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Mid-life fertility: Challenges & policy planning

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This review highlights the challenges, priority areas of research and planning, strategies for regulation of services and the need to develop guidelines and laws for fertility treatments during mid-life. The success rate of all treatments is poor in advanced age women because of declining ovarian reserve and natural fertility. There is often a need of third-party involvement which has its own ethical, legal and medical issues. Welfare of children born to older women and early death of parents are important concerns. Most of the new techniques such as the pre-implantation genetic diagnosis, oocyte augmentation, use of stem cells or artificial gametes, ovarian tissue preservation and ovarian transplantation are directed to improve, preserve or replace the declining ovarian reserve. These techniques are costly and have limited availability, safety and efficacy data. Continued research and policies are required to keep pace with these techniques. The other important issues include the patients' personal autonomy and right of self-determination, welfare of offspring, public vs. private funding for research and development of new technologies vs. indiscriminate use of unproven technology. It is important that mid-life fertility is recognized as a distinct area of human reproduction requiring special considerations.

Key words Advanced maternal age - assisted reproduction techniques - fertility policy planning - fertility services - maternal morbidity - mid-life fertility

Introduction

In the seventies, elderly primigravida was a term used for pregnant woman above 35 yr of age¹. The reason for defining them separately was the presence of increased obstetric risks in this group. Over the last 40 years, the scenario has changed. The average age of first pregnancy has risen all over the world including in India. The increase which started in the mid-seventies has led to nearly 15 per cent of all births occurring in women above 35 yr of age. Approximately 10 per cent of all first-time births occur after age 35 yr². The births in women aged >45 yr increased from 0.4 per thousand deliveries to 1.8 per thousand from 1990 to 2010 - a

rise of almost four- to five-fold. Similarly, the delivery rate in women above 50 yr increased from zero to 0.3 per thousand deliveries during the same period³. There is an entirely new category of pregnant women which had never existed in the past, *i.e.* pregnancy at very advanced age. This can be loosely defined as women aged above 45 yr.

Various reasons for this increase are (i) entry of women in the work force; (ii) availability of effective and safe contraception and abortion services; and (iii) most women are now career-oriented and therefore, delay marriage for various reasons⁴. In addition, availability of assisted reproduction techniques (ARTs) to older

women and option of fertility preservation have reinforced the idea of an infinite reproductive lifespan. Continued research on the subject has brought newer and unproven technology in the market. All these issues have opened up new ethical, social and legal challenges not only for ART practitioners and gynaecologists but also for the society at large, judiciary, government, regulatory agencies and research organizations. This review highlight key areas for research and policy planning, strategies for regulation of services and resource utilization, and need for guidelines and laws in these areas.

The key thrust areas which need attention are listed in Table I.

Definition of mid-life in relation to fertility

At present, between 40 and 65 yr is considered as the most acceptable definition for mid-life in medical literature⁵. Both upper and lower limits of age need to be defined if we consider mid-life in relation to fertility. Lower limit should start at the age where there is a serious decline in natural fertility. The menopause defines the upper limit of natural fertility. Natural fertility in female declines to <10 per cent after 40 yr of age and pregnancies are very rare after 45 yr of age⁶. With the options opening up for older women because of ARTs (*i.e.* ovum donation, surrogacy and fertility preservation), there is practically no upper limit.

There is a need to define both lower and upper limits of mid-life in relation to fertility. This would be the first step in drafting any regulatory guidelines and laws, as well as for resource allocation for research or clinical services. In the available literature, there is no

clear nomenclature of fertility status of older women. One could possibly classify these women based on natural fertility decline and likelihood of complications.

Increasing age of pregnancy

According to the Centers for Disease Control and Prevention data, the mean age of first-time mothers increased by 1.4 yr to 24.9 yr in 2000 and 26.3 yr in 2014 in the USA. From 2000 to 2014, the proportion of first birth to women aged 30-34 yr rose by 28 per cent (16.5-21.1%) and first births to women aged 35 yr and over rose by 23 per cent (7.4-9.1%). There is also a steady increase in the births in women aged above 40 and even 50 yr⁷. The changes also represent a global trend⁸.

No definite data or trends are available from India. However, an indirect interpretation can be made on the basis of increasing median age of marriage⁹. The reasons for this change are increasing migratory workforce and higher level of school enrolment in females. There is a visible trend towards a further rise in age of marriage in urban India.

Increasing demand for infertility services

There is a growing demand for fertility services in the older age group. In 1997, 44.7 per cent of women going for ART were aged below 35 yr, while it decreased to 41.4 per cent in 2010. Less than 200 embryo transfers (ETs) were reported in 1988 in women of advanced maternal age (AMA). This figure rose to >17,000 in 2012^{10,11}. The donor oocyte cycles have also nearly doubled. The addition of age group of >44 yr in the Society for Assisted Reproduction Technology (SART) data 2010 indicates this demand¹². In India, nearly 15 per cent of egg donation recipients were above 45 yr¹⁰. The reasons for increased demand in fertility services are listed in Table II.

How significant is the age-related decline in fertility?

There is a progressive decline in oocyte quality and quantity throughout the lifespan of women. This qualitative and quantitative decline is associated with a progressive decline in fertility^{11,12}. Menopause is achieved when there is almost complete depletion of follicular pool. Less than 1000 oocytes remain at menopause from nearly 3-5 lac at puberty. Even at the age of 37 yr, only 25,000 oocytes remain which are also qualitatively deselected. The menopausal transition has been very elaborately defined by the American Society of Reproductive Medicine (ASRM)¹³. The late

Table I. Key thrust areas

1. Definition of mid-life in relation to fertility
2. Increasing age of pregnancy
3. Increasing demand for fertility services
4. Age-related decline in fertility
5. Do Indian women lose fertility early?
6. Overestimation and fertile lifespan
7. Artificial extension of fertility
8. Higher failure rates of all kinds of treatments
9. Third party reproduction
10. Maternal risks
12. Impact on health and longevity
13. Perinatal morbidity and mortality
14. Welfare of the offspring
15. Use of experimental and costly treatments
16. Fertility issues of the ageing male
17. Age cut-off for fertility services

Table II. Reasons for increased demand of fertility services

1. Increasing age of marriage
2. Delayed planning of first child
3. Increasing divorce rate
4. Carrier conscious female population
5. Increasing international migration
6. High road traffic accident rate and loss of grown-up children
7. Availability of donor egg technology
8. Artificial extension of fertility due to fertility preservation
9. Increased survival of cancer patients
10. Lack of awareness regarding age-related fertility decline
11. Glamorizing of older age births by media
12. Overestimation of success of IVF outcome irrespective of age
13. Grossly inadequate infertility and ART services in government sector
14. Increased affordability in mid-life
15. Poor availability of adoption services
16. Mushrooming and commercialization of IVF centres
17. Lack of laws and guidelines

ART, assisted reproduction technique; IVF, *in vitro* fertilization

reproductive (−3), early menopausal transition (−2) and late menopausal transition (−1) are marked by significant changes in hormones, folliculogenesis and impaired fertility^{13,14}. This decline in fertility can be compensated by the use of donor eggs from younger women¹⁵⁻¹⁷. The decline in fertility may get accelerated in certain diseases because of the disease itself or the therapy required or both, *e.g.* endometriosis, leiomyoma, genital cancers, genital tuberculosis, chemotherapy and radiotherapy¹⁸⁻²¹.

In addition to decline in the probability of conception, the incidence of miscarriage and congenital malformations is also increased. This increase is related to the higher aneuploidy rate due to increased meiotic non-disjunction at AMA²². Foetal loss also increases with age even after the foetal heart rate motion has been detected by transvaginal ultrasound²³. From 9.9 per cent foetal loss rate before the age of 33 yr, the loss rate almost doubles every three years. The reported incidence is 13.7 per cent at 35-37 yr, 19.8 per cent at 38-40 yr, 19.8 per cent at 41-42 yr and 29.9 and 36.6 per cent above 44 yr²⁴.

Recommendations of the ASRM practice committee guidelines¹¹ include (i) education and awareness among young women; (ii) expedited evaluation of fertility potential in older women; and (iii) immediate evaluation of women of more than 40 yr of age.

Do Indian women lose their ovarian reserve earlier than their Western counterparts?

Various factors, *e.g.* ethnicity, nutritional, urban or rural status and education, play an important role in determining menopausal age. An elegant pan-India Survey was conducted by the Menopause Society of India²⁵. Average age of menopause of women in India is 46.2±4.9 yr as compared to 51 yr in the West²⁶. This is nearly five years earlier than their Western counterparts. The difference in the age of menopause among various ethnic groups has been highlighted earlier also²⁷. Non-White-American women achieve menopause at least two years earlier than White-American women²⁸.

There is a consistent difference in the outcome of ART cycle among various ethnic groups. Lower implantation and ongoing pregnancy rate in Black versus White women has been reported by many authors (9.8 vs. 23.4%, $P=0.009$; 14.9 vs. 38.8%, $P<0.005$, respectively)²⁹. In a comparative study, Asian women had decreased odds of clinical pregnancy (0.71) and live birth (LB, 0.69)²⁹. A similar trend of inferior outcome was reported for all non-White ethnic groups³⁰⁻³². There was significantly higher gonadotropin dose requirement in these all non-White ethnic groups. The ovarian reserve markers have also reflected a similar trend. Similar ovarian reserve markers, *e.g.* antral follicle count (AFC) and anti-Mullerian hormone (AMH), were found in Spanish and Indian women with an age difference of six years³³. Other studies have highlighted the comparatively lower AFC and AMH in Indian women as compared to Western women^{34,35}. There are no age-related nomograms for AFC and AMH values in India similar to that available in Western literature^{36,37}.

The following recommendations can be suggested for Indian women: (i) The 5-6 yr difference in the age of menopause and corresponding earlier decline in fertility of Indian women needs to be highlighted; (ii) recommendation for instituting ART in Indian women should be made on the basis of earlier menopause and not based on western age cut-offs; (iii) there is an urgent need to have population-based studies for determinants of age-specific markers of fertility such as AMH and AFC in India and determine the cut-offs for various treatment protocols; and (iv) working out the cost-effective analysis of various types of infertility treatment versus *in vitro* fertilization (IVF) in different age groups and diagnostic categories.

Overestimation of fertile lifespan and efficiency of ARTs irrespective of age

Intrauterine insemination and ART are commonly employed in women above 40 yr. The success rate of ART has steadily improved over the last 40 yr³⁸. However, the technology has not been able to circumvent the impact of ageing³⁹⁻⁴². The experience with pre-implantation genetic testing for aneuploidy (PGT-A) has revealed an alarmingly high rate of aneuploidy. The aneuploidy rate steadily rises from 30 per cent at the age of 30 yr to 90 per cent at the age of 45 yr. Almost 60 per cent of cycles end with no embryo available for transfer after PGT-A testing in AMA^{43,44}.

The American College of Obstetrics and Gynaecology and ASRM encourage counselling of reproductive age women regarding age-related fertility decline and pregnancy risks at later age¹¹. In a study assessing the awareness related to age-related fertility decline, one of five women was found to be unaware of the effect of increased age on fertility and only 30 per cent were aware of significant decrease at the age of 35. Almost one in four women (23%) regretted getting late for IVF because of lack of awareness. Unfortunately, women believed IVF can reverse age-related fertility decline⁴⁵⁻⁴⁸.

It is therefore, necessary to increase awareness among general public regarding age-related fertility decline, as well as among medical practitioners. A realistic projection of limitations of ART is also required. Awareness regarding need for third party at advanced age should be increased.

Artificial extension of fertile lifespan due to technology

The age-related decline in fertility is primarily due to depletion of ovarian pool of oocytes while the uterus retains its power to respond to endogenous and exogenous hormones almost indefinitely. Embryo freezing by slow freezing has been successfully used for almost 49 years⁴⁹. With the use of vitrification of embryos, the results have improved markedly⁴⁹. Oocyte freezing is now accepted as a standard and successful procedure ensuring almost 80 per cent oocyte survival capable of producing healthy embryos and LBs⁴⁹. This technology has created scope for women for delaying childbirth for various medical and social reasons and still having their own biological child.

Approximately 10 per cent of cancers occur in reproductive years⁵⁰. Cure and survival rates of

up to 80-100 per cent can be assured with safer and effective options available of surgery, radiotherapy and chemotherapy⁵⁰.

This improved survival has raised quality of life issues for cancer survivors. The American Society of Clinical Oncology guidelines mandate that all young patients (both males and female) undergoing gonadotoxic and reproduction affecting therapy should be given option to freeze their gametes (embryos or ovarian tissue) to preserve the fertility⁵¹⁻⁵³.

Freezing oocytes has given carrier conscious women an option of delaying their fertility till the time they are ready to take up building their families. This option has raised a huge controversy regarding the social and personal implications of such option^{54,55}.

With embryos, oocytes and sperms lying as potential future human beings, the issues related to disposition of this material in case of death, divorce or abandonment are important. Clear guidelines are needed for custody, disposition and also posthumous reproduction. Other issues regarding duration of storage, place of storage and legal liabilities of banks also need attention. Fate of these gametes in case of dissolution of the bank needs to be defined.

Futile treatment

The post-menopausal life expectancy and also quality of life are constantly improving. While cumulative pregnancy rates with ART are now above 60-70 per cent in young women, the chances of success decrease as the age advances. The quality of blastocyst decreases as the age advances⁵⁶. Even with the availability of good-quality oocytes, the implantation rate is decreased significantly as the age advances. The chances of pregnancy by blastocyst were reduced by 60 per cent in women older than 38 yr^{43,57}. The physician is caught in the dilemma of respecting patient's autonomy to decide in favour of a treatment which is not likely to result in a reasonable chance of success on the one hand and refusal of treatment based on physician judgement of the outcome.

Futile treatment can be defined when chances of achieving an LB through ART is <1 per cent or virtually no chance of success and poor prognosis when it is <5 per cent or a remote chance of success⁵⁶⁻⁵⁸. Viewpoints of the physicians who refuse futile treatment and patients who still want to avail ART treatment despite being aware of poor outcome are listed in Table III.

The following recommendations can be made for futile treatment.

Table III. Reasons for opting/refusal of ART at advanced age

Patients' viewpoint	Clinicians' viewpoint
Want to do their best efforts	Fear of litigation in case of failure
Perceive 1 per cent also as hopeful. Holding the proverbial straw	Minimizing harm to patient
Want to know if they can still produce eggs or embryos even if it does not lead to pregnancy	Avoidance of frustration associated with providing futile treatment
Perceive embryo transfer or an early abortion which removes the stigma of infertility	Right of refusal of treatment which they consider inappropriate remaining in legal framework
Satisfaction of having tried and experienced IVF	Some may believe that it is their duty to withhold a treatment which cannot fulfil its intended goal
Dissatisfaction with a previous attempt at a different centre	Matter of integrity. Wasteful or even fraudulent or misleading patients in hopeless situations
Cannot accept donor eggs	Better success rate with other options such as egg donation
IVF, <i>in vitro</i> fertilization; ART, assisted reproduction technique Source: Ref. 56	

- (i) Decision regarding refusal or continuing a treatment require thorough counselling on part of the clinician to ensure that couples have really understood the implications.
- (ii) The patients also need to know the alternate options which are available.
- (iii) The consent has to be in writing.
- (iv) The treatment should not be withheld just because of protecting a centre success rate or financial benefits.
- (v) The counselling should be evidence based.
- (vi) There should be a mechanism of referral to a centre which may have a better success rate in desperate situations and for advanced age women. This referral clause may be more relevant in Indian scenario where mushrooming of small volume centres is rampant.
- (vii) There should be clear definition of treatment guidelines to protect the clinicians and also the gullible patients.

Third-party reproduction

Ovum donation has enabled numerous women to conceive and have the pleasure of carrying a pregnancy and delivering and lactating the baby who at least is genetically related to her husband. IVF with ovum donation is a successful and acceptable option to most women⁵⁸⁻⁶¹. The procedure has encouraged demand from couples irrespective of the age and medical status of the female partner. According to the Indian data, nearly 10 per cent cycles were egg donation cycles¹⁰. This success of technology has raised many ethical, social and legal issues. Third-party reproduction has

extended the female infertility almost indefinitely creating an illusion of efficacy of IVF at any age. Most of these cycles are in women above 40 yr. Embryo donation is an acceptable option for those women who have associated male factor⁶².

Surrogacy with or without ovum donation is another technique which circumvents problem of uterus as well as ovarian reserve. The child thus produced is not related to any of the partner. There is no genetic or gestational relationship with the commissioning couple.

Third-party reproduction has raised numerous ethical and legal issues. There are issues related to the welfare of advanced age women and their offspring as well as of donors and surrogates. The method of procuring and screening surrogates and donors and monetary compensation are sensitive matters. Besides the ethics of donating oocytes and identifying a surrogate, there are numerous legal angles and disputes which can arise, especially with international contracts. The laws related to surrogacy and ovum donation vary from country to country and from State to State within many countries.

Guidelines need to be made related to a wide of range of aspects, such as eligibility requirements of commissioning couples, of donors and surrogates, upper age limit for commissioning couples, ART for single men or for single women, genetic or gestational link with at least one partner, monetary compensation guidelines, authorized law firms for such contracts, health/life policy to cover donors and surrogates, national registry of donors and surrogates, appropriate

consent and contract formats, confidentiality of surrogates and donors and commissioning couples, guidelines/laws for international couples, and also for embryo donation.

Higher maternal morbidity and mortality

There is a definite evidence of increased maternal morbidity and mortality related to advanced age⁶³. There is increased risk of diabetes, hypertension, pre-eclampsia, obesity abruption, *etc.* In addition, pre-existing comorbid medical illnesses also contribute to increase the risk⁶⁴. However, not all complications can be explained by pre-existing diseases⁶⁵.

Pregnancy at AMA brings to surface any latent or compensated disease, especially cardiovascular problems. The odds ratio (OR) of maternal deaths increased from 2.07 [confidence interval (CI) 1.78-2.40] to 9.90 (CI 5.60-15.98), respectively, from age <35 yr to above 45 yr. Similarly, OR of other serious events rose at these ages, *e.g.* myocardial infarction from 4.05 (CI 3.29-4.98) to 21.38 (CI 11.46-39.88), cardiac arrest from 2.07 (CI 1.80-2.42) to 10.84 (CI 6.48-18.14), pulmonary embolism from 1.83 (CI 1.69-1.98) to 5.01 (CI 3.47-7.23), deep vein thrombosis from 2.02 (CI 1.91-2.14) to 4.38 (CI 3.26-5.89) and acute renal failure from 1.86 (CI 1.76-1.97) to 6.38 (CI 5.06-8.04)⁶⁶.

Very high maternal complication rate was reported in a study which compared maternal outcome in women aged between 45 and 50 yr and those above 50 yr who had conceived through ovum donation and IVF⁶⁷. The complication rate was related to multiple pregnancies. The authors recommended elective single ET in these women⁶⁸⁻⁷⁰. Therefore, in addition to age, there is a need for guidelines regarding the number of embryos to be transferred in these couples⁷⁰. The complications of pregnancy increase many folds in case of multiple pregnancies. This guideline becomes very pertinent in relation to ovum donation cycles to protect these women against the additional burden of multiple pregnancy^{67,70}.

Impact on health and longevity of mother

Many women of AMA may undergo a pregnancy with or without complications. Not only the health during pregnancy and the postpartum period but also the impact on long-term health and longevity of women is a major concern⁷¹. This question has become crucial with the trend of pregnancy at later ages and AMA and very advanced maternal age (VAMA). The artificial extension of fertility has now given option to women to

delay their childbearing. Natural pregnancies at AMA have a beneficial effect on longevity of these mothers, but the same is not true of higher number of children⁷². There is some evidence that common genes may be involved in fertility, ovarian ageing and longevity^{72,73}. While pregnancy may have rejuvenating effects on female body, the complex interplay of infertility, ART and pregnancy complications is difficult to separate out⁷⁴. However, whatever evidence we have, pregnancy even at an advanced age has a beneficial effect on longevity⁷⁴. The explanation may lie in the epigenetics and changes in body which occur during pregnancy^{74,75}. The data need to be stratified according to the age at pregnancy, premorbid and comorbid conditions to arrive at definite recommendations⁷⁶.

It would be beneficial to have a databank and registry of women at AMA and VAMA, and also a long-term morbidity and mortality data registry.

Perinatal morbidity and mortality

There is a higher miscarriage and congenital malformations rate at AMA⁷⁷. However, for the children who are born at term, the perinatal outcome is fair. There is an increased risk of stillbirths (OR 1.75, 95% CI 1.62-1.89) with a population attributable risk of 4.7 per cent⁶⁸. There was also an increased risk of small for gestational age and neonatal intensive care admissions. This risk was unrelated to the use of ART or ovum donation and was higher in women above 45 yr. Age-related vascular changes in the uterus could be plausible explanation for suboptimal intrauterine environment⁶⁸. Perinatal outcome was observed to be poor even in spontaneously conceived women perhaps related to oocyte ageing. All these complications were much higher in multiple gestations^{71,77}. It is advisable to do long-term follow ups of these children to assess the impact on long-term survival and quality of life.

Welfare of the offspring

Not only the immediate pregnancy outcome is important, but also the impact of parental ageing which may affect long-term health of babies. Biological ageing of both male and female gametes may predispose these children to increased risks. There is evidence that spontaneously conceived children born to parents of advanced age have higher risk of low birth weight and preterm delivery⁷⁸.

The use of donor gametes and cryopreserved self-gametes has resulted in extension of fertile lifespan. The social impact of capabilities of child-

rearing and parental morbidity is profound. There is a 15 per cent risk of losing parents before the age of 15 yr for children born to women above 45 yr⁷⁹. Moreover, there is higher probability of losing both parents before they turn 35 yr⁷⁹. In addition to parental death, these children may have to play the role of caregivers for their sick parents. They may also suffer from loss of social and financial support and education. There is evidence that risk of bereavement of child of one or both parents in real^{40,41,79}. Decreasing financial resources at older age is also a concern. There is a possibility of legal conflicts related to inheritance issues.

Use of experimental and costly treatments

Third-party reproduction is an unpleasant and unacceptable option for most women. It is difficult to accept that there is no option left which can give them a child of their own genetic origin⁸⁰. Extensive research is on going to be able to generate a pregnancy out of every last oocyte⁸¹. PGT is a well-established reliable and safe procedure in developed countries. PGT-A screening for aneuploid embryos is one such development which promises to give these women an improved chance of pregnancy per transfer and a reduced risk of miscarriage⁸².

Data to support a final improved LB rate when intention-to-treat patients are analyzed do not support PGT-A for a routine use in AMA⁸³. The higher cancellation rate because of non-development of blastocysts or no euploid embryo available is one of the reasons⁸⁴. However, the scenario is now changing. Higher LB rate, low miscarriage rate and higher singleton term pregnancy have been reported when tested blastocysts are transferred as compared to transfer of two untested blastocysts^{85,86}.

The addition of significant cost of the procedure needs to be justified. In addition to the cost, the quality control and accreditation of IVF and genetic laboratories undertaking PGT need to be done. There is a need to emphasize that this is one technology which has a potential for sex determination of embryos. Preventive steps therefore, need to be taken.

There are other techniques which are still experimental but hold promise for the future.

- (i) *Ovarian tissue cryopreservation and reimplantation*: Instead of oocyte preservation, ovarian tissue can also be preserved and reimplanted. Natural as well as ART pregnancies have been reported through these reimplanted ovarian tissues^{52,53}.

- (ii) *Ovarian rejuvenation with stem cells taken from autologous ovarian cortex*: Ovarian tissue taken from ovarian cortex and reimplanted in ovary can provide the required niche to the stem cell which may start producing oocytes again^{79,87,88}.
- (iii) *Oocyte augments procedure*: Germinal vesicle taken from ovarian stem cells and transferred to the ooplasm of oocyte can augment the mitochondria and re-energize the oocyte^{89,90}.
- (iv) *Mitochondrial transfer*: Mitochondria from healthy donor oocytes can also be used to improve oocyte quality. The technique has ethical issues as there is a potential of mix up of DNA from three parents^{89,90}.
- (v) Regeneration of endometrium with the help of bone marrow stem cells or platelet-rich plasma⁹¹.
- (vi) Uterine transplant is a successful procedure now. However, there is high risk of graft rejection and risk of immune suppression to both mother and child.

It is to be noted that all these procedures are costly and still in experimental stage having high failure rate and side effects. There is a need to regulate these procedures. At the same time, stringent regulations or licensing can gag new research in these areas.

Fertility issues of the ageing male

Increasing trend of pregnancies at AMA is understandably associated with advanced paternal age (APA). The occurrence of higher risk of adverse pregnancy outcome is attributed only to female partner because of ageing oocytes. Extensive research has gone into studying the impact of AMA on pregnancy outcome. There is very scant literature on the subject of impact of male age on reproduction although there is some evidence that the influence is much less than female partner⁹¹.

There is no further mitosis in women after formation of mature oocytes. The spermatogonial germ cells undergo almost unlimited mitotic divisions until there is differentiation towards maturity. This repeated DNA replication predisposes to increased risk of genetically transmitted mutations, *de novo* mutations, epigenetic changes and DNA methylation. There is a selective spermatogonial selection in favour of mutated sperms giving rise to a higher incidence of fertilization with abnormal mutated spermatozoa⁹².

There is some evidence that men at age 35 yr take almost double the time for conception as compared to men aged 25 yr⁹³. There is a steady decline with age in serum testosterone and serum hormone-binding globulin⁹⁴. Semen parameters fall with age with a marked increase in DNA fragmentation⁹⁵⁻⁹⁷. There is limited evidence that APA may contribute to adverse pregnancy outcomes such as miscarriage and pre-term delivery⁹⁸.

APA is associated with increased common comorbid conditions, *e.g.* diabetes, hypertension and obesity⁷⁹. There is likely a reduction in physical capacity to work, look after children especially if associated with medical conditions. The long-term impact of impaired parenting due to physical disability associated with APA needs to be studied. Risk of parental death is most commonly feared by children of older parents⁹⁹.

Legal age limit for fertility services

Should there be an upper age limit of women to avail ART services?¹⁰⁰ Fixing up an upper limit for age of women raises the issues of personal reproductive autonomy against the welfare of women and the children born at AMA. The points in favour and against for fixing an upper legally defined age limit are listed in Table IV.

The following recommendations for limiting age of female partner can be suggested on the basis of available data: (i) No age-restriction below female

aged 45 yr; (ii) between 45 and 50 yr, pregnancy after appropriate risk assessment; (iii) no ART after 50 yr; pregnancy may be allowed after prior permission from an appropriate authority after examination by a medical board; (iv) the age limits can be revised from time to time and linked to life expectancy; (v) appropriate assessment of home situation of the concerned couple should be done by an authorized psychologist; and (vi) legal undertaking by a responsible family member for financial and social legal guardianship and protection to the children born through ART to mothers of AMA. This undertaking should be legally binding in case of bereavement.

Should there be any punishment for breaking the law or should it only be a guideline for ART specialists? This is another important question which needs to be answered.

Conclusion

The Indian Council of Medical Research (ICMR) has taken a lead in designing guidelines on assisted reproduction technology and accreditation of centres¹⁰¹. A separate statutory body can be constituted to serve as the overseeing authority of ART in India. The body should also accredit the centres as well as monitor the data. A pattern similar to SART can be followed. The role can be widened ranging from education, support groups, research, counselling guidelines and updating from time to time.

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Table IV. Upper legal age limit for availing infertility services

Points in favour of upper age limit	Points against upper age limit
Potential increased risk of maternal morbidity and mortality	Potential for natural pregnancy to the average age of menopause, <i>i.e.</i> , 47 in India. And increased overall life expectancy
Risk of bereavement of children born at advanced age	Increased in life expectancy of mothers giving birth at advanced age
Risk of psychological, social and financial burden on children	Family support
Pre-existing comorbid medical conditions which are likely to reduce life expectancy independent of pregnancy	Improving life expectancy with treatment in all medical conditions
Emotional and not well thought of decisions	Reproductive autonomy and carrier concerns
Unborn baby has no choice or rights	Same with natural pregnancy
Social pressure to bear a child at any age against women's wishes	Social pressure of abandonment and remarriage of husband
Underestimating the parenting needs at advanced age	Family support
Unscrupulous canters providing services in the absence of any law at any age	Demand and supply
State cost burden to look after these mothers and children even if self-financed	Self-financing
Guidelines for insurance companies	Countries with negative populations encouraging the trend
	At present, self-financed

Conflicts of Interest: None.

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