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TOPIC OF DISCUSSION

"Freeze-All vs Fresh Embryo Transfers in IVF-ICSI cycles"

CHAT DISCUSSIONS COMPILED BY

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SUMMARY OF SURVEY RESULTS

Discussion on Freeze-All vs Fresh Embryo Transfers in IVF-ICSI cycles

Introduction:

Embryo transfer (ET) is the final and one of the most critical steps determining the success of Assisted Reproductive Technology (ART). It involves the precise and a traumatic placement of embryos using an ET catheter into the uterine cavity at the location with the highest implantation potential (1). Implantation is a key determinant of ART outcomes and depends on three primary factors: Embryo quality, Endometrial receptivity (ER), and the synchronized interaction between the embryo and the endometrium (3).

Overview of Transfer Strategies

Fresh embryo transfer refers to the process of transferring embryos during the same cycle in which the embryos are developed via IVF after the oocytes retrieved from the ovaries.

Advantages of Fresh Embryo Transfer:

- **Shorter process duration:** The interval between egg retrieval and embryo transfer is brief.
- **Potentially reduced cost:** This approach may eliminate the need for cryopreservation and associated storage fees.

Frozen embryo transfer (FET), by contrast, involves transferring embryos that have previously been cryopreserved and later thawed. This transfer is typically performed in a subsequent cycle, which may be either a natural cycle or one prepared with hormonal support.

Advantages of the Freeze-All Strategy:

- Reduced risk of ovarian hyper stimulation syndrome (OHSS).
- Enables pre implantation genetic testing and selection of euploid embryos.
- Allows for improved endometrial preparation, facilitating better synchrony between embryo development and endometrial receptivity.

With significant advancements in cryopreservation techniques, the survival and implantation potential of frozen-thawed embryos now closely match those of fresh embryos. The primary aim of Freeze all approach is to transfer embryos into a more physiologically conducive uterine environment, thereby avoiding the potentially detrimental impact of supra physiological hormone levels on endometrial receptivity (4).

The **"window of implantation"** denotes the limited period during which the endometrium is receptive to embryo implantation (3). Evidence indicates that elevated estradiol levels and premature progesterone rise during controlled ovarian stimulation (COS) may lead to structural and biochemical changes in the endometrium, adversely affecting its receptivity. This disruption may cause embryo-endometrial asynchrony, ultimately reducing implantation rates during IVF/ICSI cycles (4).

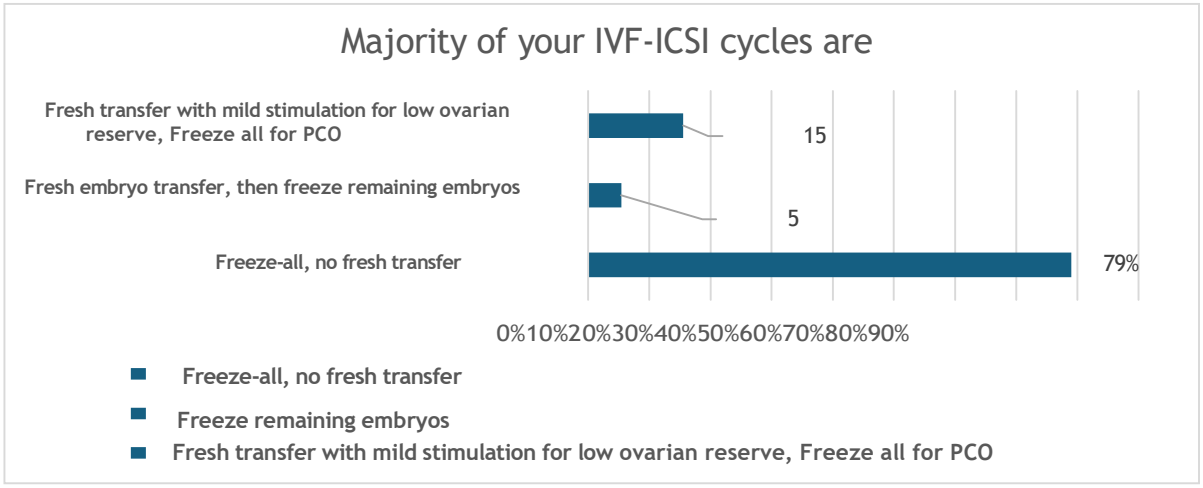
An increase in serum progesterone levels to approximately 1-2ng/mL is sufficient to induce secretory transformation in the endometrium and alter the timing of the implantation window.

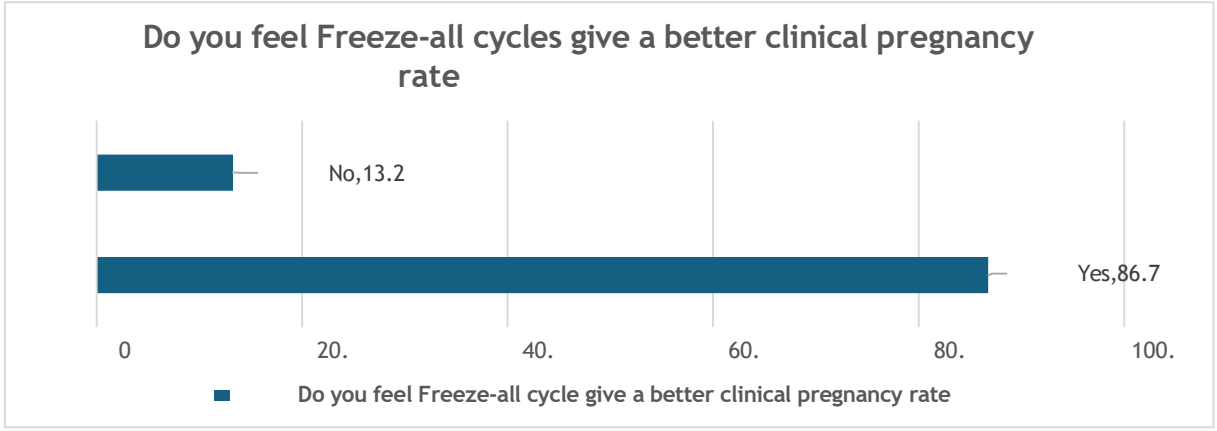
Microarray further show that premature progesterone elevation **(>1.5ng/mL)** in the late follicular phase may result in epigenetic modifications and altered gene expression in the endometrium (5).

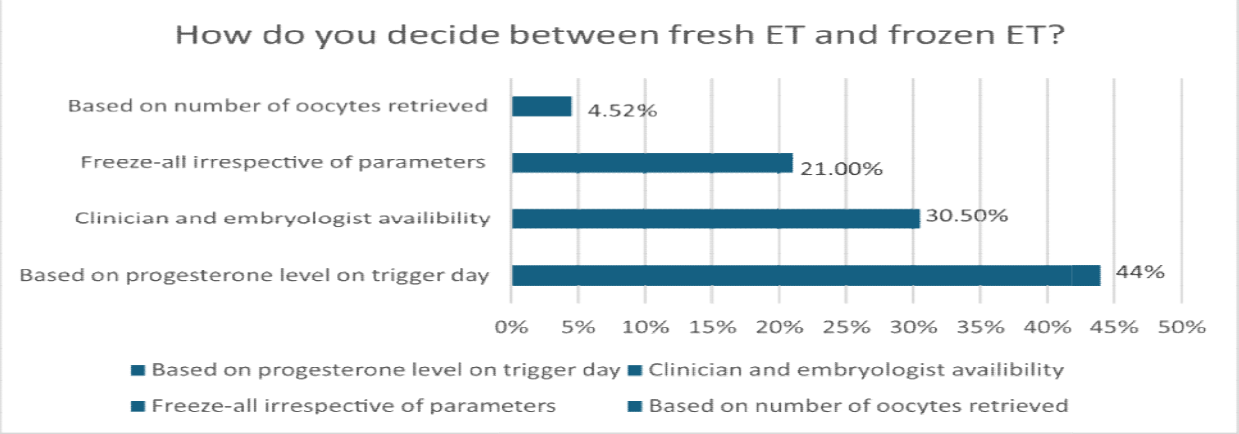
Although several strategies have been developed to prevent ovarian hyper stimulation syndrome (OHSS), the most effective approach remains the substitution of human chorionic gonadotropin (hCG)with a GnRH agonist (GnRHa) for final oocyte maturation, combined with a freeze-all strategy. hCG administration has been identified as the primary trigger for OHSS, as it stimulates a significant increase in VEGF expression, leading to heightened vascular permeability and fluid leakage into the abdominal cavity and third spaces—hallmarks of OHSS. The use of antagonist protocols with GnRHa triggers and subsequent elective cryopreservation of all embryos nearly eliminates the risk of OHSS (3).

Although the freeze-all approach is associated with improved implantation, clinical pregnancy rates (CPR), and ongoing pregnancy outcomes high responders (≥15 oocytes retrieved) ,in intermediate and low responders, FET has not shown a benefit and may even result in reduced CPR and live birth rates (2).

Poll Results:







Discussion summary on Freeze-All vs Fresh Embryo Transfers in IVF-ICSI cycles

The ongoing debate between fresh embryo transfer and the freeze-all strategy in IVF/ICSI cycles remains an area of active research and clinical interest. During a professional discussion in the **iHERA Embryo Chat group**, experienced embryologists engaged in a discussion regarding the clinical application of the freeze-all strategy. Originally employed for patients at high risk of OHSS, the freeze-all strategy has gained broader clinical applications. Many IVF centers now utilize freeze-all not just for safety but also to optimize implantation outcomes.

Benefits of Freeze-All approach:

According to poll results, most centers have adopted the freeze-all approach. In response to a question regarding its advantages, embryologists provided the following perspectives:

- Implantation success depends on precise synchrony between embryo and endometrium.
- Supra physiological levels of estradiol and early progesterone elevation during stimulation cycles may disrupt endometrial receptivity and lead to embryo-endometrial asynchrony, lowering implantation rates.
- Ovarian stimulation in fresh cycles focuses primarily on follicular growth, while endometrial preparation in frozen cycles can be better controlled and optimized, thereby improving implantation potential.
- The primary goal of IVF is not just achieving pregnancy but delivering a healthy baby. The freeze-all approach supports this goal by enabling PGT-A, which helps identify and transfer up load embryos with the highest potential for success.
- Many embryologists observed that performing ET in the same cycle as oocyte retrieval exposes patients to elevated hormone levels and psychological stress. Freezing embryos and delaying transfer allow physical and emotional recovery before proceeding with transfer.
- Freeze-all provides clinicians with better control over the timing of embryo transfer.
- Improved vitrification techniques have eliminated the negative effects of freezing, such as ice crystal formation, thus promoting the wide spread adoption of freeze-all strategies over traditional low freezing methods.

The Hormone-Driven Decision Behind ET Type

- One key reason for embryo-endometrium asynchrony is the supra physiological elevation of estrogen and pre mature progesterone rise (**>1.5ng/mL**) following trigger administration. Even minor increases in progesterone may shift the timing of the implantation window.
- It was noted that mild stimulation (lower gonadotropin doses) is associated with a lower risk of premature progesterone elevation. Several participants agreed that embryo transfer decisions should be individualized. If

- The Progestin-Primed Ovarian Stimulation (PPOS) protocol, which involves oral progestin administration to suppress premature LH surges, followed by embryo freezing and delayed FET. This approach avoids the adverse hormonal impact on endometrial receptivity and is ideal for cycles planned with freeze-all in mind.

ET Strategies for Low Responders and Poor Prognosis Patient:

A detailed discussion ensued regarding patients with low ovarian reserve. Various strategies were shared:

- Some embryologists preferred fresh ET in such cases, aligning with studies showing higher pregnancy rates with fresh transfers in low responders. These women often produce lower levels of endogenous steroids, resulting in a more physiological and receptive endometrium. Additionally, avoiding delays is critical due to the progressive nature of ovarian decline. Embryos of lower quality may be more vulnerable to freezing/thawing damage, indicating that freeze-all should not be applied in discriminately.
- Others advocated for embryo pooling, where oocytes are collected over multiple stimulation cycles to increase the total embryo yield. This approach, combined with PGT-A, can improve outcomes by identifying euploid embryos for transfer. As maternal age is the most significant factor influencing an euploidy, pooling allows for better embryo selection, flexible transfer timing, and improved pregnancy rates.

Fresh vs. Frozen in Donor Oocyte Cycles:

In donor oocyte cycles, synchronization of the recipient's endometrium with the donor's stimulation cycle is essential for performing a fresh embryo transfer. For donor oocyte recipients, fresh embryos are associated with better birth outcomes when compared with frozen embryos (10).
Some embryologists have observed high conception rates following fresh embryo transfer in donor recipients, especially when the timing between the donor's stimulation and the recipient's endometrial preparation is carefully coordinated.

Impact of Embryologist and Clinician Availability:

A question was raised about whether clinician and embryologist availability affect the choice of fresh versus frozen transfer. Freelancing embryologists may prefer fresh ET, while most clinicians base the decision on patient-specific parameters, also incorporating patient preferences and risk considerations.
Centres with skilled embryologists are more likely to offer frozen transfers due to the technical expertise required for vitrification and warming procedures.

Beyond Pregnancy: Weighing the Long-Term Outcomes of FET

FET is generally associated with lower risk of pre term delivery, low birth weight compared to fresh ET (9). However, wide spread implementation of the freeze-all policy without individualized assessment may lead to unintended consequences. Notably, a recent study reported a higher incidence of pediatric cancers in children born following FET compared to those born from fresh ET (7).

Although assisted hatching was not part of the original discussion topic, it emerged as a point of interest during the conversation. Some embryologists supported its use in specific scenarios, such as advanced maternal age, thick zona pellucida, or poor-quality embryos, citing improved clinical pregnancy and live birth rates. Others preferred waiting until natural hatching occurred on late Day 5 or early Day 6. The consensus was that AH should be considered based on embryo development

Conclusion:

The professional dialogue highlighted the increasing preference for the freeze-all strategy in modern IVF practice, driven by improved clinical outcomes and technological advancements. However, the group emphasized that freeze-all should not be universally applied. Instead, a tailored approach that considers individual patient profiles and clinical indications is essential for achieving optimal results.

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