Extended Culture of Blastocysts: Advantages and Disadvantages and In Which Patients?

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DISCLOSURES

- Catherine Racowsky, PhD, HCLD
- Extended culture of blastocyst: Advantages and disadvantages & which patients?

FINANCIAL DISCLOSURES (during last 12 months)

Consultant: World Health Organization
LifeGlobal, Inc

Speaker’s Bureau: Ferring Pharmaceuticals, Inc
LifeGlobal, Inc

UNLABELED/UNAPPROVED USES DISCLOSURE

None
Discussion Outline

1. Consider the source of the oocytes we handle
2. Review requirements for optimizing the culture conditions
3. Discuss the rationale for extending culture to the blastocyst stage
4. Review the evidence for day 3 vs. day 5 transfer
5. Outline a protocol for selection of optimal day of transfer for each patient
Please indicate the percentage of your patients who have blastocyst transfer:

A. Less than 10%
B. Approximately 25%
C. Approximately 50%
D. Approximately 75%
E. 100%
Source of the Oocytes: Follicle Growth & Selection

Adapted from Hodgen ‘82

Day of Menstrual Cycle

Egg Retrieval 36 hr post hCG

Exogenous FSH

Recruitment
Selection
Dominance

Cohort of Growing Follicles

N

DF

N-1

N-1

N-1

Atresia
Ovarian stimulation & oocyte wastage

- Only ~ 80% are mature (MII)
- Only ~ 70% of MII fertilize
- Not all embryos implant
- Not all can develop into a healthy fetus

Ovarian stimulation typically results in a high number of abnormal, developmentally incompetent oocytes
The Goals of ART

• To maximize the likelihood of pregnancy for each patient

• To produce a healthy, genetically normal full-term delivery

• To minimize the risk of a multiple gestation
The Critical Questions are ...

How can we achieve these goals for each patient by:

- Optimizing the culture conditions
- Choosing the optimal day to transfer AND
- Selecting the most developmentally competent embryo available

Our culture systems are very complex!
The Complexity of the Culture System

- Culture dish
- Embryo density
- Gas phase: $O_2$ tension
- Culture medium: type & protein
- Oil and “contact” materials
- Incubator type
- Culture platform
- Air quality

**Dynamic platforms:**
- Shaking/rotation
- Tilting
- Vibration
- Controlled fluid flow

*The in vitro environment is quite different from that in vivo*
In vivo environment is:
- Moist, not fluid
- Micro, not macro
- Moving, not stagnant
- Chemically dynamic, not static
- Epithelial surfaces are glycoprotein rich, not inert

Current embryo culture systems are non-physiological and are likely to be sub-optimal.
Requirements for Optimizing the Culture Conditions
Quality Management in the IVF Laboratory

**Policies & Procedures**
- Current, validated, implemented

**Equipment**
- Maintenance, performance, QC

**Personnel**
- Trained, certified, constantly monitored

**Patient**
- Optimal stimulation

**ENVIRONMENT**
- Contact Materials
- Air Quality

**QUALITY MANAGEMENT:**
- Control
- Assurance
- Improvement

- Game collection
- Game processing
- Insem
- ICSI
- Fert check
- Embryo eval/selection
- Embryo transfer
- Cryo
Quality Management (QM) in the IVF Laboratory

Monitor and verify acceptable lab performance through data collection and analysis with constant surveillance

Introduce and validate new protocols
QM Program: Fertilization rate as an indicator
QM Program: Embryo development as an indicator

% ≥ 7 Cell stage on day 3: <43 years
(embryos evaluated 65.0 - 68.9 hours post-insemination or ICSI)

Active, constant monitoring of laboratory performance and corrective action as indicated is essential for maximizing embryo potential

UCL=upper confidence limit, LCL =lower confidence limit
Oocyte Source and Optimizing the Culture System

Summary

- All the oocytes but 1 (or 2) in a retrieved cohort would have undergone atresia in a natural cycle
- A cohort of retrieved oocytes is typically heterogeneous in quality
- The embryology lab is challenged to identify the “best” oocyte/embryo and to optimize culture conditions
- An effective QM program, involving quantifiable indicators in the IVF lab, is mandatory
Rationale for Extending Culture
What are the key benefits of extended (i.e. blastocyst) culture?

A. This improves embryo development
B. This eliminates the non-viable embryos
C. This helps embryologists choose the better embryo(s)
The Normal Human Preimplantation Timeline

- Egg Retrieval
- Fallopian tube
- Uterus

Days After Retrieval:
- 0
- 1(am)
- 1(pm)
- 2
- 3
- 4
- 5
- 6
- ~6.5

Days:
- Day 2
- Day 3
- Day 5

Timelines:
- Egg Retrieval
- Implantation
Rationale for Extending Culture

Embryo Developmental Issues

Day 5 transfer allows self-selection of the morphologically “best” embryos

Activation of the Embryonic Genome

Day of Culture:
- 1 early
- 1 late
- 2
- 3
- 4
- 5
- 6

Egg Retrieval
Egg Retrieval

Day of Culture
1 early   1 late             2
3               4              5               6

X

Rationale for Extending Culture

Embryo Developmental Issues

Day 5 transfer allows self-selection of the morphologically “best” embryos
Aneuploidy and Female Age in the Human

Franasiak et al, ‘14

Age (yr)

% Embryos Aneuploid of Total Analyzed
Rationale for Extending Culture

Embryo Developmental Issues

Day 3: 84% aneuploidy

Day 5: 56% aneuploidy

Culture to day 5 may allow for greater selection of euploid embryos

Fragouli et al., '00
Rationale for Extending Culture

Uterine Issues

- Improved synchrony between embryonic stage and uterine environment: Disturbance due to elevated estradiol\(^1\) and progesterone\(^2\)
- Reduced uterine contractility with blastocyst transfer\(^3\)
- Reduced risk of embryo expulsion\(^4\)

\(^1\)Valbuena et al ’01; \(^2\)Healy et al ‘16; \(^3\)Fanchin et al ‘01; \(^4\)Fanchin et al ‘09

Blastocyst transfer confers advantages on uterine environment

Moore & Persaud ’98; The developing human embryo
Rationale for Extending Culture

Summary

- Self-selection of embryos results in:
  - Higher quality embryos developing to the blastocyst stage
  - A lower incidence of aneuploidy in developing embryos
- The uterine environment may be more favorable for blastocyst transfer
- Therefore, extended culture should enable transfer of fewer embryos of higher quality in a more receptive uterus
- Together, higher implantation rates and lower multiple birth rates should result following blastocyst transfer

What does the evidence from RCTs tell us?
What Is the Evidence For and Against Blastocyst Culture?
## Live Birth Rate: Fresh Transfers (RCTs)

### Odds Ratio and 95% CI

- OR: 1.48
- 95% CI: 1.20, 1.82

### Study Details

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugnon 2010</td>
<td>22</td>
<td>55</td>
<td>21</td>
<td>52</td>
<td>8.8%</td>
<td>0.98 [0.45, 2.13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dewreke 2000</td>
<td>3</td>
<td>11</td>
<td>1</td>
<td>12</td>
<td>0.5%</td>
<td>4.13 [0.36, 47.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elgindy 2011</td>
<td>52</td>
<td>100</td>
<td>35</td>
<td>100</td>
<td>11.4%</td>
<td>2.01 [1.14, 3.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emiliani 2003</td>
<td>33</td>
<td>82</td>
<td>41</td>
<td>89</td>
<td>16.0%</td>
<td>0.79 [0.43, 1.45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernandez-Shaw 2015</td>
<td>25</td>
<td>60</td>
<td>11</td>
<td>60</td>
<td>4.4%</td>
<td>3.18 [1.39, 7.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frattarelli 2003</td>
<td>15</td>
<td>29</td>
<td>8</td>
<td>28</td>
<td>2.7%</td>
<td>2.68 [0.89, 8.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levitas 2004</td>
<td>3</td>
<td>23</td>
<td>3</td>
<td>31</td>
<td>1.5%</td>
<td>1.40 [0.26, 7.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leven 2002</td>
<td>8</td>
<td>46</td>
<td>15</td>
<td>44</td>
<td>8.8%</td>
<td>0.41 [0.15, 1.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Livingstone 2002</td>
<td>14</td>
<td>30</td>
<td>11</td>
<td>29</td>
<td>4.1%</td>
<td>1.43 [0.51, 4.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papanikolaou 2005</td>
<td>38</td>
<td>80</td>
<td>23</td>
<td>84</td>
<td>8.0%</td>
<td>2.40 [1.25, 4.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papanikolaou 2006</td>
<td>56</td>
<td>175</td>
<td>38</td>
<td>176</td>
<td>17.5%</td>
<td>1.71 [1.06, 2.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rienzi 2002</td>
<td>24</td>
<td>50</td>
<td>24</td>
<td>48</td>
<td>8.7%</td>
<td>0.92 [0.42, 2.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Auwerda 2002</td>
<td>24</td>
<td>70</td>
<td>17</td>
<td>56</td>
<td>7.8%</td>
<td>1.50 [0.72, 3.15]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 811 / 819 = 100.0% | 1.48 [1.20, 1.82]

- **Total events**: 317 / 248
- **Heterogeneity**: Chi² = 21.83, df = 12 (P = 0.04); I² = 45%
- **Test for overall effect**: Z = 3.88 (P = 0.0002)

Favors day 2/3

Favors day 5/6

OR 1.48; 95% CI = 1.20, 1.82

Glujovsky et al., ‘16
Multiple Birth Rate: Fresh Transfers

Glujovsky et al., '16
### Embryo Freezing: Per Retrieval

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Day 5/6 n/N</th>
<th>Day 2/3 n/N</th>
<th>Odds Ratio M-H Fixed 95% CI</th>
<th>Weight %</th>
<th>Odds Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugnon 2010</td>
<td>42/55</td>
<td>51/52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bungum 2003</td>
<td>36/61</td>
<td>54/57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernandez-Shaw 2015</td>
<td>39/60</td>
<td>33/60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardner 1998</td>
<td>29/45</td>
<td>14/47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hreinsson 2004</td>
<td>15/64</td>
<td>34/80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karaki 2002</td>
<td>22/80</td>
<td>35/82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolibianakis 2004</td>
<td>114/226</td>
<td>145/234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leveron 2002</td>
<td>12/46</td>
<td>25/44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motta 1998</td>
<td>15/58</td>
<td>45/58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantos 2004</td>
<td>16/81</td>
<td>79/162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papanikolau 2006</td>
<td>115/175</td>
<td>126/176</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renzi 2002</td>
<td>18/50</td>
<td>42/48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ten 2011</td>
<td>20/28</td>
<td>26/27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Auwera 2002</td>
<td>26/70</td>
<td>35/66</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- Total events: 519 (Day 5/6), 744 (Day 2/3)
- Heterogeneity: $\chi^2 = 82.95$, df = 13 ($P<0.00001$); $I^2 = 81\%$
- Test for overall effect: $Z = 8.25$ ($P < 0.00001$)
- Test for subgroup differences: Not applicable

**Odds Ratio:** 0.48 [0.40, 0.57]

**Favors day 2/3**

**Favors day 5/6**

*Glujovsky et al., ‘16*
Cumulative Live Birth Rate: Undefined # CETs

Glujovsky et al., ‘16
## Fresh blastocyst versus cleavage transfers: Results

<table>
<thead>
<tr>
<th></th>
<th># Trials</th>
<th>Day 5/6 Events/Total</th>
<th>Day 2/3 Events/Total</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live birth rate (LBR)</strong></td>
<td>13</td>
<td>317/811 (39.1%)</td>
<td>248/819 (30.3%)</td>
<td><strong>1.48</strong> (1.20, 1.82)</td>
</tr>
<tr>
<td><strong>Transfer cancellation rate</strong></td>
<td>17</td>
<td>108/1274 (8.5%)</td>
<td>47/1303 (3.6%)</td>
<td><strong>2.50</strong> (1.76, 3.55)</td>
</tr>
<tr>
<td>(unselected patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Multiple birth</strong></td>
<td>8</td>
<td>81/826 (9.8%)</td>
<td>78/846 (9.2%)</td>
<td><strong>1.05</strong> (0.75, 1.46)</td>
</tr>
<tr>
<td>(equal # embryos transferred)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Embryo freezing per retrieval</strong></td>
<td>14</td>
<td>519/1099 (47.2%)</td>
<td>744/1193 (62.4%)</td>
<td><strong>0.48</strong> (0.40, 0.57)</td>
</tr>
<tr>
<td><strong>Cumulative LBR</strong></td>
<td>5</td>
<td>155/317 (48.9%)</td>
<td>164/315 (52.1%)</td>
<td><strong>0.89</strong> (0.64, 1.22)</td>
</tr>
<tr>
<td>(undefined # CETs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Glujovsky et al., 2016*
Cumulative Live Birth Rate: CETs within 1 yr of retrieval

<table>
<thead>
<tr>
<th></th>
<th>SET Day 3 (n = 377)</th>
<th>SET Day 5 (n = 623)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh cycles</td>
<td>377</td>
<td>623</td>
<td></td>
</tr>
<tr>
<td>Transfer rate (%)</td>
<td>370/377 (98.1%)</td>
<td>588/623 (94.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Deliveries with live birth per cycle&lt;sup&gt;a&lt;/sup&gt;</td>
<td>115 (30.5%)</td>
<td>229 (36.8%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Singletons</td>
<td>115</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>0</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>FET cycles&lt;sup&gt;c&lt;/sup&gt;</td>
<td>329</td>
<td>325</td>
<td></td>
</tr>
<tr>
<td>Transfer rate (%)</td>
<td>320/329 (97.3%)</td>
<td>296/325 (91.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Double embryo transfer cycles (%)</td>
<td>156/320 (48.8%)</td>
<td>91/296 (30.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deliveries with live birth per cycle&lt;sup&gt;d&lt;/sup&gt;</td>
<td>68 (20.7%)</td>
<td>70 (21.5%)</td>
<td>0.785</td>
</tr>
<tr>
<td>Singletons</td>
<td>62</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Twins</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Triplets</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cumulative live birth per patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per initiated fresh cycle&lt;sup&gt;e&lt;/sup&gt;</td>
<td>183/377 48.5%</td>
<td>299/623 48.0%</td>
<td>0.867</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;f&lt;/sup&gt;</td>
<td>51.8%</td>
<td>45.9%</td>
<td>0.103</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes singletons and twins

<sup>b</sup> One twin pregnancy

<sup>c</sup> Includes cycles with ET

<sup>d</sup> Includes singletons and twins

<sup>e</sup> Includes cycles with ET

<sup>f</sup> Adjusted for age, smoking, and weight

De Vos et al., ’16
Cumulative Live Birth Rate: CETs within 1 yr of retrieval

Time to pregnancy is shorter with blastocyst transfer

De Vos et al., ‘16
### Monozygotic Twinning from Fresh Transfers

Blastocyst transfer is associated with an increased risk of monozygotic twinning.

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of MZ Twins</th>
<th>Fold Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 3</td>
<td>Day 5</td>
</tr>
<tr>
<td>Rijinders et al ’98</td>
<td>0.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Milki et al ’03</td>
<td>2.0%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Da Costa et al ’01</td>
<td>0.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Wright et al ’04</td>
<td>0.4%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Behr et al ’00</td>
<td>--</td>
<td>5.0%</td>
</tr>
</tbody>
</table>
Day 2/3 vs. Day 5/6: Monozygotic Twinning

Table II  The association between ART parameters and monozygosity.

<table>
<thead>
<tr>
<th>Embryo stage</th>
<th>OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleavage</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Compaction</td>
<td>0.63 (0.24–1.65)</td>
<td>0.91 (0.34–2.38)</td>
</tr>
<tr>
<td>Early blastocyst</td>
<td>2.20 (1.20–4.06)</td>
<td>2.70 (1.36–5.34)</td>
</tr>
<tr>
<td>Advanced blastocyst</td>
<td>1.73 (1.12–2.65)</td>
<td>2.05 (1.29–3.26)</td>
</tr>
</tbody>
</table>

OR, univariable logistic regression odds ratio; aOR, adjusted multivariable logistic regression odds ratio.

N= 6,103 clinical pregnancies following SET

Mateizel et al., ‘16
## Day 2/3 vs. Day 5/6: Monochorionic Twinning

<table>
<thead>
<tr>
<th>Day ET</th>
<th>ICSI</th>
<th>N (cases)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>No</td>
<td>1326 (12)</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>902 (18)</td>
<td>1.87</td>
<td>0.88 – 3.97</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>245 (7)</td>
<td>4.31</td>
<td>1.59 – 11.68</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>28 (4)</td>
<td>24.42</td>
<td>7.03 – 24.42</td>
</tr>
</tbody>
</table>

Blastocyst transfer is associated with an increased risk of monochorionic twinning

Skiadas et al ’08
## Summary of Obstetrical Outcomes

<table>
<thead>
<tr>
<th>Outcome per Singleton Birth</th>
<th># Studies/Subgroups</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>3</td>
<td>1.48 (1.09-2.02)</td>
</tr>
<tr>
<td>Pre-term birth</td>
<td>13</td>
<td>1.12 (1.02-1.23)</td>
</tr>
<tr>
<td>Very pre-term birth</td>
<td>10</td>
<td>1.14 (1.04-1.24)</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>7</td>
<td>1.12 (1.03-2.51)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>8</td>
<td>0.84 (0.75-0.94)</td>
</tr>
</tbody>
</table>

However, the evidence for each of the above is of low/very low quality and most of the absolute incidences are very small.
Clinical and Obstetrical Outcomes from Day 3 vs. Day 5 ET

**Summary**

Day 5/6 transfers are associated with:
- An increase in live birth rate following fresh transfer
- No difference in the multiple birth rate
- An increase in monozygotic and monochorionic twinning rates
- A decrease in the number of embryos frozen
- No difference in cumulative live birth rate within 1 yr of retrieval
- A shorter time to pregnancy
- An increase in transfer cancellation rate in unselected patients
- Several adverse obstetrical outcomes, but absolute risks are low

However, the evidence supporting the above is of low/very low quality
Which of the following is blastocyst versus cleavage stage transfer associated with:

A. An increased risk of monozygotic and monochorionic twinning
B. An increase in live birth rate following fresh transfer
C. A decrease in the number of embryos frozen
D. A shorter time to pregnancy
E. No difference in cumulative pregnancy rate within 1 year of the retrieval
F. All of the above
Which Patients Should Have Blastocyst Culture?
Which Patients Should Have Blastocyst Culture?

PGT patients: YES ...... at least for now!

- Known genetic disorders
  - Highly accurate
  - Requires care in Bx/handling
  - Potential allelic dropout
  - Poor amplification
  - Mosaicism

![Aneuploidy screening graph](image)

- Aneuploidy
- Miscarriage
- Live Birth

Maternal Age (y)
Day 5 biopsy

Day 5 biopsy

Day 3
Day 5
No Bx
Bx

% Implanted

39% reduction

P=0.035
P=0.804

# Pts = 46 67

• One of a sibling embryo pair was biopsied & the embryos transferred in pairs
• Conceptuses were DNA fingerprinted to determine whether implanted embryo was biopsied or not
Which Patients Should Have Blastocyst Culture?

What About non-PGT patients?

- A definitive answer remains to be determined
- Appropriately powered RCTs with current technologies are required to resolve this issue
- Because of the risk of having no blastocysts to transfer, an algorithm for transfer day should be used
- Patients should be counseled regarding the pros and cons of each transfer day
Algorithm for Patient Selection to Day 3 versus Day 5 Transfer
Fertilization check

Patients < 40yr
- < 6 zygotes → Day 3 ET
- ≥ 6 zygotes → Day 5 ET

Patients ≥ 40yr
- < 8 zygotes → Day 3 ET
- ≥ 8 zygotes → Day 5 ET

Day 3 is recommended for patients with poor previous blastocyst formation
Please answer “yes” to only one of the following.

After listening to this lecture, do you think:

A. All patients should have blastocyst transfer
B. Selected patients should have blastocyst transfer
C. No patients should have blastocyst transfer
Key Points: Blastocyst versus Cleavage Transfer

• Blastocyst culture requires that a lab is “in control” through implementation of a stable QM program

• The lab must have:
  ➢ An efficacious and reliable culture system
  ➢ Adequate incubator space to keep all embryos safe
  ➢ A proven vitrification protocol for blastocyst freezing

• Acknowledgment that extended culture increases costs to the laboratory
Key Points: Blastocyst versus Cleavage Transfer

- The rationale for blastocyst culture rests on benefits from:
  - Self-selection of those embryos capable of forming blastocysts (at least in vitro) and possibly some selection of euploid embryos
  - Potentially improved uterine receptivity
Key Points: Blastocyst versus Cleavage Transfer

• Blastocyst transfer is associated with increased risks of monozygotic and monochorionic twinning, as well as some obstetrical and neonatal risks

• Blastocyst transfer is associated with a shortened time to pregnancy:
  ➢ Emotional value and reduced costs to patients

• However, cumulative pregnancy rates between day 3 and day 5 transfer are very similar, if not identical

• If a lab offers blastocyst transfer, an ET algorithm is recommended
Final Comments

We have come a long way since the birth of Louise Brown nearly four decades ago

• We have a greatly improved understanding regarding:
  ➢ The biology of human gametes and embryos, and the development of the pre-implantation embryo
  ➢ The basic requirements in running an IVF laboratory, and in culturing embryos to the blastocyst stage

• We have also made great advances in ovarian stimulation and transfer protocols

More and more patients are leaving our clinics pregnant!!

HOWEVER .........
It is currently unknown whether there are media-associated epigenome-wide alterations in human embryos during culture.

Markert-Velker et al., '10
The Barker Hypothesis

A baby's nourishment before birth and during infancy, as manifest in patterns of fetal and infant growth, "programmes" the development of risk factors such as raised blood pressure and glucose intolerance that are key determinants of coronary heart disease.

Barker DJ. Eur J Epidemiol. 2003;8:733-736
THANK YOU!!