Preovulatory follicle size and ultrasound monitoring in natural cycle

Veljko Vlaisavljević

University Clinical Centre Maribor
Gynecology and Perinatology
Department for Reproductive Medicine and Gynecologic Endocrinology
ivf.mb@uni-mb.si
www.ivf-mb.net

Ultrasound and follicle monitoring & ART

Visualization of follicle
Kretschwil 1972

Echographic monitoring of follicle growth
Hackelber 1977

Transabdominal follicle puncture
Leitz 1981

Ultrasonographically guided puncture with vaginal probe
Dellenbach 1984

Ultrasonographically guided puncture by transurethral approach
Persons 1985

Transvaginal puncture using vaginal probe
Wikland 1985
Evaluation of preovulatory follicle by ultrasound

- Follicle diameter
- Follicle growth pattern
- Follicular wall thickness
- Perifollicular vascularity
- Perifollicular blood flow

Follicular size & visualization by ultrasound

<table>
<thead>
<tr>
<th>Stage</th>
<th>Follicular size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primordial</td>
<td>0.03-0.04</td>
</tr>
<tr>
<td>Primary</td>
<td>0.05-0.06</td>
</tr>
<tr>
<td>Secondary</td>
<td>0.07-0.11</td>
</tr>
<tr>
<td>Preantral</td>
<td>0.15-0.20</td>
</tr>
<tr>
<td>Early antral</td>
<td>0.21-0.40</td>
</tr>
<tr>
<td>Antral</td>
<td>0.41-16.00</td>
</tr>
<tr>
<td>Preovulatory</td>
<td>16.1-20.00</td>
</tr>
</tbody>
</table>


Ultrasound and ovarian reserve assessment

Fluctuation in number of antral follicles in the ovulatory cycle visualized by 3D day-by-day ultrasound scan

- Dominant preovulatory follicle
  - Diameter at the time of LH surge
    18.1 – 22.6 mm
  - Linear growth rate before LH peak:
    1.4 – 2.2 mm/day
  - After the peak, growth increases very quickly

Follicle diameter and time remaining to ovulation
(d=days,h=hours)

<table>
<thead>
<tr>
<th>Mean diameter (mm)</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>7d+6h</td>
<td>1d+6h</td>
<td>2d+18h</td>
<td>5d+6h</td>
<td>7d+6h</td>
</tr>
<tr>
<td>16</td>
<td>1d+12h</td>
<td>2d+18h</td>
<td>4d+16h</td>
<td>6d+4h</td>
<td>8d+4h</td>
</tr>
<tr>
<td>17</td>
<td>1d+4h</td>
<td>2d+12h</td>
<td>5d+16h</td>
<td>6d</td>
<td>8d+4h</td>
</tr>
<tr>
<td>18</td>
<td>1d+4h</td>
<td>2d+12h</td>
<td>5d+16h</td>
<td>6d</td>
<td>8d+4h</td>
</tr>
<tr>
<td>19</td>
<td>1d+4h</td>
<td>2d+12h</td>
<td>5d+16h</td>
<td>6d</td>
<td>8d+4h</td>
</tr>
<tr>
<td>20</td>
<td>1d+6h</td>
<td>1d+16h</td>
<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
</tr>
<tr>
<td>21</td>
<td>1d+6h</td>
<td>1d+16h</td>
<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
</tr>
<tr>
<td>22</td>
<td>1d+6h</td>
<td>1d+16h</td>
<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
</tr>
<tr>
<td>23</td>
<td>1d+6h</td>
<td>1d+16h</td>
<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
</tr>
<tr>
<td>24</td>
<td>1d+6h</td>
<td>1d+16h</td>
<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
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<td>2d+18h</td>
<td>3d+18h</td>
<td>5d+18h</td>
</tr>
</tbody>
</table>
When is the correct moment to induce final oocyte maturation?
(Powell et al. 1993)

When the dominant follicle attained 16-20 mm.

or

Estradiol levels were indicating satisfactory follicular development (>1.1 - 0.73 nmol/L).

<table>
<thead>
<tr>
<th>Follicular diameter</th>
<th>Estradiol level</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 mm</td>
<td>1.1 nmol/L</td>
</tr>
<tr>
<td>18 mm</td>
<td>0.91 nmol/L</td>
</tr>
<tr>
<td>20 mm</td>
<td>0.73 nmol/L</td>
</tr>
</tbody>
</table>

Mean follicle diameter and outcome in 305 natural IVF cycles

When is the correct moment to induce final oocyte maturation?
(Maribor IVF)

When the dominant follicle attained >15 mm.

and

Estradiol levels were indicating satisfactory follicular development > 0.49 nmol/L
Correlation between serum estradiol and average follicular diameter in natural IVF/ICSI cycles
(Maribor IVF)

Estradiol = .04048 + .04712 * average follicular diameter
Correlation: r = .29464

Serum estradiol and follicular diameter on the day of hCG administration in natural cycle

<table>
<thead>
<tr>
<th>Estradiol (mean) nmol/L</th>
<th>Follicle diameter (mm)</th>
<th>Method</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.17</td>
<td>19.6 (mean)</td>
<td>Fluorimunometric</td>
<td>Cahill, 1998</td>
</tr>
<tr>
<td>1.09</td>
<td>18.6 (max)</td>
<td>RIA Pantex</td>
<td>Lindheim, 1997</td>
</tr>
<tr>
<td>1.05</td>
<td>19.3 (max)</td>
<td>RIA Pantex</td>
<td>Paulson, 1994</td>
</tr>
<tr>
<td>0.78</td>
<td>19.5 (mean)</td>
<td>DPC-RIA</td>
<td>Foulot, 1989</td>
</tr>
<tr>
<td>0.59</td>
<td>18.9 (mean)</td>
<td>Pharmacia Diapha</td>
<td>Tomažević, 1999</td>
</tr>
<tr>
<td>0.76</td>
<td>15.6 (mean)</td>
<td>Abbott AXSYM</td>
<td>Maribor, 2000</td>
</tr>
<tr>
<td>0.76</td>
<td>17.0 (max)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Growth of cohort of largest follicles in cycles stimulated with gonadotrophins

Singleton pregnancy

Nayudu et al. Hum Reprod 1991

Dynamics of follicle growth in 10 days before LH surge

Vlašanljević, Ultrazvuk 1991

Curves of follicular growth including two rapidly growing follicles and a cohort of slowly growing follicles. One follicle grew rapidly but a short time from day -2, the other from day -6 (most likely responsible for pregnancy).

Influence of dominant follicle on development of adjacent cohort

Computer reconstruction of 3D model of the same ovary using day-by-day ultrasound scans

Perifollicular angiogenesis

- Follicular growth is followed by an increase in perifollicular capillary network;
- Perifollicular blood flow may be associated with events essential for oocyte quality.

Vascularization studies in natural cycles

The value of different Doppler modalities in recognizing "pregnancy quality" follicles in unstimulated cycles by assessing perifollicular blood flow.

1. Conventional color Doppler (PI, RI, PSV)
2. Power Doppler
   - Semiquantitative analysis
   - 3D quantitative analysis

Doppler studies of perifollicular blood flow in unstimulated cycles

PSV, PI and RI in the perifollicular vessels change during the menstrual cycle.

Collins et al. Hum Reprod 1991;
Campbell et al. Fertil Steril 1993;
Lunenfeld et al. Hum Reprod 1996;
Zaidi et al. Ultrasound Obstet Gynecol 1996;
Problems in blood flow assessment in stimulated cycles

Difficulties in following the same follicle; identifying perifollicular vessels; tracing the embryo to the follicle.

Quantitative pulsed Doppler indices of perifollicular blood flow and IVF outcome in stimulated cycled

PSV of individual follicles correlated with:
- oocyte recovery rate (Nargund et al., 1996a,b);
- fertilization rate (Nargund et al., 1996a);
- developmental potential of the oocyte (van der Ven et al., 1997);
- quality of preimplantation embryos (Nargund et al., 1996a).
Power Doppler assessment of perifollicular vascularity in 141 unstimulated cycles
Semiquantitative analysis

1. Scarcely dotted vascularity;
2. Short linear segments of flow;
3. Flow in less than 30% of follicular wall;
4. Flow in 30-50% of follicular wall;
5. Flow in more than 50% of follicular wall.

Distribution of perifollicular vascularity types in 141 natural IVF cycles with and without fertilization and conception

Gavric Lovrec V. et al. WMW 2003

Dynamic PI and RI in concepted and nonconcepted 210 natural IVF cycles
Measurements performed on day 0 (hCG administration) and day +1 and day +2

Gavric Lovrec V. WMW 2003
Dinamic PSV in nonstimulated cycles

3D power Doppler quantitative analysis

Blood vessels count

**Blood vessel bifurcation**: one detected region overlaps two or more regions in the subsequent frames.

**Blood vessels join**: two or several detected region are overlapped by one region in the subsequent images.
Vascular network surrounding dominant follicles in pregnant and not pregnant IVF/ICSI natural cycles on day of oocyte pick up


<table>
<thead>
<tr>
<th>Vascular network in 5mm capsule (%)</th>
<th>Pulsatility index</th>
<th>Resistence index</th>
<th>Peak systolic velocity (cm/s)</th>
<th>Vessel 1</th>
<th>Vessel 2</th>
<th>Vessel 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>19.2 ± 16.8*</td>
<td>0.84 ± 0.2</td>
<td>0.55 ± 0.1</td>
<td>8.4 ± 3.2</td>
<td>38.6 ± 18.1</td>
<td>14.8 ± 7.1</td>
</tr>
<tr>
<td>Not pregnant</td>
<td>10.5 ± 7.1</td>
<td>0.82 ± 0.2</td>
<td>0.51 ± 0.1</td>
<td>12.8 ± 7.4</td>
<td>38.7 ± 19.1</td>
<td>14.0 ± 5.6</td>
</tr>
</tbody>
</table>

*borderline statistical significance (F=2.457, p=0.074)

Conclusion: It can be hypothesized that the follicles containing oocytes able to produce a pregnancy have a distinctive and more uniform perifollicular vascular network.

Capillary network in CL

1. Oxygen, nutrients and hormone precursors to steroidogenic cells
2. Release of progesterone
3. Damage after OPU

Mature corpus luteum (CL): Highest blood flow in any tissue in human body
Distribution of blood volume in 6 largest blood vessels in the perifollicular network pre- and 35 hours after hCG administration in 21 dominant follicles

Vlaisavljevic et al., in press

<table>
<thead>
<tr>
<th>Vessel 1</th>
<th>Vessel 2</th>
<th>Vessel 3</th>
<th>Vessel 4</th>
<th>Vessel 5</th>
<th>Vessel 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre hCG</td>
<td>3.3 ± 3.6</td>
<td>50.6 ± 28.1</td>
<td>14.0 ± 7.6</td>
<td>8.0 ± 4.8</td>
<td>5.1 ± 3.1</td>
</tr>
<tr>
<td>Post hCG</td>
<td>7.8 ± 10.1</td>
<td>28.1 ± 14.1</td>
<td>17.2 ± 8.5</td>
<td>15.5 ± 5.1</td>
<td>6.4 ± 2.5</td>
</tr>
</tbody>
</table>

Conclusions I

- Follicle diameter and growth dynamics are important factors for the prediction of LH surge (and/or hCG administration) in natural cycle
- The critical follicle diameter for LH surge also depends on the length of menstrual cycle
- Estradiol level has important role in accurate timing of hCG administration in natural cycle

Conclusions II

- Quantitative pulsed Doppler indices are not useful in recognising pregnancy quality follicles in natural cycle;
- Power Doppler assessment of perifollicular blood flow has a limited value in predicting follicle quality;
- Follicles, associated with conception, have a high percentage of volume showing power Doppler flow signal, their vascularization is more uniform.