FRESH VERSUS FROZEN EMBRYO TRANSFER OVERVIEW

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DISCLOSURES

Celmatix: sponsored research
Overview

• Definitions

• Fresh versus FET

• Fresh versus freeze-only transfer – example studies

• Cryopreservation in cancer patients
Definitions

• **Fresh transfer**: cycles where embryo(s) are transferred during the same cycle as ovarian stimulation is performed

• **Frozen embryo transfer (FET)**: cycles where embryo(s) are transferred in a subsequent natural or medicated cycle, after being frozen following an ovarian stimulation cycle
  – **Freeze-only transfer (subset of FET)**: cycles where all embryos are electively frozen and transferred in a later natural or medicated cycle (also used terms: elective FET, freeze-all)

*Note: FETs may include transfer of supernumerary embryos (after the best embryos from the cohort are already transferred in a prior fresh or FET cycle), which makes freeze-only transfers a stronger direct comparison with fresh transfer*
• Definitions

• Fresh versus frozen transfer

• Fresh versus freeze-only transfer – example studies

• Cryopreservation in cancer patients
Rate of FET increase in the United States

- **FET is on the rise**, increasing 82.5% from 2006-2012, compared to 3.1% for fresh cycles during this time\(^1\)

- Reasons for this FET increase include advances in vitrification, preimplantation genetic screening, and increased awareness of freeze-only protocols

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Fresh versus frozen transfer – maternal and fetal risks

- Frozen embryo transfer may be associated with better maternal and fetal outcomes in some parameters, including lower risk of preterm delivery, placental complications, and perinatal mortality\(^1\)\(^-\)\(^4\)

- However, some adverse outcomes may have increased likelihood with FET, including macrosomia and placenta accreta

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**Comparison of fresh transfer and FET with respect to maternal and fetal risks.**

- Reduced risks in FET:
  - OHSS
  - LBW (<2,500 g)
  - SGA
  - Preterm LBW
  - Preterm delivery (<37 wk)
  - Placenta previa
  - Placental abruption
  - Antepartum hemorrhage
  - Perinatal mortality

- Increased risk with FET:
  - Placenta accreta
  - Macrosomia (>4,500 g)
  - Large for gestational age
  - Cesarean section delivery

- Risks without a clear difference:
  - Implantation failure\(^a\)
  - Ectopic pregnancy\(^a\)
  - Pre-eclampsia
  - Very low birth weight (<1,500 g)
  - Very preterm delivery (<32 wk)
  - Neonatal intensive care unit admission
  - Congenital abnormalities

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\(^a\) May depend on the FET protocol, patient population, and cycle parameters.
Evidence also suggests that FETs may result in better transfer outcomes—1st meta-analysis

**Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis**

Meta-analysis of 3 studies (total 263 events) found that:

- FET resulted in a **statistically significant increase in the ongoing pregnancy rate** (RR 1.32, 95% CI 1.10–1.56) and **clinical pregnancy rate** (RR 1.31, 95% CI 1.10–1.56) compared to fresh transfer
- Fresh group showed a higher miscarriage rate compared with the FET group, but this difference did not reach statistical significance (33 events; RR 0.83, 95% CI 0.43–1.60)
Evidence that FETs may result in better transfer outcomes (continued)

• In conclusion, the meta-analysis suggests that there is evidence of moderate quality that the implantation, clinical, and ongoing pregnancy rates of ART cycles may be improved by performing FET compared with fresh embryo transfer.

• These results may be explained by improved embryo endometrium synchrony achieved with endometrium preparation cycles instead of controlled ovarian stimulation cycles.
• Definitions

• Fresh versus frozen transfer

• Fresh versus freeze-only transfer – example studies

• Cryopreservation in cancer patients
Freeze-only versus fresh transfer

- **Freeze-only literature more limited**: two randomized controlled trials (RCTs) until recently, several small trials, and retrospective matched cohort study all suggested improved pregnancy outcomes with freeze-only transfer\(^6\)\(^-\)\(^10\)

- RCT of 179 patients with fresh versus freeze-only transfer in euploid embryos found increased ongoing pregnancy and live birth rates in freeze-only, but no significant difference in implantation rates\(^11\)

\(^8\). NEJM 2016;375:523-33.
\(^9\). Fertility Sterility 2015;103:1190-3.
\(^10\). Reproductive Biomedicine Online 2014;29:286-90.
Freeze-only versus fresh transfer (continued)

• Few other studies have investigated frozen transfer of PGS-screened embryos but have not compared fresh vs frozen/freeze-only transfer directly\textsuperscript{12-13}

• Two large retrospective studies from Stanford and Celmatix have reported benefits of freeze-only transfer for both non-PGS and PGS embryos\textsuperscript{14-15}

\textsuperscript{13.} Human Reproduction 2011;26:1813-25.
\textsuperscript{15.} ASRM 2017
Freeze-only versus fresh transfer (continued)

- Previous studies have suggested that frozen transfer may be associated with better pregnancy outcomes due to supraphysiologic hormone levels in controlled ovarian stimulation affecting genes involved in implantation, placentation, endometrial angiogenesis, and endometrial maturation\textsuperscript{16-27}
Freeze-only versus fresh transfer RCT

Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen–thawed embryo transfer in normal responders

Bruce S. Shapiro, M.D., Ph.D., a,b Said T. Daneshmand, M.D., a,b Forest C. Garner, M.Sc., a,b Martha Aguirre, Ph.D., a Cynthia Hudson, M.S., a and Shyini Thomas, B.Sc. a

- **RCT of blastocyst transfer:** 53 fresh patients and 50 freeze-only
- All were first-time IVF patients aged <41 years, with cycle day 3 FSH <10 mIU/mL and 8-15 antral follicles.
- **Clinical pregnancy rate per transfer was 84.0% in the freeze-only (significantly greater than 54.7% in the fresh group)**
- Implantation rates were 70.8% and 38.9%, respectively, and ongoing pregnancy rates per transfer (at 10 weeks' gestation) were 78.0% and 50.9%, respectively
- Attributable risk percentage of implantation failure due to reduced endometrial receptivity in the fresh group was 64.7%.

• 1508 women with PCOS undergoing first IVF cycle randomized to either fresh or freeze-only transfer of day 3 embryos

• Freeze-only transfer resulted in a **higher frequency of live birth after the first transfer** than did **fresh-embryo transfer** (49.3% vs. 42.0%), RR 1.17 (95% CI 1.05 to 1.31; P=0.004)

• Freeze-only transfer also had a **lower frequency of pregnancy loss** (22.0% vs. 32.7%) RR 0.67 (95% CI, 0.54 to 0.83; P<0.001), and of the **ovarian hyperstimulation syndrome** (1.3% vs. 7.1%), RR 0.19 (95% CI, 0.10 to 0.37; P<0.001)

• However, FET was associated with **higher frequency of preeclampsia** (4.4% vs. 1.4%), RR 3.12 (95% CI, 1.26 to 7.73; P=0.009)

• No significant between-group differences in rates of other pregnancy and neonatal complications.
Freezing of all embryos in in vitro fertilization is beneficial in high responders, but not intermediate and low responders: an analysis of 82,935 cycles from the Society for Assisted Reproductive Technology registry

- Analysis of 82,935 SART cycles (69,102 patients had their first fresh transfer, and 13,833 had a first FET)²⁸
- High responders were found to have a higher CPR and LBR in the FET cycles compared with the fresh ET cycles (61.5% vs. 57.4%; 52.0% vs. 48.9%)
- In intermediate responders, both CPR and LBR were higher after fresh ET compared with FET (49.6% vs. 44.2%; 41.2 vs. 35.3%)
- Similarly, in low responders, CPR and LBR were higher after fresh compared with FET (33.2% vs. 15.9%; 25.9% vs. 11.5%).
- Conclusion: A freeze-all strategy is beneficial in high responders but not in intermediate or low responders, thus refuting the idea that freeze-all cycles are preferable for all patients.

• RCT of 179 patients randomized to freeze-only versus fresh transfer of euploid blastocysts

• Implantation rate per embryo transferred showed an improvement in the frozen group compared with the fresh group, but not significantly (75% vs. 67%).

• Ongoing pregnancy rates (80% vs. 61%) and live birth rates (77% vs. 59%) were significantly higher in the frozen group compared with the fresh group.

Fertility and Sterility 107.3 (2017): 723-730.
Freeze-only versus fresh embryo transfer in a multicenter matched cohort study: contribution of progesterone and maternal age to success rates

Ange Wang, M.D., Anthony Santistevan, M.S., Karen Hunter Cohn, Ph.D., Alan Copperman, M.D., John Nulsen, M.D., Brad T. Miller, M.D., Eric Widra, M.D., Lynn M. Westphal, M.D., and Piraye Yurttas Beim, Ph.D.

- Retrospective matched cohort study of 13 academic and private fertility centers in the United States
- Propensity score analysis identified 2,910 matched blastocyst transfer cycles (1,455 fresh, 1,455 freeze-only)
- For fresh cycles, luteal support was initiated after retrieval and embryos were transferred into the uterus at the blastocyst stage
- For freeze-only cycles, embryos were cryopreserved according to established practice protocols at each clinic
  - In a subsequent cycle, patients underwent blastocyst FET in either a natural or medicated cycle (using estrogen and progesterone supplementation)

METHODS

• Cohorts were matched on the following measures:
  – **Patient characteristics**: maternal age, clinic, gravidity, parity, diagnosis, body mass index
  – **Ovarian reserve**: antral follicle count, basal follicle stimulating hormone/luteinizing hormone/estradiol,
  – **Cycle characteristics**: progesterone (P) at trigger, eggs retrieved, embryo cohort size, and embryos transferred

• Generalized estimating equations modeling was used to compute the odds ratios (ORs) of ongoing pregnancy

• Receiver operating curve (ROC) analysis was used to determine cutoffs for maternal age and P at trigger
Baseline characteristics

- All characteristics were similar between the fresh and freeze-only groups after matching, as seen in Table 1
Pregnancy outcomes

- Freeze-only was only beneficial for $P > 1$ at trigger

Fertility Sterility 108, no. 2 (2017): 254-261
SENSITIVITY ANALYSIS BY MATERNAL AGE AND PROGESTERONE AT TRIGGER

- Sensitivity analysis of ongoing pregnancy shows that at higher P concentration, trend toward increasing benefit of freeze-only cycles with advancing age.
Largest study on freeze-only versus fresh transfer of euploid embryos (prelim data)

- Retrospective matched cohort study of 13 academic and private fertility centers in the United States

- Propensity score analysis identified 1,642 matched blastocyst transfer cycles (821 fresh, 821 freeze-only) that had undergone 24-chromosome PGS

- For fresh cycles, luteal support was initiated after retrieval and embryos were transferred into the uterus at the blastocyst stage

- For freeze-only cycles, embryos were cryopreserved according to established practice protocols at each clinic
  - In a subsequent cycle, patients underwent blastocyst FET in either a natural or medicated cycle (using estrogen and progesterone supplementation)

Oral presentation at ASRM 2017
## BASELINE CHARACTERISTICS

### Table 1. Baseline characteristics after propensity score matching [Mean (Stdev)]

<table>
<thead>
<tr>
<th>Metric</th>
<th>Fresh</th>
<th>Freeze-only</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>35.5 (4.3)</td>
<td>35.7 (4.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI</td>
<td>24.4 (4.8)</td>
<td>24.4 (4.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gravidity</td>
<td>0.9 (1.4)</td>
<td>0.9 (1.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Parity</td>
<td>0.2 (0.5)</td>
<td>0.2 (0.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Basal antral follicle count</td>
<td>15.7 (8.6)</td>
<td>15.5 (8.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>Day 3 LH</td>
<td>5 (3.2)</td>
<td>5.1 (3.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>Day 3 FSH</td>
<td>6.3 (2.7)</td>
<td>6.4 (2.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Day 3 E2</td>
<td>48.4 (23.8)</td>
<td>48.5 (22.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>17.6 (8.6)</td>
<td>17.1 (9.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Embryo cohort size</td>
<td>4.4 (3.2)</td>
<td>4.7 (3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>Progesterone at surge</td>
<td>1 (0.5)</td>
<td>1 (0.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>9.30%</td>
<td>10%</td>
<td>0.68</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>2.10%</td>
<td>1.30%</td>
<td>0.34</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>11.40%</td>
<td>12.50%</td>
<td>0.54</td>
</tr>
<tr>
<td>Male factor</td>
<td>13.80%</td>
<td>13.40%</td>
<td>0.89</td>
</tr>
<tr>
<td>None provided</td>
<td>6.20%</td>
<td>5.70%</td>
<td>0.75</td>
</tr>
<tr>
<td>Other</td>
<td>30.80%</td>
<td>28.40%</td>
<td>0.3</td>
</tr>
<tr>
<td>Ovulatory dysfunction</td>
<td>9.40%</td>
<td>10%</td>
<td>0.74</td>
</tr>
<tr>
<td>PCOS</td>
<td>4.80%</td>
<td>4.80%</td>
<td>1</td>
</tr>
<tr>
<td>Tubal</td>
<td>3.90%</td>
<td>4.80%</td>
<td>0.47</td>
</tr>
<tr>
<td>Uterine</td>
<td>8.40%</td>
<td>9.10%</td>
<td>0.66</td>
</tr>
<tr>
<td>Clinic</td>
<td>--</td>
<td>--</td>
<td>0.018*</td>
</tr>
<tr>
<td>ICSI</td>
<td>95%</td>
<td>97%</td>
<td>0.026</td>
</tr>
<tr>
<td>Gonadotropin dose (FSH)</td>
<td>3671(1720)</td>
<td>3857(1847)</td>
<td>0.048</td>
</tr>
<tr>
<td>N</td>
<td>821</td>
<td>821</td>
<td>--</td>
</tr>
</tbody>
</table>

- All matched categories had no significant differences
- Gonadotropin dose and ICSI usage were slightly higher in freeze-only groups (not matched)
### Table 2. Freeze-only versus fresh transfer among euploid embryos

<table>
<thead>
<tr>
<th></th>
<th>Freeze-only</th>
<th>Fresh</th>
<th>OR Freeze-only/Fresh (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing Pregnancy</strong></td>
<td>53.1%</td>
<td>42.6%</td>
<td>1.52 (1.25, 1.85), p-value &lt;0.0001</td>
</tr>
<tr>
<td><strong>Implantation rate</strong></td>
<td>50.8%</td>
<td>42.7%</td>
<td>1.38 (1.15, 1.66), p-value &lt;0.001</td>
</tr>
</tbody>
</table>

After transfer of euploid embryos, **implantation and ongoing pregnancy rates were significantly higher in the freeze-only cohort than in the matched fresh cohort** (p<0.001 and p<0.0001, respectively).
### Table 3. Freeze-only versus fresh ongoing pregnancy rate stratified by maternal age and progesterone

<table>
<thead>
<tr>
<th>Age</th>
<th>P4</th>
<th>OR Freeze-only/ Fresh (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=36</td>
<td>&lt;=1</td>
<td>1.59 (1.16, 2.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;36</td>
<td>&lt;=1</td>
<td>1.45 (1.04, 2.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;=36</td>
<td>&gt;1</td>
<td>1.60 (1.12, 2.27)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;36</td>
<td>&gt;1</td>
<td>1.45 (1.01, 2.09)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Odds of ongoing pregnancy after freeze-only transfer were significantly higher than fresh transfer for all stratifications of maternal age and P at trigger (cutoff values of maternal age = 36 years and P = 1 ng/mL determined by ROC analysis).
PROGESTERONE AND MATERNAL AGE SENSITIVITY ANALYSIS – ODDS RATIO FREEZE-ONLY/FRESH

• Sensitivity analysis of ongoing pregnancy shows no significant trend regardless of progesterone at trigger or maternal age (unlike prior study for non-PGS embryos)

• However, there may be a non-significant trend towards more benefit at higher levels of progesterone

• Freeze-only transfer with euploid embryos was associated with significantly higher ongoing pregnancy and implantation rates than fresh transfer, regardless of progesterone level at trigger or maternal age
STRENGTHS AND LIMITATIONS OF FREEZE-ONLY RETROSPECTIVE MATCHED COHORT STUDIES

• **Strengths**
  – Large sample size
  – Multicenter data set
  – Detailed information on potential confounders to create matched cohorts
  – Stratification by maternal age and progesterone at trigger
  – Wide group of diagnoses to make findings generalizable to multiple patient groups

• **Limitations**
  – Retrospective
  – Different clinics, laboratory assays, laboratory procedures, and PGS companies used
  – Lack of live birth data and perinatal outcomes
• Definitions

• Fresh versus frozen transfer

• Fresh versus freeze-only transfer – example studies

• Cryopreservation in cancer patients
Oocyte cryopreservation in cancer patients

• Literature on oncofertility outcomes is limited
• Study from 1997-2014 of 63 cancer patients, 57 cryopreserved embryos, and 21 (36.8%) returned for frozen embryo transfer (comparison: age-matched controls undergoing fresh transfer, with 23 returning for frozen embryo transfer) found that outcomes were comparable between groups²⁹
• No difference between cancer patients and controls on gonadotropin dose, number of oocytes retrieved, and number of 2pn embryos obtained
• Cumulative pregnancy rate per transfer for cancer patients compared to controls was 37 vs. 43 % respectively (p = 0.49) and cumulative live birth rate per transfer was 30 vs. 32 % respectively (p = 0.85). Cancer patients had a higher likelihood of live birth resulting in twins (44 vs. 14 %; p = 0.035).
Hot off the Press!

- Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes

Matheus Roque 1,2,*, Thor Haahr 3,†, Selmo Geber 2,4, Sandro C. Esteves 3,5,6, and Peter Humaidan 3,5

Meta-analysis of 11 RCTs (5379 patients) found that:

- FET resulted in a statistically significant increase in live birth rate in hyper-responders (RR 1.16, 95% CI 1.05–1.28) compared to fresh transfer
- No difference was found in normo-responders (RR 1.04, 95% CI 0.97–1.11)
- Risk of pre-eclampsia increased with FET (RR 1.79, 95% CI=1.03-3.09)
- No differences noted in ectopic pregnancy, miscarriage, preterm birth, congenital anomalies, or mean birthweight (low quality evidence; heterogeneity substantial)
CONCLUSIONS

• Most studies on frozen versus fresh transfer have reported benefits of frozen transfer
  – However, some maternal or neonatal outcomes may be more beneficial in fresh cycles

• Studies on freeze-only transfer are more limited but most have suggested benefits of freeze-only transfer compared to fresh transfer, though they may be beneficial for only certain populations (primarily high responders)
  – Further prospective studies and RCTs should investigate this question, including stratifications by maternal age, progesterone levels, and specific transfer protocols (natural vs medicated)

• Given advances in vitrification, evidence suggesting benefits of freeze-only, and the increasing use of PGS, there has been a shift towards freeze-only cycles
  – Other freeze-only advantages include decreased risk of OHSS
  – Disadvantages of freeze-only include increased cost and time, and possible loss of embryos during freeze-thaw
CONCLUSIONS (continued)

- These findings are encouraging in the oncofertility population, as frozen transfers are often necessitated for these patients
  - However, majority of cryopreservation cycles now for oncofertility are oocyte cryopreservation in which more study is needed (versus embryo cryopreservation)
  - Literature on oncofertility in general is limited
  - Studies are also needed on frozen transfer in cancer patients versus patients with other etiologies of infertility
REFERENCES


10. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Freeze-all can be a superior therapy to another fresh cycle in patients with prior fresh blastocyst implantation failure. *Reproductive biomedicine online* online 2014;29:286-90.


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QUESTIONS?

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