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As President of the Indian Society for Assisted Reproduction (ISAR) one of my agenda for the year 2017-2018 has been to prepare the Ethics Committee Guidelines. ISAR is in the process of developing the Guidelines on issues related to "Assisted Reproduction". An Ethics Committee was developed to help develop these Guidelines for ISAR. We invited an international Ethics expert Prof. Joanna Cains an oncologist from Mass General Hospital, Massachusetts, USA, with whom I have worked for 6 years on the FIGO Ethics Committee. Prof. Cains has great expertise on the preparation of such documents and accepted our invitation to be in Mumbai on the 7th and 8th of April 2018 to assist us in formulating the guidelines.

We developed an Ethics Committee based on requirements to develop it eg. a few IVF experts, Legal experts, Scientists & Researchers, Reproductive Social Activist. We worked on 4 Guidelines and finalized the Draft based on the ASRM Ethics Guidelines and ICMR guidance. A them and enclosed is the Draft Guidelines of the first four Guidelines which have utilized the ASRM Ethics Guidelines and ICMR guidance.

Prior to that we had worked online for 8 weeks following the discussion we prepared the Draft on 7th and 8th April 2018. Once the Draft is approved, the Guidelines will be circulated to all and will appear on the ISAR Website and In the ISAR Journal.

We have made a beginning and hope to continue making more. We do hope that these guidelines help all of us to make the right and ethical decisions in the interest of the women we treat.

Duru Shah
President, ISAR
Maximum Number of embryos to be transferred in any ART cycle

April 8, 2018 Mumbai

Overview:
There are significant harms from multifetal pregnancy for mother and fetus. This guideline balances the need to minimize the occurrence of multifetal gestation, particularly high-order multiples (HOM), with maintaining an acceptable overall pregnancy and live birth rates following In-vitro fertilization with embryo transfer (IVF-ET).

In India, elective placement of multiple embryos is influenced by several factors including the absence of insurance and associated rules for ART practice, absence of legal guidance for the practice, financial conflicts of interest for practitioners and patients to have a pregnancy success, and societal norms. Moreover, no factors have yet been identified which reliably predict occurrence of single or multiple pregnancy after single or multiple embryo transfer.

The impact of the number of embryos transferred on optimizing healthy live births from in-vitro fertilization (IVF) requires evaluation of the clinical pregnancy rate (CPR), multiple pregnancy rate (MPR), and live birth rate (LBR) correlated to the stage and number of embryos transferred. When multiple pregnancy is created, assisted reproductive technologies (ART) changes from the benefit of pregnancy success to maternal harm and neonatal complications. This makes prevention of multiple pregnancies of key importance. Even twin gestations, while attractive to parents and health professionals wanting a successful pregnancy, have significant additional morbidity compared to a singleton pregnancy.

There is an increased incidence of maternal complications with multiple pregnancy including but not limited to: pre-eclampsia, HELLP syndrome, acute fatty liver, thromboembolism, postpartum haemorrhage, and increased mortality rates. Multiple pregnancies are also associated with increased incidence of lower live birth rates, severe prematurity and its complications, small for gestational age babies, cerebral palsy and infant mortality. These complications in the babies
increase neonatal intensive care unit (NICU) admission by almost fifteen times. Although multifetal pregnancy reduction can be performed, the procedure may result in unintentional loss of additional or all foetuses.

Strict limitations on the number of embryos transferred, as required by law in some countries, do not permit individualization to each patient depending on the age, aetiology of infertility, oocyte and embryo quality, previous failures, variation in cleavage stage or blastocyst transfer, efficiency of cryopreservation program and data analysis of each clinic.

According to the ASRM guidelines, the US National data from 2013 demonstrate that clinics that perform higher rates of elective single-embryo transfer (eSET) in women aged <38 years have decreased rates of multiple gestation, with no significant impact on cumulative live-birth rates. There is no robust data presently from India on the number of embryos transferred and the occurrence of successful singleton or multiple pregnancies.

There can be conflicts of interest that need to be transparent in decision making for both health professional and patients and require careful counselling and consideration when deciding on the number of embryos to transfer. If only pregnancy rate is reported to patients, the health professional has a conflict because multiple transfers may result in a higher pregnancy rate although a lower or no different live birth rate. Patients have conflicts and vulnerability because their desire for a pregnancy often "at any cost" makes it harder for them to balance the benefits and complications of multiple pregnancy. The ethical requirement for careful truthful education and informed consent with counselling before transfer is critical for these procedures.

**Recommendations**

1. Careful education and informed consent is required in the counselling process regarding options for transfer for all patients. Transparency regarding costs including costs of care for premature babies and potential complications of twin and higher order pregnancies needs to be part of the discussion.

2. Given the potential for harm (non maleficence) for mother and fetus of multiple transfers and multifetal pregnancy, patients with a favourable prognosis should be encouraged to receive a single embryo transfer. Favourable prognosis includes factors such as:
1. young age (generally less than or equal to 35)
2. good ovarian reserve
3. presence of one or more high-quality embryos available for transfer and cryopreservation
4. previous live birth after an IVF cycle

Encouragement to receive a single embryo transfer should be offered to women with pre-existing medical conditions as multiple pregnancies would increase the morbidity and mortality.

The strategy for number of embryos transferred may vary according to age. Patients who do not meet criteria in recommendations 2 and 3 may have additional embryos transferred but not more than 3 embryos. ASRM guidelines in 2017 have recommended that the patients must be counselled regarding the additional maternal and fetal risks of twin or higher order multiple pregnancy.

In donor-oocyte cycles, the age of the donor and age and health of the recipient should be used to determine the appropriate number of embryos to transfer.

Ongoing rigorous research and cumulative and transparent reporting of all outcome data is required in the India context for this area to further define the best clinical options balancing benefit and harm for mother and neonate.

Conclusion
Each ART clinic should evaluate and report patient-specific, embryo-specific, and cycle-specific determinants to choose the number of embryos transferred to maintain acceptable pregnancy and live birth rate and also minimize occurrence of multiple pregnancies. The preferred maximum is 3 embryos. Moreover adequate and proper counselling of the couple regarding the pros and cons of transferring multiple embryos allows them to make an informed choice on the number of embryos to be transferred.
References


7. Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology; Guidance on the limits to the number of embryos to transfer: a committee opinion; Fertility and Sterility Vol. 107, No. 4, April 2017.
Provision of fertility services for women at increased risk of complications during fertility treatment

April 8, 2018: Mumbai

Overview
The introduction of ART has not only helped many young and healthy infertile couples to achieve parenthood but it has also ignited the desire of women at an advanced age and those with significant medical conditions to attempt conception. Advanced maternal age and pre-existing medical conditions like hypertension, diabetes, deep vein thrombosis (DVT), heart disease, renal dysfunction increase the risk of maternal and fetal morbidity and mortality. Cancer survivors seeking pregnancy with cryopreserved gametes with medical complications from their treatment also may have increased risks. Fetal growth restriction (FGR), small for date (SFD) babies, premature and extreme premature births contribute to increased NICU admissions and an increased neonatal mortality. The associated financial, emotional and physical burden can be devastating for the couple.

In India, societal pressures and the status of women increase the desire to have a child at any risk or cost. A childless woman is often ostracized, faces abandonment and the possibility of losing an inheritance. Women may seek to address this with ART but with significant risks. There have been many publicised cases in India of women in their 60’s and 70’s going through ART to produce an heir. It is notable that it the child who may pay a lifelong price because of the parental advanced age. Loss of a mother who does not live through their childhood to parent them or suffer the consequences of prematurity and other complications of birth will affect the child lifelong.

As per the Sample Registration System (SRS), Registrar General of India (RGI-SRS), Maternal Mortality Ratio (MMR) is 167 per 100,000 live births in the period 2011-2013\(^1\) and Infant Mortality Rate (IMR) is 34 per 1000 live births in 2016\(^2\), which is much higher than many developed nations. A maternal mortality survey conducted by FOGSI\(^3\) revealed that the leading causes of deaths were hypertension (29.4 %), haemorrhage (21.56 %), sepsis (15.05 %), and medical disorders (12 %). Though
we do not have data on the exact contribution of ART to these figures, it is likely it will increase as more high risk women seek and are offered ART services. Guidelines for offering ART to women who are at an increased risk of pregnancy complications should be based on the ethical principles of beneficence and nonmaleficence. Both the maternal and fetal consequences should be considered and bearing in mind that the goal of ART is a ‘healthy baby born to a healthy mother’4. Counselling for complications should be an integral part of ART.

**Risk assessment is critical in considering these requests including:**

1. 'High risk' women: Advanced maternal age and pre-existing medical conditions (Examples: Hypertension, Diabetes Mellitus, Heart Disease, Immunological disorders, Active treatment for cancers, Thrombophilia's, Deep venous thrombosis, Obesity, Congenital anomalies of uterus, PCOS with metabolic syndrome, Psychiatric disorders) should be evaluated to assess the risks in pregnancy4.

2. Inherent risks in ART: ART has its own risks which add to those of medical risks. These include threatened abortion, placenta Previa, placenta accrete/ percreta, premature rupture of membranes, ectopic pregnancy, pregnancy induced hypertension, gestational diabetes mellitus, operative delivery, fetal and neonatal risks4.

**Recommendations:**

1. Assessment of treatment risk before, during and throughout pregnancy, including risk to neonate must be carried out for all patients seeking ART to balance the benefits and harms.

2. A multi-disciplinary approach is essential. Patients with medical problems should be evaluated by the respective specialists. Medical clearance for ART must be obtained from them before starting treatment.

3. The patient can only make an informed choice when she understands the risks as well as the potential benefit, including the long-term risks to the child as well as herself. Because of the intense desire for pregnancy and potential coercion from family or partner, diligent counselling of the woman is critical to assure understanding.

4. Partner and family counselling to understand the risks of undertaking these procedures needs to be promoted.
5 Informed consent and counselling must always be based on the best information and clinical judgement without succumbing to personal or social bias regarding age.

6 There is no obligation for health professionals to offer treatment that is of no benefit, or likely to cause harm without substantial benefit.

7 Clinicians should counsel against or even decline ART if the risk of morbidity or mortality is high. Patient should be encouraged to seek a second opinion as desired.

8 Alternative options should be discussed, such as third party reproduction or adoption.

9 If a decision for ART is made, any modifiable risks should be corrected before starting treatment.

10 The number of embryos transferred is recommended to be limited to one given the significant risks of multiple pregnancy worsening the underlying medical conditions.

11 Pregnant patients should be managed in a tertiary centre with experience in high risk maternal and neonatal care.

12 The stigmatization of infertility causes suffering for couples and can create inappropriate pressure to reproduce even when medically inadvisable. Advocacy and education to reduce the social stigma of infertility is an important responsibility of knowledgeable health professionals.

References
2 https://community.data.gov.in/State/UT-wise Infant Mortality Rate during 2015-16
5 The Assisted Reproductive Technologies (regulation) rules - 2005, 2010; Indian Council of Medical Research New Delhi; Ministry of Health & Family Welfare Govt. Of India, New Delhi
Overview:
Effective use of Highly Active Antiretroviral Therapy (HAART) for the treatment of human immunodeficiency virus (HIV) has resulted in prolonged life expectancy (over 40 years from diagnosis) and an improved quality of life for people living with HIV. The risk of vertical HIV transmission during pregnancy has been reduced to less than 1%. As a result of these breakthroughs fertility issues for those of reproductive age are becoming increasingly important. This includes discordant HIV couples with female positive/ male negative; male positive/ female negative; as well as both positive. It is assumed for this document that all positive couples are receiving the maximal and effective treatment for HIV.

As the success of antiretroviral therapy has increased, the guidelines for treatment of HIV seropositive couples has changed:

- 1990 CDC: initially recommended against reproductive assistance HIV serodiscordant couples
- 2002 ASRM revised guidelines: HIV serodiscordant couples may seek Rx
- 2004 ESHRE ethics task force: ethically acceptable to offer sperm washing & assisted reproduction to HIV serodiscordant couples with adequate precautions
- 2009 World Health Organization (WHO) stated: All couples and individuals have the right to decide freely & responsibly the number & spacing of their children & to have access to the information, education & means to do so which includes HIV infected couples. Need to integrate guiding principles into all aspects of HIV treatment and care
- 2010 ASRM Ethics Committee guidelines: Fertility clinics should offer services to HIV couples willing for treatment and should use risk reduction therapies
- 2013 ASRM guidelines: published to reduce risk of viral transmission, basic principles include reduction of viral load in infected partner,
- decrease non-infected partner’s exposure & infection risk, discussion of risk reduction strategies with couple and obtaining informed consent before any procedure

- 2015 ASRM Ethics Committee guidelines: Current treatments for HIV can limit the risk of viral transmission to partner and offspring. Recent studies show that in HIV-infected women, the use of antiretroviral therapy, and avoidance of breastfeeding reduce the chance of new born infection to approximately 2%. In couples in which the man is infected with HIV, the use of sperm preparation techniques coupled with either inseminations or in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) has proven to be highly effective in avoiding seroconversion of uninfected women and offspring.

**HIV and Infertility:** There are clinical issues associated with HIV and its antiretroviral treatment that are relevant to infertility treatments such as menstrual irregularities, tubal factors, reduced ovarian reserve, and reduced sperm parameters. Prevention of infection: There is evidence that the risks of infection for a discordant partner can be significantly reduced. Evidence suggests that HIV does not attach or infect sperm so sperm washing can reduce risk of transmission by eliminating round cells and seminal plasma. The most rigorous and effective methods should be used for sperm washing. In a systematic review safety has been examined in both IUI and ART cycles with no seroconversion of the female partner and no neonatal transmission when the male partner is positive.

**Ethical concerns**

1. There are multiple issues of provision of just access and support in healthcare regarding HIV positive individuals seeking fertility care. HIV couples are denied treatment in various ART centers due to the potential risk of HIV transmission to the other couples undergoing treatment at the center or to the staff. Couples have been denied treatment based on a belief that transmission cannot be prevented to the newborn or uninfected partner. Concerns about the longevity of seropositive HIV patientshas also led to denial of treatment.

2. The desire to reproduce, in the HIV context, has limits (doing no harm) to what options can be offered based on the potential for risk to the uninfected partner or by vertical transmission to the fetus.
3 Harm to the potential neonate is an important ethical factor in consideration of treatment for the parents. This includes the long-term parental prognosis which impacts the well being (health, success and survival) of children. ESHRE2 and other ethics bodies have expressed concerns about the use of ART in couples with both parents HIV positive as the potential for parental loss is higher, placing the child's security and wellbeing at risk.

4 The overall benefit of the procedure chosen needs evaluation for each circumstance. Choosing the most effective option can reduce the number of cycles and exposures and reduce risks to the patient and their partner.

Recommendations HIV positive partners:

1 HIV positive couples should not be denied access to ART based on HIV seropositivity as long as quality standards to prevent transmission are met.

2 If serodiscordance or HIV positivity is discovered in the course of evaluation for fertility treatment, the provider has a responsibility to counsel the couples regarding this finding.

3 When HIV positive individuals seeking ART treatment are not maximally treated, the health professional does not have an obligation to offer ART as it risks the safety of others (patient, partner and potential offspring)

4 Maximal effort and counseling to prevent transmission to the fetus and neonate is required.

5 A multi-disciplinary team approach is essential for counseling and effective treatment.

6 ART should be carried out only in those institutions, which are able to adhere to strict quality standards such as universal precautions for infection controlwith maternal-fetal medicine specialist, HIV/AIDS specialist, fertility specialist, neonatologist / pediatrician and psychiatrist / social worker / psychologist, have appropriate laboratory facilities and separate freezing facilities for gametes and embryos.

7 Clinical evaluation of the couple is important to assess the feasibility of ART treatment in light of status of HIV treatment and coexisting disease. Optimum medical status of HIV suppression should be required before treatment to maximally reduce risks.
8 Pre-conceptual counseling and informed consent must be carefully reviewed with the partners including reproductive options available and potential treatment failure, effect of HAART on reproductive function, risk of vertical transmission, factors affecting HIV transmission and long term health outcome and support networks.

9 It is important to emphasize that no treatment option is 100% risk free. Alternate options must also be offered which include use of donor sperm in HIV positive men and surrogacy in HIV positive women.

10 Informed consent based on all the above elements is mandatory.

11 Only those couples who have high motivation for childbearing that includes strict adherence to their antiretroviral therapy resulting in well-controlled HIV, stable CD4 count, and undetectable viral load (serum and semen) should be selected for treatment.

12 Couples should be offered the most effective ART treatment with the least risk of transmission of HIV. The goal must be to prevent transmission to partner and fetus (nonmalificence).

13 When both partners are positive, counseling regarding the impact of potential parental loss for the child, should be reviewed prior to partners choosing ART.

14 Expansion of access to ART for HIV positive couples should be done. This requires advocacy for additional research and effort to provide more options for safe laboratory procedures that reduce infectious risk and expand access.

**Conclusion**

ART is safe and effective for significantly reducing horizontal and vertical transmission in HIV serodiscordant or positive couples. Good clinical status with undetectable viral load and high CD4 count is mandatory before consideration for treatment for fertility. Additionally, the risks to each partner, and the offspring needs careful exploration during informed consent and care should only be given in centers that are able to provide the level of services needed for ART management.
References


2. Taskforce 8: Ethics of medically assisted fertility treatment for HIV positive men and women, Human Reproduction, Volume 19, Issue 11, 1 November 2004, Pages 2454-2456


5. Ethics Committee of the American Society for Reproductive Medicine: Human immunodeficiency virus (HIV) and infertility treatment: a committee opinion; Fertility and Sterility, 2015; Volume 104, Issue 1, e1 - e8


Upper Age Limits for Assisted Reproductive Technologies

April 8, 2018 Mumbai

Overview:
The natural limits to reproduction for women have been extended by available reproductive technologies. With oocyte and embryo donation women well beyond menopausal age can aspire to give birth. Donation and hormonal treatments can medically overcome age related decline in egg and embryo quality. However, significant dangers from age related diseases remain which can complicate pregnancy.

Maternal and neonatal morbidity and mortality are significantly increased at advanced maternal ages. To avoid harm, fully informing women of the significant health risks and fetal risks, as part of counseling is critical for informed consent.

In India, unregulated treatment has led to many "grandmother" mothers, with a very high morbidity for the woman and the neonates as well1,2. Indian council of Medical research (ICMR) draft guidelines of 2005, state that the recipient "should be a healthy woman (determined by medical and psychological examination) having normal genitalia (as determined by physical examination) and uterine cavity (as determined by hysterosalpingography)".

The Ministry of Health, Government of India, guidelines of 20053 has no recommendation on the upper age limit for recipients of donated oocytes or embryos. However, the 2017 ICMR draft bill for ART suggest an upper age limit of 45 for women and 50 for men.

There is a need to determine when ART can be safely offered to women of advanced age and when it should be denied.

There are a number of considerations supporting childbearing for couples of advanced age:

1. Average life expectancy in India has increased significantly from 58.3 in 1990 to 70 in 20154. Women are living well beyond menopause which is 47.5 (2008)
in India. Rising life expectancy encourages women to become mothers at a later age.

2 Women may delay child bearing beyond their 40s for financial, career, and personal reasons.

3 There is no cutoff to define advanced age, but for women it may be considered as age of natural menopause.

There are also considerations against CHILDBEARING IN COUPLES OF ADVANCED AGE:

1 As age advances there are higher chances of pregnancy related complications which may become life threatening, especially after the age of 55.

2 Preterm birth, low birth weight, genetic abnormalities and higher fetal mortality increase with maternal age. Higher rates of genetic abnormalities also can be related to advanced paternal age. "Advanced paternal age" has not been defined though evidence exists of increased risks of disabilities and disorders resulting from single-gene mutations and chromosomal abnormalities in offspring of men of advancing age.

3 Social, economic, and medical fitness of the couple to raise a child to adulthood, at an advanced age may be compromised.

4 Family support may diminish with advancing age. Younger family members may have their own children to focus on and may not have the capacity to provide additional support to elderly family members who are new parents or to the children born to them.

5 Compromised medical fitness in either partner leads to a higher risk of mortality and morbidity which may ultimately affect the wellbeing of the child. Loss of a parent is the worst kind of stress for any child, and an acknowledged factor in diminishing their success in life.

The major ethical issues include whether the best medical interests (beneficence) and avoidance of harm in medical care (nonmaleficence) of the couple and the child thus born are served by pregnancy at advanced parental age. The ethical responsibility to assure careful medical evaluation with full counseling and informed consent is heightened especially when there are increased risks for short and long term harm to patients and their offspring.
Recommendations:

1. A health professional may ethically decline treatment to women of advanced maternal age based on their health status and the risk of potential harm to them or their offspring.

2. Couples of advanced age considering ART should be counseled about adoption as an additional option for child raising.

3. For women up to 45, ART could be offered after routine evaluation reveals that there are no underlying medical conditions that would significantly increase the obstetrical and neonatal risks. Expert opinion suggests that women up to 50 could potentially be medically considered with the same criteria for risk assessment based on the age of menopause and life expectancy. Additional counseling regarding the increased risks added by age for maternal and fetal health must be given.

4. For men up to 50 ART may be offered after routine evaluation reveals satisfactory parameters for sperm. Counseling regarding potential for genetic and other abnormalities needs to be provided.

5. In all circumstances where oocyte or embryo donation is offered, a careful and truthful informed consent is necessary.

6. Given the high risk of pregnancy at advanced age, couples should be counseled about the need for access to high levels of maternal and neonatal care for the pregnancy.

References:

3. The Assisted Reproductive Technologies (regulation) rules - 2005, 2010; Indian Council of Medical Research New Delhi; Ministry of Health & Family Welfare Govt. Of India, New Delhi
5. www.indianmenopausesociety.org full 2008 Consensus Statement
6. Oocyte or embryo donation to women of advanced reproductive age: an ethics committee opinion. Fertility and Sterility® Vol. 106, No. 5, October 2016 0015-0282