Maximum Number of Embryos to be Transferred in Assisted Reproductive Technologies cycle: Ethics Opinion

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, with maintaining an acceptable overall pregnancy and live birth rates (LBRs) 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 the occurrence of single or multiple pregnancy after single or multiple ET.

The impact of the number of embryos transferred on optimizing healthy live births from IVF requires evaluation of the clinical pregnancy rate, multiple pregnancy rate, and 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.[1-3] 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: preeclampsia, HELLP syndrome, acute fatty liver, thromboembolism, postpartum hemorrhage, and increased mortality rates. Multiple pregnancies are also associated with increased incidence of lower LBRs, 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 admission by almost fifteen times.

Although multifetal pregnancy reduction can be performed, the procedure may result in unintentional loss of additional or all fetuses.[4]

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, etiology 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-ET in women aged <38 years have decreased rates of multiple gestation, with

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no significant impact on cumulative live-birth rates.\textsuperscript{[5,6]}
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 counseling 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 LBR. 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 before transfer is critical for these procedures.

**Recommendations**

1. Careful education and informed consent is required in the counseling 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 (nonmaleficiency) for mother and fetus of multiple transfers and multifetal pregnancy, patients with a favorable prognosis should be encouraged to receive a single ET. Favorable prognosis includes factors such as:
   - young age generally ≤35
   - good ovarian reserve
   - presence of one or more high-quality embryos available for transfer and cryopreservation
   - previous live birth after an IVF cycle.
3. Encouragement to receive a single ET should be offered to women with preexisting medical conditions as multiple pregnancies would increase the morbidity and mortality.
4. 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 three embryos.\textsuperscript{[6]} ASRM guidelines,\textsuperscript{[7]} in 2017, have recommended that the patients must be counseled regarding the additional maternal and fetal risks of twin or higher order multiple pregnancy.
5. 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.
6. 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 LBR and also minimize the occurrence of multiple pregnancies. The preferred maximum is three embryos. Moreover, adequate and proper counseling 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.

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**Conflicts of interest**

There are no conflicts of interest.

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