Changing concepts in IVF: Are we prepared?

Today assisted reproductive technology (ART) is an established treatment of infertility with continuously evolving newer strategies to simplify and improvise the treatment. Yet still today concerns persist among the ART clinicians as the pregnancy rates continue to be static and low over the last two decades despite the advances. Also, the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies continue to daunt the clinicians. So, what we are looking for in ART? Both, the clinicians and the patients want an improved pregnancy rate, lesser time to conception, and a single healthy baby at a lower cost and with simplified protocols with no risk of OHSS.

Literature review has shown that only 15% of the transferred embryos develop into a conceptus. Improving embryo quality by blastocyst transfer (day 5) attempts to identify the embryos that have a better implantation potential. Freeze all for all is an attempt to mitigate the detrimental effect of supra physiological steroid levels on the endometrium to increase the implantation rate and avoid OHSS, and elective single embryo transfer (eSET) came in vogue with better vitrification techniques and improvised culture media to deliver a single healthy baby to a healthy mother. But all these attempts to increase the pregnancy rates have their pros and cons for uniform application. A frequent question that plagues all is—Are all the changing concepts good and practicable? Though logical, all these measures have practical limitations and before implementing them in routine practice and recommending them as good practice guidelines, they need to be reviewed critically by RCT.

BLASTOCYST TRANSFER FOR ALL

Traditionally, ART clinicians are transferring two to three cleavage stage embryos on day 2/3 in the fresh cycle and this is still the prevalent practice in most of the clinics worldwide. It has been seen that there is a considerable attrition rate (30–40%) of the embryos when observed from day 3 to day 5. The process of harvesting the embryos in an extended culture by itself does not make an embryo better. So, are these nonsurviving embryos the ones that were never destined to implant? It is speculated that this method of embryo selection helps identify those embryos that have managed to activate their embryonic genome. If it is so, then day 5 transfer is a means to identify and select better embryos from a cohort. Also, there is an added advantage of achieving physiological synchronization of the endometrium and the embryo that mimics closely the sequence of events in natural conception by delaying the transfer of embryos. Consequentially, blastocyst for all appears a logical choice.

But, is it practical in routine practice for all cycles? Blastocyst transfer is not without limitations. Blastocyst transfer improves the odds of transferring a viable embryo, but it does not guarantee euploidy and an improved live birth rate.[1] The *in vitro* survival does not equate with *in vivo* survival, there is risk of losing some or all embryos leading to a higher transfer cancellation incidence. The stipulated reason is that morphological scoring, either at blastocyst or cleavage stage, is not an accurate way of identifying chromosomal abnormalities.[2] Besides, there is a decreased probability for vitrification with extended culture as embryos that do not reach blastocyst stage are discarded and not eligible for transfer, resulting in a decreased cumulative pregnancy rate.

Cochrane Systematic Review 2016 comprising 27 RCTs with 4061 women showed a low quality evidence favouring a higher live birth rate in the blastocyst group (odds ratio (OR) 1.48, 95% confidence interval (CI) 1.20 to 1.82); It was observed that the clinical pregnancy rate was also higher in the blastocyst transfer group, following fresh transfer (OR 1.30, 95% CI 1.14 to 1.47; 27 RCTs, 4031 women, I(2) = 56%, moderate quality evidence. No evidence of a difference was observed in between the two groups in rates per couple of cumulative pregnancy following fresh and frozen-thawed transfer after one oocyte retrieval (OR 0.89, 95% CI 0.64 to 1.22; 5 RCTs, 632 women, I(2) = 71%, very low quality evidence).[3] Also another clinical aspect of relevance is the obstetrics and perinatal outcome of ART pregnancies like preterm delivery, monozygotic twins, and large for gestational age (LGA) babies associated with blastocyst culture that needs review. A

higher relative risk (95% CI) of preterm (<37 weeks) (1.27 [1.22–1.31]) and very preterm (<32 weeks) delivery (1.22 [1.10–1.35]) is confirmed in meta-analysis comparing D5 ET with D3 ET.[4,5] A systematic review of blastocyst versus cleavage-stage embryo transfer (ET) consisting of 12 studies in which 1200 women had blastocyst transfer and 1218 women had cleavage-stage ET concluded that blastocyst had no superiority over cleavage-stage ET in clinical practice.[6] However, more RCTs are required to confirm these observations. Also, there is an increased risk of monozygous twins *with* blastocyst transfer due to alteration in the *zona pellucida* induced by the extended culture with a pooled odds ratio of 3.04 (95% CI 1.54–6.01).[7,8] The type of culture media used in extended culture seems to be responsible for LGA babies, as shown by Zhu *et al*.[9] However, same is not confirmed by other studies. One postulation is that this could be due to selection bias as this study included poor prognosis patients who are known to have poor perinatal outcome.[9] Another possible explanation for poor perinatal outcome may be genetic and *epigenetic* changes in trophodermal cells that can lead to abnormal *placentation* and *implantation*. Despite all these concerns, *blastocyst* stage seems to be the preferred strategy among ART clinicians and it is being offered more frequently as conception rates are better with blastocyst transfers when compared to cleavage stage. But it is to be remembered that the cancellation rates are also higher, especially when no good blastocysts are available for transfer.

So what should be our strategy: blastocyst for all or for select group only?

In light of conflicting analysis by various RCTs and as the quality of the evidence for the primary outcomes is low, additional well-designed RCTs are still needed before robust conclusions can be drawn. Till then most ART clinicians are following an individualized approach.

One of the suggested individualized approaches gives a fair practicability and feasibility without compromising the outcome:

Age <38 years
More than four good quality embryos—d5 ET
Less than or equal to four good quality embryos—d3 ET
More than eight good quality embryos—half frozen on d3 rest goes for d 5 ET
Age >38 years
More than six good quality embryos—d5 ET
Less than or equal to six good quality embryos—d3 ET rest freeze
More than 10 good quality embryos—half frozen and half for d5 ET
All d3 if previous cycle shows poor blastocyst conversion

It is reiterated that blastocyst culture requires a reliable culture system and proven vitrification program.

Extended culture in women with very few embryos incurs the risk of either having no embryos for transfer in a fresh cycle or vitrification for future use.

Hence, we do need to consider alternative strategies and individualize on the basis of the number of good quality embryos, number of cycles that are feasible (economic and financial constraints of the patient), and risk–benefit analysis. More RCT and long-term studies on perinatal outcome are required. Till then no to blastocyst for all.

Freeze all polic is another controversial and debated issue among ART consultants. The points in favor are advancement in cryobiology, vitrification, good survival rate, improved pregnancy rate, and a more physiological environment of an unstimulated cycle yielding better results. It also avoids OHSS, a very pertinent and adverse iatrogenic complication of stimulation.

It is an established fact that there are problems of superovulation like supra physiological E2 and premature advancement of endometrium resulting in poor endometrial receptivity. Higher progesterone on OPU day is detrimental as it is associated with poor implantation potential. There is a postulated increase in adverse perinatal outcome manifested as a higher incidence of low birth weight, preterm labor, small for gestational age, and higher risk of ectopic pregnancy.

Here, again there is a pertinent question that needs an answer. Is cryopreservation risk free? There is a risk of exposure of blastomeres of cryopreservatives and complete survival is not guaranteed by any ART laboratory. Also, the associated increased risk of congenital malformation and its statistical significance should be known. A speculated higher incidence of LGA, adverse cost–benefit analysis, and patient's inconvenience are not in favor of cryopreservation for all. The associated waiting period is tiresome and stressful and most patients prefer a shorter time for outcome. Another point against freeze all policy is that ET in fresh cycle involves fewer cycles of hormonal stimulation. Moreover, optimal endometrial preparation regime for FET is still evolving. Should freezing all embryos be the

dictum? In the era of personalized medicine, we should stop following a one size fits all approach. Hence, to conclude, it is clear that some subgroups of patients would greatly benefit from a freeze all approach and all should be encouraged to recommend it. But applying a blanket freeze all approach may be considered premature.[10] The number of oocytes and day 3 embryos should be considered when recommending frozen or fresh ET. One of the largest studies evaluating the freeze all strategy in ART inferred that freeze all policy may be related to better IVF outcomes in normal responders but patients with poorer ovarian response do not benefit.[11]

Based on the current evidence, it is reasonable to recommend a freeze all approach for patients at risk for developing OHSS, PGT for genetic testing, and those with premature elevation of serum progesterone. The speculated higher incidence of LGA babies needs further evaluation. It is too premature to adopt the policy as robust vitrification program is not available in all clinics. Also, the associated increased cost is prohibitive of the policy in Indian scenario and other countries where ART is not a program of public health scheme or covered by insurance and patient has to bear the cost. So, at present, individualized approach is needed that considers clinical parameters, embryology outcomes of that cycle, and patients' characteristics rather than a "freeze all" protocol.

SINGLE EMBRYO TRANSFER

Single embryo transfer (SET) has to address the following dilemmas of the clinician:

- Is it applicable to all cases?
- Whom to offer?
- Can it be practiced with d3 also?
- Is it cost-effective?

An outcome and feasibility survey of eSET policy for the first and second IVF/ICSI attempts concludes that in a selected population, an eSET strategy decreases the twin pregnancy rate without decreasing the delivery rate, with a better outcome for the infants than DET.[12] However, eSET is well accepted by patients only for the first attempt even though the pregnancy rate is not statistically different for the second. In an analysis of global variations in the uptake of SET, a comparison of the data from 31 countries revealed a gradual increase in SET rates over a 3-year period.[13] The SET rates are highest in Sweden (69.4%) but are as low as 2.8% in the United States. Access to public funding for ART, availability of good cryopreservation facilities, and legislation appear to be the most important reasons favoring the uptake of SET. Personal choice plays a significant role as many subfertile couples have a strong preference for twins. Awareness that double embryo transfer (DET) increases live birth per fresh treatment cycle, inability to accurately identify women at high risk for twins, and limitations of existing embryos selection criteria are barriers to a wider acceptance of SET.

The current variation in the uptake of elective SET is likely to persist until there are major changes in the way ART is viewed, funded, and legislated.

As per Practice Committee of American Society of Reproductive Medicine (ASRM) recommendations, eSET is most appropriate in good prognosis patients, <35 years, with more than one top quality embryo, a previous successful IVF pregnancy, or a recipient of donor egg.

Decision for eSET in cryopreserved embryo depends on good quality embryos and credibility of vitrification program. Challenges in SET exist such as provider and patient education, cost consideration, embryo selection, successful cryopreservation, and mandated insurance coverage for ART preimplantation genetic screening (PGS) in eSET.

Though the concepts are changing, transformation is not smooth. SET offers a theoretical advantage that may not be applicable to all patients. Considering the limitation and feasibility of eSET, an individualized approach after critical analysis is suggested.

To conclude, greater insights into embryo development will improvise and simplify ART. The current knowledge and research has various gray areas in reproductive biology. Continuing advancements and research will help us demystify the existing dilemmas of the treating ART clinicians.

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