Minimal monitoring of ovarian stimulation – Is it safe?

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Monitoring serves what?

Helps the physician to:
- Choose best protocol.
- Obtain best possible outcome.
- Avoid complications.

Adds to the common pool of information, which increases our knowledge and understanding of human reproduction.
Close continues observation

- Patient's initial parameters
- Ovarian response to ovulation induction
- Completion of therapy
What do we have to consider?

- Increase patient comfort.
- Avoiding the development of OHSS.
- Reduce rate of multiple pregnancies.
- Taking advantage of significant improvements that have been achieved in embryology and laboratory science.
- Addressing the economic considerations.
Monitoring serves what?

To find the optimal dose of gonadotropins for stimulation.

To find the optimal time for hCG administration.

To follow endometrial development.

To achieve single pregnancy.

To collect optimal number of eggs.
Simplifying treatment protocols remains a most important objective

- Reduce the cost.
- Reduce time commitments.
Success rates and complication rates are not dependent on monitoring as such, but on treatment protocol used. Monitoring merely gives us the possibility to decide how far we want to go.

Methods for monitoring

• Estrogen alone.
• US measurements of follicle size and endometrial thickness.
• US and estrogen combined.

No consensus has been reached on the preferred methods and how often.
Phases of treatment

• Pituitary down-regulation.
• Stimulation (with or without GnRH antagonist)
• hCG administration
Prospective evaluation of endometrial thickness as a predictor of pituitary down-regulation after gonadotropin-releasing hormone analogue administration in an in vitro fertilization program.

Hypothesis

- Endometrial thickness - a reliable bioassay of the patient’s estrogenic status.

- Ultrasonographic assessment of the endometrium has been suggested as a predictor of estrogen status.

Shulman et al. (Hum Reprod 1989)
Morcos et al. (Fertil Steril 1991)
• 183 IVF-ET cycles.
• GnRH-a for 15-17 days (long protocol).
• E2 + US before ovarian stimulation.
• Assessment of correlation between E2 and endometrial thickness.

** Pituitary down-regulation defined  E2 ≤ 200 pmol/L
Endometrial thickness vs. Estradiol

$n = 183$
Results

• $E2 > 200 \text{ pmol/L with endometrium} > 8 \text{ mm (93.3\%)}$
• $E2 \leq 200 \text{ pmol/L with endometrium} \leq 6 \text{ mm (95.6\%)}$
Conclusion

Transvaginal sonographic measurement of endometrial thickness of \( \leq 6 \) mm predicts pituitary down-regulation in over 95% of cases.
Acute changes in endometrial thickness after aspiration of functional ovarian cysts.

This condition is usually characterized by:

# A functional ovarian follicle/cyst, usually > 15-20 mm in diameter.

# High serum estradiol levels, usually >200 pmol/L

# Increased endometrial thickness, usually > 7 mm
Results

Serum estradiol concentration

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>739.8±493.0 pmol/L</td>
<td>184.0±271.1 pmol/L</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Endometrial Thickness

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.6±2.0 mm</td>
<td>5.9±2.4 mm</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Estradiol Measurements

- Does it contribute to the safety of the patient?
- Does it add to treatment success?
- Does it influence the timing of hCG administration?
FSH Administration Regimen

**Chronic Low Dose (CLD):** S. Franks et al.

- **Days:** 7, 14, 21, 28
- **Dosage:**
  - Days 1-7: 75 IU
  - Days 8-14: 75 IU
  - Days 15-21: 112.5 IU
  - Days 22-28: 150 IU
- **hCG** injection after day 28

**Step Down (SD):** B. Fauser et al.

- **Dosage:**
  - Days 1-7: 150 IU
  - Days 8-14: 112.5 IU
  - Days 15-21: 75 IU
  - **hCG** injection after day 21

**Sequential (SE):** J.N. Hugues et al.

- **Dosage:**
  - Days 1-6: 75 IU
  - Days 7-12: 112.5 IU
  - Days 13-18: 150 IU
  - Days 19-28: 75 IU
  - **hCG** injection after day 28

**Notes:**
- **Foll ≥ 10 mm** for CLD and SD regimens
- **Foll ≥ 14 mm** for SE regimen
When did you cancel ART cycles based on Estradiol Measurements alone

Preventive attitude of physicians to avoid OHSS in IVF patients

Theoretical case was presented to 573 physicians (ESHRE file)

25 y-old
Lean
PCOS
Carrier of protein C deficiency
Multiple allergies
Stimulated with hMG
- 20 follicles
- Estradiol 6590 pg/ml = 24,180 pmol/l

- Cancel the cycle
- Take some preventive measures
  - Coasting
  - Aspiration twice 12 h and 36 h after hCG
  - Replacing hCG with r-LH
  - Give albumin or hydroxyethylstarch
  - Administering glucocorticoids
  - Cryopreservation of embryos
- Proceed to regular IVF

Results

15% Proceed to a regular IVF
65% Take some preventive measurements
20% cancel the cycle

Monitoring the patients only once during ART treatment

One US scan on stimulation day 9 or 10

Results


Take home baby/started cycle = 26%

Mild OHSS = 2.8%

Wikland – Goteborg, Sweden
Can we abandon routine evaluation of serum estradiol during control ovarian hyperstimulation for assisted reproduction

A retrospective comparison of 2 consecutive periods

Methods

1998-1999: 855 cycles (U/S alone)

1996-1997: 1130 cycles (Intensive monitoring)

Results

No sig. Dif. was found comparing any of of the monitoring parameters and treatment results

Ben-Shlomo et al. Fertil Steril 2001
A single U/S was performed after 8 or 9 days of stimulation

<table>
<thead>
<tr>
<th>TABLE 1</th>
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</thead>
<tbody>
<tr>
<td>Summary of demographic data and outcomes in minimally monitored ART patients for all cycles started.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IVF (n=81)</th>
<th>GIFT (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32.2 ± 3.7</td>
<td>34.4 ± 2.3</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubal factor, %</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>Endometriosis, %</td>
<td>20</td>
<td>77</td>
</tr>
<tr>
<td>Unexplained, %</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Oocytes (n)</td>
<td>15.4 ± 9.5</td>
<td>12.0 ± 7.4</td>
</tr>
<tr>
<td>Fertilized (n)</td>
<td>10.7 ± 6.6</td>
<td>NA</td>
</tr>
<tr>
<td>Transferred (n)</td>
<td>4.0 ± 1.0</td>
<td>4.1 ± 0.8</td>
</tr>
<tr>
<td>Clinical pregnancy, %</td>
<td>51</td>
<td>36</td>
</tr>
<tr>
<td>Implantation rate, %</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Live birth rate, %</td>
<td>42</td>
<td>29</td>
</tr>
</tbody>
</table>

Bradley S. Hurst, M.D.,a,b Kathleen E. Tucker, Ph.D.,a,b and William D. Schlaff, M.D.a

FERTILITY AND STERILITY®
VOL. 77, NO. 1, JANUARY 2002
Monitoring of in vitro fertilization–embryo transfer cycles by ultrasound versus by ultrasound and hormonal levels: a prospective, multicenter, randomized study

Amir Lass, M.D., on behalf of the UK Timing of hCG Group
<table>
<thead>
<tr>
<th>Variable</th>
<th>E₂/follicle ratio</th>
<th>Ultrasound</th>
<th>CI (95%) of the estimated difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients who received hCG</td>
<td>143</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>33.2 ± 3.4</td>
<td>33.0 ± 3.4</td>
<td>−0.64; 0.94</td>
</tr>
<tr>
<td>Height</td>
<td>164.8 ± 6.8</td>
<td>165.0 ± 6.2</td>
<td>−1.65; 1.37</td>
</tr>
<tr>
<td>Weight</td>
<td>63.4 ± 8.9</td>
<td>62.3 ± 7.8</td>
<td>−0.78; 3.07</td>
</tr>
<tr>
<td>BMI</td>
<td>23.3 ± 2.9</td>
<td>22.9 ± 2.5</td>
<td>−0.17; 1.09</td>
</tr>
<tr>
<td>No. of patients who underwent OPU</td>
<td>141</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>No. of patients who underwent ET</td>
<td>129</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Endometrium thickness (mm) on hCG day</td>
<td>11.8 ± 2.1</td>
<td>11.5 ± 2.1</td>
<td>−0.19; 0.77</td>
</tr>
<tr>
<td>Days of Gonal-F</td>
<td>10.2 ± 1.9</td>
<td>10.1 ± 1.9</td>
<td>−0.29; 0.53</td>
</tr>
<tr>
<td>Cumulative dose of Gonal-F (IU)</td>
<td>2442 ± 883.5</td>
<td>2483 ± 1044</td>
<td>−259; 163.0</td>
</tr>
<tr>
<td>No. of follicles ≥11 mm on hCG day</td>
<td>13.6 ± 7.2</td>
<td>13.4 ± 6.8</td>
<td>−1.38; 1.86</td>
</tr>
<tr>
<td>No. of follicles ≥14 mm on hCG day</td>
<td>9.6 ± 4.7</td>
<td>9.0 ± 4.4</td>
<td>−0.47; 1.65</td>
</tr>
<tr>
<td>No. of follicles ≥16 mm on hCG day</td>
<td>6.4 ± 3.4</td>
<td>6.1 ± 3.1</td>
<td>−0.47; 1.05</td>
</tr>
<tr>
<td>No. of follicles ≥18 mm on hCG day</td>
<td>3.3 ± 2.1</td>
<td>3.3 ± 1.9</td>
<td>−0.45; 0.50</td>
</tr>
<tr>
<td>E₂ level (pmol/L) on hCG day</td>
<td>4926 ± 2512</td>
<td>5302 ± 2800</td>
<td>−1007; 372.9</td>
</tr>
<tr>
<td>LH level (IU/L) on hCG day</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 0.6</td>
<td>−0.26; 0.10</td>
</tr>
<tr>
<td>No. of oocytes retrieved per OPU</td>
<td>11.4 ± 6.1</td>
<td>11.7 ± 5.9</td>
<td>−1.79; 0.99</td>
</tr>
<tr>
<td>No. of 2PN oocytes on day 1 after OPU</td>
<td>6.6 ± 4.3</td>
<td>6.4 ± 4.2</td>
<td>−0.80; 1.20</td>
</tr>
<tr>
<td>No. of embryos on day 2 after OPU</td>
<td>8.4 ± 4.1</td>
<td>8.7 ± 3.8</td>
<td>−1.27; 0.55</td>
</tr>
<tr>
<td>No. of grade A embryos on day 2 after OPU</td>
<td>2.0 ± 1.9</td>
<td>1.9 ± 1.9</td>
<td>−0.24; 0.60</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>2.3 ± 0.5</td>
<td>2.3 ± 0.6</td>
<td>−0.15; 0.12</td>
</tr>
<tr>
<td>Proportion of pregnancies</td>
<td>49 (34.3%)</td>
<td>46 (31.7%)</td>
<td>−0.60; 0.38</td>
</tr>
<tr>
<td>Proportion of OHSS</td>
<td>5 (3.4%)</td>
<td>7 (4.7%)</td>
<td>−0.83; 1.53</td>
</tr>
</tbody>
</table>

* Indicates statistical significance.
Time of hCG administration

Group I. >18 mm with 2 follicles > 14 mm

Group II. >24 h later

Group III. >48 h later

Tan et al. Fertil Steril 1992
Time of hCG administration

No differences found comparing:
- Oocytes recovered
- Fertilization and cleavage
- Embryos frozen
- Pregnancy rate

Tan et al. Fertil Steril 1992
Induction of ovulation and IVF protocols can be monitored successfully by measuring endometrial thickness and ovarian follicles.

Avoidance of E$_2$ blood tests may simplify IVF protocols, thus increasing cost-effectiveness and patient convenience.
Conclusion

It seems preferable to choose a simple method like US and combine it with estrogen only in poor responders and in patients at risk for OHSS