Ovarian Ageing and Ovarian Reserve testing

Basic Principles in Ovarian Physiology - Relevance for IVF
Lisbon, 19 & 20 september 2008

Frank J Broekmans
Reproductive Medicine
University Medical Center Utrecht

Questions

- **What do we know about Ovarian Ageing?**
- **What is the Aim of Ovarian Reserve testing?**
- **Should we test for OR before IVF?**
- **Conclusions**

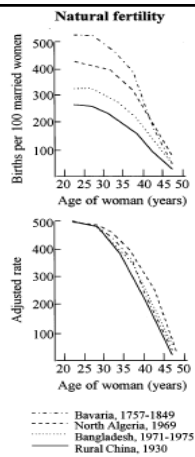**Fertility declines with female age
=
Reproductive ageing**

**Evidence from
Natural Populations**

Natural fertility
Births per 100 married women
Age of woman (years)
Adjusted rate
Age of woman (years)

Bavaria, 1757-1849
North Algeria, 1969
Bangladesh, 1971-1975
Rural China, 1930

Evidence from ART Populations

Egg donation…

Fertility declines with female age = Reproductive ageing

Singleton Live Birth per ART cycle initiated

Percentage

Female Age
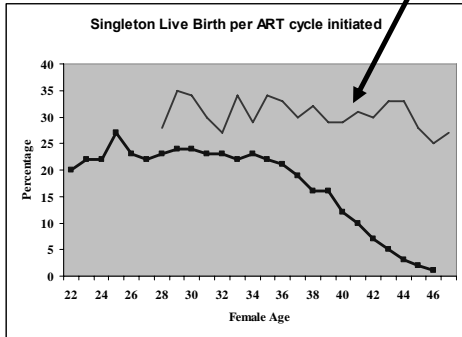
Reproductive ageing = Ovarian ageing
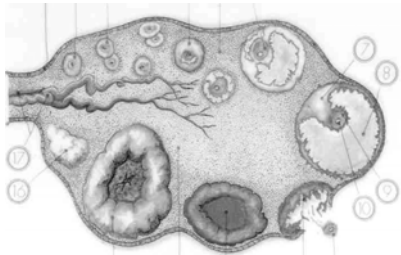
Ovarian Ageing = quantitative and qualitative decline of the ovarian follicle/oocyte pool

Optimal fertility

Declining fertility

End of fertility

Menopause

Irregular cycles

Number of follicles

Proportion of poor-quality oocytes (%)

Age (years)
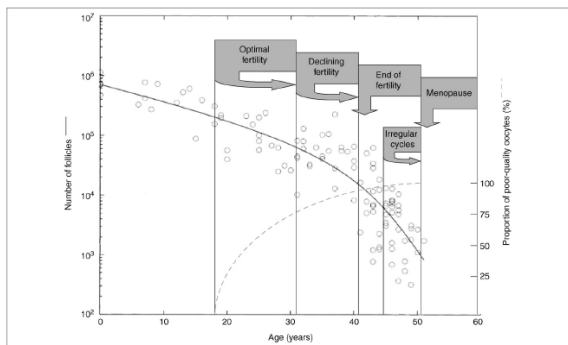
Faddy, 1995, De Bruijn, 2003, O'Connor, 2001

The newest data from autopsy or ovariectomy
Showing the same decay pattern

NGFs   Antral follicles

Menopause threshold

○ NGF
‐‐‐ 95% CI
— Power fit

Hansen, 2008
Leidy, 1998

Log(NGF) vs Age (years)

Ovarian Reserve Tests

- Mark the <u>size of the antral follicle cohort</u>

- This cohort is proportionally related the <u>primordial follicle pool</u>

Quality????

INITIAL RECRUITMENT   CYCLIC RECRUITMENT   Selection & Dominance   Ovulation

Primordial   Primary   Secondary   Antral   Graafian Follicles

human (2-5 mm)
rat (0.2-0.4 mm)   Atretic

human   ???   >120 days   71 days   14 days

Quality = determined by recombination errors in meiotic cell division of the oocyte

Meiotic Non disjunction
=
Aneuploid oocyte
=
Aneuploid embryo
=
Non implantation/EPL

Hassold and Hunt, 2008

Meiosis I   Meiosis II
Normal   Normal
'True' non-disjunction   Non-disjunction
'Achiasmate' non-disjunction
Premature separation of sister chromatids

3

Mechanism
Aneuploidy

Production line theorie

First oocytes formed in the embryo have the best recombination quality in meiotic divisions

First in first out…

Two hit theory

Part of the oocytes already has defective recombination

Another part obtains non-disjunction during resumed meiosis through

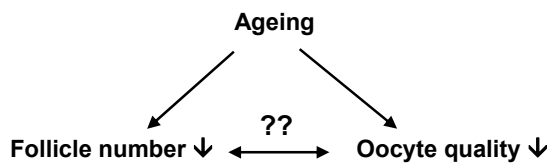   accumulated damage oocyte

    accumulated damage follicle

**Ovarian Reserve =
follicle number and oocyte quality**

Ageing

Follicle number ↓   **??**   **Oocyte quality ↓**

Follicle number	Oocyte quality
• Age at menopause (51)	• Age at natural sterility (41)
• Ovarian reserve tests poor	• Age at start of subfertility (31)
• Ovarian response in IVF ↓	• Ongoing pregnancy in IVF ↓
	• Early pregnancy loss rate ↑

Questions

- **What do we know about Ovarian Ageing?**
- **What is the Aim of Ovarian Reserve testing?**
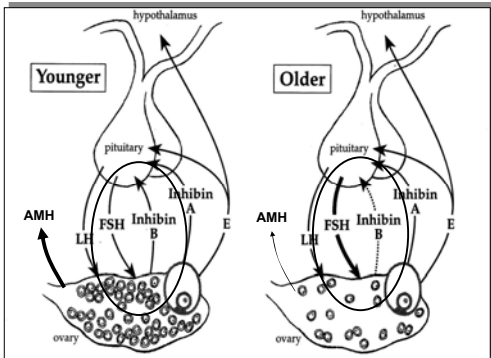- **Should we test for OR before IVF?**
- **Conclusions**

Ovarian Reserve assessment = quantity

Soules, 1998

Things could be simple……………..

Date of Birth
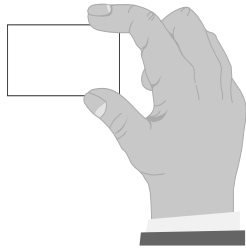
But….. Variation

Distribution for ages at menopause and last childbirth

Age at last birth

Age at menopause

Maternal Age

Variation in age at menopause and preceding reproductive events

---
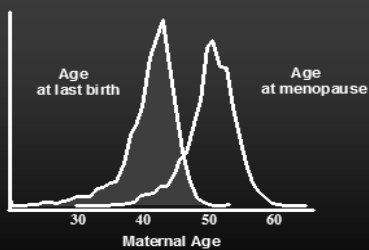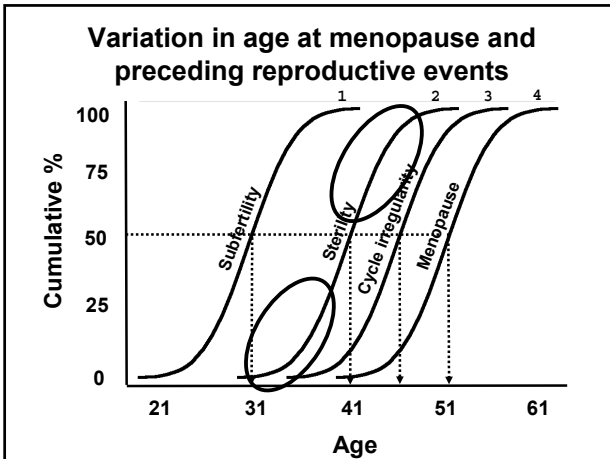
So…why ovarian reserve testing?

to identify cases with

- **severely decreased OR**

for age, and then

1) refuse treatment
2) alter treatment schedule
3) advise egg donation
4) improve the centre's results ……

So…why ovarian reserve testing?

to identify cases with

- **still highly adequate OR**

for age, and then

1) allow treatment in women of 40 years and over..
2) continue treatment after poor response..

Questions

- **What do we know about Ovarian Ageing?**
- **What is the Aim of Ovarian Reserve testing?**
- **Should we test for OR before IVF?**
- **Conclusions**

Assess ovarian reserve in ART indicated cases with regular menstrual cycle ?

Tools

- Age
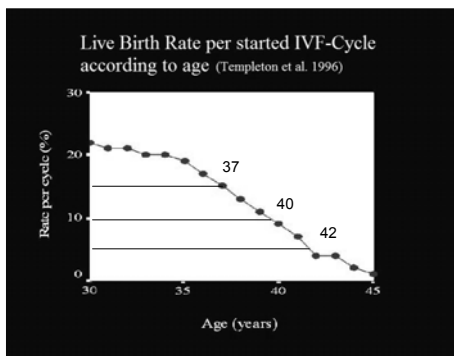- ORT: Basal FSH, AMH, AFC
- First cycle Response

Using female age alone….

Live Birth Rate per started IVF-Cycle according to age (Templeton et al. 1996)

Using female age alone….
cost explosion prevention…?

Henne, 2008

Direct health care treatment costs

Cost per live birth
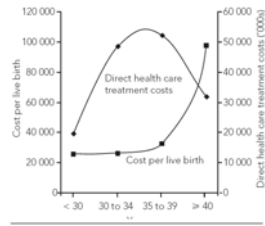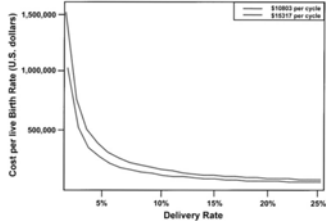
* Cost is expressed in 2005 Australian dollars.   ♦

Chambers, 2006

Although a very expensive child, there are not many…

Ovarian reserve tests…Add what? Systematic review Meta-analysis

- Accuracy of the test from aggregate analysis
- Clinical value from change in pre --- post test probability
- Clinical value from consequences of abnormal test for treatment and false positive rate

Broekmans et al, Hum Reprod Update , 2006

Prediction of Non-Pregnancy
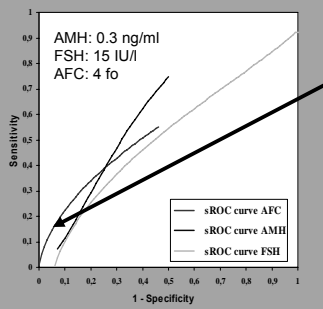
Accuracy Non Pregnancy prediction

AMH: 0.3 ng/ml
FSH: 15 IU/l
AFC: 4 fo

sROC curve AFC
sROC curve AMH
sROC curve FSH

Sensitivity

1 - Specificity

At extreme cut off:
FPrate   5%
Sens   15%
Post-test   96%
% pos tests   2-3%

Accuracy and Clinical Value: Poor

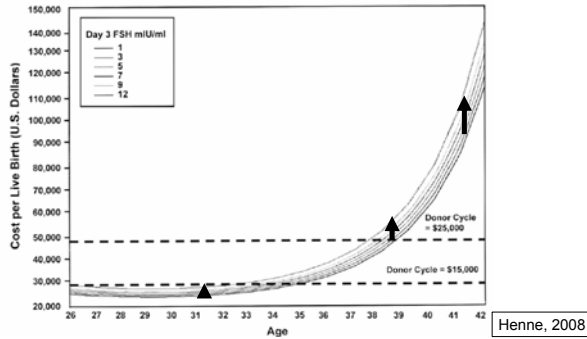**ORTs add what..??**
Effect of female age on costs are clear,
added value of basal FSH small

Henne, 2008

Pregnancy Prediction Difficult

Why?

- Quality **not** a continuous state
- Pregnancy as outcome not analysed in **series** of ART cycles
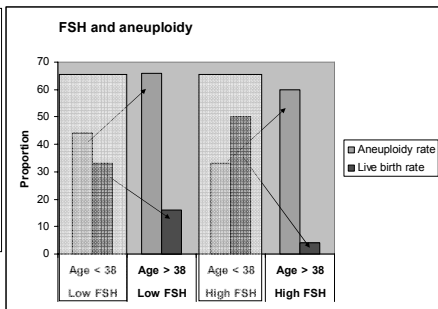- Quantity and quality not **fully** related

---

Relationship between women's age and basal
follicle-stimulating hormone levels with aneuploidy
risk in in vitro fertilization treatment

Meen-Yau Thum, M.D., Hossam I. Abdalla, F.R.C.O.G., and Deborah Taylor, Ph.D.

N = 151
1 cell FISH
5 probe set

**FSH does
not relate to
embryo
aneuploidy..**

FS, 2007

Prediction of Poor Response
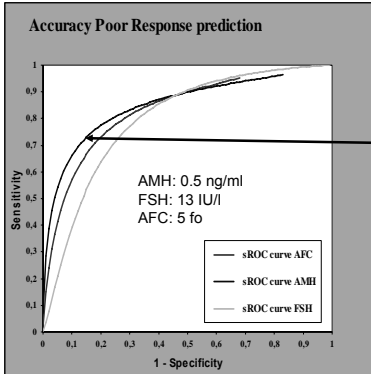
Accuracy Poor Response prediction

AMH: 0.5 ng/ml
FSH: 13 IU/l
AFC: 5 fo

— sROC curve AFC
— sROC curve AMH
— sROC curve FSH

Sensitivity
1 - Specificity

At the best cut off:	
Sens	70%
FPRate	10%
PT prob	~70%
LR+	7
AbnTests	~13%

Quite good, but
useful clinically?

Broekmans et al.

Human Reproduction Update
2006;12:685-718.

Prediction Poor Response
Individualize dose FSH?

- <u>Yes</u>: an individual stimulation dose based on a model with AFC, Ovarian volume, Ovarian flow, female Age and Smoking resulted in higher pregnancy rates compared to a standard dose (Popovic-Todorovic et al. Hum Reprod 2003).

- <u>No</u>: predicted poor responders based on AFC did not have better pregnancy rates with higher compared to normal doses (Klinkert et al. Hum Reprod 2005).
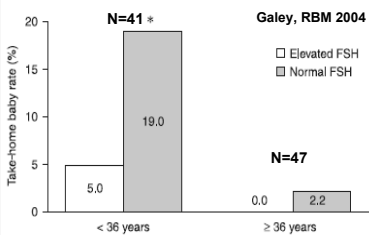

Poor Response: what does it mean?

The young (<37 years) poor responder with normal basal FSH produces quite a normal pregnancy rate: 23% per cycle   (N=66/124 poor responders. Lashen HR 1999)

Galey, RBM 2004

N=41 *

☐ Elevated FSH
☒ Normal FSH

Take-home baby rate (%)

5.0   19.0

N=47

0.0   2.2

< 36 years   ≥ 36 years

Poor Response can be due to causes other than advanced ovarian ageing….

Other biological reasons for poor response
– **excessive bodyweight**
– **FSH-receptor polymorphisms**
– **chance!!!!**

Should we test for OR prior to ART ?

- No, as…
  - Prediction of poor response does not clearly alter treatment
  - Prediction of non pregnancy is inaccurate and will hardly lead to refusal of treatment

- So, use
  - female age and
  - first cycle response??

The Expected Poor Responder approach

Klinkert, 2006

| |
|---|
| First cycle poor response = < 4 oocytes or cancel Cumulative OPR in cycle 2 and 3: 42% in Unexpected PR (age <41, Basal FSH < 15 U/l) |
| In Expected PR (age ≥ 41 Basal FSH ≥ 15 U/l) Cumulative OPR in cycle 2 and 3: 17% |
| |

Prediction of Ongoing Pregnancy in three cumulative cycles IVF

Prospective   N=222

Multivariate analysis using age, FSH, AMH, AFC and Inhibin B

ONLY female age……
is predictive but fails to identify very poor prognosis cases…
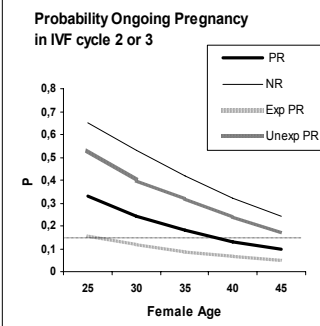
Probability Ongoing Pregnancy in IVF cycle 1, 2 or 3
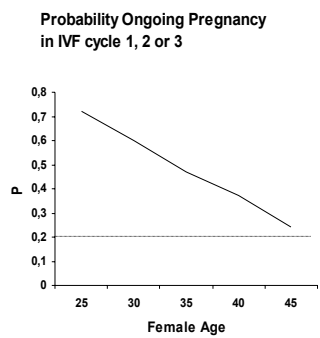
Expected Poor Responder Approach

Probabilities of Ong Preg in Cumulative cycles 2 and 3 based on

• **Female Age**
• **1st cycle Poor Response**
Classification:

Expected = abnormal ORT (FSH AMH AFC InhB)

Poor prognosis cases can be identified: *expected poor responders (10%)*

Probability Ongoing Pregnancy in IVF cycle 2 or 3

Do not screen for OR, but use it in specific conditions…

- Poor responder in first IVF/ICSI cycle
  – Diminished ovarian reserve?
  – Chance?
  – FSH receptor polymorphism?
- Apply an ORT, if abnormal: prognosis is very poor.. stop

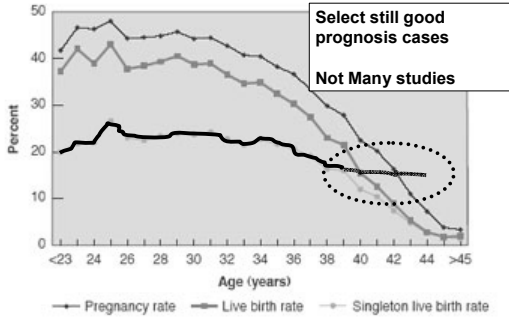**Should we test for adequate OR prior to IVF in females over 40…??**

Select still good prognosis cases

Not Many studies

Cumulative live birth rates following IVF in 41- to 43-year-old women presenting with favourable ovarian reserve characteristics

J van Disseldorp obtained his MD in 2006 from the University of Utrecht, The Netherlands. Currently, he is writing his PhD thesis at the Department of Reproductive Medicine and Gynaecology at the University of Utrecht. His thesis centres on ovarian ageing and onset of menopause.

•AFC (2-5): ≥5 fo
•FSH < 15 IU/l
•Regular cycles
Of n=144 60% allowed entry in program
Cumulative live birth in two cycles: 17%
Cost per child: 44.000 euro

Female age: when to stop?

- Tsafrir, RBM online 2007
- Cumulative Delivery rate according to Response (average of 3 cycles per couple)

Age (years)	Cycles with 1–4 oocytes		Cycles with ≥5 oocytes		P-value
	Total no. of cycles	No. of pregnancies (%)	Total no. of cycles	No. of pregnancies (%)	
40–41	172	8 (4.6)	189	35 (18.5)	<0.0001
42–43	195	16 (8.0)	148	22 (15.0)	0.04
44–45	127	2 (1.6)	100	8 (8.0)	0.016

Do not screen for OR, but use it in specific conditions…

- Female age over 40 years
  - Is ovarian reserve still adequate?
- Apply an ORT, if clearly normal: prognosis may be still be adequate... allow treatment
- Need for further studies

Take Home

- *Stop routine OR testing in IVF/ICSI populations*

- *Test in specific situations:*
  Poor response classification
  Female age ≥ 40 years (?)