Review Article

Ovarian Stimulation in Assisted Reproductive Technology Cycles for Varied Patient Profiles: An Indian Perspective

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Abstract

Controlled ovarian stimulation has been an integral part of *in vitro* fertilisation (IVF) treatment cycles. Availability of different gonadotropins for ovarian stimulation and gonadotropin releasing hormone (GnRH) analogues for prevention of premature rise of leutinising hormone during follicular phase offer an opportunity to utilise them for a successful outcome in women with different subsets of ovarian response. Further, use of GnRH agonist as an alternative for human chorionic gonadotropin improves safety of ovarian stimulation in hyper-responders. Mild ovarian stimulation protocols have emerged as an alternative to conventional protocols in the recent years. Individualisation plays an important role in improving safety of IVF in hyper-responders while efforts continue to improve efficacy in poor responders. Some of the follicular and peri-ovulatory phase interventions may be associated with negative impact on the luteal phase and segmentalisation of the treatment with frozen embryo transfer may be an effective strategy in such a clinical scenario. This narrative review looks at the available evidence on various aspects of ovarian stimulation strategies and their consequences. In addition, it provides a concise summary of the evidence that has emerged from India on various aspects of ovarian stimulation.

Keywords: *Controlled ovarian stimulation, hyper-responders, in vitro fertilization, normo-responders, poor responders*

Introduction

Controlled ovarian stimulation (COS) to obtain multiple oocytes forms the mainstay of assisted reproduction treatments (ART). While cumulative live birth rate (LBR) increases with increasing number of oocytes, an oocyte yield beyond fifteen increases the risk of ovarian hyperstimulation syndrome (OHSS) without further improvement in the pregnancy rate.[1,2] Ovarian response to COS is largely dependent on the ovarian reserve of an individual undergoing ART. While first cycle of ART was traditionally considered as the true test of ovarian reserve, pre-treatment assessment of certain ovarian reserve markers help identify women as expected normo/hyper/poor responders.[3-5] The most widely used tests to predict ovarian response to COS are anti Mullerian hormone (AMH) and antral follicle count (AFC).[6] Both have the highest accuracy for predicting poor and excessive response following COS.[3,4] Further, AMH has the advantage of minimal intra- and inter-cycle variability.[6] A cut-off value of 0.7-1.2 ng/ml for AMH and 5-7 for AFC has been proposed as predictive of poor response.[7] Serum AMH levels of >3.5 ng/mL and AFC of >16 have been shown to be the most appropriate cut-off for prediction of hyper-response.[5,8-10] A single centre study from North India has identified a higher cut-off value of 5.03 ng/ml for AMH in Indian women for the diagnosis

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of polycystic ovarian syndrome (PCOS).[11] Follicle stimulating hormone receptor (FSHR) and leutinising hormone receptor (LHR) genotype, apart from age, body mass index (BMI), ethnicity, infertility diagnosis and smoking, may influence the choice of protocol, starting dose of gonadotropins and the final oocyte yield.[12-17] However, evaluation of receptor polymorphism still remains a research interest and not a common clinical practice.

A challenging area in ART is poor response to COS, which is encountered in approximately 12-20% of women undergoing in-vitro fertilization (IVF). The most common aetiology is poor ovarian reserve (POR) with its varied, often ill-understood underlying mechanisms.[18,19] Introduction of Bologna criteria and subsequent POSEIDON classification of women with low prognosis are the most concentrated international efforts to bring uniformity to the definition of poor responders based on age and ovarian reserve markers.[20,21]

A comparison of Indian and Spanish women undergoing IVF documented an advanced ovarian age in women of Indian origin compared to Spanish women.[22] Data from national database of the United Kingdom (UK) shows a reduced live birth rate in women of Indian ethnicity compared to Caucasian women despite they being younger and with higher oocyte yield.[23] Similar outcomes have been observed in Indian women in the United States of America (USA).[24] Recent evidence suggests an association between genital tuberculosis and POR in the Indian context.[25,26]

An understanding of ovarian physiology is fundamental to optimise the COS. The pituitary gonadotrophins, follicle stimulating hormone (FSH) and luteinising hormone (LH) working in synergy regulate the folliculogenesis. FSH is involved in the initial recruitment and growth of the follicles. LH provides androgen substrate in the initial phase of the cycle and thereafter is involved in follicular growth, oocyte maturation, ovulation and corpus luteum (CL) maintenance. Cytoplasmic and nuclear maturation of the oocyte is dependent on the action of the LH surge on theca and mural granulosa cells.[27-29] It reprograms gene expression of these cells, altering the inter-cellular communication within the cumulus oocyte complex (COC) and the secretome of the oocyte and cumulus cells.[30,31] Also, acute upregulation of the epidermal growth factor (EGF) network by LH is essential to transmit LH signals from the follicular periphery to the COC since the pre-ovulatory oocyte does not express LH receptors.[32,33]

This narrative review is aimed at addressing the current evidence pertaining to ovarian stimulation in different subsets of women, factors which may influence outcomes, monitoring of IVF cycles, and current published experience of IVF in Indian women.

Methodology

A literature search using PubMed, Medline, Embase and Google Scholar was performed. The keywords included poor responders, hyper-responders, normal responders, *in vitro* fertilization, FSH, LH, gonadotropin-releasing hormone (GnRH) analogues, COS, oocyte quality, ovarian reserve, embryo quality, ART, embryo transfer, oestrogen, and progesterone. Boolean search strategy was used to perform the keyword search. English language articles published from Jan 1975 – Mar 2022 were included in the review. The review did not include case reports, case series, and articles published in text books. A flow-chart is given below for the search strategy [Figure 1].

Controlled Ovarian Stimulation in Normo-Responders

An optimal response to COS cycles is considered as an oocyte yield between 10 and 15 oocytes.[1,34] Pre-treatment with oestrogen, progesterone or oral contraceptive pills (OCP) prior to COS do not offer any benefits in normo-responders.[35,36] A recent meta-analysis showed a significantly lower ongoing pregnancy rate with antagonist compared to long agonist protocol.[37] However, this outcome was noted only with the combination of oral hormonal pre-treatment and flexible antagonist protocol, while no such difference was evident between fixed antagonist and agonist protocol.[37] Antagonist protocol is preferred in many IVF clinics worldwide considering convenience and safety aspects.[38]

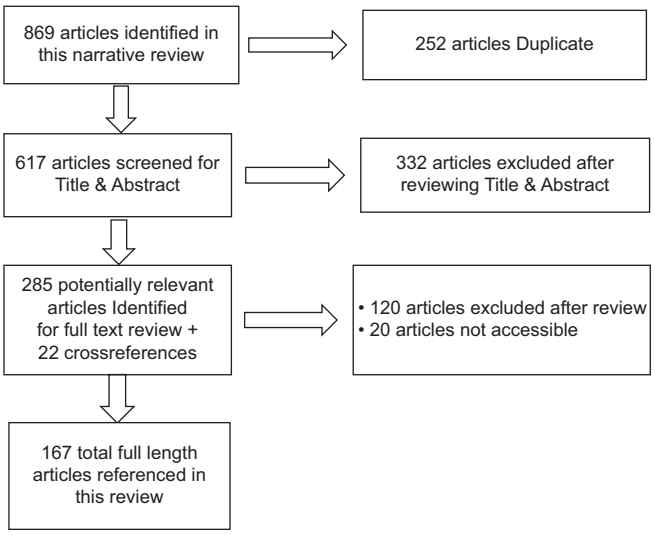

Figure 1: Flow chart of search strategy

Both recombinant follicle stimulating hormone (rFSH) and human menopausal gonadotropins (HMG) or highly purified HMG (HP-HMG) have been used for COS. A greater number of oocytes can be expected with rFSH compared to HMG.[39] Non-inferiority of HP-HMG to rFSH has been established in both antagonist and long agonist protocols in terms of ongoing pregnancy rates.[40,41] Thus, the choice of gonadotrophins in normo-responders is based on the availability, cost and clinician's discretion. There exists a positive correlation between FSH dose and oocyte yield.[42] For predicted normal responders, more oocytes are retrieved with daily dose of 200–225 IU FSH compared with 100–150 IU, with no significant difference observed between 225 IU and 300 IU. However, the current evidence suggests a similar pregnancy rate in normo-responders with starting doses of 150 IU or 200IU of FSH.[43] Available evidence does not support incorporation of recombinant LH (rLH) in rFSH protocols for young normo-responders. Role of rLH supplementation in those with profound suppression of endogenous LH remains controversial. Unexpected hyporesponse in young women (POSEIDON group I) remains a challenge. A retrospective cohort study from India reported that simple increase in dose of FSH or change of protocol may achieve LBR similar to those with good prognosis.[44] A systematic review in which two RCTs specifically addressed the issue of unexpected hyporesponse in young women reported that addition of rLH may be beneficial.[45] However, the findings should be interpreted with caution considering the limitations of these studies including relatively small numbers.

Minimal/Mild Ovarian Stimulation

Mild stimulation protocols aim to achieve an oocyte yield of <8 per cycle.[46] The data regarding the efficacy of mild/minimal ovarian stimulation in normal responders is limited.[47-49] A retrospective cohort study from India reports the cost-effectiveness of mild stimulation in a well selected group of normoresponders.[50] A recent meta-analysis shows similar live birth rate (LBR) in normo-responders with conventional or mild ovarian stimulation. However, cancellation rate was two-fold in mild stimulation and with reduced oocyte and embryo numbers.[51] This may negatively affect time to pregnancy and cumulative LBR.

Ovulation Triggering

Presence of two or three leading follicles of 18 mm diameter determines the timing of ovulation trigger. The current literature addressing the optimal length of COS is sparse. It is thought that a shorter duration may allow insufficient time for oocyte maturation and endometrial development. While some authors report a decrease in success rate with prolonged duration of stimulation,[52-54] others found no association between the length of stimulation and treatment outcome.[55,56]

The most commonly used preparation to mimic LH surge, for oocyte maturation is either recombinant or urinary human chorionic gonadotropin (HCG). Both preparations are equally effective for triggering oocyte maturation in COS.[57] A comparison of 5000 IU and 10,000 IU has not shown any difference in OHSS.[58] 4000IU and 6000 IU have shown similar oocyte maturation, with no benefit on OHSS and a possible negative impact on clinical pregnancy rate.[58,59] The most recent meta-analysis highlights the need for luteal phase optimisation when GnRHa is used as a trigger, to maintain an equivalent LBR to that with HCG.[60] Current evidence is very limited regarding the use of dual trigger in normoresponders.[61,62] Conversely, it is noted that a double dose of rHCG does not improve IVF outcomes.[63] We should consider fresh transfers in normo-responders as no difference has been observed in LBR when compared with elective frozen embryo transfer (eFET).[64] Any change in the current practise should be based on the emerging data.

Normoresponders: Summary Points

Gonadotropin Starting dose: 225 IU or lower (considering age and BMI).

Pituitary suppression: Long GnRH agonist or Fixed antagonist (based on availability, convenience and clinician's choice).

Ovulation trigger: HCG or GnRHa trigger (in antagonist protocol if hyper-response noted).

Controlled Ovarian Stimulation in Poor Responders

Poor response to COS is encountered in approximately 12-20% of women undergoing IVF. The most common aetiology is POR with its varied, often ill-understood underlying mechanisms.[19] It is important to note that more than 50% women with POR in first cycle of IVF will have normal response in subsequent cycles.[65] However, a persistently poor response of three or less oocytes is a predictor of reduced LBR in older women.[65] A comparative study in women undergoing IVF has shown that the ovarian age of Indian women is approximately six years older than their Spanish counterparts.[22] The interventions in management of this challenging group are directed towards improving the recruitment of a homogenous cohort of follicles leading to an increase in oocyte number and live birth.

Pre-Stimulation Strategies

Androgen supplementation is a widely practised approach to improve the outcome in poor responders. Transdermal or oral testosterone and oral dehydroepiandrosterone (DHEA) are the most commonly used molecules; with conflicting evidence regarding any benefit from various RCTs and meta-analyses.[66-70] Testosterone initiated before or during ovarian stimulation may improve IVF outcomes in poor responders.[69,70] Duration of its usage may have therapeutic implications.[71] Currently ongoing T-TRANSPORT trial may add to the understanding of androgen supplementation. DHEA is considered as a cost-effective alternative to testosterone and 75 mg daily in micronised form is the most widely used androgen supplement in expected or proven poor responders.[68,70] A systematic review including 17 RCTs concluded that the benefits of androgen pre-treatment were inconclusive when the studies with high risk of performance bias are removed.[72] The most recent network meta-analysis with included studies using Bologna criteria for defining poor response shows an improved clinical pregnancy rate with DHEA.[70] It is important to note that only two studies in which 82 women received DHEA were eligible for inclusion. This precluded the authors drawing conclusions on the quality of evidence.[70] A small single centre cohort study from India documents better pregnancy rates subsequent to DHEA supplementation in poor responders with previous IVF failures.[73] Another study measuring serum and follicular fluid concentrations of DHEA in poor and hyper-responders suggests an important role for DHEA in oocyte activation. Rectification of both low and high values may have a positive impact on embryo parameters and LBR.[74]

Current evidence is inconclusive on the role of growth hormone supplementation in improving LBR in poor responders.[70,76-78] Limited evidence suggests its beneficial role in long agonist protocol.[75] A single study shows possible benefit of Co-enzyme Q10 (CoQ10) in poor responders.[70,79]

RCTs including studies with uniform definition of poor response and low risk of bias are necessary to define the place of the above supplements in management of poor responders. Cost of these additions and current lack of conclusive evidence to support their use routinely in clinical practice should be considered prior to their incorporation in routine clinical practice.[80]

Steroid Pre-treatment

Progestins, OCPs and oestradiol are routinely used prior to antagonist cycles. A single study comparing antagonist cycles with and without OCP pre-treatment to GnRHa cycles in low responders showed a lower number of oocytes and embryos in untreated antagonist group compared to the other two groups. However, live birth rate was similar in all the three groups.[81]

Stimulation Protocols

Long agonist, short agonist and antagonist protocols are all utilised in IVF for poor responders. Long agonist and antagonist protocols yield similar pregnancy rates.[37] Conventional protocols in poor responders involve a higher starting dose of FSH compared to normal responders. Addition of rLH from mid cycle onwards to rFSH is a common clinical practice in poor responders to improve LBR despite lack of conclusive evidence in its support.[82,83] The ESPART trial did not show any advantage to adding rLH to rFSH in poor responders.[84] Use of urinary HCG instead of rLH appears to be a promising approach in improving clinical pregnancy rates.[85] A retrospective study suggests that early initiation of HMG with rFSH is associated with an improved LBR compared to mid-follicular HMG or rFSH alone.[86] However, this observation needs to be validated through appropriately designed RCTs.

An alternative approach to conventional stimulation is the use of mild stimulation or modified natural protocols. A low per cycle pregnancy rate, high cancellation, increased time interval to pregnancy and lack of available evidence on cumulative pregnancy rate should all be considered while choosing this option.[87] Protocols incorporating clomiphene and letrozole may be associated with low oocyte yield, high cancellation rate[88] and the lowest pregnancy rate.[70] Dual stimulation offers an attractive opportunity of increasing the number of oocytes within the span of an ovarian cycle in the context of fertility preservation. However, such an approach in the management of poor responders should be used cautiously considering the financial implications and the absence of supporting evidence.[89]

Poor Responders: Summary Points

Gonadotropin Starting dose: Usually 300 IU (age, BMI and previous response may influence the choice of starting dose).

Pituitary suppression: Fixed antagonist or long agonist.

Ovulation trigger: HCG.

Pre-stimulation strategies: Use of testosterone, DHEA, growth hormone and CoQ-10 all lack high quality evidence for their use in routine clinical practice.

Controlled Ovarian Stimulation in Hyper-Responders

Diagnosis of PCOS, a high AMH or AFC values, a previous high response or high number of retrieved oocytes (>15 oocytes) are considered as indicators of a high response. Choice of COS protocol, dose of stimulant, ovulation trigger will influence the occurrence of OHSS in hyper-responders.

Pre-Stimulation Strategies

Pre-stimulation steroid and metformin administration may have important impact on the course of ovarian stimulation in hyper-responders. Use of metformin before and during ART is a widely used intervention in women with PCOS. The most recent meta-analysis suggests a reduction in OHSS and a non-significant reduction in miscarriages. While no impact on LBR was noted in long agonist protocol, LBR was lower in the antagonist protocol in comparison to a placebo. The limitations were the low quality of evidence and no data on cumulative livebirth.[90]

Pre-treatment with OCP is a common practice in expected or proven hyper-responders to achieve pituitary suppression without increasing the risk of OHSS. Pre-treatment with OCP in antagonist cycles across the entire spectrum of ovarian response is considered to reduce pregnancy rate, LBR and miscarriages.[35] However, a retrospective study in women with PCOS suggests an improved IVF and pregnancy outcomes following pre-treatment with COCP for three months or longer.[91] This assumption needs further exploration before adopting as a standard clinical practice.

Ovarian Stimulation in Hyper-Responders

Ovarian response to urinary HMG and recombinant FSH exhibit certain differences during ovarian stimulation: rFSH results in a larger number of small and intermediate follicles, more mature oocytes, and in women with basal LH <1 IU/L, very low E2 levels with poor folliculogenesis. Results of a single RCT show that HP-HMG results in higher E2 levels but a lesser incidence of OHSS and miscarriage rate in comparison to rFSH and a similar pregnancy rate.[92] Further, a decision-tree model evaluating the financial impact of therapy per live birth after first embryo transfer in the same patient population suggests a reduced cost with HP-HMG in comparison to rFSH.[93] These reported benefits of efficacy and safety need validation through further RCTs.

A reduced starting dose of FSH is both cost-effective and safe in women expected to be hyper-responders.[94] An elective use of antagonist protocol is both effective and safe in hyper-responders.[5] A prospective study from India in a cohort of women with PCOS shows an increased risk of OHSS with long GnRH agonist protocol compared to antagonist protocol.[95] Final trigger for oocyte maturation in hyper-responders is best decided based on the ovarian response.[96] Coasting,[97] reduced dose of HCG,[58] GnRHa trigger[98] and elective embryo cryopreservation[99] have all been used in an attempt to reduce the incidence of OHSS in this subgroup of women. Prediction of OHSS based on the number of follicles and choosing the appropriate strategy for further management may help optimise the outcomes.[100] Though a 'freeze all' strategy remains the standard approach, an intensive luteal phase support with the addition of oestradiol or a small bolus of HCG to the standard progesterone therapy is necessary if fresh cycle transfer is considered following GnRHa trigger.[101]

Hyper-Responders: Summary Points

Gonadotropin Starting Dose: 150 IU or lower (based on BMI, AMH/AFC value and previous response).

Pituitary suppression: Antagonist (most widely used - fixed or flexible multiple dose).

Ovulation trigger: GnRHa (HCG if ovarian response is ≤ normal).

Pre-stimulation strategies: ? Metformin for long agonist GnRHa protocol.

The Efficacy of Stimulation Protocols to Improve Oocyte and Embryo Quality

The oocyte quality is one of the key parameters determining the embryo quality and is a good predictor of IVF outcome. Bovine and murine studies have shown that ovarian stimulation may negatively impact the fertilization and embryo development, impair implantation and increase chromosomal abnormalities.[102,103] However, an analysis of trophectoderm biopsies in a large cohort has shown that the intensity of stimulation does not influence the ploidy status.[104] In a large cohort study, a strong association is reported between the number of oocytes and live birth rate; with the best chance of a live birth at 15 oocytes.[105]

While a study from India suggested that antagonist protocols may be associated with better perifollicular vascularity and better quality embryos, it included small numbers and did not report on LBR.[106] A systematic review of 73 RCTs has not shown any difference in the LBR when antagonist or agonist was used.[107] No difference is noted in embryo morphokinetics within

individuals undergoing IVF when switched between antagonist and agonist protocols.[108]

It is plausible that gonadotropin preparations used in COS may have an impact on oocyte quality.[109] However, similar pregnancy rates have been reported while comparing rFSH and HP-HMG in the MERIT trial.[40] An RCT comparing urinary FSH (hFSH) and rFSH did not reveal any difference in the fertilization rate or implantation rate.[110] A comparison of HMG, hFSH, rFSH, and sequential hFSH/rFSH did not reveal any difference in the oocyte numbers or embryo quality amongst the different groups in a RCT.[111] Even supraphysiological E2 does not appear to have any negative impact on oocyte quality.[112] Addition of rLH to rFSH in older women has not shown to improve clinical outcomes.[113,114]

Agonists versus Antagonists in *In vitro* Fertilisation

GnRH analogues play an important role in COS to prevent premature rise in LH and premature ovulation as evident from the above discussion. A recent systematic review and meta-analysis showed that in normo-responders GnRH agonist protocols result in higher pregnancy.[37] Within this population, antagonist treatment prevents one case of OHSS in 40 patients but results in one less ongoing pregnancy out of every 28 women treated. In women with PCOS and potential high responders, GnRH antagonists do not seem to compromise ongoing pregnancy rates and are associated with less OHSS and therefore should be considered as standard treatment.[37] In addition, they offer the flexibility of using GnRHa for triggering to minimise the risk of OHSS. While antagonist protocols are widely used in the poor responders, long agonist protocol may be equally effective.[115]

Does Luteinising Hormone Activity Improve the Quality of Oocyte and Embryo?

Considering the vital role LH plays in folliculogenesis, the current trend of conducting COS in an LH-depleted environment (pituitary suppression and COS with recombinant FSH) has been questioned.[116] The role of exogenous LH in COS remains controversial since very low concentration of endogenous LH are sufficient to sustain adequate follicular growth and development.[117] However, profoundly suppressed LH may compromise the quality of oocytes and thereby ART outcome. A negative effect on the ovarian response and follicular endocrine profile in LH depleted cycles has been reported.[118,119] A reduction of apoptosis with improved chromatin quality of cumulus cells involved in oocyte maturation in women treated with r-LH has been observed.[120] A review and meta-analysis of studies comparing different gonadotrophins concluded that FSH alone resulted in higher oocyte number, HMG improved the number of mature oocytes and embryos and increased implantation rate, while rLH addition or use of HMG lead to higher pregnancy rate in GnRH agonist cycles.[121] A large retrospective study of more than 4000 patients demonstrated the beneficial effect of LH in low prognosis patients.[122] LH may improve the oocyte quality by leading to activation of ERK1/2 and AKT-pathway and a final proliferative and anti-apoptotic signal.[123]

The ultimate answer to this debate may lie in pharmacogenetics which demonstrates the effect of individual genetic variability.[124] FSH and LH receptor polymorphisms have been implicated in infertility as well as response to COS.[125] An increase in FSH requirement for COS has been demonstrated in women having an LH or AMH polymorphism.[126-128] An association between LHCGR N312S polymorphism and a higher requirement for rLH in Indian women homozygous and heterozygous for serine was noted in a cross-sectional study.[129] It is to be seen whether customised COS based on the patient's genome would possibly provide the final answer on the need for LH in COS.

Selective and Elective Freeze policy

Transfer of supernumerary cryopreserved embryos generated as a result of COS in IVF has evolved as an important strategy to enhance cumulative pregnancy rates (CPR) in ART. A shift in cryopreservation technique from slow freezing to vitrification has led to enhanced embryo survival rates.[130,131] and better reproductive outcomes in frozen embryo transfer (FET) cycles.[132-134] Consequently, a global upsurge in FET cycles of approximately 15-40% has been observed.[135-137]

High steroid levels generated during COS initiate early endometrial maturation, altering the 'window of implantation'(WOI)[138,139] leading to a negative impact on embryo implantation.[140] The improved pregnancy rate (PR) in FET cycles is presumed to be a result of better embryo – endometrial synchrony.[132] Rise in pre-ovulatory progesterone level in stimulated cycles is also detrimental to implantation.[141] A significantly reduced risk of ectopic pregnancy, preterm birth, low birthweight and small for gestational age babies has been reported in FET pregnancies.[142]

An elective freezing or a 'freeze all strategy' implies cryopreservation of all embryos generated in IVF

with subsequent FET in a natural or hormone replacement cycle. Selective freezing refers to freezing of supernumerary embryos following a fresh embryo transfer or freezing of all embryos in specific clinical scenario when an unexpected intra-uterine pathology such as endometrial fluid, polyps or thin endometrium was encountered during COS; rise in pre-ovulatory progesterone level in stimulated cycles or unexpected hyper-response. Elective freezing was initially proposed as an OHSS risk reduction strategy in hyper-responders,[143] in patients undergoing preimplantation genetic testing (PGT) and fertility preservation. Its use is extended to patients with recurrent implantation failure to improve embryo-endometrial synchrony at ET.[140]

One of the earliest systematic reviews and meta-analysis, comparing reproductive outcomes of fresh or elective frozen embryo transfer (eFET) proposed that eFET should be universally advocated because it resulted in an approximate 30% increase in CPR and ongoing pregnancy rate (OPR).[144] Two of the three trials included in this review were on high responder patients whilst one included normal responders. Many other studies followed reporting higher PRs with eFET; most of them included PCOS patients.[145-147] However, RCTs done in patient specific groups reveal that eFET does not improve results across the spectrum. An RCT in non-PCOS patients found no advantage of eFET over fresh transfer.[148] SART registry data of 82935 patients revealed that CPR and LBRs were significantly higher only in eFET in high responders (>15 oocytes recovered).[149] In normal (6-14 oocytes) and poor responders (<6 oocytes) on the other hand, CPR and LBRs were significantly higher in fresh ET cycles ($P < 0.001$). Only data of first IVF cycles and ET done within one year were used for analysis.[144] A population based study also reported significantly lower cumulative LBR in normal and sub-optimal responders with eFET.[147] In high responders, cumulative LBR was similar in fresh and eFET. A Cochrane meta-analysis of 2021 concluded that cumulative LBR between eFET and fresh ET are similar with a moderate quality of evidence. However, the meta-analysis was unable to draw any conclusions on the impact of 'freeze all' on the risk of miscarriages, multiple pregnancies and small-for-gestational age.[99]

Elective freezing has other associated disadvantages. There is an inherent risk of complete or partial degeneration of embryos during the freeze thaw process. Added to that there is a delay in cycle completion leading to increased emotional and financial burden. A high rate of treatment discontinuation has also been observed in normal and suboptimal responders (24.4% and 34.1%, respectively)[147] and an increase in pregnancy induced hypertension and large for gestational age babies has been reported.[142] In addition, the luteal support (LPS) in FET cycles may need an individualised approach to achieve the best possible outcomes rather than a standard LPS for all.[150,151]

Monitoring of Controlled Ovarian Stimulation Cycles

This section provides a brief overview of the monitoring of COS cycles during IVF. Patient comfort, cost implications and the impact on outcome influence the choice of modality. Transvaginal ultrasonography (TVS) forms the mainstay of monitoring ovarian response. Ultrasound assessment of follicular growth was first introduced in 1978 when a linear relationship between follicle size and circulating E2 levels was reported.[152] There is no evidence that cycle monitoring by TVS alone is any less effective than combined monitoring by transvaginal and oestradiol assay.[153] Till date there is no consensus regarding the optimal number of measurements for each follicle or how best they are performed; but a single measurement is less reliable than two or three measures.[154] In addition to measuring the number and the rate of growth of follicles and the endometrial thickness, a TVS may be used to evaluate follicular and endometrial blood flow.

Baseline ultrasonography (USG) is utilised to confirm that the follicular size is <10 mm, there is absence of ovarian cyst, endometrial thickness <6 mm [Figure 2]. Rate of growth of endometrium is slow during the first few days, but reaches 1-2 mm/day around 2-3 days before ovulation. Ideal thickness required varies between 8-14 mm.[155] Endometrial thickness of less than 7 mm on the day of HCG is associated with poor implantation.

Follicles with more than 75% of their surface perfused, ovarian stromal peak systolic velocity (PSV) >10 cm/s and resistance index (RI) <0.4 – 0.48 usually contain oocytes of satisfactory quality. Rising PSV with steady low RI suggests imminent rupture.[156] Ultrasound parameters evaluated to assess endometrial receptivity are endometrial thickness, endometrial pattern, endometrial volume, doppler study of uterine arteries and endometrial blood flow. Endometrial thickness and

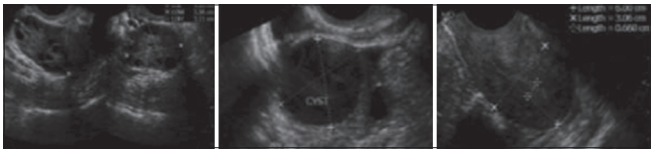

Figure 2: Criteria for initiation of controlled ovarian stimulation

pattern have low positive predictive value and specificity for ART outcome.[157,158] A volume of 2.0–2.5 ml on 3D ultrasound is considered as a good predictor of pregnancy outcome.[159,160] However, it is ineffective for predicting pregnancy in an unselected population of women undergoing ART.[161]

An endocrine evaluation has an important role to identify certain nuances of ovarian response. Baseline assessment confirms ovarian quiescence when LH is ≤4 IU/L, oestradiol (E2) levels is <50 pg/ml and progesterone level <1.5 ng/ml following pituitary downregulation with long or ultralong agonist protocol. However, such measurements have limited role in an antagonist protocol and a TVS usually suffices. Serial E2 measurement may provide additional information in predicting OHSS or poor response. The dose of gonadotropin should not be changed as long as serial E2 rise is between 50 and 100% every other day.[162] E2 levels during COS have long been used to predict the risk of OHSS.[163]

Premature progesterone elevation (PE) in the late follicular phase is identified by the serum progesterone levels of >1.5 ng/ml on the day of HCG. PE can result in advanced endometrial maturation, leading to dyssynchronous glandular and stromal differentiation in the luteal phase.[164] PE may also be associated with altered gene expression.[165] Despite lack of consensus, it is generally accepted that PE adversely affects the pregnancy rate and fresh embryo transfer is avoided.[166] Progesterone levels on the day of embryo transfer may help in defining the most optimal strategy for LPS.[167]

Conclusions

The review provides an overview of ovarian stimulation for IVF and the emerging evidence in the recent years. It also looks at the evidence available on ovarian reserve and ovarian stimulation in Indian women. An apparently increasing incidence of poor response in IVF is a frustrating situation for infertile couples and clinicians alike. Lack of definitive benefits, possible side effects of various interventions and their impact on LBR should be considered while offering them to these women.

The challenges in hyper-responders are the need for cancelation due to hyper-response and OHSS, the most serious iatrogenic complication of IVF. Safe and effective outcome can be achieved by using antagonist protocols, individualised dosing of gonadotropin, right choice of trigger and decision regarding segmented cycles. Both endocrine and ultrasound monitoring of IVF cycles contribute to improve the safety and efficacy of treatment and a prudent choice of the modality is needed as demanded by the clinical scenario. Currently an all freeze strategy cannot be advised to an unselected patient population as it is still not certain that it can improve clinical efficacy.

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Data availability statement

Not applicable.

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