Low Cost Approaches to IVF

GERARD CELIA, PHD, HCLD
Why?

- Traditional IVF is expensive
  - Average cost: $15-18,000 in US - Forbes 2014
- Cycles require extended time commitment
  - Frequently 2-3 months to initiate
  - 1-3 months between failed attempts, including FET
- Aversion to ovarian stimulation
  - Fear of needles/injections
  - Fear/high risk of OHSS
- History of low oocyte yield/evidence for diminished ovarian reserve impedes patient retention
- Access to technology/infrastructure is not universal
Introduction

  - In 2014 only 24% of infertile couples received access to adequate treatment in the US
- Barriers to care include:
  - Cost
  - Social obstructions
  - Psychological obstructions
  - Physical access to care
- Low cost options seen as a major step toward broadening access to care in the US and abroad
Introduction

- Suggested low cost approaches include:
  - Mild Ovarian Stimulation IVF
  - Natural/Modified Natural Cycle IVF
  - Vaginal Incubation (Invocell)
  - IVM
Mild Ovarian Stimulation

Definition:
The administration of low doses (fewer days) of exogenous gonadotrophins in GnRH antagonist co-treated cycles, and/or oral compounds (like anti-estrogens, or aromatase inhibitors) for ovarian stimulation for IVF, aiming to limit the number of oocytes obtained to less than eight.

Fauser et al. Human Reproduction 2010
Mild Ovarian Stimulation

- **Rationale**
  - Decreased use of gonadotropins versus conventional COH-IVF (≤150 IU/day, Fewer days of stimulation)
  - Works best with GNRH antagonist protocols to prevent premature ovulation
  - Decreased monitoring
  - Decreased demand on lab (in theory)
Stimulation Approach

Macklon et al. Endocrine Reviews 2006
Cumulative Pregnancy Rate After 12 Months

## Advantages/Disadvantages

### Advantages
- Similar live birth rate/cycle
- Reduced complexity
- Easier on patient
- Lower patient drop-out rate
- Lower cost
- Improved embryo quality

### Disadvantages
- Lower pregnancy rates/cycle
- Still require expensive medication
- Higher cancellation rates
- Fewer embryos to cryopreserve
- May result in higher overall costs when multiple cycles are required for success
Laboratory Concerns

- Prep not significantly different from conventional COH-IVF
- Hyper stimulation and excessive response risk not eliminated
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Greater pressure place on lab staff relative to outcomes
- Impact on SART/CDC statistics— a cycle is a cycle
Natural/Modified Natural Cycle IVF

Definitions:

**Natural Cycle IVF (NCIVF)** – a completely natural cycle in which the patients endogenous hormones and follicular growth is monitored until the retrieval of a mature oocyte can be attempted.

**Modified Natural Cycle IVF (MNCIVF)** – A natural cycle supplemented with antagonists to prevent ovulation and sufficient FSH to counteract the drop in pituitary gonadotropins, similar to mild stimulation, but with the goal of obtaining a single mature oocyte.

OR

-A natural cycle supplemented with clomiphene citrate with the intent of retrieving 1 or more mature oocytes.

**Controversy** – The use of HCG as a trigger is a contested point in the US with respect to categorizing a cycle as NCIVF or MNCIVF.
Natural/Modified Natural Cycle IVF

- Rationale
  - “Natural” approach
  - No risk of OHSS
  - Reduced drug and supply costs
  - Back to back cycles are possible
Approach

NCIVF

Day 3
Baseline E2, LH, Follicular scan

Day 7
Begin monitoring:
E2, LH, Follicular scan

Day 8 → Day of trigger
Continue monitoring until:
E2 >100,
LH ≥ 2x baseline,
Follicle diameter acceptable

MNCIVF

Day 3
Baseline E2, LH, Follicular scan

Day 5-7
Begin monitoring:
E2, LH, Follicular scan
Begin antagonist/rFSH

Day 8 → Day of trigger
Continue monitoring until:
E2 >100,
LH ≥ 2x baseline,
Follicle diameter acceptable

Retrieval
35-36hrs post HCG,
Multiple flushes to obtain oocyte
Natural Cycle IVF

- Considerations:
  - Patient must have regular ovulatory cycles
  - High cancelation rate relative to stimulate cycles
  - Trigger at smaller follicular size (≥15mm versus ≥18mm) to avoid premature ovulation
  - Multiple flushes may be required to retrieve oocyte (aspiration needle selection critical)
  - ICSI versus IVF
  - Day 3 versus Day 5 ET

Bourne Hall reported reasonable success using NCIVF

Other clinics unable to replicate this success, resorting to clomiphene/gonadotropin stimulate cycles

Greater oocyte yield/control of cycle has lead to the dominance of stimulated IVF throughout the world

NCIVF still widely practiced in Europe

2015: ASRM encourages the exploration of NCIVF as a low cost option
<table>
<thead>
<tr>
<th></th>
<th>England(^{13})</th>
<th>Australia(^{16})</th>
<th>United States(^{17})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopies</td>
<td>35</td>
<td>107</td>
<td>41</td>
</tr>
<tr>
<td>Cycles with eggs (%)</td>
<td>29/35 (83%)</td>
<td>62/107 (57.9%)</td>
<td>19/41 (46.3%)</td>
</tr>
<tr>
<td>Eggs fertilized (%)</td>
<td>24/25 (96%)</td>
<td>31/66 (47%)</td>
<td>9/15 (60%)</td>
</tr>
<tr>
<td>Pregnancy rate/embryo transfer (%)</td>
<td>6/24 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1: Early attempts at natural cycle *in vitro* fertilization with laparoscopic retrieval (modified from Lenton et al.\(^{15}\))
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cycles</td>
<td>775</td>
<td>397</td>
<td>NA</td>
<td>1048</td>
<td>255</td>
<td>NA</td>
<td>129</td>
<td>243</td>
</tr>
<tr>
<td>Oocyte retrievals attempted (%/cycle)</td>
<td>92.60%</td>
<td>92.70%</td>
<td>242</td>
<td>81.70%</td>
<td>87%</td>
<td>500</td>
<td>69%</td>
<td>86.80%</td>
</tr>
<tr>
<td>Successful retrieval (%/attempt)</td>
<td>79.50%</td>
<td>82.30%</td>
<td>72.70%</td>
<td>73%</td>
<td>77.9%</td>
<td>78.10%</td>
<td>85.40%</td>
<td>88%</td>
</tr>
<tr>
<td>Fertilization ICSI or IVF</td>
<td>IVF</td>
<td>IVF</td>
<td>Both</td>
<td>IVF</td>
<td>Both</td>
<td>ICSI</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Fertilization rate (%/oocyte)</td>
<td>NA</td>
<td>NA</td>
<td>73%</td>
<td>72.50%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>75%</td>
</tr>
<tr>
<td>Day of embryo transfer</td>
<td>NA</td>
<td>Blast</td>
<td>NA</td>
<td>D3</td>
<td>D2</td>
<td>NA</td>
<td>D2</td>
<td>Day 3 and Blast</td>
</tr>
<tr>
<td>Embryo transfer (n)</td>
<td>368</td>
<td>122</td>
<td>127</td>
<td>382</td>
<td>119</td>
<td>285</td>
<td>60</td>
<td>119</td>
</tr>
<tr>
<td>Embryo transfer (%/cycle)</td>
<td>47.40%</td>
<td>30.70%</td>
<td>NA</td>
<td>36.50%</td>
<td>46.70%</td>
<td>NA</td>
<td>46.50%</td>
<td>49%</td>
</tr>
<tr>
<td>Embryo transfer (%/attempt)</td>
<td>51.20%</td>
<td>33.10%</td>
<td>52%</td>
<td>44.60%</td>
<td>53.60%</td>
<td>57%</td>
<td>67.40%</td>
<td>56%</td>
</tr>
<tr>
<td>Pregnancy rate/ET (%)</td>
<td>14.40%</td>
<td>39.30%</td>
<td>18.90%</td>
<td>27.20%</td>
<td>18.50%</td>
<td>17.10%</td>
<td>26.70%</td>
<td>35%</td>
</tr>
<tr>
<td>Pregnancy rate/Retrieval attempt (%)</td>
<td>7.40%</td>
<td>13%</td>
<td>9.90%</td>
<td>12.10%</td>
<td>9.90%</td>
<td>9.60%</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Pregnancy rate/cycle (%)</td>
<td>6.80%</td>
<td>12%</td>
<td>NA</td>
<td>9.90%</td>
<td>8.60%</td>
<td>48/?</td>
<td>12.40%</td>
<td>17%</td>
</tr>
<tr>
<td>GnRH-antagonist</td>
<td>N</td>
<td>N</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>rFSH add-back</td>
<td>N</td>
<td>N</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Follicle size/E2 level</td>
<td>LH &gt; 16 mm; &gt; 0.39 nmol/l</td>
<td>17 mm</td>
<td>18 mm</td>
<td>17 mm</td>
<td>≥ 16 mm</td>
<td>≥ 15 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing (LH or hCG)</td>
<td>LH</td>
<td>hCG</td>
<td>hCG</td>
<td>hCG</td>
<td>hCG</td>
<td>hCG</td>
<td>hCG</td>
<td>hCG</td>
</tr>
<tr>
<td>Timing of retrieval (hr)</td>
<td>Varied</td>
<td>31-32</td>
<td>34</td>
<td>34</td>
<td>36</td>
<td>37 h</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Type of needle (SL, DL, NA)</td>
<td>NA</td>
<td>SL</td>
<td>DL</td>
<td>SL</td>
<td>NA</td>
<td>NA</td>
<td>SL</td>
<td></td>
</tr>
<tr>
<td>Flushing of follicle</td>
<td>NA</td>
<td>N</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td>Luteal support/Type</td>
<td>NA</td>
<td>HCG 1500 D9</td>
<td>hCG 2500 OR+2 and OR+4; prog 200 mg PV tid</td>
<td>hCG 1500 OR+5, OR+8, OR+11</td>
<td>hCG, P4 supp</td>
<td>50 mg PIO</td>
<td>NONE</td>
<td>Prog supp 100 mg, estrace 2 mg</td>
</tr>
</tbody>
</table>

D2: day 2; D3: day 3; E2: estradiol; ET: embryo transfer; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; LH: luteinizing hormone; NA: not available; OR: oocyte retrievals; rFSH: recombinant follicle stimulating hormone
Laboratory Concerns

- 1 oocyte = Greater pressure per cycle
- Prep can be greatly simplified
- Faster retrievals = faster OR turnaround
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Impact on SART/CDC statistics – slowly improving with new sorting methods
Advantages/Disadvantages

Advantages
- Similar implantation rate
- Reduced complexity
- Easier on patient
- Lower patient drop-out rate
- Lower cost

Disadvantages
- Lower pregnancy rates/cycle
- Higher cancellation rates
- Rare to have supernumerary embryos to cryopreserve
- May result in higher overall costs when multiple cycles are required for success
INVOCell

INVO bioscience
Mild, natural cycle, or modified natural cycle IVF protocol

Vaginal incubation
History

- Technique pioneered in 1985 as a means of controlling CO$_2$ and O$_2$ instability
- Pregnancy rates similar to traditional IVF
- Proposed as a means of bringing IVF to developing countries
- 2008 INVOcell device introduced
- Currently used in clinics throughout the world
- Rapidly growing use in the US
### Preliminary results

#### Initial results of INVO using the prototype device

<table>
<thead>
<tr>
<th>Number of publications</th>
<th>Countries</th>
<th>Number of INVO cycles</th>
<th>Clinical pregnancy rate/cycle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Austria, France, Germany, Japan, Netherlands, UK, USA</td>
<td>815</td>
<td>19.6</td>
</tr>
</tbody>
</table>

#### Results of the prelaunch clinical trial using the INVOcell

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cleavage rate (%)</th>
<th>Clinical pregnancy per cycle</th>
<th>Rate per transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 Oocytes retrieved</td>
<td>52.2</td>
<td>31.80% (7/22)</td>
<td>38.90% (7/18)</td>
</tr>
<tr>
<td>≥10 Oocytes retrieved</td>
<td>48.9</td>
<td>11.70% (7/60)</td>
<td>13.50% (7/52)</td>
</tr>
<tr>
<td>Total</td>
<td>49.9</td>
<td>17.10% (14/82)</td>
<td>17.10% (14/82)</td>
</tr>
</tbody>
</table>
Method

- Load inner chamber with medium containing 30,000 motile sperm/ml
  - Standard bicarbonate buffered culture media
- Place ≤10 oocytes into inner chamber
- Seal chamber and place in outer shell
- Outer shell is placed in diaphragm and inserted into the patients vagina by clinician
Method

- Vaginal incubation lasts 2-3 days (some current clinics are experimenting with blastocyst culture)
- Device is removed and a specialized holding block allows embryos to be graded prior to opening inner chamber
- Embryos are selected for transfer, removed, and rapidly loaded for ET in the absence of a CO₂ incubator
- Remaining embryos may be cryopreserved
Considerations

- No fertilization check
- CO₂ incubator greatly reduces potential failures in the process
- Presence of CO₂ incubators in developed countries may negate the logistic advantage of INVOcell
Laboratory Concerns

- Specific training required
- Prep can be simplified
- Decreased equipment demand
- Perceived reduction in laboratory workload and income per cycle may lead to decreased support for staffing
- Potential impact on SART/CDC statistics
- Growing use of ICSI and IVF insemination
Advantages/Disadvantages

Advantages
- Reports of similar pregnancy rates to tradition culture
- Reduced process complexity
- Resistance to equipment failure
- Decrease infrastructure needed
- Lower cost

Disadvantages
- No fertilization check
- Cannot verify development until day of ET
- Uncomfortable for some patients
- Cost benefit in existing US lab unclear
**in vitro Maturation (IVM)**

- **Definition (ASRM):** maturation in culture of immature oocytes after their recovery from follicles which may or may not have been exposed to FSH, but were not exposed to either LH or hCG prior to retrieval to induce meiotic resumption.
**in vitro Maturation (IVM)**

Vuong Thi Ngoc Lan, M.D., MCE, ASRM Access to Care Whitepaper, 2015
1935: Pincus and Enzmann perform successful IVM on rabbit oocytes
1944: Culture of human oocytes for 22-28hrs prior to fertilization and cleavage (Rock and Menkin)
1965: First reported IVM of human oocytes (Edwards)
1989: First reported human birth using IVM (Cha, et al.)
1994: First treatment of PCO patients (Trounson et al.)
Method

- Follicles monitored in a natural or FSH supplemented cycle until they reach 10-12mm
- Aspiration of COCs followed by 30-48hrs of \textit{in vitro} culture prior to stripping
  - Culture media may contain FSH, LH or HCG, Estradiol, serum.
  - No consensus on media enrichment
- Insemination by ICSI of MII oocytes
  - Zona Hardening concerns
Results

Maturation, fertilization and developmental competence (expressed as pregnancy and implantation rates) of human oocytes derived from invitro maturation cycles and matured invivo (blue bars) or in vitro (red bars). Percentages are cumulative frequencies. See also text for further details (Dal Canto et al., 2012).

* p < 0.0001, ** p < 0.0001.
### Clinical Concerns

<table>
<thead>
<tr>
<th>Citation (authors, ref no.)</th>
<th>Year</th>
<th>Number of included births</th>
<th>Obstetric and perinatal outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cha et al. [35]</td>
<td>2005</td>
<td>20 Singleton, 4 twin live births after IVM</td>
<td>3 Congenital anomalies (5.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Major (omphalocele: miscarriage, hydrops fetalis: termination, normal chromosome)</td>
</tr>
<tr>
<td>Mikkelsen [39]</td>
<td>2005</td>
<td>47 Births after IVM</td>
<td>No specific abnormalities related to the IVM procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One 46 XX with CCNH gene variation, inherited paternally (no clinical significance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One IUFD, induction failure, and asphyxia</td>
</tr>
<tr>
<td>Soderstrom-Anttila et al. [40]</td>
<td>2006</td>
<td>40 Singletons, 3 sets of twins</td>
<td>8 (19%) Minor developmental problems expressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One optical glioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuropsychological development within the normal range at 2 yr of age</td>
</tr>
<tr>
<td>Shu-Chi et al. [37]</td>
<td>2006</td>
<td>21 IVM births</td>
<td>Growth and developmental scale comparison with non IVM, no developmental delay</td>
</tr>
<tr>
<td>Buckett et al. [36]</td>
<td>2007</td>
<td>55 IVM, 217 IVF, and 160 ICSI babies compared</td>
<td>Risk of congenital anomalies (odd ratios) 1.42, 1.21, and 1.69, respectively</td>
</tr>
<tr>
<td>Fadini et al. [38]</td>
<td>2012</td>
<td>200 Babies born following IVM</td>
<td>No detected major congenital abnormalities</td>
</tr>
</tbody>
</table>

**IVM, in vitro maturation; ref no., references number; IUFD, intrauterine fetal death; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.**

Chang, et al. Clinical and Experimental Reproductive Medicine, 2014
Laboratory Concerns

- Increased culture complexity
- Longer duration in laboratory
- Increased training needed to identify and isolate COCs
- Methodologies not standardized
- Potential impact on SART/CDC statistics
Advantages

- Reduced cost to patient
- Reduced risk of OHSS
- More gentle approach for patient

Disadvantages

- Clinical outcome concerns
- Increased demand on lab/cycle
- Physiologic differences between in vivo and in vitro maturation unknown
- Cost benefit to lab/clinic is unclear
<table>
<thead>
<tr>
<th>Approach</th>
<th>Target patients</th>
<th>Key benefits</th>
<th>Drawbacks</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Stim</td>
<td>All, OHSS</td>
<td>Cost, Comfort</td>
<td>↓embryos</td>
<td>Cumulative cost, OHSS?</td>
</tr>
<tr>
<td>NCIVF</td>
<td>Normal cycling</td>
<td>Cost, Comfort</td>
<td>1-2 embryos</td>
<td>Cumulative cost</td>
</tr>
<tr>
<td>INVOCell</td>
<td>All</td>
<td>Decreased infrastructure requirements</td>
<td>Embryo monitoring</td>
<td>Actual savings?</td>
</tr>
<tr>
<td>IVM</td>
<td>All, OHSS, PCOS</td>
<td>Drug cost, Comfort</td>
<td>↓PR ↑demand on lab ↑clinical cost</td>
<td>Outcomes (perinatal concerns)</td>
</tr>
</tbody>
</table>
Access to infertility care is seen as a major health issue for the 21st century, both in the US and internationally.

Multiple strategies are being refined to address this shortcoming.

No single strategy offers a complete solution.
The End

Questions?