Predicting fertility: ovarian reserve testing

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Key infertility questions

• What’s wrong with me/us?

• Can you put it right, Doc? ie will I get pregnant?
Summary

- What is the ovarian reserve?
- How does it relate to fertility?
- How can you measure it?
- What does it tell you?
- Can it predict fertility?
Essentials of fertility: post-ovulatory

and that’s assuming normal ovulation, semen quality, sex......
The ovarian reserve: what is it?

• The number of
  oocytes within the ovaries
  growing follicles
  small antral follicles
  follicles that can be stimulated by FSH
  oocytes that can be recovered after FSH

• What are we trying to predict?
  • natural fertility now
  • IVF outcome
  • Duration of fertility/age of menopause
Humans have a limited reproductive lifespan

Modified from A. H. Schultz (1969) The Life of Primates (20), 149
The ovarian follicular complement

Data from Block 1952; Baker 1963
Current model of follicular depletion

Wallace and Kelsey 2010 PLoS One 5; e8772
Age and reproductive success

Live birth rate per ET

<29  30-34  35-39  40-44  >45

0  5  10  15  20  25  30

Templeton et al 1996 Lancet 384; 1402
Age and reproductive success

Live birth rate per ET

Donated eggs

Own eggs

<29 30-34 35-39 40-44 >45

Templeton et al 1996 Lancet 384; 1402
The role of ovarian response prediction: improving balance

Van der Gaast et al, RBM Online, 2006
Progressive follicle selection

Scaramuzzi R et al 1993 Reprod Fertil Develop 5: 459-478
Prediction of ‘ovarian reserve’

• Age: cheap and hard to beat!
• Biophysical: Antral follicle count and ovarian volume
• Biochemical: basal and stimulated
Predictive tests: basic biology

- Age: a surrogate, but includes ‘quality’.
- FSH: indirect, reflects growing follicles
- Stimulation tests (CC, EFORT) largely superceded
- AFC: relatively large, committed follicles
- AMH: mass of granulosa cells, also relatively large follicles
- (AFC and AMH are essentially measuring the same thing)

Where is there a mention of oocyte quality?
Assessment of ovarian age

Age: a surrogate, but includes ‘quality’.
FSH: indirect, reflects feedback

Stimulation tests (CC, EFFORT)
AFC: relatively large, committed follicles
AMH: mass of granulosa cells, also relatively large follicles
(AFC and AMH are essentially measuring the same thing)
The growing follicle produces changing hormones.

- AMH
- Inhibin B, oestradiol

Stages:
- Primordial
- Preantral
- Antral
- Preovulatory
## Age, FSH and inhibin B

<table>
<thead>
<tr>
<th></th>
<th>Oocytes recovered</th>
<th>After downreg.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>-0.2 (ns)</td>
<td></td>
</tr>
<tr>
<td><strong>FSH</strong></td>
<td>-0.51 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibin B</strong></td>
<td>0.24 (ns)</td>
<td>0.65 (&lt;0.001)</td>
</tr>
<tr>
<td><strong>stim Inhibin B</strong></td>
<td>0.44 (0.002)</td>
<td>0.69 (&lt;0.001)</td>
</tr>
<tr>
<td><strong>AFC</strong></td>
<td>0.42 (0.004)</td>
<td>0.44 (0.002)</td>
</tr>
</tbody>
</table>

Yong PYK et al Human Reprod 2003, 18, 35
AMH is expressed in small but not larger follicles

Macaque ovary, courtesy of Prof Hamish Fraser
AMH expression in human ovary


<1mm 6.1 and 2.5 mm
Changes in markers of the ovarian reserve with age

In COS, AMH predicts no of oocytes (better than inhibin B)
Conveniently, AMH does not vary across the menstrual cycle

Seifer et al., 2002: Fanchin et al., 2003
Anti-Mullerian hormone and prediction of oocyte yield

Any better than (stimulated) inhibin B? Probably not!

There is a relationship between oocyte number and pregnancy rate

Van der Gaast et al, RBM Online, 2006
Prediction of menopause

50 women followed prospectively (Michigan Bone Health and Metabolism Study) 6 annual assessments

Mean initial age 42 yr

The association of age at FMP with AMH and inhibin B profiles

<table>
<thead>
<tr>
<th></th>
<th>$\beta \pm SE$</th>
<th>P value</th>
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<tbody>
<tr>
<td>Log AMH intercept</td>
<td>0.83 $\pm$ 0.38</td>
<td>0.035</td>
</tr>
<tr>
<td>Log AMH slope</td>
<td>0.75 $\pm$ 3.52</td>
<td>0.83</td>
</tr>
<tr>
<td>Log Inhibin B intercept</td>
<td>1.83 $\pm$ 1.77</td>
<td>0.31</td>
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<tr>
<td>Log Inhibin B slope</td>
<td>$-0.07 \pm 3.52$</td>
<td>0.98</td>
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Poor responders = earlier menopause

<table>
<thead>
<tr>
<th></th>
<th>IVF poor responders</th>
<th></th>
<th>IVF normal responders</th>
<th>OR or HR</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median follow-up</td>
<td>% menopausal</td>
<td>n</td>
</tr>
<tr>
<td>Retrospective cohort</td>
<td>636</td>
<td>6 years</td>
<td>22</td>
<td>3675</td>
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<tr>
<td>Retrospective cohort</td>
<td>118</td>
<td>5 years</td>
<td>50</td>
<td>265</td>
</tr>
<tr>
<td>Case control</td>
<td>12</td>
<td>7 years</td>
<td>92</td>
<td>24</td>
</tr>
</tbody>
</table>

Data from De Boer et al 2002, 2003; Nikolaou et al 2002; Lawson et al., 2003
AMH and AFC reflect primordial follicle number

Stereological analysis following oophorectomy, n=42

Hansen et al 2010 Fertil Steril
Intercycle variability in AFC and AMH

AFC (<10mm)  AMH

AMH: 89% of variation is between-subject, 11% is true individual cycle fluctuation.
AFC: 71% of variation is between-subject, 29% is individual cycle variation.

Intracycle variability

AFC (2-5mm)
Same quintile: 41% and 45% (2–5 and 2–10 mm).
Different q: 21% and 16%.

AFC (2-10mm)

AMH
Same quintile 72%
Different q: 1%

FSH vs AMH and ovarian response

AMH discriminates between response groups better than FSH

At the best cut off:

Sensitivity 70%
False pos rate 10%

Accuracy of ORTs: pregnancy

Accuracy is poor: only at extreme cut-off levels can a few zero prognosis cases be identified

n=558 meta-analysis

Conclusions

• Ovarian ageing: mostly genetic and unavoidable
• The various markers predict oocyte number
• Of course they do: by their nature they indicate the number of growing follicles
• How to improve prediction of oocyte quality?
What is the ‘ovarian reserve’?

Scaramuzzi R et al 1993 Reprod Fertil Develop 5: 459-478
Indirect evidence for AMH prediction of pregnancy

Age related decline
Good compared to UK standards

Clinical pregnancy rates for N=1217 cycles started
Versus national UK data

Data courtesy of Prof Scott Nelson, University of Glasgow
Indirect evidence for AMH prediction of pregnancy

Just treat AMH >5pmol/l
(50% centile at age 40)
Improvement in success rates for all ages
Consistent with independent prediction
Indirect evidence for AMH prediction of pregnancy

If AMH <5pmol/l
Poor ovarian reserve at young ages very poor results

Clinical pregnancy rates for N=1217 cycles started
National UK data
GCRM clinical pregnancy rates for AMH >5pmol/l
GCRM clinical pregnancy rates for AMH <5pmol/l
So can AMH predict live birth?

Paper 1:
• N = 340
• Increasing AMH associated with higher live birth
• Conversely higher FSH lower LB rate
• AMH AUC 0.62 95% CI 0.55 – 0.68

Paper 2:
• N = 336
• Increasing AMH but again threshold effect

Nelson et al Hum Repro (2007)
Lee et al Rep Biology and Endocrinology (2009)
Conclusions

• Prediction models to date have been limited in their applicability

• Multiple factors influence live birth success rates

• The decline in AMH parallels the reduction in follicles

• AMH can predict live birth

• Large cohorts to establish accurate measures of degree to which AMH can enhance the current best prediction models

• Still trying to equate egg quality with quantity: a real test of quality is elusive