A new protocol of stimulation in IVF eliminating OHSS risk and increasing implantation rate

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Disclosure of Interest: Nothing to Disclose
• Freeze-all policy

• Mild stimulation

• Luteal-phase ovarian stimulation

• Double stimulation
Our clinic replaced fresh ET by frozen-thawed ET since March 2011. The data prove the better pregnancy outcome in FET compared with fresh ET.

A total of 20 cases of OHSS among 10,300 OPU cycles in 2013.
• ‘Freeze-all’ as a primary policy
  • Simplify the ovulation induction
  • Avoid later OHSS
  • Reduce the risk of early OHSS
Non-down regulation protocol

- Natural cycle
- Mild stimulation (LE+CC-HMG)
- GN/GnRH antagonist
- Luteal-phase ovarian stimulation
- Double stimulations
Mild stimulation

- Letrozole+CC-HMG
  - Moderate oocyte retrieval
  - Less drugs
  - Good oocyte/embryo quality
  - High cancel rate (20-40%)
## Cycle characteristics of mild stimulation

<table>
<thead>
<tr>
<th></th>
<th>Diminished ovarian reserve (n=197)</th>
<th>Normal ovarian function (n=3127)</th>
<th>PCOS (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>37.2 ± 5.3</td>
<td>33.9 ± 5.0</td>
<td>29.7 ± 3.6</td>
</tr>
<tr>
<td><strong>bFSH (IU/L)</strong></td>
<td>9.2 ± 4.1</td>
<td>6.6 ± 3.1</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td><strong>No of follicles &gt;10 mm on trigger day</strong></td>
<td>2.5 ± 1.3</td>
<td>4.0 ± 2.4</td>
<td>4.5 ± 4.2</td>
</tr>
<tr>
<td><strong>No of follicles &gt;14 mm on trigger day</strong></td>
<td>1.8 ± 1.1</td>
<td>2.8 ± 1.8</td>
<td>3.1 ± 2.6</td>
</tr>
<tr>
<td><strong>No. of oocytes retrieved</strong></td>
<td>1.9 ± 1.1</td>
<td>3.2 ± 2.3</td>
<td>3.4 ± 3.0</td>
</tr>
<tr>
<td><strong>No. of MII oocytes</strong></td>
<td>1.7 ± 1.0</td>
<td>2.9 ± 2.1</td>
<td>3.0 ± 2.7</td>
</tr>
<tr>
<td><strong>No. of fertilized oocytes</strong></td>
<td>1.4 ± 1.0</td>
<td>2.3 ± 1.8</td>
<td>2.3 ± 2.1</td>
</tr>
<tr>
<td><strong>No. of cleaved embryos</strong></td>
<td>1.3 ± 1.0</td>
<td>2.2 ± 1.7</td>
<td>2.3 ± 2.1</td>
</tr>
<tr>
<td><strong>No. of viable embryos</strong></td>
<td>1.1 ± 1.1</td>
<td>1.8 ± 1.6</td>
<td>1.9 ± 2.0</td>
</tr>
<tr>
<td><strong>Cancel rate (%)</strong></td>
<td>39% (77/197)</td>
<td>24.4% (764/3127)</td>
<td>27% (35/129)</td>
</tr>
</tbody>
</table>
## Pregnancy outcome using embryos derived from mild stimulation in FET

<table>
<thead>
<tr>
<th></th>
<th>Diminished ovarian reserve (n=93)</th>
<th>Normal ovarian function (n=1214)</th>
<th>PCOS (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>36.6 ± 5.2</td>
<td>33.7 ± 5.2</td>
<td>30.7 ± 4.5</td>
</tr>
<tr>
<td><strong>Infertility duration (yr)</strong></td>
<td>5.4 ± 4.1</td>
<td>4.3 ± 3.3</td>
<td>3.5 ± 2.9</td>
</tr>
<tr>
<td><strong>No of transferred embryos</strong></td>
<td>1.7 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td><strong>Clinical pregnancy rate (%)</strong></td>
<td>40.9% (38/93)</td>
<td>46.0% (558/1214)</td>
<td>56.4% (22/39)</td>
</tr>
<tr>
<td><strong>Implantation rate (%)</strong></td>
<td>32.0% (49/153)</td>
<td>28.8% (616/2142)</td>
<td>41.1% (29/70)</td>
</tr>
<tr>
<td><strong>Miscarriage rate (%)</strong></td>
<td>7.9% (3/38)</td>
<td>9.0% (50/558)</td>
<td>9.1% (2/22)</td>
</tr>
</tbody>
</table>
- Freeze-all policy
- Mild stimulation
- Luteal-phase ovarian stimulation
- Double stimulation
Antral follicles

- Many antral follicles in the periovulation time.
- It is good opportunity to retrieve oocytes in the luteal phase, especially for poor responders.

A case of 42 years with primary infertility, basal FSH 24 IU/L, no antral follicles appeared on cycle day 3. After treatment with ethinyl estradiol and progestin, ultrasound examination showed that a dominant follicle accompanied with four antral follicles.
Protocol of luteal-phase ovarian stimulation

- **Ovulation/OPU**
  - Letrozole 2.5mg qd
  - HMG 225IU/L qd

- **HMG 225IU/L (MPA when necessary)**

- **GnRHa 0.1mg trigger**
  - 36-38h OPU

- **Freeze-all**

- **AFC > 3**

- **Dominant follicle ≥18mm or More than three follicles ≥16mm**
The cyclic characteristics of luteal-phase ovarian stimulation and short protocol

OHSS incidence in luteal-phase ovarian stimulation is 0.04% (1/2413) compared with 0.5% (15/3730) in short protocol (P<0.05)
FET pregnancy outcome using embryos derived from luteal-phase ovarian stimulation and short protocol

<table>
<thead>
<tr>
<th></th>
<th>Luteal-phase ovarian stimulation (n=1631)</th>
<th>Short protocol (n=4180)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.5 ± 5.0</td>
<td>32.1 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>Infertility duration (yr)</td>
<td>4.1 ± 3.1</td>
<td>4.0 ± 2.9</td>
<td></td>
</tr>
<tr>
<td>FET cycle</td>
<td>1631</td>
<td>4180</td>
<td></td>
</tr>
<tr>
<td>Thawed embryo survival rate (%)</td>
<td>97.7% (3061/3134)</td>
<td>99.2% (8103/8166)</td>
<td>0.00</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>47.8% (780/1631)</td>
<td>45.6% (1904/4180)</td>
<td>0.063</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>36.4% (1110/3050)</td>
<td>31.1% (2517/8103)</td>
<td>0.00</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>11.2% (87/780)</td>
<td>12.8% (244/1904)</td>
<td>0.235</td>
</tr>
<tr>
<td>Ectopic pregnancy rate (%)</td>
<td>2.2% (17/780)</td>
<td>2.4% (46/1904)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Live birth 422 healthy babies using luteal-phase stimulation up to now.
LH decrease into 1.9 IU/L on trigger day.
Our data show that luteal-phase ovarian stimulation is feasible for producing potential oocytes/embryos, with potential pregnancy outcomes in subsequent FETs.

Advantages: No spontaneous LH surge

lower OHSS incidence

- Freeze-all policy
- Mild stimulation
- Luteal-phase ovarian stimulation
- Double stimulation
Double stimulation

- Combination of two stimulations in one menstrual cycle.
- Targeted for antral follicles in the follicular phase and luteal phase.
- Two chances of OPU achieve more oocytes and viable embryos
Double stimulation:

Mild stimulation-luteal-phase ovarian stimulation (Mild stimulation-LPS)
The results of double stimulation in three populations

- **POR**: normal ovarian function
- **POR**: mild stimulation
- **PCOS**: luteal-phase ovarian stimulation

**No of viable embryos**

- POR: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18
- POR (mild stimulation): n=38
- POR (luteal-phase ovarian stimulation): n=288

**No of oocyte retrieval**

- POR: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18
- POR (mild stimulation): n=38
- POR (luteal-phase ovarian stimulation): n=288
- PCOS (luteal-phase ovarian stimulation): n=26
Patient characteristics of mild stimulation-LPS in POR

- Poor ovarian responders (Bologna criteria, n=38)
  - Age: 37.2 ± 5.4 years
  - Basal FSH: 6.5 ± 1.6 mIU/ml
  - Previous failed IVF treatments: 26/38 (68.4%)
  - AFC: 3.9 ± 1.8 on cycle day 3
68.4% of poor responders had 1–6 embryos cryopreserved after double stimulations.

Pregnancy rate: 56.5% (13/23); Implantation rate: 36.6% (15/41)
# Results of mild stimulation-LPS in POR

<table>
<thead>
<tr>
<th></th>
<th>Mild stimulation (n=38)</th>
<th>Luteal-phase Stimulation (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation duration (day)</td>
<td>10.2 ± 2.4</td>
<td>10.8 ± 3.1</td>
<td>0.265</td>
</tr>
<tr>
<td>HMG dose (IU)</td>
<td>326.4 ± 248.9</td>
<td>1802.5 ± 712.7</td>
<td>0.00</td>
</tr>
<tr>
<td>No of &gt;14mm follicles on trigger day</td>
<td>1.5 ± 0.6</td>
<td>3.5 ± 2.0</td>
<td>0.00</td>
</tr>
<tr>
<td>No of oocyte retrieved</td>
<td>1.7 ± 1.0</td>
<td>3.5 ± 3.2</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>No of MII oocytes</td>
<td>1.4 ± 1.0</td>
<td>2.7 ± 2.7</td>
<td>0.008</td>
</tr>
<tr>
<td>No of fertilized oocytes</td>
<td>1.0 ± 1.0</td>
<td>2.1 ± 2.5</td>
<td>0.019</td>
</tr>
<tr>
<td>No of cleaved embryos</td>
<td>1.0 ± 1.0</td>
<td>2.0 ± 2.4</td>
<td>0.045</td>
</tr>
<tr>
<td>No of top-quality embryos</td>
<td>0.7 ± 1.0</td>
<td>1.2 ± 1.5</td>
<td>0.155</td>
</tr>
<tr>
<td>No of cryopreserved embryos</td>
<td>0.9 ± 1.0</td>
<td>1.3 ± 1.4</td>
<td>0.171</td>
</tr>
</tbody>
</table>
Figure: The hormone profile of double stimulation. The figure indicated that the relative ovarian insensitivity to GnRHa stimulation during the luteal phase compared with the follicular phase.
Double stimulation

- **Advantages**
  - More oocytes retrieval and reduce cancel rate
  - More flexible stimulation protocol
  - Especially useful for poor responders, cases that repeatedly no viable embryos and cancer patients needing emergency fertility preservation.
Prospective research

- The mechanism of ovarian folliculogenesis is not fully elucidated.
- Different ovarian response between follicular phase and luteal phase.
- Two enigmas: no spontaneous LH surge and lower OHSS incidence in luteal-phase ovarian stimulation.