

Clinical Consensus

Best Practice Recommendations for Infertility Management

1. **Dr. Jaideep Malhotra,**
Managing Director - Rainbow IVF, Agra, U.P., President ISAR (2019),
Email Id: jaideepmalhotraagra@gmail.com;
2. **Dr. M. Gouri Devi,**
President, Indian Fertility Society, Director, Ridge Fertility and IVF Group
3. **Dr. Madhuri Patil MD, FCPS, DGO, DFP, FICOG**
Address: No1, Uma Admiralty, Bannerghatta Road, Bangalore, India.
Email Id: drmadhuripatil59@gmail.com. Mobile: +919845542819.

on behalf of the Fertility Preservation Society (India)

Corresponding Author: Dr. Jaideep Malhotra and Dr. Madhuri Patil

Abstract

Aim: The objective of this document is to provide guidance to the infertility specialist, gynecologist, embryologist, and counselors on the management of sub-fertility and brief them with the recent advances in the field. These recommendations will aid the aforementioned healthcare professionals in everyday clinical decisions about appropriate and effective care of their patients with the best available evidence.

Participants: Extensive deliberations, discussion, and brainstorming was done between different reproductive medicine (RM) specialists, to develop the recommendations.

Evidence: A systematic review of the literature published up to June 2019 was carried out using PubMed and Cochrane Collaboration Library. International guidelines, cohort studies, case series, observational studies, and randomized controlled trials currently available in the literature were reviewed. Indian data whatever available was also reviewed.

Process: Primary meetings were held with leading reproductive medicine specialists. Each topic was brainstormed on by a group of reproductive medicine experts, who then prepared the first draft of the recommendation. These recommendations then were reviewed by Dr. Jaideep Malhotra, Dr. Gouri Devi, and Dr. Madhuri Patil along with the chief co-ordinator of each consensus to finalize the final draft.

Conclusions: From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient, or non-existing. For the benefit of couples undergoing several treatments, the working committee recommends that future research, where possible in well-designed RCTs, will help in establishing evidence for a particular practice. In the Indian context, one also needs to take into consideration facilities and options available, cost, lack of insurance coverage, experimental nature of some advanced techniques used.

Key Words: Infertility, IVF, ICSI, investigations, ultrasound, genetics, unexplained infertility, poor responders, endocrinopathies, ovulatory disorders, polycystic ovary syndrome, IUI, IVF, ICSI, recurrent implantation failure, fertility preservation, third party reproduction, safety, ethical issues

Published: 15-02-2024

How to cite this article: Malhotra J, Gauri Devi M, Patil M. Best Practice Recommendations for Infertility Management. J Hum Reprod Sci 2024;17:S1-240.

Access this article online	
Quick Response Code: 	Website: www.jhrsonline.org
	DOI: 10.4103/jhrs.JHRS_ISAR_IFS

Chapter 1: Investigating a Sub-fertile couple

OVERVIEW

Infertility can be caused by a number of underlying conditions including ovulatory disorders, tubal damage, male factors, and uterine or peritoneal problems. Before treatment is started, it is important that a clinical assessment, namely history taking and physical examination, is undertaken. In most cases, further diagnostic investigations are also undertaken to establish if a pathological condition is present. This guideline offers recommendations on the investigations for sub-fertile couples. The investigations are detailed for the couple together, as well as for the male and female partners individually.

1. Introduction

- Begin infertility investigations if a woman of reproductive age has failed to conceive after 12 months of regular (2–3 times per week) unprotected vaginal sexual intercourse, in the absence of any known cause of infertility
- The number and quality of oocytes are shown to decline with a woman's age. Besides, there is clear evidence that overall fertility declines with age, which is in part related to a decline in ovarian reserve, but also a lower rate of embryo implantation and an increased chance of pregnancy loss. It has been established that the fecundity of women decreases gradually, but significantly beginning approximately at age 32 years and decreases more rapidly after 37 years
- Because of the decline in fertility and increased time to conception related to advanced age, several international societies have recommended that women >35 years should receive expedited evaluation and treatment after 6 months of failed attempts to conceive, or earlier if clinically indicated
- Several studies published during last few years have reported faster ovarian ageing in Indian women with 5–6 years difference in age of menopause, and corresponding earlier decline in fertility, when compared with their counterparts in western countries
- Ethnic differences are reported to exist with ovarian ageing, as shown in a study by Iglesias C et al 2014. It was observed that similar ovarian reserve markers and ovarian response existed in women with a 6-year age difference in favor of the Spanish
 - » In a Pan-India survey conducted by the Menopause Society of India, average age of menopause in Indian women was reported as 46.2 ± 4.9 years compared to 51 years in their western counterparts
- A cut-off age of 32 years should be taken as risk factor for diminished ovarian reserve and fertility for Indian women as discussed in detail and agreed with consensus
- Follow specific factors that may mandate earlier investigations (after 6 months of failed attempts to conceive or earlier if clinically indicated) in Indian women:
 - » If woman is aged ≥ 32 years
 - » A known cause of infertility or a history of predisposing factors for infertility exists
- The term primary infertility is used when a woman has never conceived, and secondary infertility is the incapability to conceive in a couple who have had at least one successful conception in the past. Globally, most infertile couples suffer from primary infertility
- Infertility affects up to 15% of the couples of reproductive age worldwide
 - » According to the World Health Organization estimate, the overall prevalence of primary infertility in India is between 3.9% to 16.8%

- » In Indian states prevalence of infertility varies from state to state such as 3.7% in Uttar Pradesh, Himachal Pradesh, and Maharashtra, to 5% in Andhra Pradesh, and 15% in Kashmir, and prevalence varies in same region across tribes and caste
- A detailed medical history of both partners and physical examination of female partner are mandatory and helpful to decide the extent of investigations necessary in individual infertile couple
- Provide all infertile couples with pre-pregnancy counseling and offer general investigations to assess general health and detect medical and heritable genetic disorders having potentials to impact mother and/or child's health
- Focus basic standard investigations for the infertile couple on the major causes of infertility such as semen abnormalities, ovulation dysfunction, and fallopian tube obstruction/impaired function. Also, include the appropriate ovarian reserve tests under standard/basic infertility evaluation for women aged >32 years or those <32 years with risk factors for early/ expedited oocyte depletion.
- Counsel the infertile couple that only some of the causes of infertility are known, and after a conventional diagnostic assessment, in approximately 30% (reported range 15%-40%) of couples, subfertility remains unexplained. Further, even the most sophisticated array of diagnostic tests cannot reveal the defect causing infertility in many patients, with these causes remaining undiscovered at this time
- Counsel the infertile couple that even subnormal tests/investigation reports may not always mean absolute infertility and some couples will achieve pregnancy even without treatment

2. Standard investigations for sub-fertile couples

- General investigations for both partners

- Investigations for female partner
 - » Assessment of ovulation
 - » Ovarian reserve tests
 - » Tubal and uterine assessment
- Investigations for male partner

2.1 General investigations for both partners

The tests of general investigations are categorized under following headings:

- Tests to assess general health and exclude common medical disorders having impact on mother or child during pregnancy
- General investigations in male partner
- Tests to exclude existing or significant risk of contacting common infections with serious risk of vertical transmission
- Indications for genetic evaluation in subfertile couple
- To assess fitness in advanced age women
- Investigations in women with complex medical disorders

2.1.1 Tests to assess general health and exclude common medical disorders having impact on mother or child during pregnancy

2.1.1.1 Anemia

2.1.1.2 Urine analysis

2.1.1.3 Blood group and Rhesus typing

2.1.1.4 Impaired glucose tolerance and diabetes mellitus (DM)

- WHO criteria 2 hour 75 gm OGTT
 - » Impaired glucose tolerance (IGT): 140–199 mg/dl
 - » DM \geq 200 mg/dl
- American Diabetic Association (ADA) criteria fasting glucose level
 - » Impaired fasting glucose (IFG) 100–125 mg/dl
 - » DM \geq 126 mg/dl
 - » HbA1c measures the efficacy of glucose lowering treatment. A normal HbA1c cannot exclude DM or IGT

2.1.1.5 Thyroid dysfunction

- There is reasonable evidence that overt hypothyroidism may be associated with infertility and pregnancy complications. Universal screening rather than a targeted screening is recommended in subfertile Indian women considering high incidence of thyroid disorders in India
- Further evaluate women with subclinical hypothyroidism [serum thyroid stimulating hormone (TSH) between 2.5 and 10 mIU/L with normal FT4 concentration] detected during preconception by anti-thyroid peroxidase antibodies to decide regarding the need for treatment

2.1.1.6 Cervical cancer screening

2.1.1.7 Rubella immune status

2.1.1.8 Thalassemia and other hemoglobinopathies

- Majority of β -thalassemia carriers will have a mean corpuscular volume (MCV) of <80 fl and mean corpuscular hemoglobin (MCH) of <27 pg with relatively high red blood cell (RBC) counts for the level of Hb and these indices can be used for initial screening. HbA2 levels of $>4.0\%$ along with reduced RBC indices are indicative of β -thalassemia carriers. Borderline HbA2 levels (3.3%–3.9%) must be interpreted with caution and may need confirmation by DNA methods. Atypical β -thalassemia carriers may have a normal MCV and/or MCH sometimes, and these individuals may be missed on screening using RBC indices. Carriers of variant HbS like Hb E and Hb S may also have normal indices in 20%–30% of cases. In cases with microcytosis, iron deficiency anemia, and anemia of chronic disease should be ruled out and specific investigations for thalassemia and other hemoglobinopathies considered

2.2 General investigations in male partner

- Blood Hb estimation
- Urine analysis
- Blood group and Rhesus typing

- Screening for blood sugars and / or HbA1c
- Thyroid hormones

2.2.1 Tests to exclude existing or significant risk of contracting common infections with serious risk of vertical transmission

- Offer universal preconception screening for HIV, syphilis, hepatitis B, and hepatitis C for both partners
- In serodiscordant couples, additional tests would be required after a specialist consultation to assess the disease status and transmission risk. Additional or alternate procedures, counselling and decisions would be required to treat these couples
- Routine TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes simplex) panel should not be done except to check for Rubella immune status

2.3 Indications for Genetic evaluation in sub-fertile couple

- Offer peripheral blood Karyotype and Y chromosome microdeletion testing to infertile male patients diagnosed to have non-obstructive azoospermia or severe oligozoospermia (sperm density ≤ 10 million/ml)
- Offer genetic counselling and testing to men with congenital absence of unilateral or bilateral vas deference, since they need cystic fibrosis transmembrane receptor gene (CFTR) screening
- The patients with hypogonadotropic hypogonadism may need genetic tests and counselling according to clinical features
- Investigate primary amenorrhea by karyotype analysis and selected mutation screening according to the patient's clinical features
- Consider karyotype analysis and FMRI gene screening in cases of Premature Ovarian Failure (POF)
- Indicate detailed genetic testing and counselling in cases of consanguineous marriages, advanced age (either partner), family history of genetic diseases, mental retardation, genital malformations, previous affected baby, recurrent miscarriages, and recurrent

implantation failures. Peripheral blood Karyotype is minimum basic investigation

- Next generation sequencing (NGS) screening is a preferred method testing
- Carrier screening based on prevalence of common genetic diseases after proper genetic counseling should be offered
- All genetic analysis should be accompanied by expert counseling by a clinical geneticist both in male and female patients

2.4 Additional tests that may be required in women older than 35 years

- Oocyte and embryo donation are accepted treatments of age related fertility decline. Pregnancies in advanced age are complicated by increased risks of maternal and perinatal morbidity and mortality. Common causes are diabetes, hypertensive disorders, and cardiac and thromboembolic events. It is mandatory for the care takers to evaluate these women completely to exclude or control any pre-existing medical disease

2.4.1 Recommended tests

- Oral glucose tolerance test
- Lipid profile
- Liver function tests
- Renal function tests
- Electrocardiogram
- X-ray chest
- Echocardiography in post-menopausal women
- USG/ mammogram
- Whole abdomen ultrasound for abdominal organs

2.5 Investigations in women with specific medical disorders needing complete evaluation are:-

- Turner's syndrome
- Cardiomyopathy
- Treated malignancies
- Hereditary thrombophilias with h/o thromboembolism
- Bleeding disorders
- Severe respiratory insufficiency

- Ischemic heart disease
- Renal transplant or chronic renal failure
- Portal hypertension

2.6 General investigations for female partner

2.6.1 Assessment of ovulation

- Although regular menstruation is strongly suggestive of ovulation, it should be confirmed by mid luteal progesterone (MLP)
- Progesterone on day 21 in 28 day cycle/ progesterone every 7 days after day 21 in patients with irregular menstrual cycles till until the next menstruation
- Values of ≥ 3 ng/ml are suggestive of ovulation and values of ≥ 10 ng/ml are suggestive of normal progesterone production
- Urinary LH Kit
- Ultrasound guided follicular monitoring

2.6.2 WHO classification of ovulation disorders

- The WHO classifies ovulation disorders into three groups (Table 1)

Table 1. WHO classification of ovulatory disorders

Group I: Hypothalamic/pituitary failure	Kallmann's syndrome hypogonadotrophic hypogonadism	5%
Hypothalamic causes (hypogonadotropic hypogonadism)	Weight loss Exercise Chronic illness Psychological distress Idiopathic	
Causes of hypothalamic/pituitary damage	Tumours (e.g. cranio-pharyngiomas) Cranial irradiation Head injuries Sarcoidosis Tuberculosis	
Systemic causes	Chronic debilitating illness Weight loss	
Endocrine disorders	Thyroid, Cushing's syndrome	
	Hyperprolactinemia Hypopituitarism	
Group II: H/P dysfunction	Polycystic ovary syndrome	90%
Group III: Ovarian failure	Premature ovarian failure (POF) Resistant ovary syndrome (ROS)	5%

- The table below shows the diagnostic hormonal levels in anovulatory infertility

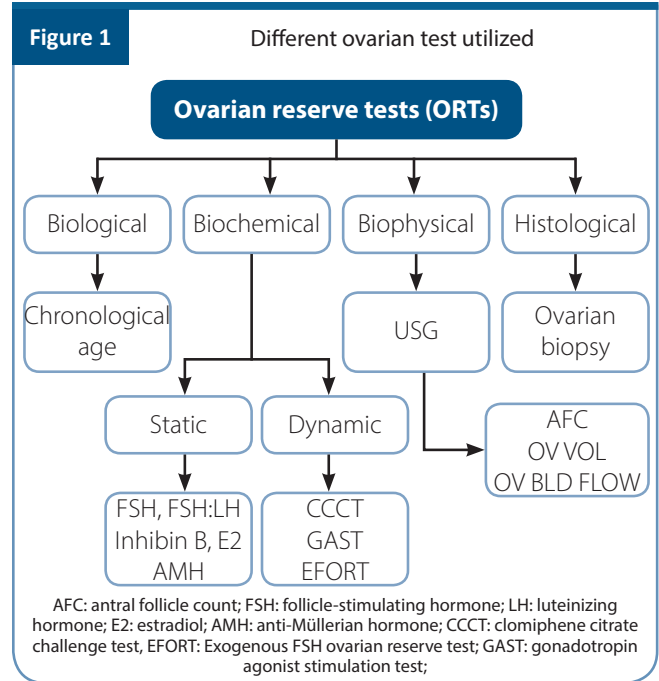
Table 2. Diagnostic Hormonal levels in anovulatory Infertility	
Hypothalamic: underweight	↓FSH, ↓ LH, ↓E2 n FSH, ↓ LH, ↓ E2
Hyperprolactinaemia	↓ FSH, ↓ LH, ↓ E2
Ovarian failure / menopause:	↑↑ FSH, ↑ LH, ↓E2
Mid-cycle	↑ FSH, ↑↑ LH, ↑ E2
PCOS	↓/n FSH, ↑/n LH, ↑/n E2
FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; PCOS: polycystic ovary syndrome.	

2.6.3 Ovarian reserve tests

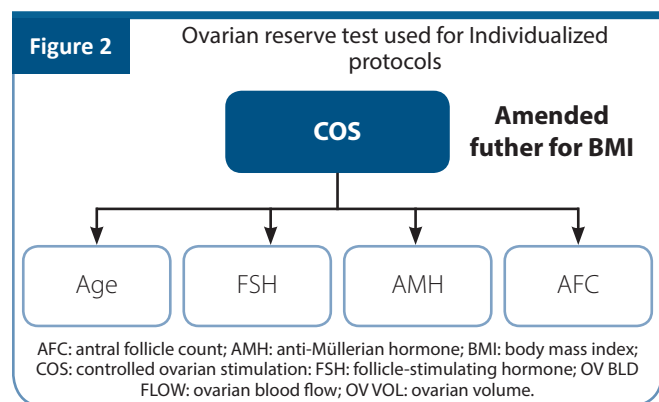
- Ovarian reserve test are used to
 - » Improve efficacy, safety and cost effectiveness of treatment
- Predict response to tailor correct stimulation regimen for adequate response so as to prevent complications and improve pregnancy outcomes
- Response to the first cycle of controlled ovarian stimulation (COS) is the most important predictor of ovarian response
- Ovarian reserve testing help for a strategic approach to ovarian stimulation (Table 3)

Table 3. Use of ovarian reserve test for strategic approach to ovarian stimulation in hyper and poor responders	
Anticipated excessive ovarian response, clinicians can provide guidance on the <ul style="list-style-type: none"> AMH >3.5 ng/mL-high risk of OHSS, regardless of age Potential risks of OHSS and multiple pregnancy associated with treatment Advise on low dose gonadotropin antagonist protocols GnRHa trigger Stringent monitoring during treatment 	Predicted poor ovarian response, clinicians may decide to counsel patients not to proceed with treatment <ul style="list-style-type: none"> Alter their treatment protocol Exogenous agents Not feasible to deny treatment based on low (1.0 ng/mL) AMH level Combination of low AMH levels & POR in the first IVF cycle suggest unfavourable prognosis and one must avoid further IVF Suggest egg donation at an early stage in their management
AMH: anti-Müllerian hormone; OHSS: ovarian hyperstimulation syndrome; IVF: in-vitro fertilization; GnRHa: gonadotropin-releasing hormone agonist; POR: poor ovarian response.	

- The figure 1 gives the different ovarian test that can be utilized to assess the ovarian reserve. The choice of the test will depend on local provision, such as laboratory resources and availability of a skilled ultrasonologist



Of these test only age, AMH, AFC, and FSH are used to select the correct stimulation protocol. The dose of gonadotropin used depending on these ovarian reserve test is further amended for BMI (Figure 2)



2.6.3.1 Limitations of ovarian reserve tests (Table 4)

2.6.3.2 Key points

- AMH an excellent marker of ovarian response and can predict extremes of response as compared to FSH, but a weak predictor of clinical pregnancy

- High accuracy for AMH and AFC in predicting poor response but only moderate accuracy for FSH
- Significant negative interaction between age and AMH
- AMH and age independent determinants of oocyte yield
- Accuracy of AMH, AFC, and FSH in predicting zero prognosis cases is poor and can be possible only at extreme cut-off levels
- All three Ovarian reserve tests (ORTs) have only a very small or no predictive effect on pregnancy rates
- Sexually transmitted infections (STIs) are the leading preventable cause of infertility by causing 70% of PID responsible for tubal damage
- Other causes are endometriosis, previous surgery for ruptured appendix or other abdominal surgeries including surgery for ectopic pregnancies
- The tests used to diagnose tubal factor infertility are hysterosalpingography, sonosalpingography, hysterosalpingo contrast sonography, and laparoscopy
 - » Hysterosalpingography (HSG)
 - » Sonosalpingography (SSG)
 - » Hysterosalpingo contrast sonography (HyCoSy) is same as SSG, the only difference is instead

2.6.4 Tubal and uterine assessment

2.6.4.1 Tubal factors

- Tubal factor infertility accounts for 25%–35%. The most common cause of tubal factor infertility is infection pelvic inflammatory diseases (PID)

Table 4. Limitations of the ovarian reserve tests used

Ovarian reserve tests (ORTs)	Limitations
FSH	<ul style="list-style-type: none"> • Does not diagnose poor ovarian reserve until high thresholds reached • Does not explain oocyte quality decline • Inter-cycle and inter-sample variations may result in a disparity in FSH measurements • Role limited in the evaluation of young healthy Women • Elevated day 3 FSH - heterogeneous group <ul style="list-style-type: none"> » true reduced ovarian reserve » due to the presence of heterophile antibodies » FSH receptor polymorphism in patients with otherwise normal ovaries
Estradiol	<ul style="list-style-type: none"> • Prediction of ovarian reserve is still debatable • No relationship has been found between serum E2 levels and pregnancy rates • Very low predictive accuracy, both for the poor response or excessive response
Inhibin B	<ul style="list-style-type: none"> • Better predictor for cancellation than the ovarian response • It is influenced by the amount of fat in an individual with levels lower in obese women
AMH	<ul style="list-style-type: none"> • AMH concentrations able to predict the number of oocytes collected after ovarian stimulation • No role in predicting oocyte quality or LBR • Expensive • Lack of standardization of AMH assay • Variable AMH measurements made by the different AMH assays, even when using the same clinical sample • Women with higher basal AMH concentration experience greater variation in AMH values over time
AFC	<ul style="list-style-type: none"> • Access to quantity but not quality • Inter/Intra-observer differences – may be reduced by 3D USG • Losing track of measured or not yet ---- One or two adjacent follicles • Inter-cycle variability • Poor predictive value for pregnancy
Ovarian Volume	<ul style="list-style-type: none"> • Wide range in the definition of normal ovarian volume in the reproductive age group • Predictive value for pregnancy limited (1.0–1.4) • Has high false-positive test therefore not suitable as a routine test for ovarian reserve assessment
Dynamic test	<ul style="list-style-type: none"> • More expensive and invasive, time-consuming • Done only in the research setting
Ovarian Biopsy	<ul style="list-style-type: none"> • Invasive • Follicular density varies • Long-term consequences

of normal saline, a radiocontrast dye is instilled inside the uterine cavity.

» Laparoscopy

2.6.4.2 Uterine factors

- Ultrasonography (2D & 3D)
- Hysterosalpingography has a sensitivity of between 50% for intracavitary lesions and it is unable to reliably distinguish between submucosal myomas and endometrial polyps. HSG has low sensitivity (50%) and a positive predictive value of 30%. It cannot differentiate between septate and bicornuate uterus hence MRI or 3D USG is necessary
- Saline Infusion sonography and HSG have similar diagnostic accuracies (52% vs. 60%). It has a high positive predictive value (90%) for detecting intrauterine pathology. It does not involve radiation
- Hysteroscopy
- MRI

2.7 Investigations for male partner

2.7.1 Investigations

2.7.1.1 Semen analysis

Table 5. WHO lower reference limits* for semen characteristics

Criteria	Lower reference value
Serum morphology (normal forms, %)	1.5 (1.4–1.7)
Total sperm number (106 per ejaculate)	39 (33–46)
Sperm concentration (106 per ml)	15 (12–16)
Total motility(PR + NP, %)	40 (38–42)
Progressive motility(PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other consensus threshold values	
ph	≥ 7.2
Peroxidase-positive leukocytes (106 per ml)	< 10
MAR test (motile spermatozoa with bound beads, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	≥ 2.4
Seminal zinc	≥ 13
Seminal fructose (micromole/ejaculate)	≥ 20
Seminal neutral glucosidase (milli units ejaculate)	
*5th centiles and their 95% confidence intervals, who: world health organization, 2010	

2.7.1.2 Microscopic examination

• Initial microscopic examination

» This provides an overview of the sample, to reveal:

- Mucus strand formation.
- Sperm aggregation or agglutination (the presence of agglutination is not sufficient evidence to deduce an immunological cause of infertility, but is suggestive of the presence of anti-sperm antibodies; further testing is required. Severe agglutination can affect the assessment of sperm motility and concentration)
- The presence of cells other than spermatozoa, such as epithelial cells, “round cells” (leukocytes and immature germ cells) and isolated sperm heads or tails

• Detailed microscopic examination

» Sperm motility

- Grade the motility of each spermatozoon as follows:
 - # Progressive motility (PR): Spermatozoa moving actively, either linearly or in a large circle, regardless of speed
 - # Non-progressive motility (NP): All other patterns of motility with an absence of progression, such as swimming in small circles, the flagellar force hardly displacing the head, or when only a flagellar beat can be observed
 - # Immotility (IM): No movement

» Sperm vitality

- The presence of a large proportion of vital but immotile cells may be indicative of structural defects in the flagellum; a high percentage of immotile and non-viable cells (necrozoospermia) may indicate epididymal pathology

» Sperm Numbers

- It is recommended to calculate and report the total number of spermatozoa per ejaculate, as this parameter provides a

measure of the capability of the testes to produce spermatozoa and the patency of the male tract.

» **Sperm morphology**

- Strict Kruger's criteria are used to evaluate the morphology
- Coiled tails ($>360^\circ$) may indicate epididymal dysfunction
- Abnormal spermatozoa generally have a lower fertilizing potential, depending on the types of anomalies, and may also have abnormal DNA
- Morphological defects have been associated with increased DNA fragmentation, an increased incidence of structural chromosomal aberrations, immature chromatin, and aneuploidy

» **Presence of leucocytes/peroxidase positive cells**

- Excessive numbers of leukocytes in the ejaculate (leukocytospermia, pyospermia) may be associated with infection and poor sperm quality

» **Assessment of immature germ cells in semen**

- Germ cells include round spermatids and spermatocytes, but rarely spermatogonia. They can be detected in stained semen smears, but may be difficult to distinguish from inflammatory cells when the cells are degenerating

» **Testing for antibody coating of spermatozoa**

- The diagnosis of immunological infertility is made when 50% or more of the motile spermatozoa (progressive and non-progressive) have adherent particles. Particle binding restricted to the tail tip is not associated with impaired fertility and can be present in fertile men

2.7.1.3 Biochemical tests on seminal plasma

• **Seminal fructose**

- » The lower reference limit for fructose is 13 mol per ejaculate
- » Low fructose in semen is characteristic of ejaculatory duct obstruction, bilateral congenital absence of the vas deferens, partial retrograde ejaculation, and androgen deficiency
- » Other biochemical tests such as zinc, alpha-glucosidase are optional and not of much clinical significance

2.7.1.4 Computer aided sperm analysis (CASA)

- CASA, including assessment of motility, concentration and morphology, has two advantages over manual methods:
 - » Has high precision
 - » Provides quantitative data on the kinematic parameters of spermatozoa (forward progression and hyperactivated motility, characteristic of capacitated cells)
- The use of fluorescent DNA stains with CASA allows the concentration of motile sperm and percentage motility to be determined accurately, but scrupulous adherence to technique is required
- The CASA instrument detects and counts fluorescent sperm heads. Without microscopic evaluation, there is no way of knowing if the spermatozoa are intact (the head is attached to a tail)
- Semen analysis will provide the direction for further evaluation and treatment. If semen analysis is abnormal we need to evaluate further (Table 6)
- In presence of low volume, the male partner is evaluated as follows (Figure 3)

2.7.1.5 Diagnosis based on hormonal tests

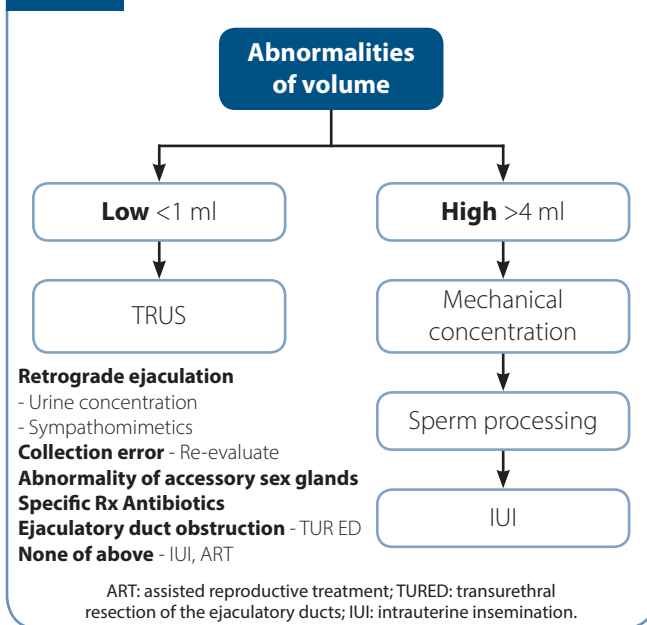
- In case of an abnormal semen analysis the diagnosis can be achieved by performing hormonal investigations. (Figure 4)

Table 6. Investigations for male partner

Medical and Sexual history	<ul style="list-style-type: none"> • Coital frequency and timing • Duration of infertility and prior fertility • Childhood illnesses and developmental history • Systemic medical illnesses • Prior surgeries • Sexual history including sexually transmitted diseases • Gonadal toxin exposure including heat
Physical Examination Recommended in cases of : Abnormal Male history Abnormal semen analysis Unexplained Infertility Treated female factor with persistent infertility	<ul style="list-style-type: none"> • Secondary sexual characters • Examination of penis • Palpation of testis and measurement of size • Presence and consistency of vas and epididymis • Evaluation for varicocele • Digital rectal examination
Ultrasound	For determination of <ul style="list-style-type: none"> • Size of testis • Varicocele • Hydrocele • Epididymal cyst • Spermatocele • Epididymitis • Orchitis • Testicular torsion • Cryptorchidism
Endocrine Evaluation Initially recommended in cases of Low sperm count especially if less 10 mill/ml Impaired sexual function Clinical findings suggestive of a endocrinopathy	Minimal: <ul style="list-style-type: none"> • FSH • Testosterone Additional in cases of low testosterone: <ul style="list-style-type: none"> • Repeat testosterone • SHBG • Prolactin • LH No role for evaluating AMH and Inhibin B
Karyotyping	Klinefelters syndrome XXY and variants Translocations Balanced Unbalanced
Molecular genetics	<ul style="list-style-type: none"> • Y-chromosome microdeletion • Cystic Fibrosis Gene mutations
Sperm function test Diagnose some subtle changes and help clinically to direct therapy	<ul style="list-style-type: none"> • Trial Wash • HOS • TZI • CASA • DFI • Acrosome reaction • Mucus Penetration test • Estimation of ROS Not regularly performed prior to ART treatment because they are <ul style="list-style-type: none"> • complex • expensive • not rigorously tested • do not always provide clinically useful information • typically do not affect treatment • cannot be performed with good repeatability and reliability and at minimal cost
Testicular Biopsy	Diagnostic / therapeutic testicular biopsy for ultimate differentiation between obstructive and non-obstructive azoospermia Should be done only when facilities for cryopreservation are available
Post ejaculation urine examination	To differentiate between retrograde ejaculation and an ejaculation

Figure 3

Evaluation of male with low volume



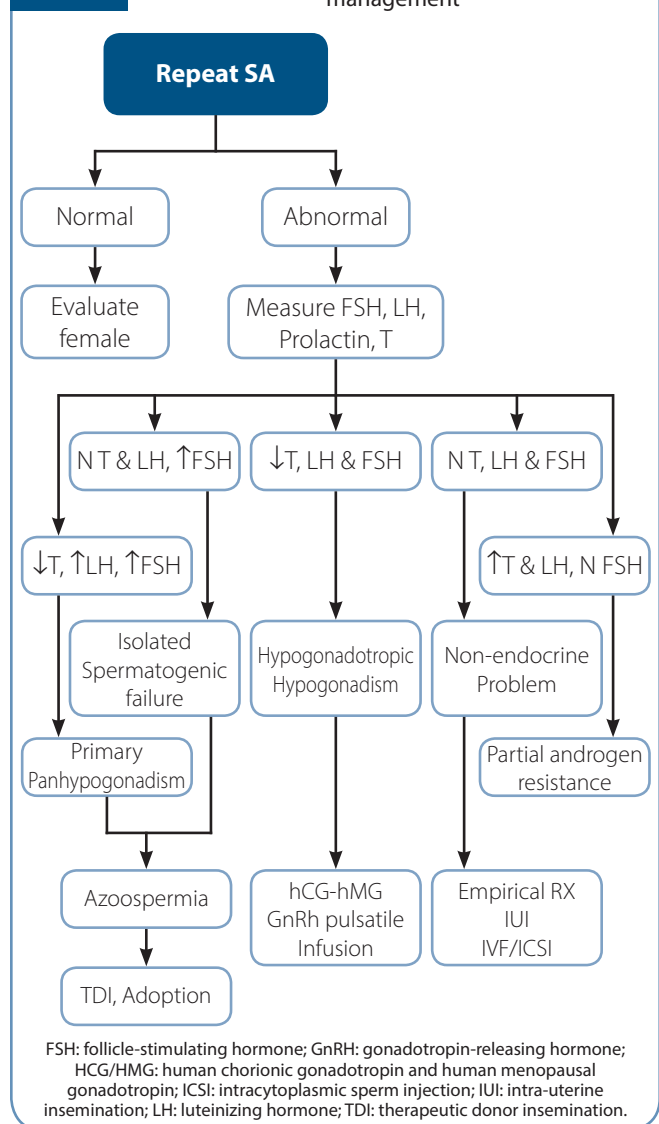
- Evaluation of azoospermic male (Figure 5)

Summary of recommendations

- Begin infertility investigations if a woman of reproductive age has failed to conceive after 12 months of regular (2–3 times per week) unprotected vaginal sexual intercourse, in the absence of any known cause of infertility
- Several published reports suggest faster ovarian aging in Indian women, it is recommended that all Indian women >32 years of age should be considered for expedited evaluation after 6 months of failed attempts to conceive, or earlier, if there is a known cause of infertility or a history of predisposing factors for infertility
- All infertile couples must be provided pre-pregnancy counseling, detailed medical history, physical examination and general investigations to assess general health and detect medical and heritable genetic disorders having potentials to impact the mother and/or child's health
- Given the high incidence of thyroid disorders in Indian population, routine screening by measurement of thyroid stimulating hormone (TSH) is recommended in all Indian subfertile women

Figure 4

Hormonal tests in the male for final diagnosis and management

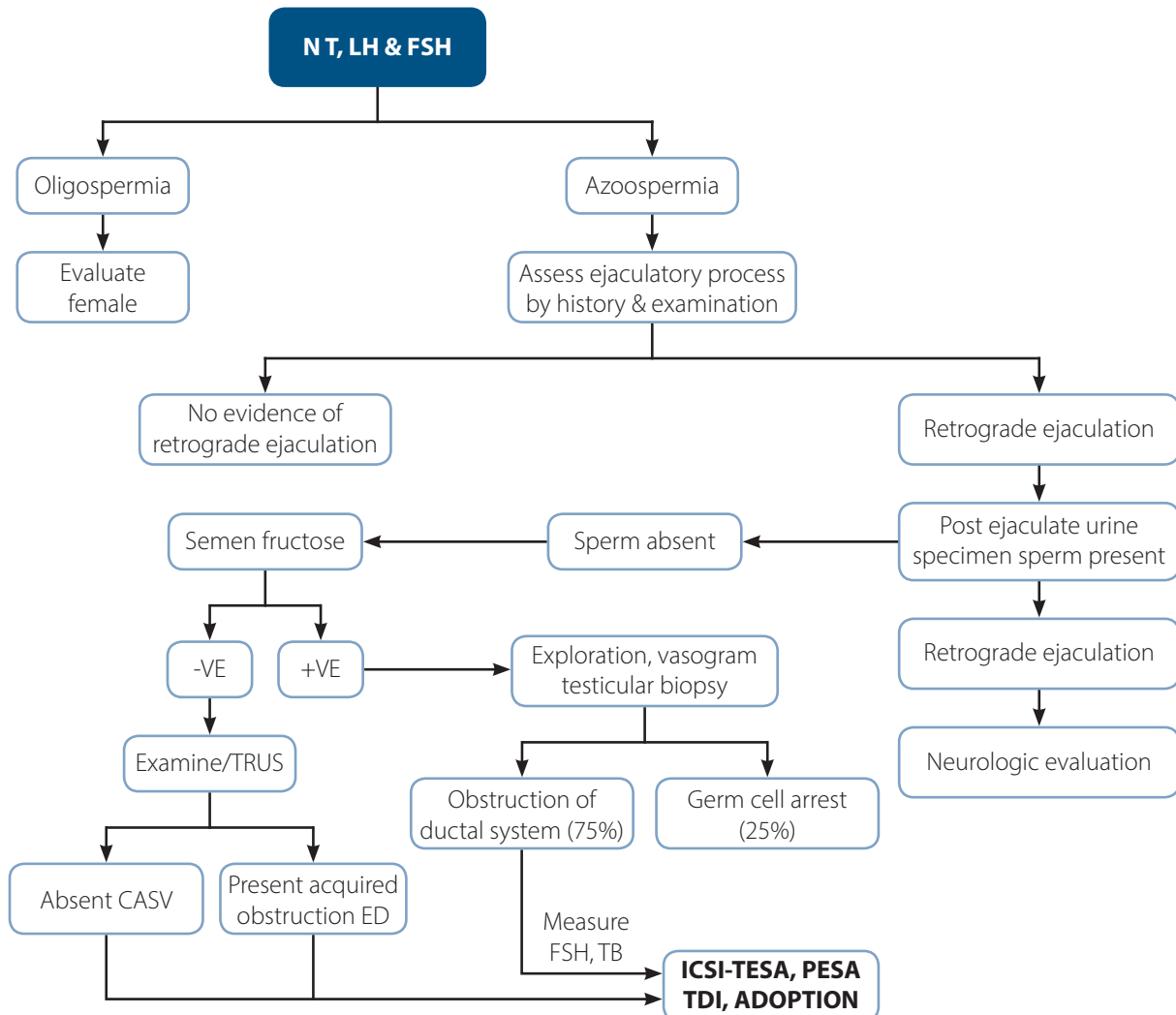


- As the major causes of infertility are semen abnormalities, ovulation dysfunction and fallopian tube obstruction/impaired function, the basic/preliminary investigations for the infertile couple should be focused on these only. However, it is recommended that for women aged >32 years or those <32 years with risk factors for early/expedited oocyte depletion, appropriate ovarian reserve tests, should also be included under standard/basic infertility evaluation
- At mid-luteal phase (day 21 of a 28-day cycle), serum progesterone should be checked to confirm ovulation even if the woman has regular menstrual cycles

Figure 5

Evaluation of Azoospermia

Azoospermia with normal FSH, LH and Testosterone



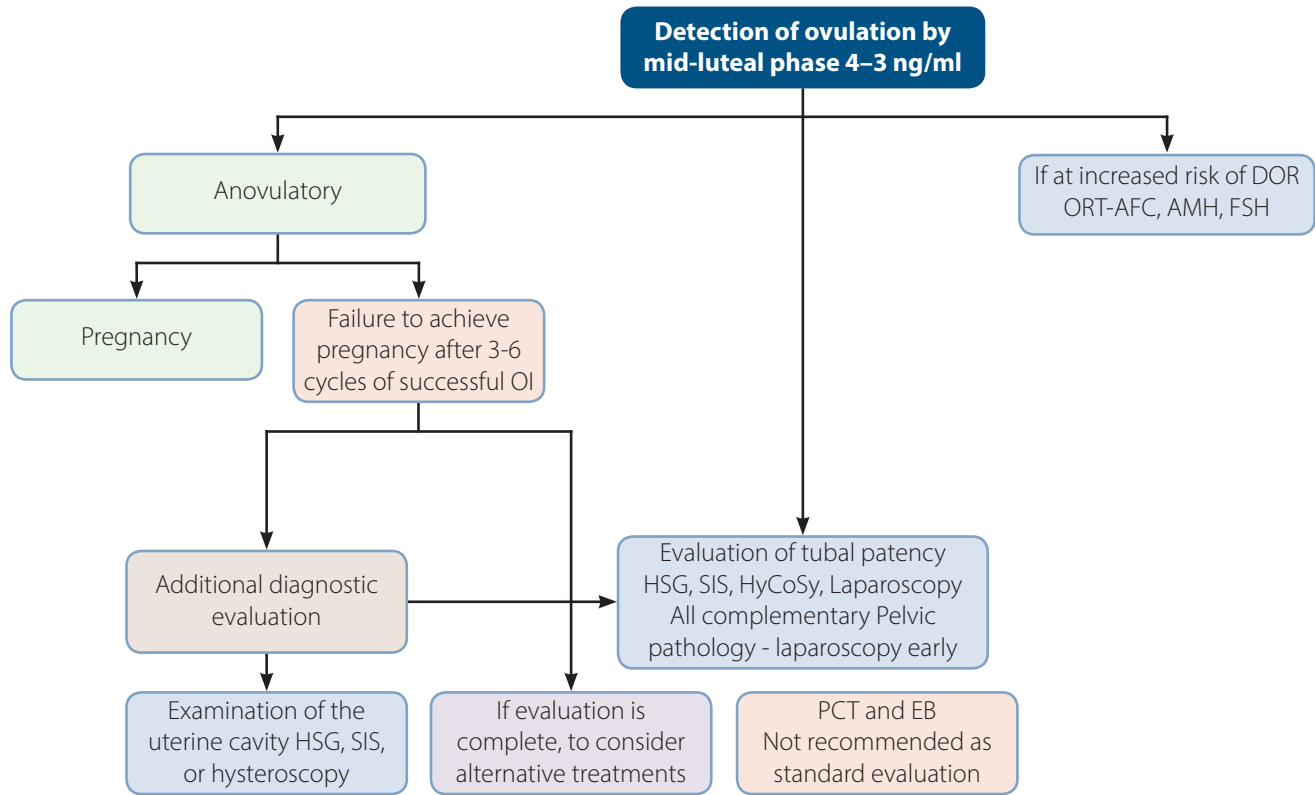
CASV: congenital agenesis of the seminal vesicle; FSH: follicle-stimulating hormone; ICSI: intracytoplasmic sperm injection; LH: luteinizing hormone; PESA: percutaneous epididymal sperm aspiration; TESA: testicular sperm aspiration; TDI: therapeutic donor insemination; TRUS: Transrectal ultrasound.

follicular ultrasound examination (follicle monitoring) is an accepted option to assess ovulation

- Endometrial biopsy for histologic endometrial dating is not recommended, however, endometrial biopsy should be performed in women with suspected pathology, such as chronic endometritis or neoplasia
- Women with irregular menstrual cycles and/or suspected of ovulation disorder should be offered serum gonadotropins (FSH and LH) and other relevant hormones including estradiol, AMH, and prolactin
- Ovarian reserve testing may be considered for women aged >32 or for women <32 with risk factors for decreased ovarian reserve, such as those with previous ovarian surgery, poor response to FSH, endometriosis, previous exposure to chemotherapy or radiation, or unexplained infertility
- Ovarian reserve tests are also helpful prior to ART treatment to predict poor responders and over-responders and may be used for counseling and selecting appropriate controlled ovarian stimulation protocol. However, these tests cannot predict

Figure 6

Algorithm for investigating the female



AMH: anti-Müllerian hormone; DOR: diminished ovarian reserve; FSH: follicle stimulating hormone; HSG: hysterosalpingogram; HyCoSy: hysterocontrast salpingography; OI: ovulation induction; ORT-AFC: ovarian reserve tests-antral follicle count; PCT: post-coital test; SIS: saline-infusion sonohysterograph.

Figure 7

Algorithm for investigating the male

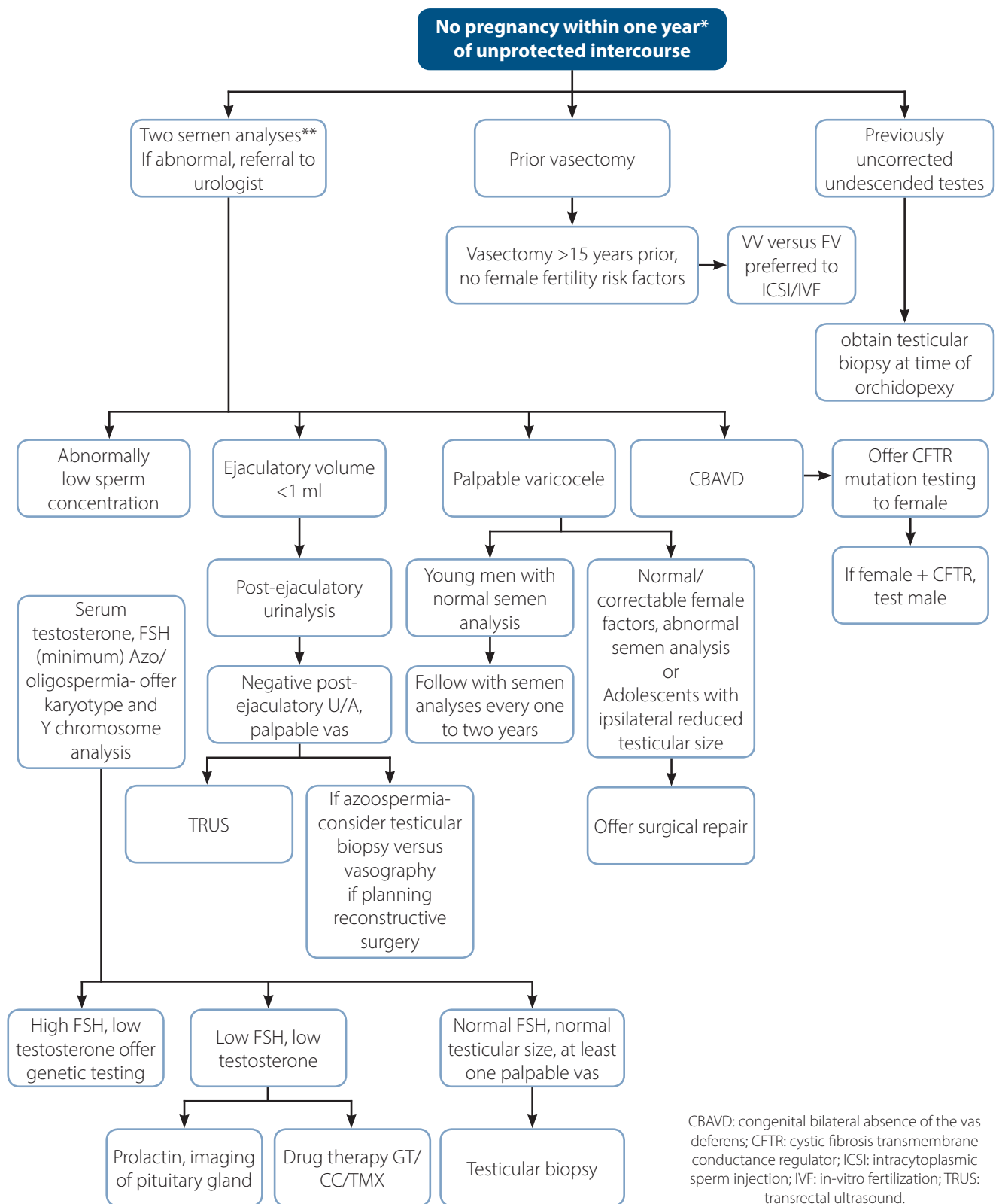


Table 7. Important female reproductive hormone levels in blood and their clinical relevance (normal values should be guided by reference range of the laboratory used)

Hormone Test	Timing	Normal range	Clinical relevance
Follicle stimulating hormone (FSH)	Day 3 of cycle	4–8.9 IU/L	FSH>8.9 IU/L low ovarian reserve. FSH > 25 IU/L indicates Premature Ovarian Insufficiency (POI). Extremely low levels indicate hypogonadotropic hypogonadism.
Estradiol (E2)	Day 3	30–80 pg/ml	Abnormally high levels on day 3 (>80pg/ml) may indicate existence of a functional cyst or diminished ovarian reserve. Extremely low levels will be found in WHO Group 1 & Group 3
Estradiol (E2).	Surge/hCG day	>200 pg/ml	The levels should be 150-200pg/ml per mature (18mm) follicle.
Luteinizing hormone (LH)	Day 3	3–10 IU//L	LH: FSH ratio >2 is an indication of PCOS. Extremely low levels of LH are seen in hypogonadotropic hypogonadism.
Luteinizing hormone (LH)	Surge day	>20 mIU/ml	The LH surge leads to ovulation within 48 hours.
Prolactin		2–29 ng/ml	High levels >50- 100 ng/ml need further investigations to exclude prolactinoma
Progesterone	Day 3	<1.0 ng/ml	An elevated level may indicate a lower success rate for pregnancy.
Progesterone	Day 21	>5 ng/ml (>15.9 nmol/L)	A level over 5 ng/ml indicates ovulation, but a level over 10ng/ml in a natural cycle indicates an adequate luteal phase
Anti-Mullerian hormone (AMH)	Any day of cycle	1.2–3.5 ng/ml	There is no universal consensus on normal or cut off levels. AMH levels <0.75 – 1.2 ng/ml predict low response and ≥3.5 ng/ml predict high response in IVF cycles.
Thyroid stimulating hormone (TSH)		0.35–5 mu/L	Subclinical hypothyroid in women desiring to become pregnant should be treated with the aim of keeping TSH <2.5mu/L
Total testosterone		8–70 ng/dl (0.5–3 nmol/L)	More than >2 SD above the mean for the assay used can suggest presence of androgen secreting ovarian or adrenal tumor
Free testosterone	Follicular phase	0.45–3.18 pg/ml	High quality assays such as LCMS/mass spectrometry and extraction/ chromatography immunoassays should be used for the most accurate assessment of total or free testosterone FAI or CFT are more reliable to assess biochemical hyperandrogenism in PCOS
	Luteal phase	0.46–2.48 pg/ml	
Dehydroepian-drosterone sulfate (DHEAS)	20–24 yrs age	< 407 µg/dl	High levels can suggest an adrenal tumor
	25–34 yrs age	< 340 µg/dl	
	35–44 yrs age	< 337 µg/dl	
Androstenedione		0.7–3 ng/ml (2.0–11 nmol/L)	Could be tested while investigating hyperandrogenism, if total or free testosterone not elevated
Sex hormone binding globulin (SHBG)		18–144 nmol/L	Increased androgen production often leads to lower SHBG. Free androgen Index (FAI) = (Total Testosterone ÷ SHBG) X 100 Normal FAI = 0.5%–6.5%
17 Hydroxy-progesterone (17-OHP)	Follicular phase	0.32–1.47 ng/ml (<80 ng/dL)	Used for screening of congenital adrenal hyperplasia (CAH) due to 21–hydroxylase deficiency
	Luteal phase	0.25–2.91 ng/ml (<285 ng/dL)	Early morning 17– OHP levels of >200 ng / dL should prompt further evaluation.

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Begin infertility investigations if a woman of reproductive age has failed to conceive after 12 months of regular (2–3 times per week) unprotected vaginal sexual intercourse, in the absence of any known cause of infertility	A	II
EBR	In view of the several published reports suggesting faster ovarian ageing in Indian women, it is recommended that all Indian women >32 years of age should be considered for expedited evaluation after 6 months of failed attempts to conceive, or earlier, if there is a known cause of infertility or a history of predisposing factors for infertility	B	II
EBR	All infertile couples must be provided pre-pregnancy counselling, detailed medical history, physical examination and general investigations to assess general health and detect medical and heritable genetic disorders having potentials to impact mother and/or child's health	A	II
EBR	In view of high incidence of thyroid disorders in Indian population, routine screening by measurement of TSH is recommended in all Indian subfertile women	A	II
EBR	As the major causes of infertility are semen abnormalities, ovulation dysfunction and fallopian tube obstruction/impaired function, the basic/preliminary investigations for the infertile couple should be focused on these only. However, it is recommended that for women aged >32 years or those <32 years with risk factors for early/ expedited oocyte depletion, appropriate ovarian reserve tests, should also be included under standard/basic infertility evaluation	A	II
EBR	At mid-luteal phase (day 21 of a 28-day cycle), serum progesterone should be checked to confirm ovulation even if the woman has regular menstrual cycles	C	IV
EBR	Follicular ultrasound examination (follicle monitoring) is an accepted option to assess ovulation.	B	III
EBR	Endometrial biopsy for histologic endometrial dating is not recommended, however, endometrial biopsy should be performed in women with suspected pathology, such as chronic endometritis or neoplasia.	B	II
EBR	Women with irregular menstrual cycles and/or suspected of ovulation disorder should be offered serum gonadotropins (FSH and LH) and other relevant hormones including estradiol, AMH and prolactin.	B	III
EBR	Ovarian reserve testing may be considered for women aged >32 or for women < 32 with risk factors for decreased ovarian reserve, such as those with previous ovarian surgery, poor response to FSH, endometriosis, previous exposure to chemotherapy or radiation, or unexplained infertility	B	II
EBR	Ovarian reserve tests are also helpful prior to ART treatment to predict poor responders and over-responders and may be used for counseling and selecting appropriate controlled ovarian stimulation protocol. However, these tests cannot predict clinically important outcome such as pregnancy and should not be used to exclude an infertile couple from seeking ART	B	II
EBR	Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or severe endometriosis) should be offered hysterosalpingography (HSG) or SIS as an initial screen test for tubal occlusion under initial investigations, because this is a reliable test to rule out tubal occlusion, and less invasive	A	II
EBR	Women who are thought to have comorbidities should be offered laparoscopy and dye test, so that tubal and other pelvic pathology can be assessed and treated at the same time	B	II
EBR	Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated	A	I
EBR	The results of semen analysis conducted as part of an initial assessment should be compared with the World Health Organization 2010 reference values	A	II
EBR	If the semen analysis is normal, there is no need for a repeat analysis. If azoospermia or severe oligozoospermia is reported in the initial semen analysis, a repeat test should be undertaken within two to four weeks	A	I
CCR	Advice further relevant investigations, counselling and referral to specialist for men who have two abnormal semen analyses	B	-
EBR	Genetic tests may be required in selected cases of subfertile men and women based on medical history, clinical features and standard investigation reports, and should be accompanied by expert counselling by a clinical geneticist in all cases	B	III

clinically important outcomes such as pregnancy and should not be used to exclude an infertile couple from seeking ART

- Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or severe endometriosis) should be offered HSG or saline infusion sonohysterography (SIS) as an initial screen test for tubal occlusion under initial investigations, because this is a reliable test to rule out tubal occlusion, and less invasive
 - Women who are thought to have comorbidities should be offered laparoscopy and dye test so that tubal and other pelvic pathology can be assessed and treated at the same time
 - Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated
 - The results of semen analysis conducted as part of an initial assessment should be compared with the World Health Organization 2010 reference values
 - If the semen analysis is normal, there is no need for a repeat analysis. If azoospermia or severe oligozoospermia is reported in the initial semen analysis, a repeat test should be undertaken within two to four weeks
 - Advice further relevant investigations, counseling and referral to a specialist for men who have two abnormal semen analyses
 - Genetic tests may be required in selected cases of subfertile men and women based on medical history, clinical features, and standard investigation reports, and should be accompanied by expert counseling by a clinical geneticist in all cases
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Chapter 2: Ultrasound for Infertility

OVERVIEW

This guideline offers recommendations on the technique and safety of ultrasound scanning. It also provides recommendations for the use of the ultrasound scan for the evaluation of various gynecological pathologies. In addition to this, it provides recommendations for using the ultrasound for early first-trimester scan, ectopic pregnancy, evaluation of tubal patency, and sub-fertile man.

1. Overview of techniques and safety statement

1.1 Need for ultrasound in infertility:

- To optimize the traditional anatomic diagnosis of the infertile male and female
- To stratify patient care: expectant vs. medical vs. surgical vs. newer technique
- Appropriate counseling of the patients in their specific infertility scenario
- Ultrasound images provide a road map for surgery by determining the needed instruments, equipment's, expertise, duration of surgery, cost and recovery time
- Provides information to the patients with respect to the limitations associated with the success of the surgery and treatment.
- Providing a fast decision on whether to perform surgery/surrogacy in women with uterine factor
- The technique is cost-effective

1.2 Safety of ultrasound

- Evidence suggests that ultrasound scanning has not produced any harm to patients from the time (over four decades) it is being used
- Transvaginal scans and 3D/4D scans are also found to be safe
- The embryonic heart should be evaluated by M-mode
- Keep the examination times as short as required to produce a useful diagnostic result
- Keep the output levels as low as is reasonably achievable (ALARA principle) while producing a useful diagnostic result

1.3 Category of infertility ultrasounds

The category of infertility ultrasounds should be specified in the requisition and in the report. The categories include: (Figure 1)

1.4 Components of a detailed gynecological scan

- A detailed gynecological scan includes following components:
 - » Cervix and uterus–endometrium , myometrium
 - » Ovaries – antral follicle count, ovarian reserve, polycystic ovaries, follicular development,

Figure 1

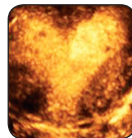
Category of infertility scans



To prove normalcy



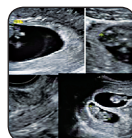
Follicular monitoring and response to treatment



To detect structural problems



Ultrasound guided procedures



Confirmation and progress of pregnancy after treatment for infertility

corpus luteum development, presence of physiological and pathological ovarian cyst

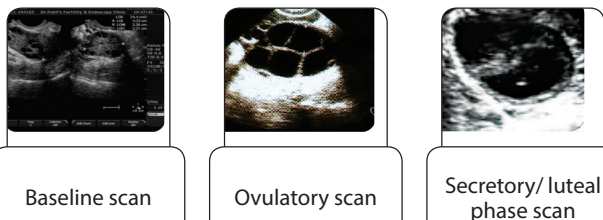
- » Tubes – USG guided procedures to establish patency (SIS, HyCoSy), diagnosis of pathology (hydrosalpinx, ectopic pregnancy)
- » Peritoneum, lymph nodes
- » Abnormalities if any

1.5 Points be considered while performing a gynecological scan

- » In order to minimize chances of missing large lesions, wandering fibroids, and high located ovaries, a transabdominal scan is encouraged as a scout procedure
- » Transvaginal scanning should commence at the introitus
- » Each component of pelvic anatomy should be scanned from superior to inferior, medial to lateral, and anterior to the posterior extent; mobility of viscera is particularly important
- » During scanning, all negative and positive findings must be imaged and documented
- » Any variation from the protocol should be supported by valid reason and this should be documented in the report
- » Every institution/clinic can have its own limited protocol if there is resource restriction, shortage of staff or compromised equipment. The patient must be made aware of this institutional limitation

1.6 Assessment of the cycle should include the following (Figure 2)

Figure 2 Ultrasound assessment of menstrual cycle in a sub-fertile women



2. Guidelines for the first visit scan

- A detailed scan at the first visit of the patient can offer tremendous insight into the cause of infertility
- Cervical scan: Position, direction and abnormality (Figure 3 A, B, C, D, E, F, and G)

Figure 3 A & B

Cervical scan for position and direction

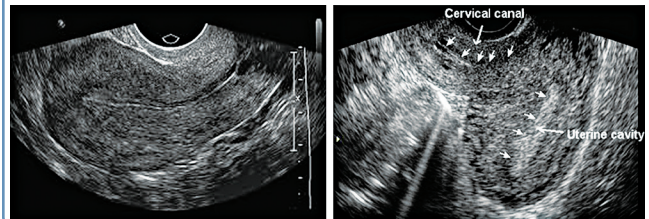


Figure 3 C, D, & E

Vascular Cervical Polyp

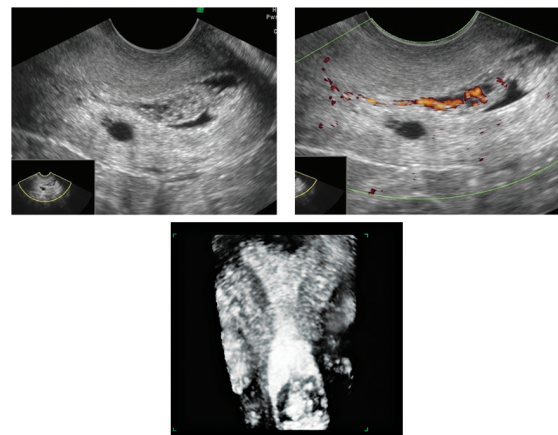
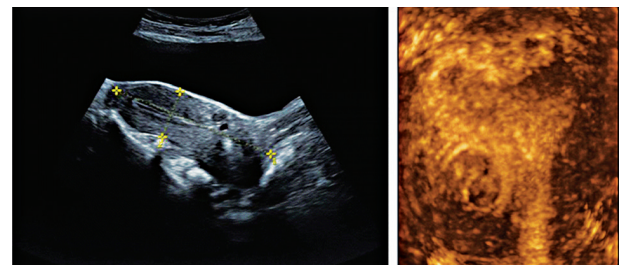


Figure 3 F & G

Cervical Fibroid

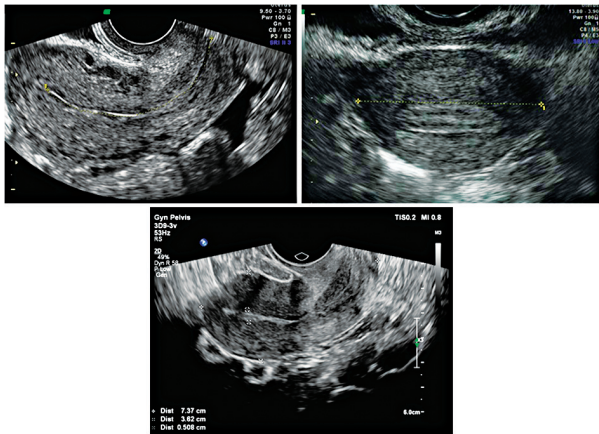


2.1 Evaluation of uterus (Figure 4 A, B and C)

- » Longitudinal, AP, and Transverse measurement
- » Uterocervical length

- » To identify uterine abnormalities – myoma, adenomyosis, polyps, intrauterine adhesions, endometrial abnormalities, congenital anomalies

Figure 4 A: Longitudinal, B: Transverse, C: Endometrial thickness

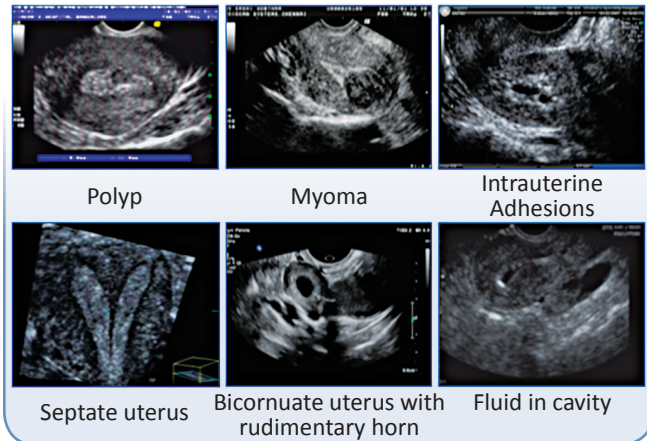


2.2 Evaluation of Uterine cavity

- » The intrauterine abnormalities that need to be looked for are shown in Figure 5 A–F

Figure 5

Abnormalities of uterine cavity A: Polyp; B: Myoma; C: Intrauterine adhesions, D: Septate uterus; E: Bicornuate uterus with rudimentary horn; F: Fluid in cavity



2.3 Female congenital uterine anomalies

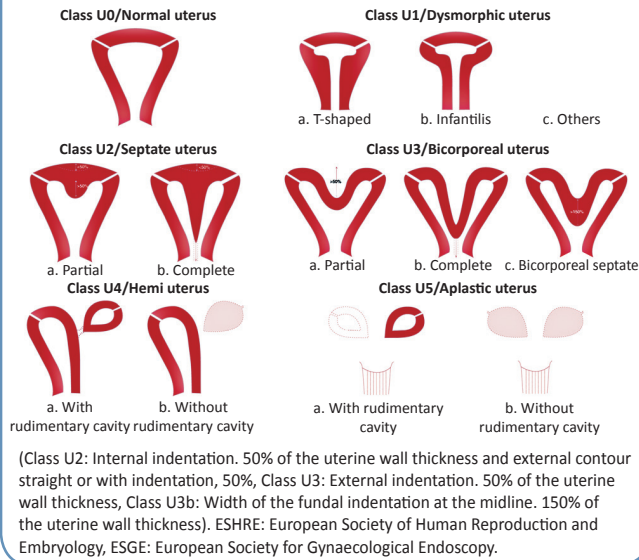
- » The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) classification for the female genital tract anomalies is given in table 1 and Figure 6

Table 1: The ESHRE/ESGE classification for the genital tract anomalies

	Uterine anomaly		Cervical or vaginal anomaly
	Main class	Sub-class	Co-existent class
U0	Normal uterus		C0 Normal cervix
U1	Dysmorphic uterus	a. T-shaped b. Infantilis c. Others	C1 Separate cervix
U2	Septate uterus	a. Partial b. Complete	C2 Double normal cervix
U3	Bicorporeal uterus	a. Partial b. Complete c. Biocorporeal septate	C3 Unilateral cervical aplasia
U4	Hemi-uterus	a. With rudimentary cavity (communicating or horn) b. Without rudimentary cavity (horn without cavity/ no horn)	C4 Cervical aplasia
U5	Aplastic	a. With rudimentary cavity (bilateral or unilateral horn) b. Without rudimentary cavity (bilateral or unilateral uterine remnants/aplasia)	V0 Normal vagina
U6	Unclassified malformation		V1 Longitudinal non-obstructing vaginal septum
			V2 Longitudinal obstructing vaginal septum
			V3 Transverse vaginal septum and/or imperforate hymen
			V4 Vaginal aplasia

Figure 6

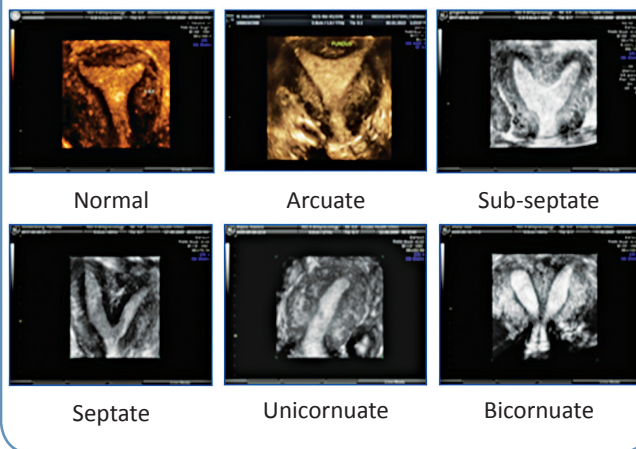
ESHRE/ESGE classification of uterine anomalies schematic representation



- Combination of both 2D and 3D reveal the accurate diagnosis of uterine anomalies. (Figure 7)

Figure 7

3D pictures of uterine anomalies

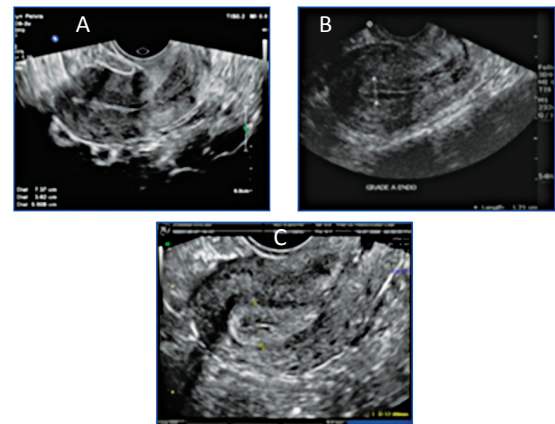


- The uterine cavity ultrasound is also done for evaluating the endometrial development when monitoring an ovulation induction cycle (Figure 8 A–C). In the proliferative phase, after day, 7 the endometrium should be multilayered endometrium consisting of

prominent outer and midline hyperechogenic lines and inner hypoechogenic regions. Under the influence of progesterone, the endometrium will be entirely homogenous and hyperechogenic. This pattern is usually seen in the luteal phase or when there is progesterone elevation in the late follicular phase

Figure 8

Endometrial lining during the menstrual cycle. A Day 2, B Proliferative phase, C Luteal phase



2.4 Evaluation of myometrial pathologies

Reporting protocol

- The presence or absence of the fibroids
- Location of the fibroid
- Number of fibroids
- Size of the fibroids
- Presence of pedicles
- Echogenicity/calcification of the fibroids
- Degree of vascularization

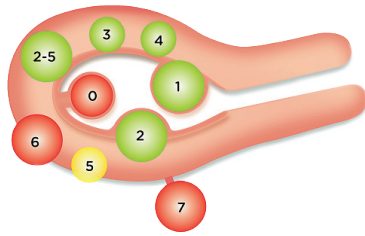
2.4.1 Classification system for fibroids

The International Federation of Gynaecology and Obstetrics (FIGO) classification is the most employed nowadays (Figure 9)

Figure 9

The International Federation of Gynaecology and Obstetrics (FIGO) classification system for fibroids.

Leiomyoma subclassification system



FIGO classification of uterine fibroids

SM-submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	>50% intramural
O-other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal >50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify eg, cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium, while the second refers to the relationship to the serosa. One example is given below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities respectively

only after degeneration and are large, solitary and irregular in outline

- » Adenomyosis is characterized by uterine enlargement: Anterior/posterior
- » The enlargement can be focal/diffuse in the absence of fibroid
- » Presence of improperly defined hyperechogenic (heterotopic endometrial glands) and hypoechogenic areas (smooth muscle hyperplasia)
- » Presence of small anechoic cysts in the myometrium
- » In distinct endometrial/myometrial margin
- » Minimal mass effect on the cavity/serosa compared to the size of the lesion
- » The myometrium is diffusely echogenic
- » Presence of echogenic nodules or linear striations radiating out from the endometrium into the myometrium
- » An increased number of tortuous vessels that penetrate throughout the involved myometrium

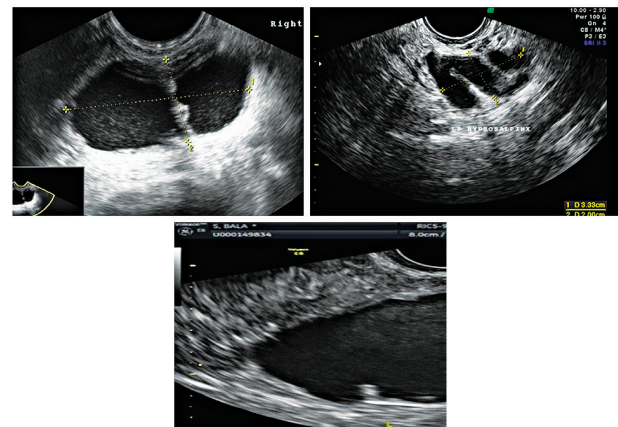
Figure 10 shows the ultrasound pictures of fibroid uterus and adenomyosis

2.5 Ultrasound features of adenomyomas

- Checklist for labelling
 - » The shape of focal lesions is elliptical rather than globular
 - » Rim vascularization is absent
 - » Presence of spoke wheel vascularization or radial arteries running through the lesion
 - » Calcification is absent in the lesions
 - » A mild mass effect disproportionate to the size of the abnormal area
 - » Adenomyomas can be associated with multiple, small, regular cysts vs. cystic fibroids which occur

Figure 10

A Hydrosalpinx, B Haematosalpinx



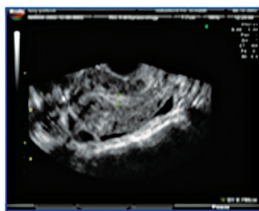
2.6 Tubal evaluation

The fallopian tubes can be visualized only in the presence of a pathology.

- Hydrosalpinx
- Sonographic features diagnostic for hydrosalpinx include a tubular or S-shaped cystic mass separate from the ovary, with “beads on a string” or “cogwheel” appearance. (Figure 11)

Figure 11

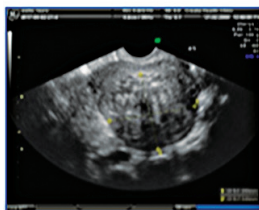
Myometrial Pathology: A submucous myoma; B Intramural myoma impinging on cavity; C: Intramural myoma without endometrial distortion; D: Adenomyosis



Submucous myoma



Intramural myoma impinging on the endometrial cavity



Intramural myoma with no endometrial distortion



Adenomyosis

2.7 USG assessment of ovarian reserve

- Antral follicle count (AFC): (Figure 12)
 - » Good correlation small follicle count and primordial pool and responsiveness. The AFC should be the first choice test
 - » The number of small antral follicles (2–6 mm) represents functional ovarian reserve

Figure 12

Antral follicle count in low, normal, and excessive ovarian reserve



Low AFC
<5 AFC per ovary



Normal AFC
AFC 5-10 per ovary



Excessive AFC
AFC >12 per Ovary

- Ovarian volume (OV) :
 - » Good correlation between OV and age and primordial follicle pool
 - » Weak correlation with ovarian
- 4 D USG–Sono AVC
 - » It determines the hypoechoic aspect of the ultrasound, display is inverted to demonstrate fluid-filled areas within the 3D dataset which are the follicles
 - » *Best model in predicting the number of oocytes retrieved*
 - » Oocyte retrieval rate–60%

2.8 Ultrasound assessment of PCO

2.8.1 Rotterdam consensus

- » Polycystic ovary contains 12 or more follicles measuring 2–9 mm in diameter on day 2 or 3 of MC

and/or

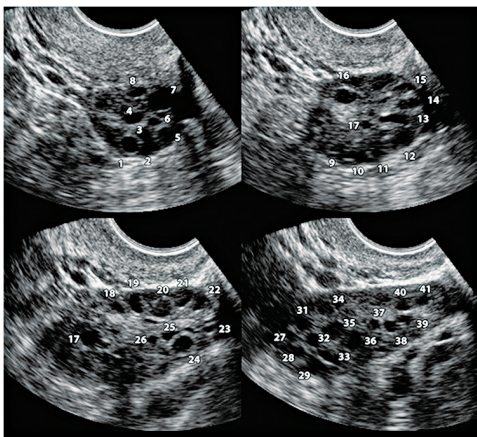
- » Increased ovarian volume ($>10\text{ cm}^3$)
- » No dominant follicle $> 10\text{ mm}$ or CL

These features do not apply to women taking OCP, as ovarian size is reduced, even though the polycystic appearance may persist. Ultrasound is also not reliable in the diagnosis of polycystic ovaries in adolescent girls.

- Ultrasonography criteria for diagnosing PCOS
 - » Transvaginal ultrasound is preferred because it often provides optimal visualization of the internal structure of the ovary
 - » Regularly menstruating women should undergo scanning during the early follicular phase (days 2–5)
 - » Oligomenorrhoeic or amenorrhoeic women may be scanned at random
 - » The entire ovary and both must be scanned
 - » One or both ovaries demonstrate 20 or more follicles measuring 2–9 mm in diameter (Figure 13), or
 - » The ovarian volume exceeds 10 cm^3

Figure 13

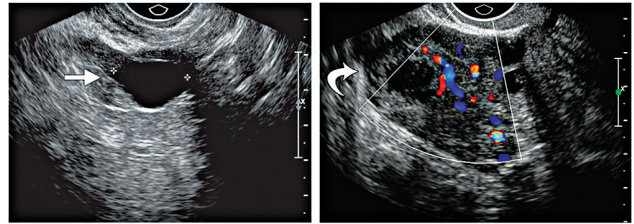
Selected images from a three-dimensional ultrasound examination of the right ovary demonstrate determination of the number of follicles present (follicles numbered 1–41) across the entire volume of the ovary



- » If there is evidence of a dominant follicle ($>10\text{ mm}$) or a corpus luteum, the scan should be repeated in the next cycle between 2–4 (Figure 14)

Figure 14

Findings in the US assessment of polycystic ovaries that should prompt repeat US during the next menstrual cycle



A: Ultrasound images of the left ovary demonstrates a dominant follicle (arrow) with an average diameter of more than 10 mm. B: Sagittal colour doppler ultrasound image of the right ovary in a different patient demonstrates the presence of a corpus luteum (arrow).

- » Only one ovary meeting either of these criteria is sufficient to establish the presence of polycystic ovaries
- » To identify a polycystic ovary, subjective appearance should not be used in place of ovarian volume and follicle count (follicle distribution and increase in stromal echogenicity are omitted) (Figure 15)

Figure 15

Transverse ultrasound image of the right ovary demonstrates the classic “string of pearls” appearance of a polycystic ovary



- » Ovarian volume should be calculated based on the simplified formula for a prolate ellipsoid ($0.5 \times \text{length} \times \text{width} \times \text{thickness of the ovary}$)
- » The mean of the diameters of any large cystic area should be used in ovoid structures and not the maximum diameter
- Clinical consensus recommendations (CCR) and clinical practice points (CPP) for the assessment of PCOS includes:

» CCR

- Ultrasound should not be used for the diagnosis of PCOS in those with a gynecological age of <8 years (<8 years after menarche), due to the high incidence of multifollicular ovaries in this life stage
- The threshold for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined
- A transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.
- Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8 MHz

» CPP

- If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10 ml on either ovary
- In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype
- In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥ 10 ml, given the difficulty of reliably assessing follicle number with this approach

2.9 Prediction of response

Table 2. Ultrasound markers of high and low response

Markers of high response	<ul style="list-style-type: none"> • Increased AFC • Color doppler – Increased stromal velocity • Increased AMH
Markers of low response	<ul style="list-style-type: none"> • High FSH and E2 • Low AMH, Inhibin B, • AFC < 5 • Ovarian volume • Low flow at color doppler

AMH: anti-Mullerian hormone; AFC: antral follicle count; FSH: follicle stimulating hormone; E2: estradiol.

3. Ultrasound for ovarian lesions

- Morphological features of adnexal lesion
 - » An adnexal lesion is the part of an ovary or an adnexal mass that is judged from an assessment of ultrasound images to be inconsistent with normal physiologic function.
 - » Adrenal lesion arises due to the presence of cysts. The features of cystic content are given in Figure 16.
 - » The morphological features of various types of cysts that may be observed in an adnexal mass are given in Figures 17,18,19, 20, and 21

Figure 16

The dominant feature of the cystic contents in complete septum

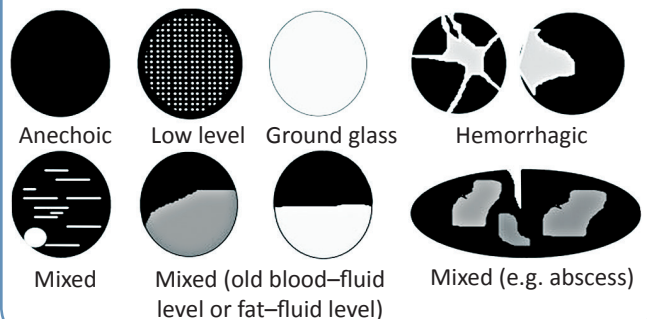
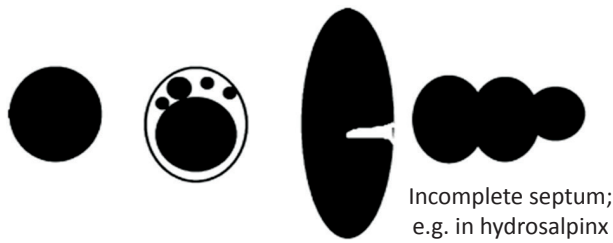
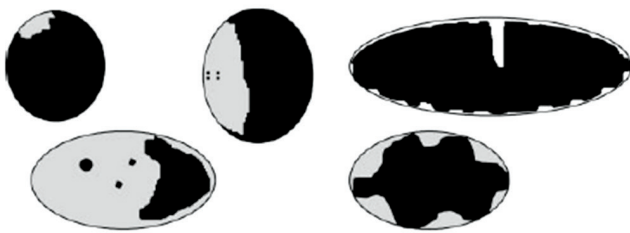


Figure 17

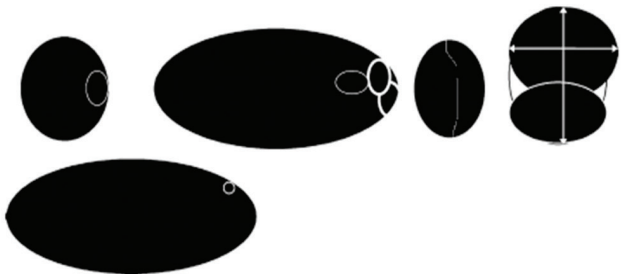
Examples of different kinds of unilocular cysts. A unilocular cyst is a cyst without septa and without solid parts or papillary structures

**Figure 18**

Examples of different kinds of unilocular–solid cysts. A unilocular–solid cyst is a unilocular cyst with a measurable solid component

**Figure 19**

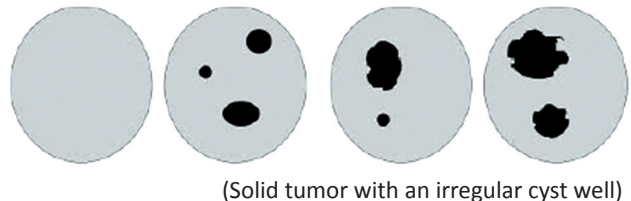
Examples of different kinds of multilocular cysts. A multilocular cyst is a cyst with at least one septum but no measurable solid components or papillary projections. The 'lesion' is measured in the planes indicated by the arrows

**Figure 20**

Examples of different kinds of multilocular–solid cysts. A multilocular–solid cyst is a multilocular cyst with a measurable solid component or at least one papillary structure (solid tumour with an irregular cyst wall)

**Figure 21**

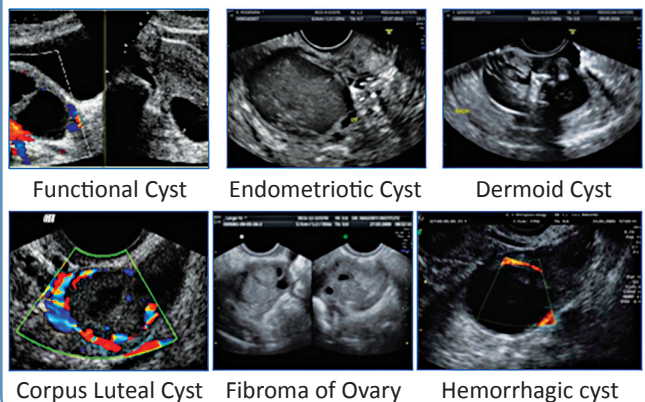
Examples of different kinds of solid tumours. A solid tumour is a tumour where the solid components comprise 80% or more of the tumour when assessed in a two-dimensional section. A solid tumour may contain papillary projections protruding into internal small cysts



- Differential diagnosis of adnexal masses: It is important to remember that all adnexal or pelvic masses are not of gynecologic origin (Figure 22)

Figure 22

Ovarian lesions in infertile women



- Fimbrial and paraovarian cysts (Figure 23)
 - » Fimbrial and paraovarian cysts are a common finding in women of reproductive age and represent embryological remnants
 - » These are small, round, unilocular, and thin walled
 - » No proven significance for fertility
 - » These should be separate from the ovaries
 - » Gentle pressure with the transducer will displace the cyst(s) away from the homo- lateral ovary, unless there are adhesions

Figure 23

Paraovarian cyst



4. Protocol for tubal patency evaluation

- For patients presenting with infertility, tubal assessment is essential
- To exclude hydrosalpinx and adhesions, transvaginal ultrasound scan is the primary investigation, especially for those females who also have other pathologies like pelvic inflammatory disease, previous history of ectopic pregnancy and endometriosis
- For tubal occlusion, hysterosalpingography (HSG) is still considered a primary screen. This is a reliable test to rule out tubal occlusion and is less invasive
- Screening for tubal occlusion using hysterosalpingo contrast ultrasonography (HyCoSy) should be considered when appropriate expertise is available. It

is an effective alternative for women who are known to have other pathologies like pelvic inflammatory disease, previous history of ectopic pregnancy, and endometriosis

- Where facility and expertise are available, HyCoSy can also be offered with 3D ultrasound. This can add to the information available with 2D HyCoSy
- Laparoscopy with dye test is the investigation of choice for patients with pathologies that are likely to cause tubal damage. It is considered as a gold standard for the evaluation of tubal patency

5. Guidelines for the day 2 scan

- Checklist for baseline scan (done on day 2 or day 3/ day 4) when the ovaries are silent with no follicles >8 mm
 - » Follicular size is <10 mm
 - » Residual cystic areas should be excluded
 - » Assessment of pelvic pathology, if any
 - » Assessment of uterine cavity configuration if not done earlier
 - » To confirm that endometrium is <6 mm
 - » To perform antral follicle count

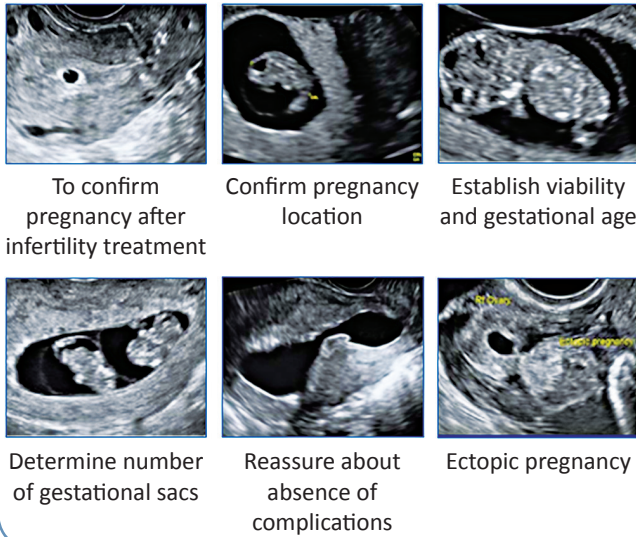
6. Imaging with Doppler and 3D/4D

The requirement from ultrasound where doppler & 3D/4D plays a significant role includes:

- » To confirm or exclude a lesion
- » Provide an anatomical diagnosis
- » Helps to identify pointers toward histopathology
- » Assess extent and contralateral involvement
- » To look for borderline tumours
- » Assess the rest of the abdomen and the pleura on either side.

7. Early first trimester scan

Aims of the early pregnancy USG (Figure 24)

Figure 24**Aim of early pregnancy scan****7.1 Systematic approach****Figure 25****Approach to early pregnancy scan**

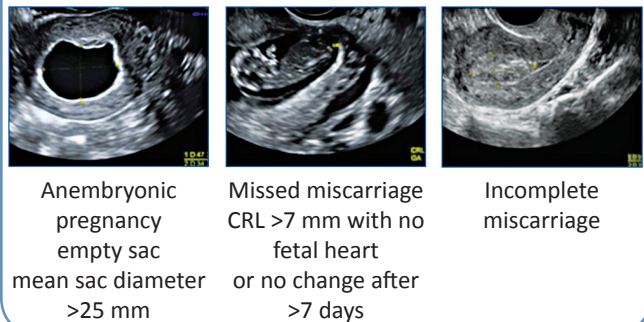
Longitudinal view of the uterus	
Transverse view of the uterus	
Visualization of the gestational sac	
Assessment of embryonic structures	
Visualization of the right ovary	
Visualization of the left ovary	
Assessment of the adnexa	
Inspection of the pouch of Douglas	
Other sites	

- Early sonographic markers which are found to be associated with poor pregnancy viability includes:
 - » Embryonic bradycardia
 - » Suboptimal embryonic growth
 - » Abnormal yolk sac

- » Chorionic hematoma
- » Peritrophoblastic hyperemia

7.2 Diagnosis of miscarriage

- Criteria for non-viability in the first trimester of pregnancy (Figure 26)

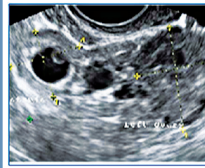
Figure 26**Criteria for non-viability of pregnancy****8. Ectopic pregnancy after assisted reproductive technology (ART)**

- The incidence of ectopic pregnancy after IVF ranges from 2.1% to 9.4% of all clinical pregnancies
- Even if one pregnancy is located in the uterus, do not stop looking at the adnexa: There may be a concurrent adnexal gestation
- Even if one pregnancy is located in the adnexa, keep looking: There may be a concurrent second adnexal gestation
- Ultrasound technique for ectopic pregnancies
 - » Transabdominal ultrasound can be used
 - » Transvaginal scan: Preferably high frequency transducer with power doppler should be used
 - » Try 3D ultrasound
 - » Thoroughly inspect uterine cavity, ovaries, rest of adnexa, and the pouch of Douglas
 - » Assess the free fluid

- Presentation of tubal ectopic pregnancy (Figure 27)
- Other locations of ectopic pregnancy (Figure 28)
- Heterotopic pregnancy (Figure 29)
 - # An ectopic pregnancy with an intra-uterine pregnancy
 - # 1 in 7,500–30,000 spontaneous conceptions
 - # 1–3 in 100 pregnancies conceived via ART
 - # Heterotopic pregnancy (Figure 27)
- Pregnancy of unknown location
 - # Working diagnosis only
 - # All women need follow-up to determine final outcome
 - # PUL rates should be < 15%
 - # Features of pregnancy of unknown location are seen in Figure 30
- Diagnostic algorithm for ectopic pregnancy is given in Figure 28

Figure 27

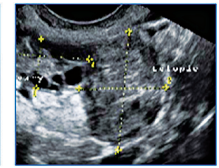
Presentation of tubal ectopic pregnancy



Gestational sac
and CRL or yolk sac
~20%



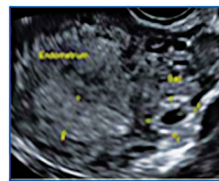
Empty gestational
sac ~20%



Inhomogeneous
mass ~60%

Figure 28

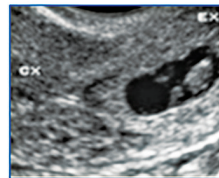
Criteria for non-viability of pregnancy



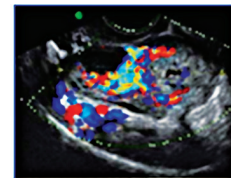
Interstitial ectopic
pregnancy



Cornual ectopic
pregnancy



Cervical ectopic
pregnancy



Ovarian ectopic
pregnancy

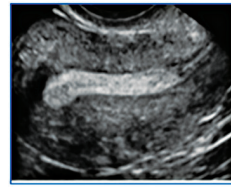
Figure 29

Heterotopic pregnancy

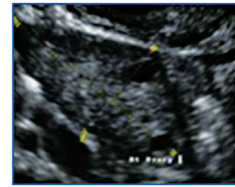


Figure 30

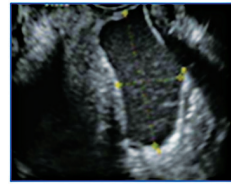
Features of pregnancy of unknown location



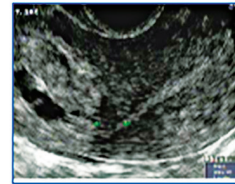
Absence of an intra-uterine pregnancy



Clear visualization of both ovaries and adnexae



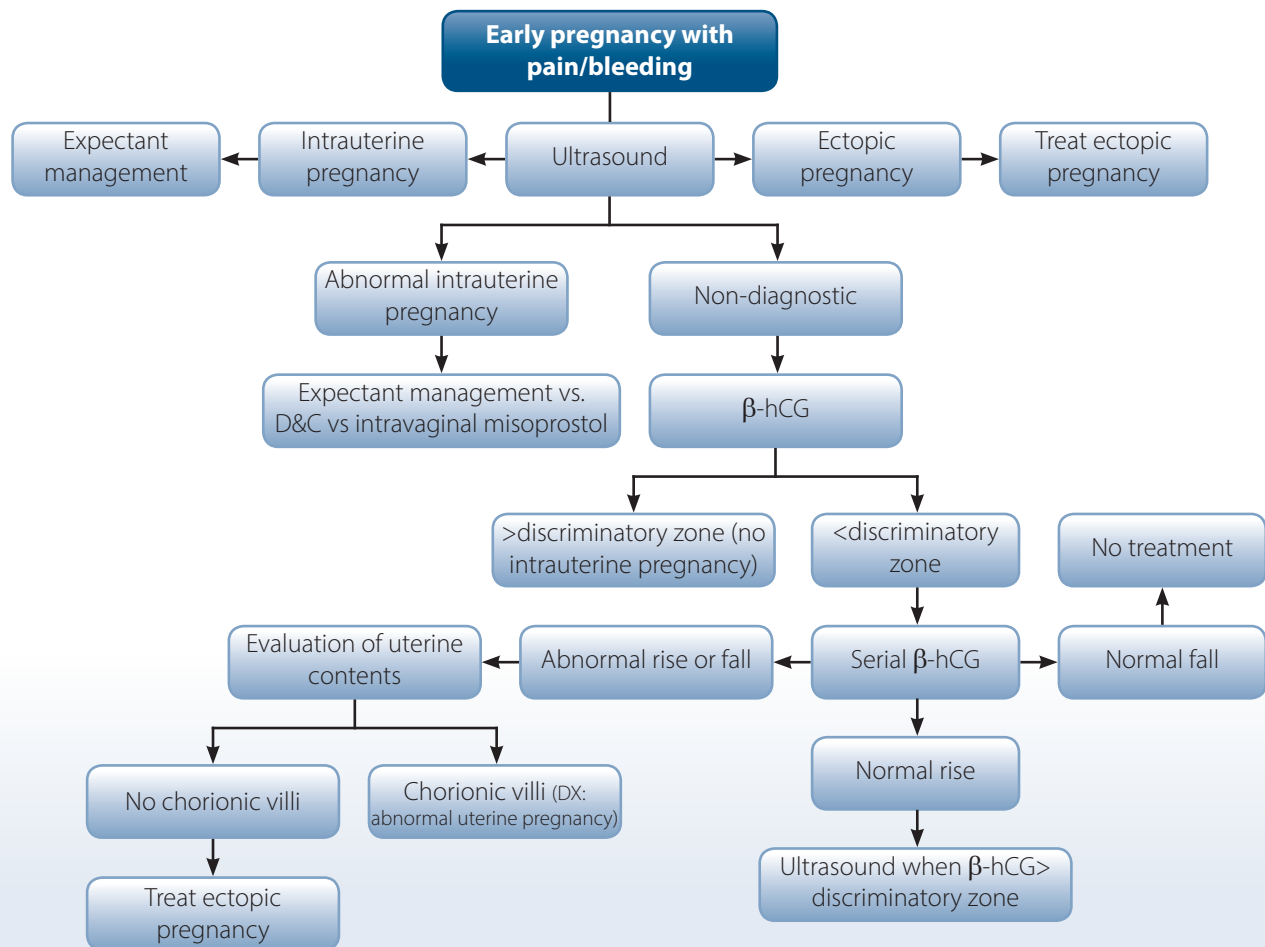
Inspection of pouch of Douglas for echogenic free fluid



Inspection of interstitial portion of fallopian tubes

Figure 31

Diagnostic algorithm for ectopic pregnancy



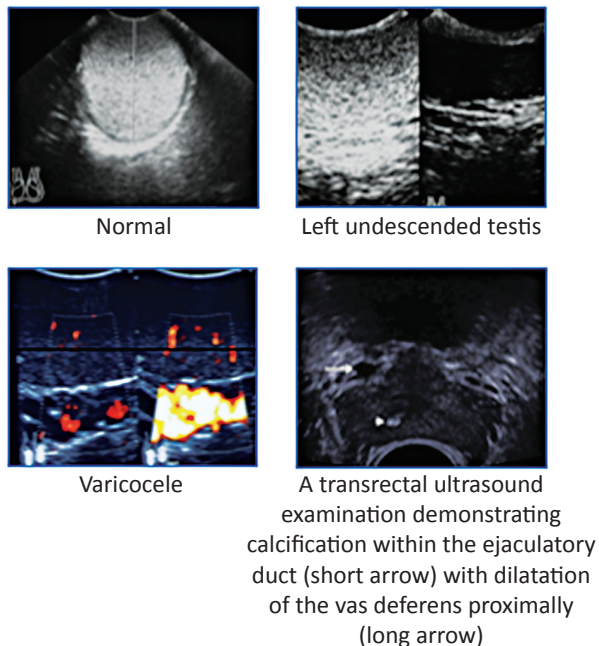
D&C: dilatation & curettage hCG: human chorionic gonadotropin

9. Imaging in the infertile male

- Imaging in infertile men is necessary in presence of abnormal semen analysis—low volume, severe oligoasthenospermia, azoospermia, hydrocele, and in those with a suspicion of absent vas, undescended testis, and varicocele
 - » Imaging helps to identify the causes of infertility, such as congenital anomalies and disorders that obstruct sperm transport and may be correctable
 - » Scrotal ultrasound is excellent for initial evaluation of male reproductive system and reproductive system, including the testes and extratesticular structures such as the epididymis for presence/absence, calcification, masses, cysts, hydrocele, and varicocele
 - » To assess the seminal vesicles and prostatic cysts, a transrectal scan is recommended

Figure 32

Ultrasound in the male



Recommendations

- Appropriate selection of imaging modalities and accurate characterization of the various underlying reproductive abnormalities and treatment helps to guide individual management decisions and maximize infertility treatment outcomes
- Two-dimensional US is the most widely available method for female evaluation and easiest to perform
- Two-dimensional US should be performed in all women who present with sub-fertility
- 3D/4D USG and SIS—increase the specificity and sensitivity
- If available 3D US should be done along with 2D US
- 2D USG in conjunction with HSG, increases accuracy particularly in the absence of 3D US, or where SIS is not practiced
- All techniques are complementary to each other for accurate diagnosis and appropriate management
- Baseline USG between 2–4 should be done in all before initiation of treatment in every cycle as it provides invaluable information on ovarian morphology and allows to choose appropriate stimulation regimen to prevent OHSS and multiple pregnancies and prediction of patients response to ovarian stimulation
- USG monitoring of follicular growth is the most important tool in assessment of progress in ovarian stimulation and should be used in all patients undergoing ovulation induction
- Ultrasound improves chance of safe and effective treatment
- USG also allows diagnosis of disorders and complications of ovulation
- Monitoring luteal phase helps confirm ovulation and pregnancy by β -hCG assay and USG documentation of pregnancy (20 days post ovulation when β hCG is 1000 mIU/ml), an end-point desired of tracking ovulation
- Ultrasound in the male should be done in all with azoospermia, oligoasthenospermia, hydrocele, and suspicion of absent vas deferens, undescended testis, and varicocele

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	Appropriate selection of imaging modalities and accurate characterization of the various underlying reproductive abnormalities and treatment helps to guide individual management decisions and maximize infertility treatment outcomes	-	-
CPP	Two-dimensional US is the most widely available method for female evaluation and easiest to perform	-	-
CPP	Two-dimensional US should be performed in all women who present with sub-fertility	-	-
CPP	3D/4D USG and SIS–increase the specificity and sensitivity	-	-
CPP	If available 3D US should be done along with 2D US	-	-
CPP	2D USG in conjunction with HSG, increases accuracy particularly in the absence of 3D US, or where SIS is not practiced	-	-
CPP	All techniques are complementary to each other for accurate diagnosis and appropriate management	-	-
EBR	USG at first visit evaluates the cervix, uterus, ovaries, and adnexa to provide diagnostic information and guidance to management	B	II
EBR	Baseline USG between 2–4 should be done in all before initiation of treatment in every cycle as it provides invaluable information on ovarian morphology and allows to choose appropriate stimulation regimen to prevent OHSS, multiple pregnancies, and prediction of patients response to ovarian stimulation	B	II
EBR	USG monitoring of follicular growth is the most important tool in assessment of progress in ovarian stimulation and should be used in all patients undergoing ovulation induction	A	II
EBR	Ultrasound improves chance of safe and effective treatment	C	III
EBR	USG also allows diagnosis of disorders and complications of ovulation	B	III
EBR	Monitoring luteal phase helps confirm ovulation and pregnancy by β -hCG assay and USG documentation of pregnancy (20 days post ovulation when beta hCG is 1000 mIU/ml), an end point desired of tracking ovulation	B	II
EBR	Ultrasound in the male should be done in all with azoospermia, oligoasthenospermia, hydrocele and suspicion of absent vas deferens, undescended testis, and varicocele	B	III

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Chapter 3: Genetic Analysis for Infertility Detection

OVERVIEW

This guideline offers recommendations on the requirement of genetic analysis for the detection of infertility in adult male and females. It also gives an overview of few tests recommended for the genetic analysis required for infertile patients.

1. Introduction

- Chromosomes carry genes that determine the existence and form of organisms
- Genes are made of DNA, where the particular DNA sequence determines the function of the gene
- Genetic disease or disorder is the result of changes or mutations, in an individual's DNA which can be inherited or acquired/De novo (spontaneous or induced by UV light/chemicals/radiation)
- Chromosomal abnormalities as a result of abnormal chromosome number, structure, or rearrangement can result in infertility
- Infertility is genetic in origin in at least 10%–15% of men and 5%–10% of women
- Genetic defect seen in >20% of cases with azoospermia
- 20% of cases of genetic counselling is related to fertility problems
- Genetic testing helps to finalize a causal diagnosis; and to assess the genetic risk for the offspring in case of successful treatment
- But only few genetic tests are routinely applied in clinical practice

2. Genetic abnormalities associated with infertility

2.1 In males

- Genes can interfere with male fertility during gonads development (in utero life). Eg: Testicular dysgenesis, gonadotrophin action (hormones and receptors), eg: Kallmann syndrome, organs malformations, eg: Cystic fibrosis (CBAVD and CFTR), at gametogenesis level, eg: Y microdeletion and sexual behaviour abnormalities.

Chromosomal aberrations are responsible for 5%–10% cases of azoospermia and severe oligospermia

- » Chromosomal aberrations–sex chromosome
 - 47,XXY and mosaicisms (Klinefelter syndrome)
 - 47,XYY and other YY–aneuploidies
 - 46,XX and 45, X males
 - Structural Y chromosomal aberrations (del, rings, inversions, etc)
 - Chromosomal aberrations–autosomes
- Translocations (Robertsonian, reciprocal)
- Inversions
- Other structural anomalies
- Clinical syndromes (Trisomy 21, etc)
 - » Gene mutations–sex chromosome
 - Y-linked–microdeletions Yq11 (5%–10% case of azoospermia and severe oligospermia)
 - X-linked–Kallmann syndrome, androgen insensitivity syndrome, Kennedy disease (2%–3% cases of azoospermia and severe oligospermia)
 - » Gene mutations–Autosomal
 - Complex genetic syndromes with infertility as minor manifestation or major manifestation (with mutation of CFTR, FSH- β , LH- β , FSH-R, LH-R genes) responsible for 5% male Infertility and 60%–70% cases of CBAVD

2.2 In females

- Incidence: 1.5%–3.3% among sub-fertile women versus 0.16% in general population. These are mostly aneuploidies and rearrangements involving sex

chromosomes with small to moderate reproductive risk

- Chromosomal aberrations of sex chromosomes
 - » Turners syndrome with/without mosaicism
 - » Gonadal dysgenesis with Y cell line
 - » X-autosomal translocation
 - » 47, XXX with/without mosaicism
- Autosomal chromosomal aberrations
 - » Robertsonian translocation
 - » Reciprocal translocation
 - » Inversions
- X-linked gene mutations
 - » Fragile X syndrome
 - » Kallmann syndrome
 - » Complete androgen sensitivity syndrome
- Gene mutations in autosomal chromosomes resulting in complex genetic syndromes with infertility as minor manifestation or major manifestation
 - » With mutation of FSH β gene, FSHR gene, LHR gene, GnRHR gene, steroid enzyme genes (CYP17, CYP19, HSD17B3, autoimmune regulatory (AIRE) gene, FOXL2 gene, HOXA13 gene, BPES
- Presence of globozoospermia or round head syndrome also require genetic testing
- FSH and testosterone should be done and if abnormal test for SHBG, prolactin, LH, E2, and repeat testosterone
- Karyotype analysis and Y-chromosomal microdeletion screening should be performed in patients with azoospermia or severe oligozoospermia in order to rule out structural chromosomal abnormalities, Klinefelter syndrome, and Y chromosome microdeletions
- Men with azoospermia with decreased seminal volume, pH and markers of epididymal (α -glucosidase), and seminal vesicle (fructose) function in the presence of normal luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone levels. need CFTR gene screening
- If clinical findings suggest hypogonadotropic hypogonadism (HH) like low sex steroid and low gonadotropin levels, perform HH mutation screening
- Oligozoospermic men with hypospermatogenesis and normal FSH levels (<8 IU/L) should be evaluated for FSH and LH receptor polymorphism
- If Kennedy syndrome suspected androgen receptor CAG repeats abnormalities should be tested for

3. Genetic screening for infertility: When should it be done?

3.1 Male

- Depending on semen analysis and clinical findings, the infertile male patient needs genetic evaluation to identify pattern of inheritance (autosomal-dominant, autosomal-recessive or X-linked)
- In men with severe oligo-astheno-teratozoospermia and azoospermia physical examination for secondary sexual characteristic, testicular size, and consistency, epididymal abnormalities, varicocele, a per rectal examination for seminal vesicular, and prostatic abnormalities should be done

3.2 Females

- Genetic testing in the female is required in presence of primary or secondary amenorrhea, polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), poor ovarian reserve or response, hyper-response, recurrent implantation failure or pregnancy loss (RPL), endometriosis, adenomyosis, leiomyoma, unexplained infertility, hypogonadotropic hypogonadism (HH), and those who would be subjected to gonadotoxic chemotherapy or radiotherapy
- Immense clinical variability in features associated with GnRH deficiency resulting in hypogonadotropic hypogonadism may be due to mutations of two distinct genes in an individual, which may generate a

more severe phenotype than a single-gene alteration.

- Look for symptoms and signs of diminished ovarian reserve, early menopause, endometriosis, and hyperandrogenemia
- Look for symptoms and signs of Turner's syndrome (short stature, webbed neck, puffiness or swelling (lymphedema) of the hands and feet, skeletal abnormalities, heart defects, high blood pressure, and kidney problems
- Kallmann syndrome—primary amenorrhoea, anosmia, hypogonadism, bimanual synkinesia, and renal anomalies
- Familial premature ovarian failure (POF), the incidence of which varies from 4% to 31% associated with hypergonadotropic hypogonadism. The inheritance of POF may be autosomal dominant sex-limited or X-linked. The POF risk is 2-fold higher in women with the FMR1 premutation
- Congenital absence of the uterus and vagina (Mayer-Rokitansky-Kuster-Hauser) syndrome – There is complete aplasia of the vagina and uterus with two rudimentary horns and normal fallopian tubes or vaginal aplasia with either symmetric uterine hypoplasia or aplasia of one horn, tubal malformation, and other associated malformations. Tendency to familial distribution suggests the potential for a genetic link (mutation of the WNT4 gene)
- Hemoglobinopathies
- Genetic conditions like galactosemia, cystic fibrosis, Prader Willi etc. also cause the genetic changes and may induce infertility

Recognition of mosaic turners and Klinefelter' syndrome early will enable us to cryopreserve the gametes, thus preserving fertility.

4. Genetic tests for the detection of infertility

4.1 Genetic testing done by

- Comprehensive chromosome screening (CCS)

- aCGH
- SNP microarray
- qPCR
- NGS

4.2 For males

- Karyotype in non-obstructive azoospermia and severe oligospermia
- "Y" microdeletion in non-obstructive azoospermia and severe oligospermia
- CFTR gene mutation in obstructive azoospermia
- Androgen receptor mutation in non-obstructive azoospermia and severe oligospermia
- INSL3/RXFP2 gene mutation in cryptorchidism
- HH gene mutation in HH and Kallmann syndrome
- Testing for sperm aneuploidy and DNA fragmentation is still debatable

4.3 For females

- Karyotype–Turner syndrome (46X) and Swyer syndrome (46XY)
- Diagnosis of Kallmans syndrome (KAL1, FGFR1, and CHD7 genes)
- CFTR mutation
- POI - FMR1 mutation in Fragile-X Syndrome

5. What is the need of these recommendations?

- These recommendations will help in providing options for couples with increased genetic risk
 - » Genetic counselling
 - » To accept the risk
 - » Refrain from having children
 - » Adoption
 - » Sperm or oocytes donation
 - » Prenatal diagnosis (PND)
 - » Preimplantation genetic diagnosis/screening (PGD/PGS)

6. Preimplantation genetic testing (PGT)

6.1 PGT Test

- It is a test performed to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA-typing or for determining genetic abnormalities
- PGT for aneuploidies (PGT-A): Formerly known as PGS or CCS—screens for the presence of all 46 chromosomes. PGT – A is done in good prognosis patients (adequate number of embryos) and indications being advanced age (>37 years), recurrent implantation failure, recurrent pregnancy loss (without known genetic abnormality), severe male factor infertility, and embryo selection
- PGT for monogenic/single gene defects (PGT-M): Formerly known as PGD for single gene disorders or HLA typing – Examples: Cystic fibrosis, BRCA, Huntington's disease

- PGT for chromosomal structural rearrangements, X linked and autosomal chromosomal abnormalities (PGT-SR). Formerly known as PGD for chromosome rearrangements; examples: chromosome translocations, and inversions

6.1.1 Day of biopsy

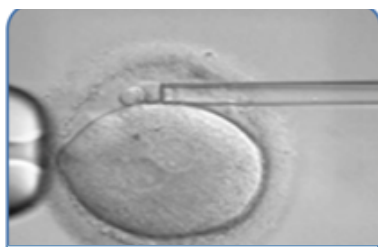
- One could do a polar body, blastomere biopsy on day 3 or trophectoderm biopsy on day 5. The advantages and disadvantages of the same are given in the Figure 1
- Therefore, whenever possible, trophectoderm biopsy should be the method of choice in embryo biopsy and should be performed by experienced hands
- No increase in live birth rate (LBR) but fewer miscarriages

6.1.2 Disadvantages to PGT

- Poor lab condition might hamper blastocyst formation, mandating a state of ART lab conditions
- Poor morphology embryos—may degenerate at biopsy

Figure 1

Embryo biopsy at different stages of embryo development



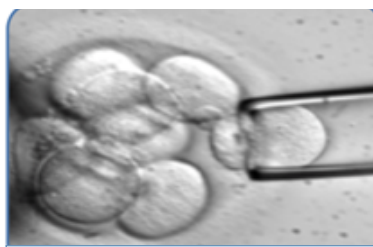
Characteristics

8–12 h after ICSI

Performed where embryo biopsy is considered illegal

Detects only maternal anomalies—aneuploidies

30% of post-meiotic anomalies not detected



PROS

Worldwide expensive

Enough time for fresh ET

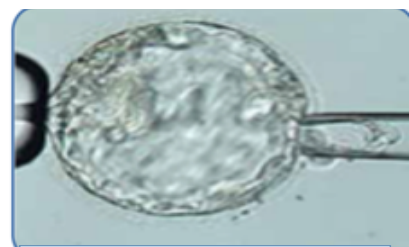
Suitable for many patients

CONS

Less DNA

High rate of mosaicism

Less implantation



PROS

More DNA: Less no results

Less mosaicism: Less error rate

No impact of embryo biopsy

Less embryos to test: Lower cost

eSET possible

Frozen ET: Better endometrial receptivity

CONS

Not all embryos reach blastocyst

Requires experience

- Failure to amplify
- Embryo loss during long-term in vitro culture, embryo cryopreservation, and inter-clinic variability in expertise.
- Less transfers
- Less embryos cryopreserved
- No effect on time to pregnancy
- Mosaicism is still a possibility and there is no consensus on degree of mosaicism and the best practice. Risk of having false positive results due to mosaicism.
- Long-term safety of children born after embryo biopsy still needs further research
- Invasive procedure with increased cost

7. Genetics in recurrent pregnancy loss (RPL)

- The rate of cytogenetic abnormalities is lower in cases of RPL (30%–50% of losses) compared to up to 70% in sporadic early pregnancy losses
- Approximately 50% of all clinically recognized spontaneous miscarriages have a chromosome abnormality. Of these, about 9% have a 45,X constitution, 30% have trisomy, 10% are either triploid or tetraploid, and 2% have a structural rearrangement
- Numerical and structural chromosomal abnormalities are important causes of RPL
- Balanced translocations or inversions can lead to unbalanced gametes depending on specific recombination and segregation patterns. The attendant reproductive risk depends on the type of rearrangement and its parental origin
- Single Gene Disorders: Uncommon e.g. metabolic disorders (typically autosomal recessive with RPL e.g. storage disorders) and hemoglobinopathies (especially alpha thalassemia major)
- Couples with recurrent miscarriage (RM) are twice as likely as controls to have single gene defects like hereditary thrombophilias due to Factor V Leiden defect and prothrombin gene (G20210A) mutations, C677T polymorphism in the MHFTR gene which controls DNA methylation associated with

7.1 Who needs testing?

- Threshold of >3 losses should be used for epidemiological studies while clinical evaluation to be offered after two consecutive first trimester pregnancy losses
- A putative diagnosis should be made and treated in approximately 50% of patients with RPL
- Balanced parental chromosome rearrangements are found in 3% to 5% of couples with RPL (5- to 10-fold more common than general population) therefore parental karyotype test is recommended based on genetic history (e.g. previous birth of child with congenital abnormalities, offspring with unbalanced chromosome abnormalities in the family, or detection of a translocation in the pregnancy tissue). This test also provides an idea of likelihood of a subsequent pregnancy loss or healthy live birth which depends on the chromosome involved and the type of rearrangement
- Conventional karyotype and fluorescence in situ hybridization (FISH) is not recommended referred currently because of limitations (Karyotype limitation: Failure of tissue culture; FISH: Limited as it only uses probes for certain chromosomes)
- Use array comparative genomic hybridization (CGH) test over conventional karyotype

Summary of recommendations

- All genetic analysis should be accompanied by expert counseling by a clinical geneticist both in male and female patients
- Parental karyotype is carried out after individual assessment of risk
- Depending on the clinical findings, the infertile male patient needs genetic evaluation. Karyotype analysis and Y-chromosomal microdeletion screening should be performed in patients with azoospermia or severe oligozoospermia in order to rule out structural

chromosomal abnormalities, Klinefelter syndrome, and Y-chromosome microdeletions

- Infertile patients with obstructive azoospermia need CFTR gene screening
- Patients with HH mutation screening may be performed according to clinical features which suggest hypogonadotropic hypogonadism
- Primary amenorrhea should be investigated by karyotype analysis and selected mutation screening according to the patient's clinical features
- Karyotype analysis and FMR1 gene screening is recommended in cases of POF early diagnosis by genetic investigation in turners and POI may instead lead to the advice of early conception or oocyte harvesting and preservation
- For women with hypergonadotropic hypogonadism, it is important to consider Turner syndrome, but in those with 46,XX ovarian failure, about 15% of women may have mutations in genes
- For eugonadal disorders, test for FSHR mutations in abnormal ovarian response, WNT4 mutations in mullerian aplasia, and estrogen receptor gene (ESR1) mutation in complete estrogen insensitivity syndrome (CEIS)
- Karyotype analysis of both partners is recommended in all couples with recurrent implantation failure and RPL
- Chromosomal defects explain a high proportion of pregnancy failures
- No routine genetic test can be recommended so far in patients with PCOS
- Single gene defects which cause infertility are conditions associated with hypogonadotropic hypogonadism e.g. Kallmann syndrome, defective signalling through the kisspeptin
- PGT-A is not recommended routinely but may be done in women with advanced maternal age, recurrent pregnancy loss, or recurrent implantation failure
- PGT-M is recommended in all patients known for single gene disorders
- PGT-SR for abnormal karyotype reduces the miscarriage rate

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Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	All genetic analysis should be accompanied by expert counselling by a clinical geneticist both in male and female patients.	-	-
CPP	Parental karyotype is carried out after individual assessment of risk.		
EBR	Depending on the clinical findings, the infertile male patient needs genetic evaluation. Karyotype analysis and Y-chromosome microdeletion screening should be performed in patients with azoospermia or severe oligozoospermia in order to rule out structural chromosomal abnormalities, Klinefelter syndrome and Y-chromosome microdeletions.	A	I
EBR	Infertile patients with obstructive azoospermia need CFTR gene screening.	A	I
EBR	Patients with HH mutation screening may be performed according to clinical features which suggest hypogonadotropic hypogonadism.	B	II
EBR	Primary amenorrhea should be investigated by karyotype analysis and selected mutation screening according to the patient's clinical features.	A	I
EBR	Karyotype analysis and FMR1 gene screening is recommended in cases of POF.	A	I
EBR	Early diagnosis by genetic investigation in Turner and POI may instead lead to the advice of early conception or oocyte harvesting and preservation.	B	II
EBR	For women with hypergonadotropic hypogonadism, it is important to consider Turner syndrome, but in those with 46,XX ovarian failure, about 15% of women may have mutations in genes.	C	III
CCR	For eugonadal disorders, test for FSHR mutations in abnormal ovarian response, WNT4 mutations in mullerian aplasia, and ESR1 mutation in CEIS.	C	-
EBR	Karyotype analysis of both partners is recommended in all couples with RIF and RPL.	A	I
EBR	Chromosomal defects explain a high proportion of pregnancy failures	A	I
EBR	No routine genetic test can be recommended so far in patients with PCOS.	B	III
EBR	Single gene defects which cause infertility are conditions associated with hypogonadotropic hypogonadism e.g. Kallmann syndrome, defective signalling through the kisspeptin.	C	IV
EBR	PGT-A is not recommended routinely but may be done in women with advanced maternal age, RPL or RIF	B	II
EBR	PGT-M is recommended in all patients with known for single gene disorders.	A	I
EBR	PGT-SR for abnormal karyotype reduces the miscarriage rate.	A	II

Chapter 4: Guidelines on Endoscopy in Infertility & ART

OVERVIEW

Indian Society for Assisted Reproduction (ISAR) has dedicated this year towards better practices, better outcomes and keeping that in mind the three organizations ISAR, IFS, & ACE have come together to prepare *Minimum Standards of Infertility Practice: A Consensus Statement*. This paper provides advice for clinicians regarding role of fertility enhancing endoscopic surgeries in infertility patients.

1. Introduction

- 30% of infertility cases are due to presence of pelvic factors of infertility
- Therapeutic options for infertility in presence of adequate seminal and ovarian functions is reproductive surgery for pelvic factor or invitro fertilization (IVF)
- Aim of reproductive surgery in infertility is to optimize the implantation of the blastocyst in the uterine cavity for an optimal outcome
- Fertility enhancing endoscopic surgery is a broad spectrum, multifaceted approach which encompasses all minimal access surgery techniques adopted in order to improve the fertility rate of a couple
- It primarily involves the use of hysteroscopy and laparoscopy to confirm and treat the causes of female infertility
- In a couple with infertility, female infertility contributes to almost 40% cases. These can be attributed to problems from ovarian issues [polycystic ovary (PCO), cysts-simple, hemorrhagic, dermoid], tubal factors (hydrosalpinx, distal or proximal tubal block, excessively tortuous tube), uterine factors (fibroid, adenomyosis, poor endometrial growth), or infections in genital tract, or pelvic adhesions
- A laparoscopy coupled with hysteroscopy can evaluate all these factors as a single procedure

2. Laparoscopy related surgeries

- Myomectomy
- Endometriosis related surgery

» Cystectomy, ablation/fulguration of endometriotic spots

- Adhesiolysis
- Tubal de-linking
- Tubal anastomosis
- PCO drilling

3. Hysteroscopy related surgeries

- Polypectomy
- Hysteroscopic adhesiolysis
- Hysteroscopic septal resection and metroplasty
- Submucous myoma resection
- Lateral metroplasty

4. Combined approach

- Diagnostic hysterolaparoscopy with selective chromopertubation
- Tubal cannulation

In this guideline, different gynecological conditions and the recommendations for their surgical management in infertility patients will be discussed

5. Guidelines in management of myomas/fibroid uterus

Summary of evidence

- Fibroids may or may not impact the fertility potential significantly
- Accepted indications for removal of fibroids are:
 - » The presence of a submucous fibroid 2–5 cm
 - » Intramural fibroid >4 cm/distorting the cavity or close to the junctional zone

- » Infertility of >3 years
- » Prior to ART
- » Large fibroid altering tubo-ovarian relationship
- Relative/optional
 - » Multiple large fibroids (space problem for pregnancy)
 - » Low large cervical fibroid likely to obstruct labour
 - » History of repeated abortions with fibroids of significant size

Subserosal fibroids do not appear to have an impact on fertility. Submucous fibroid adversely affect reproductive outcome and its removal improves the outcome. There are insufficient high quality studies on the impact of intramural (IM) fibroid or removal of IM fibroid on reproductive outcome. Some studies have shown a negative effect on IVF results, while others have concluded that IM myoma does not affect IVF results. Junctional zone (JZ) IM myomas have unfavourable ART outcomes compared to other IM myoma and myomectomy should be considered for JZ myomas.

Recommendations for assessment of fibroids

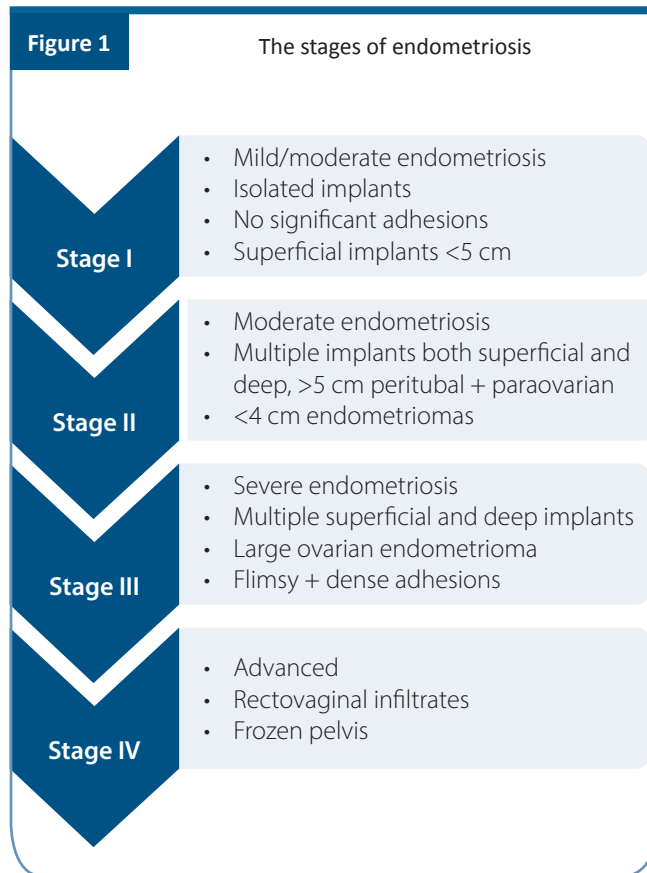
Category	Recommendation	Grade	Quality of Evidence
EBR	Adequately evaluate and classify fibroids in women with infertility, particularly those impinging on the endometrial cavity, using transvaginal ultrasound, hysteroscopy, hysterosonography, or magnetic resonance imaging	A	III
EBR	In addition to an assessment of fibroid size and location within the uterine cavity, include evaluation of the degree of invasion of the cavity and thickness of residual myometrium to the serosa as preoperative assessment of submucosal fibroids. A combination of hysteroscopy and transvaginal ultrasound or hysterosonography are the modalities of choice	B	III
EBR	A hysterosalpingogram is not an appropriate exam to evaluate and classify fibroids.	D	III
CCR	Preoperative assessment of submucosal fibroids is essential to the decision on the best approach for treatment	C	—

Recommendations for management of fibroids

Category	Recommendation	Grade	Quality of Evidence
EBR	Submucosal fibroids are managed hysteroscopically. The fibroid size should be <5 cm, although larger fibroids have been managed hysteroscopically, but repeat procedures are often necessary	B	III
EBR	In women with otherwise unexplained infertility, submucosal fibroids should be removed in order to improve conception and pregnancy rates	A	II
EBR	There is little evidence on the use of Foley catheters, estrogen, or intrauterine devices for the prevention of intrauterine adhesions following hysteroscopic myomectomy	B	III
EBR	Removal of subserosal fibroids is not recommended	D	III
EBR	There is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and unexplained infertility, regardless of their size	D	II
EBR	If the patient has no other options, the benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized	C	III
EBR	If fibroids are removed abdominally, efforts should be made to use an anterior uterine incision to minimize the formation of postoperative adhesions	A	II
EBR	Widespread use of the laparoscopic approach to myomectomy may be limited by the technical difficulty of this procedure. Patient selection should be individualized based on the number, size, and location of uterine fibroids and the skill of the surgeon	A	III
CCR	In the infertile population, cumulative pregnancy rates by the laparoscopic and the mini-laparotomy approaches are similar, but the laparoscopic approach is associated with a quicker recovery, less postoperative pain, and less febrile morbidity. (II-2)	B	—

6. Guidelines in management of endometriosis

The incidence of endometriosis in the reproductive age group is 6%–10%, however, laparoscopic incidence of this condition can be as high as 9%–50%. The stages of endometriosis are enumerated in Figure 1.



6.1 Diagnosis of endometriosis

Summary of evidence

- Endometriosis associated symptoms, include dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclical intestinal complaints, fatigue/weariness, and infertility. The evidence on the value of clinical examination for the diagnosis of endometriosis is weak. Vaginal examination can facilitate the detection of nodules of the vagina, uterosacral ligaments or pouch of Douglas. Rectovaginal digital examination may allow the detection of endometriosis of rectovaginal septum. Use of transvaginal sonography (TVS), and magnetic resonance imaging (MRI) helps in diagnosing ovarian and deep endometriosis. TVS is useful for both identifying and ruling out rectal endometriosis
- Laparoscopy with or without histological verification is widely used to diagnose and rule out the presence of endometriosis. Laparoscopy with histology as a diagnostic intervention is safe and predictive of disease
- The evidence concludes that serum CA-125 measurement in the diagnosis of endometriosis grade I/IV is limited, whereas it has some role in the diagnosis of endometriosis grade III/IV
- Barium enema, transvaginal sonography, transrectal sonography and MRI should be used to diagnose and know the extent of disease in deep endometriosis

Recommendations for the diagnosis of endometriosis

Category	Recommendation	Grade	Quality of evidence
CPP	It is recommended that clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, and fatigue in the presence of any of the above	—	—
CPP	It is recommended that clinicians should consider the diagnosis of endometriosis in women of reproductive age with non-gynecological cyclical symptoms (dyschezia, dysuria, hematuria, rectal bleeding, shoulder pain)	—	—
CPP	Perform a thorough clinical examination including per abdominal, per vaginal, per rectal and rectovaginal examination after proper counselling in women with suspected endometriosis	—	—
CCR	Suggest diagnosis of deep endometriosis in patients with deep pelvic pain and findings of nodules and/or induration of the rectovaginal wall	C	—
CCR	Suspect endometrioma during examination and finding of adnexal mass	C	—
CCR	Absence of clinical evidence during examination does not rule out the disease	C	—
CCR	A transvaginal USG can exclude or diagnose an ovarian endometrioma typically seen as a simple or complex cyst with internal echoes to solid masses but usually without internal vascularity	A	—
CCR	In women with symptoms of endometriosis, TVS is useful to identify rectovaginal involvement	A	—
EBR	Laparoscopy remains the gold standard for diagnosis of endometriosis	A	II
CCR	CA-125 is poorly sensitive for diagnosis. However, it has a role in treatment follow-up	A	—
CPP	One should assess ureter, bladder, and bowel involvement by additional imaging techniques (barium enema, transvaginal sonography, transrectal sonography, and MRI) if there is a clinical suspicion of deep endometriosis based on history or physical examination	—	—

6.2 Treatment guidelines

Surgical management for endometriosis associated pain

- Laparotomy and laparoscopy (excision/ablation) are equally effective in the treatment of endometriosis-associated pain. Laparoscopy may be a better option compared to laparotomy as it is associated with less pain, shorter hospital stay and quicker recovery. Both ablation and excision of peritoneal disease are equally effective for treatment of endometriosis-associated pain
- Laparoscopic uterosacral nerve ablation (LUNA) does not offer any beneficial effect compared to ablation or excision in endometriosis associated pain. Presacral neurectomy (PSN) may be beneficial in reducing pain but associated with increased risk of adverse effects such as bleeding, constipation, and urinary urgency
- Cystectomy is superior to drainage and coagulation or CO₂ laser vaporization of ovarian endometrioma (≥ 3 cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometrioma. Surgery for deep endometriosis is effective in reducing pain but is associated with substantial intraoperative and postoperative complications

Recommendation for surgical treatment in endometriosis-associated pain

Category	Recommendation	Grade	Quality of Evidence
CCR	Endometriosis identified at laparoscopy, should be surgically treated to reduce endometriosis-associated pain Laparoscopic approach is better than laparotomy for both diagnosis and treatment	A	--
CCR	Both ablation and excision are effective in reducing endometriosis pain in women with peritoneal endometriosis pain Fulguration of cyst wall should be avoided in cases with poor ovarian reserve	C	-
EBR	Laparoscopic uterosacral nerve ablation (LUNA) should not be performed to reduce endometriosis-associated pain	A	III
CCR	Presacral neurectomy (PSN) though effective in reducing endometriosis-associated midline pain, requires a high degree of skill and is associated with potentially hazardous complications	A	-
CCR	Cystectomy is better than drainage and coagulation or as it reduces endometriosis-associated pain and decreases recurrence rate of the endometrioma	A	-
CCR	Surgical removal of deep endometriosis, reduces endometriosis-associated pain, and improves quality of life	B	-
EBR	Preoperative hormonal therapy does not improve operative outcome	A	II
EBR	Postoperative hormonal treatment does not improve the outcome of surgery for pain and should be avoided	A	II
EBR	Postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months, should be used for the secondary prevention of endometriosis-associated dysmenorrhea	A	III
CPP	Avoid repeated surgery in these patients as this can reduce ovarian reserve	-	-

6.3 Management of infertility in women with endometriosis**Summary of evidence**

- The pregnancy rate (PR) is reduced to halve in women with endometriosis undergoing ART treatment. Detrimental effect of endometriosis was seen on implantation and PRs. Moreover one needs to balance the beneficial and harmful effects of surgery for endometriosis on the reproductive outcomes of ART
- In stage I and II endometriosis operative laparoscopy is more effective than diagnostic laparoscopy in improving ongoing pregnancy rates. Ovarian endometriosis ablation, cyst wall cauterization, and vaporization with CO₂ laser decrease anti-Müllerian hormone (AMH) and antral follicle count (AFC)
- Place for surgery for DE before ART is only if there is no pregnancy after three IVF-intracytoplasmic Sperm Injection (ICSI), whereas in women >35 years, removal of DE might be proposed after failure of 2 IVF–ICSI cycles

Figure 2

Management of stage I and II endometriosis in infertility

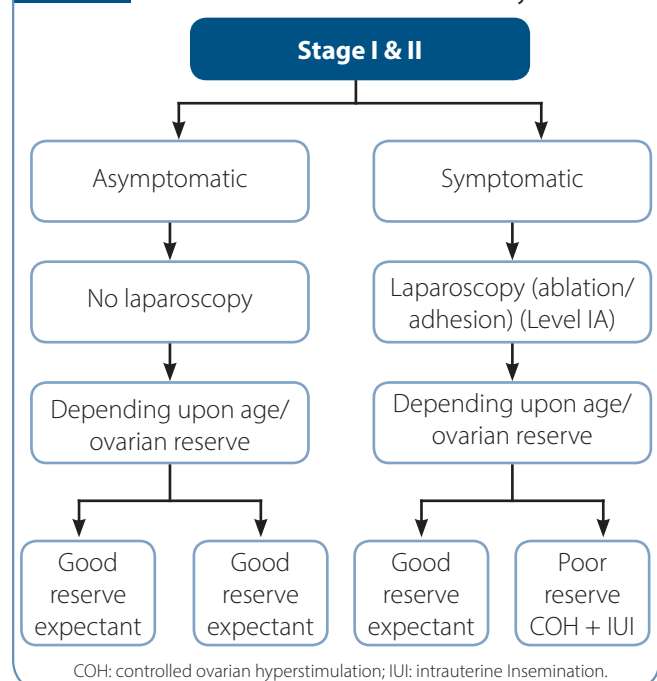
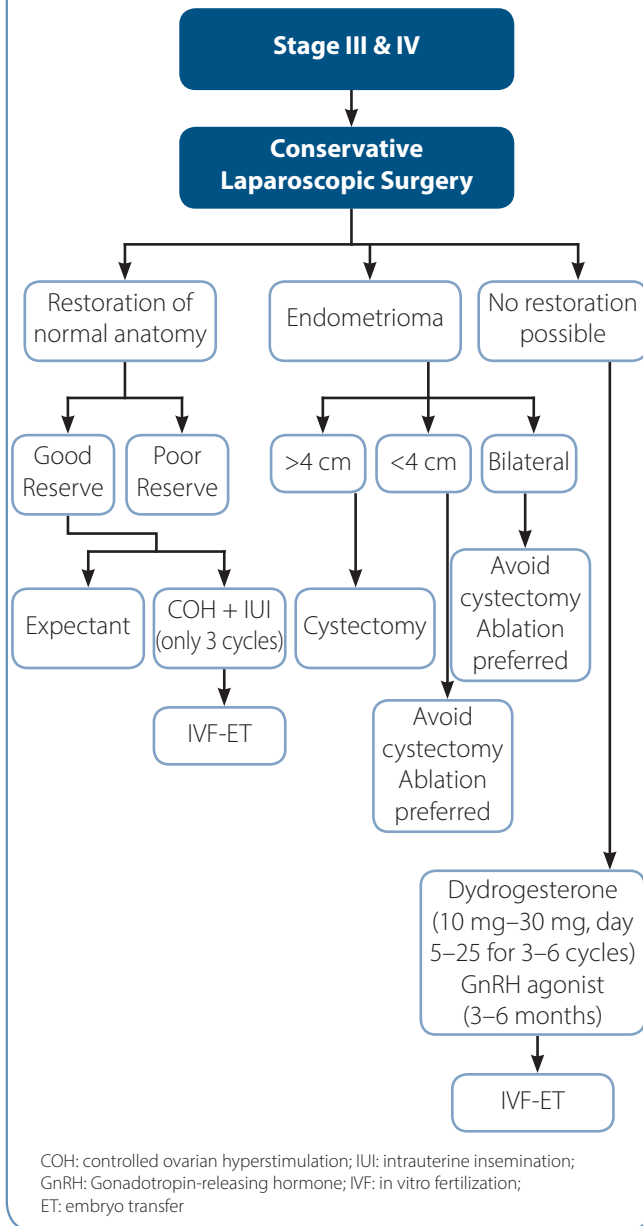
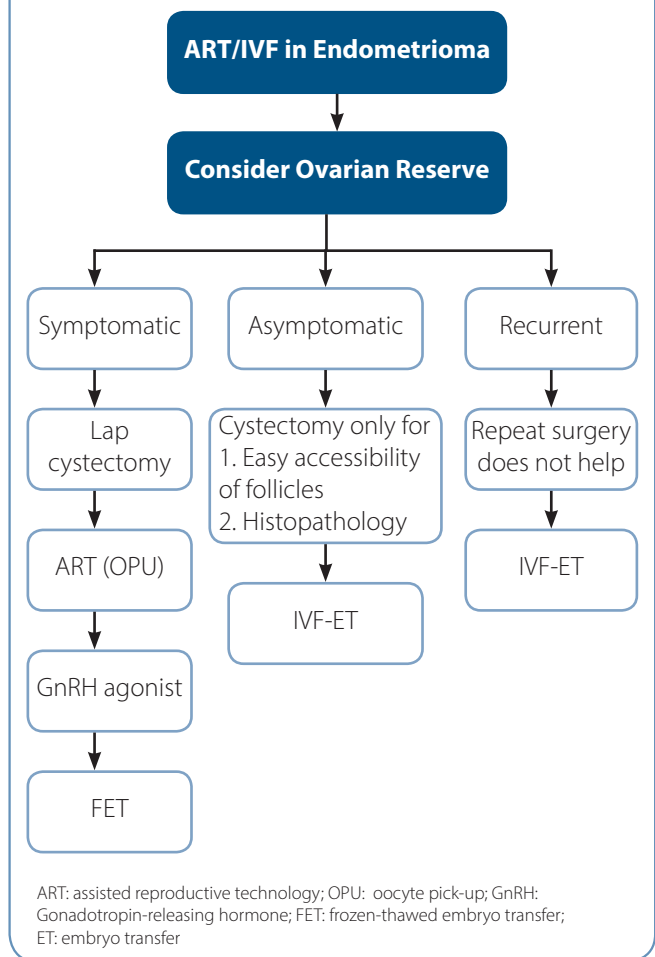


Figure 3

Describes the management of stage III and IV endometriosis in infertility

**Figure 4**

Management of endometrioma before ART



Recommendations for management of infertility in women with endometriosis

Category	Recommendation	Grade	Quality of evidence
EBR	In infertile women with AFS/ASRM stage I/II endometriosis, operative laparoscopic viz excision or ablation of the endometriosis lesions and adhesiolysis, rather should be performed to increase ongoing pregnancy rates	A	II
EBR	In infertile women with endometrioma larger than 3 cm, there is no evidence that cystectomy prior to treatment with ART to improves PRs	A	II
EBR	In stage III/ IV: Operative laparoscopy instead of expectant management increases chances of spontaneous pregnancy	A	III
CPP	In women with endometrioma larger than 3 cm, clinicians should consider cystectomy prior to ART only to improve endometriosis-associated pain or the accessibility of follicles	—	—
CPP	Counselling of women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of ovary is essential. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery	—	—
CCR	The effectiveness of surgical excision of deep nodular lesions before treatment with ART in women DE is not well established with regard to reproductive outcome	C	—
CPP	ART should be recommended in presence of tubal dysfunction or in presence of male factor or if other management options fail	B	—
CPP	Recurrence rate of endometriosis is not increased with controlled ovarian stimulation	—	—

*AFS: American Fertility Society (AFS); ASRM: American Society for Reproductive Medicine.

7. Guidelines in the management of adenomyosis

Summary of evidence

- Prevalence ranges from 8% to 27% and in endometriosis the prevalence is about 54%. Adenomyosis could be either diffuse or focal and may not affect implantation, but may be associated with pelvic pain, infertility, and early pregnancy loss. Adenomyosis can be diagnosed by 2D and 3D USG, MRI, histopathology, and at hysteroscopy
- In adenomyosis detection of junctional zone (JZ) involvement is very important as JZ has emerged as a hormone-dependent structure that governs uterine peristalsis outside pregnancy. Adenomyosis is associated with lower clinical and ongoing pregnancy rates and higher miscarriage rate. Medical management includes COC's, gonadotropin-releasing hormone (GnRH) agonists, Progestins, [medroxyprogesterone acetate (MPA), dienogest, danazol, levonorgestrel intrauterine system (LNG-

IUS)], selective progesterone receptor modulators (SPRM), and selective estrogen receptor modulators (SERM) which may avoid surgery but is not very effective in relief of pain. The chance of conception remains low in these cases

Surgical management

Summary of evidence

- The conservative surgical techniques involved excision of the adenomyotic tissue or adenomyoma and hysteroplasty either laparoscopically or via laparotomy. Conservative surgery can result in the reduction in myometrial capacity with higher incidence of abortion, premature labour, uterine rupture, and caesarean section. There is no fixed duration for which the patient needs be given contraception after surgery but is beneficial to be given for 6 months
- In women with adenomyosis planning to undergo IVF treatment, the following management strategies should be considered

1. GnRH analogue therapy for 2–6 months before IVF
 2. Long GnRH analogue protocol rather than GnRH antagonist should be considered as it helps to induce decidualization of the adenomyotic
 3. Two–Staged IVF could be considered. Patients can undergo ovarian stimulation, oocyte retrieval, and fertilization and embryo freezing followed by frozen–thawed embryo transfer (FET) at a later stage. Prior to the FET, GnRH analogue suppression therapy
 4. Single embryo transfer to prevent multiple pregnancies is preferred in adenomyosis as it has been associated with increased incidence of preterm delivery, preeclampsia, and second trimester miscarriage when compared with the control group
- Moreover, in women who have undergone adenomyomectomy prior to IVF should have single embryo transfer (SET) to avoid multiple pregnancy with a view to minimize the risk of scar rupture.

Recommendations for surgical management of adenomyosis

Category	Recommendation	Grade	Quality of evidence
CPP	Focal adenomyosis can be treated by laparoscopy. However, for diffuse adenomyosis laparotomy is preferred as the junction of normal and abnormal tissue is better delineated by palpation	—	—
CPP	Laparoscopic adenomyomectomy results in incompletely repaired muscle defects, compared with laparotomy surgery. Thus, the risk of uterine rupture is believed to increase during subsequent pregnancies following laparoscopic procedures	—	—
CPP	Energy sources can cause extensive tissue denaturation, making the tissue hard and difficult to heal after repair	—	—
CPP	Women after surgery for adenomyosis should be advised contraception for 6 months	—	—

8. Laparoscopy in PCOS

8.1 Laparoscopic ovarian drilling

Summary of evidence

- Laparoscopic ovarian drilling is as effective and safe as gonadotrophin therapy with less incidence of multiple pregnancy, ovarian hyperstimulation syndrome (OHSS). It is indicated in women who hypersecrete luteinizing hormone (LH), either in natural cycles or in response to clomiphene citrate (CC), anovulatory women with polycystic ovary syndrome (PCOS) who need laparoscopic assessment of their pelvis and in those women it is not possible to monitor a gonadotropin treatment cycle. Laparoscopic ovarian drilling not recommended for prevention of hyperresponsiveness to exogenous gonadotropins or management of menstrual irregularity or hyperandrogenism
- Poor reproductive outcome after laparoscopic ovarian drilling seen in women who are
 - » Obese (body mass index >25 kg/m²)
 - » Longer duration of infertility (>3 years)
 - » Low basal LH levels (<10 IU/L)
 - » Marked biochemical hyperandrogenism (testosterone levels ≥4.5 nmol/L, free androgen index >15)
 - » High basal anti-mullerian hormone (AMH) (≥7.7 ng/ml)

Recommendation for laparoscopic ovarian drilling in PCOS

Category	Recommendation	Grade	Quality of evidence
EBR	Laparoscopic ovarian surgery could be second line therapy for women with polycystic ovary syndrome (PCOS), who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors	C	III
CCR	Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors	C	—
CPP	<p>Risks of laparoscopic ovarian drilling need to be explained where laparoscopic ovarian surgery is to be recommended, the following need to be considered:</p> <ul style="list-style-type: none"> • Comparative cost with gonadotropins expertise required for use in ovulation induction • Intraoperative and postoperative risks are higher in women who are overweight and obese • There may be a small associated risk of lower ovarian reserve or loss of ovarian function • Periadnexal adhesion formation may be an associated risk 	—	—

9. Bariatric surgery in PCOS

Summary of evidence

- There is a direct causal relationship between PCOS, visceral obesity and metabolic syndrome.¹ It is not a fertility treatment for inducing ovulation but can correct menstrual irregularities, result in hormone normalization and improved reproductive function with reduced need for fertility treatment post bariatric surgery has been noted. Pregnancy should be avoided for 12 months post surgery
- Further methodologically rigorous trials are important to address the efficacy, safety and role of bariatric surgery in PCOS, which includes improving fertility

Recommendations for bariatric surgery in PCOS

Category	Recommendation	Grade	Quality of evidence
CCR	Bariatric surgery should be considered as an experimental therapy in women with polycystic ovary syndrome (PCOS), for the purpose of having a healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy	C	-
CCR	Bariatric surgery could be considered as a second line therapy to improve fertility outcomes in adult women with PCOS who are anovulatory, have a body mass index ≥ 35 kg/m ² , and who remain infertile despite undertaking an intensive (frequent multidisciplinary contact) structured lifestyle management program involving reducing dietary energy (caloric) intake, exercise, behavioural and/or drug interventions for a minimum of 6 months	C	-
CPP	<p>If bariatric surgery is to be prescribed, the following need to be considered:</p> <ul style="list-style-type: none"> • Comparative cost • The need for a structured weight management program involving diet, physical activity, and interventions to improve psychological, musculoskeletal, and cardiovascular health to continue postoperatively • Perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality • Potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes • Recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception • If pregnancy occurs, the following need to be considered: <ul style="list-style-type: none"> » Awareness and preventative management of preoperative and postoperative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting » Monitoring of fetal growth during pregnancy 	-	-

10. Laparoscopic ovarian surgery for dermoid and simple cyst

Summary of evidence

- When surgery is required for any type of ovarian cysts, it should be conservative and excision is preferred than ovariectomy. Moreover, laparoscopy is the preferred mode with the use of bipolar rather than

monopolar cautery when required. Coagulation of the cyst walls should be avoided

- Needle aspiration of a dermoid cyst must not be considered, owing to the risk of chemical peritonitis, and for this reason only excision is appropriate. No evidence also to support the utility of fine-needle aspiration of a unilocular cyst. These cysts should be treated by either surveillance or excision, depending on their size

Recommendations for laparoscopic ovarian surgery for dermoid and simple cyst

Category	Recommendation	Grade	Quality of Evidence
CPP	Imaging techniques which include 2D and 3D ultrasound should be used for assessment of ovarian cyst to decide between expectant and surgical management	—	—
CPP	Expectant management should be followed in moderate sized dermoid cysts (4–6 cm) which are asymptomatic	—	—
CPP	When surgery is required for any type of ovarian cysts, it should be conservative and excision is preferred than ovariectomy	—	—
CPP	Laparoscopy is the preferred mode with the use of bipolar rather than monopolar cautery Coagulation of the cyst walls should be avoided	—	—
CPP	No evidence for needle aspiration of either a dermoid or simple cyst	—	—

11. Tubal surgery

Summary of evidence

- Tubal surgery is done for hydrosalpinx, proximal tubal obstruction, sterilization reversal, and adhesiolysis. One could perform either salpingectomy, salpingostomy, proximal tubal occlusion/ligation or aspiration of fluid from hydrosalpinx to treat hydrosalpinx before IVF. It is best to avoid tubal surgery and opt for IVF as a treatment modality if patients is >37 years, presence of decreased ovarian reserve, abnormal tubal mucosa, and lack of in training in tubal surgery
- Reconstructive tubal surgery for hydrosalpinx can still be considered for selected women younger than 35 years, with mild tubal disease and no other co-existing infertility factors, and for those who cannot or refuse to undergo IVF treatment. In the presence of hydrosalpinx, the pregnancy rate was higher in the salpingectomy group, thus there is a definite beneficial effects of pre-IVF salpingectomy. Salpingectomy could be challenging, especially in the presence of dense periadnexal adhesions. Moreover, salpingectomy could also affect the ovarian blood flow and reduces the ovarian response during consequent IVF cycles
- Proximal tubal occlusion with electrocoagulation or with clips is another option of treatment but the concern with method is that it may lead to an increased size of hydrosalpinx, as the fluid can no longer drain through the uterus. For this reason, consideration may be given to widely fenestrating the hydrosalpinges at the time of proximal occlusion
- Laparoscopic sterilization reversal required shorter hospitalization compared to laparotomic reversal and was less expensive compared to robotic reversal. One must remember that for older women IVF could be a more cost effective than reversal of sterilization
- Tubal anastomosis should not be considered when
 - » Final tubal length is less than 4 cm
 - » There are significant tubo-ovarian adhesions with mucosal damage
 - » In presence of stage 3–4 endometriosis
 - » Presence of male factor
- Pelvic adhesions could be due to post pelvic infection, endometriosis and postsurgery. Salpingo-ovariolysis could be an option in the presence of tubal adhesions and the success of tubal surgery depends on extent of tubal damage, tubal wall thickness, distal ampullary diameter, health of distal tubal endothelium, extent and type of adhesions, and experience of the surgeon

Recommendations for tubal surgery in infertility

Category	Recommendation	Grade	Quality of Evidence
CPP	<p>Assessment for tubal surgery</p> <ul style="list-style-type: none"> The patient's age and declining fertility should be considered when advising a patient to undergo tubal assessment or corrective surgery Couples should be screened to exclude ovulatory disorders and semen abnormalities as these factors may preselect a couple for IVF treatment With a known history of pelvic inflammatory disease, pelvic surgery, ectopic pregnancy or endometriosis, laparoscopy and dye studies is preferred for pelvic assessment in preference to hysterosalpingography or hysterocontrastsonography (HyCoSy). A finding of proximal tubal obstruction by hysterosalpingography necessitates confirmation by either fluoroscopic or hysteroscopic selective tubal catheterisation Practitioners should have the necessary skills for and be prepared to undertake interventional procedures as part of a diagnostic laparoscopy procedure and the patient consented appropriately Laparoscopic staging of tubal pathology as to site, type and extent of disease process particularly in relation to hydrosalpinx is important for prognosis and deciding to have tubal surgery or IVF 	—	—
EBR	<p>Open microsurgery and laparoscopic tubal surgery</p> <ul style="list-style-type: none"> There is insufficient evidence to recommend one particular approach to surgery. The technique adopted should be determined by the skill of the surgeon and the available equipment 	C	III
EBR	<p>Proximal tubal disease</p> <ul style="list-style-type: none"> When available, selective salpingography and tubal catheterization or hysteroscopic tubal cannulation should be considered as they are less invasive treatment options with proven pregnancy results Tubocornual anastomosis should only be attempted by surgeons trained in microsurgical techniques and with the appropriate equipment. Alternatively, IVF should be considered 	C C	III III
CCR	<p>Distal tubal occlusion</p> <ul style="list-style-type: none"> Consider salpingoneostomy for <3 cm diameter thin walled hydrosalpinges free of adhesions which gives best results compared to fallopian tubes with both external and internal pathology Intraoperative or preoperative salpingoscopy enabling direct endoscopic evaluation of tubal mucosa may facilitate a decision to perform conservative salpingoneostomy or on the basis of extensive tubal pathology salpingectomy in preparation for IVF There was no improvement in pregnancy rate with use of postoperative hydrotubation with antibiotics and steroids or by carrying out second look laparoscopy and adhesiolysis Commencing IVF concomitantly or after this period of time seems a sensible progressive step 	C	—
EBR	<p>Hydrosalpinx and IVF</p> <ul style="list-style-type: none"> Consider salpingectomy for women with hydrosalpinges prior to IVF treatment. This should be undertaken laparoscopically with great care taken not to interfere with ovarian blood supply via the infundibulopelvic fold 	A	II

Category	Recommendation	Grade	Quality of Evidence
EBR	<p>Reversal of sterilization</p> <ul style="list-style-type: none"> Surgical reversal of sterilization offers a high chance of tubal patency and fertility and should be offered to women wishing to conceive after Filshie or Hulka clip and Falope ring sterilization Request for renewed fertility arises because of a new partner, improved economic circumstances or more rarely death of a child To enable couples to reach a decision regarding IVF or reversal, data on cumulative live birth rates after invitro fertilization should be presented The main factors influencing successful reanastomosis are the site of anastomosis, length of residual fallopian tube, and surgical technique. For the most commonly encountered Filshie or Hulka clip and Falope ring sterilization microsurgery offers a high chance of tubal patency and fertility The live birth rate in patients aged over 40 following reanastomosis suggest that conception may occur more readily with natural ovulatory cycles than in stimulated cycles The reversal procedure can be performed via a 3–5 cm suprapubic incision and uterine manipulation enabling patients to be discharged the same day or following an overnight hospital stay In younger women, particularly when they wish to consider having only one child in a new relationship, IVF may be a more realistic option because sterilization will continue to provide contraception following a successful birth 	B	II
CCR	<p>Tubal adhesions</p> <ul style="list-style-type: none"> Surgical correction of peritubular adhesions, preferably with minimal access techniques is recommended when the adhesions are American Fertility Society (AFS) stage I and II and in the absence of distal tubal occlusion 	C	-
CPP	<p>Adhesion prevention</p> <ul style="list-style-type: none"> Careful tissue handling is essential in reproductive surgery, however, adjuvant therapies do not improve the chance of pregnancy Teaching and maintenance of preventative surgical technique for laparotomy and laparoscopic surgery are pivotal in reducing postoperative surgical adhesions These techniques encompass gentle tissue handling, meticulous haemostasis, minimising ischemia and tissue dryness, use of nonreactive sutures, and prevention of infection Successful adhesion preventive measures in the experimental animal including the use of hypothermia and insufflation with 3% oxygen should be considered for routine use following confirmation of usefulness in clinical studies Whilst effective in reducing adhesion, there is no evidence from published studies that surgical barriers influence fertility, pain, and incidence of postoperative adhesions 	—	—

12. Hysteroscopy in infertility and ART

12.1 Routine hysteroscopy in all infertility patients, before IVF or RIF

Summary of evidence

- Hysteroscopy is a gold standard technique for uterine factor evaluation since it enables direct visualization of the uterine cavity and its relevant pathological disorders as well as the treatment of any detected abnormality. It has been shown to have no role in routine evaluation of infertility. There was also no impact on the pregnancy rates in women undergoing intrauterine insemination (IUI)
- There is also no evidence for routine hysteroscopy before first ever IVF. It is done early in the presence of an abnormal hysterosalpingogram (HSG) or history or symptoms suggestive of endometrial or uterine pathology. Routine hysteroscopy does not improve live birth rates (LBRs) in infertile women with a normal TVS of the uterine cavity scheduled for a first IVF treatment. Therefore, women with a normal transvaginal ultrasound should not be offered routine hysteroscopy. The TROPHY trial concluded that outpatient hysteroscopy before IVF in women with a normal ultrasound of the uterine cavity and a history of unsuccessful IVF treatment cycles does not

improve the livebirth rate. Moderate quality evidence indicates that endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle is associated with an improvement in LBR and CPR in women with more than two previous failed ETs. When confounding factors like age and number of failed IVF cycles were removed, there was no statistical difference in the LBR and miscarriage rate. Thus, the two recent meta-analysis concluded that endometrial injury should be used restrictively and not as a routine procedure

Recommendations for use of routine hysteroscopy before first IVF or RIF

Number	Category	Recommendation	Grade	Quality of Evidence
8.1.1	CRR	No role of routine hysteroscopy prior to IUI as it does not have any impact on pregnancy rates	B	—
8.1.2	EBR	Hysteroscopy before (first or subsequent) IVF/ ICSI attempt in infertile women without intrauterine abnormalities does not improve LBR and therefore should not be performed	A	II

IUI: intrauterine insemination; IVF: in vitro fertilization; ICS: intracytoplasmic sperm injection;

12.2 Operative hysteroscopy

Summary of evidence

- Hysteroscopic diagnosis and treatment of intrauterine abnormalities may improve pregnancy rates after ART, at least when compared with controls not receiving hysteroscopy but the quality of evidence is low

- Endometritis can cause delayed endometrial maturation, leading to asynchrony with implantation, which can result in RIF and RPL. Endometritis can easily be identified at hysteroscopy and once identified it can effectively be treated with a course of doxycycline and normal fertility restored
- Intrauterine synechiae can be a source of abnormal placentation, recurrent miscarriage, and preterm labour. PRs can be improved and miscarriage rates decreased with hysteroscopic adhesiolysis. Postoperative estrogen followed by progesterone and second-look hysteroscopy with adhesiolysis have all been used for treatment of recurrent synechiae after initial adhesiolysis. Intrauterine balloon application after operative hysteroscopy is of great value in preventing intrauterine adhesions. Mechanical agent like intrauterine device may not be helpful in prevention of postop adhesions
- Auto-cross linked hyaluronic acid gel (ACP) significantly reduces the development of intrauterine adhesions postoperatively and its use is likely to be associated with reduction in severe adhesion. Intercoat gel has also been tried and it has shown to prevent de novo formation of IUAs and to improve the patency of the internal uterine ostium at follow-up hysteroscopy
- Poor prognostic indicators for surgery in women with IUA include:
 - » Adhesions obliterating both ostia
 - » Age >35 years
 - » Amenorrhea/oligomenorrhea
 - » Abnormal ultrasound appearance
 - » Reformation of adhesions at second look

Recommendations for operative hysteroscopy in infertility

Category	Recommendation	Grade	Quality of evidence
CCR	Intrauterine abnormalities can be diagnosed by 2D and 3D ultrasound, saline infusion sonogram (SIS), and HSG	B	—
CCR	MRI should not be routinely advised for diagnosis of intrauterine abnormalities	C	—
EBR	Operative hysteroscopy in infertile women improves clinical pregnancy rate in women diagnosed with intracavitary abnormalities (i.e. endometrial polyps and submucous fibroids) detected at US, HSG or SIS/gel instillation sonography (GIS)	A	III
CPP	Asymptomatic polyps in non-infertile women, less than 10 mm in size and at low risk of malignancy may be followed up without surgery. Polyps larger than 10 mm are unlikely to regress spontaneously. All symptomatic polyps require removal	—	—
CPP	Direct removal of polyps either by resection or hysteroscopic scissors is reported to reduce recurrence rate compared to visualising the polyp followed by removal by a polyp grasping forceps or curettage	—	—
CCR	Diagnosis and treatment of endometritis and adenomyosis at hysteroscopy allows treatment with improvement in the clinical pregnancy rate (CPR) and LBR	B	—
CCR	PRs can be improved and miscarriage rates decreased with hysteroscopic adhesiolysis in mild-to-moderate intrauterine adhesions	B	—
CCR	There is no role of blind cervical probing or blind curettage in these patients	C	—
CCR	The use of concomitant modalities like ultrasound and laparoscopy does not provide additional benefit. However, in expert hands and in properly selected patients, these may marginally reduce the complication (e.g. perforation) rate	B	—
CCR	PRs and LBRs do not improve much after hysteroscopic adhesiolysis of severe intrauterine adhesions	C	—
CCR	Postoperative estrogen followed by progesterone, balloon therapy, and second-look hysteroscopy with adhesiolysis may prevent recurrent synechiae formation after initial adhesiolysis	C	—
CCR	Adhesion barriers used post procedure is known to have short-term benefit. However, long-term benefit on overall fertility rate remains questionable	A	—
CCR	Role of preoperative, intraoperative or postoperative antibiotics has no proven benefit	C	—
CCR	Intrauterine devices (IUD) are not recommended.	C	—
CCR	Newer adhesive barriers like hyaluronic acid and auto-cross-linked hyaluronic acid gel reduce adhesion reformation Their efficacy in terms of post-treatment pregnancy rate is unknown	A	—
CCR	Use of stem cell therapy as an adjunctive treatment has limited evidence and should not be applied outside research settings	C	—
CCR	Relook hysteroscopy is advocated to assessment of uterine cavity after adhesiolysis	B	—

12.3 Mullerian duct abnormalities

Summary of evidence

- Septate uterus is associated with higher first-trimester abortion, pre re-look hysteroscopy term delivery and lower term births. Earlier surgery was recommended when sub-septation was 10 mm, but the new cut off for correction of septate uterus is 5.9 mm. Hysteroscopic septal resection reduces the incidence of first-trimester abortions, pre-term deliveries and increases the live birth rate, and also improves post IVF pregnancy rates
- Management of patients with a T-shaped uterus is controversial and the beneficial effect of hysteroscopic

metroplasty is questionable with no prospective studies or RCTs

- One must remember that lateral metroplast may be associated with cervical incompetence, hysteroscopic endometritis in 1% to 5% of cases, destruction of normal endometrium due to use of monopolar cautery, and development of intrauterine adhesions. Uterine perforation at surgery and

increased incidence of uterine rupture during pregnancy, increased risk of miscarriage (22%) and premature delivery (20%) adherent placenta, and cesarean section is also noted

- Lateral metroplasty may be performed only in cases of repeated miscarriages, longstanding and unexplained infertility unrelated to the uterine anomaly, or following failed ART

Recommendations for surgery in mullerian duct abnormalities

Category	Recommendation	Grade	Quality of Evidence
CCR	Hysteroscopic septal resection reduces the incidence of first trimester abortions, pre-term deliveries, and increases the live birth rate.	B	—
CCR	Earlier correction of uterine sub-septations was done when it was longer than 10 mm New cut off for correction of septate uterus is 5.9 mm	B	—
CPP	In a patient with no history of infertility or prior pregnancy loss, it may be reasonable to consider septum incision after counselling about the potential risks and benefits of the procedure	—	—
CPP	Performing enlargement metroplasty by making incisions on the lateral myometrial walls to a depth of 5 mm to 7 mm appears to improve the obstetrical prognosis only in cases of repeated miscarriages, longstanding and unexplained infertility, and should not be done in all cases	—	—
CCR	Arcuate uterus have no adverse impact on early pregnancy and therefore hysteroscopic resection is not necessary	B	—

Summary of recommendations

Infertile women undergoing IUI, there is no evidence of a treatment effect of laparoscopy prior to IUI for the ongoing pregnancy rate per patient (compared to immediate treatment with IUI)

- Reproductive surgery may be complimentary before IVF to enhance its success and not all surgeries can improve IVF outcome. Surgeries that may help are:
 - » Adhesiolysis so that the ovary can be accessed by TVS
 - » Removal of large endometriomas, which preclude access to follicular aspiration
 - » Hydrosalpinx
- Reproductive surgery indicated beyond a reasonable doubt

- » Adhesions around the fallopian tube, ovaries or the ampulla (Level B-C)
- » Intramural myomas >5 cm and those close to the junctional zone (Level B)
- » Hydrosalpinx (Level A)
- » Tubectomy reversal. (Level B-C)
- » Hysteroscopic surgery for polyps, submucous myoma (Level A)
- » IUA and metroplasty (Level B-C)

- Reproductive surgery having contradictory evidence
 - » In PCOS—laparoscopic ovarian drilling is second-line treatment for OI in PCOS
 - » Endometriosis and endometrioma or recurrent endometrioma
 - » Deep rectovaginal endometriosis without pain

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Infertile women undergoing IUI, there is no evidence of a treatment effect of laparoscopy before IUI for the ongoing pregnancy rate per patient (compared to immediate treatment with IUI)	B	III
EBR	Reproductive surgery may be complimentary before IVF to enhance its success and not all surgeries can improve IVF outcome. Surgeries that may help are:	B	III
EBR	• Adhesiolysis so that the ovary can be accessed by TVS	B	II
EBR	• Removal of large endometriomas, which preclude access to follicular aspiration	C	IV
	• Hydrosalpinx	A	I
EBR	Reproductive surgery indicated beyond a reasonable doubt	A	I-III
EBR	• Adhesions around the fallopian tube, ovaries or the ampulla	B	III
EBR	• Intramural myomas >5 cm and those close to the junctional zone	B	II
EBR	• Hydrosalpinx	A	I
EBR	• Tubectomy reversal.	B	III
EBR	• Hysteroscopic surgery for polyps, submucous myoma	A	I
EBR	• IUA and metroplasty	B	III
EBR	Reproductive surgery having contradictory evidence		
EBR	• In PCOS–laparoscopic ovarian drilling is second–line treatment for OI in PCOS	B	II
EBR	• Endometriosis and endometrioma or recurrent endometrioma	B	III
EBR	• Deep rectovaginal endometriosis without pain	C	IV
CCR	• Adenomyosis	C	IV
EBR	• Severe tubal disease or occlusion due to disease	C	III
EBR	• Routine laparoscopy, hysteroscopy	A	I
EBR	• Endometrial scratch	A	I

- » Adenomyosis
- » Severe tubal disease or occlusion due to disease
- » Routine laparoscopy, hysteroscopy
- » Endometrial scratch

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Chapter 5: Advice on Preconception Care

OVERVIEW

This guideline offer recommendations to highlight the benefits of preconception care by outlining the interventions that are effective and beneficial. This guideline will act as a blueprint to the standards of preconception care in India. These recommendations highlight the benefits of preconception care, outline preconception interventions, and provide the evidence to make the case for preconception care. It is aimed primarily at women aged 18 years or older presenting to healthcare professionals or general practitioners or any maternity service providers.

1. Definition of preconception care

- Preconception care comprises a range of interventions aimed at identifying and modifying medical, behavioral, and social risks to women's and men's health during their reproductive years
- Preconception care is aimed at identifying, preventing, and managing risk factors that adversely affect maternal-fetal outcomes before conception

2. Need for preconception care

- Health inequalities is a global problem and more so in India. The reason behind this is the diversity in:
 - » Socioeconomic status
 - » Access to education
 - » Culture
 - » Social makeup
 - » Dietary habits
 - » Beliefs and way of life in general
- There is ample evidence to prove that timely preconception interventions correlate positively with improved maternal and neonatal outcomes as it focuses on health irrespective of an individual's reproductive plans. The preconception period is a singular unique time to address health inequalities before they set in
- A woman's health at conception is the biggest predictor of pregnancy outcomes. Correcting it at this time ensures a better start for infants in life and sustained efforts will make the benefit percolate through generations

3. Some Indian statistics

- In 2015, India was declared maternal and neonatal tetanus free, similar accolades remain to be achieved on other accounts
 - » One in two pregnancies in India is unintended as opposed to 2 in 5 globally
 - » 53% of women in the reproductive age group in India have iron-deficiency anemia
 - » 40% of Indian women have a lifetime risk of suffering domestic violence, especially during pregnancy
 - » Approximately 11.8 million teenage pregnancies occur in India per year
 - » The neonatal mortality rate remains at about 28 per 1000 live births and is as high as 50% in teenage pregnancies
 - » Around 3.2% of Indian women smoke i.e. about 12 million women. The ones that do smoke take more than 7 puffs a day. Indian girls start smoking at 17.7 years of age as opposed to boys at 18.5 years

4. Benefits of preconception care

- Reduces maternal and child morbidity and mortality
- Prevent unplanned pregnancies
- Prevent preterm birth, low birth weight, and stillbirths
- Prevent birth defects
- Prevent neonatal infections
- Prevent underweight and stunting

- Prevent vertical transmission of human immunodeficiency virus (HIV); sexually transmitted infections (STIs)

5. Barriers in preconception care implementation in India

- Fragmented health care service delivery system
- Poor health care budgets
- Lack of identification and treatment services for high-risk behaviors
- Inadequate availability and penetration of counseling services
- Lack of practice guidelines and protocols for uniformity of care
- Not all preconception interventions supported by robust evidence
- End-user diversity leading to women most in need of preconception care least likely to receive it

6. Constituents of preconception care

- It encompasses if and when a couple will like to choose to be parents and their fitness for pregnancy. Preconception care includes the following:
 - » Management of pre-existing health conditions
 - » Assistance in ceasing risky behaviors
 - » Promoting healthy behaviors

7. Preconception care recommendations

7.1 Reproductive planning

- Opportunistically discuss reproductive goals–
 - a. Discuss factors that will affect the optimum outcome–medications, lifestyle, habits, activities, and health conditions
 - b. Discuss about effecting of ageing on ovarian reserve and oocyte quality and aneuploidy in the embryos

- c. Also, discuss the possibility of premature ovarian insufficiency at a younger age

7.2 Contraception

- When not planning for a pregnancy, counsel for and offer a full range of contraception–Cafeteria approach
- Counsel for and support birth spacing
- Encourage late age for first conception

7.3 Genetic and family history

- Take a thorough personal and family history. Especially ask for consanguinity and ethnic background (thalassemias)
- Identify risk factors for genetic conditions
- Offer genetic counseling and carrier screening and testing to a high-risk population
- Advice about the age-related increased risk of genetic issues e.g. Down's syndrome

7.4 Psychosocial issues

- Screen for depression and anxiety disorders
- Counsel and treat preexisting depression
- Explain the risks of antidepressant medications
- Look for signs of, and actively ask about exposure to domestic violence. Evaluate the patient's safety and offer help as appropriate
 - » Ask about alcohol use and abuse and counsel about alcohol cessation
 - » Ask about tobacco use and offer counseling and treatment for the cessation of smoking
 - » Ask for use of recreational drugs
 - » Educate about fetal alcohol syndrome and the risks of smoking to the fetus
 - » Provide access to behavioral interventions to reduce tobacco, alcohol, and drug use

7.5 Infection screening

- Screen and treat all women who are at risk of infection f–Chlamydia, gonorrhea, all high-risk women, herpes

simplex virus infection, HIV, syphilis, and tuberculosis

- » Counsel about the risk of vertical transmission
- » Universal screening for HIV

» Treat women with active and latent disease before pregnancy. Screen for periodontal and urinary infections and treat accordingly

7.6 Vaccination

Name of the vaccine	Recommendation
Hepatitis B	<ul style="list-style-type: none"> • Vaccinate all high-risk women • Counsel chronic carriers about the prevention of vertical transmission
Influenza	<ul style="list-style-type: none"> • Vaccinate all women during influenza season and women at risk of influenza-related complications
MMR	<ul style="list-style-type: none"> • Screen for immunity • Vaccinate all non-immune women non-pregnant women • Consider vigorous counselling in patients to avoid pregnancy for 3 months post vaccination
DPT	<ul style="list-style-type: none"> • Tetanus vaccination may protect against neonatal tetanus • Vaccinate with Tdap* between 27 to 36 weeks' gestation to reduce the risk of neonatal tetanus
Varicella	<ul style="list-style-type: none"> • Screen for immunity • Vaccinate all non-immune women who are not pregnant • Subject to patient counselling to avoid pregnancy for 1 month post vaccination
*Tetanus, diphtheria, and pertussis (whooping cough)	

7.7 Exercise, diet, nutrition and supplements

- Assess BMI and consider counselling of women in those with obesity, overweight, or underweight regarding achieving a healthy body weight before pregnancy
- Screen for anemia and diabetes
- Supplement iron and folic acid
- Monitor nutritional status

7.7.1 Exercise

- Moderate-intensity physical exercise, 30 minutes/day
- No detrimental effect of moderate exercise in the preconception period
- High contact sports are contraindicated e.g. mountaineering, deep sea diving, etc
- Promoting exercise
- Consider use of iodized salt

7.7.2 Recommended supplements

Nutrient	Target population	Recommended dose	Helps
Folic acid	All women preconception high risk (previous NTD, an anticonvulsant medication, GDM, malabsorption, obese)	400–500 µg daily for at least four weeks before pregnancy and the first 12 weeks of gestation, 5 mg daily for at least four weeks before pregnancy and the first 12 weeks of gestation	Prevention of NTD such as spina bifida and anencephaly
Iodine	All women	150 µg daily while pregnant and breastfeeding	Production of maternal thyroid hormone, fetal brain, and CNS development
Vitamin D	Women with vitamin D deficiency	1000 IU/day (vitamin D 30–49 nmol/L) 2000 IU/day (vitamin D <30 nmol/L)	Reduces the risk of small-for-gestational-age babies and impaired fetal skeletal development
Iron	Women with iron deficiency	Oral supplement with at least 60 mg of elemental iron daily	Prevention of anemia
Vitamin B12	Vegans and vegetarians	2.6 µg/day or intramuscular injection 1000 µg/ampoule	Infant neurological sequelae
Calcium	Women with an inadequate dietary intake (<1000 mg daily)	At least 1000 mg daily	Prevention of pre-eclampsia
CNS: central nervous system; GDM: gestational diabetes mellitus; NTD: neural tube defects.			

7.7.3 Nutrients to restrict

Nutrient	Target population	Recommended limitation	Why?
Vitamin A	All women	Dietary sources do not pose a risk at normal levels Limit vitamin A supplements to 3000 IU per day All synthetic derivatives of retinol should be ceased at least one month before conception	Increased risk of miscarriage and CNS malformations
Mercury-containing fish	All women	Avoid fish containing high levels of mercury and eat two to three serves of other types of fish per week	Increased risk of negative effects on the fetal brain and CNS
Caffeine	All women	Limit to 300 mg or less per day (i.e., 2 or 3 cups)	Increased risk of fetal growth restriction
CNS: central nervous system.			

7.8 Chronic medical conditions

- Optimize control of any preexisting medical condition
- Where possible make the patient medication free
- Where not possible use the least harmful drug at the least possible needed for control
- Prefer monotherapy to polypharmacy
- Inform and counsel that one-third of preexisting medical conditions can worsen in pregnancy
- Offer TOP if the pregnant patient was already exposed to known teratogenic agent

7.8.1 Diabetes

- » Discontinue most oral hypoglycemic and start insulin
- » Metformin may be continued
- » Advice weight loss where indicated
- » Inform and counsel about the risk of miscarriage and fetal macrosomia
- » Avoid ACE inhibitors, statins due to the risk of fetal renal damage and fetal demise seen in animal studies, limited data available in humans

7.8.2 Hypertension

- » Counsel for the risk of superadded preeclampsia.
- » Advice regular BP checkups
- » Counsel about the risk of low birth weight baby and intrauterine growth restriction (IUGR)
- » Avoid ACE inhibitors, alpha receptor blockers due to fetal renal complications

7.8.3 Hypo and hyperthyroidism

- » TSH screening is a must for all women preparing for a pregnancy
- » In cases of active thyroid disease, it is desirable to aim for TSH in the range of 2–3.5 mIU/L (≤ 2.5 mIU/L) for better outcomes

» Propylthiouracil (PTU) is preferred in preconception and the first trimester

- Methimazole may be used in second and third trimesters
- There is a risk of teratogenicity in the first trimester
- If surgery is needed for goiter this may be done in the preconception period
- If radioiodine has been used to avoid pregnancy for 3 months

7.8.4 Asthma

- Inhaled steroids and β -agonists are safe for use
- Oral steroids are associated with increased risk of pre-eclampsia, reduced birth weight, and oral clefts

7.8.5 Seizure disorder

- Postpone conception until seizure free for a year
- Most antiepileptics are teratogenic
- Higher doses and polytherapy increase the risk of congenital anomalies
- Monotherapy at least effective dose should be achieved before conception
- Where possible it is best for the patient to be medication free and disease under control

7.8.6 Thrombophilia

- Warfarin is teratogenic
- Shift to heparin during preconception care
- Low-molecular-weight heparin (LMWH) is preferred anticoagulant for preconception and pregnancy

7.8.7 Preconception care for men

- Enquire about male reproductive health issues at the preconception visit
- When the couple is planning for a pregnancy, discuss medical conditions, activities, and lifestyle issues
- When not planning for pregnancy offer contraception

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
	Lifestyle		
CPP	• The use of illicit drugs and alcohol during pregnancy has adverse effects on the neonate, and these children are at risk for altered neurodevelopmental outcome and poor health status. Detection of drug and alcohol abuse is essential to counsel them preconceptionally about the effects on mother and fetus	-	-
CPP	• Screening of women and girls for tobacco use (smoking and smokeless tobacco) at all clinical visits and also informing about passive smoke and harmful effects on pregnant women and unborn children	-	-
CPP	• Counsel about health risks associated with smoking during pregnancy include intrauterine growth restriction, placenta previa, and abruptio placentae. Additionally, adverse pregnancy outcomes may occur including premature rupture of membranes, low birth weight, and perinatal mortality. Smokers of reproductive age should be counselled about the associated risks of smoking and the negative outcomes associated with pregnancy	-	-
CPP	• Intervention, known as the 5 A's, is appropriate for use during routine prenatal office visits and includes the following five steps: Ask, Advise, Assess, Assist, and Arrange	-	-
CCR	• Providing brief tobacco cessation advice, pharmacotherapy (including nicotine replacement therapy, if available) and intensive behavioural counselling services	C	-
CCR	• Treating substance use disorders, including pharmacological and psychological interventions	C	-
CPP	• Counsel on healthy balanced diet. Inform that women needs around 2,000 kcal to maintain her weight. Being obese (body mass index [BMI] >30) increases the risk of hypertension in pregnancy and gestational diabetes by almost 11 times, as well as other pregnancy complications, such as miscarriage, shoulder dystocia, blood clots, and still birth	-	-
	• Recommend regular moderate exercise		
	Nutritional Conditions		
CPP	• Screening for anemia and diabetes	-	-
CCR	• Supplementing iron and folic acid	A	-
CCR	• Information, education, and counselling	-	-
CPP	• Monitoring nutritional status	-	-
CPP	• Supplementing energy- and nutrient-dense food	-	--
CPP	• Management of diabetes, including counselling people with diabetes mellitus	-	-
EBR	• Promoting exercise	A	II
EBR	• Iodization of salt	-	-
CPP	• Counsel on the importance of vitamin D for calcium absorption, and maintenance of healthy bones and teeth is widely known. Inform that insufficient vitamin D during pregnancy results in calcium deficiency, which can lead to maternal osteomalacia (softening of bones), pre-eclampsia, low birth weight, and increased risk of neonatal tetanic seizures and childhood rickets	-	-
CCR	• Supplement Vitamin D if required	C	-
	Environmental health		
CPP	• Providing guidance and information on environmental hazards and prevention	-	-
CPP	• Protecting from unnecessary radiation exposure in occupational, environmental, and medical settings	-	-
CPP	• Avoiding unnecessary pesticide use/providing alternatives to pesticides	-	-
CPP	• Protecting from lead exposure	-	-
CPP	• Informing women of childbearing age about levels of methyl mercury in fish	-	-
CPP	• Promoting use of improved stoves and cleaner liquid/gaseous fuels	-	-
CPP	• Occupational exposures–Material Safety Data Sheets for employer	-	-
CPP	• Counsel on effects of chemotherapy and radiation exposure in early pregnancy	-	-

Category	Recommendations	Grade of Recommendation	Quality of Evidence
	Genetic conditions		
CPP	• Taking a thorough family history to identify risk factors for genetic conditions	-	-
CPP	• Family planning	-	-
CPP	• Genetic counselling	-	-
CPP	• Carrier screening and testing of racial/ethnic background/family history	-	-
EBR	» Sickle cell anemia		
	» Cystic fibrosis	B	III
	» Thalassaemia		
	» Tay–Sachs disease		
CCR	• Appropriate treatment of genetic conditions	C	-
CPP	• Community-wide or national screening among populations at high risk	-	-
	Sexually transmitted infections (STIs)		
CPP	• Providing age-appropriate comprehensive sexuality education and services	-	-
CPP	• Promoting safe sex practices through individual, group, and community-level behavioural interventions	-	-
CPP	• Promoting condom use for dual protection against STIs and unwanted pregnancies	-	-
CCR	• Ensuring increased access to condoms	C	-
CPP	• Screening for STIs	-	-
	• Increasing access to treatment and other relevant health services		
	HIV		
CPP	• Family planning	-	-
CPP	• Promoting safe sex practices and dual method for birth control (with condoms) and STI control	-	-
CPP	• Provider-initiated HIV counselling and testing, including male partner testing	-	-
EBR	• Providing antiretroviral therapy for prevention and pre-exposure prophylaxis	A	II
CPP	• Providing male circumcision	-	-
EBR	• Providing antiretroviral prophylaxis for women not eligible for, or not on, antiretroviral therapy to prevent mother-to-child transmission	B	I
CCR	• Determining eligibility for lifelong antiretroviral therapy	C	-
	Vaccine-preventable diseases		
EBR	• Vaccination against rubella	A	II
EBR	• Vaccination against tetanus and diphtheria	A	II
EBR	• Vaccination against hepatitis B	A	II
	Mental health		
CPP	• Assessing psychosocial problems	-	-
CPP	• Providing educational and psychosocial counselling before and during pregnancy	-	-
CPP	• Counselling, treating, and managing depression in women planning pregnancy and other women of childbearing age	-	-
CPP	• Strengthening community networks and promoting women's empowerment	-	-
CPP	• Improving access to education for women of childbearing age	-	-
CPP	• Reducing economic insecurity of women of childbearing age	-	-
	Too-early, unwanted, and rapid successive pregnancies		
CPP	• Influencing cultural norms that support early marriage	-	-
CPP	• Providing age-appropriate comprehensive sexuality education	-	-
CPP	• Providing contraceptives and building community support for preventing early pregnancy and contraceptive provision to adolescents	-	-
CPP	• Engaging men and boys to critically assess norms and practices regarding gender-based violence and coerced sex	-	-
CPP	• Educating women and couples about the dangers to the baby and mother of short birth intervals	-	-

Category	Recommendations	Grade of Recommendation	Quality of Evidence
	Chronic disease		
CPP	• Identification and management of chronic diseases like asthma, diabetes mellitus, hypothyroidism, heart disease, obesity, and dental disease	B	-
CCR	• If on any medication, its use should be continued to control disease in women during the preconception period. Switching medication may be appropriate during the preconception period if suitable alternatives exist with less risk to the pregnant woman or fetus	B	-
EBR	• Certain drugs taken preconceptionally may be a risk factor for negative pregnancy outcomes and therefore should be used with caution.	B	
	• Isotretinoin: If used in pregnancy to treat acne, it can result in miscarriage and birth defects.	B	II
EBR	• Anti-epileptic drugs: Certain types e.g. valproic acid are teratogens	A	III
EBR	• Oral anticoagulants such as warfarin have shown to be teratogenic. Early exposure during pregnancy could be avoided preconceptionally by switching to safer drugs	A	II
EBR	• In presence of chronic medical conditions	B	II
EBR	• Diabetes—optimize control	A	I
EBR	• Hypertension—avoid ACE inhibitors, angiotensin II receptor antagonists	B	II
EBR	• Epilepsy—consider increased dose of folic acid	A	I
EBR	• DVT—switch from warfarin (Coumadin) to heparin	B	III
EBR	• Acne—stop isotretinoin (e.g. Accutane)		
	• Depression/anxiety and other mental health issues—discuss current benefit/risk medication data	C	IV
	Assess any complications from previous pregnancies		
CPP	• Cesarean section • Premature delivery • Hypertensive disorder of pregnancy • Diabetes • Rh incompatibility • Postpartum hemorrhage • Thrombotic event (DVT/PE)	-	-
	Other pre-conceptional advice		
CPP	Screen for domestic violence	-	-
CPP	Screen for social issues (e.g. place to live, child care, transportation)	-	-
CPP	Counsel on the use of over-the-counter medications, nutritional supplements, and naturopathic substances	-	-

ACE: angiotensin-converting enzyme; DVT: deep venous thrombosis; HIV: human immunodeficiency virus; PE: pulmonary embolism.

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Chapter 6: Medical & Surgical Management of Male Infertility

OVERVIEW

This guideline is of relevance to:

- The professional groups who share in caring for couples seeking advice and treatment for fertility problems, such as gynecologists, andrologists, GPs, counselors, and nurses
- Those with responsibilities for commissioning and planning fertility services in primary care trusts and Health Commission
- People seeking advice and treatment for possible infertility

1. Introduction

- Male factor is present in nearly 50% of cases
- Offer examination and evaluation of all males coming to an infertility clinic
- Infertility platform affords an opportunity to evaluate young males for other problems such as diabetes, hyperlipidemia, ischemic heart disease (IHD), renal failures, pituitary tumors, and testicular cancers

- Semen analysis should be performed and further andrological assessments should be done if at least two semen analysis reports show abnormality
- WHO parameters of semen analysis are not sufficient to interpret the fertility status or chance of pregnancy in either natural or assisted conception and male infertility workup thus goes far beyond a simple semen analysis
- Reference values are shown in Table1 below

2. Investigations

2.1 Semen analysis

- The most basic investigation is a good standardized semen analysis report with an abstinence period of 3–4 days
- Semen analysis should be performed and further andrological assessments should be done if at least two semen analysis reports show abnormality
- WHO parameters of semen analysis are not sufficient to interpret the fertility status or chance of pregnancy in either natural or assisted conception and male infertility workup thus goes far beyond a simple semen analysis
- Reference values are shown in Table1 below

2.2 Hormonal investigations

- Endocrine laboratory diagnosis is recommended in cases of low sperm count especially if less 10 mill/ml, impaired sexual function and clinical findings suggestive of an endocrinopathy
- When semen parameters are abnormal assessment for serum follicle-stimulating hormone (FSH), and

Table1. Reference values of semen parameters in different WHO manuals

	WHO laboratory manual for the examination of human semen and sperm–cervical mucus interaction 1992	WHO laboratory manual for the examination of human semen and sperm–cervical mucus interaction 1999	WHO laboratory manual for the examination and processing of human semen 2010
Volume	2.0	1.5	1.5 (1.4–1.7)
pH	7.2–7.8	7.2	≥7.2
Concn (x 10 ⁶ ml)	20	20	15 (12–16)
Total count	40	40	39 (33–46)
Prog motility(%)	50	50	32 (31–34)
% Normal morph	30	-	4 (3.0–4.0)
Vitality (alive)	75	75	58 (53–63)
WBC (x10 ⁶)	1.0	1.0	<1.0
%MAR	20	50	<50

MAR: mixed antiglobulin reaction; WBC: white blood cells; WHO: World Health Organization.

serum testosterone should be done. Additional luteinizing hormone (LH), prolactin & estradiol (E2), sex hormone binding globulin (SHBG) is done in men with low testosterone levels

- An elevated FSH level greater than twice the normal upper limit is a reliable indicator of abnormal spermatogenesis and severe testicular dysfunction
- However, focal areas of spermatogenesis may be present in patients with highly elevated FSH levels
- Recently a stronger correlation has been demonstrated between inhibin B, anti-Müllerian hormone (AMH), and spermatogenesis as they reflect Sertoli cell function
- Do not consider routine inhibin B and AMH estimation in andrological evaluation. Though levels correlate with testicular cytology but are not superior to FSH as predictors for the presence of sperm in testicular sperm extraction (TESE)/ fine needle aspiration (FNA) in men with azoospermia

2.3 Sperm function Test

2.3.1 Hypo-osmotic swelling test

- Provides information on membrane integrity of sperm and has a good correlation exist between spermatozoa showing positive HOS reaction and FR at IVF

2.3.2 Teratozoospermia index (TZI)

- Normal values for TZI is <1.6. If TZI is >1.8. ICSI is beneficial irrespective of count and motility
- **Sperm survival test**
- Sperm survival tests are helpful in assessing IVF outcome and PRs.
- **Computer-assisted sperm analysis (CASA):** A semi-automated technique for semen analysis. CASA is not superior to conventional semen analysis (Grade A). Advantages and disadvantages of CASA are given in Table 2

CASA is not superior to conventional semen analysis (Grade A)

Table 2. Advantages and disadvantages of CASA

Advantages	Disadvantages
<ul style="list-style-type: none"> • High precision • Quantitative assessment of sperm kinetics • Provides data on sperm density, motility, straight-line and curvilinear velocity, linearity, and average path velocity, amplitude of lateral head displacement, flagellar beat frequency, and hyperactivation 	<ul style="list-style-type: none"> • Sperm concentration, sample preparation and frame rate can affect accuracy of CASA • Stains used also affect the accuracy of determining morphology • Does not add any advantages in clinical practice • Requires expensive equipment and still requires the active participation of a technician

CASA: Computer-assisted sperm analysis

2.3.3 Sperm DNA fragmentation test

- There is evidence linking sperm DNA fragmentation to poor reproductive outcome and has impact on embryo/blastocyst development, progress of pregnancy, and pregnancy loss. It may contribute to the development of novel and more personalized approaches to test and treat male factor infertility
 - » Tests that measure the extent of DNA damage
 - SCD (Halo Test)
 - Acridine Orange Assay (AO)
 - Sperm chromatin structure assay (SCSA)
 - Comet Assay (single cell gel electrophoresis assay) quantifies the amount of DNA damage per spermatozoon.
 - TUNEL–Terminal deoxynucleotidyl transferase dUTP nick end labeling–directly measures single or double strand breaks in DNA
 - » DNA fragmentation index (DFI)–Threshold values

0–15%	High fertility potential
>15% and <30%	Good to fair fertility potential
30% and higher	Low to poor fertility potential

- TUNEL assay was reported to have the higher precision specificity (91.6%) positive predictive value at a cutoff point of 16.8% as compared to other tests.
 - » SCSA and SCD test have a poor predictive value.
 - » TUNEL assay and Comet assay have fair predictive value after ART

2.3.3.1 Limitations of DNA fragmentation testing

- Consider the following limitations of DNA fragmentation testing:
 - » Poor accuracy
 - » Poor reproducibility and assessment
 - » Lack of standardized protocols for different tests
 - » Intra assay variability
 - » Inter observer variability
 - » Variability in chosen cut off values
 - » Variable specificity and sensitivity

2.3.3.2 Sperm DNA fragmentation testing

- Indications and evidence for testing
- Not enough data to recommend routine sperm DNA testing

Table 3: Indications for DFI testing

Indication	Evidence
SDF is recommended in patients with grade 2/3 varicocele with normal conventional semen parameters and in patients with grade 1 varicocele with borderline/abnormal conventional semen parameter results	C
SDF testing may allow clinicians to better select varicolectomy candidates among those men with clinical varicocele and borderline to normal semen parameters	
High DFI may provide a possible explanation for UI, RPL and IUI failure, therefore, it is reasonable to offer SDF testing to these infertile couples as these couples may be better served by IVF or ICSI sooner rather than later	C
DFI testing in patients with recurrent ART failure is indicated as it can provide useful prognostic information on subsequent ART cycles	C
Several studies have shown some benefit in using testicular sperm rather than ejaculated sperm in men with oligozoospermia, high SDF and recurrent IVF failure	B–C
Infertile men with evidence of exposure to pollutants or those found to have a modifiable lifestyle risk factor during evaluation should be offered SDF testing	C
DFI can help reinforce the importance of lifestyle modification, predict fertility, and monitor the patient's response to intervention	C
ART: assisted reproductive technology; DFI: DNA fragmentation index; RPL: recurrent pregnancy loss; SDF: sperm DNA fragmentation; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilization; UI: unexplained infertility.	

2.4 Genetic tests

- Karyotyping: In all men with impaired spermatogenesis–moderate to severe oligospermia (5 million/ml) and azospermia
 - » Klinefelters syndrome XXY and variants
 - » Translocations
 - Balanced
 - Unbalanced
- Molecular genetics: In men with obstructive and non-obstructive azospermia, severe oligoasthenoteratozoospermia
 - » Y-chromosome microdeletion–AZFc variable phenotype, AZFa, and AZFb in non-obstructive azospermia
 - » Cystic fibrosis transmembrane conductance regulator (CFTR) mutation in presence CBAVD and obstructive azospermia

ASA (antisperm antibody tests) is not recommended routinely

2.5 Ultrasound in male infertility

- Ultrasound for evaluation of male infertility, should be done in following conditions:
 - » Accurate measurement of testicular volume,
 - » Testicular and epididymal inflammatory and neoplastic lesions
 - » Diagnosis and doppler imaging of varicoceles.
 - » TRUS in seminal vesicular and prostatic abnormalities
 - » Penile blood flow evaluation in erectile dysfunction
 - » Location of the block in RTO by vasography
 - » Locating undescended testes

2.6 Testicular biopsy

- Diagnostic/therapeutic testicular biopsy is done for ultimate differentiation between obstructive and testicular azospermia. It should be done only

when facilities are available for cryopreservation of obtained sperms

- Testing for sperm oxidative stress:
 - » Laboratory signs suggesting possible sperm oxidative stress
 - Poor sperm motility
 - Teratozoospermia
 - High number of round cells (? leukocytes) in semen
 - Increased semen viscosity
 - Poor sperm membrane integrity on HOST
 - Poor fertilization on routine IVF
 - Poor sperm motility after overnight incubation with the oocyte
 - Poor blastocyst development in the absence of a clear female factor (advanced maternal age/poor ovarian reserve)

2.7 Measurement of ROS

- Chemiluminescence, which measures total seminal ROS (from WBC, abnormal spermatozoa, and seminal fluid). As the standardization of testing and the availability of these tests remain limited, it will be some time before this test will become a part of regular evaluation for male sub fertility
- Cut Off values for ROS: Normal ROS levels in washed sperm suspensions range from 0.10 to 1.03×10⁶ cpm per 20×10⁶ sperm
- ROS why not a mainstream investigation in the evaluation of male infertility
 - » Normal or reference values are not established at this point
 - » Use of seminal WBC levels as basis of ROS levels, although proven and well-accepted, has yet to establish definite cut-off points
 - » Even low WBC levels (below the WHO cut-off) are associated with ROS

2.8 Other sperm function tests

- Other sperm function test like acrosome reaction, acrosin activity test, creatine kinase, sperm penetration assays, and sperm zona binding tests are usually not done
 - » Emerging technologies like microarray, proteomics, epigenetics (aberrant DNA methylation, and RNA assay technologies including RNA-sequencing may help in elucidating the functional role of the spermatozoa
- » Consider using hMG instead of FSH to reduce cost and ensure compliance
- » Consider that treatment may have to be given for longer periods of 12 to 18 months
- » Not beneficial in men with normal gonadotropin levels

3.1.3 Anti-estrogen therapy-CC/Tamoxifen

- CC Clomiphene citrate (CC) 25 mg or Tamoxifen 20 mg for 6 months. Tamoxifen is preferred to CC as it exerts a weaker estrogenic action
- Most results controversial with some studies report benefit, while others do not
- Establishment of clear-cut guidelines for use necessary

3.1.4 Aromatase inhibitors

- High estrogen levels in combination with low testosterone levels impair proper spermatogenesis as elevated levels of E2 lead to feedback inhibition of the HPG axis, thus decrease LH, which is necessary for the production of testosterone, and FSH to optimize sperm production. Anastrozole 1 mg daily, or letrozole 2.5 mg daily increase testosterone, decrease estrogen levels, and inhibit the peripheral metabolism of testosterone. It is this effective in restoring LH, FSH, and testosterone levels, improving semen parameters, and re-establishing fertility

3.1.5 Androgens

3.1.5.1 Mesterolone

- Suppress tubular testicular function resulting in temporary oligospermia or azospermia allowing function to rebound after treatment is stopped. No benefit reported and therefore not used

3.1.5.2 Testosterone undecanoate

- To promote androgen bioactivity in epididymis and in accessory glands as it results in amplification in bioavailability of DHT in peripheral blood
 - » Not used any more as it can lower FSH & LH & thus inhibit spermatogenesis by negative feedback mechanism.

3. Medical management

- Abnormalities that can be seen in the male after semen testing
 - » Volume-Low or high
 - » Viscosity-Hyper viscous
 - » Count-Absent or low
 - » Motility Hyper viscous-Low or absent
 - » Morphology-High Teratozoospermia index
 - » Agglutination-Anti-sperm antibody
 - » Infection

3.1 Medical management of male sub-fertility

3.1.1 GnRH

- Indicated only in hypothalamic hypogonadism. GnRh therapy is given with the use of micropumps either SC/IV. Administration with micropumps for several months makes compliance difficult

3.1.2 Gonadotropin therapy

- Indicated only in hypothalamic hypogonadism with low FSH & LH levels
 - » Offer gonadotropin therapy with 2000 units of hCG twice a week with hMG 75 IU or rFSH 100-150 IU two to three times a week for 3 months
 - » First spermatozoa appear in the ejaculate after a median of 7 months in 80% of azospermic men (Borgress et al)
 - » Offer therapy 6 months prior to planned fatherhood

- » According to Anne Jecquier (male infertility, 2003) 6–10 injections of testosterone administered daily can render a normospermic male, azoospermic
- Do not offer testosterone replacement for treatment of male infertility
- Testosterone replacement therapy (TRT) should be provided for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood
- Offer TRT in Late-onset hypogonadism (LOH) (andropause) and in hypogonadism for steroidogenesis

3.1.6 Food and vitamin supplementation

- Carnitine, zinc, folic acid, astaxanthin, vit C, vit E, COQ may improve male infertility
- Direct effect on sertoli cells & epididymal function and improves spermatogenesis
- Involved in cellular respiration, improving motility, and preventing oxidative stress
- The Table 4 below gives the overview of management of male sub-fertility

Table 4: Overview of management of male sub-fertility

Medical treatment	Surgical treatment	Assisted reproduction	Third part reproduction
GnRh	Varicocele ligation	IUI	Donor insemination
Gonadotropins	Microsurgical repair of vasal obstruction	IVF	Adoption
Anti-estrogen therapy–CC, Tamoxifen	Epididymal obstruction	ICSI	
Androgens–Mesterolone and testosterone	Transurethral resection of the ejaculatory ducts (TURED)	TESA–ICSI	
Sperm Vitalizers: l–carnitine, CoQ10			

CC: clomiphene citrate; TESA: testicular sperm aspiration; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilization

3.1.7 Other endocrinopathies and systemic diseases

- Thyroid, adrenal, hypothalamus, and pituitary

- Diabetes, hypertension, renal disease, and malignancy
- Antibiotics for genital tract infection

3.2 Management of oxidative stress (OS)–related infertility

3.2.1 Lifestyle management is considered as the first and main treatment of OATS

- In >80% of males, medical treatment is ineffective. Consider the following general measures:
 - » Lifestyle modification (smoking, poor diet, alcohol, obesity, stress)
 - » Minimize environmental exposure to heat, pollutions, and toxins
 - » Control diabetes, hypercholesteremia, and weight reduction
 - » Avoid activities heating the scrotum
 - » Proper ventilation/use of personal protective equipment to reduce exposure to chemicals/metals linked with OS
 - » Direct treatment of the underlying stimulus for sperm OS. For example, antibiotic treatment infection
 - » Surgery–Varicocele ligation or the use of TESA ICSI improve sperm DNA quality
 - » Vitamin and antioxidant supplements and food supplementation, with or without the addition of anti-inflammatory medications to decrease leukocyte ROS production
 - » Optimize laboratory procedures
 - » Minimization of iatrogenic OS by limiting semen centrifugation time and avoidance of use of cryo-preserved sperm if possible

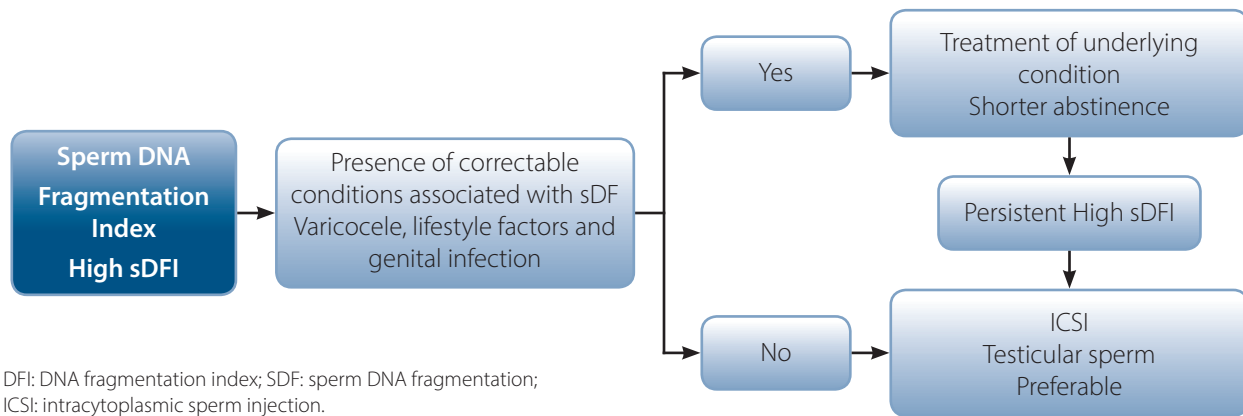
3.3 Management of high DFI

3.3.1 What can be done to avoid iatrogenic sperm DNA fragmentation?

- Short abstinence periods (1 day) and serial ejaculation
- Patients should be instructed to deliver specimens just before performing ART

Figure 1

Algorithm for the management of high sperm DFI



- Sperm sample should be processed as soon as possible
- Incubation time after processing should not exceed 4 hours
- Thawing of cryopreserved specimens should be done just before performing ART
- Use of testicular sperm should be considered in preference to ejaculated sperm

3.4 Management of high sperm DFI (Figure 1)

3.4.1 Evidences on sperm DNA damage with ejaculated sperm vs. testicular sperm

- Sperm DNA damage is reported to be higher in ejaculated sperm as compared to testicular sperm. DNA damage occurs during transit through epididymis due to ROS which are released from leukocytes, immature sperms, or by dysfunctional mitochondrial metabolism
- SDF levels measured by TUNEL assay were found to be lower in testicular sperm as compared to ejaculated sperm. Using testicular sperm in ICSI (44.4%) also led to higher pregnancy rate as compared to ejaculated sperm (23%)
- When 81 testicular sperm cycles were compared with 91 ejaculated sperm cycles in couples where male partner had OATS with high SDF (as measured by SCD method). The birth weight was significantly higher and the miscarriage rate was significantly lower in the testicular group

3.5 Medical treatment in leucocytospermia

- Leucocytospermia is characterized by pus cells $>1 \times 10^6$
 - » Neutrophil granulocytes need to be differentiated from round cells and immature sperm cells and hence a stained smear is needed
- The WHO cutoff is 1×10^6
 - » Many authors Agarwal et al, Cleveland Clinic–2014 have challenged the value and suggested the lower cutoff 1 to 1
- Occurs usually due to prostatitis/seminal vesiculitis (as per WHO criteria). i.e., accessory gland infection
- Bacteriospermia may or may not be present
- Consider performing semen culture
- Leucocytospermia causes production of ROS and free radicals which causes sperm DNA fragmentation and reduces sperm motility
- Common organisms involved are *E. coli*, urea plasma, Chlamydia, Klebsiella, and Pseudomonas.
- Antibiotics used – Doxycycline, auinolones, Mikacin, azithromycin
- It is an important cause of OATS hence needs to be treated
- Results of treatment are satisfactory and results in increased sperm count and motility

- Offer antibiotic therapy in combination with antioxidant treatment
- Offer antibiotics for minimum 15 to 21 days. Dose of antibiotic should be according to body weight

Table 5. Main antibiotics and their eradication rates

Antibiotic	Eradication rate (%)
Ciprofloxacin	40–77
Levofloxacin	75
Azithromycin	80
Doxycycline	77
Clarithromycin	80
Azithromycin + ciprofloxacin	62–77

3.6 Medical treatment in hyperprolactinemia

- Consider MRI to rule out pituitary microadenoma for levels above 100 ng/ml
- High prolactin levels inhibit GnRh
- Offer bromocriptine 2.5–5 mg/day for 1–3 months or cabergoline 1 mg/week or 0.5 mg/twice a week for 1–3 months
- Monitor PRL levels

3.7 Medical treatment in immunologic infertility

- Characterized by immotile sperms or agglutinated sperms
- May benefit with intrauterine insemination (IUI) and assisted reproductive treatment (ART)

3.8 Erectile dysfunction

- PDE5 inhibitors such as sildenafil–viagra, tadalafil–Cialis, vardenafil–Levitra or udenafil–Udezire

3.9 Situational anejaculation

- Offer simple methods like comfortable room, getting the sample from home, accompaniment of the partner, masturbation with visual stimulation, silastic condoms, use of stimulants like sildenafil, and vibrators to treat and prevent it

3.10 Ejaculatory dysfunction (ED)

- Ejaculatory dysfunction is the inability of a man to efficiently ejaculate semen from the penis at the moment of sexual climax
- Ejaculatory dysfunction is the most prevalent form of male sexual dysfunction and is a common cause of male infertility
- Ejaculatory dysfunction is classified into four types: premature ejaculation, delayed ejaculation, retrograde ejaculation and anejaculation (no ejaculation)
- Treatments for ejaculatory dysfunction include medications, behavioral therapy (for premature ejaculation) and sometimes surgery
- Behavioral therapy (pause, squeeze, stop, and start)–masters and Johnsons exercises
- Topical treatment with xylocaine and prilocaine spray
 - » Drug treatment with tramadol, dapoxetine, clomipramine, and other SSRI

3.11 Retrograde ejaculation

- Occurs when the semen enters the bladder instead of coming out through the urethra during orgasm

3.11.1 Diagnosis

- It is diagnosed when the patient gets dry orgasm and the antegrade ejaculate is minimal or absent
- Urine may be cloudy after orgasm due to semen
- Post orgasm urine shows presence of sperms
- It is usually harmless but maybe the cause of male infertility

3.11.2 Treatment

- Treatment is not always necessary and many people live with this problem with normal sex life.
- Consider treatment when the resulting male infertility becomes an issue
- Drugs are available for toning the internal sphincter (Table 6 below); however, drugs may not work and have a number of side effects

Table 6. Drug treatment for retrograde ejaculation

Generic name	Dose	Frequency
Pseudoephedrine	120 mg	90 min prior to ejaculation
Pseudoephedrine	60 mg	4x daily x 2 days prior to ejaculation
Imipramine	20–50 mg	Daily for 1 month
Phenylephrine	Nasal	1–2 hours prior to ejaculation
Ephedrine	30–60 mg	1–2 hours prior to ejaculation
Ephedrine (inhalers)		1–2 hours prior to ejaculation
Chlorpheniramine		Twice daily x 1 month
Bromopheniramine		Twice daily x 1 month

3.11.3 Harvesting sperms to restore fertility in retrograde ejaculation

- Administer oral alkalinizing agents to alkalize the urine
- Urine is collected by voiding or catheterization immediately after an orgasm
- Concentrate the sperms by centrifugation and maybe used for IUI, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)
- ICSI is the procedure of choice in case of sperms retrieved from patients with retrograde ejaculation

3.12 Management of non-obstructive azoospermia (NOA)

- Hypergonadotropic hypogonadism or eugonism
- FSH raised, testosterone low or normal
- There is an imbalance between circulating testosterone and estrogen with an altered (low) T/E ratio <10
- Administration of aromatase inhibitor for 2–3 months prior to retrieval can result in significant improvement in T/E ratio and subsequent retrieval rates in both TESE and micro TESE

3.13 Antioxidants in the management of Male sub-fertility

- Two types on the basis of their actions
 1. Preventive anti-oxidants are metal chelators or binding proteins, such as lactoferrin and transferrin, which prevent the formation of ROS

2. Scavenging antioxidants, like vitamins C and E, remove the ROS that is already present

Table 7 highlights the type of antioxidants used for management of male sub-fertility

Table 7: Types of antioxidants used in male sub-fertility management

Enzymatic antioxidants	Non-enzymatic antioxidants	Other antioxidants
Glutathione reductase and glutathione peroxidase	Vitamin E	Albumin
	Vitamin C	Taurine/hypotaurine
	Carnitine	Inositol
Superoxide dismutase	Carotenoids	Selenium
	Cysteines	Zinc
Catalase	Pentoxifylline	Coenzyme Q10
	Astaxanthin	

Key points on anti-oxidant therapy

- Proper dose should be administered to prevent pro-oxidant effect resulting in an abrupt fall in sperm motility and viability and an increase in lipoperoxidation
- High doses of vitamin C may cause kidney stone formation and therefore should be given with caution

4. Surgical management

4.1 Varicocele

- Varicocele associated with substantial risk of deteriorating testicular function
- Consider operating the palpable varicoceles with male sub fertility
- Efficacy of varicocelectomy as a treatment is controversial but beneficial in severe and symptomatic cases
- Microsurgical varicocelectomy comes nearest to being the ideal operation and is the gold standard
- Do not offer treatment for varicoceles in infertile men who have normal semen analysis and in those with subclinical varicocele

- Offer treatment for varicoceles in adolescents with progressive failure of testicular development documented by serial clinical examination.

Varicocele and azoospermia

- Varicocele is present in 5%–10% of azoospermic men
- Do not suggest surgery for all
- Varicocele ligation is effective in NOA only in cases of late maturation arrest and hypospermatogenesis and ineffective in early maturation arrest and SCO (sertoli cell only syndrome)
- Post varicocelectomy, sperms in ejaculate may be found in 21%–50% of patient and TESE may be avoided

4.2 Surgical sperm retrieval (SSR)

4.2.1 Goals of SSR

- Minimal damage to reproductive tract, there by reserving chances for repeat retrieval attempts

To obtain good quality sperm for immediate use for ICSI + cryopreservation

- To preserve Leydig cell function & avoid LOH
- The different sperm retrieval techniques are highlighted in Tables 8 and 9

Table 8. Sperm retrieval techniques

Open biopsy	MESA	TESE
Percutaneous	PESA PESE	TESA Percutaneous biopsy TEFNA Mapping

MESA: microsurgical epididymal sperm aspiration; PESA: percutaneous epididymal sperm aspiration; TESA: Testicular Sperm Aspiration, TEFNA: Testicular Fine-Needle Aspiration.

Table 9. Indications for sperm retrieval techniques

Technique	Acronym	Indications
Percutaneous epididymal sperm aspiration	PESA	Obstructive azoospermia (OA)
Microsurgical epididymal sperm aspiration	MESA	OA
Open epididymal fine-needle aspiration	Not defined	OA
Percutaneous testicular sperm aspiration; percutaneous testicular fine-needle aspiration	TESA; TEFNA	Obstructive azoospermia, Failed epididymal retrieval in OA cases; Epididymal agenesis in CAVD cases; Favorable testicular histopathology ¹ in NOA cases; Previous successful TESA/TEFNA attempt in NOA cases
Testicular sperm extraction (single or multiple biopsies)	TESE	Obstructive azoospermia; Failed epididymal retrieval in OA cases; Failed TESA/TEFNA in OA cases; Non-obstructive azoospermia
Single seminiferous tubule biopsy	Not defined	Obstructive azoospermia; Failed epididymal retrieval in OA cases; Failed TESA/TEFNA in OA cases; Non-obstructive azoospermia
Microsurgical testicular sperm extraction	Micro-TESE	Non-obstructive azoospermia

MESA: microsurgical epididymal sperm aspiration; NOA: non-obstructive azoospermia; PESA: percutaneous epididymal sperm aspiration; TESA: Testicular Sperm Aspiration, TEFNA: Testicular Fine-Needle Aspiration.

4.2.2 SSR-in NOA

- Efficiency of sperm retrieval in non-obstructive azoospermia (NOA) depends on method of sperm collection
- If TESA fails, then TESE should be avoided because of chance of hematoma and increased bleeding

- TESE may be done on the opposite side
- Micro TESE is a better technique
- TESE has a better successful retrieval rates (SRR) than TEFNA (testicular fine-needle aspiration)

4.3. Micro TESE

- Micro TESE is based on the premise that potential areas of spermatogenesis are present even in the smallest of testes and even in cases of high FSH
- **Indications**
 - » Hypovolemic testis (<10 cc), small gonads
 - » Repeated negative outcome in routine TESE
 - » Klinefelter syndrome
 - » Hypogonadotropic hypogonadism
 - » Torsion testis, damaged testis

4.3.1 Micro TESE in NOA

- The reported micro TESE retrieval rate range from 35%–77%
- Multiple controlled studies demonstrated that micro TESE performs significantly better than TESA or TESE with minimal damage to testicular tissue
- Micro TESE is more effective in SRR in men with testicular volume of <10 ml (42% vs. 27%)
- Up to 37% of success rate was achieved when operating time was increased from 2 hours to 4 hours
- SRR with TESA and micro TESE is comparable when testicular volume is more than 10 ml, hence TESA, TESE is first choice in such cases

4.4 Surgical reconstruction procedures in obstructive azoospermia

- Treatment of obstructive azoospermia
 - » Microsurgical repair of vasal obstruction: patency rate of 80% and conception rate of 40%
 - » Epididymal obstruction: low success rate
 - » Low volume ejaculate and severe oligozoospermia: Transurethral resection of the ejaculatory ducts (TURED)

- Extremely cost effective in carefully selected cases in centers of microsurgical excellence
- In obstructive azoospermia (OA) and microsurgery is restricted to vasovasal anastomosis and TURED

4.5 Retrieval vs. reconstruction

- Better pregnancy rates are achieved with sperm retrieval technique with ICSI than following reconstructive surgery. However, this is more expensive and has a single event impact
- Reconstructive surgery is cheaper in the long run and has a multiple event impact
- Retrieval is preferred to reconstruction because of the following reasons:
 - » Even after reconstruction the sperm count and motility remains low
 - » Late surgical failures are known
 - » There is a chance of antibody formation
 - » Reverse motility is sometimes seen
 - » Reconstruction requires greater surgical expertise

4.6 Testicular biopsy

- Testicular biopsy should be performed when the information obtained will directly help future therapy or enable sperm retrieval
- The testicular tissue should be collected in culture media. Formalin should not be used as it will distort histological features
- The tissue should be cut with fine sharp iris scissors

In the era of ICSI and sperm retrieval, diagnostic testicular biopsy has become obsolete:

- Every attempt at testicular biopsy produces an area of fibrosis and avascularity which jeopardises further chances of sperm retrieval
- Today a testicular biopsy is restricted to a micro biopsy combined with retrieval

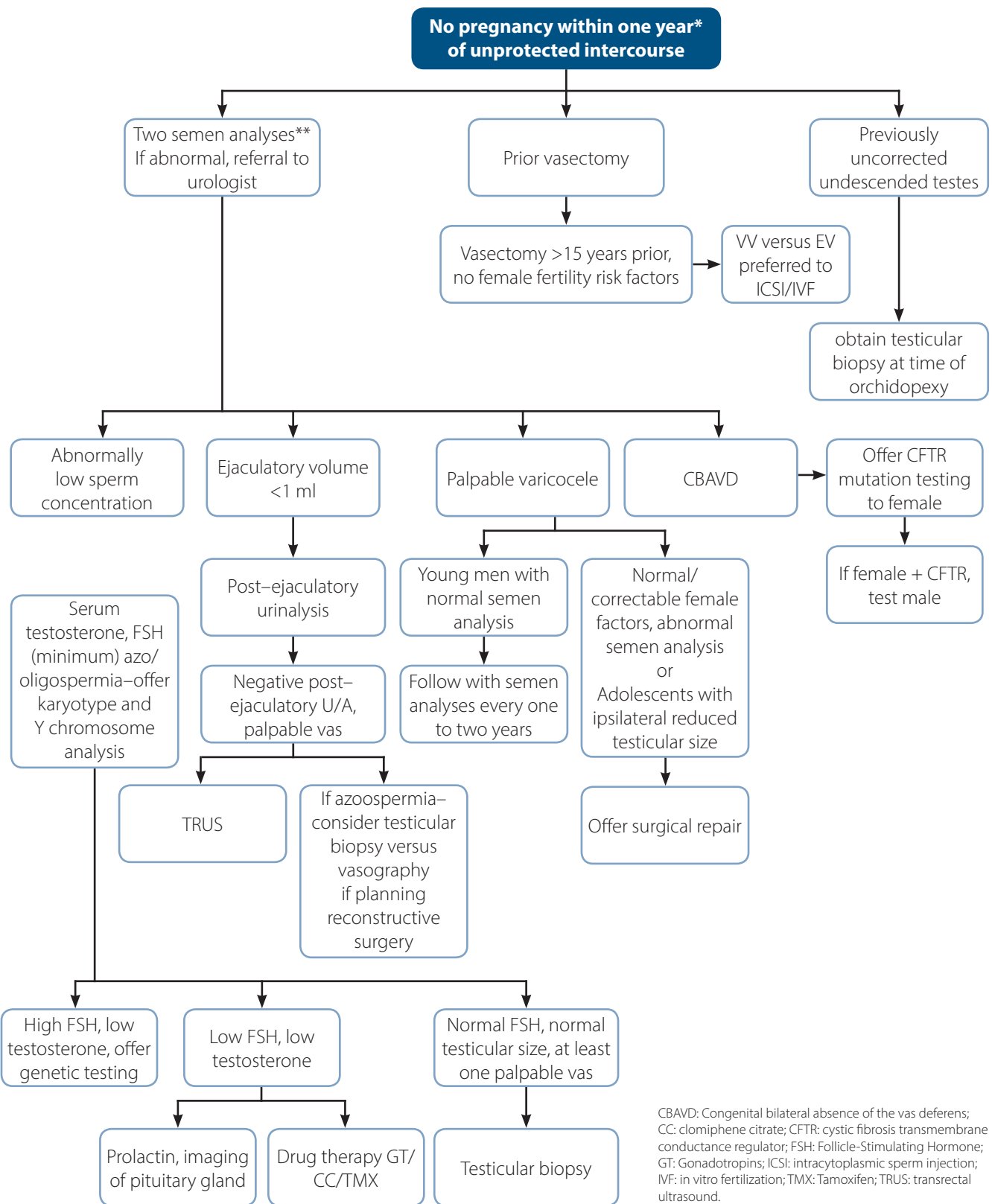
Genetic counselling should be done in all cases of azoospermia when sperm retrieval is attempted,

in all couples with a genetic abnormality in clinical and genetic investigations and in patients who carry potential inheritable disease.

- Consider providing long-term endocrine follow-up for all men with KLFS and androgen replacement therapy, which is considered to be necessary
- Men with Yq microdeletion and their partners who wish to proceed with ICSI should be informed that microdeletions will be passed to sons, but not to daughters
- Consider using sperm retrieval techniques only when cryostorage of the material obtained is available
- Consider genetic counseling needed in CBAV where both the man and his partner carry the CFTR gene mutation
- Testicular biopsy and cryopreservation should be performed in all cases of testicular microcalcification (TM), who belong to one of the high risk groups– Infertility, spermatogenic failure bilateral TM, atrophic testes (<12 CC), history of undescended testes, and testicular germ cell tumour (TGCT)
- Offer cryopreservation of semen or sperms for all candidates going for chemotherapy, radiotherapy or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders

Figure 2

Algorithm for investigating the male infertility



Summary of recommendations

Category	Recommendation	Grade of evidence	Quality of evidence
CCR	Perform semen analyses according to the guidelines	A	-
CCR	Perform further andrological assessment when semen analysis is abnormal in at least two tests	A	-
EBR	An initial endocrine evaluation should include at least a serum testosterone and FSH. It should be performed if there is: (1) an abnormally low sperm concentration, especially if less than 10 million/ml; (2) impaired sexual function; or (3) other clinical findings suggestive of a specific endocrinopathy	A	II
EBR	Insufficient evidence in the literature to support the routine use of DNA integrity testing in the evaluation and management of the male partner of an infertile couple	B	III
EBR	There is insufficient data to support the routine use of reactive oxygen species testing in the management of the male partner of an infertile couple	A	III
EBR	For men with OA, NOA, and severe OAT, perform karyotyping and appropriate genetic testing and offer genetic counselling	A	II
CCR	Karyotype testing should be performed on all males with severe oligozoospermia ($<5 \times 10^6$ /ml) or NOA prior to any therapeutic procedure	A	-
EBR	Do not test for microdeletions in men with OA when ICSI is used because spermatogenesis should be normal	A	I
EBR	Inform men with Yq microdeletion and their partners who wish to proceed with ICSI that microdeletions will be passed to sons, but not to daughters	A	I
EBR	In men with structural abnormalities of the vas deferens (unilateral or bilateral absence), test the man and his partner for CFTR gene mutations	A	I
EBR	Specialized sperm function tests (tests for anti-sperm antibodies, CASA, sperm cervical mucus interaction) on semen are not required for diagnosis of male infertility. They may be useful in a small number of patients for identifying a male factor contributing to unexplained infertility, or for selecting therapy, such as assisted reproductive technology	B	-
CCR	Scrotal ultrasonography is indicated in those patients in whom physical examination of the scrotum is difficult or inadequate or in whom a testicular mass is suspected	B	--
EBR	Use sperm retrieval techniques, such as MESA, TESE, and PESA only when cryostorage facilities of the material obtained is available	B	II
EBR	For azoospermia caused by vasal or epididymal obstruction, perform microsurgical vasovasostomy or tubulovasostomy	B	III
EBR	Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele	A	II
EBR	Treat varicoceles in men with a clinical varicocele, oligospermia and otherwise unexplained infertility in the couple	A	III
EBR	Testosterone replacement therapy should be offered only for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood	A	II
EBR	Do not use testosterone replacement for the treatment of male infertility	A	II

Category	Recommendation	Grade of evidence	Quality of evidence
EBR	In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG/hMG/rFSH)	A	I
EBR	If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy for detection of intratubular germ cell neoplasia of unclassified type (ITGCNU)	B	II
EBR	Do not use hormonal treatment of cryptorchidism in adults	A	II
EBR	Use medical treatment of male infertility only for cases of hypogonadotropic hypogonadism.	A	I
EBR	No recommendation can be made for treatment with gonadotropins, antiestrogens and antioxidants for treatment of idiopathic male infertility	B	II
EBR	There are insufficient data to recommend the use of supplemental antioxidant therapies for the treatment of men with abnormal semen parameters and/or male infertility	C	IV
EBR	Offer simultaneous sperm cryopreservation if testicular biopsies are performed for fertility diagnosis.	A	I
EBR	Offer cryopreservation of semen to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders	A	I
EBR	Offer specific treatments for ejaculatory disorders before performing sperm collection and ART	A	III
EBR	IVF with or without ICSI may be considered the primary treatment option when such treatment is required to treat a female factor, regardless of the semen parameters	A	I
EBR	IVF can be attempted provided that more than approximately 2 million motile sperm can be harvested from an ejaculate, with an expectation of success close to that of IVF for other indications	A	I
EBR	ICSI should be offered if there is a chance of failure of fertilization with IVF: Less than 2 million motile sperm per ejaculate, less than 4% of sperm with normal morphology, less than 5% of sperm with progressive motility, sperm autoimmunity, and defects of sperm-oocyte interaction	A	I

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Chapter 7: Management of Pelvic Infections and Pathologies

OVERVIEW

This guideline offers recommendations on the diagnostic tests, treatment regimens, and health promotion principles needed for the effective management of pelvic inflammatory disease (PID) covering the management of the initial presentation, as well as how to reduce transmission and future infection. It is aimed primarily at women aged 16 years or older presenting to health care professionals.

1. Introduction

- Pelvic infection is one of the most common, serious infections in non-pregnant women of reproductive age
- Goals of the therapy include:
 - » Resolution of clinical symptoms and signs
 - » Eradication of pathogens from the genital tract
 - » Prevention of sequel including infertility, ectopic pregnancy, and chronic pelvic pain
 - » Prevention of recurrence
- *Neisseria gonorrhea* and *Chlamydia trachomatis* (*C. trachomatis*) have been identified as the causative agents. *C. trachomatis* is the commonest identified cause accounting for 14%–35% of cases, whilst *Gardnerella vaginalis*, anaerobes and other organisms commonly found in the vagina may also be implicated. *Mycoplasma genitalium* has been associated with upper genital tract infections in women and is a very likely cause of PID. Pathogen negative PID is common. Genital tuberculosis is one of the causes of PID in India

2. Factors associated with PID

2.1 Factors related to sexual behavior

- Young age not using barrier contraception, having multiple partners, recent new partner (within previous 3 months), past history of sexually transmitted infections (STIs) in the patient or their partner

2.2 Instrumentation of the uterus/ interruption of the cervical barrier

- Termination of pregnancy, insertion of intrauterine device within the past 6 weeks, hysterosalpingography,

in vitro fertilization (IVF), intrauterine insemination (IUI), hysteroscopy

2.3 Genital tuberculosis

- Genital tuberculosis (GTB) is a chronic disease with low-grade symptoms. *Mycobacterium* reaches the genital tract by hematogenous spread from the foci, lungs being the most common primary focus
- Presenting symptoms are infertility, menstrual irregularities, chronic pelvic pain, and abnormal vaginal discharge
- Organ involvement in GTB involves fallopian tubes, 90%–100%; endometrium, 50%–80%; ovaries, 20%–30%; and the cervix, 5%–15%

2.3.1 Fallopian tubes

- The infection in tuberculous endosalpingitis with the hematogenous route of spread starts from endosalpinx making tubes swollen, edematous, and irregular with the formation of hydrosalpinx, pyosalpinx, tubo-ovarian masses, and dense adhesions
- The infection in tuberculous exosalpingitis starts in the muscularis mucosa of oviducts with hyperemia, flimsy adhesions, and miliary tubercles on the surface of the tubes. Beading, closed tubes, tubo-ovarian masses, hydrosalpinx, pyosalpinx, and the development of synechiae formation occurs later

2.3.2 Ovaries

- Ovaries are affected in 20%–30% of the patients with adhesions, caseation, adnexal cyst, or mass formation with defective ovarian function and reserve, and sometimes complete destruction of ovary

- Tubo-ovarian cyst can sometimes manifest as an acute abdomen simulating acute appendicitis and may be diagnosed on laparoscopy or laparotomy

2.3.3 Peritoneum

- Various types of adhesions are formed in the pelvis and abdomen, such as perihepatic synechiae (Fitz-Hugh-Curtis syndrome), hanging gallbladder sign and ascending colonic synechiae and frozen pelvis in the abdomino-pelvic tuberculosis

3. Clinical features

3.1 Acute PID staging

3.1.1 Centre of Disease Control (CDC) diagnostic criteria

- Presence of one or more of the following minimum clinical criteria on pelvic examination:
 - » Lower abdominal tenderness
 - » Adnexal tenderness
 - » Cervical movement
- One or more of the following additional criteria can be used to enhance the specificity of the minimum clinical criteria and support a diagnosis of PID:
 - » Oral temperature $>38.3^{\circ}\text{C}$
 - » Abnormal cervical or vaginal discharge
 - » Elevated erythrocyte sedimentation rate
 - » Elevated C-reactive protein
- Laboratory documentation of sexually transmitted diseases (STDs) is recommended
- Definitive criteria for diagnosis of PID
- Histopathological evidence of endometritis on endometrial biopsy (curatage not recommended)
- Tubo-ovarian abscess on sonography or other radiological test
- Laparoscopy abnormality consistent with PID

3.2 Stages

Stage 1

- Women who fulfill the Centers for Disease Control and Prevention (CDC) major diagnostic criteria and ≥ 1 of its minor criteria, but who do not have overt peritonitis and who do not have prior documented STD upper track infections

Stage 2

- The above said criteria plus peritonitis

Stage 3

- Women with demonstrable tubo-ovarian complex or tubo-ovarian abscess evident on physical or ultrasonographic examination

Stage 4

- Women with ruptured tubo-ovarian abscesses

4. Investigations

- Complete blood count
- C-reactive protein
- Erythrocyte sedimentation rate
- Test for syphilis
- Test for human immunodeficiency virus (HIV)
- Urine pregnancy test
- Urine analysis
- Urine culture

4.1 Vaginal wet mount

- Presence of white blood cells (WBC) suggests PID but their presence is nonspecific, whereas absence of WBCs has a good negative predictive value.
- Cervical chlamydia and gonorrhea testing for organisms if facilities are available

4.2 Imaging

- Consider chest x-ray in suspected cases of GTB (genital tuberculosis). Active pulmonary TB (fibrocavitary disease, infiltrations, mediastinal or hilar lymphadenopathy, miliary tuberculosis) or old healed lesions of past TB can be detected with chest x-ray

- Consider ultrasonography (USG) to investigate:
 - » Tubo-ovarian masses
 - » Fluid in pouch of Douglas
 - » Hydrosalpinges
 - » Heterogeneous or thin endometrium
 - » Endometrial fluid
 - » Intrauterine synechiae
- Computerized axial tomography scan can be considered to diagnose masses in the abdomen and pelvis with ascites, thickened and enhanced peritoneum, with lesions in the abdominal viscera and lymph nodes
- Higher resolution obtained with magnetic resonance imaging (MRI) can be considered to show presence of tubo-ovarian masses
- Hysterosalpingography (HSG) can be considered as a part of infertility evaluation. HSG shows evidence of GTB in the form of tubal occlusion, diverticula, pouching, hydrosalpinx, and multiple constrictions
- HSG findings of uterine tuberculosis include irregular margins, filling defects, and signs of intra uterine synechia
- HSG should be avoided in women with acute infection

4.3 Blood test

- Full blood count is considered to diagnose anaemia, raised leucocytes and lymphocytes, and raised ESR in tuberculosis
- Serological tests are not considered sensitive and specific

4.4 Microbiological tests

- Consider endometrial biopsy, curettage or aspirate performed in the luteal phase (day 21) for the diagnosis of GTB
- Perform the WHO approved rapid diagnostic tests (WRDT) which are cartridge based nucleic acid amplification test (CBNAAT/GeneXpert MTB/RIF) and

liquid culture by mycobacterial growth indicator tube (MGIT) on endometrial sample sent in saline and histopathology (available in all government hospital free of charge)

- High false positivity of polymerase chain reaction (PCR) is reported. Avoid starting antitubercular treatment (ATT) only on positive PCR unless there is evidence of FGTB (female genital tuberculosis) clinically on examination, or on radiology or endoscopy. A positive CBNAAT (cartridge based nucleic acid amplification test) result is a useful confirmation

4.5 Diagnostic laparoscopy

- » Consider laparoscopy and look for typical findings of tubal congestion, hydrosalpinx, rigid tubes, and tubercles on the surface
- » During a diagnostic laparoscopy, consider taking a biopsy, or perform drainage, removal of hydrosalpinx and tubo-ovarian masses

5. Complications requiring admission to hospital

- The three reported complications of PID are:
 - » Acute/chronic pelvic pain
 - » Infertility
 - » Ectopic pregnancy
- Approximately 25% of patients with a history of PID may suffer from chronic pelvic pain, which is related to cyclic menstrual changes, but it also may be the result of adhesions or hydrosalpinx
- Note that PID may produce tubo-ovarian abscess (TOA) and may progress to peritonitis and Fitz-Hugh-Curtis syndrome (perihepatitis)
- It is important to note a rare but life-threatening complication of acute rupture of a TOA may result in diffuse peritonitis and necessitate urgent abdominal surgery
- Ectopic pregnancy should be ruled out
- In women with immunosuppression secondary to HIV, symptoms associated with PID may be more

severe, but may respond well to standard antibiotic therapy

- Note the right upper quadrant pain associated with perihepatitis with the Fitz–Hugh Curtis syndrome

6. Differential diagnoses

- Ectopic pregnancy, acute appendicitis, endometriosis, complications of an ovarian cyst, urinary tract infection, irritable bowel syndrome, functional pain
- Tuberculosis is suspected if there is no response to the initial management

7. Management

7.1 General measures

- Advise rest for those with severe disease, offer appropriate analgesia
- Offer intravenous therapy for patients with more severe clinical disease such as pyrexia $>38^{\circ}\text{C}$, clinical signs of tubo–ovarian abscess, or signs of pelvic peritonitis
- Advise patients to avoid intercourse to avoid reinfection, until they and their partner(s), have completed the treatment
- Outpatient therapy is as effective as inpatient treatment for patients with clinically mild to moderate PID
- Choice of treatment regimen should be influenced by following:
 - » Offer oral therapy for mild and moderate cases as outpatients
 - » Offer intravenous therapy, which should be continued until 24 hours after clinical improvement and switched to oral therapy
- Arrange all the investigation as appropriate, ensure that sexual partner is treated
- Prescribe drug treatment, such as:
 - » Ibuprofen/paracetamol to provide pain relief
 - » Empirical antibiotics as soon as presumptive diagnosis of PID is made clinically

- » Screen women for STI before starting antibiotics
- » Manage sexual partner of women appropriately

In women with intrauterine contraceptive (IUD or levonorgestrel system present with PID)

- Consider removal of the device if patient request or if symptoms do not resolve within 72 hour after a review of 48–72 hours in situ
- Offer emergency hormonal contraception if the device is removed

7.2 Antibiotics

7.2.1 First line regimens

- If risk of gonococcol infection is low
- Offer ceftriaxone 1 gm as a single intramuscular dose followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days
or
- Offer ceftriaxone 1 gm intramuscular followed by oral ofloxacin 400 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days
- If none of the above first line regimen is suitable then alternative regimen
 - » Offer ceftriaxone 1 gm as a single intramuscular dose followed by oral azithromycin 1 gm per week for 2 weeks, but there is less evidence to support this
- If risk of gonococcal infection is high
 - » Offer ceftriaxone 1 gm as a single intramuscular dose followed by doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days
 - » Do not recommend azithromycin for gonococcal PID
 - » Do not recommend the regimen of doxycycline and metronidazole without intramuscular ceftriaxone
 - » Do not replace intramuscular ceftriaxone with oral cephalosporin

- » Offer same treatment for women infected with HIV as those of not infected with HIV

7.2.1.1 In-patient regimens

- Offer ceftriaxone 2 gm IV/IM once daily, doxycycline 100 mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily to complete 14 days
- Offer clindamycin 900 mg IV three times a day plus IM/IV Gentamicin (3–6 mg/kg as a single daily dose with renal monitoring)
- This may be followed by either:
 - » Oral clindamycin 450 mg four times daily for 14 days
 or
 - » Oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days

7.2.1.2 Alternative regimen

- Offer ofloxacin 400 mg IV twice daily plus IV metronidazole 500 mg three times daily for 14 days
- or
- Offer ceftriaxone 500 mg intramuscular single dose plus oral azithromycin 1 gram single dose followed by a second dose of oral azithromycin 1 gram after one week

7.3 Surgical management

- Reevaluate for possible laparoscopic or surgical intervention in patients who do not improve in 72 hours and reconsider for other possible diagnoses
- Perform laparoscopic pelvic lavage, abscess drainage, and adhesion lysis when necessary
- USG guided or CT guided drainage may be considered under appropriate circumstances
- Most TOAs (60%–80%) resolve with antibiotic administration
- Reserve laparotomy for patients experiencing surgical emergencies (abscesses that have ruptured or that

have not responded to medical management and laparoscopic drainage) and for patients who are not candidates for laparoscopic management. Consider guiding the treatment by intraoperative findings and the patient's desire for fertility maintenance

- Discuss various surgical treatment options, such as unilateral or bilateral salpingo-oophorectomy or hysterectomy. Perform the operation after the acute infection and inflammation have resolved. In patients with recurrent PID, dense pelvic adhesions may render surgery difficult
- Infertility patients presenting with hydrosalpinx, perform a salpingectomy before ART to achieve better outcomes

7.4 Treatment of genital tuberculosis

- Offer first-line drugs in combination:
 - » Four drugs isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) for two months (HRZE), followed by H, R and E (HRE) daily for four months
 - » Thrice-weekly regimen is no longer used
- In patients with advanced stage with scarring, severe fibrosis, and adhesions, treatment outcomes especially for infertility are poor. Offer early diagnosis and correct treatment to avoid complications and to restore fertility in such patients

7.5 Managing sexual partner

- Contact the current and recent partner of women within last 6 months and offer advice, screening, treatment, and contact tracing
- Offer screening for chlamydia and gonorrhea
- Offer empirical treatment with broad spectrum antibiotic while waiting for result
- Suggest abstinence for both the partner till the disease is cured
- Discuss the use and offer barrier methods, and broad spectrum empirical treatments to all male partners

7.6 Advice to women

- Provide advice to women to complete the course, screen for other sexually transmitted infections, the need for contact tracing and treat other partner
- Discuss about risk of ectopic pregnancy, infertility, chronic pelvic pain, even if fertility is maintained
- Discuss about severe, recurrent attacks and lack of proper treatment, contraceptive (dual contraception barrier with any other contraception), additional information about PID, that may compromise fertility

7.7 Follow up in women after PID treatment

- Consider follow-up of women within 72 hours, If there is:
 - » No clinical improvement (decrease in tenderness) –consider admission, check antibiotic sensitivity

from swab test, and adjust antibiotic treatment if necessary

- Consider review after 2–4 weeks—confirm response of treatment, confirm sexual contact has been screened and treated, discuss the potential sequel of PID

At follow-up perform

- Routine repeat testing after 2–4 weeks if initial testing for chlamydia was positive
- Test of cure if initial testing for gonorrhea was positive.
- Repeat testing after 3–5 week if possibility of persisting infection or recurrent infection is present
 - » Repeat testing after 4 weeks if initial test for *Mycoplasma genitalium* is positive
- Repeat testing if symptoms persist, and during the presence of antibiotic resistance, poor compliance, possibility of reinfection, or if sensitivity testing is not done

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CCR	Clinical criteria for diagnosis of PID	C	
CCR	Pain on cervical movements or in posterior or lateral fornices	C	-
CCR	Oral temperature >101° F (38.3 °C >)		-
CCR	Mucopurulent cervical discharge or abnormal vaginal discharge	B	-
CCR	Pain associated with fever and mucopurulent cervical or vaginal discharge	C	-
	Complex tubo-ovarian mass at ultrasound	B	-
CCR	Laboratory criteria for diagnosis of PID		
	The presence of abundant numbers of white blood cells (leukocytes) on saline microscopy of vaginal secretions	C	-
CPP	Elevated erythrocyte sedimentation rate	-	-
EBR	High C-reactive protein	B	III
CCR	Acute or chronic salpingitis or endometritis in histological evaluation of biopsy	B	-
EBR	demonstrates integration <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> in the genital tract	B	II
EBR	Diagnostic laparoscopy or laparotomy for PID	C	II
EBR	Isolation of pathogenic bacteria from a bacterial specimen from the upper genital tract	B	II
EBR	Laparoscopy has substantial value in the confirmation of the diagnosis of PID but is not sensitive enough to be considered a gold standard of diagnosis.	B	II
	Is required when		
	• The symptomatic patient with high suspicion of other pelvic pathologies like ectopic pregnancy, ovarian cyst, endometrioma, ovarian torsion, appendicitis, cholecystitis, constipation, gastroenteritis, inflammatory bowel disease, perforated peptic ulcer, acute pancreatitis, Meckel diverticulitis, intestinal obstruction	-	-
CPP	• Woman with the acute disease, which did not respond to outpatient treatment to PID	-	-
CPP	• Any patient showing no improvement after approximately 72 h of hospital treatment to PID	-	-
CPP	Laparoscopic abnormalities consistent with PID include erythema, edema, tubal adhesions, purulent exudate or purulent fluid in POD	-	-
	Diagnostic Tests		
CCR	Pregnancy test	B	-
EBR	Microscopic examination of vaginal discharge in saline solution	B	III
CPP	Complete blood count		-
CCR	Nucleic acid amplification tests for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>	-	II
CPP	Urine test	B	-
EBR	C-reactive protein	-	II
EBR	HIV tests	A	II
EBR	Surface antigen and hepatitis B surface antibodies	A	II
EBR	Test for syphilis.	B	II
CCR	Ultrasound of pelvis and abdomen using both trans vaginal and transabdominal route	B	
CCR		C	III
EBR	MRI in indicated cases	B	II
EBR	Endometrial biopsy with histopathological evidence of endometritis	B	II
	Laparoscopy		

Category	Recommendations	Grade of Recommendation	Quality of Evidence
	Treatment		
CPP	• Rest, hydration, and sexual abstinence during treatment	-	-
CPP	• Symptomatic treatment—analgesics, antipyretics, and non-hormonal anti-inflammatory drugs	-	-
CPP	• Convene partners for clinical evaluation	-	-
CPP	• Guidance on the risks of new episodes of PID and other STDs	-	-
CPP	• Avoid unprotected sex	-	-
	• Outpatient antibiotic therapy—		
EBR	» Offer ceftriaxone 1 gm as a single intramuscular dose followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days	B	III
EBR	» Offer ceftriaxone 1 gm intramuscular followed by oral ofloxacin 400 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days	B	III
EBR	» Offer ceftriaxone 1 gm as a single intramuscular dose followed by oral azithromycin 1 gm per week for 2 weeks, but there is less evidence to support this	B	III
EBR	• Inpatient antibiotic therapy – indicated when there is lack of response to oral therapy, severe clinical disease, PID complicated with pelvic abscess, possible need for surgical intervention	B	II
EBR	• Offer ceftriaxone 2 gm IV/IM once daily, doxycycline 100 mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily to complete 14 days	B	III
EBR	• Offer clindamycin 900 mg IV three times a day plus IM/IV gentamicin (3–6 mg/kg as a single daily dose with renal monitoring) followed by either: Oral clindamycin 450 mg four times daily for 14 days or oral doxycycline 100 mg twice daily plus oral metronidazole 400 mg twice daily for 14 days	B	III
EBR	• Surgical treatment is indicated for clinical treatment failure, presence of pelvic mass that persists or increases, despite the clinical treatment, suspected rupture of tube-ovarian abscess; hemoperitoneum or POD abscess	B	II
EBR	• In chronic PID with development of hydrosalpinx, either the tube is removed or disconnected from the cornual end to increase the chance of pregnancy	A	I
EBR	In Indian context it is important to rule out genital tuberculosis	B	II
	Follow-up		
EBR	• Review with 72 hours to evaluate clinical improvement. Admit to hospital if there is no substantial improvement	B	III
EBR	• Consider review after 4 weeks after therapy to evaluate adequate adherence and response to treatment	B	III
EBR	• Screening and treatment of male partner	B	III
EBR	• Discuss potential sequelae of PID	C	III

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Chapter 8: Managing Endometriosis –The Indian Perspectives

OVERVIEW

This guideline covers diagnosis and management of endometriosis. It aims to raise awareness regarding the signs and symptoms of endometriosis, and provides clear advice on actions to be taken when women with such signs and symptoms first present in healthcare settings. It also provides advice on the range of treatments available.

1. Introduction

- Endometriosis is a benign disease and is defined by the presence of endometrial glands and stroma outside the uterus
- Microscopically, the endometrial glands and stroma are seen with hemosiderin-laden macrophages

Prevalence of endometriosis

- Endometriosis affects the women from menarche to menopause. The prevalence of endometriosis varies with age and clinical presentation
- The prevalence of asymptomatic endometriosis is 1%–7%
- The overall prevalence of endometriosis in reproductive aged women is between 3%–10%
- Among women in reproductive age group, 12%–32% women with complaint of pelvic pain have endometriosis, and 9%–50% women with infertility have endometriosis
- It is estimated that 176 million women all over the world suffer from endometriosis. In India, 26 million is reported to have endometriosis
- Association with endometriosis: The reported association is with fibroids (26%), Mullerian anomalies (20%) and ovarian malignancy (1.3%–1.9%)

2. Risk factors, protective factors, and sites for endometriosis

2.1 Various risk factors associated with endometriosis are:

- Infertility

- Early age at menarche
- Shorter menstrual cycle
- Heavy menstrual bleeding
- Nulliparity
- Mullerian anomalies
- Diethylstilbestrol exposure
- Dioxin exposure
- Endometriosis in first degree relative
- Prior medical or surgical therapy for endometriosis

2.2 Various protective factors are:

- Multiparity
- Lactation
- Increased body mass index (BMI)
- Increased waist-to-hip ratio
- Diet high in vegetable and fruit

2.3 Sites of endometriosis

- Pelvic
- Ovaries
- Posterior cul-de-sac
- Broad ligament
- Uterosacral ligament
- Extra pelvic: Abdominal wall, the urinary and gastrointestinal tract, thorax and nasal mucosa

3. Signs and symptoms of endometriosis

Symptoms of endometriosis

- Endometriosis can be asymptomatic.

- Pain is the most common presenting feature. Patient can present with dysmenorrhea, dyspareunia, and chronic pelvic pain, dysphasia, and disturbances in menstrual cycle
- Endometriosis also presents frequently with infertility. Almost 50% women with infertility have endometriosis

Extra pelvic endometriosis

- » Colon and rectum is the most common site of extra pelvic disease
- » Extra pelvic endometriosis presents as abdominal and back pain, abdominal distension, cyclic rectal bleeding, constipation, and obstruction
- Ureteral involvement can lead to obstruction and cyclic pain, dysuria, and hematuria
- Pulmonary endometriosis manifests as pneumothorax, hemothorax or hemoptysis during menses
- In umbilical endometriosis, umbilical mass is palpated with cyclic pain in umbilical region
- Scar endometriosis manifests as cyclic pain and swelling at scar site

Signs of endometriosis

- External genitalia
 - » Normal or episiotomy scar endometriosis
- On per speculum examination
 - » Blue coloured implants or red proliferative lesions
- Pelvic tenderness
- Focal thickening, nodularity, and induration of uterosacral ligaments
- Adnexal mass
- Retroverted fixed uterus

4. Differential diagnosis of endometriosis

Consider the following for differential diagnosis of endometriosis:

- » Pelvic inflammatory disease (PID)/tubo-ovarian mass
- » Ectopic pregnancy
- » Ovarian cysts
- » Ovarian malignancy

5 Diagnosis of endometriosis

5.1 Ultrasonography

- Consider using ultrasonography to diagnose or rule out an ovarian endometrioma
- The typical ultrasonography feature of endometrioma is a cystic lesion with diffuse low-level internal echoes, described as “ground-glass appearance”
- Multilocularity and echogenic foci in the wall are also seen in endometrioma
- Overlapping of sonographic imaging of endometrioma and hemorrhagic cyst may be observed, hence, consider performing a followup ultrasound after 6–12 weeks

5.2 Magnetic resonance imaging (MRI)

- Consider MRI for detection and differentiation of ovarian endometrioma from other cystic ovarian masses. MRI detects only 30%–40% peritoneal lesions observed at surgery
- MRI helps to differentiate between acute hemorrhage and blood clots
- Consider MRI for assessing endometriomas for enhancing mural nodules and for restricted diffusion in those suspected of undergoing malignant transformation

5.3 Cancer antigen (CA) 125

- Do not use serum CA 125 as a marker for screening of endometriosis, as the levels of CA 125 are elevated in advanced endometriosis, but the overall sensitivity and specificity is low
- Serial CA 125 determinations may be useful to predict the recurrence of endometriosis as the levels decrease after treatment of endometriosis

5.4 Laparoscopy

- Laparoscopy is the standard technique for inspection of pelvis and to establish a definitive diagnosis of endometriosis
- Perform a complete inspection in a clockwise or counterclockwise direction with a blunt probe, with palpation of lesions to check for nodularity as a sign of deeply infiltrative endometriosis of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, or broad ligament

Laparoscopic appearance

- Superficial peritoneal lesions
- These are located on the pelvic organs or pelvic peritoneum
- Classically seen as bluish or blue–brown lesions and are associated with hemosiderin deposits
- Observed laparoscopic appearances are as follows:
 - » Typical powder burn or gunshot
 - » Dark brown puckered lesions
 - » Red implants
 - » Small cysts with old hemorrhage
 - » Serous or clear vesicles
 - » Scarring or white plaques
 - » Characteristic findings include typical powder–burn or gunshot lesions on the serosal surfaces of the peritoneum
- Endometrioma (endometriosis cyst)
 - » These are formed by the invagination of ovarian cortex and are characterized by fibrosis and retraction of cortex
 - » There is presence of glandular endometrial tissue and blood clots. These are also called as “chocolate cyst”
 - » Deep endometriosis is defined as endometriosis infiltrating deeper than 5 mm. This may give the appearance of minimal disease, thus resulting in underestimation of severity

6 Classification of endometriosis

- Revised American Society for Reproductive Medicine classification (Figure 1)

Endometriosis fertility index (Figure 2)

- The endometriosis fertility index (EFI) is used to predict fecundity after endometriosis surgery
- In addition to providing a detailed score to the appendix (fallopian tubes, fimbriae of fallopian tubes, ovaries) by calculating the least–function scores, the EFI also combines conception–related factors such as age, duration of infertility, and gravidity history
- The EFI score ranges from 0–10 (0–poorest prognosis, 10–best prognosis)

7 Endometriosis and infertility

- The mechanisms of infertility associated with endometriosis remain controversial and include distorted pelvic anatomy, altered hormonal and cell-mediated function, altered peritoneal function, endocrine and ovulatory abnormalities, and abnormal uterotubal transport
- These factors lead to poor oocyte quality, impaired fertilization, and implantation

8 Recurrent endometriosis

- Risk factors of recurrent endometriosis are:
 - i. Younger age at the time of surgery (<25 years)
 - ii. Bilaterality
 - iii. Size of endometriotic lesion
 - iv. Revised AFS score >24
 - v. Pre-operative cyst rupture
 - vi. Type and extent of surgery (laparoscopy less risk vs laparotomy)

9. Endometriosis and cancer

- Some cancers (ovarian cancer, specially endometrioid and clear cell cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis
- Women with endometriosis have lower risk of cervical cancer

Figure 1

Revised American Society for Reproductive Medicine classification of endometriosis 1985

Patient's Name _____ Date: _____

Stage I (Minimal) 1–5 Laparoscopy _____ Laparotomy _____ Photography _____

Stage II (Mild) 6–15 Recommended treatment _____

Stage III (Moderate) 16–40 _____

Stage IV (Severe) >40 _____

Total _____ Prognosis _____

PERITONIUM	Endometriosis	<1 cm	1–3 cm	>3 cm
	Superficial	1	2	4
OVARY	Deep	2	4	6
	R superficial	1	2	4
	Deep	4	16	20
	L superficial	1	2	4
OVARY	Deep	4	16	20
	Posterior cul-de-sac obliteration	Partial	Complete	
		4	40	
OVARY	Adhesions	<1/3 Enclosure	1/3–2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
TUBE	Dense	4	8	16
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
TUBE	Dense	4*	8*	16

•If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____ Associated Pathology: _____

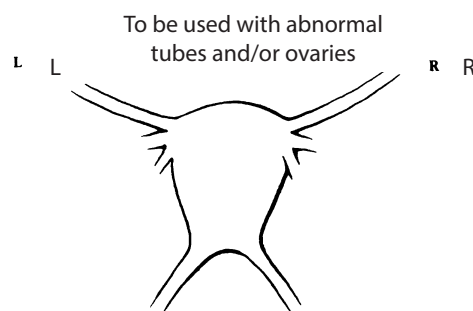
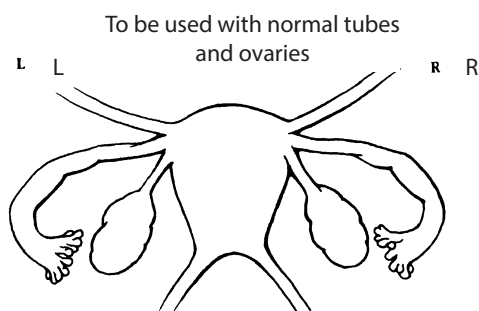


Figure 2

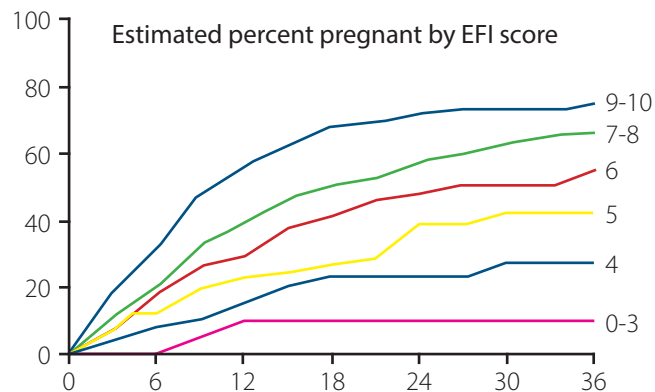
Endometriosis Fertility Index for women with endometriosis for whom future fertility is a consideration

**ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM****LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY**

Score	Description		Left	Right	
4	= Normal				
3	= Mild dysfunction	Fallopian tube	<input type="text"/>	<input type="text"/>	
2	= Moderate dysfunction	Fimbria	<input type="text"/>	<input type="text"/>	
1	= Severe dysfunction	Ovary	<input type="text"/>	<input type="text"/>	
0	= Absent or nonfunctional				
To calculate the LF score, add together the lowest score for the left side and the lowest score of the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.		Lowest score	<input type="text"/>	+	<input type="text"/>
			Left		Right
				=	<input type="text"/>
					LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical factors			Prior pregnancy		
Factor	Description	Points	Factor	Description	Points
<u>Age</u>	If age is ≤ 35 years	2	<u>LF score</u>	If LF score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF score = 1 to 3 (low score)	0
<u>Years infertile</u>	If years infertile is ≤ 3	2	<u>AFS endometriosis score</u>	If AFS endometriosis lesion score is <16	1
	If years infertile is >3	0		If AFS endometriosis lesion score is ≥16	0
<u>Prior pregnancy</u>	If there is a history of prior pregnancy	1	<u>AFS total score</u>	If AFS total score is <71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥71	0
Total historical factors			Total surgical factors		
ER = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:			<input type="text"/>	+	<input type="text"/>
			Historical		Surgical
					= <input type="text"/>
					EFI Score



- Endometriosis is not associated with an altered risk of uterine cancer
- The relationship between endometriosis and breast cancer is uncertain

10. Management of endometriosis

Consider the following management strategies:

- Medical
- Surgical
- ART [intrauterine insemination (IUI); in vitro fertilisation (IVF); intracytoplasmic sperm injection (ICSI)]

Approach to a patient:

- Perform a detailed infertility workup in a patient with endometriosis and any other cause related to infertility other than endometriosis should be ascertained, as despite enormous amount of information there is still uncertainty regarding etiologies and treatment
- Management is still challenging in patients of endometriosis with subfertility
- Treatment depends on
 - » Age of the patient
 - » Extent of the disease
 - » Stage of endometriosis
 - » Duration of infertility
 - » Previous therapy
- Priority of the patient and cost of treatment should also be taken under consideration
- Treatment modalities and preferences vary in patients based on classification. Patients with mild endometriosis on one end can be treated like those with unexplained infertility and those with severe disease require IVF

10.1 Medical management

- Medical management improves the quality of life for patients with endometriosis

- Therapies for endometriosis cause hormonal suppression and most of them have contraceptive effects
- According to Cochrane review, subfertile women should not be prescribed hormonal ovarian suppression to improve fertility as first-line treatment in endometriosis patients who wish to conceive

a. Preoperative medical management

- Not recommended
 - » Changes appearance of endometriosis
 - » Leads to delayed diagnosis
 - » Expensive and may cause side effects
 - » Delay in attempting pregnancy
 - » No difference for pain relief or infertility

b. Postoperative medical management

- No evidence of benefit is reported
 - » Leads to ovulation suppression
 - » It works well for pain but does not appear to improve fertility
 - » As ovulation and periods are stopped, fertility may be reduced

c. Current place of dienogest in the treatment of endometriosis

- Dienogest is a fourth-generation progestin of 19-nortestosterone derivative
- It is well tolerated with no androgenic, glucocorticoid or mineralocorticoid activity
- It binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule
- Dienogest is associated with relatively moderate inhibition of gonadotropin secretion, leading to a reduction in the endogenous production of estradiol
- When given continuously, dienogest induces a hypoestrogenic, local endocrine environment,

causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions

- It also inhibits aromatase and COX-2 expression as well as prostaglandin E2 production in endometriotic stromal cells
- It also normalizes the activity of natural killer cells and decreases the release of interleukin-1b by macrophages
- Dienogest increases progesterone receptor expression and decreases proinflammatory cytokines
- Dienogest at 2 mg once daily is used as the optimal dose in the treatment of endometriosis for duration of 12–F24 weeks
- Several trials assessed the role of dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF; no significant difference was noted in number of oocyte retrieved, pregnancy, and miscarriage rate. The dienogest pretreatment was less expensive than the GnRH ultra-long protocol

10.2 Surgical management

10.2.1 Is surgery effective for infertility associated with endometriosis?

- Surgical management is warranted for women with symptoms of dysmenorrhea, dyschezia, and chronic pelvic pain
- Operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis is indicated in infertile women with the American Fertility Society (AFS)/ American Society for Reproductive Medicine (ASRM) stage I/II endometriosis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates
 - » Consider CO₂ laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates
 - » Nowadays bipolar electrocoagulation is considered safe over monopolar energy source,

as there is less likelihood of complications with the same

- » As per the Cochrane review, it has been agreed that operative laparoscopic surgery improves ongoing pregnancy rate in stage I and II endometriosis when compared to diagnostic laparoscopy alone [evidence level A]
- » Consider the conservative surgical management through laparotomy or laparoscopic approach
- » With development of fine surgical skills, laparoscopy is now considered as gold standard in the surgical management of endometriosis
- » Laparoscopic approach to the management of endometrioma is preferred over laparotomy, as laparoscopy offers benefits of magnification and illumination, shorter hospital stay, faster postoperative recovery, less analgesic requirement, and less morbidity

10.2.2 Managing ovarian endometrioma

- The decision for operative ovarian endometrioma is taken based on clinical symptoms and ovarian reserve
- In case laparoscopy is done
 - Excision of the endometrioma capsule (>3 cm) is recommended instead of drainage and electrocoagulation of the endometrioma wall, to increase clinical pregnancy rates
- Counsel women with endometrioma regarding the reduction of ovarian reserve following surgery
- Malignancy should be ruled out, as it is associated with endometrioma in 0.8% of cases
- In recurrent endometrioma there is no role of USG guided aspiration and the side effects include leakage, pelvic adhesion, and ovarian abscess

10.2.3 Intraoperative steps to prevent complications

- Preservation of the vascular blood supply to the ovary is important, as proper blood supply is vital for the preservation of ovarian volume and antral follicular counts

- So it is postulated that when approaching the hilus, where the ovarian tissue is more functional and the plane of cleavage is less visible, partial cystectomy is performed and the remaining tissue is electro coagulated or CO₂ laser is used for vaporization
- Adhere strictly to the principles of microsurgery
- Remove all visible endometriotic disease
- Identify the plane of dissection clearly between the cyst wall and normal ovarian tissue to avoid inadvertent injury to normal ovarian tissue. Use hydrodissection or dilute vasopressin injection beneath the capsule
- Identify the ureters clearly during adhesiolysis and release of ovaries from ovarian fossa
- Avoid spillage of endometriotic contents as this may increase the risk of recurrence of the disease and adhesion formation

Agents for preventing adhesion during surgery:

- Promote the use of oxidized regenerated cellulose during operative laparoscopy for endometriosis as it prevents adhesion formation
- Anti-adhesion agents like polytetrafluoroethylene surgical membrane, hyaluronic acid products, have been effective for adhesion prevention in pelvic surgeries, although their specificity is yet to be proven in women with endometriosis

11. ART in endometriosis

- Perform IUI with COS, instead of expectant management in infertile women with AFS/ASRM stage I/II endometriosis, as it increases live birth rates

11.1 Ovulation induction and IUI

- Age, duration of infertility, ovarian reserve, and male factor should also be taken under consideration
- Advise patients to begin attempting to conceive soon after laparoscopic surgery

- Clomiphene citrate (CC) and IUI is an effective treatment option resulting in a higher clinical pregnancy rate compared to natural contact and timed intercourse
- Treatment with gonadotrophins and IUI results in a higher clinical pregnancy rate compared to CC and IUI
- Endometriosis and infertility have decreased per cycle conception rate compared with male factor and unexplained infertility
- Also, repetitive superovulation with IUI (3–4 cycles) may have a plateau effect over time, so timely decision for IVF to be considered

11.2 Indication for IVF

- Primarily IVF would be suggested if during laparoscopy severe endometriosis is found compromising tubal function
- Secondly, after cystectomy if no conception even after superovulation and IUI for 3–4 cycles
- Early referral for IVF in case of reduced ovarian reserve, tubal factor, and male factor

11.2.1 Stimulation protocol for IVF

Ultra-long protocol

- Down regulation for 3 months with gonadotropin-releasing hormone (GnRH) in women with endometriosis increases the odds of clinical pregnancy by more than 4-fold
- With the use of GnRH agonist and transvaginal oocyte retrieval, there is increased success in use of IVF for endometriosis associated infertility
- Controlled ovarian stimulation (COS) using GnRH agonists or antagonists is effective in IVF patients with mild-to-moderate endometriosis and in those with endometrioma who did not undergo surgery

GnRH agonist protocol

- » Women with all stages of endometriosis who underwent luteal phase GnRH agonist down-

regulation followed by IVF/ICSI treatment had a similar pregnancy and live birth rate and lower miscarriage rate when compared with women with tubal factor infertility

GnRH antagonist protocol

- A good choice for poor responders, patients with poor ovarian reserve due to ovarian endometrioma or after its surgical excision in IVF cycles as they cause immediate suppression of luteinizing hormone (LH) surge
- Similar implantation and clinical pregnancy rates have been reported in both the agonist and antagonist groups but higher number of embryos was available for cryopreservation in those patients treated with GnRH agonist

OCP'S

- The preoperative use of OC before IVF/ICSI given for a period of 6–8 weeks in patients with severe endometriosis have reported higher clinical pregnancy rates compared to endometriosis patients treated without OCs and comparable to that of control patients without endometriosis

11.2.2 Precautions during ovum pick-up with endometrioma

- In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval to reduce the risk of ovarian abscess

- Vaginal preparation with better bactericidal substances as well as stronger antibiotic prophylaxis might be useful in the prevention of PID - To decide
- Other preventive measures during ovum pickup are the use of strict asepsis in the surgical field, avoiding successive punctures of the vaginal wall and ovarian capsule, avoiding puncture, and aspiration of the endometrioma

11.3 Need for oocyte donor

- If ovarian reserves are poor, the couple has to be counseled regarding need for oocyte donor

11.4 Role of frozen embryo transfer (FET)

- Frozen–thawed embryo transfer (FET) achieves higher pregnancy rates as compared to fresh transfers as it improves endometrial receptivity

Conclusion

- Do not offer hormonal suppressive therapy to women with endometriosis who are trying to conceive
- In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform IUI with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates
- IVF–ET is better therapeutic option in moderate–to–severe endometriosis
- Repeated surgery to be avoided

Summary of recommendation

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CCP	Clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, fatigue or non-gynecological cyclical symptoms (dyschezia, dysuria, hematuria, rectal bleeding, shoulder pain).	-	--
EBR	Recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma and rectovaginal endometriosis	A	II
EBR	Recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis	A	II
EBR	For endometriosis-associated pain it is recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)]	A-B	II
EBR	For pain from rectovaginal endometriosis refractory to other medical or surgical treatment, one can prescribe aromatase inhibitors in combination with oral contraceptive pills, progestagens, or GnRH analogues	B	III
EBR	Recommended to ablate and/or excise peritoneal endometriosis	C	III
EBR	When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation to prevent decrease in ovarian reserve	A	I
EBR	In infertile women with endometriosis, recommended not prescribe hormonal treatment for suppression of ovarian function to improve fertility	A	II
EBR	In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates	C	III
CPP	It is recommended to offer ART for infertility associated with endometriosis, especially if tubal function is compromised, in the presence of male factor infertility, and/or other treatments have failed.	-	-
CCR	In women with endometrioma, it is beneficial to use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess following follicle aspiration is low.	D	-
EBR	GnRH agonists for a period of 3 to 6 months prior to COS for ART may improve CPRs	B	III
EBR	In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rate.	A	
EBR	Removal of endometrioma should be considered in presence of endometrioma larger than 3 cm only to improve endometriosis-associated pain or the accessibility of follicles.		II

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Chapter 9: Endocrinopathies and its Management in Infertility

OVERVIEW

Endocrinopathies are common in women of childbearing age. These disorders are also known to have adverse effects on reproductive functions, resulting in subfertility. Therefore, it is necessary to recognize symptoms and make a correct diagnosis for proper management to avoid adverse effects on outcome of infertility treatment. The following recommendations are based on latest guidelines/recommendations from global societies, the Cochrane database, large meta-analysis, available Indian literature, prevalent practices in India, and consensus amongst experts in the field of infertility and reproductive endocrinology.

1. Thyroid disorders

1.1 Hypothyroidism

1.1.1 Preconception hypothyroidism and sub fertility

- The effects of hypothyroidism on female reproductive hormones include decrease in sex hormone binding globulin (SHBG), decrease in total estradiol, increase in the unbound fraction of testosterone and estradiol, and decreased metabolic clearance of estrone and androstenedione. These changes may lead to alteration of the pituitary ovarian axis. Pulsatile gonadotrophin releasing hormone (GnRH) secretion is impaired. Hyperprolactinemia is a well-known finding in hypothyroidism especially when thyroid underactivity is profound
- Overt hypothyroidism is known to be associated with anovulatory cycles and subfertility, while the association between subclinical hypothyroidism, and subfertility is uncertain (Negro, 2018). Hypothyroid women may have no menstrual disturbances or may present with features of oligovulation or anovulation. Oligomenorrhea or amenorrhea and menorrhagia may be seen probably reflecting estrogen breakthrough bleeding. Treatment of hypothyroidism with thyroxine usually reverses hormonal alterations, and restores ovulation and normal menstrual pattern

1.1.2 Preconception screening for hypothyroidism

- Screening can be targeted based on presence of risk factors (Table 1) or can be undertaken universal-irrespective of any risk factors

Table 1. High risk factors for hypothyroidism^{1,6}

- Women residing in geographic areas with high prevalence of thyroid disorders
- Women over age 30 years of age
- **Women with infertility**
- Obesity (pre-pregnancy/first trimester body mass index (BMI) ≥ 23 kg/m²) [BMI= weight in kg/height in m²]
- Women with a family history or autoimmune thyroid disease or hypothyroidism
- Women with a goiter
- Women with thyroid antibodies, primarily thyroid peroxidase antibodies
- Women with symptoms or clinical signs suggestive of thyroid hypofunction
- Women with type 1 DM or other autoimmune disorders
- Women with a prior history of miscarriage or preterm delivery
- Women with prior therapeutic head or neck irradiation or prior thyroid surgery
- Women currently receiving levothyroxine replacement
- Women living in a region with presumed iodine deficiency

Recommendation

- It is recommended to do targeted screening for hypothyroidism women presenting for preconception counselling. (Grade B)
- It is recommended to do universal screening for hypothyroidism in women presenting with infertility and/or planned to undergo any form of infertility treatment. (Grade B)

Two Indian studies found the incidence of hypothyroidism to be 23.9% (TSH>4.2) and 53.7% (TSH>4.6) in women with infertility (Mohana Priya, Verma Indu). While other studies have shown that the incidence of subclinical hypothyroidism (SCH) is similar in infertile women and the general population, with higher mean TSH in the infertile population (Lincoln, Poppe).

1.1.3 Preconception treatment of hypothyroidism Recommendation

- It is recommended to treat all women with overt hypothyroidism and planning to conceive or undergoing any form of infertility treatment. (Grade A)
- It is recommended to treat subclinical hypothyroidism in women undergoing any form of infertility treatment, if serum TSH is higher than the first trimester pregnancy specific range. (Grade B)
- Hypothyroid women already on thyroxine, undergoing infertility treatment should be readjusted on thyroid replacement doses to maintain TSH levels below the reference range for first trimester. (Grade B)

Hypothyroid women undergoing controlled ovarian stimulation (COS) for assisted reproductive techniques (ART) may need an increment of thyroxine dosage. TSH level is known to increase during COS. Therapeutic regimens used for COS induce a deterioration of thyroid function especially in TPO antibody positive women. On the other hand, SCH likely adversely affects ART outcomes in a dose related fashion.

Overt hypothyroidism should always be treated with hormone replacement in women planning to conceive. Women already on thyroxine generally need escalation of thyroid dose by 30% when pregnancy is diagnosed

1.2. Hyperthyroidism

1.2.1 Preconception hyperthyroidism

Reported prevalence of overt hyperthyroidism in India ranges from 1.2% to 2.5% (22-24).

The commonest cause of maternal thyrotoxicosis is Graves' disease associated with thyroid stimulating immunoglobulin G antibodies.

Hyperthyroidism if diagnosed prior to conception should be managed prior to advising the woman to conceive. Contraception should be used till euthyroid state is achieved.

Preconception recommendations

- Thyrotoxic women should be stabilized to a euthyroid state before attempting pregnancy. (Grade A)

2. Hyperprolactinemia

Prolactin (PRL) secretion in excess may suppress the activity of the hypothalamic–pituitary–ovarian axis in the nonpregnant state. Hyperprolactinemia leads to a decrease in gonadotropin secretion with decreased LH pulse frequency and amplitude. This may result in oligo/anovulation and hence infertility. A prolonged and marked suppression of hypothalamic–pituitary–gonadal axis by chronically elevated prolactin levels may lead to signs of estrogen deficiency, most important being osteoporosis. Among women with infertility, prevalence of hyperprolactinemia was found to be 46%. Another study found the prevalence of hyperprolactinemia to range from 0.4% in an unselected normal adult population to as high as 9%–17% in women with reproductive disorders.

Hyperprolactinemia can be physiologic, iatrogenic, pituitary related, systemic or idiopathic (Table 2). Medications that are responsible are the ones that act as dopamine antagonists or the ones that interfere with dopamine secretion. Regardless of etiology, hyperprolactinemia may remain asymptomatic or it may present with hypogonadism, infertility, and galactorrhea. Bone loss occurs in many women secondary to hyperprolactinemia–mediated sex steroid attenuation.

2.1 Recommendations for diagnosis of hyperprolactinemia

Table 2. Etiology of hyperprolactinemia (21)

Physiologic	Medications	Pituitary	Systemic
Pregnancy	Metoclopramide	Prolactinomas	Primary hypothyroidism
Lactation	Domperidone	Stalk transection	Renal failure
Sleep	Antipsychotic agents (phenothiazines, haloperidol, risperidone, paliperidone)	Stalk effect in patients with non-functioning sellar and suprasellar masses	Adrenal insufficiency
Coitus	Opioids	Somatotropinomas and other co-secreting tumors	Spinal cord lesions
Food consumption	Cocaine	Radiation therapy	Chest wall lesions
Stress	Verapamil		PCOS
	Alpha methyl dopa		Ectopic prolactin secretion
	Monoamine oxidase inhibitors		Prolactin receptor gene mutations
	Fluoxetine		Nipple stimulation

- In women presenting with oligo/anovulatory infertility (irregular menstrual cycles), it is recommended to test for serum prolactin levels. (Grade A)
- Single measurement of serum prolactin level 2.5 times above the reference range limit confirms the diagnosis of hyperprolactinemia. (Grade B)
- Excessive venipuncture stress should be avoided. Sample may be taken at any time of the day. (Grade C)

The initial determination of serum prolactin should avoid excessive venipuncture stress and can be drawn at any time of the day. A single determination is usually enough to establish the diagnosis, but when in doubt, sampling can be repeated on a different day at 15 to 20 min intervals to account for possible prolactin pulsatility. Normal values are higher in women than in men and are generally lower than 25 mcg/liter.

- In patients with asymptomatic hyperprolactinemia, assessment for macroprolactin should be done using polyethylene glycol precipitation test. (Grade C)

Patients with asymptomatic hyperprolactinemia, should be assessed for the presence of macroprolactin. Retrospective studies have shown that approximately

40% patients with hyperprolactinemia have macroprolactinemia. Since, macroprolactinemia is a common cause of hyperprolactinemia, routine screening for macroprolactin will eliminate unnecessary diagnostic testing and treatment. Polyethylene glycol precipitation is the test done to detect the presence of macroprolactin in the serum.

- In presence of a very large pituitary tumor and a mildly elevated prolactin level, serial dilution of serum samples is recommended to eliminate an artifact that can occur in patients with exuberant PRL secretion leading to a falsely low prolactin value ("hook effect") (Grade A)

Serum prolactin levels are known to parallel prolactinoma size. Macroprolactinomas are generally associated with prolactin levels greater than 250 mcg/l. Many a times, there may be a dissociation between the size of prolactinoma and serum prolactin levels. A common cause of such discrepancy is the 'hook effect', which is an assay artifact that may be observed when high serum prolactin concentrations saturate antibodies in the immunoradiometric assay used to estimate serum prolactin level.

- In women with elevated prolactin, it is recommended to rule out pregnancy, rule out causative medicine use, to get serum TSH and free/total T₄ testing, and to do renal function test in order to establish the etiology (Table 2) (Grade A)
- If other causes are ruled out, contrast-enhanced MRI head with pituitary images is recommended. (Grade A)

In women with confirmed elevated prolactin level, pregnancy should be ruled out in those of childbearing age, medication use should be excluded, levels of thyrotropin and free T₄ should be measured, and renal function should be assessed.

Imaging: Once other possible causes of an elevated prolactin level have been ruled out, MRI of the head should be performed, with the use of contrast material, and pituitary images obtained.

2.2. Preconception Hyperprolactinemia management

2.2.1 Drug induced hyperprolactinemia

- Asymptomatic drug induced hyperprolactinemia does not require treatment. (Grade A)
- In symptomatic women with drug induced hyperprolactinemia, if feasible, consideration should be given to discontinuation or substitution of the drug for 3 days and recheck prolactin levels. (Grade B)
- When discontinuation of the drug is not feasible, use of dopamine agonists is controversial. (Grade C)
- Oral contraceptives may be used in symptomatic women with drug-induced hyperprolactinemia to regularize cycles and to improve symptoms of estrogen deficiency. (Grade B)

If possible, establish temporal relation between prolactin elevation and initiation of medication. Obtain a pituitary magnetic resonance image (MRI) if the onset of the hyperprolactinemia does not coincide with therapy initiation. In patients with symptomatic hyperprolactinemia related to medication, attempt discontinuation of the medication for 3 days or substitution of an alternative drug, followed by remeasurement of

serum prolactin. Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient's physician.

If discontinuation or substitution of the drug is not feasible in symptomatic women, use of dopamine agonists in such women is controversial. Studies suggest that dopamine agonist therapy is effective only in 75% of such patients but may lead to exacerbation of the underlying psychosis. Use of oral contraceptives in women may improve symptoms of estrogen deficiency but not those of hyperprolactinemia.

2.2.2 Idiopathic hyperprolactinemia and prolactinomas

- Dopamine agonists are recommended for the management of macroprolactinomas and for symptomatic microprolactinomas as well as idiopathic hyperprolactinemia. (Grade A). Symptomatic micro-prolactinomas as well as idiopathic hyperprolactinemia with amenorrhea may also be managed with oral contraceptives. (Grade B)
- Cabergoline is preferred over other dopamine agonists in the presence of hyperprolactinemia of idiopathic origin or with prolactinomas. (Grade A)
- It is recommended to monitor therapy with serum prolactin level at 1 month after starting dopamine against to make dose adjustments as required. (Grade B)
- Women with prolactinomas who are controlled on dopamine agonists, require repeat MRI at 1 year
- Women with macroprolactinomas and with persistent high prolactin levels or with new onset of symptoms despite receiving dopamine agonists should have repeat MRI at 3 months. (Grade B)
- Dopamine agonist may be discontinued after 2 years of initiation of treatment if serum prolactin has normalized and there is no visible remnant tumor on MRI. (Grade A)

Dopamine agonist therapy lowers prolactin levels, decreases tumor size, and restores gonadal function for

patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas. Cabergoline is preferred to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage. The incidence of unpleasant side effects is lower with cabergoline; hence drug compliance may be superior for this medication. With careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 years, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI.

Asymptomatic patients harboring microprolactinomas or with idiopathic hyperprolactinemia do not need treatment with dopamine agonists.

2.3 Subfertility and hyperprolactinemia

- It is recommended that, women with hyperprolactinemia presenting with oligo/anovulation and infertility, be managed with dopamine agonists. Women with high prolactin levels with normal ovulation do not need treatment with dopamine agonist. (Grade A)

Patients with asymptomatic hyperprolactinemia, should be assessed for the presence of macroprolactin. Retrospective studies have shown that approximately 40% patients with hyperprolactinemia have macroprolactinemia which has no biological activity. With dopamine agonists cyclic menses are restored in 70%–90% women, within 6–8 weeks of initiation of treatment and ovulatory cycles return in 50%–75% of treated women. Cabergoline is more effective than bromocriptine in achieving and maintaining normal prolactin levels, restoring ovulatory cycles and is better tolerated.

- Those failing to ovulate with dopamine agonists or in women with drug induced hyperprolactinemia where drug cannot be discontinued or prolactin levels should not be reversed, may be considered for ovarian stimulation with gonadotropins. (Grade B)

Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient's physician. Reversing prolactin levels to normal may negate the drug effect also. Those failing to ovulate with dopamine agonists can be treated with gonadotropin for ovarian stimulation.

Comparison between cabergoline and bromocriptine

	Bromocriptine	Cabergoline
Half-life	6–20 h	63–69 h
Duration of action	24 h	7–14 h
Dosing	Twice daily	Once or twice weekly
Recommended dose	5–7.5 mg daily	1–2 mg weekly
Normalization of prolactin (%)	48–59	83–93
Restoration of fertility (%)	48–52	72

3. Adrenal disorders

3.1 Congenital adrenal hyperplasia (CAH)

CAH consists of a group of inherited disorders that result from decreased cortisol synthesis due to deficiency of one or more of the enzymes involved in steroidogenesis or affecting steroidogenic pathways. Decrease in cortisol production leads to feedback rise in adrenocorticotrophic hormone (ACTH) release with resultant chronic adrenal stimulation and hyperplasia. The precursors of steroid synthesis before the enzymatic block are increased in concentrations. This may include increased synthesis of adrenal androgens. The symptoms of the disease generally result from deficiency of cortisol and/or mineralocorticoids and excess of androgens, depending on the enzyme/enzymes that are deficient and whether any residual enzyme activity is present.

All forms of CAH are inherited as autosomal recessive disorders. The most common form results from deficiency of 21-hydroxylase (21-OHD), responsible for more than 90% of the cases. Other enzyme deficiencies that may result in CAH are: 11- β hydroxylase, 3- β hydroxysteroid dehydrogenase, 17 hydroxylase, 17- β hydroxysteroid

dehydrogenase, aromatase, P450 oxidoreductase, steroid acute regulatory protein.

3.1.1 Classification

CAH due to 21-hydroxylase deficiency can be classified as under (Table 4).

Treatment mainly consists of glucocorticoid (GC) with or without mineralocorticoid (MC) supplementation. This lowers production of ACTH and hence reverses adrenal hyperfunctioning and its effects. In young girls and adults presenting for the first time in adolescence or later non-classic CAH (NCCAH) is the one mostly seen which is the mildest form of CAH owing to of 21-hydroxylase deficiency.

3.1.2 Diagnosis of CAH and NCCAH

- In symptomatic individuals, screen with early-morning (before 8 AM) baseline serum 17-hydroxyprogesterone measurement. (Grade A). In menstruating women sampling should be done in the early follicular phase. (Grade B)
- In individuals with borderline 17-OHP level, it is recommended to get co-syntropin stimulation test done. (Grade A)
- Genotyping should be considered only when (Grade B)

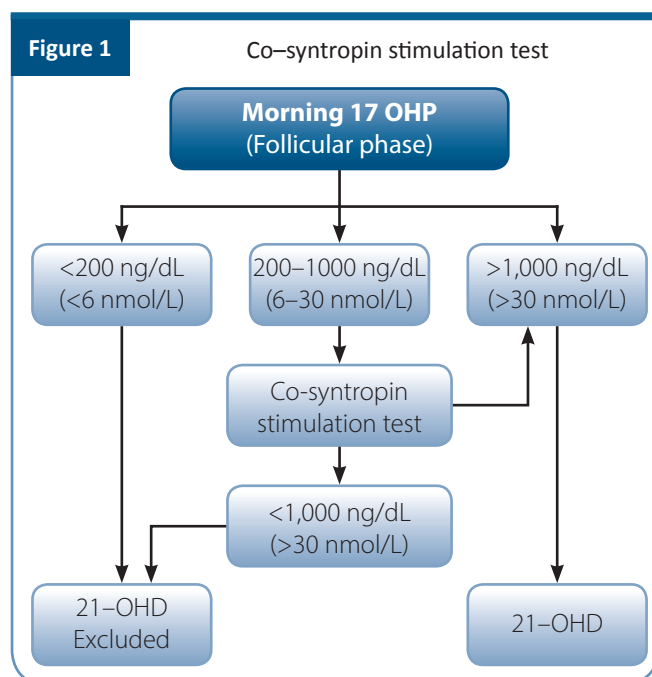
- » Results of the adrenocortical profile after a co-syntropin stimulation test are equivocal, or
- » Co-syntropin stimulation cannot be accurately performed (i.e., patient receiving glucocorticoid), or
- » For purposes of genetic counseling

In symptomatic individuals, past infancy, screening with an early-morning (before 8 AM) baseline serum 17-hydroxyprogesterone (17-OHP) measurement is recommended. Random measurements of 17-OHP have not been shown to be helpful since these often yield normal levels in patients with NCCAH. In menstruating females, it is recommended to sample in the early follicular phase. Co-syntropin stimulation test: Baseline samples are collected for 17-OHP after which synthetic ACTH (co-syntropin) is administered with a standard dose of 250 µg for older children and adults. (Figure 1). Repeat blood work is collected 60 minutes after administration to determine the stimulated values of 17-OHP. While stimulated 17-OHP levels with classic CAH typically exceed 20,000 ng/dl, those with NCCAH will have 17-OHP levels within the range of 1,500–10,000 ng/dl post stimulation.

For patients with nondiagnostic stimulated 17-OHP values, genotyping may confirm the diagnosis.

Table 4. Classification of congenital adrenal hyperplasia (CAH)

Classification	Residual enzyme activity	Presentation	Aldosterone	Cortisol
Classic-salt wasting type	0% to 1%	<ul style="list-style-type: none"> • Symptoms of gluco-corticoid & mineralocorticoid deficiency since birth • Virilized external genitalia in girls at birth 	Low	Low
Classic-simple virilizing type	2% to 20%	<ul style="list-style-type: none"> • Virilized external genitalia in girls at birth 	Normal	Low
Non classic CAH (NCCAH)	20% to 50%	<ul style="list-style-type: none"> • Symptoms of hyperandrogenism in adolescent and adult females 	Normal	Normal



3.1.3 Management of CAH and NCCAH

Young women not planning pregnancy

- Women diagnosed as NCCAH and presenting with hyperandrogenism and menstrual irregularities may be managed with oral contraceptives and antiandrogens if required. (Grade B)
- Asymptomatic non-pregnant women with NCCAH do not require treatment. (Grade A)

Clinically, many young women with NCCAH are asymptomatic. When symptomatic, the presentation is quite variable among individuals and varies with age in the same individual. Initial clinical presentation of NCCAH is before the age of 10 years in 11% of cases and between the ages of 10 and 40 years in 80%.

Symptomatology includes premature pubarche, under 8 years of age in girls and under 9 years in boys. Incidence of NCCAH among children with precocious puberty ranges from 5%–30% according to different studies. Rapid progression of bone age and truncated final height may also be seen. During adolescence and adulthood, women with NCCAH generally have symptoms like PCOS. Presenting symptoms include hirsutism (78%), menstrual dysfunction (54.7%), and decreased fertility (12%), and alopecia (Witchel). Acne is reported in about

33% of NCCAH patients. The presence of hirsutism correlates with increasing age, indicating progressive nature of the disease. Osteoporosis may be a late feature, as a consequence of prolonged corticosteroid therapy.

- Young women with classic CAH should continue glucocorticoid and mineralocorticoid therapy as prescribed by endocrinologist. (Grade A). A baseline bone mineral density (BMD) measurement should be considered in young women. (Grade C). Oral contraceptives may be added to improve symptoms of hyperandrogenemia

During the transition from adolescence to adulthood in girls with classic CAH, need for continuation of glucocorticoid and mineralocorticoid for long term benefits, should be stressed to prevent noncompliance. Addition of oral contraceptive pills to the regimen might help to reduce androgen concentrations, should be especially considered in heterosexually active women, not desiring pregnancy. Osteoporosis prophylaxis, including vitamin D and calcium supplementation should also continue.

3.1.4 Young women planning pregnancy

- In women with classic CAH who are trying to get pregnant, dexamethasone should be substituted with hydrocortisone or prednisolone. (Grade A)

Fertility treatment in classic CAH with optimized GC therapy to normalize androgen and progesterone levels, most women desiring pregnancy will achieve spontaneous conceptions. Women who fail to ovulate despite adequate treatment may be given oral ovulation induction agents. Women with low sex steroid production may need COS with IVF with adequate hormone replacement. In some women with uncorrected or partially corrected virilized external genitalia, genitoplasty may be required to improve sexual function.

- In infertile women (anovulatory infertility) with NCCAH or those with a history of miscarriage, and currently planning to conceive, treatment with a GC that does not cross placenta is recommended. (Grade B)

- Infertile women with NCCAH who fail to ovulate with glucocorticoids may be treated with oral ovulogens or with gonadotropins. (Grade B)
- Table 5 enumerates the different glucocorticoids that can be used whereas table 6 elicits dose for the maintenance therapy

In women with Infertility with NCCAH hydrocortisone seems to be the appropriate treatment; as it lowers adrenal androgen secretion, normalizes menstrual

cycles, and reduces the incidence of miscarriages (Bidet, Pham, Smith). Twice-a-day hydrocortisone dose schedule is considered reasonable (Table 3). The clinical criteria for therapeutic efficacy are regular cycles and rise in P4 indicating resumption of ovulation; the biochemical criteria consist of fall in plasma testosterone and androstenedione values to normal levels (Feldman). Women who fail to ovulate with hydrocortisone therapy may be considered for ovulation induction with clomiphene citrate.

Table 5: Choice of glucocorticoids (GC) in infertile women with NCCAH

Glucocorticoids	Usage in	Features
Short acting GC: Hydrocortisone	<ul style="list-style-type: none"> • Neonates and children • Treatment of pregnant women with CAH 	<ul style="list-style-type: none"> • Multiple daily dosing required • Closely resembles cortisol in action. • Does not cross placenta
Long acting GC: Dexamethasone	<ul style="list-style-type: none"> • Prenatal treatment of fetal CAH with aim to prevent female fetal virilization at birth 	<ul style="list-style-type: none"> • Highest suppression of steroid synthesis • Greatest decrease in BMD and highest weight gain tendency • Crosses placenta
Long acting GC: Prednisolone	<ul style="list-style-type: none"> • Adults 	<ul style="list-style-type: none"> • Side effect profile: less severe than dexamethasone • Crosses placenta but fetal uptake is limited

Table 6. Maintenance in infertile women with NCCAHt

Long-acting corticosteroid	Dose (mg/d)	Daily doses
Hydrocortisone	15–25	2–3
Prednisone	5–7.5	2
Prednisolone	4–6	2
Methylprednisolone	4–6	2
Dexamethasone	0.25–0.5	1
Fludrocortisone	0.05–0.2	1–2

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Endocrine disorders should be identified, addressed, treated and body weight normalized	B	II
EBR	It is recommended to do targeted screening for hypothyroidism women presenting for preconception counselling	B	II
EBR	It is recommended to do universal screening for hypothyroidism in women presenting with infertility and/or planned to undergo any form of infertility treatment	B	III
EBR	Anti-thyroperoxidase (TPO) and/or anti-thyroglobulin (TPG) antibodies have a negative impact on fertility and pregnancy, which makes it mandatory to measure the thyroid antibodies in women who wish to conceive or those who have had BOH despite euthyroid status	B	III
EBR	Women with hypothyroidism and thyroid antibodies should be treated with L-thyroxine,	A	I
CCR	• It is recommended to treat all women with overt hypothyroidism and planning to conceive or undergoing any form of infertility treatment	B	III
EBR	• It is recommended to treat subclinical hypothyroidism in women undergoing any form of infertility treatment, if serum TSH is higher than the first trimester pregnancy specific range	B	II
EBR	• Hypothyroid women already on thyroxine, undergoing infertility treatment should be readjusted on thyroid replacement doses to maintain TSH levels below the reference range for first trimester		
EBR	Hyperthyroidism	A	I
EBR	Thyrotoxic women should be stabilized to a euthyroid state with the average dose of radioactive iodine (370 MBq), before attempting pregnancy	B	
EBR	No significant damage to the gonads noted with this dose but conception is avoided until 6 months after administration		
EBR	Hyperprolactinemia	A	II
CCR	In women presenting with oligo/anovulatory infertility (irregular menstrual cycles), it is recommended to test for serum prolactin levels	C	IV
CCR	In patients with asymptomatic hyperprolactinemia assessment for macroprolactin should be done using polyethylene glycol precipitation test	A	I
EBR	In women with elevated prolactin, it is recommended to rule out pregnancy, rule out causative medicine use, to get serum TSH and free/total T4 testing, and to do renal function test in order to establish the etiology	A	II
EBR	If other causes are ruled out, contrast enhanced MRI head with pituitary images is recommended	A	I
EBR	Hyperprolactinemia should be treated with dopamine agonists	A	II
EBR	Cabergoline is preferred over other dopamine agonists in the presence of hyperprolactinemia of idiopathic origin or with prolactinomas		
EBR	It is recommended to monitor therapy with serum prolactin level at 1 month after starting dopamine against to make dose adjustments as required	B	II
EBR	Congenital adrenal hyperplasia (CAH)	A	I
EBR	In symptomatic individuals, screen with early-morning (before 8 AM) baseline serum 17-hydroxyprogesterone measurement	B	III
EBR	In menstruating women sampling should be done in the early follicular phase	A	II
EBR	In individuals with borderline 17-OH Progesterone level, it is recommended to get co-syntropin stimulation test done	B	III
EBR	Women diagnosed as non-classical CAH (NCCAH) and presenting with hyperandrogenism and menstrual irregularities may be managed with oral contraceptives and antiandrogens if required	A	II
EBR	Asymptomatic non pregnant women with NCCAH do not require treatment	A	I
CCR	Young women with classic CAH should continue glucocorticoid and mineralocorticoid therapy as prescribed by endocrinologist	C	-
CCR	A baseline bone mineral density (BMD) measurement should be considered in young women	C	
EBR	Oral contraceptives may be added to improve symptoms of hyperandrogenemia	B	
EBR	Infertile women with NCCAH who fail to ovulate with glucocorticoids may be treated with oral ovulogens or with gonadotropins		

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Chapter 10: Ovulatory Disorders

OVERVIEW

This document highlights good practice recommendations on ovulatory disorders for practicing gynecologists in India. Management of ovulatory disorders poses a constant challenge in practicing gynecologists, embryologists, and infertility specialists. These recommendations are based on several guidelines/recommendations from global societies, the Cochrane database, large meta-analysis, available Indian literature, prevalent practices in India, and consensus amongst experts in the field of ovulatory infertility. These recommendations concentrate on the need to strengthen and promote meaningful research that will be applicable to Indian patients and Indian practice.

1. Introduction

- Ovulatory disorders account for infertility in up to 40% of women. In most of the cases, ovulatory disorders are associated with irregular periods (oligomenorrhea) or an absence of periods (amenorrhea)
- A cut-off age of 32 years should be taken as a risk factor for diminished ovarian reserve
- Normal BMI: 18.0–22.9 kg/m²
- Overweight: 23.0–24.9 kg/m²
- Risk/high-risk: >25 kg/m² (risk of obesity); and >27.5 kg/m² (high-risk)
- » Waist circumference (women)
 - 72 cm (avoid gaining weight and maintain physical activity)
 - >80 cm (seek medical help to manage obesity-related risk factors)

2. Classification of anovulatory infertility

- World Health Organization (WHO) classification of ovulatory disorders (Table 1)
- Underweight may signify a hypothalamic cause and overweight could indicate endocrinopathy like PCOS
- Other signs of endocrinopathy–alopecia, hirsutism, acne, stigmata of thyroid dysfunction
- Clinical hyperandrogenemia should be assessed and scored for severity

3. Diagnosis of anovulatory infertility

3.1 Menstrual irregularity

- Menstrual irregularity may suggest the presence of ovulatory disorders. In women with ovulatory disorders, oligomenorrhea, amenorrhea and/or prolonged cycles are very common
- » To evaluate hirsutism, a modified Ferriman Gallwey score (mFG) can be used: A score of ≥4 is relevant but relevance may vary with ethnicity

3.2 Physical examination

- According to WHO Consensus Statement,
 - » BMI
 - » To evaluate alopecia, the Ludwig visual score can be used

Table 1. Classification of ovulatory disorders

Group I: Hypothalamic/pituitary failure	Weight loss, systemic illness, Kallmann's syndrome, hypogonadotrophic hypogonadism	5%
	Hyperprolactinaemia, hypopituitarism	
Group II: Hypothalamic/pituitary dysfunction	PCOS	90%
Group III: Ovarian failure	Premature ovarian failure (POF) Resistant ovary syndrome (ROS)	5%

3.3 Laboratory investigations

3.3.1 Diagnostic hormonal levels in anovulatory infertility

Table 2. Hormone levels in different anovulatory disorders

Hypothalamic: Underweight	↓ FSH, ↓ LH, ↓ E2 n FSH, ↓ LH, ↓ E2
Hyperprolactinaemia	↓ FSH, ↓ LH, ↓ E2
Ovarian failure/menopause	↑↑ FSH, ↑ LH, ↓ E2
Mid-cycle	↑ FSH, ↑↑ LH, ↑ E2
PCOS	↓/n FSH, ↑/n LH, ↑/n E2

- Testosterone will be low or normal in women classified under group I WHO. Testosterone testing in women with the group I and III is not helpful. In women with group II, assessment of biochemical hyperandrogenism by assessing free androgen index (FAI), calculated free testosterone (cFT), and calculated bioavailable testosterone (cBT) should be considered in diagnosing PCOS
- Women on oral contraceptive pills have an altered testosterone level due to alteration in sex hormone-binding globulin. Contraceptive should be withdrawn for 3 months before measuring androgens

3.3.2 Tests for confirming ovulation

- Follicular monitoring by ultrasound is a reliable option
- Progressive growth and collapse of the follicle with increased internal echoes and fluid in the cul-de-sac are markers of ovulation
- Serum progesterone in the mid-luteal phase on day 21 of a 28 days menstrual cycle
- Women with prolonged, irregular cycles if day 21 progesterone suggests anovulation test after day 28th weekly till menstruation
- A value of >3 ng/mL is considered as ovulation. Progesterone has a pulsating release thus single level may not be useful unless elevated. Values of >= 10ng/ml are suggestive of normal progesterone production
- Urinary LH kit

3.3.3 Baseline pelvic scan

Baseline scan is the scan done between from 2nd to 4th day of the cycle time when the ovaries are quiescent with no follicles > 8mm. It is done to

- » Assess endometrium < 7 mm
- » Identify adnexal abnormalities
- » Identify uterine abnormalities
- » Identify ovarian cyst
- » To identify the type of the ovary
- » Assess ovarian reserve by AFC
- » Decide stimulation protocols for adequate response and avoid OHSS

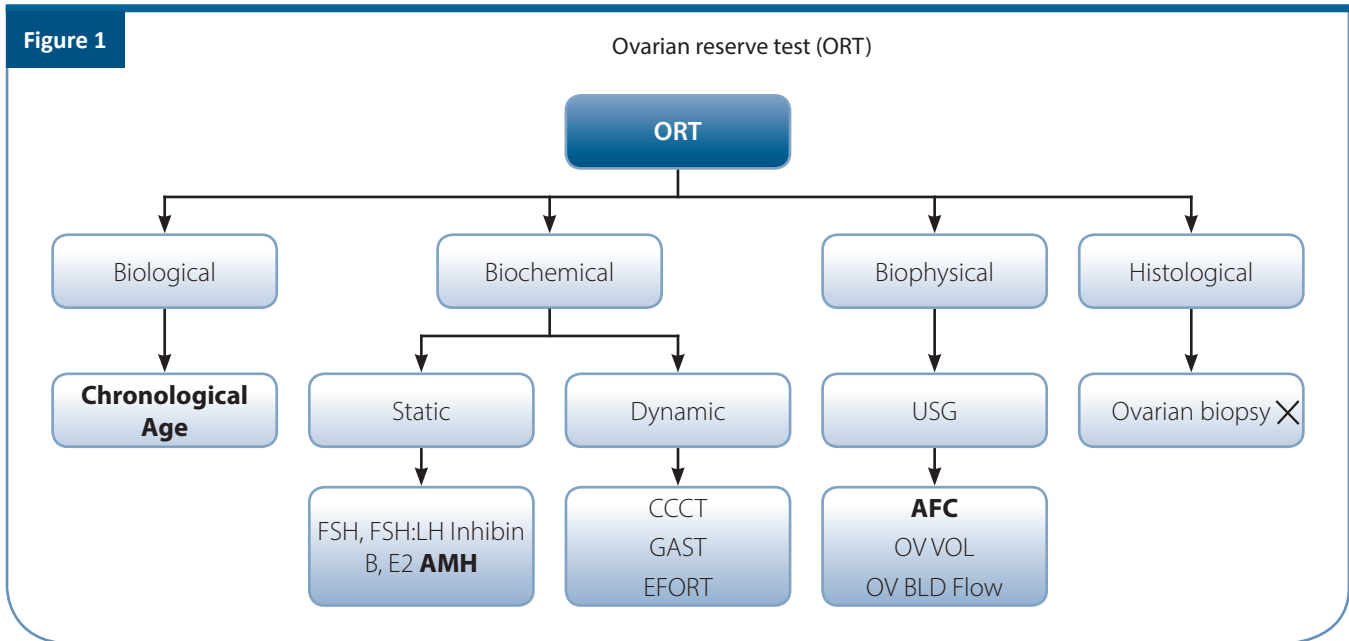
Prerequisites for OI: OI initiated on Day 2/3 only if:

- » Follicular size is <10 mm
- » Absence of ovarian cyst
- » Endometrial thickness <6 mm

3.3.4 Testing ovarian reserve status

- The figure 1 enumerates all available ovarian test
- Analysis of ovarian reserve should be done before starting the ovarian stimulation to select the correct stimulation protocol to decide dose to prevent ovarian hyperstimulation or poor response. Most Individualized protocols are based on age, AMH, AFC, and FSH, which are further amended according to the BMI
- Ovarian reserve testing is beneficial in determining the dose of gonadotropins in women undergoing ovarian stimulation. Ovarian reserve also helps to prevent ovarian hyperstimulation or poor response
- Specific factors must be followed that may mandate earlier investigations (after 6 months of failed attempts to conceive or earlier if clinically indicated) in Indian women:
 - » Aged ≥32 years
 - » Family history of early menopause or a known cause of infertility
 - » Unexplained infertility

Figure 1



- » Ovarian surgery, chemotherapy or radiotherapy
- » Show signs of shortened menstrual cycles or oligomenorrhea or amenorrhea
- » Poor ovarian response and AFC on a basic scan

3.3.5 Other investigations

- Prolactin/thyroid function test
- Androgen profile if PCOS
- SHBG and GTT
- Lipid profile
- Semen analysis
- Tubal patency assessment

3.4 Predictors of ovarian response

- Response can be predicted based on AMH, AFC, FSH. Additional test like Inhibin B, estradiol, day 10 progesterone values, and ovarian volume are used to predict poor response. The table 3 gives the predictor of high and poor ovarian response

Table 3. Predictors of ovarian response

Markers of normal response	<ul style="list-style-type: none"> • AFC - > 8 < 14 • AMH – 1.25–3.5 ng/ml
Markers of high response	<ul style="list-style-type: none"> • AFC > 4 • AMH > 3.5 ng/ml • Color doppler – Increased stromal velocity
Markers of low response	<ul style="list-style-type: none"> • Age – > 36 years • FSH > 10 mIU/ml • E2 > 75 pg/ml • AMH < 1.25 ng/ml • Inhibin B < 45 pg/ml • P4 on day 10 of COS > 1.1 ng/ml • AFC < 5 • Ovarian volume – < 3 cm³ • Large inter-cycle variability in basal FSH • Low flow at color Doppler

AFC: antral follicular Count; AMH: anti-Müllerian Hormone; E2: estradiol; FSH: follicle stimulating hormone.

- AMH and AFC along with age the good predictors of response to COS but do not predict ART outcomes “Live birth rate”

- FSH alone is not a good predictor of ovarian response
- Ovarian volume, ovarian blood flow, inhibin B, estradiol E2 clomiphene challenge tests are not to be considered as they are not beneficial in testing. Basal estradiol values are not used singularly but only to interpret FSH values

4. Treatment of anovulatory disorders

Etiology and treatment of anovulatory disorders is highlighted in Table 4.

Table 4. Etiology and treatment of anovulatory disorders

Etiology	Examples	Suitability for ovulation induction treatment	Drug treatment	Next step
Group I Hypogonadotropic ↓FSH, ↓LH, and ↓E2	Underweight, anorexia; intense exercise as in athletes, ballerinas	Not unless correction of weight, reduction in exercise (as appropriate) is achieved	Gonadotropins: LH + FSH or pulsatile GnRH pump	ART – IVF/ICSI
	Cranial tumors, irradiation, and hypophysitis	Not until the primary disease is treated with medical or surgical measures as indicated	Gonadotropins	
	Sheehan syndrome	Yes	Gonadotropins	
	Kallmann's syndrome, idiopathic	Yes, after addressing lifestyle if necessary	Gonadotropins or pulsatile GnRH pump	
Hyperprolactinemia (this can result in secondary hypothalamic hypogonadism)	Pathological: drugs (e.g. phenothiazines, metoclopramide), pituitary microadenomas or macroadenomas. Other causes: stress, exercise, physical examination, PCOS	No, hyperprolactinemia should be corrected first either by medical or surgical means as indicated	Dopamine agonists, e.g. bromocriptine	
Group II Normogonadotropic ↔FSH, ↔ or ↑LH, ↔ or ↑E2	PCOS, idiopathic	Yes, after correcting weight and lifestyle factors	Letrozole 2.5 - 5 mg day 3 - 7 is first line therapy Clomiphene citrate 50-150 mg Day 2-6 for 6- 9 cycles if ovulatory	Gonadotropins or LOD; last option is IVF
Group III Hypergonadotropic ↑FSH and LH, ↓E2	Premature ovarian failure: Genetic causes: Turner syndrome, fragile X syndrome, gonadal dysgenesis. Iatrogenic: surgery, chemotherapy, and radiation Autoimmune causes: polyendocrinopathy syndrome Infections (rare): viral oophoritis Idiopathic autoimmune disorders	No	Egg donation program	Long-term HRT

↑ = increased; ↓ = decreased; ↔ = normal E2 = estradiol; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HRT = hormone replacement therapy; IVF = in vitro fertilization; LH = luteinizing hormone; LOD = laparoscopic ovarian drilling; PCOS = polycystic ovary syndrome.

4.1 WHO Group I–Anovulatory infertility due to hypogonadotropic hypogonadism

Choice of therapy (Table 5)

- The choice between pulsatile GnRH or gonadotropins in this category depends on the intactness of the pituitary. Pulsatile GnRH may be used if the pituitary is intact. It is given subcutaneously or intravenously every 90 minutes. Its place in current practice needs to be evaluated
- Gonadotropin therapy is ideal and more cost-effective that can be considered even when the pituitary is not functioning. Both FSH and LH are required for ovulation induction as there is no endogenous LH. With only FSH, follicles may grow but results in inadequate estrogen production. The dose of gonadotropin to achieve monofollicular growth, a low-dose step-up must be considered to avoid hyperstimulation
- Counselling for prolonged stimulation is also recommended and luteal support is needed after ovulation induction as endogenous gonadotropin secretion is likely to be inadequate to support normal luteal function. Follicular monitoring should be a must
- Treatment with exogenous progesterone or additional small doses of hCG–2000 IU every 3 days during the luteal phase of ovulation induction cycles has been shown to increase the pregnancy rates
- Assisted reproductive technology (ART)
- Intrauterine insemination (IUI) may be combined with ovulation induction if there is no pregnancy. If ovulation induction along with IUI does not lead to pregnancy, then IVF can be considered

Table 5. Treatment of anovulatory infertility

Condition	Treatment
Hypothalamo-pituitary failure	<ul style="list-style-type: none"> • Gonadotrophins 75 – 225 IU hMG • GnRH pulses Dose - 15 ug or 20-25 ug either IV or SC respectively at 90 minutes interval till hCG administration
Hyperprolactenemia	Dopamine agonists <ul style="list-style-type: none"> • Bromocriptine 2.5 – 20 mg daily • Cabergoline 0.25 - 1 mg twice weekly • Quinagolide 25 – 150 daily
Hypothalamo – Pituitary dysfunction PCOS	<ul style="list-style-type: none"> • Weight loss • Clomiphene citrate (CC)/Letrozole/Tamoxifen • CC – 50- 150 mg Day 2-6 • Letrozole 2.5 – 5 mg Day 3-7 • Gonadotrophins IUI cycle - start with 37.5 – 75 IUI and increase if necessary • Gonadotrophins IVF cycle – Start with dose of 100- 225 IU depending on age, BMI, AFC and AMH • GnRH analogues - GnRH antagonist preferred in PCOS women • Others one can use GnRH agonist Long or short protocol or GnRH antagonist depending on AMH and AFC • Ovarian surgery – LOD Beneficial in Lean PCOS and those with high LH concentrations • Insulin sensitizers: May have a role in PCOS women • Metformin can be used in the dose of 500 mg twice or three times a day can be increased by 500 mg till a maximum dose of 2500 mg per day • A dose of 850 mg twice a day may also be used
Hypergonadotrophic hypogonadism	<ul style="list-style-type: none"> • Success rate poor • GnRHa in ultra short protocol with hMG • Oocyte donation/Adoption • HRT to prevent osteoporosis and CVS disease

- WHO Group II anovulatory infertility principles of treatment
- Before treatment, the underlying disorders such as hyperprolactinemia, hypothyroidism, and adrenal disorders should be treated before commencing infertility therapy
- Lifestyle modifications such as optimization of BMI, blood glucose levels, smoking cessation to be optimized, diet, exercise, sleep, anxiety, mental, social, and sexual health, and minimization of alcohol consumption are needed to be considered in the success of the treatment
- Weight loss of 5% improves insulin sensitivity and may lead to spontaneous ovulation
- The lowest effective dosage of fertility drugs is to be considered to achieve monofollicular ovulation
- Counseling is essential as the number of days taken to ovulate may be more
- Ovulation induction therapy should be administered monthly until pregnancy is achieved or for up to six cycles. In cases of unsuccessful therapy prolonged use of ovulation induction agents should be avoided, due to poor success rates

4.2 Ovulatory drugs for PCOS

- Table below highlights the drugs used for ovulation induction

Table 6. Medication used for ovulation induction	
Drugs used for ovulation Induction	GnRH analogues
Anti Estrogens 1. Clomiphene citrate 2. Tamoxifen/Raloxifene Aromatase inhibitors 1. Letrozole 2. Anastrozole Gonadotropins • Urinary or highly purified hMG • Purified or highly purified u-FSH • Recombinant FSH (r-FSH) • Recombinant LH Combinations of oral agents with gonadotropins	• GnRH agonists • GnRH antagonists
<small>FSH: follicle stimulating hormone; GnRH: gonadotropin-releasing hormone; hMG: human menopausal gonadotropin; LH: luteinizing hormone.</small>	

4.2.1 First-line pharmacological management in women with anovulatory infertility

4.2.1.1 Role of letrozole in ovulation induction in anovulation infertility

- Letrozole can be considered as the first-line drug in the therapeutic management of ovulation induction in women with PCOS with anovulatory infertility to avoid multiple pregnancy and ovarian hyperstimulation with clomiphene
- Dose 2.5–5mg daily from day 3–7
- Letrozole use is associated with a reduced risk of multiple pregnancy in comparison to clomiphene citrate

4.2.1.2 Clomiphene citrate

- Starting dose 50 mg; maximum dose –150 starting on any day between day 2–5 and given for 5 days
- Dose correlates with body weight, age, indication for use (anovulation, PCOS, COH), and past history
- Dose cannot be accurately predicted
- Requires empiric incremental titration to establish lowest effective dose
- To be discontinued if two consecutive cycles anovulatory with maximum dose or If endometrial thickness <7 mm at ovulation
- CC failure could be due to
 - » Failure to ovulate due to high BMI, Free androgen index, LH or Insulin levels
 - » Ovulation but no conception due to
 - » antiestrogen effects on cervical mucus or endometrium
 - » High LH
 - » Improvement of results with CC if
 - Monitor for antioestrogen effects:
 - Decrease insulin
 - weight loss
 - insulin lowering medications

4.2.1.3 Adjuvants: hCG, dexamethasone, dopamine agonist

- » Decrease LH

- » Pretreatment suppression of LH and androgens with OC/progesterone
- » LOD

4.2.1.4 Addition of metformin to clomiphene citrate

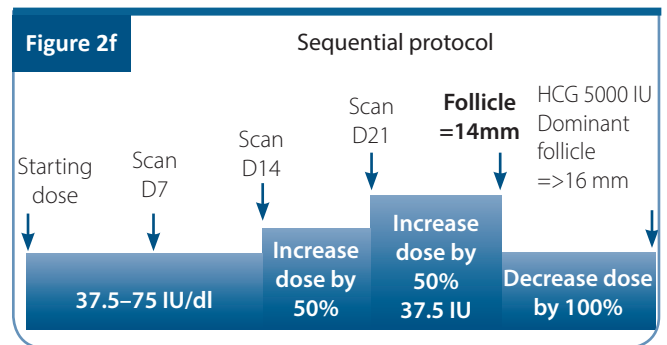
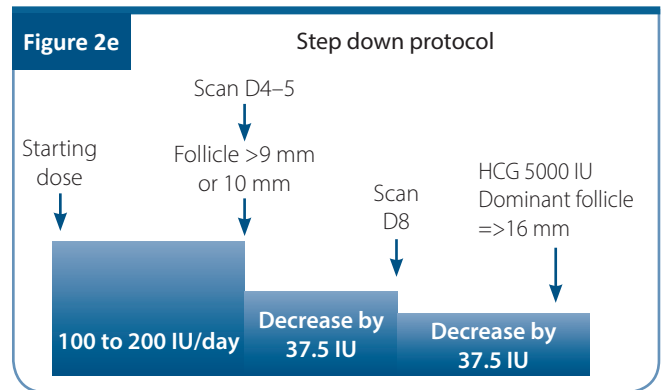
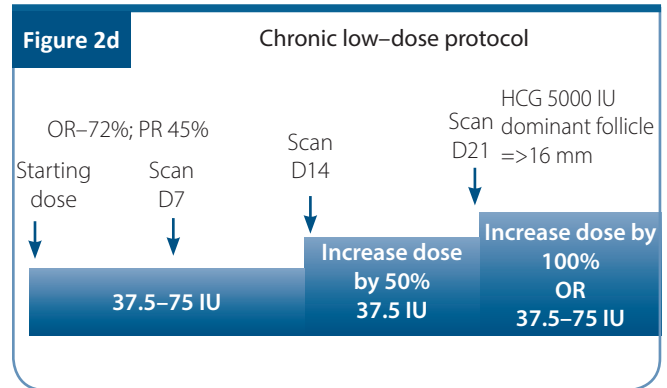
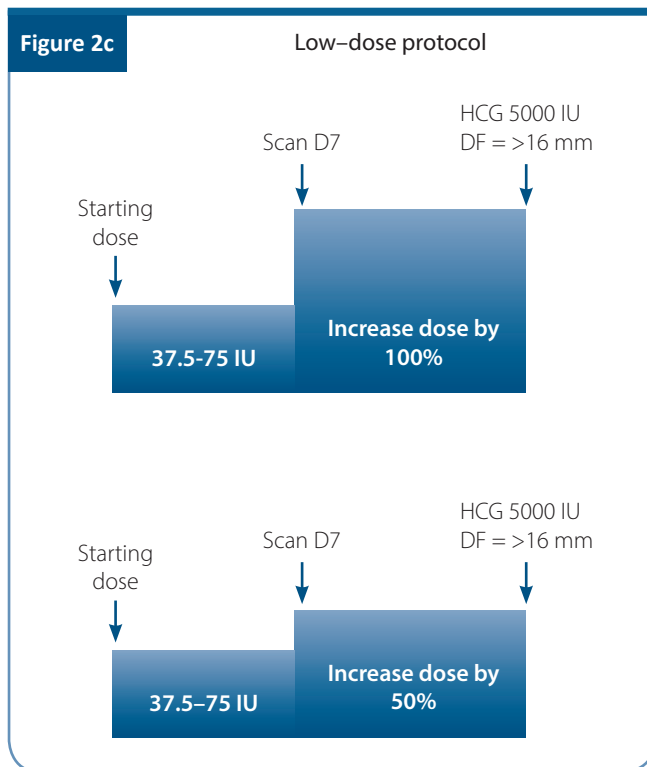
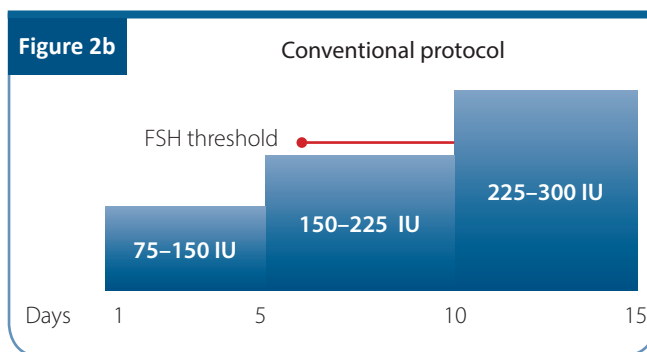
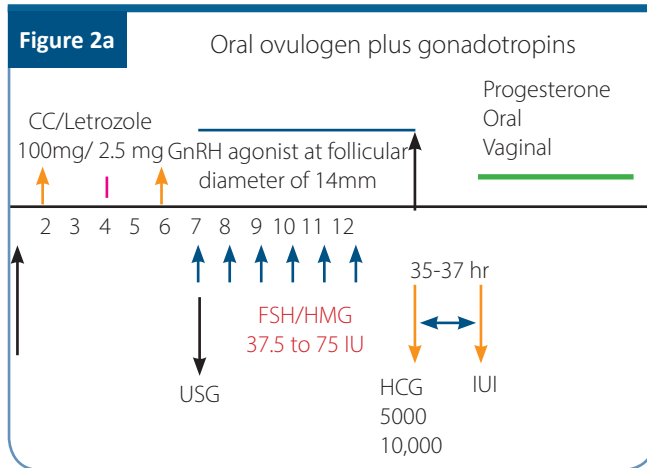
- Clomiphene improves ovulation and pregnancy rates and is preferred to administer along with metformin. Metformin alone in women with PCOS improves ovulation and pregnancy but not live birth rates due to increased pregnancy complications. Also, in most cases metformin is not used as an ovulation-inducing agent rather it is used as an insulin sensitizer
- Women prescribed metformin should be informed of the side-effects (such as nausea, vomiting, and other GI disturbances) associated with its use
- Clomiphene could be combined with metformin, rather than persisting with clomiphene alone as it improves ovulation, pregnancy, and live birth rates in women with PCOS who are obese (BMI ≥ 30 kg/m²)
- Monitoring is needed with clomiphene to avoid multiple pregnancy and hyperstimulation
 - » Ultrasound monitoring during the first cycle of treatment must be considered to ensure that they are taking a dose that minimizes the risk of multiple pregnancy, ensure a positive response, and adequate endometrial development
- Importantly, while using clomiphene, the healthcare professional should be aware that
- Routine luteal support not required unlike WHO group I
- 15% of women do not respond to clomiphene and are resistant

4.2.2 Second-line pharmacological/surgical management in women with anovulatory infertility

Gonadotropins or laparoscopic ovarian surgery is recommended as second-line therapy in women with group II anovulatory infertility with clomiphene-resistance after counseling on the benefits and risks of each therapy

4.2.2.1 Gonadotropins can be considered as second-line management

- In specific selected cases, gonadotropins can be used as first-line treatment, provided that women can undergo monitoring and are counseled about risk and cost
- Gonadotropins can be used in different ovulation induction regimens either a low-dose step-up or a step-down regimen. The risk of multiple pregnancy and ovarian hyperstimulation syndrome with the use of gonadotropins is very tough to establish. However, considering the low-dose step-up regimen (37.5–50 IU), the risk can be reduced and unifollicular development can be achieved in non-ART cycles
- The Figure 2 a-f below show the different protocols with gonadotropins
- In women with clomiphene-resistance, gonadotropin with the addition of metformin can be used along with considering the aspects such as patient counselling on cost, monitoring, risk of multiple pregnancy and ovarian hyperstimulation
- According to the Leeds study (>10-year period; 1998–2008), gonadotropin ovulation induction showed an overall ovulation rate of 67.4% (523/775 cycles). The overall cumulative clinical pregnancy rate after 5-cycles was 47.7% (Figure 4) with a twinning rate of 10.8%



4.2.2.2 Laparoscopic ovarian surgery

- The results with ovarian drilling are similar to gonadotropins but have the advantage of no intensive monitoring and spontaneous conception
- The risks, advantages, and disadvantages should be explained to all women and decisions should be taken after comparing costs, recurrence of treatment, the existence of a person with expertise in chosen treatment side-effects, and risks like adhesions and decreased ovarian reserve which may occur with surgery
- Laparoscopic ovarian drilling can be considered as first-line in Indian rural women who cannot come back repeatedly for monitoring

4.2.3 Anti-obesity agents and bariatric surgery in women with anovulatory infertility

- To improve fertility, pharmacological anti-obesity agents and bariatric surgery can be used as an experimental therapy in PCOS women with anovulatory infertility who do not ovulate with maximum dose of ovulation induction drugs

4.2.4 Third-line management in women with anovulatory infertility

Role of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)

- In PCOS women with anovulatory infertility where first- or second-line ovulation induction therapies have failed, IVF/ICSI can be recommended as third-line therapy in the absence of an absolute indication for IVF/ICSI
- Women who are recommended to IVF/ICSI treatment, the GnRH antagonist protocol must be preferred and an elective frozen embryo transfer strategy could be considered
 - » Women with PCOS undergoing IVF ± ICSI therapy should be counseled before starting treatment, including on cost and risk of ovarian hyperstimulation syndrome and methods of tackling it
- Either urinary or recombinant FSH can be used as there is insufficient evidence to suggest a difference between various FSH preparations. No significant

differences were seen between human menopausal gonadotropins (hMG) and urinary FSH in rates per cycle of pregnancy, multiple pregnancy, miscarriage, ovulation, or overstimulation

- Recombinant LH not recommended for use in combination with FSH therapy. Unlike the WHO I category, these women do not require LH during stimulation
 - » GnRH antagonist protocol is preferred in women with PCOS to avoid OHSS by using agonists trigger and freeze all policy
 - » Also, the GnRH agonist protocol should not be offered as it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. If GnRH agonist protocol is used, then human chorionic gonadotropins (hCG) smallest dose (1000 mg to 1500 mg daily) to trigger final oocyte and adjunct metformin therapy should be used as it reduces the risk of OHSS

4.2.5 Is fertile window extended in women with polycystic ovarian syndrome

- » Despite a higher oocyte yield in all age groups, women with PCOS over age 40 had similar CPR and LBR when compared to women with tubal factor infertility
- » Reproductive window may not be extended in PCOS and that patients with infertility should be treated in a timely manner despite indicators of high ovarian reserve

4.2.6. Long-term health outcomes of ovulation induction and ovarian stimulation

- » No direct association has been found between these treatments and invasive cancer
- » Information about long-term health outcomes in women and children is still awaited
- » For a better outcome, the use of ovulation induction or ovarian stimulation agents should be limited to the lowest effective possible dose and duration

4.3 WHO Group III anovulatory infertility principles of treatment:

- » The only realistic treatment option for women classified as WHO group III anovulatory infertility is egg donation. Besides, they require long-term hormone replacement therapy to prevent the deleterious effects of hypoestrogenism on their bones

are rare in the field of ovulation induction. Also, there is a lack of RCTs or multicentre trials from India

- There is a strong need to strengthen and promote meaningful research so we can have enough data to formulate our guidelines, otherwise, we will continue to depend on the guidelines and recommendations which may not apply to our patients and our practice in India

Conclusion and future perspectives

- Even though the evidence-based approach is practiced by the gynecologists, embryologists, and infertility specialists in reproductive medicine for a long-period, large multicenter, randomized controlled trials (RCTs)

Summary of recommendations

- Increase safety and effectiveness
- Optimizing response to increase live birth rate
- Minimize risk of OHSS and multiple pregnancy by stimulation individualization

Recommendations for ovulation induction, trigger, and LPS

Category	Recommendation	Grade of Recommendation	Quality of evidence
EBR	For predicting high and poor response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests	A	I
CCR	Pre-treatment with estrogen and progesterone or COCP in an GnRH antagonist cycle is not recommended	C	-
EBR	GnRH antagonist protocol is recommended for PCOS women and for predicted high responders to improved safety and equal efficacy	A	I
EBR	There is insufficient evidence to recommend the addition of letrozole to gonadotropins in stimulation protocols for predicted high responders	C	IV
EBR	The GnRH antagonist protocol is recommended for predicted high responders. However, if GnRH agonist protocols are used, a reduced gonadotropin dose is probably recommended to decrease the risk of OHSS	C	III
EBR	The GnRH antagonist protocol is recommended for predicted normal responder women and in general IVF/ICSI population with regards to improved safety	B	II
EBR	GnRH antagonists and GnRH agonists are equally recommended for predicted poor responders	C	III
CCR	Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are equally recommended for predicted poor responders	A	-
CCR	The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted poor responders	C	-
EBR	A gonadotropin dose higher than 300 IU is not recommended for predicted poor responders	A	II
CCR	The use of modified natural cycle is probably not recommended over conventional ovarian stimulation for predicted poor responders	D	-
EBR	If GnRH agonists are used, the long GnRH agonist protocol is probably recommended over the short or ultrashort GnRH agonist protocol	C	III

Category	Recommendation	Grade of Recommendation	Quality of evidence
EBR	The use of recombinant FSH (rFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended	A	I
EBR	No advantage in using recombinant LH (rLH) + recombinant FSH (rFSH) for ovarian stimulation over hMG in regards to safety	C	III
EBR	Routine use of adjuvant metformin before and/or during ovarian stimulation is not recommended with the GnRH antagonist protocol for women with PCOS	A	II
CCR	Use of adjuvant growth hormone before and/or during ovarian stimulation is probably not recommended for poor responders	C	III
EBR	Use of testosterone or DHEAS before ovarian stimulation is probably not recommended for poor responders	C	III
CCR	Random-start ovarian stimulation is probably not recommended for the general IVF/ICSI population Should be reserved for ovulation Induction in cancer patients	C	-
Research point	Double stimulation in poor responders should only be used in the context of clinical research Can be considered for urgent fertility preservation cycles	Research point	-
CCR	All ovulation induction should be monitored by ultrasound The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended	D	-
CPP	The decision on timing of triggering in relation to follicle size is multi-factorial, taking into account the size of the growing follicle cohort, the hormonal data on the day of pursued trigger, duration of stimulation, patient burden, financial costs, experience of previous cycles, and organizational factors for the centre. Most often, final oocyte maturation is triggered at sizes of several of the leading follicles between 16–22 mm		-
CCR	A poor response to ovarian stimulation alone is not a reason to cancel a cycle	B	-
EBR	The use of recombinant hCG and urinary hCG is equally effective and either can be used for triggering final oocyte maturation during ovarian stimulation	A	II
EBR	hCG 5000 IU is preferred to 10,000 IU in an GnRH agonist cycle	C	III
EBR	A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS	B	I
CCR	It is not recommended to administer recombinant LH for triggering final oocyte maturation	B	-
EBR	The use of GnRH agonist for final oocyte maturation with conventional luteal support and fresh transfer is not recommended in the general IVF/ICSI population	A	II
CCP	If the GnRH agonist trigger with triptorelin is applied, dosages ranging of 0.1–0.4 mg can be chosen		-
EBR	The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for predicted normal responders	C	II
EBR	Progesterone is recommended for luteal phase support after IVF/ICSI	A	I
CPP	Starting of progesterone for luteal phase support should be in the window between the evening of the day of oocyte retrieval and day 3 post oocyte retrieval	-	-
EBR	The addition of oestradiol to progesterone for luteal phase support is probably not recommended.	C	III

Category	Recommendation	Grade of Recommendation	Quality of evidence
Research point	A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles can only be used in the context of a clinical trial.	Research only	-
CPP	A freeze-all strategy is recommended to eliminate the risk of late-onset OHSS and is applicable in both GnRH agonist and GnRH antagonist protocols.		-
EBR	If a GnRH agonist trigger with freeze-all strategy is not used in patients at risk of OHSS, should be followed by luteal phase support with LH-activity	C	IV
EBR	In women classified as WHO group III anovulatory infertility, egg donation is the only realistic treatment option. Along with this, they must be considered for long-term hormone replacement therapy to prevent the deleterious effects of hypoestrogenism on their bones.	C	IV

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Chapter 11: Polycystic Ovarian Syndrome and Infertility Management Recommendations

OVERVIEW This guideline offers recommendations on diagnosis, pharmacological, and surgical management of infertility associated with polycystic ovarian syndrome (PCOS). It also covers recommendations on counselling required for an infertile woman with anovulatory PCOS.

1. Introduction

- PCOS is a complex endocrine, metabolic, reproductive, and psychological system disorder affecting women of reproductive age group
 - The prevalence rate of PCOS in India is 3.7%–22.5%
 - Cardinal features of PCOS include:
 - » Chronic anovulation
 - » Androgen excess
 - » Polycystic ovarian morphology (PCOM)
- are present in varying combinations, the resultant phenotypes are also many and varying
- Based on the presence of anovulation, hyperandrogenemia, and PCOM, women with PCOS were divided into four phenotypes (as per Rotterdam criteria), Table 1
 - Clinical manifestations of PCOS
 - » Amenorrhea/oligomenorrhea (Table 2)
 - » Ovulatory dysfunction with Infertility (Table 2)
 - » Hirsutism
 - » Acne
 - » Alopecia
 - » Sub-fertility
 - » Early pregnancy loss

2. PCOS and infertility

Clinical–pathological basis of infertility

- Two out of the three criteria if present, qualify the patient as having PCOS. Since these symptoms

Table 1. Characters of PCOS phenotype

	Androgen levels	LH levels	Ovarian size	AMH levels	Body weight	Insulin resistance
PHENOTYPE A (Classic)	Increased	Increased	Increased	Increased	Increased	Increased
PHENOTYPE B (Classic, normal ovaries)	Increased	Moderately increased	Normal	Mild increase	Increased	Increased
PHENOTYPE C (Ovulatory)	Moderately increased	Normal	Moderately increased	Mild increase	Moderately increased	Moderately increased
PHENOTYPE D (Normo-androgenic)	Mild increase	Normal	Moderately increased	Normal	Normal	Normal

Table 2. Summary of recommendations for defining irregular cycles

Category	Recommendation	Grade
CCR	When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines <ul style="list-style-type: none"> • Normal in the first year post menarche as part of the pubertal transition • >1 to <3 years post menarche: <21 or >45 days • >3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year • >1 year post menarche >90 days for any one cycle • Primary amenorrhea by age 15 or >3 years post thelarche (breast development) 	A
CCR	In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors	A
CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche	—
CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured	—

PCOS: polycystic ovary syndrome.

- Metabolic aspects:

- » Obesity
- » Insulin resistance
- » Type 2 diabetes (10% by age 40s)
- » Cardiovascular disease

appearance may persist

- Androgen profile (Tables 4 and 5)
 - » Testosterone – Total and free <5.0 nmol/l
 - » FAI
 - » +/- 17OH-P, adrenal profile
 - » SHBG–surrogate for insulin resistance (16–119 nmol/l)

3. Investigations

- Ultrasound scan (Table 3)

- » Rotterdam diagnostic criteria: Polycystic ovary contains 12 or more follicles measuring 2–9 mm in diameter on day 2 or 3 of MC and/or increased ovarian volume (>10 ml) with no dominant follicle >10 mm or CL
- » Does not apply to women taking OCP, as ovarian size is reduced, even though the polycystic

- Follicle-stimulating hormone (FSH), luteinizing hormone (LH)
- Anti-Mullerian hormone (AMH): Evidence for assessment of AMH as a diagnostic modality is highlighted in Table 6
- Assessment glucose intolerance/insulin resistance and lipid profile
- Prolactin/Thyroid Function Test (TFTs)

Table 3. Recommendations for assessment of PCOS on ultrasound

Category	Recommendation	Grade
CCR	Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of <8 years (<8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage	A
CPP	Transabdominal ultrasound should primarily report ovarian volume with a threshold of >10 ml, given the difficulty of accurately assessing follicle number.	—
CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed	A
CPP	If using lower resolution USG transducers (frequency <8 MHz) the threshold for PCOM should be FNPO of ≥ 12 and/or ovarian volume of ≥ 10 ml.	—
CCR	Using endovaginal USG transducers with frequency bandwidth > 8 MHz the threshold for PCOM should be FNPO of ≥ 20 and/or an ovarian volume ≥ 10 ml on either ovary, ensuring no corpora lutea, cysts or dominant follicles are present	B
CPP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.	—
CPP	Clear protocols are recommended for reporting AFC per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include: <ul style="list-style-type: none"> • Last menstrual period • Transducer frequency • Approach/route assessed • Total follicle number per ovary measuring 2–9 mm • Three dimensions and volume of each ovary • Reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology • Other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles \geq equal 10 mm. 	—

FNPO: follicle number per ovary.

Table 4. Recommendations for clinical hyperandrogenism

Category	Recommendation	Grade	Quality
CCR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism, in adolescents, severe acne, and hirsutism.	A	—
CCR	Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.	A	—
CCR	Standardized visual scales are preferred when assessing hirsutism, such as the <u>modified Ferriman Gallwey score (mFG)</u> with a level ≥ 4 –6 indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common, and can limit clinical assessment.	A	—
CCR	The <u>Ludwig visual score</u> is preferred for assessing the degree and distribution of alopecia.	A	—
CPP	There are no universally accepted visual assessments for evaluating acne.	—	—
CPP	The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism, and the severity of hirsutism varies by ethnicity (In Indian women $>/=7$).	—	—
CPP	As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus hair is confused with terminal hair; only terminal hairs need to be considered in pathological hirsutism, with terminal hairs clinically growing >5mm in length if untreated, varying in shape, and texture and generally being pigmented.	—	—

Table 5. Recommendations for biochemical hyperandrogenism

Category	Recommendation	Grade	Quality
EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS	A	III
EBR	High quality assays such as liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS	B	III
EBR	Androstenedione and DHEAS could be considered if total or free testosterone are not elevated—provide limited additional information in the diagnosis of PCOS	B	III
CCR	Direct free testosterone assays, (radiometric or enzyme–linked assays) should not be used in assessment of biochemical hyperandrogenism in PCOS—demonstrate poor sensitivity, accuracy, and precision	A	—
CPP	Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone–binding globulin, and altered gonadotrophin–dependent androgen production		
CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non–hormonal alternative is needed during this time		
CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent		
CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotype healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages		
CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen–secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.		

Table 6. Assessment of AMH as diagnostic criteria

Category	Recommendation	Grade	Quality
EBR	Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.	B	III
CPP	There is emerging evidence that with improved standardization of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOM.	—	—

3.1 Other assessments for PCOS

Metabolic screening

- Clinical - Acanthosis nigricans and truncal obesity
- Fasting Lipids –1–3 yearly
- Screening for glucose tolerance in PCOS
- WHO criteria
 - » 2 hour 75 gm glucose tolerance test (OGTT)
- » Impaired glucose tolerance (IGT) 140–199 mg/dl
- » Diabetes mellitus (DM) ≥ 200 mg/dl
- ADA criteria
 - » Fasting glucose level
 - » IFG 100–125 mg/dl
 - » DM ≥ 126 mg/dl

- » Insulin levels not done due to assay variability (depending on age, gender, and feeding status) and inaccuracy (absence of validated assay)
- Recommendations for diagnosing impaired glucose tolerance and diabetes mellitus is shown in Table 7.
- Consensus for defining an Asian Indian for metabolic syndrome is highlighted in Table 8

Table 7. Recommendations–Impaired glucose tolerance and type 2 diabetes

Category	Recommendation	Grade
CCR	Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of GDM, IGT, and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by, obesity	A
CCR	Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors	A
CCR	An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. In high-risk women with PCOS (including a BMI >25kg/m ² or in Asians >23kg/m ² , history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended	A
CCR	A 75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia, and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at <20 weeks gestation, and all women with PCOS should be offered the test at 24–28 weeks gestation	A

Table 8. Consensus for definition of Asian Indian for metabolic syndrome

Definition	Abdominal obesity (cm)	Dysglycemia FBS mg/dl	Hypertension mm Hg	High Triglycerides mg/dl
International Diabetic Federation (IDF)	>80 Non-obligatory criteria	≥ 100	≥130/≥85	≥150
IDF	>80 Obligatory criteria	≥ 100	≥130/≥85	≥150
Modified national cholesterol education program, adult treatment plan III (NCEP, ATP III)	>88 Non-obligatory criteria	≥ 100	≥130/≥85	≥150

Diagnosis of PCOS is that of exclusion. One needs to exclude other causes of menstrual irregularity and hyperandrogenaemia. (Table 9)

Table 9. To diagnose PCOS exclude other disorders therefore PCOS is diagnosis of exclusion

Condition	Exclude by
Pregnancy	Beta human chorionic gonadotropin
Ovarian failure	Follicle-stimulating hormone
Hypothyroidism	Thyroid-stimulating hormone
Hyperprolactinemia	Prolactin
Congenital adrenal hyperplasia	17-OH progesterone
Ovarian tumor	Total testosterone (especially if >200 ng/dl)
Adrenal tumor	Dehydroepiandrosterone sulfate (especially if >800 mcg/dl)
Cushing's syndrome	Serum cortisol

4. Management of infertility

4.1 Strategies

- Preconceptional counselling
- Lifestyle modifications
- Pharmacological interventions
- Surgical management
- Assisted reproductive technologies

4.2 Pre-conceptional counselling

Clinical need/Rationale/Existing guidelines

- Quality of life may be compromised in women with PCOS as the symptoms are associated with anxiety, depression, low self-esteem, perception of loss of feminine identity, and sexual dysfunction and this may trigger social isolation
- Health care providers should be well aware of the physiological and emotional wellbeing of the woman with PCOS. Psychological co-morbidities require respectful consideration and assessment
- Prior to initiating therapy, explanation on the purpose, proper information regarding the treatment, implication, expected results should be provided for patients. Although this may increase the consultation time, but it may help in building trust and rapport with the patient and justifies their right of being informed
- Patient counselling prior to therapies should include:
 - » Identify and rectify risk factors (cease smoking and limit alcohol consumption)
 - » Offer education regarding the behavioral changes and chances of pregnancy
 - » Importance of multivitamins, vitamin D, folate, iron, and calcium
 - » Advice on healthy weight for obese women
 - » Encourage exercise in PCOS women; however, exercise interventions do not always require clinical centers, expensive gyms and fitness centers
 - » Ovarian hyperstimulation syndrome (OHSS), long term

- » Avoid pregnancy for 12–18 months after bariatric surgery

Recommendations

- Consider counselling prior to initiating therapies for PCOS women in order to identify and correct the long term risk factors associated with fertility (Grade A, EL 4)
- Provide pre-treatment counselling for PCOS women on weight reduction using lifestyle modification (Grade A, EL 4)
- During the course of therapy, emphasis the role of a husband and family in the emotional wellbeing of subfertile PCOS women (Grade B, EL4)
- Advise the patients on the duration of the procedure, types, side effects, success rate, and cost of treatment (Grade B, EL 4)

4.3 Lifestyle modifications

Clinical /Rationale/Existing guidelines

- Evidence defines obesity as a BMI ≥ 25 for Asian Indians (Reference)
 - » Additionally, obesity is strongly associated with PCOS and can occur in up to 50% of the patients
 - » Compared to thin women with PCOS, obese women with PCOS are more likely to experience anovulation
 - » There is an increased risk of the poor obstetric outcome, spontaneous abortion, preterm labor, maternal complications, thromboembolism, gestational diabetes mellitus, wound infection, and gestational hypertension in obese women
 - » Therefore awareness, monitoring, early intervention are vital and there is a need for health care professionals in helping obese women with empathy to control their weight

4.3.1 Treatment of obesity is multifaceted

4.3.1.1 Diet and exercise

- 7% weight loss is recommended

- Diet and exercise go hand in hand in achieving best outcomes in weight reduction
- Consider yoga and meditation as a holistic approach for treating the root cause of PCOS (obesity and stress)

4.3.1.2 Diet and exercise along with pharmacological ovulation-inducing agents

- Lifestyle management in comparison to clomiphene citrate alone or in combination with metformin showed a higher pregnancy rate

4.3.1.3 Pharmacological weight-reducing agents

- Both orlistat and sibutramine have displayed weight loss resulting in improvement in cardiovascular risk factors, hyperandrogenemia, and insulin resistance (IR)
- Do not consider these as first-line therapy in obese women with PCOS for reducing weight

Recommendations

- Consider lifestyle modification as a first-line treatment for reducing weight before attempting pharmacological methods of ovulation induction in subfertile women with PCOS. (Grade A, EL 1)
- Lifestyle modification should include
 - » Calorie restriction with any hypocaloric diet (reduced by 500 kcal/day)
 - » Moderate physical activity of 45–60 min/day
 - » Restriction of excessive caffeine intake, alcohol consumption, and smoking (Grade A, EL 2)
- Consider appropriate age-related decline in fertility when considering the duration of lifestyle management interventions (Grade B, EL 4)
- PCOS patients who are morbidly obese should avoid pharmacological methods of ovulation induction prior to weight reduction (Grade B, EL 4)
- Consider pharmacological preparations in morbidly obese patients under medical supervision in case of unsuccessful weight reduction with diet or exercise alone (Grade B, EL 1)

4.4 Ovulation Induction

4.4.1 Aromatase inhibitors

Recommendations

- Consider letrozole (2.5 mg/day for 10 days) as a first-line treatment for ovulation induction in women
 - » Who have PCOS with anovulatory and no other infertility factors
 - » Who has breast cancer and PCOS requiring oocyte cryopreservation
- Consider other ovulation induction agents in case letrozole is not available or its use is not permitted

4.4.2 Clomiphene citrate

Recommendations

- Consider clomiphene citrate as a first-line pharmacological agent in anovulatory PCOS women with subfertility at a starting dose of 50–100 mg/day starting from day 2 to day 5 of the menstrual cycle for 5 days. Clomiphene citrate (CC) recommended for ovulation induction is gradually increased by 50 mg/day at each cycle to a maximum of 150 mg/day for a maximum of six cycles (Grade A, EL 1)
- Consider ultrasound monitoring in infertile PCOS women who are on clomiphene citrate for ovulatory response and also to reduce the risk of multiple pregnancies. Monitoring of LH levels can be another alternative in case ultrasound monitoring is not available. (Grade B, EL3)

4.4.3 Addition of Insulin-sensitizing agent-metformin

Clomiphene and insulin

Recommendation

- Consider metformin in the following circumstances:
 - » In PCOS patients with impaired glucose intolerance
 - » In obese PCOS women co-administered with clomiphene citrate
 - » In clomiphene citrate resistant PCOS women
 - » In PCOS women who are at high risk of hyperstimulation

- Sustained release preparations are recommended for better compliance

4.4.4 Gonadotropins and GnRH analogs

Recommendations

- Offer gonadotropins as a second-line treatment for not more than three ovulatory cycles in PCOS women with CCR or who failed to conceive with no other subfertility factors (Grade A, EL 2)
- Advise patients on the need for strict monitoring of cycle, the risk of OHSS and multiple pregnancies, treatment cost, and cycle cancellation criteria prior to initiating gonadotropin therapy (Grade B, EL 4)
- Consider low-dose step-up protocol over step-down protocol when gonadotropins are indicated for reducing the chances of OHSS in PCOS patients with subfertility (Grade A, EL 2)
- Consider gonadotropin at an initial dose of 37.5–75.0 IU/day for 7–10 days depending on BMI and previous response. In the case of follicle ≥ 12 mm is not developed or ovulation is triggered with the development of follicle ≥ 18 mm in size, then consider small dose increments of 50% of the initial or previous dose. (Grade B, EL 4)
- Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse. (CPP)
- Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates. (Grade B, EL 2)
- Where gonadotrophins are prescribed, considerations include: (Grade B, EL 3)
 - » Cost and availability
 - » Expertise required for use in ovulation induction

- » Degree of intensive ultrasound monitoring required
- » Lack of difference in clinical efficacy of available GT preparations
- » Low dose gonadotrophin protocols optimise monofollicular development
- » Risk and implications of potential multiple pregnancy

4.5 Surgical management

4.5.1 Bariatric surgery

Recommendations

- Consider bariatric surgery in obese subfertile PCOS women who are unsuccessful in reducing weight by lifestyle management as a second-line option (Grade B, EL 4)
- Bariatric surgery is recommended as first-line therapy for weight reduction in PCOS patients with BMI >40 kg/m² (Grade B, EL 4)
- Advise to avoid conception after bariatric surgery for at least 12 months for PCOS women with subfertility as the effects of these interventions on the evolution of early pregnancy are not yet known (Grade B, EL 4)

4.5.2 Laparoscopic drilling

Recommendations

- Consider laparoscopic ovarian drilling as a second-line therapy over gonadotropin therapy in anovulatory PCOS women who have failed first-line oral ovulation induction therapy or who have CCR (clomiphene resistant) and hypersecretion of LH levels with no other subfertility factors. (Grade A, EL 1)
- LOD (laparoscopic ovarian drilling) should be considered in anovulatory PCOS women with CCR with no other subfertility factors, or who cannot access hospital facility for intensive monitoring, or required gonadotropin therapy or laparoscopic assessment of their pelvis (Grade C, EL4)
- The number of punctures should be limited to a maximum of 4–6 depending on the size of the ovary at wattage 40 (Grade B, EL 4)

- Where laparoscopic ovarian surgery is to be recommended, the following need to be considered:
 - » Comparative cost
 - » Expertise required for use in ovulation induction
 - » Intra-operative and post-operative risks are higher in women who are overweight and obese
 - » Are may be a small associated risk of lower ovarian reserve or loss of ovarian function
 - » Periadnexal adhesion formation may be an associated risk
- In non-fertility indications, severe male factors and in obstructive tubal disease, laparoscopic ovarian drilling (LOD) should not be considered

4.6 Assisted reproductive technology

4.6.1 Intrauterine insemination

Recommendations

- Consider IUI along with ovulation induction in anovulatory subfertile PCOS women with associated male factor subfertility
- Recommend IUI in anovulatory subfertile PCOS women with unsuccessful conception despite ovulation induction

4.6.2 In vitro fertilization

Recommendations

- IVF is considered as third line treatment options who have failed to conceive or who have other indications for IVF (Grade A, EL 2)
- Consider GnRH antagonist protocol over the GnRH agonist long protocol in anovulatory subfertile PCOS women undergoing IVF for reducing the incidence of severe OHSS at similar clinical pregnancy rates (Grade A, EL 2)
- Gonadotropin should be considered at an initial

dose of 75–225 IU/day for 7–10 days based on age and follicle size (Grade B, EL 4)

- GnRH agonist should be used for trigger. Either single dose of Triptorelin 0.3mg (Decapeptyl®) or 1 mg of leuprolide acetate or buserelin

4.6.3 In vitro maturation

Recommendation

- Consider IVM in units with sufficient expertise to achieve pregnancy and live birth rates in women with PCOS who are at standard IVF/ICSI treatment without the risk of OHSS, where an embryo is generated, vitrified, thawed, and transferred in a subsequent cycle

4.6.4 Luteal phase support

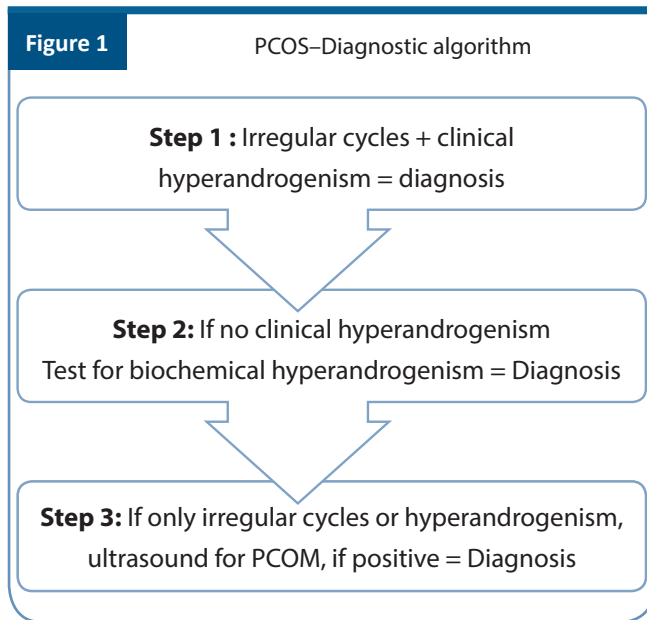
Recommendation

- Offer luteal phase with progesterone in subfertile PCOS women who are undergoing ovulation induction or assisted reproduction (Grade A, EL 1)
- HCG as LPS should be avoided

Table 10: Assessment of PCOS

Clinical assessment	Androgen profile	Exclude secondary causes
<ul style="list-style-type: none"> • Menstrual cycle • Progesterone if cycles regular • Ovarian morphology (absence of HA and Irregular cycles) • AMH not recommended • Androgen excess • Impaired glucose tolerance 	<ul style="list-style-type: none"> • Free testosterone • Free androgen index • SHBG 	<ul style="list-style-type: none"> • Clinical history and examination • Thyroid function test • Prolactin • FSH • 17-OH progesterone

AMH: anti-müllerian hormone, FSH: follicle-stimulating hormone; HA: hyper androgenism; SHBG: sex hormone binding globulin.



- PCOS is an insulin resistance (IR) syndrome, a gender-specific form of Metabolic Syndrome, hence also called “Syndrome X”
- There is ONE defect that is IR with consequent hyperinsulinemia
- There are TWO underlying hormonal factors: Hyperinsulinemia and hyperandrogenemia
- Its THREE key features are:
 1. Oligo –/ anovulation
 2. Hyperandrogenism
 3. PCO morphology
- There are FOUR possible phenotypes
- Assessment of PCOS is based on clinical assessment, androgen profile and by excluding secondary causes (Table 1)
- The diagnostic algorithm for PCOS is highlighted in Figure 1
- Life-style modifications should be advised before OI in obese PCOS women
- Dietary intervention and increased physical activity in overweight/obese improve IR and hyperandrogenism, menstrual function and fertility
- Aromatase Inhibitors is as effective as CC and should be used as first line drug

- CC still may be used for OI in women with AI resistance or failure
- Metformin alone is less effective than CC in inducing ovulation in women with PCOS
- Addition of metformin to CC may be indicated in specific sub-group of PCOS women
- GT in low dose protocols aiming at monofollicular development is an effective treatment option
- COS regimens offer an opportunity to correct abnormal systemic endocrine environment in vivo
- Safer to use low dose step-up protocol
- When the ovarian response has been previously documented, the threshold dose can be initiated from the start
- LOD is as effective as GT for OI and achievement of pregnancy but with significantly less multiples
- Management of anovulatory infertility in PCOS is depicted in Figure 2

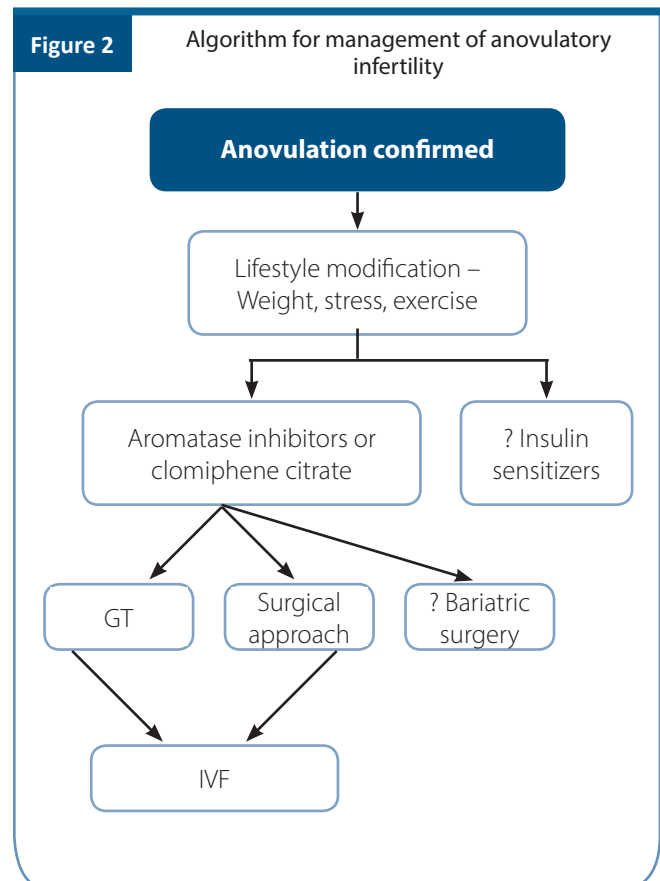


Figure 3

Summarizes the management of infertility in women with PCOS

1st line non-pharmacological management for infertility in PCOS



1st line pharmacological management



2nd line pharmacological/surgical management



3rd line management

1. Preconception counselling
2. Lifestyle modifications
3. Bariatric surgery

1. Pretreatment with COCPs
2. Letrozole
3. Clomiphene citrate

1. Gonadotropins
2. Laparoscopic surgery (LOD)

1. IUI
2. IVF

COCP: combined oral contraceptive pills; IUI: intrauterine insemination;
IVF: in vitro fertilization.

- iCOS with eSET should be order of the day to achieve optimal outcome after ART and Reduce complications
- Modifying conventional stimulation protocols according to patients' characteristics and ovarian reserve makes it patient-friendly and optimizes the chance of LBR
- Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents
- If metformin is being used for ovulation induction in women with PCOS who are obese ($\text{BMI} \geq 30\text{kg/m}^2$) with anovulatory infertility and no other infertility factors, CC could be added to improve ovulation, pregnancy and live birth rates
- Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF \pm ICSI therapy with a GnRH agonist protocol, to improve the clinical pregnancy rate, and reduce the risk of OHSS
- In a GnRH agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF \pm ICSI treatment, the following could be considered:
 - » metformin commencement at the start of GnRH agonist treatment
 - » metformin use at a dose of between 1000mg to 2550 mg daily
 - » metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)
 - » metformin side-effects
- In IVF \pm ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a GnRH antagonist protocol to reduce risk of OHSS
- No conclusions is drawn regarding other insulin-sensitizing drugs as no studies reported primary outcomes
- Vitamin D binds to vitamin D receptor and activates peroxisome proliferator activator receptor- δ (PPAR δ) which stimulates the expression of insulin receptor and enhances insulin-mediated glucose transport

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CCR	Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility. (Previous abdominal or pelvic sepsis, previous pelvic and/or abdominal surgery, cases of recurrent acute pelvic pain, history of sexual transmitted diseases or pelvic inflammatory disease, or endometriosis)	B	-
EBR	Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity, and insulin resistance	B	III
CPP	Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing assessment and monitoring is important during weight loss and maintenance in all women with PCOS	-	-
CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight	A	-
CPP	Pregnancy needs to be excluded prior to ovulation induction	-	-
EBR	Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates	A	III
CPP	Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals can use other ovulation induction agents	-	-
EBR	Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates	B	IV
EBR	Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents	B	II
EBR	Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI is ≥ 30 kg/m ²) with anovulatory infertility and no other infertility factors	B	III
EBR	If metformin is being used for ovulation induction in women with PCOS who are obese (BMI ≥ 30 kg/m ²) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates	B	III
EBR	Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate-resistant, with anovulatory infertility and no other infertility factors, to improve ovulation and pregnancy rates	B	III
CPP	The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered	-	-
EBR	Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors	B	III
EBR	Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy, and live birth rates	B	II
CPP	Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse	-	-

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Laparoscopic ovarian surgery could be second-line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors	B	III
CCR	In the absence of an absolute indication for IVF \pm intracytoplasmic sperm injection (ICSI), women with PCOS and anovulatory infertility could be offered IVF as third-line therapy where first or second line ovulation induction therapies have failed	B	-
CPP	Women with PCOS undergoing IVF \pm ICSI therapy need to be counselled prior to starting treatment including on: availability, cost and convenience increased risk of ovarian hyperstimulation syndrome options to reduce the risk of ovarian hyperstimulation	-	-
CPP	In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used multiple pregnancies can be minimised	-	-
CCR	Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF \pm ICSI, with insufficient evidence to recommend specific follicle stimulating hormone (FSH) preparations	B	
EBR	A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF \pm ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS)	B	III
CPP	Human chorionic gonadotrophins is best used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF \pm ICSI cycle to reduce the incidence of OHSS	-	-
CPP	Triggering final oocyte maturation with a gonadotropin-releasing hormone (GnRH) agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned	-	-
CPP	In IVF \pm ICSI cycles in women with PCOS, consideration needs to be given to an elective freeze of all embryos	-	-
EBR	Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF \pm ICSI therapy with a GnRH agonist protocol, to improve the clinical pregnancy rate, and reduce the risk of OHSS	B	III
CCR	In a GnRH agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF \pm ICSI treatment, the following could be considered: Metformin commencement at the start of GnRH agonist treatment metformin use at a dose of between 1000 mg to 2550 mg daily metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)	B	-
CCR	In units with sufficient expertise, IVM could be offered to achieve pregnancy and live birth rates approaching those of standard IVF \pm ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle	B	-
CCR	Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy	D	

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Chapter 12: Unexplained Infertility

OVERVIEW

This guideline offers recommendations on the identification criteria for detection of unexplained infertility. It also gives an overview of few diagnostic tests and management recommended for patients with unexplained infertility.

1. Definition of unexplained infertility

- A couple whose routine standard, basic investigations of infertility showed no abnormality can be labelled as having unexplained infertility (UI). Diagnostic terminology of UI is not used to describe presence of a medical condition, but a void or a negative. Negatives are however, practically impossible to prove

Diagnosis of UI was appropriate, as long as

- Ovulation is confirmed but even apparently normally ovulating women may produce poor quality oocytes and embryos
- Tubal patency has been proven but patent fallopian tubes do not necessarily function normally
- Semen analysis is normal but fertilization potentials of sperm still may be affected

So subtle abnormalities need to be identified before labelling the couple to be having unexplained infertility

Prevalence: 25%–30% of all infertility

Introduction

- Infertility is unexplained when the following criteria are met:
- Normal ovulatory function confirmed by basal body temperature measurement, cervical mucus changes, serum/urinary luteinizing hormone (LH) surge or mid-luteal progesterone levels, or evidence of follicular rupture during ultrasound
 - » Normal semen analysis, as per the WHO 2010 criteria
 - » Bilateral patent tubes

- The above criteria definition does not include the normal semen analysis, and therefore consider the following definition to identify patients
- Infertility in spite of normal ovarian function, tubes, uterus, cervix, and pelvis in female partner, with normal semen analysis and genitourinary anatomy in male partner with normal coitus and coital frequency
- Although, the above definition provides an idea to identify unexplained infertility, more evidences are required to resolve the queries regarding change in nomenclature of unexplained infertility to sub-fertility or adding women with minimal and mild endometriosis and men with subtle abnormal semen parameters and duration of infertility in the definition.
- Six common conditions when not diagnosed tend to be labeled as UI. These include:
 - » Mild endometriosis
 - » Subtle tubal pathology
 - » Premature ovarian ageing
 - » Age related infertility
 - » Immunological infertility
 - » Sperm dysfunction

2. Evaluation of a couple with unexplained infertility

- Consider performing a thorough, systematic and physical examination along with detailed review of history of both male and female partners
- Consider carrying out the following tests for the evaluation of unexplained infertility
 - » Tests of ovulatory function
 - Consider performing serial trans-vaginal ultrasonography (TVS), mid-luteal serum

progesterone estimation (>3 ng/ml) or use urinary luteinizing hormone (LH) kits

- Assess the antral follicle count (AFC) while performing the baseline transvaginal USG
- AMH to be done if AFC is less or if women is more than 35 years

2.1 Husband's semen analysis

- Consider assessment of sperm concentration, motility, morphology, and vitality of male partner as per WHO 2010 criteria
- Testing for DFI may provide a possible explanation for UI, therefore, it is reasonable to offer the same to these infertile couples as these couples may be better served by IVF or ICSI sooner rather than later (grade of evidence C)
- Sperm survival test – The number of spermatozoa recovered after swim-up and the percentage of spermatozoa that maintain their motility after 24 hours were both helpful in assessing fertility potential of the sperms

2.2 Tests to assess tubal patency (hysterosalpingography/laparoscopy/saline infusion sonography)

- Consider hysterosalpingography (HSG) as a first-line investigation for tubal patency evaluation when there is no of suspicion of pelvic pathology. It is traditional, less expensive and less invasive method
- When pelvic pathology is suspected from either history, pelvic examination or USG
- (e.g. endometriotic cyst, hydrosalpinx), diagnostic laparoscopy/hysteroscopy should be advised as first line investigation for evaluation of tubes and pelvis.
- Laparoscopy may prove beneficial in unexplained infertility as it evaluates fallopian tubes, ovaries, tubo-ovarian relationship, pelvic peritoneum, periovarian and peri-tubal adhesions and also in mild to minimal endometriosis

2.3 Detection of Ovulation

Documentation of ovulation can be done by

- Urinary LH kit - determines the LH surge and therefore time of ovulation
- Mid luteal progesterone levels - Values of > or = 10ng/ml are suggestive of normal progesterone production
- Trans vagina USG - Serial scan from day 9 for follicular grown and ovulation after an baseline scan on day 2 or 3
- BBT - Not used these days

3. Differential diagnosis of unexplained infertility : Six common conditions when not diagnosed tend to be labeled as UI

- Mild endometriosis
- Subtle tubal pathology
- Premature ovarian
- Age related infertility associated with change in fertilizability & implantation potential of oocytes and embryos, Increased risk of embryonic chromosomal abnormalities, and Spontaneous abortions–Assess AFC, AMH and FSH, PGT-A to rule out aneuploidy
- Immunological infertility – Most autoimmune disorders may be etiologically associated with infertility and so require evaluation. Testing of antiphospholipid, antinuclear, antithyroid, and antisperm antibodies may help.
- Sperm dysfunction – Despite normal count and motility there could be reduction in acrosome reaction, oocyte binding, and zona penetration or there could be ultrastructural abnormalities of head and neck

4. Management of unexplained infertility

- UI may be associated with subtle abnormalities or pathologies unidentified making management difficult and controversial. Selection of treatment

depends on the prediction models for occurrence of spontaneous pregnancy. Cut-off point between good and poor prognosis was 30% when women's age, duration of sub-fertility, type of sub-fertility, referral status, sperm motility, and post-coital status were taken into account. Those having a chance of conceiving spontaneously being $\geq 30\%$ (good prognosis) were offered expectant line of treatment where as those with a chance of conceiving spontaneously being $< 30\%$ (poor prognosis) should be offered IUI if female age was < 38 years, for three to six COH/ IUI cycles before IVF. If female age is ≥ 38 years, IVF was offered directly

4.1 Life style changes

- Counsel patients to maintain normal BMI ($18-25 \text{ kg/m}^2$) by conscious calorie intake and exercise, reduce caffeine intake, alcohol, smoking, and other illicit substances
- Advise couples to increase coital frequency (at least 2–3 times a week)

4.2 Expectant management

- Expectant management for 2 years is the best choice for good prognosis when the woman's age is less than 35 years with less than 2 years of infertility and normal ovarian reserve test. When expectant management is offered women needs to be aware of their ovulation time and the best period for unprotected intercourse
- Consider age factor for infertility treatment because as per published study, approx 60% couples with unexplained infertility of 3 years duration where woman's age is less than 25 years, chances of pregnancy is improved in first 3 years of expectant management. However, if woman's age is more than 31 years, chances of pregnancy reduce by 10% on each subsequent year

4.3 Ovulation induction y

- Clomiphene citrate and aromatase inhibitors does not offer any benefit over expectant management

and should not be offered to couples with UI (Level 1A)

- There is insufficient evidence to recommend gonadotropin-OS alone in the management of UI (Level III C)

4.4 Superovulation with intrauterine insemination

- Natural-cycle IUI does not offer any benefit over expectant management and should not be offered in UI (Level 1A)
- Either letrozole or clomiphene citrate (CC) can be used for IUI with oral agents (Level 1A)
- COS with IUI is the treatment of choice if there is no pregnancy with expectant management, no pregnancy with OI with CC/letrozole and TI, age is more than 30 years and less than 35 years
- Gonadotropin/IUI can be offered to couples with UI (Level IB)
- Patients should be aware that gonadotropin/IUI is associated with a higher pregnancy rate per cycle and a higher multiple pregnancy rate per cycle than IUI with oral agents (Level IA)

4.5 Assisted reproductive technology (ART)– In vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI)

- ART may be offered as first-line treatment if women's age is more than 35 years or when ovarian reserve is poor or infertility > 4 years
- Serves as a diagnostic method for assessing egg quality and embryogenesis and split IVF and ICSI for those with no male factor
- IVF should be offered to couples with UI after three cycles of ovarian stimulation/IUI have failed (Level 1A)
- Consider options of study of embryo morpho-kinetics through time lapse technology and pre-implantation genetic testing for aneuploidies for selection of good embryo(s) for transfer wherever possible

5. Laboratory management

Evaluation and selection of sperm

- Advanced sperm selection techniques are not recommended as routine. These need larger trials before being incorporated in routine clinical practice
- Oocyte quality
 - Evaluate oocyte quality to minimize fertilization failure
- Abnormal cleavage/development/embryo quality
- Options of study of morphokinetics through time lapse technology and PGTA may be given to patients for selection of good embryo(s) for transfer where ever possible
- Consider pre-implantation genetic testing for evaluation of oocyte quality

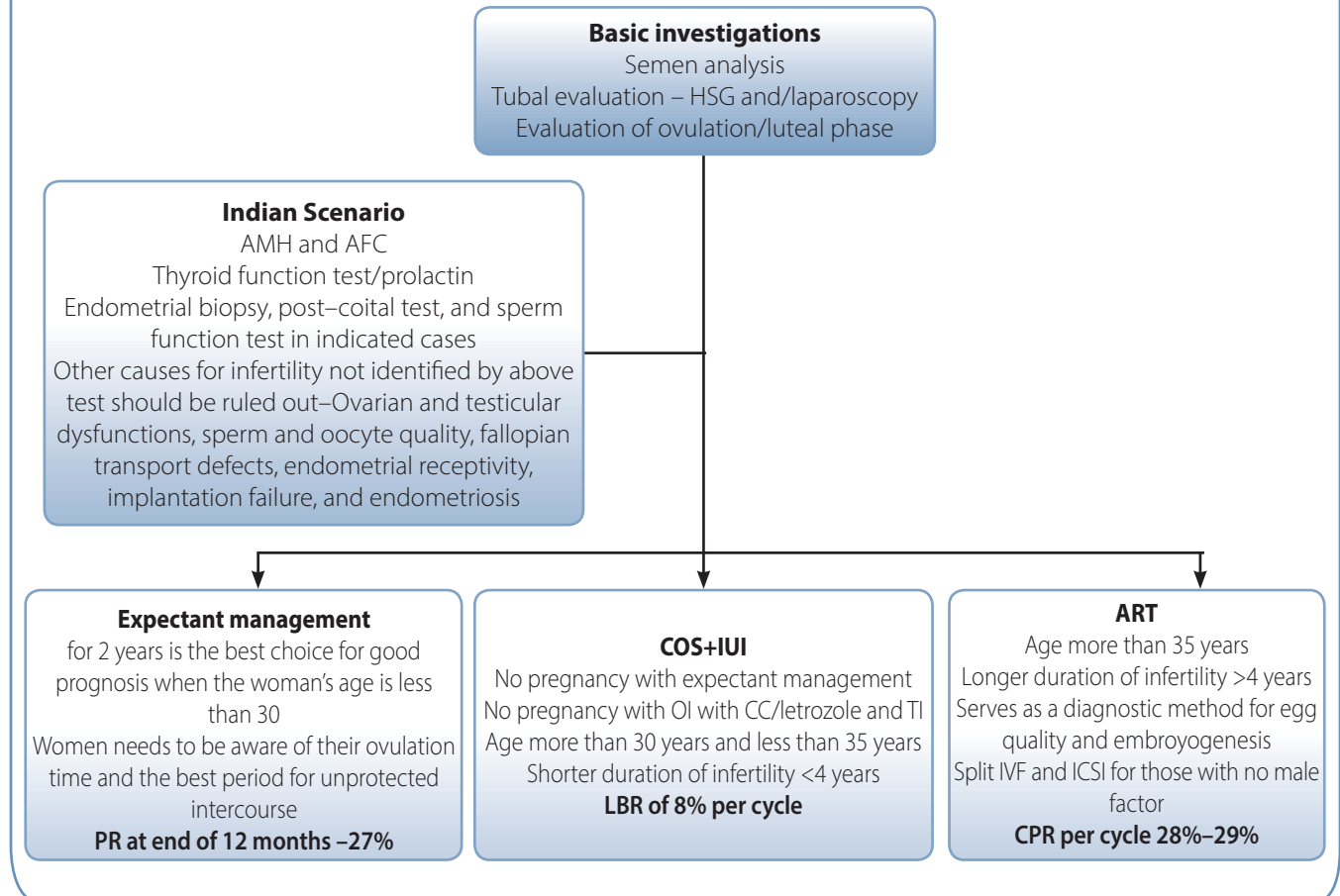
Summary

- Perform a thorough and systematic history and physical examination of both female and male partner
- Better effort should be undertaken to develop reliable tools to diagnose, often undiagnosed conditions of endometriosis, tubal disease, premature ovarian ageing, and immunological infertility, which are often misdiagnosed for UI
- A range of treatment options is available for unexplained infertility; however, the right treatment strategy needs to be customized according to the individual situation. Factors like the age of the female partner, duration of infertility, and previous pregnancies should be considered in choosing the optimal treatment protocol
- Use serial transvaginal USG, mid-luteal serum progesterone estimation (>3 ng/ml) or by urinary LH kits for tests of ovulation
- Consider estimation of ovarian reserve based on female's age, AFC, and AMH, which may help in avoiding inadvertent delay in definitive treatment
- Consider performing diagnostic laparoscopy/hysteroscopy assessment as first-line investigation if there is suspicion of pelvic pathology
- Sperm survival and DFI testing may provide some clue to sperm dysfunction
- Expectant management may be offered for a woman <30 year of age and normal ovarian reserve with duration of infertility being less than 3 years.
- Perform controlled ovarian stimulation (with clomiphene/letrozole/gonadotropins) along with IUI for 3–4 cycles when expectant management has failed or as first line in case of >30 year old lady, poor ovarian reserve or longer duration of infertility (>3 years)
- Consider IVF/ICSI if IUIs have failed
- Perform split IVF/ICSI of sibling oocytes to prevent total fertilization failure in first cycle itself as current evidence about universal application of ICSI for unexplained infertility except in cases of previous history of total fertilization failure yields conflicting results
- Use sperm DNA fragmentation testing to customize treatment
- Do not completely rely on the use of advanced sperm selection techniques for routine assessments; these need larger trials before being incorporated in routine clinical practice
- Consider options of study of embryo morphokinetics through time lapse technology and PGT A for selection of good embryo(s) OR for transfer wherever possible

Summary of management of unexplained Infertility (Figure 1)

Figure 1

Summary of management of unexplained Infertility



Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Perform a thorough and systematic history and physical examination of both female and male partner	B	II
EBR	Better effort should be undertaken to develop reliable tools to diagnose, often undiagnosed conditions of endometriosis, tubal disease, premature ovarian ageing, and immunological infertility, which are often misdiagnosed for UI	B	III
EBR	A range of treatment options is available for unexplained infertility; however, the right treatment strategy needs to be customized according to the individual situation. Factors like the age of the female partner, duration of infertility, and previous pregnancies should be considered in choosing the optimal treatment protocol	A	I
EBR	Use serial transvaginal USG, mid-luteal serum progesterone estimation (>3 ng/ml) or by urinary LH kits for tests of ovulation	B	III
EBR	Consider estimation of ovarian reserve based on female's age, AFC and AMH which may help in avoiding inadvertent delay in definitive treatment	B	II
EBR	In the absence of evidence for tubal or other pelvic pathology, laparoscopy is not warranted in UI	B	II
EBR	Consider performing diagnostic laparoscopy/hysteroscopy assessment as first-line investigation if there is suspicion of pelvic pathology	A	II
EBR	Sperm survival and DFI testing may provide some clue to sperm dysfunction	D	IV
EBR	Expectant management may be offered for a women <30 year of age and normal ovarian reserve with duration of infertility being less than 3 years	A	I
EBR	Natural-cycle UI does not offer any benefit over expectant management and should not be offered in UEI	A	I
EBR	Clomiphene citrate or letrozole alone does not offer any benefit over expectant management and should not be offered to couples with UI	A	I
EBR	Perform controlled ovarian stimulation (with clomiphene/letrozole/gonadotropins) along with IUI for 3–4 cycles when expectant management has failed or as first line in case of >30 year old lady, poor ovarian reserve or longer duration of infertility (>3 years)	A	I
EBR	Patients should be aware that gonadotropin/IUI is associated with a higher pregnancy rate per cycle and a higher multiple pregnancy rate per cycle than IUI with oral agents	A	I
EBR	Consider IVF/ICSI if IUIs have failed	A	I
EBR	IVF can be offered as an effective first-line treatment in unexplained infertility	B	I
EBR	There is insufficient evidence to recommend the routine addition of ICSI in couples with UEI undergoing IVF to increase the live birth rate, although the addition of ICSI in IVF for UEI may reduce the incidence of TFF	B	I
CCR	Perform split IVF/ICSI of sibling oocytes to prevent total fertilization failure in first cycle itself as current evidence about universal application of ICSI for unexplained infertility except in cases of previous history of total fertilization failure yields conflicting results	C	-
EBR	Use sperm DNA fragmentation testing to customize treatment	C	IV
EBR	Do not completely rely on the use of advanced sperm selection techniques for routine assessments; these need larger trials before being incorporated in routine clinical practice	C	III
EBR	Consider options of study of embryo morpho-kinetics through time lapse technology and PGT A for selection of good embryo(s) OR for transfer wherever possible	C	IV

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Chapter 13: Intrauterine Insemination

OVERVIEW

Intrauterine insemination (IUI) is an office procedure in which prepared semen sample with motile spermatozoa is placed directly into a woman's uterus to produce pregnancy, with or without ovarian stimulation to produce multiple oocytes. This guideline offers recommendations on the rationale, indications for IUI, required pretreatment workup for female and male factors, contraindications for IUI, details regarding ovarian stimulation in IUI, and luteal phase support during IUI.

1. Introduction

- Intrauterine insemination (IUI), with or without ovarian stimulation, is an indispensable part of infertility treatment because it is a noninvasive, cost effective and often successful treatment

2. Rationale

- Deposition of a concentrated pellet of motile and mature sperms into the uterine cavity close to the tubal ostia, around the time of ovulation
- Increases the density of sperm near the site of fertilization which increases the likelihood of pregnancy

3. Indications

- IUI with partner's sperm can be used as a potentially effective treatment for infertility of all causes in women under about age 40 except in women with tubal blockage, severe tubal damage, very poor egg quality, premature ovarian insufficiency, and severe male factor infertility
- IUI with or without ovarian stimulation is considered to be indicated for a broad range of diagnostic conditions

3.1 IUI with husbands semen

- Indications for IUI with husbands semen are highlighted in Table 1

Table 1. IUI with husband semen

Consider female factors such as
<ul style="list-style-type: none">• Minimal or mild endometriosis• Sexual dysfunction (vaginismus)• Cervical hostility/factor• Ovulatory dysfunction ?• Unexplained Infertility (in stimulated cycles) (Grade of evidence A)• Anatomic defects of vagina or cervix
Consider male factors such as
<ul style="list-style-type: none">• Anatomic defect of penis, e.g. hypospadias• Sexual or ejaculatory dysfunction• Erectile dysfunction/impotence• Mild to moderate male factor (Total motile sperm count (TMSC) of 3–10 million) (Grade of evidence A)• Immunological factors• HIV/HBsAg/HCV discordant couples• Cryopreservation of sperm in cases of cancer treatment
Others
<ul style="list-style-type: none">• Unexplained infertility

3.2 IUI with donor semen

- Azoospermia
- Genetic conditions (e.g. haemophilia, Huntington's chorea)
- Severe male factor (cannot afford assisted reproduction(ART))
- Severe Rh incompatibility

4. Factors that will guide the choice of IUI as treatment modality

- Semen Parameters (TMC >5 million/ml)

- Other Factors which affect the chance to pregnancy
 - » Presence or absence of cervical factor
 - » Endometriosis
 - » Tubal pathology
 - » Uterine pathology – Congenital anomalies, polyp, sub-mucous myoma, IUA
 - » Pelvic factor – History of previous pelvic or abdominal surgeries
 - » Age of the women – above 37 years one should consider IVF early in the treatment protocol
- Special situations

5. Contraindications

IUI is contraindicated in women with:

- Cervical atresia
- Acute cervicitis/vaginitis
- Pelvic inflammatory disease
- Severe endometriosis
- Bilateral tubal obstruction

IUI is contraindicated in men with:

- Severe male factor infertility
- Heritable genetic disorders

6. Pre-treatment workup

- Accurate detection of underlying reproductive abnormalities helps to guide individual management decisions and maximize treatment outcomes

6.1 Workup for female partner (Figure 1)

6.1.1 Baseline transvaginal sonography

- For evaluation of the uterus, uterine cavity, endometrium, and adnexa
- Measurement of antral follicle count (AFC) for ovarian reserve
- Doppler in presence of any uterine and adnexal pathology

6.1.2 Hysterosalpingography (HSG)

- Has low sensitivity but its high specificity thus, makes it a useful screening test for ruling out tubal obstruction

6.1.3 Laparoscopy

- It is not cost effective to do diagnostic laparoscopy as part of the initial infertility evaluation when history, physical examination, TVS, HSG, and mid-luteal progesterone are all normal and should be done only if patient fails to conceive after 6 ovulatory cycles (Grade B). Laparoscopy has positive predictive value of 98.4 %
- Laparoscopy is considered early if
 - » Age >35 yrs
 - » Married > 3 yrs
 - » Presence of an abnormal HSG
 - » History or symptoms suggestive of pelvic disease
 - » Presence of dyspareunia and dysmenorrhea
 - » History of previous pelvic surgery

6.1.4 Ultrasound for assessment of tubal factor

- Assessment of tubal factor by USG can be done either by saline infusion sonosalpingography (SIS) or hysterosalpingo-contrast sonography (HyCoSy). Both have a good sensitivity and specificity but HyCoSy is more efficient than SIS in detecting tubal obstruction (Grade A) and has a better predictive value as compared to SIS. Results of SIS correlated positively with laparoscopy in 97% and with HSG in 94%

6.1.5 Hysteroscopy

- Hysteroscopy is indicated as initial workup of infertility before IUI only in presence of
 - » Abnormal HSG/USG
 - » Unexplained infertility to detect any subtle endometrial abnormalities?

- » history or symptoms suggestive of endometrial or uterine pathology

6.1.6 Endocrine parameters

- Offer analysis of endocrine parameters such as:
 - » Thyroid stimulating hormone (TSH)
 - » Antithyroid antibody
 - » Prolactin
 - » Anti-müllerian hormone (AMH) if AFC < 5
 - » Follicle stimulating hormone/luteinizing hormone (FSH/LH) on day 2–3 of menstrual cycle if indicated
 - » Androgen profile – DHEAS, ASD, testosterone (total and free) and 17-OH progesterone in presence of signs of hyperandrogenemia, and PCOM at USG

6.1.7 Assessment of pelvic TB required when

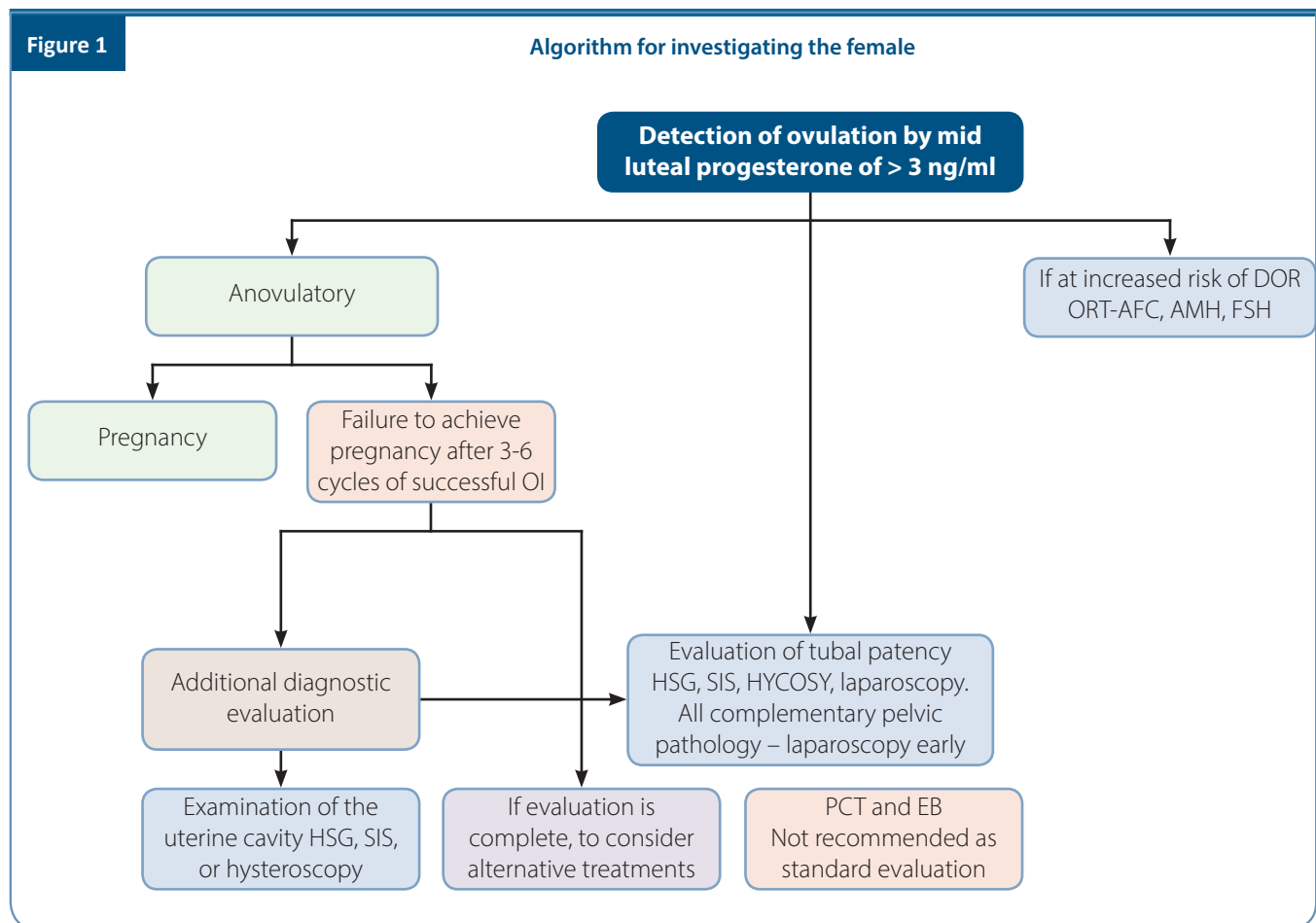
- Previous history of extragenital tuberculosis
- Persistent thin endometrium despite good follicular cycles and E2 levels
- USG suggestive of IU adhesions
- HSG suggestive of IU adhesions or tubal pathology
- Hysteroscopy suggestive of endometritis

6.1.8 Others

- Offer workup for:
 - » Hemoglobin
 - » Blood sugar
 - » OGTT if PCOS
 - » Lipid profile if PCOS
 - » Rubella screening

Figure 1

Algorithm for investigating the female



DOR: diminished ovarian reserve; FSH: follicle stimulating hormone; HSG: hysterosalpingography; OI: ovulation induction; OR-AFC: ovarian reserve-antral follicle count; PCT: post-coital testing; SIS: saline infusion sonohysterography.

- » Thalassemia screening
- » Pap smear
- » Viral markers
- » Serum chlamydial antibodies

6.2 Workup for the male partner

6.2.1 Semen analysis

- Consider the following for semen analysis:
 - » Total motile sperm count (prewash): >5–10 million
 - » Inseminating motile count (IMC) >1 million
 - » Sperm morphology using strict criteria >4%
 - » Total motility >30%

6.2.2 Viral markers

- Couples and individuals undergoing IUI and males providing semen samples for IUI should be screened for infectious agents based on local, regional, and national standards and regulations. (Grade of evidence D)

7. Counselling

- Consider counselling of the couples before the procedure begins regarding the indication of IUI, timing and number of visits required, cost involved, chances of success, what is sperm preparation, technique of insemination and complications
- Offer reassurance to the couple about confidentiality and consent form by ICMR should be signed by both the partners

8. Ovarian stimulation in IUI

- Consider using the following stimulating agents in IUI cycle
 1. Oral ovulation induction agents: Clomiphene citrate/letrozole
 2. Gonadotropins
 3. Clomiphene citrate/letrozole+ gonadotropins
 4. Gonadotropin releasing hormone (GnRH) agonists and antagonists with gonadotropins

8.1 Oral ovulation induction agents

8.1.1 Clomiphene citrate (CC)

- Clomiphene is a selective estrogen receptor modulator (SERM) that binds to the estrogen receptors at multiple sites throughout the reproductive tract, and can act as an estrogen agonist or as an antagonist
- Clomiphene binds to estrogen receptors in the hypothalamus, inhibiting negative feedback of estrogen on gonadotropin release
- Subsequent up-regulation of the hypothalamic–pituitary–gonadal axis leads to growth of the ovarian follicle(s)
- Consider the dose of 50–100 mg per day for five days up to a maximum of 150 mg per day, which can begin from day 2–5 of a normal period or a withdrawal bleed

8.1.2 Aromatase inhibitors

- Aromatase inhibitors suppress estrogen production but do not have the anti-estrogenic effect of clomiphene citrate in the late follicular phase and they may have fewer side effects than clomiphene
- Letrozole is the most commonly used aromatase inhibitor for ovulation induction
- Consider the dose of 2.5 mg/day orally from day 2–3 of the cycle for 5 days
- No significant difference in pregnancy rates between anti-estrogens with aromatase inhibitors, in non-PCOS women undergoing IUI

8.1.3 Gonadotropins

- They stimulate follicular growth by acting directly on ovarian FSH receptors and have no anti-estrogenic effect on cervical mucus or endometrium such as clomiphene
- Consider low dose regimens with 75 IU or lower because higher doses have similar pregnancy rates but increase the multiple pregnancy rates and risk of ovarian hyperstimulation (OHSS)
- COS using gonadotrophins might be the most effective drug for IUI cycles

8.1.4 Clomiphene citrate/letrozole plus gonadotropins

- Combination protocols reduce the cost of treatment and equally effective, with potentially fewer multiple births than with gonadotropins alone
- Consider a sequential use of clomiphene citrate or Letrozole with gonadotropin. CC 50–100 mg/letrozole 2.5 mg from day 3 to day 7 followed by gonadotropins daily from day 8 till the size of the dominant follicle became 18 mm

8.1.5 Gonadotropin releasing hormone (GnRH) agonists and antagonists

- Premature LH surges also occur in 25%–30% of stimulated IUI cycles
- Antagonist or agonist use in IUI cycles did not show any significant increase in pregnancy rates and are not cost effective to use in all IUI cycles

8.2 Ideal ovarian stimulation for IUI

- Clomiphene citrate/letrozole is considered to be the most cost effective, especially considering the cost of monitoring, and risk of ovarian hyperstimulation syndrome

No. of follicles recruited	2 – 4 follicles 18–20 mm
Endometrial thickness	≥9 mm thick and trilaminar
Day of IUI	IUI between cycle Day 13–16

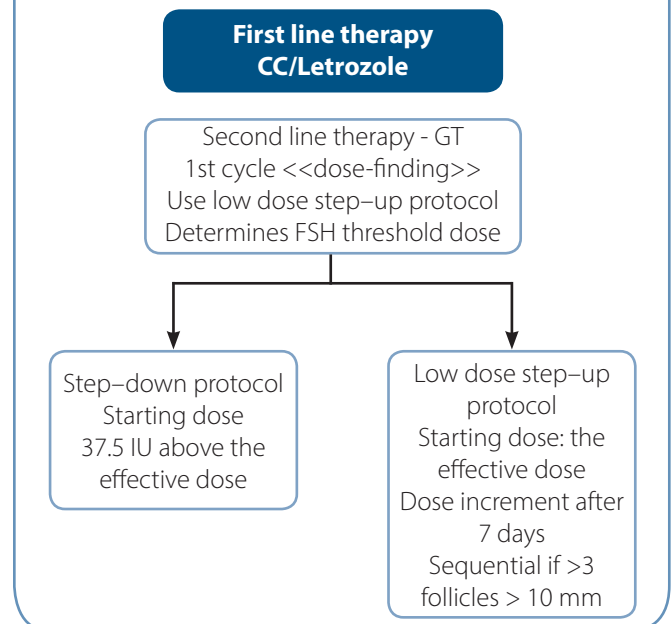
9. Consensus on OI in IUI (Figure 2)

- Anti-estrogens appear to be cost effective in IUI programs, although less effective compared to GT. (Grade of evidence B)
- Both letrozole and CC have similar results
- When GT used – given on daily basis
- Low dose protocols do not differ significantly in success, when compared to high dose, which, increase risk of multiples and OHSS
- In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates. (Grade of evidence B)

- When gonadotrophins are used in IUI, regiments with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates. (Grade of evidence A)
- No difference in the probability of conception whether one uses urinary or Rec GT
- Addition of GnRH agonist to gonadotrophins in IUI–OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates, OHSS and increased costs. (Grade of evidence B)
- Role of GnRH–antagonists in mild COS/IUI programs needs to be determined (GPP)

Figure 2

Summary of OI in IUI cycles



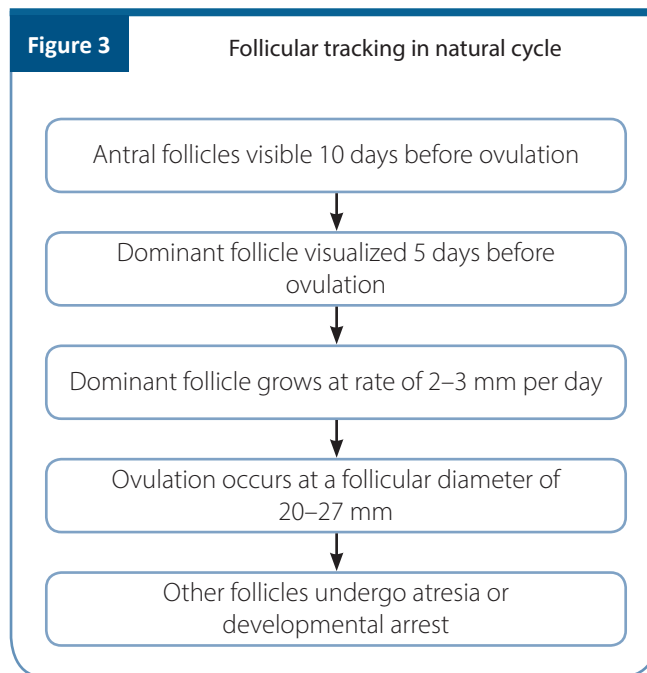
10. Monitoring in IUI cycle

- Different methods like luteinizing hormone (LH kits, serum estradiol levels, and ultrasonography (USG) to time IUI has been used
- Ultrasonography and LH kits are the most economical form of monitoring
- If ultrasonography is used for monitoring size of follicle, endometrial thickness should also be recorded

- Normal Follicular growth correlates with E2 measurements and a mature follicle secretes 250 – 300 pg/ml of E2. Follicular size more accurate than E2 in predicting ovulation

10.1 Monitoring in natural cycle (Figure 3)

- Natural cycles with IUI require least amount of monitoring. LH predictor kits are used to determine LH surge and ovulation and the IUI is timed accordingly
- Alternatively, transvaginal ultrasound can be used between cycle days 10 – 14 to determine development of mature follicle with administration of HCG for trigger at follicular diameter of 18–20 mm followed by IUI between 24 – 42 hours



10.2 Monitoring in stimulated cycle (Figure 4)

- Perform an ultrasound on cycle days 2/3 in order to confirm that no ovarian cysts are present prior to starting the ovarian stimulating agents
- Perform serial ultrasound scans from day 8 (gonadotropin stimulating cycle) or day 10 (oral ovulation induction drug cycle) till the day of trigger

Figure 4A

Follicular tracking in Stimulated cycle

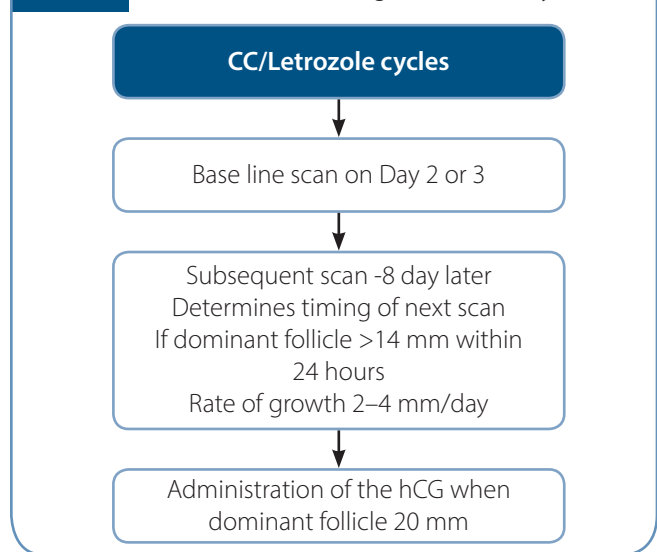
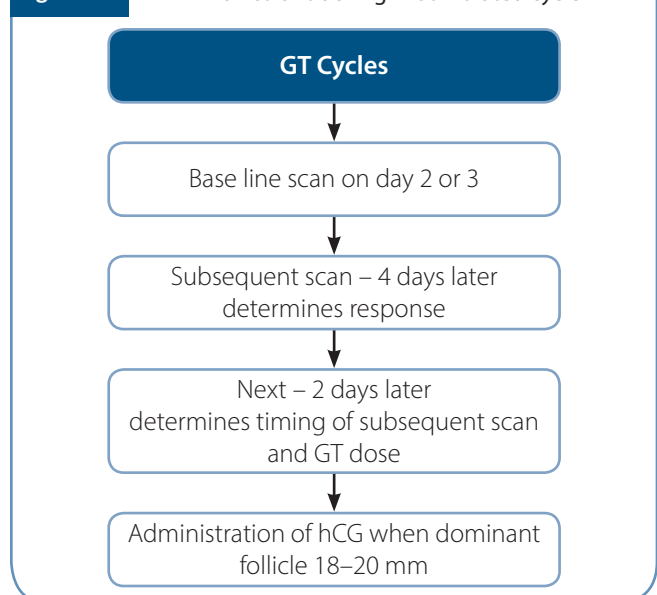


Figure 4B

Follicular tracking in Stimulated cycle



11. When to cancel IUI cycle or convert to IVF

- Consider cancelling the IUI cycle or converting to IVF in the following situations:
 - » In order to prevent high rates of multiple gestation pregnancies in IUI–OS, IUI should be withheld when more than three dominant follicles

>15 mm on the day of HCG injection or LH surge are present. (Grade of evidence B)

» Estradiol \geq 1500 pg/ml

12. Trigger and timing of IUI

- Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method while comparing hCG and natural LH surge (Grade of evidence B)
- Human chorionic gonadotropin (hCG) 5000–10,000/ recombinant human chorionic gonadotropin (rec-hCG) –250 mcg SC is used as trigger in stimulated cycle. No evidence to repeat the trigger in case of non-rupture of follicle.
 - » Trigger should be given when dominant follicle (DF) is 20–22 mm in a clomiphene citrate/letrozole cycles and 18 mm for gonadotropin cycle
- IUI should be performed 24 to 40 hours after administration of hCG trigger. (Grade of evidence B)
- Perform IUI 1 day after detection of spontaneous LH surge in natural cycle or after confirmation of ovulation. (Grade of evidence B)

13. Efficacy of IUI varies widely because of different variables related to:

- Use of technique
- Environment in laboratory
- Equipment's
- IUI catheters
- Consumables

13.1 Semen collection

- Semen collection should be done according to standard recommended procedure

13.2 Semen preparation techniques that are routinely used worldwide are as follows

- A simple dilution and washing technique

- Swim-up technique
- Density gradient centrifugation

13.3 Choice of technique will depend on

- Count
- Motility
- Morphology and TZI index
- Source of sample
- Debris & other cellular contamination
 - » Sperm concentration >15 million/ml with good forward progressive motility, swim-up performed
 - » Borderline samples, and samples with large amount of debris, extreme oligozoospermia, severely compromised motility best prepared by gradient separation
 - » Samples collected by electroejaculation – low motile sperm concentration best suited for gradient separation
- According to the available evidence, it is not possible to recommend any semen preparation technique over another for a normal semen samples (swim-up, gradient, wash and centrifugation). (Grade of evidence C)

13.4 Environment in laboratory

- Sperm preparation requires a clean room with air conditioning with no free access to toxic fumes and has sufficient space to accommodate necessary equipment's

Equipment's and consumables of highest quality and reliability should be used

- Maintenance of equipment's and optimal working environment in the lab is required for good IUI results. Special care should be taken to maintain the temperature at 37°C
- Damage to the sperm from following factors must be minimized
 - » Dilution – performed slowly
 - » Temperature change – should be gradual
 - » Centrifugation – Centrifugal forces should be low

- » Limit oxidative damage caused by free oxygen radicals released from leucocytes or abnormal sperms
- » Exposure to potentially toxic material

14. IUI procedure

- Special dedicated room for the IUI procedure – with sterilized instruments which would give adequate exposure of cervix for insemination is needed. The factors that affect the IUI success rate are seen the table below

Table 2. The factors that affect the IUI success rate

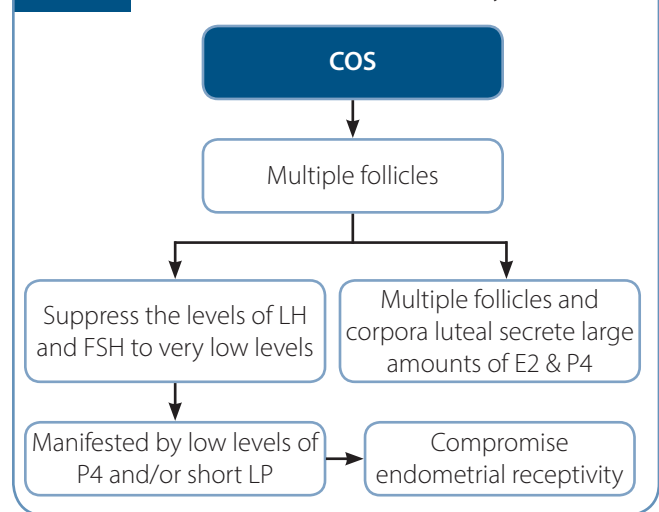
Type of catheter (soft/firm)	<ul style="list-style-type: none"> • Open ended/rounded tip teflon catheters least traumatic and most efficient • No significant difference in PR with type of catheter • Gentle, atraumatic technique with no touch to fundus is the essence of successful IUI
Volume of insemination	0.3–0.5 ml
Insemination	Immediately after the sample is ready and loaded in the syringe
Ultrasound guided	<ul style="list-style-type: none"> • No difference in cumulative pregnancy rates • Ultrasound guided helpful in cases of difficult IUIs
Single or double insemination	<ul style="list-style-type: none"> • Single well timed IUI recommended. (Grade of evidence B) • Double IUI in cases of male factor infertility may be performed but insufficient evidence. (Grade of evidence B)
Bed rest after IUI	<ul style="list-style-type: none"> • A 10–15 minutes bed rest after IUI has a positive effect on CPR. (Grade of evidence B)
Number of treatment IUI cycle	<ul style="list-style-type: none"> • Perform at least three consecutive IUI cycles in couples with an indication for IUI. (Grade of evidence B) • There is insufficient evidence to recommend a maximum number of IUI treatment cycles. (Grade of Evidence B) • Maximum PRs are seen in the first 4 IUI cycles

15. Luteal phase support after IUI

- Required definitely with use of gonadotrophins and GnRH analogs - Agonist and Antagonist (Figure 5)

Figure 5

Rationale for LPS in GT cycles



- Insufficient evidence to recommend use of LPS in natural or clomiphene/letrozole stimulated IUI cycle
- Start from next day of IUI or after ovulation is confirmed on ultrasound
- Offer for 2 weeks, if pregnant; continue till 8–10 weeks of gestation

16. IUI outcome

The IUI outcome can be linked to female factor and semen parameter's

16. 1 Female factor

- Age of women
- Ovarian reserve – Poor outcome with decreased ovarian reserve
- Duration of infertility – Pregnancy rates decrease if duration. More than 4 years
- Cause of infertility – best results in unexplained and mild male factor infertility and least with endometriosis

16.2 Semen parameters

- It is not possible to define clear lower cut-off levels of pre–or post–wash sperm parameters below which IUI should be withheld. (Grade of evidence B–C)
- High motile count before preparation (>15 million/ml)
- High Inseminating Motile Count (IMC) ≥ 5 million/ml
 - » CPR per couple TMS count
 - » 28.5% < 5 million
 - » 44.3% > 5 million
- 24 hour survival of processed sperm - > or = 70%
- Better Sperm morphology (>4%) in unprocessed and processed sample
- CPR per couple decreased from 40.7% to 21.4%, percentage of teratospermia was higher
- TZI <1.85
- HOS >60 %
- DFI <15 %

Summary of recommendations

- IUI is a simple and non–invasive technique it can be performed without expensive infrastructure with a reasonable success rate within three or four cycles
- IUI is safe and easy treatment with minimal risks and monitoring with good couple compliancy (low drop–out rate) and a very low risk for complications such as OHSS
- IUI is most cost–effective strategy especially in couples with mild male factor and unexplained infertility
- In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%)
- IUI could be postponed for at least 6 months (Grade of evidence A)
- In couples with unexplained infertility and men with a total motile sperm count (TMSC) >10 million and a prognosis of spontaneous pregnancy <30% within a year, it is recommended that IUI plus ovarian stimulation (OS) is the treatment of first choice. (Grade of evidence A)
- In couples with solely a poor sperm quality in the male partner, it is not recommended either for or against use of IUI. (Grade of evidence A)
- In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates. (Grade of evidence B)
- It is not possible to define clear lower cut–off levels of pre–or post–wash sperm parameters below, which IUI should be withheld. (Grade of evidence B–C)
- Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method. (Grade of evidence B)
- Providers can determine the method of timing IUI in natural cycles (no OS) as there is no evidence to recommend for or against a method. (Grade of evidence B)
- If a HCG injection is used, single IUI can be performed any time between 24 and 40 hours after HCG injection without compromising pregnancy rates. (Grade of evidence B)
- IUI in a natural (not ovarian stimulated) cycle should be performed 1 day after LH rise. (Grade of evidence B)
- The intervention FSP, when compared to IUI, should not be the treatment of choice. (Grade of evidence A)
- In both unexplained and male infertility there is insufficient evidence that the intervention, a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI within a cycle. (Grade of evidence B)
- Women undergoing IUI should be offered a single insemination per cycle. (Grade of evidence B)
- Women undergoing IUI, should have 10 to 15 minutes of bed rest after an insemination. (Grade of evidence B)

- In couples with an indication for IUI at least three consecutive IUI cycles should be performed. (Grade of evidence B)
- There is insufficient evidence to recommend a maximum number of IUI treatment cycles. (Grade of evidence B)
- According to the available evidence, it is not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation). (Grade of evidence C)
- In couples with unexplained infertility and men with a TMSC of >10 million and a prognosis of a pregnancy without assistance <30% within a year, at least three cycles of IUI-OS is the most effective option. (Grade of evidence A)
- Good practice point: Couples and individuals undergoing IUI and males providing semen samples for IUI should be screened for infectious agents based on local, regional and national standards, and regulations. (Grade of evidence D)
- In order to prevent high rates of multiple gestation pregnancies in IUI-OS, IUI should be withheld when more than two dominant follicles >15 mm or more than five follicles >10 mm at the time of HCG injection or LH surge are present. (Grade of evidence B)
- When gonadotrophins are used in IUI, regimens with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates. (Grade of evidence A)
- Clomiphene citrate or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple pregnancy and birth rates and with lesser costs, although at a lower live birth rate than with gonadotrophins. (Grade of evidence B)
- Addition of GnRH agonist to gonadotrophins in IUI-OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates and increased costs. (Grade of evidence B)
- Good practice point: As an alternative to cycle cancellation, aspiration of excess follicles at the time of HCG injection or LH surge might be additional options for reducing the risk of multiple pregnancy in IUI-OS. (Grade of evidence C)
- Individuals with infertility undergoing treatment with IUI-OS should be informed about a possible increased risk for preterm birth and low birth weight in singletons and twin pregnancies when compared to pregnancies in fertile couples not requiring assistance. (IVF/ICSI outcome comparisons are assessed in the IVF/ICSI prioritized guideline.) (Grade of evidence D)

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	IUI is a simple and non-invasive technique it can be performed without expensive infrastructure with a reasonable success rate within three or four cycles	-	
CPP	IUI is safe and easy treatment with minimal risks and monitoring with good couple compliancy (low drop-out rate) and a very low risk for complications such as OHSS	-	
CPP	IUI is most cost-effective strategy especially in couples with mild male factor and unexplained infertility	-	
EBR	In couples with unexplained infertility with a prognosis of becoming pregnant without assistance within the next 12 months (estimate >30%), IUI could be postponed for at least 6 months	A	I
EBR	In couples with unexplained infertility and men with a total motile sperm count (TMSC) >10 million with prognosis of spontaneous pregnancy <30% within a year, it is recommended that IUI plus ovarian stimulation (OS) is the treatment of first choice	A	I
EBR	In couples with solely a poor sperm quality in the male partner, it is not recommended either for or against use of IUI.	A	I
EBR	In couples with unexplained infertility and men with a TMSC above 10 million, IUI should be combined with OS to improve live birth rates	B	II
EBR	It is not possible to define clear lower cut-off levels of pre- or post- wash sperm parameters below which IUI should be withheld	B	III
EBR	Providers can determine the method of triggering in IUI stimulated with gonadotrophins as there is no evidence to recommend for or against a method	B	II
EBR	Providers can determine the method of timing IUI in natural cycles (no OS) as there is no evidence to recommend for or against a method	B	II
EBR	If a HCG injection is used, single IUI can be performed any time between 24 and 40 hours after HCG injection without compromising pregnancy rates	B	II
EBR	IUI in a natural (not ovarian stimulated) cycle should be performed 1 day after LH rise	B	II
EBR	The intervention FSP, when compared to IUI, should not be the treatment of choice	A	II
EBR	In both unexplained and male infertility there is insufficient evidence that the intervention, a double IUI, within the same cycle will lead to better pregnancy rates than a single IUI within a cycle	B	II
EBR	Women undergoing IUI should be offered a single insemination per cycle	B	II
EBR	Women undergoing IUI, should have 10 to 15 minutes of bed rest after an insemination	B	III
EBR	In couples with an indication for IUI at least three consecutive IUI cycles should be performed	B	II
EBR	There is insufficient evidence to recommend a maximum number of IUI treatment cycles	B	III
EBR	According to the available evidence, it is not possible to recommend any semen preparation technique over another (swim-up, gradient, wash and centrifugation)	C	III
EBR	In couples with unexplained infertility and men with a TMSC of >10 million and a prognosis of a pregnancy without assistance <30% within a year, at least three cycles of IUI-OS is the most effective option	A	II
EBR	Good practice point: Couples and individuals undergoing IUI and males providing semen samples for IUI should be screened for infectious agents based on local, regional and national standards and regulations.	D	IV
EBR	In order to prevent high rates of multiple gestation pregnancies in IUI-OS, IUI should be withheld when more than two dominant follicles >15 mm or more than five follicles >10 mm at the time of HCG injection or LH surge are present.	B	II
EBR	When gonadotrophins are used in IUI, regiments with 75 IU or lower should be used because higher doses have similar pregnancy rates but increase multiple pregnancy rates.	A	I

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Clomiphene citrate or tamoxifen are acceptable alternatives to low dose gonadotrophins for low multiple pregnancy, and birth rates and with lesser costs, although at a lower live birth rate than with gonadotrophins	B	II
EBR	Addition of GnRH agonist to gonadotrophins in IUI-OS is not recommended because there is no increase in pregnancy rate despite increased multiple pregnancy rates and increased costs	B	II
CCR	Good practice point: As an alternative to cycle cancelation, aspiration of excess follicles at the time of HCG injection or LH surge might be additional options for reducing the risk of multiple pregnancy in IUI- OS	C	-
EBR	Individuals with infertility undergoing treatment with IUI-OS should be informed about a possible increased risk for preterm birth and low birthweight in singletons and twin pregnancies when compared to pregnancies in fertile couples not requiring assistance. (IVF/ICSI outcome comparisons are assessed in the IVF/ICSI prioritized guideline)	D	V

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Chapter 14: IVF/ICSI

OVERVIEW

This guideline offers recommendations on assisted reproduction technologies (ART) such as in-vitro fertilization (IVF) and intracytoplasmic sperm Injection (ICSI) in couples with infertility problems. This guideline will act as a blueprint to the standard of care in ART and also overcome the technical challenges inappropriate management of infertility. The recommendations are aimed primarily at women aged 21 years or older presenting to healthcare professionals with infertility problems. This guideline may help fill the gap and help in the proper maintenance of ART procedures in India.

1. Introduction

- Infertility is the inability to conceive after having regular unprotected intercourse at least for >1 year
- The exact burden of infertility in India is unknown. However, a multinational study by the World Health Organization (WHO) including India showed that the incidence of infertility was found to be 10%–15%
- Different types of infertility infections such as reproductive tract infections (RTI) and genital

2. Definitions

2.1 Assisted reproductive technology (ART)

- ART envelops all the techniques involved in obtaining a pregnancy by manipulating the sperm and oocyte outside the body and transferring the gamete or embryo into the uterus for fertilization
- IVF-ET (*In vitro* fertilization–embryo transfer)
- IVF-ET is the fertilization of an oocyte in vitro and the transfer of the fertilized oocyte or embryo to the uterus of a woman

2.2 ICSI (Intracytoplasmic Sperm Injection)

- In ICSI, a single sperm (ejaculated or extracted (PESA and TESA)) is injected directly into the cytoplasm of the oocyte to aid in fertilization

3. Factors that will guide the choice of treatment between IVF and ICSI will depend on

- Semen Parameters – sperm count, motility, morphology, DFI
- Other Factors which affect the chance to pregnancy
 - » Presence or absence of cervical factor
 - » Endometriosis
 - » Tubal pathology
 - » Uterine pathology – Congenital anomalies, polyp, sub–mucous myoma, IUA
 - » Anti–sperm antibody in male and female partner
 - » Pelvic factor – History of previous pelvic or abdominal surgeries
 - » Age of the women – above 40 years should consider IVF early in the treatment protocol
- Special situations

4. Indications

4.1 IVF –ET

- Irreversible pathology of the fallopian tubes/blocked tubes
- Ovulatory dysfunction who have failed to conceive with conventional methods
- Subnormal malefactor
- Unexplained infertility

- Endometriosis.
- Infertility of immunological origin
- Fertility preservation
- Candidates for preimplantation genetic diagnosis

4.2 ICSI with ejaculated spermatozoa

- Oligoasthenoteratozoospermia
- Fertilization failure after standard IVF treatment
- The newer indications for ICSI include – poor-quality oocytes, low oocyte yield, PGT, IVM, fertilization of cryopreserved oocytes
- Poor post-thaw parameters after sperm freezing
- Increased DFI
- Anejaculation because of spinal cord injury
- Retrograde ejaculation

4.3 Indications for ICSI with testicular sperm (TESA)

- Germ-cell hypoplasia (hypo spermatogenesis)
- Germ-cell aplasia with focal spermatogenesis

4.4 Use of IVF as a first-line versus last resort in certain conditions is debatable and include

- Unexplained infertility
- Mild male factor infertility
- Endometriosis without tubal disease
- Unilateral tubal blockage
- Diminished ovarian reserve
- Age >40 years with good ovarian reserve

4.5 Contraindications to ART procedures

- Any medical condition where pregnancy is contraindicated

5. Procedure

Recommended procedure for IVF, and ICSI IVF

- Oocytes are aspirated from mature Graafian follicle after controlled ovarian stimulation to produce multiple follicular developments. Oocytes must be aspirated and maintained in an environment that maintains the temperature at 37°C

5.1 Prerequisites

- Female partner – age >21 –<45 years, 23–50 years in male
- Investigations needed for administration of anesthesia must be done
- Baseline scan
- Counselling and consent for complete treatment plan, complications and adverse outcomes. The model consent forms are to be adapted from the ICMR guidelines
- Fitness for general anesthesia and pregnancy
- Back up semen sample is advisable

5.2 COS

- The treatment protocol for COS can be individualized according to need of the couple. One need to decide on the dose and type of gonadotropin used and the GnRH analogue used to prevent LH surge

5.3 Procedure for lab preparation

- All culture media, oil, hyaluronidase, PVP, vitrification and thaw solutions are to be maintained at 4°C and discarded upon expiry
- All the consents in the checklist has to be verified before the patient is taken to OT for the procedure
- All culture media should be appropriately equilibrated for temperature, pH and osmolarity

5.4 Oocyte retrieval procedure

- Transvaginal follicle puncture under USG control
 - » Method of choice worldwide
 - » less invasive
 - » Less complications

- Time of retrieval–hCG or GnRH agonist is can be administered at any time 34 to 36 hours before OR without affecting the results of IVF
- Patient ID checked
- Oocyte pick has to be done under conducive conditions using standard procedures
 - » Analgesia/anaesthesia
 - » Cleaning of vagina
 - » Use of TVS with a needle guide
 - » Aspiration of all visible follicles from both ovaries with a suction pump delivering 100–120 mmHg pressure
 - » Differentiating between follicle and internal iliac vessels important during OR and when in doubt turn the probe the vessel will become elongated, where as the follicle will remain round, and If still in doubt add color which will identify the internal iliac vessel
 - » Follicular fluid containing oocytes is collected into sterile tubes maintained at 37°C and then rapidly transported to the laboratory
 - » Confirming haemostasis at vaginal puncture sites
- Follicular flushing results in no significant difference in the number of oocytes retrieved, fertilization rate, PR. It significant increases the operating and aspiration time
- In the laboratory, oocytes are screened picked up, and incubated at 37°C for insemination
- Complications of oocyte retrieval are rare but may occur
 - » Severe intra–abdominal bleeding seems to occur in <1 in 1000 procedure
 - » Infectious complications such as pelvic infections or pelvic abscesses, second most common complications with 2–6 cases per 1000 ORs
 - » Injury of pelvic structures, such as the ureter, the bowel or the appendix, happens in 1 in 1000 procedures
 - » 3% of patients experience severe to very severe pain and 2% of patients still suffer from severe pain 2 days after the procedure
 - » The pain level increases with the number of oocytes retrieved

5.5 Procedure for insemination

- The procedure for insemination depends on the technique selected. In IVF, sperm and eggs are mixed and incubated together. Whereas, for ICSI, spermatozoa are injected into the cytoplasm of the oocyte

5.5.1 IVF

- Sperm count and motility should be normal
- Prepare semen as described and dilute to final concentration 1×10^6 per ml
- Place in the incubator before use for capacitation and initiation of acrosome reaction
- Insemination after 4–6 hours of OR
- Inseminate with 10000 sperms per oocyte either in central well dish or micro droplets

5.5.2 ICSI

- Done in patients with severe OAT, failed fertilization, high DFI; surgically retrieved sperm
- Oocyte denudation is performed via enzymatic action of hyaluronidase, and mechanical pipetting
- Injection of the sperm in the denuded oocyte should be done within 40 hours of ovulation induction trigger
- Sperm immobilized, aspirated in injection needle, and then injected into the oocyte with polar body at either 6 or 12 O'clock position
- Injected oocytes washed and cultured in microdroplets

5.6 Fertilization check

- Fertilization check occurs between 16–18 hours post insemination – Check for 2 PN or syngamy

5.7 Embryo evaluation and transfer

- Embryos are analyzed for the rate of development, level of fragmentation, and quality using a quality score till embryo transfer
 - On the day of transfer, select embryo on the basis of embryo score for transfer, and the remaining good quality embryos are cryopreserved
 - The Table below shows the timeline of embryo development

Table. Embryo check	
2PN	16–18 hours
2 Cell	25–27 hours
4 Cell	42–46 hours
8 Cell	66–72 hours
Morula	90–100 hours
Blastocyst	114–120 hours
Hatching Blastocyst	1–140 ur

5.8 Embryo transfer procedure

- Patient ID checked
- Number of embryos to be transferred decided – not more than 2 if women <35 years and not more than if women >35 years

- Embryo transfer should be done under ultrasound guidance
- Embryo transfer can be done at cleavage cell stage (4 or 8 cells) or blastocyst stage

6. Documentation

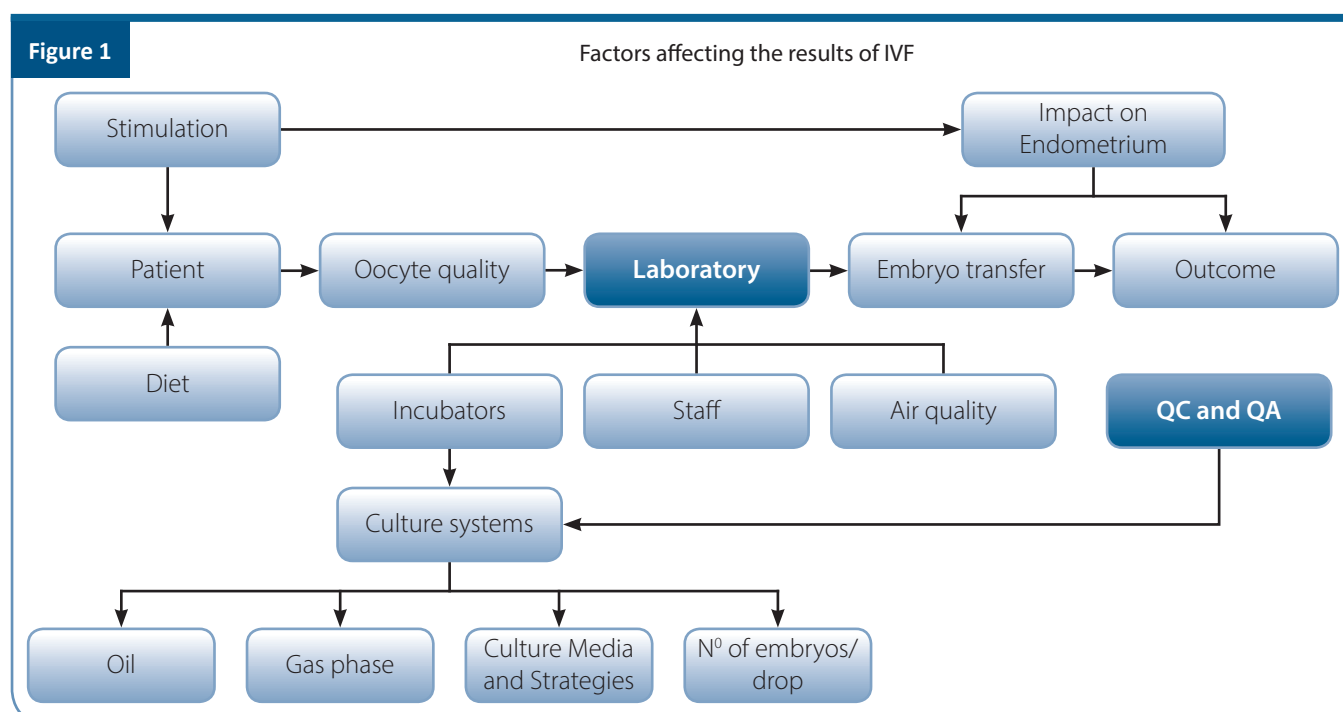
- All IVF/ICSI procedures should also be documented in the EMR. These should clearly state the patients' details; the number of oocytes collected and used, quality assessment of oocytes and embryos formed, number of embryos transferred, and cryopreserved and the transfer details.

7. Maternal risks

- Maternal risks involved in ART are ovarian hyperstimulation syndrome (OHSS), increased risk of multiple pregnancy if more number of embryos are transferred, ectopic pregnancy, pre-eclampsia, placenta previa, placental abruption, gestational diabetes, and cesarean delivery

Summary of recommendations

- Time of oocyte retrieval should be 34 to 36 hours after ovulation trigger without affecting the results of IVF



- Transvaginal follicle puncture under USG control is the method of choice worldwide
- Oocyte retrieval performed under intravenous sedation or under GA using intravenous fentanyl and propofol as well as assisted mask ventilation with oxygen
- Aspiration pressure level should be maintained between 100–120 mm of Hg
- Differentiating between follicle and internal iliac vessels important during OR
- No benefit in total oocytes retrieved or oocyte yield with follicle flushing but associated with a significant increase in the procedure time for oocyte retrieval
- Follicular fluid containing oocytes is collected into sterile tubes maintained at 37°C and then rapidly transported to the laboratory where it is screened for presence of cumulus oocyte complexes
- At the end of the procedure, the vagina was thoroughly examined with a speculum and if necessary local compression was applied to allow haemostasis
- Factors that will guide the choice of treatment between IVF and ICSI depend on semen parameters, other Factors which affect the chance to pregnancy, and special situations
- OCCs are then transferred to media with bicarbonate and incubated/cultured for at least 4 hours
- In IVF Insemination after 4-6 hours of OR and then inseminated with 10000 sperms per oocyte either in central well dish or micro droplets. Denude after 16–18 hours and check for fertilization
- ICSI should be done after 40 hours after oocyte trigger. Injected oocytes washed and cultured in microdroplets and checked for fertilization after 16-18 hours
- Embryos are analyzed for the rate of development, level of fragmentation, and quality using a quality score till embryo transfer
- Embryo transfer can be done at cleavage or blastocyst stage and the remaining embryos cryopreserved.
- Number of embryos depends on the age, cause of subfertility stage of transfer, quality of embryos, and policy
- Use of USG guided soft catheter embryo transfer technique improve results and lower the variability of the results by making it less traumatic, standardized, and technically precise

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Time of oocyte retrieval should be 34 to 36 hours after ovulation trigger without affecting the results of IVF	A	II
EBR	Transvaginal follicle puncture under USG control is the method of choice worldwide	A	I
EBR	Oocyte retrieval performed under intravenous sedation or under GA using intravenous fentanyl and propofol as well as assisted mask ventilation with oxygen	B	III
EBR	Aspiration pressure level should be maintained between 100–120 mm of Hg	B	II
EBR	Differentiating between follicle and internal iliac vessels important during OR	A	I
EBR	No benefit in total oocytes retrieved or oocyte yield with follicle flushing but associated with a significant increase in the procedure time for oocyte retrieval	A	II
EBR	Follicular fluid containing oocytes is collected into sterile tubes maintained at 37°C and then rapidly transported to the laboratory where it is screened for presence of cumulus oocyte complexes	A	I
EBR	At the end of the procedure, the vagina was thoroughly examined with a speculum and if necessary local compression was applied to allow haemostasis	A	II
EBR	Factors that will guide the choice of treatment between IVF and ICSI depend on semen parameters, other factors which affect the chance to pregnancy and special situations	B	II
EBR	OCCs are then transferred to media with bicarbonate and incubated/cultured for at least 4 hours	A	I
EBR	In IVF Insemination after 4–6 hours of OR and then inseminated with 10000 sperms per oocyte either in central well dish or micro droplets. Denude after 16–18 hours and check for fertilization	A	I
EBR	ICSI should be done after 40 hours after oocyte trigger. Injected oocytes washed and cultured in microdroplets and checked for fertilization after 16–18 hours	A	II
EBR	Recommendation for routine prophylactic antibiotics before embryo transfer cannot be made	B	III
EBR	Embryos are analysed for the rate of development, level of fragmentation, and quality using a quality score till embryo transfer	A	I
EBR	Embryo transfer can be done at cleavage or blastocyst stage and the remaining embryos cryopreserved	A	I
EBR	Number of embryos depends on the age, cause of subfertility stage of transfer, quality of embryos and policy	B	II
EBR	Use of USG guided soft catheter embryo transfer technique improve results and lower the variability of the results by making it less traumatic, standardized, and technically precise	A	I

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Chapter 15: Management of Poor Ovarian Responders

OVERVIEW

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of poor ovarian response (POR) covering defining women with POR and its new classification, and a focus on the management options.

1. Introduction

- The success of an ART cycle in most cases is directly proportional to the number of oocytes retrieved
- Patients with a diminished ovarian reserve or poor ovarian response (POR) to exogenous gonadotropin stimulation have been a therapeutic challenge for reproductive specialists
- Besides the limited understanding of the pathophysiology, there is wide heterogeneity in the definition of poor responders as well as overall disappointing outcomes in assisted reproductive technology
- Various strategies have been employed for the management of poor responders which will be covered in this guideline

2. Definition of POR

- Initially the Bologna criteria were used to define poor responders. At least two of the following three features must be present to label the patient as a poor responder
 1. Advanced maternal age (≥ 40 years) or any other risk factor for POR
 2. A previous POR – ≤ 3 oocytes with a conventional stimulation protocol
 3. An abnormal ovarian reserve test – AFC < 5 –7 follicles or AMH – 0.5 – 1.1 ng/ml

Supplemental criteria includes two episodes of POR after maximal stimulation in the absence of advanced maternal age or abnormal ORT

Bologna criteria is not ideal as it does not address the heterogeneity of subgroups, specific profiles of abnormal ovarian response (hypo and sub-optimal)

are not included, does not take into consideration age-related aneuploidies

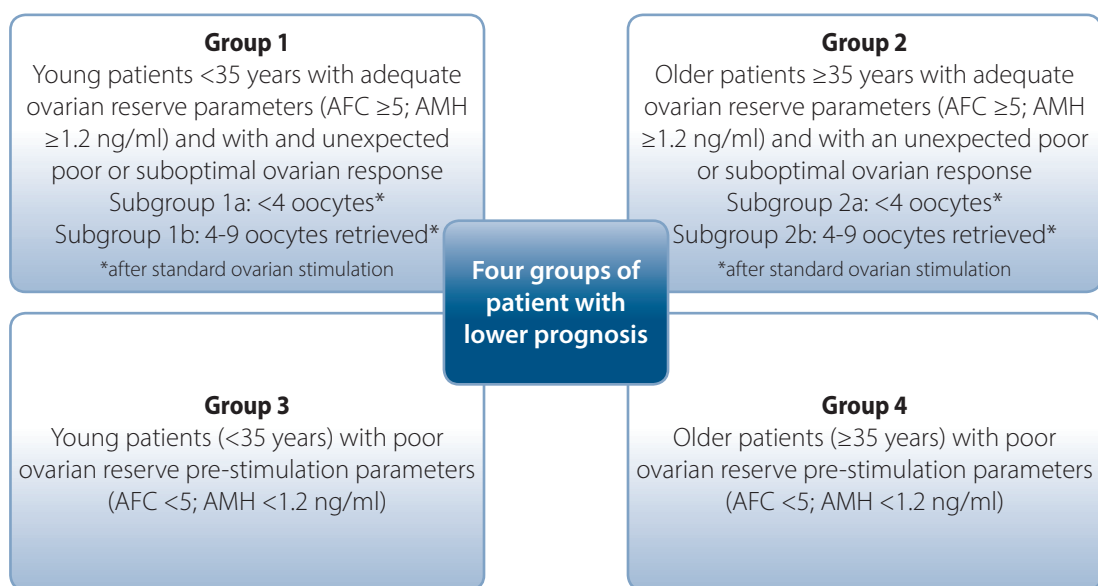
To resolve the shortcomings in the Bologna criteria, recently, the POSEIDON group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) proposed a new classification and coined a new definition of poor ovarian responders (POR) as “Low Prognosis” to guide patient management based on the ability to retrieve the number of oocytes necessary to obtain at least one euploid embryo (Figure 1).

3. Diagnosis and investigations

- For the diagnosis of poor ovarian response, the patient is required to have undergone controlled ovarian stimulation and oocyte retrieval
- By now it is too late and no intervention can be done in the current cycle and therefore prediction of poor ovarian response is important
- Although difficult, it is extremely important to predict poor response to individualize the stimulation protocol for the patient
- Choice of marker used may depend on the organization, setting, availability of equipment or patient-related conditions
- Offer tests to help in diagnosing and predicting response to ovarian stimulation. Tests are as follows:
 - » High levels of serum FSH (> 12 or > 15 mIU/mL) on cycle days 2 or 3
 - » Elevated levels of serum estradiol (> 30 or 75 pg/mL) on cycle days 2 or 3
 - » Decreased levels of serum inhibin B (45 pg/mL) on cycle days 2 or 3

Figure 1

POSEIDON working group classification



- » Decreased serum concentrations of anti-müllerian hormone (AMH) of <0.5-1.1 ng/ml
- » Decreased ovarian volume (OVVOL)
 - Ovarian volume measurement with a cut-off value of 3 cm³
- » Decreased antral follicle count (AFC)
 - Antral follicle count <5-7
- Currently only serum AMH and AFC are to be considered as standard methods of diagnosing poor reserve which can be used to predict a poor response
- It is possible to measure the submerged part of the iceberg of follicle growth, i.e. the intrinsic, so-called 'acyclic' ovarian activity by evaluating AMH
- Single test is considered sufficient and AFC seems to be efficient and most used

4. Controlled ovarian stimulation (COS) protocols in poor responders

- Despite a large number of papers over the last two decades on COS in poor responders, it remains an enigmatic task with the most efficient protocol yet to be defined

- Consider using the following protocols for POR

A. GnRH analogues

4.1 Agonist protocol

4.1.1 Long protocol

- Mid-luteal, lower dosage (0.1-0.5mg)

4.1.2 Flare-up-short

- Follicular start of agonist, gonadotropins 2-3 days later

4.1.3 Ultra short

- Stop after 2-3 days of gonadotropins

4.1.4 Stop agonist

- Mid-luteal start and stopped on day of menses

4.1.5 Micro dose

4.2 Antagonist protocol

4.2.1 Fixed protocol

When GnRH antagonist is started on day 6 of stimulation

4.2.2 - Flexible protocol

When GnRH antagonist is started when dominant follicle is 14 mm

4.3 Evidence comparing protocols

4.3.1 Antagonist versus long agonist protocol

1. No difference in OR, embryos transferred, PR/ET, CPR
2. Antagonist protocol is shorter in duration and is associated with higher cancellation rate (hence, the agonist protocol is preferred)
3. Antagonist protocol is associated with fewer oocytes retrieved. Lower E2, thinner ET
4. Cancellation rate similar

4.3.2 Micro dose protocol vs. antagonist protocol

- Micro dose protocol is associated with:
 - a. Significantly higher number of oocytes and peak E2 levels
 - b. No significant difference is observed in fertilization rate, implantation rate, and PR
 - c. Antagonist protocol is associated with shorter duration of stimulation and lower gonadotropin requirement
- 4 RCT till date

4.3.3 Mild stimulation using oral ovulogens with gonadotropins and GnRH antagonist protocol vs long agonist protocol

Mild using CC protocol is comparable to GnRH-antagonist with

- a. Significantly shorter duration and lower consumption of gonadotropins
 - b. IVF outcome in IR, CPR
 - c. Economical advantage
 - d. More cycle cancellation rate with mild stimulation
- Lower E2 peak and thin ET with CC use is observed in mild stimulation

4.3.4 Long agonist versus short (flare, ultrashort) agonist

1. No difference is observed in gonadotropins used, or number of embryos transferred between flare agonist and antagonist

2. CPR and live birth rate (LBR) are reported to be similar in both protocols

4.3.5 COH protocols (long agonist vs short flare vs stop vs antagonist)

1. No benefit of any COS protocol over the other
2. No trials (RCT/retrospective) comparing natural versus conventional stimulation
3. Dual stimulation (prospective non-inferiority observational study)– May be of benefit in POR

Recommendations

- In women with low ovarian response, no differences exist in terms of safety and efficacy between the GnRH agonist and GnRH antagonist protocol
- All protocols have similar outcome in terms of OR, embryos transferred, cancellation rate, PR, and LBR
- Antagonist protocol is preferred for benefit of shorter duration
- Natural/modified natural have no role in COS in POR

B. Gonadotropins (type and dosage) for POR

- Conventional (150–300 IU) vs higher dosage (>300 IU)
 - » Higher doses result in more oocytes and therefore more embryos for transfer but not higher IR or PR
 - » No benefit of higher dosage > 300 IU is reported in POR
- Recombinant versus urinary Gonadotropins
 - » No RCT compares urinary and recombinant gonadotropins
 - » Only small retrospective study compares hMG vs. rLH and rFSH
 - » hMG vs. rLH and rLH (retrospective)
- Addition of rLH to rFSH
 - » Addition of r-LH to r-FSH has shown to offer benefit in women with:
 - Advanced age

- Women defined as POR by Bologna's criteria and POSEIDON group 1 and 2 (hypo-responders)

Recommendations

1. Doses higher than 300 IU is of little advantage in increasing CPR and LBR
 - » May give additional oocytes but data on cumulative LBR from surplus embryos lacking
2. Choosing Recombinant over urinary gonadotropins is not supported by strong evidence
3. Addition of rLH may benefit women with advanced age or hypo-responders

5. Management based on POSEIDON classification

5.1 Group 1

- Adding LH and increasing rFSH are effective in improving FORT
- Hypo-response may reflect polymorphisms of Gn and their receptors
- Possible pharmacogenomic approach helpful

5.2 Group 2

- LH can be effective in increasing oocyte/embryo quantity and competence
- Blastocysts accumulation (double stimulation) can be an option

5.3 Group 3

- iCOS Treatment
 - » Long GnRHa protocol
 - » GnRH antagonist (E2, OCP)
 - » Stimulation with 300 IU/day GT
 - » Androgens?
- Embryo Transfer strategy
 - » Fresh transfer
 - » Oocyte/embryo accumulation and FET

- » Measure of success – Total of 4–7 oocytes needed to obtain 1 euploid blastocyst

5.4 Group 4

- iCOS Treatment
 - » Long GnRHa protocol
 - » GnRH antagonist (E2, OCP)
 - » Stimulation with 300 IU/day GT/addition of LH
 - » Androgens?
- Embryo Transfer strategy
 - » Fresh transfer
 - » Oocyte/embryo accumulation and FET
 - » Measure of success – Total of 12 oocytes needed to obtain 1 euploid blastocyst
- In group 3 and 4, if ovarian reserve is low and FORT is high, no GTs can compensate!!!
- DuoStim can be an option in young patients where aneuploidy rates are still low

6. Adjuvant therapy

6.1 Androgens

- i. Testosterone in the form of gel/ spray/patch
- ii. Dehydroepiandrosterone (DHEA)

Rationale for use of androgens

- Expression of IGF-1 in the serum improves the response to gonadotropins
- Androgens modulate ovarian physiology, promote oocyte and follicle maturation.
- Exerts local effects on the endometrium during ovulation, and implantation to improve pregnancy

Dosage of testosterone

- Offer testosterone– Tablets 12.5 mg/day; 1% gel, spray, and patch
- Consider the treatment to be started 5–21 days until stimulation is initiated

Evidences for testosterone

- 2 RCTs suggest that addition of testosterone increases CPR and LBR
- Testosterone is reported to improve LBR compared to placebo (32% vs. 10%)
- Recent meta-analysis showed significantly improved CPR (OR 2.41; 95% CI 1.16–5.04) and LBR (OR 2.18; 95% CI 1.01–4.68), but the number of oocytes retrieved was not statistically significant (mean difference 0.94; 95% CI 0.24–1.64)
- ESHRE guidelines on COS indicates that use of testosterone before COS is probably not recommended in low responders (as quality of evidence from meta-analysis of low quality)

Dosage of DHEAS

- Offer DHEAS 75 mg for 12 weeks prior to ovarian stimulation in poor responders

Evidences for DHEAS

- A Cochrane database demonstrated that, DHEA compared to placebo revealed:
 - » Higher LBR (12% vs. 15%–26%) and ongoing PR
 - » No difference in miscarriage rate
 - » However, in a sensitivity analysis removing trials at high risk of performance bias, the effect size was reduced and no longer reached significance (5 RCT, 1913 OR 1.50, 95% CI 0.88–2.56, 306 women)
 - » The ESHRE Reproductive Endocrinology Guideline Group recommends:
 - Use of DHEAS before or during controlled stimulation is probably not recommended for low responders

6.2 Growth hormone (GH)

Rationale

- High levels of GH in follicular fluid result in oocytes with good morphology, rapid cleavage, and therefore is considered to have better implantation potential

Evidences for GH use

- A recent systematic review and meta-analysis reported
 - » Significantly higher live birth rate (9 RCT, RR 1844 1.73, 95% CI 1.25–2.40, 562 women) in the GH group compared to control group in poor responders undergoing IVF treatment
 - » Significantly higher number of oocytes retrieved (6 RCT, SMD 1.09, 95% CI 0.54 to 1.64, 523 women) and mature oocytes (5 RCT, 1847 SMD 1.48, 0.84 to 2.13, 469 women) in the GH group compared to control group in poor responders undergoing IVF treatment
- An RCT, more recent than the above-mentioned meta-analysis, including 127 Bologna criteria poor 1850 responders, compared adjuvant GH with no adjuvant treatment in the GnRH antagonist protocol
 - » No significant difference in ongoing pregnancy rate (8.1% (5/62) vs. 9.2% (6/65)) or number of retrieved oocytes (3.7±2.6 vs. 3.4±2.5) was observed with GH compared to control group
- The ESHRE Reproductive Endocrinology Guideline Group recommends

6.3 Aspirin

- Use of adjuvant GH during/before controlled ovulation stimulation is probably not recommended in low responders
 - » Doses of aspirin used in the studies varied between 75 mg daily, 80 mg daily or 100 mg daily
 - » Continue aspirin was until hCG administration for final oocyte maturation, 12 weeks of pregnancy or until delivery

Evidence for aspirin

- A Cochrane meta-analysis combining 3 RCTs including 1053 women

- » No significant difference in the live birth rate (3 RCT, RR 0.91, 95% CI 0.72-1.15) or ongoing pregnancy rate (2 RCT, RR 0.94, 95% CI 0.69-1.27) was observed between the aspirin and control group
- The ESHRE Reproductive Endocrinology Guideline Group recommends:
 - » Use of adjuvant aspirin during/before controlled ovulation stimulation is probably not recommended in low responders

6.4 Vasoactive substances like arginine

- It is recommended that the empirical use of adjuvants should be avoided pending good quality evidence from well-designed studies

6.5 Antioxidants

- Insufficient number of studies has examined the associations of nutritional factors and ovarian reserve, especially measuring AMH as a marker, and timing of menopause
- The findings of some studies suggest modest associations of some single nutrients or food items with ovarian reserve and age at menopause
- To better understand this issue, more studies examining the associations of dietary intakes and dietary patterns with concentrations of AMH and age at menopause are needed

7. Laboratory issues

ICSI for low oocyte yield

- Low egg number is not an indication to perform ICSI in the presence of normal semen parameters
- The use of ICSI over conventional IVF is not supported to improve proportion of embryos per obtained oocyte, cycle cancellation rate, fertilization rate, implantation rate, clinical pregnancy rate (PR), live birth rate (LBR), cumulative PR, and cumulative LBR
- ICSI doesn't show advantages over IVF even when only one oocyte was retrieved

8. Pre-implantation genetic screening or PGT-A for poor responders

- Low oocyte numbers as well as rise in aneuploidy of embryos contribute to poor reproductive outcomes in advanced age women
- Age-related effects on aneuploidy rates seem to be driven by impaired mitochondrial function, increased granulosa cell apoptosis, and increased levels of oxidative stress in germline cells
- At least 12 oocytes would be required in order to produce one euploid embryo
- PGT-A has shown to significantly decrease time to live birth by an average of three months in patients with diminished ovarian reserve
- Further, PGS appears to have a decreased risk for ongoing aneuploid gestations
- Offering embryonic screening paradigm to patients with POR serves as a way to decrease time to live birth and may decrease the risk of clinical miscarriage and abnormal ongoing gestations
- Still there is no consensus related to employing blastocyst culture and PGS in poor responders

9. Ideal day of embryo transfer

- Higher pregnancy and implantation rates have been reported with blastocyst compared to cleavage stage embryo transfers
- The Cochrane review 2016 of 12 randomized controlled trials demonstrated that live birth rates can be optimized by performing blastocyst transfer compared to cleavage stage embryo transfers
- Chromosomal abnormalities are largely reduced at the blastocyst stage compared to cleavage embryo stage
- Even though the cancellation rate in the blastocyst (day 5) strategy is significantly higher than in the cleavage stage (day2/3) strategy, the PR, clinical PR, and even LBR per oocyte retrieval still remains significantly higher in the blastocyst

- Women with POR can be offered blastocyst transfer after adequate counselling for possibilities of cancellation of transfer

10. Numbers of embryo transfer

- Elective single embryo transfer allows less burden and complications (i.e., miscarriage and multiple gestations)
- Success of eSET is comparable to double cleavage stage embryo transfer
- The real focus in patients with poor ovarian response should be on strategies to obtain oocytes with genetic and cytoplasmic competence, rather than on strategies to obtain more oocytes

11. Oocyte donation

- In patients with a clear depletion of the ovarian reserve, or in presence of recurrent IVF failures, especially after multiple euploid ETs, the only options left are adoption or ovum donation
- The ethical and moral uncertainties are the main concerns related to the transfer of an embryo partially non-self
- Despite the high success rate of OD, recent evidences from reviews and meta-analyses suggest that pregnancies achieved by this strategy show a significant increase in the likelihood of several obstetrics and maternal complications with respect to pregnancies achieved through IVF with own eggs
- Interestingly, all these risks are independent of maternal age, suggesting that their causes might be ascribed to an immunological mechanism, e.g., host vs. graft rejection phenomenon
- OD-derived embryos are in fact totally allogenic to the mother and may cause the onset of an immunologic reaction in the recipient that could impair the process of placentation

12. Newer advances

- On a more experimental basis the future handling of the expected POR patient might include

- Intra-ovarian androgen priming
- In vitro activation
- Stem cell therapy – intraovarian injection of stem cells
- *In vitro* oogenesis
 - » Development of oocytes from stem cells of the patient.
 - » The successful reconstitute of oogenesis *in vitro* includes the initial phase of meiosis,
 - » follicular assembly, and appropriate conditions to support sufficient oocyte growth, and complete maturation
 - » This is probably the most promising future treatment
- Autologous mitochondrial transfer
 - » To improve the implantation potential and quality of the embryo
- Pharmacogenomics
 - » Taking the genome of the patient into consideration when designing drugs and planning a treatment

Summary of recommendations

- Compared to Bologna criteria, POSEIDON gives a better overview of POR patients
- The diagnosis is by AFC<5, AMH<1.2, and FSH>15
- E2, and ovarian volume per say is not diagnostic
- A single prior IVF cycle gives a lot of insight to POR
- There is no ideal protocol for poor ovarian reserve and poor responder patients, hence a large no of protocols have been tried. The common used protocols seem to be:
 1. Antagonist protocol
 2. Agonist short protocol
 3. Microdose flare protocol
 4. Letrozole/ CC-HMG protocol
 5. Agonist stop –antagonist protocol

6. Rec.FSH vs rFSH+rLH (this seems to help the subgroup POSEIDON Group 1 & 2)
- Using more than 300 IU of gonadotrophin does not seem to increase the oocyte yield
 - Synchronize the follicle pool with premenstrual estrogen/P4 treatment or long protocol
 - Use a combination of FSH and LH
 - Dual stimulation or pooling when appropriate
 - Adjuvants:
 - » Testosterone: Recent meta-analysis showed increased CPR and LBR, but the number of oocyte retrieved were not significant
 - » ESHRE guidelines on COS indicates that use of testosterone before COS is probably not recommended in low responders (as quality of evidence from meta-analysis of low quality)
 - Role of DHEA and GH is debatable. The ESHRE Reproductive Endocrinology Guideline Group
 - Recommends: 1. Use of DHEAS before or during controlled stimulation is probably not recommended for low responders
 - Use of adjuvant GH during/before controlled ovulation stimulation is probably not recommended in low responders
 - ICSI does not show advantages over IVF even when only one oocyte was retrieved
 - There is no consensus related to employing blastocyst culture and PGS in poor responder
 - Day 3 vs. Day 5 transfer: Women with POR can be offered blastocyst transfer after adequate counselling for possibilities of cancelation of transfer
 - Oocyte donation: With a clear depletion of the ovarian reserve, or in presence of recurrent IVF failures, especially after multiple euploid ETs, the only options left are adoption or ovum donation
 - The newer advances like intraovarian activation, ovarian tissue freezing, activation and reimplantation, stem cell/PRP injection to ovarian cortex, autologous mitochondrial transfer are still experimental

Conclusion

- Management of POR still represents a therapeutic challenge for the clinician. POR are a heterogeneous group with no uniform protocol and one cannot recruit follicles that do not exist in a case of DOR. Moreover, oocyte quality fundamentally cannot be altered with different treatment modalities

16 Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	Compared to Bologna criteria, POSEIDON gives a better overview of POR patients	-	-
EBR	The diagnosis criteria used are AFC<5, AMH<1.1, and FSH>15	A	II
EBR	E2 and ovarian volume per say is not diagnostic	C	III
EBR	A single prior IVF cycle gives a lot of insight to POR	B	II
CCR	There is no ideal protocol for poor ovarian reserve and poor responder patients, hence a large no of protocols have been tried. The common used protocols seem to be: 1. Antagonist protocol 2. Agonist short protocol 3. Microdose flare protocol 4. Letrozole/ CC–HMG protocol 5. Agonist stop–antagonist protocol 6. Rec.FSH vs rFSH+rLH (this seems to help the subgroup POSEIDON Group1 & 2)	C	-
EBR	Using more than 300 IU of GTP does not seem to increase the oocyte yield	B	III
EBR	Synchronize the follicle pool with premenstrual estrogen/P4 treatment or long protocol	C	III
EBR	Use a combination of FSH and LH	B	II
EBR	Dual stimulation or pooling when appropriate	C	III
EBR	Adjuvants: • Testosterone: Recent meta-analysis showed increased CPR and LBR, but the number of oocyte retrieved were not significantly higher	B	III
EBR	• ESHRE guidelines on COS indicates that use of testosterone before COS is probably not recommended in low responders (as quality of evidence from meta-analysis of low quality)	C	III
EBR	• Role of DHEA and GH is debatable		
EBR	• Use of DHEAS before or during controlled stimulation is probably not recommended for low responders	B	III
EBR	• Use of adjuvant GH during/before controlled ovulation stimulation is probably not recommended in low responders	C	IV
		C	III
EBR	ICSI doesn't show advantages over IVF even when only one oocyte was retrieved	B	II
EBR	There is no consensus related to employing blastocyst culture and PGS in poor responder	C	IV
EBR	DAY3 vs. D5 rransfer: Consider day 3 embryo transfer to limit the culture time	B	II
EBR	Women with POR can be offered blastocyst transfer after adequate counselling for possibilities of cancelation of transfer.	C	IV
EBR	Limit the use of PGS in patients with very few available embryos	B	I
CPP	Oocyte donation: With a clear depletion of the ovarian reserve, or in presence of recurrent IVF failures, especially after multiple euploid ETs, the only options left are adoption or ovum donation	-	-
Research points	The newer advances like intra-ovarian activation, ovarian tissue freezing, activation and reimplantation, stem cell/PRP injection to ovarian cortex, autologous mitochondrial transfer are still experimental	-	-

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Chapter 16: Advances in Infertility

OVERVIEW

Infertility is a prevalent condition that affects over 80 million people globally. A variety of lifestyle choices and genetic issues have been implicated in the condition. These recommendations covers the advanced techniques for treating fertility problems. It aims to reduce variation in practice and improve the way fertility problems are investigated and managed.

1 Recommendations

1.1 Thin endometrium

- Thin endometrium is defined as endometrial thickness <7 mm or <8 mm on the day of human chorionic gonadotropin (HCG) administration
- Measurement of thin endometrium
- Ultrasound is the ideal noninvasive tool to evaluate the endometrium

1.1.1 Platelet rich plasma (PRP) for thin endometrium

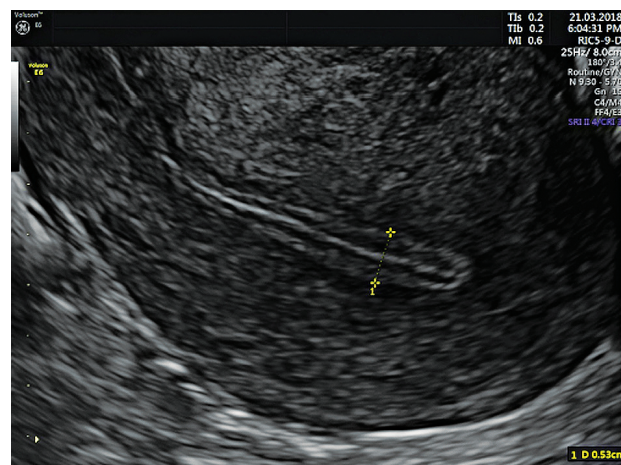
- The definition and cut-off for thin endometrium differs between studies, although most studies use endometrial thickness <7 mm or <8 mm on the day of human chorionic gonadotropin (HCG) administration
- PRP plays an active role in promoting endometrial proliferation improving embryo implantation rate and clinical pregnancy rates
- The benefits of PRP for these infertile women with thin endometrium may be due to the 4 times higher platelets and significant greater amounts of growth factors as platelet-derived growth factor (PDGF)-AB, PDGF-BB, and transforming growth factor (TGF)- β in PRP than peripheral blood ($p < 0.01$)
- PRP is beneficial but further studies are required

1.1.2 Intrauterine stem cell perfusion for thin endometrium

- Bone marrow-derived cells are implicated as possible endometrial progenitors.
 - » Origination of the cells from bone marrow mesenchymal stem cells or, alternatively, is circulating endometrial cells originally derived

Figure 1

Measurement of thin endometrium



from the endometrium and harboured in bone marrow is unknown

- » Regardless of their origin, these cells may serve as a source of reparative cells for the reproductive tract
- » Both stromal and epithelial cells were derived from bone marrow origin
- Researches show the potential for stem cells to have a role in the regeneration or repair of this tissue after injury
- Significant engraftment of endometrium by bone marrow is likely to occur after endometrial injury or inflammatory insult
- Severe Asherman's syndrome cases involving damaged basal endometrium layer are reported to have better response with autologous stem cells than with PRP
- Adipose tissue derived stem cells are also found to be very promising in one of the recent studies in cases of thin endometrium

1.2 Summary of recommendations

Category	Summary statements	Quality of evidence	Justification	
CCR	Various factors can limit the accuracy of endometrial measurements such as fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries, uterine contractions, ultrasound machine quality, interobserver and intra-observer variability, and patient intolerance	II		
	Recommendations	Strength	Quality of evidence	Justification
EBR	The endometrium should be measured transvaginally in the sagittal plane at the thickest portion near the fundus	B	III	Recommendation is based on commonly accepted practice and to ensure consistency in measurements to aid in clinical assessment, research, and reporting
EBR	Repeat any thin endometrium measurement.	D	IV	Recommendation is based on commonly accepted practice and intra-observer variability
EBR	Uterine cavity assessment by hysteroscopy or sonohysterogram may be performed in the assessment of a patient with thin endometrium to assess for pathological cause	D	IV	Consensus opinion from the Committee for Practice Guidelines: Although the incidence of intrauterine adhesions in patients with thin endometrium is unknown, uterine assessment may identify patients who may benefit from surgical management

- As far as ethical aspect is concerned, as per The Gazette of India published in April 2018, use of autologous stem cells does not need any special licence by treating hospital

1.2 Poor ovarian reserve

1.2.1 Platelet rich plasma (PRP) in ovarian rejuvenation

- Premature ovarian insufficiency (POI) affects around 1%–3% of women in the reproductive age below 40 years, and around 0.1% in women below 30 years of age
- Only around 5%–10% of POI women conceive spontaneously due to fluctuations in ovarian functions. First data on intra-ovarian injection of calcium gluconate activated autologous platelet rich

plasma was published in 2018. There is still a debate regarding volume of PRP that should be injected in cases of premature ovarian failure

- Two different routes for injecting PRP are as follows:
 - » Transvaginal under ultrasound guidance
 - » Laparoscopy routes
- There are scanty studies supporting use of PRP for ovarian rejuvenation therapy

1.2.2 Intra ovarian stem cells for premature ovarian failure and ovarian rejuvenation

- Stem cell (SC) therapy has emerged enormously, particularly for indications where not much can be done medically or surgically to improve the condition

- SCs are the foundation cells for every organ, tissue and cell in the body, and it can either reproduce into a SC or differentiate into specialized types of cells
- Recently, Herraiz et al conducted a study to assess if infusion of human BMDSCs (bone marrow derived stem cells) could promote follicle development in the patients with impaired ovarian functions
 - » The researchers conducted the experiments in mice and obtained promising results which raised the possibility that promoting ovarian angiogenesis by BMDSC infusion could be an alternative approach to improve follicular development in women with impaired ovarian function
- The world's first baby following use of intraovarian stem cells injection in a 45 year old lady is reported in India
- Still larger studies and data are needed to support the use of stem cells in ovarian rejuvenation

1.3 Noninvasive chromosomal analysis of embryos

- Chromosomal abnormalities are known to cause recurrent implantation failure, early pregnancy loss or severe chromosomal diseases. Around 50% of miscarriages are due to aneuploidy.
- One of the major limitations of PGS-TE (preimplantation genetic screening- trophoectoderm) biopsy is not only its technically challenging and invasive procedure, there is still alarming presence of chromosomal mosaicism within the developing embryo
- Although there appears to be a high concordance rate between TE cells and inner cell mass (ICM) cells in selected blastocysts, a TE biopsy may not always represent the remainder of the TE or the ICM
- Detection of mosaicism can be up by 30% when next-generation sequencing (NGS) is applied for chromosomal analysis
- Circulating cell-free embryonic DNA is present in the blastocoel fluid (BF) and spent culture media of blastocysts which can be used for non-invasive screening of chromosomes. Therefore, BF may represent a source of embryonic genetic material that is routinely discarded during vitrification
- Obtaining BF is not only noninvasive but also technically easy and a very cost effective option. It is also found that the amount of DNA found in BF is of the same extent at times better than TE biopsy obtained DNA
- Recently, cell-free embryonic DNA has also been found in blastocyst culture condition medium (BCCM) and has shown good results for preimplantation genetic diagnosis and preimplantation genetic screening were only recently published

1.4 Uterine transplant

- Advise the women with uterine factor infertility (UFI) having a nonfunctional or absent uterus to explore in vitro fertilization (IVF) with a gestational carrier (where legal), adoption, foster parenting, or to lead a life without children
- Uterus transplantation is currently considered an experimental procedure and should not be performed outside of an Institutional Review Board approved research protocol. These trials should be listed on Clinicaltrials.gov
- Multidisciplinary transplantation team should include a transplant surgeon, gynaecologic surgeon, maternal-fetal medicine specialist, anesthesiologist, infectious disease specialist, psychiatrist or psychologist, neonatologist, pathologist, radiologist, bioethicist or professional with bioethics expertise, social worker, living donor advocate as described by United Network for Organ Sharing (UNOS) regulations, research nurse/coordinator transplant medicine specialist
- As a surgical team prepares for transplantation attempts in human subjects, surgical practice specific to uterus transplantation is required
- Surgical training and preparation may involve either large animal research or cadaver practice to optimize

the surgical approach and team training for obtaining and implanting a uterus graft

1.4.1 Ethical concern

- Human uterus transplantation is considered a vascularized composite allograft (VCA) similar to transplantation of the face, limbs, abdominal wall, and other non-lifesaving organs, and present unique ethical and logistical considerations
- VCAs are regulated in a manner similar to other solid organs and require specialized consent to allow removal of the specified organ as well as its use in research or transported to donors in all series of living donors to date
- Care should be taken to avoid undue emotional and psychological pressure in living donors, who are often family members of the recipient seeking transplantation
- Inclusion and exclusion criteria should be strictly followed as per ASRM position statement on uterus transplantation, a committee opinion 2018
- The organ used during uterus transplantation can be for living or deceased donors; with each approach having its own challenges and strengths
- It is necessary for all donors to be blood-type compatible with their intended recipient. All recipients should be screened for preformed anti-human leukocyte antigen (HLA) antibodies prior to transplantation

1.5 Ovarian tissue transplant

- Ovarian tissue transplant and cryopreservation is accepted. It still remains an option for patient undergoing gonadotoxic treatment especially for prepubertal girls
- Do not offer ovarian tissue transplant for benign conditions or to women who want to delay their child bearing
- Ovarian tissue can be stored as cortical biopsies or strips or whole ovaries
- Ovarian tissue can be transplanted to pelvic (orthotopic) or extrapelvic site (heterotopic site)
- No pregnancies have been obtained from thawed ovarian tissue transplanted to heterotopic site
- Pregnancies have been documented from orthotopic site transplant
- Clearly state that ovarian tissue transplant does carry a risk of reintroduction of malignancy

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	For patients with a history of thin endometrium in ART treatment undergoing endometrial preparation for embryo transfer, there is insufficient evidence that any specific protocol (natural cycle or hormone replacement) for endometrial preparation provides better pregnancy outcomes	C	III
EBR	In patients with thin endometrium undergoing embryo transfer Weak cycles, we suggest against the use of pentoxifylline, HCG, gonadotropin-releasing hormone agonists, platelet-rich plasma or stem cells to improve pregnancy rates	C	IV
EBR	PRP therapy is investigated in women with POF, infertile women more than 35 years of age, and women with low ovarian reserve	D	IV
CCR	Noninvasive preimplantation genetic testing (NIPGT) for chromosomal abnormalities assessment has the potential to be an accurate and reliable option for preimplantation genetic testing of human embryos	D	-
CCR	Uterus transplantation from live donors became a reality to treat infertility for treatment of absolute uterine factor infertility	D	-
EBR	Ovarian tissue transplantation for: 1. Fertility preservation for cancer patients 2. Rare genetic diseases-confirmed potential in children 3. Known causes of POI 4. Endometriosis 5. Postponing menopause 6. Social freezing – alternative to mature oocytes 7. In combination with <i>in vitro</i> follicle activation 8. Anovulatory PCOS women – modern wedge resection Is no longer experimental and can be used in the above conditions	B	III

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Chapter 17: Recurrent Implantation Failure

OVERVIEW

The guideline provides an overview of suggested treatments for RIF, and which of those are recommended. Furthermore, recommendations are made on the investigations that could be helpful to identify the origin of implantation failure and possible therapeutic targets. In addition, recommendations are written regarding organization of care for couples faced with RIF.

1. Scope of the guideline

- To examine the causes, potential treatments, and recommendations for patients suffering from RIF

2. Definition of RIF

- RIF is as the failure of clinical pregnancy after 4 good quality embryo transfers, with at least three fresh or frozen IVF cycles, in women under the age of 40
- An internationally agreed consensus on the definition is yet to be reached

3. Incidence of RIF

- Due to variations in definitions for recurrent implantation failure and biochemical pregnancy, there is scarce data that accurately represents the incidence or prevalence

4. Causes

4.1 Gamete/embryo factors

4.1.1 Oocyte quality

- Age-related decline in oocyte quality is associated with increased chromosomal non-dysjunction, resulting in aneuploid embryos, decrease in mitochondrial membrane potential, and increase of mitochondrial DNA damage
- There is evidence to suggest that aggressive ovarian stimulation protocols may lead to the production of poor-quality oocytes and a higher rate of fertilization failure
- Co-culture of embryos with cumulus cells produced improved implantation and pregnancy in women with repeated implantation failure compared with conventional culture without cumulus cells

4.1.2 Poor quality embryos

- Older women have more mitochondrial DNA mutations and increased incidence of aneuploidy may be responsible for poor embryonic development
- COH and *in vitro* culture may contribute to poor or retarded embryonic development

4.1.3 Zona hardening

- The zona pellucida, hardens naturally after fertilization to prevent polyspermic fertilization, and to protect the integrity of the preimplantation embryo
- Increased zona thickness and zona hardening induced by *in vitro* culture or by *in vivo* ageing, affect hatching, and associated with lower implantation rates

4.1.4 Sperm quality

- High DNA fragmentation may be associated with an increased risk of miscarriage, but its association with RIF has not yet been established

4.1.5 Suboptimal culture conditions

- Sophisticated and tailored specific culture conditions and optimal laboratory facilities are needed for optimal embryonic development and lack of these conditions result in RIF

4.2 Parental chromosomal and genetic anomalies

- Chromosomal abnormalities are significantly more likely in women who had RIF. The most common abnormality is translocation

4.3 Uterine factors – Anatomical abnormalities

- Congenital uterine anomalies
- Acquired intracavity conditions

- » Submucous fibroids
- » Intramural fibroids
- » Endometrial polyps
- » Intrauterine adhesions
- » Adenomyosis

4.4 Altered expression of adhesive molecules

- Local dysregulation of normal expression or action of various cytokines, interleukins and integrins
- Elevated endometrial NK cells
- High levels of aromatase p450 mRNA
- Changes in pinopode expression and high matrix metalloproteinases

4.5 Thin endometrium

- Thin or hyperechogenic endometrium or persistent endometrial fluid impaired the outcome after ART

4.6 Hydrosalpinges

- Hydrosalpinx fluid – alkaline and contains cytokines, PG or other inflammatory compounds – have direct embryo-toxicity or adversely affect the endometrium reflux of hydrosalpinx fluid into uterine cavity result in diminishing embryonic endometrial apposition
- Hydrosalpinges can have a negative impact on implantation in women undergoing IVF

4.7 Immunological factors

- Principal pathogenic mechanisms mediated by immunological factors are highlighted in the table below

Table1. Principal pathogenic mechanisms mediated by immune factors

Interference with:	
a) Soluble coagulation factors:	Protein C/S pathway inhibition fibrinolysis inhibition
b) Coagulation cells:	Induction of a pro-adhesive, pro-inflammatory and pro-coagulant endothelial phenotype induction of a procoagulant phenotype in monocytes
Interference with:	
a) Trophoblast cells:	Reduction of proliferation and differentiation GT secretion impairment

4.8 Thrombophilic condition

- A strong association exists between anti- $\beta 2$ glycoprotein 1 and anti-nuclear antibodies and implantation failure⁹
- But no evidence exists to suggest that these antibodies directly cause the implantation failure
- Inherited thrombophilias such as methylene tetrahydrofolate reductase (MTHFR) deficiency, factor V Leiden, prothrombin deficiency, and antithrombin III deficiency are seen in higher rate in women with RIF, but they do not have a significant role in IVF embryo transfer implantation failure

4.9 Infection

- Diagnose chronic endometritis with on histological examination, on visualization with hysteroscopy, and by bacterial culture
- Use immunohistochemistry stain for syndecan-1 (CD 138), a plasma cell marker to provide a more accurate diagnosis

4.10 Suboptimal ovarian stimulation

- COH associated with supraphysiological E2 –affect oocyte quality & endometrial receptivity

- Altered endometrial receptivity due to premature expression of pinopodes and integrins, resulting in precocious luteal transformation
- Abnormal luteal phase steroid secretion

4.11 Suboptimal embryo transfer

- Suboptimal ET technique can reduce the implantation rate (IR) and pregnancy rate (PR) significantly
- It is estimated that poor embryo transfer technique may account for as much as 30% off all failures in assisted reproduction

5. Investigation of recurrent implantation failure

Table 2. Investigation of recurrent implantation failure

Recommended investigations	Investigations of research value
Hysteroscopy	Hereditary/acquired thrombophilia
Hysterosalpingography	Sperm DNA fragmentation
Pelvic ultrasonography	Endometrial receptivity markers
Parental karyotype	Embryo biopsy with PGT-A
Ovarian reserve and function: FSH, anti-Müllerian hormone, antral follicle count	
Thyroid antibody	

6. Management

- Through history and examination
- Transvaginal ultrasound (2d and 3D) to rule out uterine and adenexal pathology
- Ovarian reserve testing
- Hysteroscopy to evaluate uterine cavity
- Thrombophilia and APLA screen
- Karyotyping of both parents
- Thyroid antibody evaluation
- Sperm DNA fragmentation evaluation
- Adopt a multidisciplinary approach in the management of a couple with RIF

- Review couples with RIF by an experienced fertility specialist
- Offer appropriate counselling of the couple with RIF, which is of the utmost importance prior to proceeding with further treatment

6.1 The uterus

6.1.1 Hysteroscopy

- There is convincing evidence that hysteroscopy improves the outcome of women with RIF¹¹

Intracavity lesions

- Submucous fibroids
 - » Submucous fibroids significantly reduced the implantation rate, clinical pregnancy rate and live birth rate and significantly increased the miscarriage rate¹²
 - » Hysteroscopic removal of submucous fibroids distorting the uterine cavity recommended

Endometrial polyps

- Remove the endometrial polyps in women with RIF.
- Removal of endometrial polyps in women undergoing intrauterine insemination resulted in doubling of the clinical pregnancy rate.¹³

Uterine septum

- Uterine septal resection in women with RIF, regardless of the size improves pregnancy rates and decreases miscarriage rate.¹⁴

Intrauterine adhesions

- It is accepted that intrauterine adhesions would interfere with the implantation process and adversely affect the implantation rate and so, if present in women with RIF, should be removed (March, 2011)
- Nevertheless, there are as yet no firm literature data to confirm that removal of intrauterine adhesions improves the implantation rate

6.2 Myometrial pathology

6.2.1 Intramural fibroids

- The final decision of myomectomy must be individualized, and the involvement of a reproductive surgeon in the decision-making process is recommended.¹⁵
- Removal of all intramural myomas close to junction zone alter endometrial peristalsis hampering implantation and therefore removal recommended

6.2.2 Adenomyosis

- The role played by adenomyosis in reproductive failure is receiving increasing attention and is now recognized to be a cause of RIF¹⁶

6.3 Thin endometrium

- Endometrial thickness, ≤ 7 mm is associated with compromised success rates.¹⁷

6.3.1 Treatment of Endometritis

- Treatment of bacterial and tuberculosis endometritis
 - » **Antibiotics for infection**
 - In patients who have had CE diagnosed via hysteroscopy and culture, antibiotic therapy has been shown that antibiotic therapy to be an effective intervention to improve endometrial thickness and implantation rate
 - » **5.3.4 Tuberculosis endometritis**
 - Premenstrual endometrial sampling for smear, culture, PCR, and histopathology
 - Positive for TB requires treatment
 - # Intensive phase treatment for 2 months with isoniazid, rifampicin, pyrazinamide, and ethambutol
 - # Followed by 4 months of isoniazid, rifampicin

6.3.2 Adjuvant empirical therapies used to improve endometrial thickness

- Low-dose aspirin
 - » Low dose aspirin at least hypothetically *might* enhance endometrial growth and embryo implantation via a triple mechanism of actions reducing subendometrial contractility

minimising inflammation by inhibiting cyclooxygenase and prostaglandin biosynthesis and improving uterine endometrial blood flow¹⁹

- » The evidence to support the beneficial impact of low dose aspirin in patient with a thin endometrium is scare and controversial as no effect on endometrial thickness or uterine blood has been demonstrated.
- Heparin, corticosteroids
 - » Not many studies on improving endometrial thickness
 - » Drugs to increase uterine radial artery blood flow – sildenafil, L-arginine, and Vitamin E
- Sildenafil
 - » Sildenafil citrate has also been proposed in the women with RIF associated with a thin endometrium
 - » The hypothesis behind the use of sildenafil is that it increases endometrial blood flow, but results of observation studies have not yet been confirmed by any RCT
- L-arginine (no substrate)
 - » Relaxes vascular smooth muscells by activating cGMP
- Vitamin E
 - » Increases capillary blood flow and protects endometrium from oxidative stress
- Intrauterine injection of hCG
 - » Intrauterine injection of 500 IU of hCG before embryo transfer improved pregnancy rate compared to control group but was not significantly different.
- Granulocyte colony-stimulating factor (G-CSF)
 - » Infusion of G-CSF in endometrial cavity is a safe and may be effective method to increasing endometrial thickness in patients with thin and unresponsive endometrium
- Autologous platelet rich plasma

- » PRP intrauterine infusion might be a new alternative for patients with poor endometrial growth although still better solid evidence is expected
- Stem cell treatment in implantation failure
 - » Stem cell therapy may be effective for Asherman's syndrome and thin endometrium (<5 mm) though the evidence is sparse
 - » Stem cells used for treatment of a thin endometrium include mesenchymal stem cells, human embryonic stem cells, endometrial stem cells, and non-hematopoietic bone marrow-derived stem cells (BMDSCs) could induce endometrial regeneration
 - » BMDSCs induce regeneration of endometrial cells by paracrine signalling and this effect is two fold higher if used during uterine injury
- Luteal support with GnRHa
 - » Administration of GnRHa on day of oocyte recovery, on the day of embryo transfer and 3 days later appeared to have significantly higher estradiol, progesterone concentrations, thicker endometrium, higher implantation and pregnancy rates, and may be advocated in women with RIF
- » Salpingectomy and in some cases tubal occlusion procedures in the presence of hydrosalpinges have been shown to increase the likelihood of implantation success in future IVF cycles.²²
- » Removal of USG visible unilateral or bilateral hydrosalpinges recommended

6.5 Optimal IVF treatment

6.5.1 Tailoring the stimulation protocols

- Softer OI protocols, demonstrate improved IRs
- Use of GnRH-antagonist protocols improved blastocyst quality and pregnancy outcome after RIF with GnRH-agonist protocols
- Step-down protocol for OI where the FSH 'window' is shortened results in reduction in number of recruited and mature follicles and lower E2
- In women with endometriosis and adenomyosis, the use of ultra-long protocol involving the administration of gonadotrophin-releasing hormone (GnRH) agonists for a few months prior to IVF or ICSI may increase the pregnancy rate
- Optimal luteal phase support recommended

6.5.2 Embryo factor

- Preimplantation genetic screening–Data suggests that patients with RIF have more chromosome abnormalities within their embryos
 - » PGT-A for selecting chromosomally normal embryos for ET may increase IRs
 - » Preimplantation genetic testing for monogenic (single gene) disorders (PGT-M) can be used to evaluate specific chromosomal diseases among IVF patients with specific risk factors
 - » Preimplantation genetic testing for structural rearrangements (PGT-SR) is recommended in patients with balanced translocations

6.5.3 Assisted hatching

- Hatching of the blastocyst plays an integral role in the implantation process and failure to hatch (due to intrinsic abnormalities in either the blastocyst or zona pellucida) is a possible cause of implantation failure

6.3.3 Endometrial injury

- The possibility that local injury of the endometrium in the cycle preceding IVF treatment increases the success rate of implantation.²⁰
- It is not exactly clear why the endometrial biopsies helps the implantation rate. It is speculated that the healing process following endometrial biopsy may release cytokines and growth factors which facilitate the process of implantation

6.3.4 Microbiota of the uterus

- Uterine microbiota may contribute to healthy endometrial physiology and is responsible for receptive fertile endometrium

6.4 Salpingectomy

- Assisted hatching involves the artificial thinning or breaching of the zona pellucida and has been proposed as one technique to improve implantation and pregnancy rates following IVF²⁵
- Available evidence does not support the routine application of assisted hatching in all IVF cycles
- Assisted hatching may be clinically useful in patients with poor prognosis, including those with a history of two or more unsuccessful IVF cycles, poor embryo quality, thick zona, frozen embryo transfers and older women (38 years of age) and

6.5.4 Blastocyst transfer

- Blastocyst transfer is more physiological, it examines the property of embryonic genome with improved embryo selection, and uterine receptivity

6.5.5 Frozen vs. fresh embryo transfer

- Freeze-all policy is a potentially effective paradigm to improve RIF outcomes, in particular the rates of implantation and clinical and ongoing pregnancy in patients with risk of OHSS, progesterone rise, genetic testing, abnormal endometrium

6.6 Endometrial receptivity array

- Transcriptomic signature of ERA test reveal that the endometrial factor is responsible for 25% of cases of patients with RIF. Thus WOI is displaced in 25% of RIF patients, and pET can normalize clinical results
- ERA and pET were effective for a subset of patients with unexplained RIF, and by transferring euploid embryos in a personal WOI, with better PRs
- It is still questionable whether ERA will be cost-effective as the first diagnostic line for the endometrial factor

6.7 Transfer methods

- Improving ET technique – higher PRs obtained with USG guided atraumatic technique and embryos being deposited in middle part of the uterine cavity
- Use of fibrin glue may improve pregnancy rates in RIF

- A trial embryo transfer should be considered where a prior embryo transfer has been described as difficult or where difficulty may be anticipated
- Cervical dilatation undertaken prior to COH in women with previous H/O difficult ET

Sequential embryo transfer

- Sequential embryo transfer has been proposed as a means of improving implantation rates²⁹
- The concept behind this strategy is to overcome the problem of embryo–endometrium asynchronicity as a potential cause of implantation failure
- Till date, there appears to be preliminary evidence to suggest that double–embryo transfer may be of benefit, but carefully designed randomized controlled trials are required to confirm its value, if any, in women with RIF

6.8 Luteal phase support

Progesterone therapy

- Progesterone and specifically orally administered dydrogesterone used in IVF protocols, may have a significant role in improving pregnancy, and live birth rates among patients with RIF mainly when started in the luteal phase. More studies are needed to support this

6.9 Antithrombotic agents

- Aspirin irreversibly inhibits cyclooxygenase activity and prostaglandin production, reduces the inflammatory response, promotes vasodilatation, and increases uterine blood flow but its use in RIF is still controversial
 - » Heparin has been evaluated for use in RIF patients, though there is not yet evidence to recommend its use for improved pregnancy outcomes in these patients
 - A group of RIF patients treated with low molecular weight heparin had almost identical implantation, clinical pregnancy, and live birth rate outcomes when compared with controls³¹

6.10 Immunotherapy

6.10.1 Intravenous immunoglobulin (IVIG)

- IVIG treatment has also been regarded as a possible immunological therapy for women suffering from repeated implantation failure with an elevated Th1/Th2 ratio, elevated NK cells, an abnormal TNF α /IL-10 ratio, and auto-antibodies
- Expensive interventions, the optimal protocol for the administration of IVIG is undefined, and the overall benefits of IVIG are still controversial

6.10.2 Granulocyte colony-stimulating factor (G-CSF)

- The subcutaneous injection of G-CSF can improve the outcome of patients with recurrent miscarriage
- Intrauterine peripheral blood mononuclear cell (PBMC) administration:
 - » Intrauterine administration of autologous PBMC activated by human chorionic gonadotropin (hCG) effectively improves embryo implantation and IVF outcomes in patients with RIF
 - » Mechanism of intrauterine hCG-activated PBMC administration may be that it can promote trophoblast cell spreading and invasion into endometrium and can increase the expression of endometrial factors which facilitate implantation
 - » There is insufficient evidence to recommend intrauterine infusion of autologous peripheral mononuclear cells prior to ET to improve IVF outcome

6.10.3 Steroids

- Administration of a high dose of methylprednisolone for four consecutive days at the time of oocyte retrieval may improve IVF outcomes

6.10.4 Intralipid infusion

- Intralipid infusion is a 20% fat emulsion that reduces the Th1/Th2 ratio and suppresses the abnormal NK cytotoxicity of peripheral NK cells, thereby increasing the likelihood of implantation and clinical pregnancy.

- » Further studies are needed to determine the efficacy of intralipid infusion in women with RIF

6.10.5 Tacrolimus: An immunosuppressive drug

- Inhibits antigen-induced lymphocytic proliferation, cytotoxic T-cell formation, IL-2 receptor expression, and the production of IL-2 and interferon-gamma
- 1 to 3 mg tacrolimus 2 days prior to ET may improve clinical pregnancy and live birth rates
- There is insufficient evidence to recommend tacrolimus to improve IVF-ET outcome in RIF

6.10.6 Adalimumab (tumor necrosis factor alpha [TNF α] blocking antibody)

- Insufficient evidence to recommend adalimumab treatment to improve IVF outcome and should only be used in the context of research as Institutional Review Board (IRB)-approved studies

6.11 Treatment in the male

- In addition to maternal factors playing a role in RIF, male factor, particularly spermatozoal morphology also can play a part
- Antibody-free preparation of spermatozoa has been investigated to reduce the potential impact of anti-sperm antibodies on fertilization rates in couples with anti-sperm antibody-positive male partners. But there is insufficient evidence to support the recommendation either for or against antibody-free preparation of spermatozoa in improving IVF outcome in RIF
- Intracytoplasmic morphologically selected sperm injection (IMSI) selects morphologically normal sperms for ICSI and may be of use in RIF but the evidence is sparse to recommend its use routinely in RIF
- Role of PICSI to choose sperms with low DFI is controversial and should not be used

6.11.1 Lifestyle modifications

- » Evidence suggests that smoking, obesity, and high cortisol levels also play a role in implantation failure.

- » Achieving healthy BMI through exercise and diet
- » Psychological interventions and various relaxation techniques recommended
- » Cessation of Smoking is advised in both partners as it has a negative impact on sperm quality, fertilization rate, implantation rate, and live birth
- » Women with RIF should be advised to abstain from alcohol

6.12 Psychological assistance

- » Psychotherapy (group and individual) reduces anxiety and depression and enhances conception success

6.13 Gamete donation and surrogacy

- » Advice gamete donation if the likely source of the problem lies with the embryo
- » Discuss surrogacy if the problem lies in the uterus, for example multiple small fibroids or Asherman's syndrome which has failed to respond to surgical treatment

Summary of recommendations

Category	Recommendation	Grade of recommendation	Quality of evidence
CCR	Appropriate investigations should be carried out to determine the cause of RIF depending on the history and examination	C	-
CCR	Hysteroscopy should be carried out to exclude any intracavity uterine pathology; it has been shown to improve outcome	A	-
EBR	Submucosal fibroids have been shown to reduce implantation, pregnancy and live birth rates; removal of submucosal fibroids improves implantation rate	A	I
EBR	Endometrial polyps should be removed; although there is no data on its impact on women undergoing IVF, it has been shown to improve outcome in women undergoing intrauterine insemination	B	I
EBR	Appropriate investigations should be carried out to exclude hydrosalpinx as it has been shown to reduce implantation rate, increase miscarriage rate and reduce live birth rate; removal of hydrosalpinges has been shown to improve the outcome	A	I
EBR	Endometrial scratch should be considered in the luteal phase of the cycle immediately preceding IVF treatment; it improves implantation rate and outcome in women with unexplained RIF	B	III
EBR	Uterine septum increases miscarriage rate; its removal improves outcome	B	II
EBR	Intramural fibroid of more than 5 cm and those close to junctional zone should be removed	C	III

Category	Recommendation	Grade of recommendation	Quality of evidence
CCR	Intrauterine adhesions are a recognized cause of thin endometrium not responding to ovarian steroid stimulation; if present, intrauterine adhesions should be removed	D	-
EBR	The use of ultra-long protocol may improve outcome in women with endometriosis and adenomyosis	C	III
CCR	Softer OI protocols, demonstrate improved IRs	C	-
EBR	Use of GnRH-antagonist protocols improved blastocyst quality and pregnancy outcome after RIF with GnRH-agonist protocols	B	III
EBR	No clear evidences published yet about the real efficacy of IMSI and PICSI in improving CPR or LBR in RIF	C	III
EBR	PGT-A may increase IR in RIF by selecting euploid embryos for transfer	B	II
EBR	Assisted hatching may improve outcome in RIF	C	I
EBR	Soft catheters should be routinely used as statistically significant higher CPR and LBR reported	A	II
CCR	Removing cervical mucus at the time of embryo transfer to improves CPR and LBR	B	-
CCR	Ultrasound guidance during embryo transfer improve CPR and LBR and is recommended	A	-
EBR	Proper placement at a distance >10 mm to <20 mm seems to be the best site for embryo transfer to achieve higher PRs	A	II
EBR	Minimize embryo stress by minimizing transfer time (<120 seconds), maintaining temperature/pH which is associated with significant increase in IR and PR	B	II
EBR	Easy, atraumatic and technically precise transfer without blood or mucus transfers improve IR	B	III
CCR	Optimize implantation, minimize contractions by performing day-5 ET, FET cycles and avoiding trauma to cervix or fundus Piroxicam 10 mg 2 hrs before ET reduces contractions	B	-
CCR	Adherence compounds such as hyaluronic acid are valuable in improving the success rate of assisted reproductive technologies such as IVF and ICSI with increase in LBRs in RIF	B	-
CCR	There is no evidence to suggest screening for immunological conditions in an asymptomatic population.	B	-

Category	Recommendation	Grade of recommendation	Quality of evidence
CCR	Immunotherapies reviewed in the present document are either not associated with improved live-birth outcome in IVF or have been insufficiently studied to make definitive conclusions regarding benefits and risks. In the absence of well-designed adequately powered RCTs, patients must be informed of uncertain benefits and risks associated with immunotherapy	B	-
CCR	Empirical therapies should, whenever possible, be considered only in the setting of carefully conducted clinical trials	D	-
CCR	PRP and stem cells Stem cell therapy may be effective treatment for Asherman's syndrome and thin endometrium (<5 mm) though the evidence is sparse	D	-
CCR	Lifestyle changes may improve IR in RIF	D	-
CCR	A multidisciplinary approach should be adopted in the management of RIF	D	-

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Chapter 18: Third-Party Reproduction

OVERVIEW

This document highlights good practice recommendations on third-party reproduction for practicing gynecologists, embryologists, and infertility specialists in India. Third-party reproduction poses a constant challenge as it is socially, ethically, and legally complex. These recommendations are based on several guidelines from global societies, the Cochrane database, large meta-analysis, available Indian literature, prevalent practices in India, and consensus amongst experts in the field of third-party reproduction. These recommendations strengthen and promote meaningful research that will apply to Indian patients and Indian practice.

1. Sperm donation

1.1 Introduction

- In couples with infertility, male infertility affects about 25% of couples. Therapeutic donor insemination (TDI) is the most widely used artificial reproductive technique (ART) to treat male infertility; until the availability of intracytoplasmic sperm injection (ICSI). TDI is best indicated when a male partner is likely to pass on an:
 - » Inheritable genetic condition
 - » Infections (e.g. human immunodeficiency virus [HIV])
 - » Severe rhesus incompatibility

1.2 Indications for considering donor insemination

- Male partner with azoospermia, severe oligospermia, or other significant sperm or seminal fluid abnormalities
- Male partner with ejaculatory dysfunction or ineradicable sexually transmissible infection
- If a male partner is Rh-positive and the female partner is Rh-negative
- The partner is either affected or a carrier of genetic abnormality; or in cases where the partner's history of carrier status is unknown

1.3 Information and counseling

- Couples should be counseled about merits of ICSI and donor insemination that allows equal access to both the treatments

- Counseling regarding the physical and psychological implications on the couples and their children must be considered from someone independent of the treatment unit

1.4 Screening of sperm donors

- Gametes produced by a person aged <21 should not be used. Also, the accepted age of the sperm donor must be between 21 and 45 years
- Individuals must be free of infections and diseases such as sexually transmitted diseases (HIV), hepatitis B and C infections, hypertension, diabetes, and other common genetic disorders (thalassemia)
- An analysis of the semen of the individual must be done using a semen analyzer according to the world health organization (WHO) manual
- Psychological assessment by a qualified healthcare professional is recommended for all sperm donors
- Comprehensive medical history to be taken down
- Sperm donation by relative or friend is not permitted
- Donor samples should be taken from a registered gamete bank

1.5 Assessment of the female partner

- To attain effective donor insemination, women must be ovulating with at least one patent tube. Factors affecting the donor insemination success rates such as age, history must be evaluated as the fertility declines with age. Before donor insemination, menstrual cycles and a mid-luteal phase progesterone assessment must be considered to confirm ovulation.

In women with anovulation, appropriate treatment with ovulation agents must be considered

- Tubal status should be evaluated either by HSG, SIS or laparoscopy

Recommendations

- Therapeutic donor insemination is effective in male infertility associated with obstructive azoospermia, non-obstructive azoospermia, and severe defects in semen quality in couples that do not wish to undergo ICSI
- Donor insemination should be considered when there is a:
 - » High-risk of a genetic disorder or infectious disease to the offspring or mother from the father
 - » Severe rhesus isoimmunization
- ART procedures should not be considered without a spouse's consent
- Single women can undergo donor insemination
- Anonymity of the donor should be maintained
- Couples considering donor insemination should be offered counseling from someone independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children.
- ART banks should provide following information about donor to the recipient couple
 - » Profile matching should be done
 - » Colour of skin, eyes, hair, height, and weight
 - » Record of blood group, major illness including any psychiatric and familial disorders genetic, and hereditary diseases
 - » Screen for communicable disease including HIV, hepatitis, other sexually transmitted diseases, hypertension, diabetes
 - » Educational qualification and profession
 - » Ethnicity
- Women undergoing DI should be tested for thalassemia
- The data of every accredited ART clinic must be accessible to an appropriate authority of the ICMR for collation at the national level. An ART bank should not use the sperm from a single donor for multiple instances; there should be a limit in the number of sperm donation (25 times)
- No splitting and mixing of the sample are allowed and intrauterine insemination (IUI) should be limited to 6–12 IUI cycles
- All ART banks shall cryopreserve sperm donations after quarantine period before being used. After expiry, the sperm should not be supplied to any ART clinic unless the sperm donor is tested for sexually transmitted diseases, infections, or otherwise as may be prescribed

1.6 Welfare of children born after sperm donation

- Addresses the risks associated with medically assisted conception and its implications on the mental and physical health of the child
- Child will have identical legal rights as a legitimate child born through sexual intercourse
- The birth certificate of a child born through ART shall contain the name or names of the parent or parents
- The child born to a foreigner by sperm donation will not get Indian citizenship though he or she is born in India
- A child may, upon reaching the age of 18, ask for any information, excluding personal identification, relating to the donor. Personal identification of the genetic parent may be released only in cases of life-threatening medical conditions, which require physical testing or samples of the genetic parent or parents. Such personal identification will not be released without the prior informed consent of the genetic parent or parents

2. Egg donation

2.1 Introduction

- The recipient will have a biological but not genetic relationship to the child; her partner (if he provided the sperm) will be both biologically and genetically related

2.2 Indications

- Premature ovarian failure
- Diminished ovarian reserve
- Ovarian failure due to iatrogenic causes
- Prevent transmission of a genetic disorder
- Repeated IVF failures

2.3 Pre-requisites of oocyte donors

- The age of donors should be between 23 to 35 years. By restricting the oocyte donors to women <35 years, it decreases the risk of aneuploid offspring
- The donor should be a married woman with at least 1 child of ≥ 3 years
- A comprehensive history and physical examination is required
- The gamete donor should be screened for the infectious profile, communicable disease (HIV, hepatitis B surface antigen [HbsAg], hepatitis C virus [HCV], and venereal disease research laboratory [VDRL])
- A donor should be assessed for basic wellbeing and pre-anesthesia check before considering ovarian stimulation and oocyte isolation
- Donors should be screened for HbA2 – to rule out any hemoglobinopathies or to avoid genetic transmission of any inheritable diseases
- The psychological and mental wellbeing of the donor must be assured. The donor should be aware of the procedure and counseled about the same and a consent be taken

2.4 Ethics in oocyte donation

- Donor to be obtained from certified ART banks

- Women should not be allowed to donate oocytes more than three times in her lifetime with at least 3 months gap between each donation
- Eggs from one donor can be shared between 2 recipients only, provided that at least 7 oocytes are available for each recipient
- If married, donor requires her spouse's consent to donate eggs

2.5 Recipient characteristics and rights

- The recipient couple or the commissioning couple should be healthy, mentally sound (man >21 years, and woman >18 years, married)
- Either party seeking ART should be entitled to acquire specific information concerning donor of gametes (height, weight, ethnicity, skin color, educational qualifications, and medical history of the donor) provided that the details should be kept confidential
- If the recipient mother belongs to an advanced reproductive age, she should be counseled about the increased medical risks related to pregnancy. The counseling process must involve a physician familiar with managing a high-risk pregnancy
- The couple should be explained and counseled regarding the variation in the genetic make-up of the offspring resulting from the oocyte of a different parent. Oocyte donation should be strongly discouraged in the presence of obstetrical and neonatal risks (hypertension or diabetes)

Recommendations

- The highest possible standards must be followed in storing and handling of gametes and embryos. All unused oocytes must be preserved by ART banks for use on the same recipient, or given for research organizations registered under ART act along with written consent from both partners of the commissioning couple
- The gamete of a donor shall be stored for a period of > 5 years, and at expiry, the oocytes can be discarded or donated to research organizations registered under the ART act

- The sale, transfer or use of gametes, zygotes, and embryos, or any part thereof or information related directly or indirectly to any party within and outside India is prohibited; except in the case of transfer of own gametes and embryos for personal use according to the rules of the land
- Legal rights
 - » Children born through ART shall be deemed a biological child of the commissioning couple, and the child shall be entitled to all the rights, and privileges available to a natural child only from the commissioning couple under any law for the time being in force
 - » A donor shall relinquish all parental rights over the child or children born from his or her gamete
 - » Identity of the recipient should not be revealed to the donor
- Health issues: As donors can have following risk they should be counselled for the same and an informed consent is essential
 - » OHSS
 - » Pain and bleeding due to OR
 - » Damage to adjacent structures
 - » Infection
 - » Long term health consequences
 - » Psychological problems
 - » Risk of Ca breast, endometrium, and ovaries
- No ART clinic is allowed to:
 - » Sell human gametes, run an agency, a racket or an organization for selling, purchasing or trading in human gametes
 - » Import or shall help in acquiring imported gametes in any manner
 - » Exploit the commissioning couple or the gamete donor in any form
- National guidelines by ICMR suggest that embryo donation in ART should be used in the treatment of infertility only in indicated cases
- Left over embryos cannot be used for embryo donation

3.2 Embryo donation with frozen embryos

- In embryo donation, certain guidelines need to be considered such as anonymity, standards of screening, testing, and counseling of potential gamete donors and recipients

Financial compensation for gamete donors

- Financial compensation to be provided to gamete donors through ART banks

Ethical, moral, and legal issues

- The use of embryo donation in ART raises ethical, moral, and legal issues as it involves three different sides (donor, recipient, and the rights of the child)
- The anonymity of the donor
 - » An gamete donor has the right to remain anonymous under the Indian law. Thus it remains the duty of the ART clinic/bank to maintain the anonymity

ICMR consent forms for third party reproduction

- According to ICMR, the consent forms that need to be signed by the gamete donor, recipients, are mentioned below
- Consent forms for oocyte donors:
 - » Along with form K (consent form for the egg donation), ART bank/clinic needs to keep a record of form R1 (contract between the ART bank and oocyte donor summarizing the payment details, risk issues, medico-legal concerns, and also weaving off the parental rights), and M1 (information on egg donor; physical, and pathological findings)
- Consent forms for sperm donors:
 - » Along with form L (consent form for the sperm donor), ART bank/clinic needs to keep a record of form R1 and M

3. Embryo donation

3.1 Introduction

Recommendations

- The decision to proceed with donated gametes is complex, and both donors and recipients benefit from psychological counselling to aid in this decision
- Psychological counselling offered by a qualified mental health professional to all couples and may require psychological consultation for those couples in whom there appear to be factors that warrant further evaluation
- Before the onset of the treatment, the counselling should involve thorough explaining of, limitations, success rate of the treatment, possible side effects and risk to the women, psychological impact and the child born, possible disruption of the domestic life, cost of the treatment, alternative options etc.
- The patient should be given the liberty to take the decision on their own and they should not be forced to opt for any treatment. The patient should give the consent for the treatment in writing before starting the treatment
- Consent form signing and proper counseling of the treatment:
 - » The recipient/donor should be explained in detail about the treatment and its medical implications which should be recorded
 - » Record of all the notarized appropriate consent forms and counseling details should be attached to the patient's file. Consent from both husband and wife is necessary for any procedures
- Compulsory record keeping and track of all the embryos
 - » According to ICMR, there should be a record of all gamete donors, along with the recipient's information. The ICMR form N, O(a), O(b), O(c), and P helps in binding all the records and maintaining it easily
- All ART clinics shall maintain detailed records, in the following manner:
 - » As may be prescribed by ICMR of all IUI and ART cycles
 - » Sperm, oocytes or embryos used
 - » The manner and technique of their use
 - » The individual or couple or surrogate mother in respect of whom it was used
 - » Of all donor oocyte and embryo cycles
 - » Records should be maintained for at least a period of ten years
- ART clinic should obtain donor gametes from ART banks that have ensured that the donor has been medically tested for sexually transmitted and communicable diseases which may endanger the health of the parents, or any one of them, surrogate or child
- The ART bank shall keep a record of all the gametes received, stored and supplied, and details of the use of the gametes of each donor. If not otherwise ordered by a court of competent jurisdiction, all ART banks shall ensure that all information about clients and donors is kept confidential and that information about gamete donation shall not be disclosed to anyone
- Using sperm or oocyte donated by a relative or known friend of either of the parties seeking assisted reproductive technology treatment or procedures is prohibited

4. Surrogacy

Age of commissioning couple should be

- Female – 23–50 years
- Male 26–55 years

4.1 Indications for surrogacy

- Indications can be both medical and social. In India, medical indications are accepted for surrogacy. These include:
 - » Congenital absence of uterus (Mayer–Rokitansky–Kuster–Hauser syndrome)
 - » Surgical removal of the uterus
 - » Asherman's syndrome

- » Woman with Rh incompatibility
- » Malformed uterus
- » Significant medical conditions in which carrying a pregnancy is a threat to life
- Surrogacy is recommended as a last resort treatment when other modalities have been exhausted
 - » Repeated failure of IVF treatment
 - » Recurrent miscarriages

4.2 Types of surrogacy

4.2.1 Gestational surrogacy:

- In India, gestational surrogacy is practiced gestational surrogate is a woman who carries a pregnancy for another couple or woman where pregnancy created by transferring an embryo created with the sperm and egg of the intended parents. It is an arrangement in which a woman agrees to a pregnancy, achieved through ART (IVF), in which neither of the gametes belongs to her or her husband, to carry the pregnancy and hand over the child to the person or persons for whom she is acting as a surrogate

4.2.2 Traditional surrogacy

- Surrogate is inseminated with sperm from the male partner of the intended parent and is not allowed

4.3 Selection of a Gestational Carrier is based on

- Known/anonymous
- Minimum of 21 years of age and <38 years
- Preferably in a stable marriage
- Delivered a live-born child at term
- STI-screening—once when she agrees and once before embryo transfer
- Medical and psychological assessment

4.4 ICMR guidelines for surrogacy

- Legal contract should be made between intending or commissioning parents by ART banks as the law
- Agreement regarding

- » Fetal reduction
- » Therapeutic abortion
- » Declaration of parentage of child's birth obviating the need for adoption proceedings

4.5 Counselling

4.5.1 Surrogate

- Emotional Issues
- Impact on family
- Financial compensation
- Possibility of hospitalization
- Possibility of multiple pregnancy

4.5.2 Intended Parents

- Maintaining a respectful relationship with surrogate
- No. of embryos for transfer
- Fetal reduction and abortion
- Importance of obtaining legal advice
- Success rate and cost

4.6 Legal aspects of surrogacy

- Legal guidelines are necessary to safeguard the interests
- Surrogate mother should be from same generation and between of 21–35 years
- Woman can become a surrogate mother for upto 1 live birth excluding her own
- Genetic parents legally bound to accept the custody of the child irrespective of any abnormality, and the refusal to do so shall constitute an offence
- Surrogate mother shall not act as an oocyte donor for the couple or individual
- If a surrogate is married, the consent of her spouse shall be required
- A couple or an individual shall not have the service of more than one surrogate at any given time
- A couple shall not have simultaneous transfer of embryos in the woman and in a surrogate

- Surrogacy arrangement should provide for financial support for surrogate child in the event of death of the commissioning couple or individual before delivery of the child, or divorce
- Surrogacy contract should necessarily take care of life insurance cover for surrogate mother for a total duration of 36 months
- One of the intended parents should be a donor as well. In case the intended parent is single, he or she should be a donor
- Legislation itself should recognize a surrogate child to be legitimate child of the commissioning parent(s) without there being any need for adoption
- The birth certificate of the surrogate child should contain the name(s) of the commissioning parent(s) only
- Right to privacy of donor as well as surrogate mother should be protected
- Art clinics offering surrogacy services will not import human embryos for offering surrogacy services except for Indian residents who can import their own embryos
- Foreign nationals and overseas citizens of India (OCI) cannot commission surrogacy
- Provide surrogacy only to married Indian couples
- Therapeutic donor insemination is best indicated to avoid the high-risk of transmitting genetic disorders or infections to the offspring or mother from the father. Also during severe rhesus isoimmunization
- All ART banks need to quarantine cryo-preserve sperm samples for at least 6 months. After this period it cannot be supplied to any ART clinic unless it is tested for sexually transmitted diseases and infections
- Storing and handling of gametes must be carried out with the highest standards. The gametes of the donor can be stored for a period of >5 years; after, that the oocytes can be discarded or donated to research organizations registered under the ART act with consent
- The sale, transfer or use of gametes, zygotes, and embryos, or any part thereof or information related directly or indirectly to any party within and outside India is prohibited; except in the case of transfer of own gametes and embryos for personal use with the permission of the National Registry.
- Children born through ART must be entitled to all the rights. Children should be deemed a biological child of the commissioning couple
- ART clinics or banks are not allowed to sell human gametes, zygotes, and embryos. Also, any ART clinic should not exploit the commissioning couple or the gamete donor in any form

4.7 Financial transactions

- The financial aspect of the process has to be decided upon independently by the woman and the couple and the ART center can in no way become involved in the money that the surrogate mother receives
- In ART, clinical counseling with a trained and experienced counselor is a compulsion for the couple or anyone involved in the transfer of gametes, zygotes, or embryos

Summary of recommendations

- Infertility in couples with male infertility linked to obstructive azoospermia, non-obstructive azoospermia, and severe defects in semen quality can best be treated with therapeutic donor insemination in couples who do not wish to undergo ICSI
- According to ICMR, there should be a record of all gamete donors along with the recipient's information.
- Also, notarized consent from the recipient and the donor should be emphasized.
- Only gestational surrogacy is allowed.

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CCR	Infertility in couples with male infertility linked to obstructive azoospermia, non-obstructive azoospermia, and severe defects in semen quality can best be treated with therapeutic donor insemination in couples who do not wish to undergo ICSI	B	-
CCR	Therapeutic donor insemination is best indicated to avoid the high-risk of transmitting genetic disorders or infections to the offspring or mother from the father. Also during severe rhesus isoimmunization	C	-
CCR	All ART banks need to quarantine cryopreserve sperm samples for at least 6 months. After expiry, this period it cannot be supplied to any ART clinic unless it is tested for sexually transmitted diseases and infections	B	-
CCR	Storing and handling of gametes must be carried out with the highest standards. The gametes of the donor can be stored for a period of >5 years; after, that the oocytes can be discarded or donated to research organizations registered under the ART act with consent	B	-
CPP	The sale, transfer or use of gametes, zygotes, and embryos, or any part thereof or information related directly or indirectly to any party within and outside India is prohibited; except in the case of transfer of own gametes and embryos for personal use with the permission of the National Registry	-	-
CPP	Children born through ART must be entitled to all the rights. Children should be deemed a biological child of the commissioning couple	-	-
CPP	ART clinics or banks are not allowed to sell human gametes, zygotes, and embryos. Also, any ART clinic should not exploit the commissioning couple or the gamete donor in any form	-	-
CPP	In ART, clinical counselling with a trained and experienced counsellor is a compulsion for the couple or anyone involved in the transfer of gametes, zygotes, or embryos	-	-
CPP	According to ICMR, there should be a record of all gamete donors along with the recipient's information. Also, notarized consent from the recipient and the donor should be emphasized	-	-
CPP	Only gestational surrogacy is allowed in India	-	-

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Chapter 19: Fertility Preservation

OVERVIEW

The goal of this update is to provide health care providers and caregivers with recommendations regarding fertility preservation for patients with oncological and non– oncological conditions compromising fertility.

1. Introduction

- The cancer burden in India is estimated to be 1.45 million new cases each year, as per the ICMR registry data
- The most common female cancers are breast, and cervical cancers, and the most common male cancers are prostate, rectum and colon
- Leukemias and lymphomas are the commonest malignancies encountered in childhood
- Breast cancer which has the highest incidence of all cancers in females has also become frequent in a population younger than 50 years
 - » In most hospital–based series reports, median age of breast cancer patients is a decade younger than the western series
- At times, breast and ovarian cancer occurs due to inherited genetic mutations (called the hereditary breast and ovarian cancer syndrome) (ICMR).
- More than 140,000 cancer patients are diagnosed in their reproductive years; up to the age of 45 years. Childhood cancer too seems to be increasing

2. What is meant by fertility preservation (FP)

- Fertility preservation refers to the expansion of the reproductive window through preservation of gamete and gonadal tissue (oocyte, sperm, embryo, ovarian and testicular tissue) for use at a later date. It also includes fertility preserving reproductive surgeries.

3. Indications for fertility preservation

Fertility Preservation is offered to individuals at risk of losing their gametes (sperm/oocytes) prematurely

due to disease or its treatment. This technology has been extended to women wanting to delay childbearing, and to overcome the effect of age on ovarian reserve.

3.1 Oncofertility – Patients in reproductive age

- Undergoing gonadotoxic chemotherapy in cancer and noncancer conditions
- Undergoing RT leading to gonadal damage

3.2 Prevention of age–related decline in fertility in women

3.3 Decline in fertility in autoimmune, genetic disorders, and ovarian pathology.

- Autoimmune disease
- SLE
- Behcet's disease
- Steroid resistant glomerulonephritis
- Inflammatory Bowel diseases
- Rheumatoid arthritis
 - » Pemphigus vulgaris
- a. Genetic disorders and ovarian pathology leading to premature ovarian insufficiency
- b. Turner mosaic
- c. Beta–thalassaemia
- d. Galactosaemia
- e. Endometriosis
- f. Benign ovarian tumours

3.4 Patients undergoing hemopoietic stem cell transplantation

- Autoimmune diseases unresponsive to immunosuppressants
- Hematological diseases like:
 - » Sickle cell anaemia
 - » Thalassaemia major
 - » Aplastic anaemia

4. Need for fertility preservation

4.1 Effect of cancer treatment on fertility

- Approximately 40%–80% of females and 30%–70% males face possible infertility as a result of cancer treatments such as chemotherapy (CT), radiation (RT), and surgery
- In men, CT leads to Leydig cell dysfunction, germ cell failure, and sexual and ejaculatory dysfunction
- In women, CT can lead to ovarian failure, premature menopause, and premature ovarian insufficiency (POI) and infertility due to the apoptotic effect on oocytes. RT causes uterine damage by fibrosis and effect on vascularity, increasing the chances of subsequent infertility and adverse pregnancy outcome. These effects are drug and dose dependent

4.2 Effect of age on fertility

- Decline in fertility is a result of the decrease in ovarian reserve (OR) or egg numbers that occurs with aging as well as the increased rate of aneuploidies seen in oocytes of women over 35 years

4.3 Relevance of FP

- Modern cancer treatment has increased the survival rates in young cancer patients over the last two decades. Unfortunately, the gonadotoxic effects of these treatments can impair the reproductive ability in young cancer survivors
- Preservation of gametes allows cancer survivors to fulfil their reproductive desires after completing treatment

- Fertility preservation is becoming increasingly important to improve the 'quality of life' in cancer survivors
- Despite guidelines suggesting that discussion of fertility preservation should be done prior to starting cancer therapies there is a lack of implementation in this area
- Cryopreservation of sperm should be offered to all cancer patients in reproductive age regardless of the risk of gonadal failure
- Individualize recommendation of fertility preservation in women based on as the urgency of starting cancer treatment, the drug and dosage of CT and age of the patient

5. Multidisciplinary team assessment prior to embarking on FP

- Involve a multidisciplinary team, which includes
 - » Oncologist for treatment regimen and oncological risk assessment
 - » Reproductive medicine specialist to assess feasibility of FP
 - » Counsellors and geneticist to discuss genetic and psychological issues

6. Assessment for Feasibility of procedure

- Assessment of general condition is essential since General Anaesthesia is required for Fertility Preservation procedures in women
 - » In women, carry out fertility assessment by ovarian reserve testing this includes antral follicular count by vaginal ultrasound and AMH
 - » In men,
 - Advise for semen analysis (same sample can be cryopreserved)
 - Need for assisted ejaculation
 - Testicular tissue CP

7. Fertility preservation in males–best practice recommendations

- Research has shown that people with cancer are interested in discussing fertility preservation options
- Patients should be made aware of the options of fertility preservation and future reproduction prior to initiation of treatment
- Patients should be counseled on high risk of genetic damage in their sperm even after a single course of chemotherapy
- The discussions regarding fertility preservation should be documented in the medical records
- Efforts should be made to start and complete fertility preservation promptly, without causing any delay in the treatment of cancer
- Cryopreservation of spermatozoa obtained via ejaculation or surgical sperm retrieval is the only established method of fertility preservation in males. If initial sperm count is below WHO standard, then preferably preserve 2–3 samples (to account for post thaw loss). If sperm counts are normal, 1 sample may suffice. However, 1–3 samples recommended
- In sexually mature men unable to provide an ejaculate, sperm can be retrieved by epididymal or testicular aspiration or testicular biopsy
- When ejaculation is not possible due to medical, social or religious reasons, suggest performing penile vibratory stimulation (PVS), electroejaculation under general anesthesia, or surgical retrieval from the epididymis or the testis
- In prepubertal boys, cryopreservation of immature testicular tissue (ITT) as cell suspension or whole testicular tissue followed by autografting, xenografting or *in vitro* spermatogenesis is an option. Consider ITT experimental and only perform under institutional review board–approved protocols
- In patients who are minors, parents may consent for surgical sperm retrieval. However, assent of the child should be taken, if possible

New point – Concerns have been raised over the reintroduction of cancerous cells in the ITT after transplantation

- Provide clear instructions duly signed by the patient about the disposition of stored sperm or testicular tissue in the event of the patient's death, unavailability, or other contingency
- Suggest discarding the gametes if the child does not survive to adulthood, unless there are written instructions to preserve it

7.1 Indian scenario

Current statistics

- In 2018 over 1.1 million new cancer patients in India were registered, of which 0.57 million were males
- The deaths due to cancer stood at 0.78 million

7.2 Challenges in management with solutions

- The limitations are urgency to commence treatment, limited resources, and perceived high cost and ignorance on part of the medical provider
- There is apprehension in the patients mind that fertility preservation will delay cancer treatment and worsen their prognosis
- Fertility preservation does not contribute to a significant delay in the initiation of cancer treatment

8. Fertility preservation techniques in females

- Options for fertility preservation are oocyte and embryo cryopreservation and ovarian tissue freezing
- Ovarian tissue preservation is the only option for prepubescent girls

8.1 Oocyte cryopreservation

- Mature oocyte cryopreservation by vitrification is a well-established technique
- Similar success rates have been reported between IVF with vitrified warmed oocytes and IVF with fresh oocytes

- Congenital abnormalities are reported to be similar in infants born, following oocyte vitrification to pregnancies by regular IVF, and natural conception
- Mature oocyte cryopreservation is necessary which requires ovarian stimulation which can delay cancer treatment and is also contraindicated in patients with hormone receptive cancer
- Alternative to mature oocyte cryopreservation in such patients is to cryopreserve immature oocytes
- *In vitro* maturation of immature oocytes requires special culture media and expertise
- Clinical efficiency of these techniques is yet to be proven and should be attempted under expert guidance only after counseling the patients regarding the survival and outcome
- CT for breast cancer is damaging to the ovary, since most regimes use alkylating agents
- Advise early referral to RM specialists should be advised as there is time available between surgery and CT to do FP
- Ovarian tissue preservation for women requiring co-adjuvant CT should be offered keeping in mind the risk of concomitant ovarian cancer in BRCA mutated women

Ovarian stimulation protocols in estrogen-sensitive cancers

- Ovarian stimulation protocols in estrogen-sensitive cancers
 - » Tamoxifen, letrozole suppress plasma oestradiol levels
 - » Avoid delay in stimulation (random start protocol)

Pregnancy after cancer

- Recommended after 2 years because most disease recurrences occur within this time, 5 years for women with HR+ disease
- Pregnancy in BC survivors does not increase risk of recurrence and does not decrease survival rates in long term followup studies

8.2 Embryo cryopreservation

- Cryopreservation of cleavage and blastocyst stage embryos is a widely used
- Vitrification has enabled the scope of maximizing pregnancy potential even from very few embryos
- For women without a male partner, acceptance of donor sperm is the only option

8.3 Ovarian tissue cryopreservation

- Technique involves slicing ovarian cortex tissue into thin slices and exposure to cryoprotectants, which negates the need for ovarian stimulation, male partner and can also be performed in prepubertal cancer patients
- Successful freezing outcome has been reported both by slow freezing and vitrification
- Immature oocytes are aspirated subject to IVM
- The efficacy of ovarian tissue freezing is age dependent

8.4 Fertility preservation in gynecological cancers

8.4.1 Breast cancer

Current statistics reveal

- Premenopausal women 11% to 15% of individuals are diagnosed annually

8.4.2 Ovarian tumours

- Offer fertility sparing surgery may be offered for borderline tumours desiring fertility at a later date
- Offer radical trachelectomy may be offered to women with early stage cervical cancer keen on completing their family
- Offer unilateral salpingo-oophorectomy (USO) can be offered to women with early stage ovarian malignancy (ovarian epithelial cancer stage I, grade 1) though risk of recurrence is high. A completion surgery should be done as soon as possible

8.4.3 Cervical cancer

Current statistics

- Cervical cancer is the second most common cancer in India in women accounting for 22.86% of all cancer cases in women.

- Treatment often leads to sexual dysfunction, loss of fertility, and significant dyspareunia

Options

- Part of uterosacral lig, 1–2 cm of vaginal cuff, pelvic lymph nodes

Eligibility criteria

- Lesion size <2.5 cm, no metastasis to regional lymph nodes

8.4.4 Endometrial cancer

Current statistics

- Constitutes 7.1% of all new cancer in females
- Proper myometrial evaluation by MRI is recommended
- Definitive treatment includes hysterectomy with BLSO

Options

- For early stage endometrial cancer fertility options can be considered after medical treatment of early stage (stage 1 wave 1)
- FP can be offered to women subsequent to progesterone therapy or prior to surgery since definitive treatment needs to be carried out
- Letrozole can be added for ovarian stimulation among women with estrogen-sensitive tumors

Summary of recommendations

Males

- Semen cryopreservation is recommended for all post-pubertal males scheduled for cancer treatment
- Semen cryopreservation should be done prior to treatment
- If initial sperm count is below WHO standard, then preferably 2–3 samples should be preserved (to account for post-thaw loss). If sperm counts are normal 1 sample may suffice. 1–3 samples recommended
- Vibrators – mechanical or electrical can be used to collect the ejaculate
- TESA can be offered to post-pubertal males when collection is not possible with any of the above methods

- Immature testicular tissue should be offered to pre-pubertal males with the counselling that as yet it is an experimental procedure only
- No role for gonadal protection by GnRH analog

Females

- Effects of cancer therapy should be discussed with all women who need to undergo cancer therapy, in the reproductive age group
- FP counselling should be done prior to start of cancer therapy in all women desirous of future fertility
- FP procedures should be carried out prior to start of cancer therapy
- FP procedures include oocyte, embryo and ovarian tissue CP
- Use GnRH analogues are recommended along with CT to aid in preservation of ovarian reserve. It cannot be used as an effective method of FP
- Post-pubertal females should be offered oocyte cryopreservation (CP)
- Post-pubertal females who are married or have a partner may be offered embryo freezing though oocyte CP offers autonomy on subsequent use
- Ovarian tissue cryopreservation (OTC) is the only procedure that can be offered to pre-pubertal girls.
- Oocyte and embryo CP necessitates ovarian stimulation (OS) with gonadotrophins for 9–10 days and an approximate delay of 12–14 days is expected in starting cancer treatment
- In ER+ve breast cancers letrozole or tamoxifen can be added to the OS regime
- OTC is the only procedure that can be done after initial CT, though it may be less effective
- Safety of OS in FP has been established
- Pregnancy in cancer survivors is safe
- There is no increased risk of birth defects or genetic diseases in infants delivered after previous CT treatment

9. Consent

- Detailed consent for procedure should be taken
- Consent form should include options for gamete disposition in the event of demise of the patient

10. Limitations and suggestions in the Indian context

10.1 Late diagnosis is a problem in India

- Implementation of cancer screening for early detection is suggested

10.2 Poor survival rates due to late diagnosis

- Early diagnosis will lead to early treatment

10.3 Cost of procedure – cancer treatment is expensive. Family wants to save all resources for treatment

- Insurance should be made available – currently not given by majority of agencies for infertility treatment.

10.4 Reluctance of family to discuss or implement fertility preservation

- Fertility preservation and genetic counseling should be made available in oncology centres and oncologists should encourage patients to discuss this aspect

10.5 Information about fertility preservation options

- Through public awareness campaigns

10.6 Many oncologists, gynaecologists and physicians do not have adequate knowledge of fertility preservation .

- Enhancing knowledge of oncologists, gynaecologists and general physicians through CME programs

10.7 Availability of good centres performing fertility preservation

- Training of RM specialists in counseling and managing such patients and embryologists in fertility preservation procedures

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
	Males		
EBR	• Semen cryopreservation is recommended for all post pubertal males scheduled for cancer treatment	A	III
EBR	• Semen cryopreservation should be done prior to treatment	A	II
EBR	• If initial sperm count is below WHO standard, then preferably 2-3 samples should be preserved (to account for post-thaw loss). If sperm counts are normal 1 sample may suffice. 1-3 samples recommended	B	III
CPP	• Vibrators – mechanical or electrical can be used to collect the ejaculate	-	-
CPP	• TESA can be offered to post-pubertal males when collection is not possible with any of the above methods	-	-
CCR		C	-
CCR	• Immature testicular tissue should be offered to pre-pubertal males with the counselling that as yet it is an experimental procedure only	C	-
CCR		C	-
EBR	• No role for gonadal protection by GnRH analogue	D	IV
	Female		
EBR	• Effects of cancer therapy should be discussed with all women who need to undergo cancer therapy, in the reproductive age group	A	V
EBR	• FP counselling should be done prior to start of cancer therapy in all women desirous of future fertility	A	V
CPP	• FP procedures should be carried out prior to start of cancer therapy	-	-
EBR	• FP procedures include oocyte, embryo and ovarian tissue CP.	A	II
EBR	• Use GnRH analogues are recommended along with CT to aid in preservation of ovarian reserve. It cannot be used as an effective method of FP	B	II
EBR	• Post-pubertal females should be offered oocyte cryopreservation (CP)	B	III
EBR	• Post-pubertal females who are married or have a partner may be offered embryo freezing though oocyte CP offers autonomy on subsequent use	B	II
EBR	• Ovarian tissue cryopreservation (OTC) is the only procedure that can be offered to pre-pubertal girls	A	II
EBR	• Oocyte and embryo CP necessitates ovarian stimulation (OS) with gonadotrophins for 9-10 days and an approximate delay of 12-14 days is expected in starting cancer treatment.	C	III
EBR	• In ER +ve breast cancers letrozole or tamoxifen can be added to the OS regime	B	II
CCR	• OTC is the only procedure that can be done after initial CT, though it may be less effective	B	-
EBR	• Safety of OS in FP has been established	B	II
EBR	• Pregnancy in cancer survivors is safe	A	III
EBR	• There is no increased risk of birth defects or genetic diseases in infants delivered after previous CT treatment	B	IV
CPP	Consent	-	-
	• Detailed consent for procedure should be taken		
	• Consent form should include options for gamete disposition in the event of demise of the patient		

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Chapter 20: Patient Factors Affecting Fertility Outcomes

OVERVIEW

Infertility is a relatively common condition, greatly affecting couples medically and psychologically. This guideline offers recommendations on the causes of Infertility and female, male and combined factors such as age, obesity, use of lubricants, body weight, occupation, drugs, and smoking affecting fertility outcomes.

1. Introduction

- Infertility affects up to 15% couples of reproductive age worldwide
- According to World Health Organization (WHO), the overall prevalence of primary infertility in India is between 3.9% to 16.8%
- In Indian states, the prevalence of infertility varies from state to state such as 3.7% in Uttar Pradesh, Himachal Pradesh and Maharashtra, to 5% in Andhra Pradesh, and 15% in Kashmir, and the prevalence varies in same region across tribes and caste
- Low fertility is becoming more common worldwide, particularly in many urban settings where women are planning their first babies at older age

2. Causes of infertility

- Infertility can be caused by a number of underlying conditions including ovulatory disorders, tubal damage, male factors, and uterine or peritoneal problems
- It is important to consider clinical assessment, namely history taking and physical examination before the treatment is started
- Offer further diagnostic investigations in order to establish if a pathological condition is present in most cases
- No cause of fertility problems can be established in approximately 25% of the cases, even after investigations, and it is termed as term 'unexplained infertility'
- Offer a management approach that can be established with an individual or the couple in an attempt to improve their chances of conception after the assessment and investigations are performed

- Patient-related factors which affect fertility outcomes can be divided into female, male and combined causes

3. Female factors affecting fertility outcomes

3.1 Tubal factors

- The tubal factor is reported to account for 25%–35% of sub-fertility in the western literature, but the prevalence appears to be higher in India due to the higher rates of unrecognized pelvic inflammatory disease (PID) and tuberculosis
- PID may be responsible for more than 50% of the causes of tubal factor infertility
- Other factors include cornual polyps, chronic salpingitis, endometriosis, salpingitis isthmica nodosa, intrauterine synechiae, and parasite infection

Key points

- For women with mild tubal disease, tubal surgery may be more effective than no treatment
- For women with proximal tubal obstruction, selective salpingography with tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment option because these treatments improve the chance of pregnancy
- Offer salpingectomy preferably by laparoscopy, to women with hydrosalpinges, before IVF treatment because this improves the chance of a live birth

3.2 Uterine Factors

- Uterine abnormalities such as adhesions, polyps, submucous leiomyomas, and septae have been found in 10% to 15% of women seeking treatment for fertility problems

- Compared with HSG, hysteroscopy is recognised as the 'gold standard' test for identifying uterine abnormalities
- Congenital uterine anomalies (CUAs) do have reproductive implications. - infertility, recurrent miscarriages, preterm delivery and fetal malpresentation
- A causal relationship between leiomyoma and infertility has not been established
- In women undergoing assisted reproduction, the presence of submucous, intramural leiomyoma close to the junctional zone and multiple myoma is associated with a reduced chance of clinical pregnancy or delivery
- However, the effectiveness of surgical treatment of uterine abnormalities to enhance pregnancy rates is not established
- Consider expectant management or superovulation and intrauterine insemination (SO/IUI), as first-line therapy in younger women (<37 years) with stage I/II endometriosis-associated infertility
- Consider more aggressive treatment, such as SO/IUI or IVF for women more than 37 years of age or older
- Conservative surgical therapy with laparoscopy or possible laparotomy followed by ART is beneficial in women with stage III/IV endometriosis-associated infertility

Key points

- Offer hysteroscopic adhenolysis to women with amenorrhea or scanty menses who are found to have adhesions
- Offer hysteroscopic resection in women with diagnosed uterine septum, submucous myoma, and polyps

3.3 Endometriosis

- Endometriosis is a common, chronic disease. Although women may be asymptomatic, most women typically present with pelvic pain, infertility, or an adnexal mass
- A reasonable body of evidence demonstrates an association between endometriosis and infertility
- Endometriosis can result in adhesions or distorted pelvic anatomy that precludes fertility
- The fecundity rate of untreated women with endometriosis is difficult to quantify, given the wide range reported in the literature (2% to 10%)

Key points

- Consider female age, duration of infertility, and stage of endometriosis for formulating the management plan
- Benefits of laparoscopy for diagnosis in minimal and mild endometriosis is not reported, however, if performed, ablation or excision should be done

3.4 Ovulatory factors

- Ovulatory dysfunction has been identified in approximately 15% of infertile couples and accounts for up to 40% of infertile women
- It commonly results in obvious menstrual disturbances
- The underlying cause should be sought because specific treatment may be indicated, and some conditions may have other implications and consequences
- The most common cause of ovulatory dysfunction include PCOS, obesity, weight gain or loss, strenuous exercise, thyroid dysfunction, and hyperprolactinemia

4. Male factors affecting fertility outcomes

- Approximately 1% of men are permanently sterile, with about 20% of men having sperm quality below the threshold compatible with normal fertility
- In couples undergoing fertility treatment, male factor may solely be implicable from 20%–50% of cases
- Impaired semen parameters alone cannot be used to predict fertility as these men still have a chance of being fertile, except when a man has azoospermia, necropermia or globozoospermia
- Abnormal semen characteristics are usually idiopathic. Idiopathic semen abnormalities occur in about 26% of infertile men
- The spermatozoa are mostly dysfunctional and unable to fertilize but a proportion are often

functionally normal. Sperm function may also be impaired by anti-sperm antibodies

4.1 Sexual disorder

- Erectile dysfunction and anorgasmia may lead to decreased sexual pleasure and decreased frequency of sexual intercourse
- Retrograde ejaculation can occur because of laxity of bladder neck muscle due to surgery on prostate, or retroperitoneal lymph node dissection
- Depression as a side effect of medication used for prostate enlargement
- Nerve damage by medical condition like diabetes, multiple sclerosis, Parkinson disease

Key points

- Administer medical management and proper counselling for males with erectile dysfunction
- Intercourse of 2–3 times a week is reported to improve chance of conception
- Treat ejaculatory failure to restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed

4.2 Primary testicular dysfunction

- The most common cause of male infertility is idiopathic primary testicular dysfunction with abnormal spermatogenesis
- Other common causes include:
 - » Testicular damage due to systemic chemotherapy for cancer
 - » Klinefelter syndrome
 - » Genetic mutations
 - » Testicular cancer
 - » Pelvic irradiation or surgery
 - » Trauma
 - » Cryptorchidism
 - » Infection

» Autoimmune destruction and drugs

Key points

- Consider ART, as it represents the best or only chance for conception for men with subfertility due to primary testicular defects
- Consider giving antibiotics only in cases of proved infection as there is no evidence that men with leukocytes in their semen after giving antibiotics show improve pregnancy rate

4.3 Endocrinopathies that are associated with reduced spermatogenesis

- Hypothalamopituitary disorders are the most common cause of male subfertility due to an endocrinopathy
- Because normal secretion of both FSH and LH is required for quantitatively and qualitatively normal spermatogenesis, any disease that affects hypothalamic secretion of GnRH or Pituitary secretion of FSH or LH will impair spermatogenesis
- Tumors and infiltrative diseases of the hypothalamus, hyperprolactinemia, hemochromatosis, Kallmann syndrome, and idiopathic hypogonadotropic hypogonadism are classic endocrine causes of male subfertility
- Hypothyroidism and hyperthyroidism and adrenal disorders also may cause male subfertility via a variety of mechanisms

Key points

- Offer gonadotrophin drugs to men with hypogonadotropic hypogonadism because these drugs are effective in improving fertility
- Strong evidence does not exist that men with idiopathic semen abnormality will have any benefits from gonadotrophin antiestrogens, androgens, bromocriptine or kinin-enhancing drugs

5. Combined factors

5.1 Age

- Fertility varies among populations and declines with age in both men and women, but the effects of age are much more pronounced in women
- Although semen parameters in men also decline detectably after 35 years of age, male fertility does not appear to decrease appreciable before approximately age 50

Key points

- Inform the couples that fertility potential decline with increasing age
- Females above 35 years of age who has not conceived after 6 months of unprotected sex should consult a doctor for fertility evaluation
- Inform men who are concerned about fertility that semen parameters decline with age

5.2 Frequency of intercourse

- Although there are evidences which suggest that daily intercourse has some advantage on fecundity, it may unnecessarily lead to stress

Key point

- Inform the couple that reproductive efficiency increases when intercourse occur every 1 or 2 days, however, optimum frequency of intercourse should be decided by their own preferences

5.3 Coital position and lubricants

- There is no evidence that coital position affects fecundability
- Sperm can be found in the cervical canal seconds after ejaculation, regardless of coital position
- There is also no convincing evidence to indicate any relationship between specific coital practices and infant gender
- Some vaginal lubricants may decrease fertility, based on their observed effects on sperm survival in vitro
- Although there is no evidence to indicate that use of any vaginal lubricant decreases fertility, it seems prudent to recommend mineral oil, canola oil, or

hydroxyethylcellulose-based lubricants when they are needed

Key points

- Inform the patients that different coital position has no effect and fertility rate
- Mineral oil, canola oil, or hydroxyethylcellulose-based vaginal lubricants can be used if needed

5.4 Obesity

- Obesity impairs reproduction in both women and men, leading to infertility in couples trying to conceive, subsequent complications in pregnancy, and adverse effects on their offspring
- The internationally accepted range for BMI is from less than 18 kg/m² (underweight) to 25 kg/m² or over (obese)
- A BMI of 25 or over was reported to be an independent risk factor for spontaneous abortion in women who were oocyte recipients
- An increased risk of miscarriage has been reported in moderately obese women (BMI 25–27.9 kg/m²) undergoing ovulation induction

5.4.1 In females

5.4.1.1 Menstrual cycle abnormalities

- Menstrual irregularity is reported to occur more frequently in women above 175% of ideal body weight compared with women below 150% of ideal body weight (54% vs. 19%), respectively

5.4.1.2 Ovulatory dysfunction

- Obese women with a BMI >28 kg/m² are reported to have a relative risk (RR) of anovulatory infertility of 3.1 (95% CI, 2.2–4.4) compared with their lean counterparts with a BM 18–23 kg/m². (put Indian reference here)

5.4.1.3 Altered ovarian responsiveness and oocyte quality

- Obesity alters oocyte morphology, reduces fertilization, and impairs embryo quality in women >37 years of age

- Specifically, women with a BMI $>23 \text{ kg/m}^2$ have smaller oocytes that are less likely to complete development post-fertilization, with embryos arrested before blastulation containing more triglycerides than those forming blastocysts
- Moreover, the blastocysts developed from oocytes of high-BMI women are smaller, contain fewer cells, and have higher triglyceride content, lower glucose consumption, and altered amino acid metabolism compared with embryos from normal weight women (BMI)

5.4.1.4 Altered endometrial function

- Obesity also appears to alter endometrial receptivity during IVF with a BMI more than 25

5.4.2 Obesity in males

- Not all obese men have infertility, but those who do can have reduced semen quality, impaired erectile function, and other physical problems, including sleep apnea, and increased scrotal temperatures
- Obesity in men is associated with an increased incidence of oligozoospermia and asthenozoospermia in some, but not all.
- Moreover, increased abdominal adiposity in men of subfertile couples has been associated with reduced sperm count, concentration, and motility
- An observational study reported an inverse relationship between BMI and the total number of normal-motile sperm cells
 - » There was a significant reduced number of normal-motile sperm cells in men who were overweight (BMI 24–28) and obese (BMI greater than 28) when compared with men of normal weight
 - » A higher incidence of sperm DNA fragmentation has also been observed in men with a BMI of over

Key Points

- Inform women with BMI >25 that they may take longer to conceive

- In women with high BMI >27 , losing weight will improve ovulation and hence chances of conception
- Advise women that exercise and dietary adjustment are effective in achieving pregnancy
- Obese men are more likely to have reduced fertility and sexual dysfunction

5.5 Low bodyweight

- Low bodyweight in female is a recognized cause of hypo-estrogenic amenorrhoea. Women having extremely low amounts of body fat have more chances of ovarian dysfunction and infertility
- In women, weight loss of over 15% of ideal body weight is associated with menstrual dysfunction and secondary amenorrhoea when over 30% of body fat is lost
- Restoration of body weight may help to resume ovulation and restore fertility
- Men who are underweight are also at risk of infertility
- Men who are underweight tend to have lower sperm concentrations than those who are at a normal BMI
- As most of literature focuses on impact of obesity more research is needed to established role of low body weight on male fertility

Key points

- Women who have a BMI of less than 18, and who have irregular menstruation, or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception

5.6 Increased temperature

- Increased scrotal temperature is related to reduction in semen quality
- Important determinants of testicular temperature such as a sedentary work position and clothing have been associated with abnormal semen quality
- There are some evidences stating altered semen parameters in men wearing tight underwear

- Effect of impaired sperm quality on pregnancy outcome is not being established
- Literature review concluded that sauna bathing does not decrease female fertility and is safe during uncomplicated pregnancy
- In normal men, recommendations for behavioural modifications aimed at controlling or decreasing exposure of the testicles to heat is recommended

Key points

- Inform men that there exists an association between elevated scrotal temperature and reduced semen quality
- Inform women that sauna bathing does not decrease female fertility

5.7 Occupation and endocrine disruptors

- Endocrine disruptors like bisphenol A, pesticides, heavy metals, radiation and electromagnetic waves have an effect on male and female fertility

Key point

- A specific enquiry about occupation and exposure to endocrine disruptors should be made.

5.8 Drugs

5.8.1 Illicit drugs

- Use of illicit drugs appears to have a negative impact on fertility, though more indepth research in this area is required to make a clear link
- Marijuana is one of the most commonly used drugs around the world
 - » It acts both centrally and peripherally. In males it is reported to reduce testosterone levels, spermatogenesis sperm motility, sperm capacitation, and acrosome reaction
 - » Females using marijuana have increased risk of primary infertility
- Similarly Cocaine and opiates show negative impact on male and female fertility potential

5.8.2 Prescription and over-the-counter drugs (Table 1)

- A number of prescribed drugs and over-the-counter drugs impair fertility and sexual function. There use, benefits and adverse effects should be judged cautiously
- Anti-inflammatory, immunosuppressive, anti-depressants, tranquilizer or asthma medications lead to increased anovulation in females
- Medication such as cimetidine and sulfasalazine and long term daily use of some antibiotics and androgen injections can affect semen quality and cause oligozoospermia
- The effect is generally reversible after three months following withdrawal of medication
- Use of beta-blockers and psychotropic drugs may lead to impotence,
- Chemotherapy treatment can induce azoospermia and reduce ovarian reserve

Key point

- A number of prescriptions, over-the-counter and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered

5.9 Diet and lifestyle

5.9.1 Diet

- Fertility rates clearly are decreased in women who are either very thin or obese, but data regarding the effects of normal variations in diet on fertility in ovulatory women are few
- Whereas a healthy lifestyle may help to improve fertility for women with ovulatory dysfunction, there is little evidence that dietary variations such as vegetarian diets, low-fat diets, high-protein diet, vitamin-enriched diets, antioxidants, or herbal remedies improve fertility or affect infant gender

Table 1. Over-the-Counter Medications impacting spermatogenesis

Drug category	Generic name of drug	Effect on spermatogenesis
Analgesic	Methadone hydrochloride	Decrease in sperm motility and seminal vesicle secretions, abnormal sperm morphology
	Pregabalin	Epididymitis
Anti-arrhythmic agent	Amiodarone	Inhibit spermatogenesis and increase sperm head abnormalities
Anti-bacterial agents	Nitrofurantoin	Spermatogenic arrest/decreased sperm count
Anti-convulsants	Lamotrigine	Epididymitis(rare)
Anti-depressants	Clomipramine	Reversible suppression of spermatogenesis
	Paroxetine	Decreased sperm quality
	Fluoxetine maleate	Haemospermia
Antihypertensive agent	Nifedipine	Reversible reduction in ability to fertilize ova
Anti-Inflammatory agents	Colchicine	Azoospermia or oligospermia
	Cortisone acetate	Changes in motility and number of spermatozoa
	Dexamethasone	Changes in motility and number of spermatozoa
	Prednisone	Changes in motility and number of spermatozoa
	Sulfasalazine	Reversible oligospermia
Anti-viral agents	Ganciclovir	Testicular hypertrophy and aspermatogenesis
Hormones	Methyl testosterone	Oligozoospermia and suppressed spermatogenesis
	Testosterone enanthate/ Testosterone undecanoate	Suppressed spermatogenesis/oligozoospermia, Testosterone undecanoate may also cause spermatocele formation
Treatment of peptic ulcer and gastroesophageal reflux disease (GERD)	Cimetidine Has anti-androgenic action	Reversible impotence Gynecomastia
PDE-5 Inhibitor	Tadalafil	Decreased sperm concentration
Chemotherapeutic agents	Methotrexate given for rheumatoid arthritis	Decreased sperm concentration
	Other anticancer drugs	Decreased sperm concentration

Over-the-Counter Medications impacting female fertility

Drug	Effect on female fertility
NSAID's	Effect ovulation
Natural or herbal remedies	Contain substances that act like estrogen or progesterone

Over-the-Counter Medications to be avoided in Pregnancy

Drug Category	Drugs	Effects
Anti-diarrheal	Bismuth Subsalicylate	Salicylate absorption
	Loperamide	Fetal cardiac malformations
	Atropine/diphenoxylate	Teratogenic in animal studies. Insufficient evidence in humans.
Decongestants and expectorants	Chlorpheniramine	
	Pseudoephedrine hydrochloride	Vasoconstriction of uterine arteries and decreased blood flow to the fetus.
	Guaifenesin	Neural tube defects
	Diphenhydramine	Oxytocin like effects in high doses
Analgesics	Aspirin	Neonatal hemorrhage, low birth weight, prolonged gestation and labor. Low dose aspirin is found to be safe.
	Ibuprofen	Avoid in third trimester
	Naproxen	Avoid in third trimester
	Indomethacin	Oligohydramnios, premature closure of ductus arteriosus, Fetal nephrotoxicity and periventricular hemorrhage
	Diclofenac	Premature closure of ductus arteriosus

- Advice women attempting to conceive to take a folic acid supplement (at least 400 mg daily) to reduce the risk for neural tube defects

Key Point

- There is little evidence that diet variation affects fertility, however, healthy diet and life style does improved fertility in thin or obese men and women

5.9.2 Smoking

- Female smoking decreases fecundity by accelerating ovarian follicular depletion
- Active smoking by either partner had adverse effects, and the impact of passive cigarette smoke exposure alone was only slightly smaller than for active smoking by either partner

Key points

- There is good evidence that semen parameters and results of sperm function tests are poorer in smokers than in non-smokers and the effects are dose dependent
- There is good evidence that smokers require nearly twice the number of IVF attempts to conceive as nonsmokers
- The adverse effects of side stream and passive smoking are now established, and there is good evidence that nonsmokers with excessive exposure to tobacco smoke may have reproductive consequences as great as those observed in smokers

5.6.3 Alcohol

- The effect of alcohol on female fertility has not been clearly established
- In men, alcohol consumption has no adverse effect on semen parameters. Three to four units per day for men is unlikely to affect their semen quality

Key Points

- Avoid higher levels of alcohol consumption (>2 drinks/day, with 1 drink >10 g of ethanol) when attempting pregnancy, but there is limited evidence to indicate that more moderate alcohol consumption adversely affects fertility

- Three to four units per day alcohol consumption for men is unlikely to affect their semen quality but excessive intake could be detrimental to sperm parameter

5.6.4 Caffeine

- Caffeine is present in coffee, tea, colas, and chocolate. The association between caffeine and female infertility is inconsistent
- High levels of caffeine consumption (500 mg; >5 cups of coffee/day or its equivalent) have been associated with decreased fertility

Key points

- Moderate caffeine consumption (1 to 2 cups of coffee per day or its equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes
- In men caffeine consumption has no effect on semen parameters

5.6.5 Stress

- Stress has become prominent part of our society be it physical, social or psychological, there is a complex relationship between stress and fertility problems
- Stress such as job, life events and even social strain have shown significant impact on sperm motility, count and morphology
- Stress and depression leads to decreased libido, affects couple's relationship leading to delayed conception
- Physical and psychological stress has shown to influence female fertility
- Psychological stress such as anxiety or depression can be reduced with counselling and holistic management

Key Points

- When couples have fertility problems, inform both partners that stress in the male and/or female partner can affect the couple's relationship and are likely to

reduce libido and frequency of intercourse which can contribute to the fertility problems

- Offer counselling to people who experience fertility

problems because fertility problems themselves, and the investigations and treatment of fertility problems, may cause psychological stress.

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	Lifestyle factors, including age when starting a family, nutrition, weight management, exercise, psychological stress, cigarette smoking, recreational and prescription drugs use, alcohol and caffeine consumption, preventative care, and other behaviours are modifiable and may impact fertility	-	-
EBR	Exposure to occupational and environmental disruptors is associated with reduced fertility in both males and females	C	III
CPP	Attempting pregnancy before the age of 30 for women and before 35 for men may provide the highest chances of success	-	-
CPP	Men and women who are underweight or overweight are also at risk for negative side effects, including changes in hormone levels that heavily influence their fertility	-	-
CPP	Overweight and obese women are at increased risk of infertility and their outcome after ART is not very optimistic.	-	-
CPP	Recreational and prescription substances also appear to have significant impact on fertility. Though clear links are yet to be determined, there are negative trends, including decreased semen parameters or decreased ovarian re-serve, associated with smoking and fertility	-	-
CPP	Caffeine appears to have a negative effect on fertility, additional research is needed to elucidate if there is a definitive relationship	-	-
CPP	Decreasing or ceasing alcohol consumption may provide a better chance of achieving a viable pregnancy for the couple	-	-
CPP	Identifying, eliminating, or minimizing even one factor of the many environmental exposures may have significant positive effects on fertility for both men and women	-	-
EBR	Thyroid disorders in both the male and female are associated with reduced fertility and in the female may affect the progress of pregnancy as well	B	II
CCR	Sexual dysfunction and frequency of coitus may also influence the occurrence of pregnancy	C	
EBR	Method of fertilisation, age, reactive oxygen species, sperm quality parameters and DNA fragmentation may influence ART outcome	B	II
EBR	ICSI for male factor infertility had a worse outcome for clinical pregnancy rate and trend for lower LBR than non-male factor infertility cycles and non-ICSI male factor infertility cycles	B	II
EBR	The ICSI cycles with ejaculated and aspirated sperm for male factor infertility had better pregnancy outcomes than non-male factor infertility cycles	B	II
EBR	After adjustments for female age, male and female race/ethnicity, day of ET, number of embryos transferred, and with non-ICSI cycles as the reference group, models showed ICSI to have a lower clinical pregnancy rate, but not a lower LB rate	B	III

Category	Recommendations	Grade of Recommendation	Quality of Evidence
EBR	Men suffering from NOA undergoing TESE are to be counselled that not only are the sperm recovery rates limited but also the fertilization, implantation and conception rates are decreased compared to men with normal spermatogenesis	B	II
EBR	Diminished ovarian reserve was likely associated with decreased chance of clinical pregnancy	A	II
EBR	The impact of endometriosis on assisted reproductive technology (ART) outcomes is variable Mild endometriosis ie, stage I/II disease does not appear to negatively impact ART outcomes whereas stage III/IV disease appears to negatively impacts ART outcomes	A	II
CPP	Severe endometriosis was associated with lower oocyte retrieval, implantation, and pregnancy rates in women undergoing IVF as compared with women with mild endometriosis	-	-
CPP	Women with endometriomas, often have lower ovarian reserve and produce fewer oocytes, which reduces ART success	-	-
EBR	In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART to improves PRs	A	II
EBR	Endometriosis are associated with follicle number and oocytes retrieved but not on embryo quality or pregnancy outcomes	A	II
EBR	Presence of hydrosalpinx has a negative effect on ART outcome, salpingectomy or disconnection of tube at the cornua improves the outcome	A	I
EBR	Intramural myomas >5 cm and those close to the junctional zone have a negative impact on ART outcome and therefore should be removed	B	II
EBR	Uterine polyps and sub-mucous myoma can influence the ART outcome and therefore hysteroscopic surgery for polyps, sub-mucus myoma improves the outcome	A	I
EBR	IUA decrease the PRs significantly and adhesiolysis may improve the outcome	B	III
EBR	Congenital malformation of the uterus may influence the occurrence of infertility and increase the incidence of miscarriage, pre-term delivery, and fetal malformation	B	III
EBR	Septal resection improves fecundity significantly with increase in term delivery and decrease in spontaneous abortion rate improves the outcome	B	II
EBR	"T" shaped uterus may impact the success rate of ART, but lateral metroplasty may not improve the outcome	B	III
EBR	PCOS with obesity is associated with reduction in fertility which is multifactorial <ul style="list-style-type: none"> Reduced fertilization, impaired embryo quality and blastocyst formation (higher intracellular triglycerides) Altered Endometrial responsiveness BMI is inversely related to intrafollicular HCG concentrations, embryo quality and IVF outcome 	B	II
EBR	Abnormalities in circulating hormones in PCOS women (high androgens, LH and insulin) is associated with reduced pregnancy rates, and high miscarriage rate	B	II
EBR	There was no evidence of a significant difference in CPR, LBR or miscarriage rate in women with CC-resistant PCOS undergoing LOD compared to other medical treatments and ART	B	II

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Chapter 21: Long Term Safety

OVERVIEW

This guideline offers recommendations to highlight the long-term safety of assisted reproduction treatments in women with infertility and their children. It is aimed primarily at women aged 21 years or older presenting to healthcare professionals with infertility problems. The guideline also concentrates on the information regarding understanding the long-term impact of these treatments, which have been linked with several potential complications affecting both the mother and the child. The field of this study poses a constant challenge for the scientific community. We have to evaluate the patient to understand various other medical risk.

1. Introduction

- The treatment of infertility for decades has seen the development of revolutionary new assisted reproductive technologies (ART)
- The *in vitro* fertilization (IVF) was first achieved in 1978 with the birth of baby Louise Brown
- Later on, microassisted reproduction using techniques such as intracytoplasmic sperm injection (ICSI) and the development of preimplantation genetic diagnosis (PGD) has emerged. Despite greater inventions, questions regarding the safety of ART persist
- Understanding the long-term impact of these treatments, which have been linked with several potential complications affecting the mother and the child, poses a constant challenge for the scientific community
- The treatment of infertility for decades has as seen the development of revolutionary new assisted reproductive technologies (ART)
- There is a paucity of data in the literature and no adequate prospective randomized controlled trials (RCTs) of sufficient power available to assess the efficacy and safety of the various forms of assisted reproduction
- There is a need for assessment of the safety of various forms of assisted reproduction technology, especially long-term safety
- The definition of success in IVF started shifting from pregnancy rate per cycle towards achieving healthy singleton child per started course of treatment
- For achieving this aim the first change had to be in the stimulation protocols with the aim of less pain or stress, less cost and complications, and obtaining a good oocyte/embryo/implantation rate
- Further progression of technology aimed at minimizing complication rates yet maintaining optimal pregnancy rates

2. Long-term risks of ovulation induction and ovarian stimulation in mother

- There is no evidence of transmission of prion disease by any presently used gonadotropin
- Gynecological cancer: Carcinoma in women undergoing ovulation induction
 - » It is not easy to be determined due to many confounding factors. These include the facts that–
 - » Infertility
 - » Age
 - » Drugs for ovulation induction (either alone or in combination)
 - » Ovulation induction does not increases the risk of gynecological cancer. Moreover, the risk of ovarian cancer is not increased with ovulation induction, even though few concerns are raised due to borderline ovarian tumors
 - » More information is required about the relationship between ovulation induction and breast cancer before firm conclusions. Also, a

higher risk of uterine cancer is related to infertility status rather than to the ovulation induction

- Borderline ovarian tumor
 - » There is no strong link between the use of fertility drugs and risk for borderline ovarian tumours
 - » One cohort study concluded that ovarian stimulation for IVF may increase the risk of ovarian malignancies, especially borderline ovarian tumours
 - » Infertility drugs could be used safely in patients who experience infertility after conservative management of an early-stage BOT
 - » In patients with advanced stage BOT, the risk of lethal recurrence is increased
- IVF and ovarian cancer
 - » Collective data regarding the risk of developing cancer from use of fertility medications are reassuring
 - » No association between fertility drug use and risk of ovarian cancer
 - » Effects of long-term fertility drug use and the effects of fertility treatment on women who have a BRCA1 or BRCA2 gene mutation is currently scarce
- IVF and breast cancer
 - » There was no significant association between IVF and breast cancer in the infertility treated group

2.1 Recommendations for ovulation induction or ovarian stimulation

- Provide up-to-date information about the long-term health outcomes
- No direct association was found among IVF treatment and invasive cancer
- No association was found in the short-to medium-term among IVF and adverse outcomes (including cancer) in children born from ovulation induction

- Information regarding long-term health outcomes in women and children is still awaited
- The use of ovulation induction or ovarian stimulation agents should be limited to the lowest effective dose and duration
- Women subjected to IVF should be informed that the absolute risks of long-term adverse outcomes of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), are low, a small increase in the ovarian stimulation for IVF may increase the risk of ovarian malignancies, especially borderline ovarian tumours
- More large cohort studies are needed to confirm this findings and to examine the effect of IVF treatment characteristics

3. Long-term outcomes in children born after assisted reproduction

- The outcomes that were included in various research publications were
 - » Malformations in children
 - » Chromosomal abnormalities in children
 - » Childhood tumors growth disturbances
 - » Neurological development disturbance
 - » Autism spectrum disorders
 - » Transmission of subfertility to male offspring

3.1 Congenital abnormality and major birth defects

- NTD, esophageal atresia, omphalocele, hypospadias, and cardiac septal defects.
- The incidence was 8% with a two-fold increased risk. This was due to reasons such as increased maternal age during IVF which involves exposure of the embryo to the mechanical, thermal and chemical alterations, ICSI, cryopreservation
- Chromosomal anomalies: Slight increase in ICSI predominantly sex chromosomes
- Imprinting disorders such as Beckwith-Wiedemann syndrome and Angelman syndrome

3.1.1 Congenital anomaly

- ART was associated with 1.5 times increased risk when compared with spontaneously conceived pregnancy. The adjusted odds ratio (OR) for IVF was 1.07 and for ICSI 1.57. There were no differences among ICSI using ejaculated, testicular and epididymal sperm. Also, the ICSI Fresh embryo transfer has a greater risk than frozen transfers
- The vast majority of births resulting from ART were free of birth defects, treatment with the use of ART has higher risk of birth defects compared with spontaneous conception which is attributed to sub fertility

3.1.2 ICSI and genetic abnormalities

- "Y" chromosome micro deletions observed in 3%–15% of men with severe oligospermia may be transmitted to ICSI conceived male off springs
- More boys conceived by ICSI were found to have undescended testes required urogenital surgery

3.1.3 Imprinting disorders

- Genetic imprinting is rare with every 1 from 12000 births due to ART. The genetic imprinting disorders are Prader–Willi syndrome, Angelman syndrome, and Beckwith–Wiedeman syndrome (BWS)
- Infants and children obtained through IVF/ICSI are associated with a higher risk of epigenetic diseases compared to naturally conceived children.

3.2 Oncogenic risk

- There is very limited data and hence further research is needed. The possible mechanism may include structural similarity of antiestrogens with diethylstilbestrol (DES) and alteration of DNA methylation by gamete culture media resulting in embryonic cancers
- Based on the evidence, patients should be counseled that infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, the use of infertility drugs does not appear to increase this risk

- In children with IVF, there is a higher possibility of leukemia, lymphoma, neuroblastoma, retinoblastoma, and hepatoblastoma
- ART–conceived children do not appear to have an increased cancer risk after a median follow-up of 20 years. However, more research work is needed to investigate the cancer risk in adults and children conceived by cryopreserved embryos and/or ICSI

3.3 Neurological/autistic risk

- ART may be an independent risk factor for autism spectrum disorders (ASD)

3.4 Perinatal risks

- Pre-term birth: Single and more so in multiple pregnancy is a clear risk factor for preterm birth. A statistically significant 23% increase in the relative risk of preterm birth occurs in IVF twins compared to natural twins. Similarly, in singletons, there is an estimated two-fold increased risk of preterm birth following IVF
- Early term births (37–38 weeks) are associated with adverse neonatal outcomes primarily respiratory problems in comparison to the 39 weeks pregnancy
- Low birth weight: singleton IVF pregnancies still demonstrate an increased risk of low birth weight compared with naturally conceived singletons (RR 1.6 95%, CI 1.29–1.98)
- IVF twin pregnancies, this increased risk is still evident compared with natural twins
- Perinatal mortality: Perinatal risks associated with ART and ovulation induction are higher in multifetal gestation. Even singleton pregnancies are at a higher risk compared to naturally conceiving spontaneous pregnancies
- However, it is unclear to what extent these associations might be related to underlying causes of infertility
- Before initiation ART, couples should undergo a thorough medical checkup and counsel about these risks

4. Recommendation for monitoring preterm delivery

- Consideration of a transvaginal scan to determine the cervical length is recommended between 16 to 24 weeks
- If cervical length is found to be <25 mm, prophylactic vaginal progesterone and prophylactic cerclage is recommended
- Unless indicated routine cervical cerclage is not recommended

5. Multiple pregnancy

5.1 ART carries a substantial increase in the risk of multiple pregnancy

- Multifetal gestation is associated with an increased risk of maternal and fetal morbidity and mortality as a result of preterm birth, preeclampsia, and other pregnancy complications recommend restricted number of embryos' to be transferred

5.2 Monozygotic twinning is associated with increased perinatal morbidity and mortality

- In ART, monozygotic twinning is a common condition, while it is rare in natural conception
- ART has been associated with an increased risk of monozygotic twinning that increases the risk of growth abnormalities and twin-to-twin transfusion
- Monozygotic twinning remains speculative. Given the possible complications, adequate pre-conception counseling is advocated

5.3 Guideline recommendations for an upper limit of embryos transferred

5.3.1 Patients with a favorable prognosis

- » The transfer of single euploid embryo should be single recommended
- » A single-embryo transfer is suggested in patients under the age of 37, regardless of the embryo stage

5.3.2 Patients with unfavorable prognosis

- For patients between 38 and 40 years of age, no more than three cleavage-stage embryos or two blastocysts are recommended. In cases where euploid embryos are available, a single-blastocyst embryo transfer is suggested
- In patients 41–42 years of age, no more than four cleavage-stage embryos or three blastocysts are suggested. In cases where euploid embryos are available, a single-blastocyst transfer is recommended

5.4 Recommendations

- The risk of multiple pregnancy can be reduced by considering the Limitation of the number of transferred embryos to two or even one
 - » Also, consideration of eSET helps in reducing the number of twin pregnancies in ART

6. Recommendations for follow-up

- Both the mother and child should be requested to report to IVF centers as well as a pediatrician to assess physical health, mental health, and other complications

7. Recommendations for counseling before IVF

- The etiology of risk in ART is likely multifactorial and the magnitude of this risk has not been precisely identified for all women or specific subgroups
- Many questions remain including the magnitude of risk of ICSI in non-male factor infertility, the effect of prolonged embryo culture, the effect of embryo biopsy, and elucidation as to why risk is lower after a frozen embryo transfer
 - » All patients considering ART should be informed of the risk
- As scientists and physicians, it is our responsibility to provide safe care. Optimizing the environment at the time a woman conceives will likely have an effect on gestation as well as the health of children.

Reproduction effects health and health effects reproduction

Summary of recommendations

- ART exposes patients and professionals to delicate psychosocial issues and situations
- Psychological counselling should be offered to all infertile couples independent of their individual diagnoses or the stage of medical treatment and independent of treatment
- Giving basic information concerning individual treatment and the emotional implications helps patients to integrate the process which enhances quality patient care, personal and team satisfaction
- Psychosocial care, infertility counselling and psychotherapy are not clearly distinct categories
- Screening instruments are helpful for identifying patients which have to be referred into psychotherapy.

Exact criteria when to refer have to be developed yet

- Caring for the emotional needs of the patient demands continuity and should not be treated as a single event. Holistic patient care should be the aim whilst they undergo treatment
- Important to discuss about options available, cost, success rate of different procedures and must emphasize that failures are more than successes

Recommendations for incident reporting

- All IVF centers must maintain a follow-up of all their pregnancies by ART
- Also, complications must be reported to a central database and records maintained for at least 10 years
- The obstetrician should report any adverse events in an ART pregnancy to the centre concerned and records to be maintained for 10 years

Summary of recommendation

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	ART exposes patients and professionals to delicate psychosocial issues and situations	-	-
CCR	Psychological counselling should be offered to all infertile couples independent of their individual diagnoses or the stage of medical treatment and independent of treatment	B	-
CCR	Giving basic information concerning individual treatment and the emotional implications helps patients to integrate the process which enhances quality patient care, personal and team satisfaction	B	-
CPP	Psychosocial care, infertility counselling, and psychotherapy are not clearly distinct categories	-	-
CPP	Screening instruments are helpful for identifying patients which have to be referred into psychotherapy. Exact criteria when to refer have to be developed yet	-	-
CPP	Caring for the emotional needs of the patient demands continuity and should not be treated as a single event. Holistic patient care should be the aim whilst they undergo treatment	-	-
CPP	Important to discuss about options available, cost, success rate of different procedures, and must emphasize that failures are more than successes	-	-
CPP	Recommendations for incident reporting		
CCR	• All IVF centers must maintain a follow-up of all their pregnancies by ART	-	-
CCR	• Also, complications must be reported to a central database and records maintained for at least 10 years	C	-
CCR	• The obstetrician should report any adverse events in an ART pregnancy to the centre concerned and records to be maintained for 10 years	C	-

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Chapter 22: Ethical Issues: Assisted Reproductive Technologies

OVERVIEW

This guideline offers recommendations on the importance of assisted reproductive technologies in treating infertility. It also covers resolution on ethical issues encountered while providing ART benefits to respective patients.

1. Introduction

1.1 ART in Infertility

- Infertility cases are increasing day by day throughout the world and create social and mental trouble to the suffering couple. The success ratios of pharmacological treatments in improving the infertility problems are not up to the mark hence require an alternative.
- Assisted reproductive technology (ART) majorly utilizing *in vitro* fertilization (IVF) technique for treating infertility has raised hopes for several couples throughout the world. Most ARTs are recommended because these do not treat the biological problems that give rise to infertility but circumvent them and offer ways to have children despite underlying fertility problems
- » Discarding excess embryos
- » Expensive technology, not affordable for common man
- » Creating embryos, freezing them, and storing
- » Destroying embryos for research
- » Selective selection of embryos for transfer
- Currently, ART is recommended throughout the world for the treatment of infertility and therefore, the chances of ethical misconduct at the same time are also high. In such scenario, it is recommended to create certain regulatory policies for use of ART to protect the medical, social and legal rights of women and the unborn child
- These regulations may advise in providing couples with the best possible management of their problems, while at the same time ensuring that there are no unnecessary risks or ineffective treatments

1.2 Necessity of ethical issues and regulation

- Specific clinical setup is required to provide such techniques for which regulatory guidelines have to be followed
- Regulatory interference is mandatory as it is accompanied by ethical and societal concerns. The majority of new techniques, which provide infertility solutions, require gamete (spermatozoa or the oocytes) handling outside the body. This may result in unethical practices affecting the recipient of the treatment, medically, socially, and legally
- Ethical issues which may arise during the use of ART are:
 - » Bypassing the natural method of conception
 - » Creating life in laboratory
 - » Fertilizing more embryos than will be needed

2. Best practice recommendations

2.1 Clinical facility registration

- Register all ART clinics with central registration authority and provide all necessary details of techniques and procedures of ART practiced at clinics
 - » Clinics performing IUI should also register
 - » Only clinics that meet certain physical infrastructure requirements and have prescribed technical expertise are allowed to enroll in the registry
- Monitor quality and quantity of all assisted reproduction procedures. It is recommended to submit annual reports of all treatment cycles and their outcome to central database

- Monitor ART procedures data at individual clinics and with central registry to understand the improvement in efficacy, safety and success rates of the fertility treatments

2.2 Age, eligibility criteria, and ART treatments

- Make ART treatments available to each needy person accordingly to the law of the land
- Do not offer ART to women with age above 45 years and Men above 50 years
- Do not suggest ART for the women with age below 21 years and men below 23 years
- ART should be offered to the couple keeping in mind the best interests of a particular patient or their potential offspring to proceed with IVF because of
- Associated safety issues
- Older women are more prone to develop chronic disorders like diabetes which may affect off springs
- Chances of chromosomal abnormalities particularly after 35 years of maternal age

2.3 Counseling during ART

- Offer professional counseling to all patients undergoing fertility treatments
- Explain various treatment alternatives available with reason for recommendation of particular treatment to arrive at informed decision
- Counsel patients regarding the implications and chances of success of ART procedures in India and internationally from the available reference data being updated regularly (6–12 months)
- Counsel patients about merits and demerits of ART procedures, side effects of drugs used during procedures, risks including the complications of multiple pregnancy, and ovarian hyperstimulation syndrome (OHSS)
- Inform patients about the costs of proposed and alternative treatments. Do not hide any charges to be applied for treatment

- Counsel patients about the associated benefits and loss of continuing treatment after a certain number of attempts
- Discuss the possibility of adoption with patients whenever required
- Counsel couples or individual about their rights of a child born through the use of ART
- Provide clear, precise and honest information (in the form of pamphlets) about the procedures to patients in local language and English
- The counseling should help the patient/s in taking an informed decision

2.4 Documentation, record keeping, and consenting

- Obtain written informed consent from all individuals/ couples before initiating any ART treatment or procedures
- Start freezing procedures of embryo only after obtaining informed consent from all individual seeking ART and also discuss about the management of frozen gametes or embryos in case of death or incapacity of any of the parties
- Allow individual seeking ART to withdraw consent any time before embryos or the gametes are transferred to the woman's uterus
- Maintain detailed records of all procedures performed at clinic. These records should be maintained for a period of 10 years at least
- This data will automatically get transferred to national ART registry to be set up by the Department of Health Research at the Headquarters of the ICMR
- As may be prescribed by ICMR of all IUI and ART cycles
- Sperm, oocytes or embryos used
- The manner and technique of their use
- The individual or couple or surrogate mother in respect of whom it was used

- Of all donor oocyte and embryo cycles
- Maintain the clinic's data of all infertility and ART procedures including adverse outcomes
- Record details of all the gametes or embryos received, used and stored
- Maintain proper records along with its identification during and after storage of gametes and embryos. Security of the stored gametes and embryos should also be provided
- Provide discharge certificate with details of ART performed
- Maintain confidentiality of all the patients who have undergone ART procedures
- Inform about legal right of born child and parents
 - » In case of married couples, the child born to them through ART is considered legitimate child of couple
 - » In case of a single woman the child should be considered as the legitimate child of the woman
 - » In case a married couple separates or gets divorced, after both parties consented to the ART treatment but before the child is born, the child shall be the legitimate child of the couple
 - » A child born to a woman artificially inseminated with the stored sperm of her dead husband with prior consent should be considered as the legitimate child of the couple
- Unused embryos can be used for research with approval of the couple
- Mixing of sperms or oocytes from more than one person is not allowed

2.5 Gender selection in ART

- Do not offer the facility to identify/predetermination of sex of child before birth to recipient of ART
- Do not provide, prescribe or administer anything that would ensure or increase the probability that an

embryo shall be of a particular sex except to diagnose a sex-linked disorder or disease

- Do not perform any procedure to separate, or yield fractions enriched in sperm of X or Y variations
- Human reproductive cloning is not allowed

2.6 HIV and ART

- ART cannot be refused to a HIV discordant couples however it is recommended to have facilities available to prevent horizontal and vertical spread of HIV
- Prevalence of HIV infected people is increasing day by day where majority of the infected patients are of reproductive age group. In such cases, couple should be counseled not opt for natural conception process because of associated risk to offspring
- ART procedures are recommended for HIV positive couples because
 - » When male partner is sero-positive, modified density-gradient centrifugation and swim-up method for sperm preparation coupled with either inseminations or in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) can be used as these techniques have proven to be highly effective in avoiding seroconversion of uninfected women and offspring
 - » When female partner is seropositive, a healthy conception can be achieved with help of antiretroviral treatment followed by intrauterine insemination or IVF
- Consider the preexposure prophylaxis of antiretroviral drugs before commencing fertility treatments, which may further reduce the susceptibility of the uninfected female partner and child. Research has shown that, once pregnant, the use of antiretroviral therapy and avoidance of breastfeeding in HIV infected women may reduce chance of newborn infection to approximately 2%

- Ensure safety through evaluation of clinical part of the program (oocyte retrieval) and of the laboratory conditions during IVF cycle
- Consider having separate tanks for storage of infected material

2.7 Multiple pregnancy and ART

- The incidence of multiple pregnancies is higher in ART, hence it recommended to not transfer more than 2 embryos in young women and note more than 3 in older women and in recurrent implantation failure

2.8 ART and welfare of the unborn child

- Consider the medical risks, family environment, and social environment before initiating ART procedures
- Consider the best interest of unborn child before proceeding for ART

2.9 ART and preimplantation genetic diagnosis

- Inform and counsel couple undergoing (IVF/ICSI) preimplantation genetic diagnosis (PGD) cycle about its complexities and uncertainties, including possible dilemmas and conflicts regarding embryo transfer after PGD
- Offer PGD only to screen the embryo for known, preexisting, heritable or genetic diseases. PGD in order to select for handicap/disability is morally unacceptable
- Aneuploidy screening should be done in high risk patients

2.10 Ethical aspect of gamete donation:

- Gamete donors should be free of all communicable diseases, sexually transmitted diseases, and identifiable genetic disorders
- Semen donors should be between 21 to 45 years (both inclusive). Donor sperm should be cryopreserved for at least six months (quarantine period) before being used and, at the expiry of such period, the

ART bank shall not supply the sperm to any assisted reproductive technology clinic unless the sperm donor is tested for such diseases, sexually transmitted disease or otherwise, as may be prescribed

- Single donor sample can be used for 25 times
- One sample of semen supplied by an ART bank shall be used by the assisted reproductive technology clinic only once on only one recipient
- Oocyte donors should be between 23 to 35 years (both inclusive)
- Oocyte donor can donate oocytes for maximum of one time in her lifetime
- Eggs from one donor can be shared between two recipients only, provided that at least seven oocytes are available for each recipient
- All unused oocytes would be either appropriately preserved by the assisted reproductive technology clinic for use on the same recipient(s), or given for research to a bonafide organization
- An ART bank shall obtain all necessary information in respect of a sperm or oocyte donor, including the name, identity and address of such donor or surrogate, and shall undertake in writing to the donor to keep such information confidential
- No ART bank shall divulge the name, identity, or address of any sperm or oocyte donor to any person or assisted reproductive technology clinic except in pursuance of an order or decree of a court of competent jurisdiction
- Any person or ART bank who divulges the name, identity or address of a sperm donor shall be guilty of an offence
- The collection of gametes from a person whose death is imminent shall only be permissible if such person's spouse intends to avail assisted reproductive technology to have a child

2.11 Research & ART

- Only those gametes and embryos donated for research purpose

- Maintain prior regulatory approval (Department of Health Research) before conducting any research studies

2.12 Code of practice

- Code of Practice deals with all aspects of the treatment provided and the research done at registered clinics.
- Any information about clients and donors must be kept confidential, except with the consent of the person to whom the information relates, or in a medical emergency or a court order
- All relevant information must be given to the patient before a treatment is given
- No treatment should be given without the written consent of the couple
- A standard consent form recommended by the accreditation authority should be used by all ART clinics
- Specific consent must be obtained from couples who have their gametes or embryos frozen, in regard to what should be done with them if he/she dies or becomes incapable of varying or revoking his or her consent
- People seeking registered treatment must be given a suitable opportunity to receive proper counseling about the various implications of the treatment

Summary of recommendations

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	Accreditation and supervision of ART Clinics and Banks necessary to ensure that services provided by the ART Clinics and Banks are ethical	-	-
CPP	To ensure Medical, social and legal rights of all those concerned are protected with maximum benefit to the infertile couples or individuals within a recognized framework of ethics and good medical practice	-	-
CPP	All ART clinics handling gametes need to enroll in a national registry (ICMR) before they are allowed to operate, therefore clinics performing IUI are also included	-	-
CPP	Only clinics that meet certain physical infrastructure requirements and have prescribed technical expertise are allowed to enroll in the registry	-	-
CPP	Do not offer ART to women with age above 45 years and Men above 50 years because of <ul style="list-style-type: none"> • Associated safety issues • Older women are more prone to develop chronic disorders like diabetes which may affect off springs • Chances of chromosomal abnormalities particularly after 35 years of maternal age 	-	-
CPP	Do not suggest ART for the women with age below 21 years and men below 23 years	-	-
CPP	All infertile couples undergoing treatment especially those who are going to undertake third party procedures should have a psychosocial counselling	-	-
CPP	Counselling about the investigations, management, complications and cost will help the patient/s in taking an informed decision	-	-
CPP	No ART clinic shall perform any treatment or procedure of ART without the consent in writing of all the parties seeking ART	-	-
CPP	No ART clinic shall freeze any human embryos without specific instructions and consent in writing from all the parties seeking ART	-	-
CPP	All ART clinics shall maintain detailed records, in the following manner: <ul style="list-style-type: none"> • As may be prescribed • Of all donor oocytes • Sperm, oocytes or embryos used • The manner and technique of their use • The individual or couple or surrogate mother in respect of whom it was used 	-	-
CPP	All ART clinics will, as and when such central facilities are established put online all information available to them in regard to progress of the patient (such as biochemical and clinical pregnancy), which should be done within seven days of the information being available, withholding the identity of the patient	-	-
CPP	Records maintained for at least a period of <u>ten years</u> , upon the expiry of which the ART clinic shall transfer the records to a central database of a, national ART registry to be set up by the Department of Health Research at the Headquarters of the ICMR	-	-
CPP	ART cannot be refused to a HIV discordant couples however it is recommended to have facilities available to prevent horizontal and vertical spread of HIV	-	-
CPP	The incidence of multiple pregnancies is higher in ART, hence it recommended to not transfer more than 2 embryos in young women and note more than 3 in older women and in recurrent implantation failure.	-	-
CPP	Sex selection No ART clinic shall offer to provide a couple with a child of a pre-determined sex No assisted reproductive technology clinic will carry out any ART procedure to separate, or yield fractions enriched in sperm of X or Y variations Any contravention of stipulation under subsection 1, 2, 3 and 4 of this section shall amount to an offence under this Act	-	-

Category	Recommendations	Grade of Recommendation	Quality of Evidence
CPP	Preimplantations genetics screening or diagnosis indicated for screen the embryo for known, pre-existing, heritable or genetic diseases or life-threatening condition Aneuploidy screening	-	-
CPP	Unused embryos should be destroyed or given for research only with the approval of the patient	-	-
CPP	Mixing of sperms or oocytes from more than one person not allowed	-	-
CPP	In the event of the closure ART bank immediately transfer the records to a central database of a, national ART registry to be set up by the Department of Health Research at the Headquarters of the ICMR	-	-
CPP	Sperm or semen, oocytes or oocyte donors and surrogate mothers should be obtained by the ART clinics or their patients from Assisted Reproductive Bank	-	-
CPP	Semen donors should be between 21 to 45 years (both inclusive). Donor sperm should be cryopreserved for at least six months (quarantine period) before being used and, at the expiry of such period, the ART bank shall not supply the sperm to any assisted reproductive technology clinic unless the sperm donor is tested for such diseases, sexually transmitted disease or otherwise, as may be prescribed	-	-
CPP	Single donor sample can be used for 25 times	-	-
CPP	Oocyte donors should be between 23 to 35 years (both inclusive). Oocyte donor can donate oocytes for maximum of one time in her life time	-	-
CPP	Eggs from one donor can be shared between two recipients only, provided that at least seven oocytes are available for each recipient	-	-
CPP	The collection of gametes from a person whose death is imminent shall only be permissible if such person's spouse intends to avail assisted reproductive technology to have a child	-	-
CPP	Gamete donation from relatives and friends is not allowed	-	-
CPP	Surplus embryos cannot be used for embryo donation	-	-
ICMR reference not added			

References

1. Human immunodeficiency virus (HIV) and infertility treatment: a committee opinion. Ethics Committee of the American Society for Reproductive Medicine American Society for Reproductive Medicine, Birmingham, Alabama. Fertil Steril 2015.
2. Guidelines for infertility counselling in different countries: Is there an emerging trend? Eric Blyth, Human Reproduction, Volume 27, Issue 7, July 2012, Pages 2046–2057.
3. National Draft Guidelines for Accreditation, Supervision & Regulation of ART Clinics in India - Indian Council of Medical Research (ICMR) at www.icmr.nic.in