A Novel Minimal Stimulation ("Mini-IVF") Protocol:

For Older Women, Women With Low Ovarian Reserve, And Less Expensive

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Infertility Center of St Louis
# Cost Comparison

Conventional Stimulation vs. Mini-IVF

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<th>Total Cost 1st cycle</th>
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<td>$7,500 + $800(Meds) = $8,300</td>
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LESS IS MORE?

• Several reports of improved egg quality in IVF protocols with less medication (Collins 2009; Verberg et al., 2009a; Verberg et al., 2009b; Pelinck et al., 2007; Heijnen et al., 2007; Baart et al., 2007; Verberg et al., 2008; Fauser et al., 1999).

• The question is: whether the already demonstrated improvement in percentage of good quality embryos with a mild stimulation protocol is sufficient to outweigh the larger number of embryos obtained with conventional stimulation.
HOW CAN YOU EXPECT ALL THESE EGGS TO BE GOOD?

<table>
<thead>
<tr>
<th>#</th>
<th>Follicle Sizes</th>
<th>E2 Level</th>
<th>LH Level</th>
<th>FSH Level</th>
<th>Prog Level</th>
<th>HCG Level</th>
<th>Uterine Lining</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Right Ovary: FSH = 4.1; LH = 10; E2 = 60; Prog = 16.2; Quant Beta HCG = &lt;5</td>
<td>20.6 &lt; 1.1</td>
<td>20 &lt; 1.0</td>
<td>20</td>
<td>2.7</td>
<td>4.3</td>
<td>0.6 &lt; 5 4mm</td>
</tr>
<tr>
<td>2</td>
<td>Left Ovary: FSH = 4.1; LH = 10; E2 = 60; Prog = 16.2; Quant Beta HCG = &lt;5</td>
<td>20 &lt; 1.0</td>
<td>0.6 &lt; 5 !</td>
<td>7mm</td>
<td>1L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Right Ovary: FSH = 4.1; LH = 10; E2 = 60; Prog = 16.2; Quant Beta HCG = &lt;5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>Left Ovary: FSH = 4.1; LH = 10; E2 = 60; Prog = 16.2; Quant Beta HCG = &lt;5</td>
<td>1.0</td>
<td>1.0</td>
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Patient MUST begin menstrual cycle prior to ovarian stimulation. Day 1 = 1-21-04. Ovarian stimulation begins on date scheduled as long as menstrual cycle occurs in advance.
Heterogeneous Cohort of Follicles

(Oehninger & Hodgen, 1990)

Human menopausal gonadotrophin

Follicular aspiration

Immature follicles

DAYS OF MENSTRUAL CYCLE
## Mini-IVF and Conventional IVF Average Number of Eggs Per Retrieval

<table>
<thead>
<tr>
<th>Year</th>
<th>Mini</th>
<th>Conventional</th>
</tr>
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<tbody>
<tr>
<td>2008</td>
<td>369/108 = 3.4</td>
<td>1748/177 = 9.9</td>
</tr>
<tr>
<td>2009</td>
<td>392/97 = 4.0</td>
<td>1708/167 = 10.2</td>
</tr>
<tr>
<td>2010</td>
<td>298/65 = 4.6</td>
<td>506/48 = 10.5</td>
</tr>
<tr>
<td>2011</td>
<td>898/257 = 3.5</td>
<td>2048/158 = 13.0</td>
</tr>
<tr>
<td>2012</td>
<td>1281/346 = 3.7</td>
<td>2519/163 = 15.5</td>
</tr>
<tr>
<td>2013</td>
<td>1281/346 = 3.6</td>
<td>2473/182 = 13.6</td>
</tr>
<tr>
<td>Total</td>
<td>Mean = 3.8 +/- 0.44*</td>
<td>Mean = 12.1 +/- 2.3*</td>
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* p<.001
1) The “mini-IVF” protocol was designed in Japan originally to provide more natural stimulation for in vitro fertilization (IVF). (A different “mild” stimulation protocol was designed and studied in depth in Netherlands.)

2) Clomiphene citrate (50 mg), a competitive inhibitor of estradiol, is begun on day 3, to stimulate the ovary by elevating FSH AND LH secretion.

3) Clomiphene citrate is continued beyond the usual 5 days to inhibit the LH surge (Teramoto and Kato, 2007).

4) Thus, two different effects were achieved by the prolonged anti-estrogen effect of clomiphene: a longer period of FSH and LH elevation, and suppression of premature LH surge.
Mini-IVF Protocol (con’d)

- A very low supplemental dose of FSH is added every other day from day 3.

- When the lead follicles are 18 mm, a GNRH agonist is administered to trigger an LH surge for final oocyte maturation.

- Follicle aspiration is performed 36 hours later.
Avoidance of Premature Ovulation and Cancellation

- Two additional methods were used to avoid premature ovulation when clomid does not completely block the LH surge:

  - Indomethacin 50mg p.o. is given on the day of GNRHa administration to delay ovulation without preventing LH induced maturation.

  - If the LH level begins to rise before the follicles are mature, a tiny dose (8 micrograms) of GNRH antagonist is added for a day or two before triggering with GNRH agonist.
Preceed Stimulation With BC Pills

- Must destroy all non-ovulated, non-atretic, mid size follicles.

- 19 days or more of suppression of FSH with BC pills will reduce and finally eliminate these residual follicles.

- Assures only a cohort of fresh eggs.
Reasons For Using GnRHa To Trigger Oocyte Maturation.

- It stimulates the pituitary to produce a more natural surge of LH.

- It is potent enough to induce maturation in larger follicles, but it never stimulates small follicles.

- Its half life is short, which allows the ovary to preserve those smaller follicles for upcoming cycles, rather than stimulate them prematurely, and allows women to cycle repeatedly without taking breaks.

- This is especially advantageous for older patients having limited ovarian reserve.
Frozen Transfer Better Than Fresh

- The reliance on continuous clomiphene citrate, with its negative impact on the endometrium, required a simplified, cheap, reliable method for embryo cryopreservation.

- The Kuwayama method of vitrification (Kuwayama et al, 2005) solves this problem.

- Poorer quality eggs is defined as a lower “implantation rate per egg” rather than “per embryo” (Collins 2009; Verberg et al., 2009a; Verberg et al., 2009b).

- However, the lower quantity of eggs means that no embryo can be wasted with a less than perfect cryopreservation method.
VITRIFICATION OF EMBRYOS: KUWAYAMA METHOD
Advantages of Mini-IVF

1) less medication
2) fewer injections
3) fewer eggs, but eggs of higher quality
4) lower cost
5) virtually no complications
6) much more patient friendly
   (dropouts are rare)
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Mini-IVF Question

• Is it really possible to achieve pregnancy rates with retrieval of only two to five eggs with mini-IVF, that is comparable to what you can achieve with 10 to 20 eggs using conventional stimulation protocols?

• It is well established that with gentle ovarian stimulation, there is a greater percentage of good quality eggs (although a smaller number) than with higher dose conventional stimulation (Verberg et al., 2009a, 2009b).

• But can this concept translate into favorable results with gentle stimulation IVF protocol compared to general expectations?
**Figure 6** Cumulative term live-birth rate within 12 months after starting IVF treatment. Mild: mild ovarian stimulation with GnRH antagonist and single embryo transfer. Standard: standard ovarian stimulation with GnRH agonist long protocol along with the transfer of two embryos. The shaded area represents the singleton live birth rates after 12 months for which the study was designed and powered to compare (Heijnen et al., 2007).