

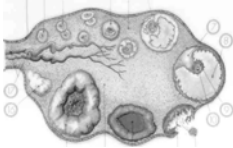
Ultrasound markers of ovarian reserve

Modena April 18-19, 2008



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UMC Utrecht

Impact study: stop OR tests or Soft catheters ??



Stop OR screening,
cost reduction 21 euro per IVF
indicated couple



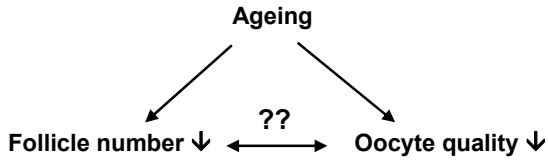
Stop using soft echogenic ET catheter,
but use stif catheter, cost reduction 21
euro per IVF treated couple

Your choice is.....

Questions

- What is Ovarian Reserve?
- What is the Aim of Ovarian Reserve testing?
- Ultrasound marks Ovarian Reserve?
- What does Ultrasound offer in OR Testing ?
- Conclusions

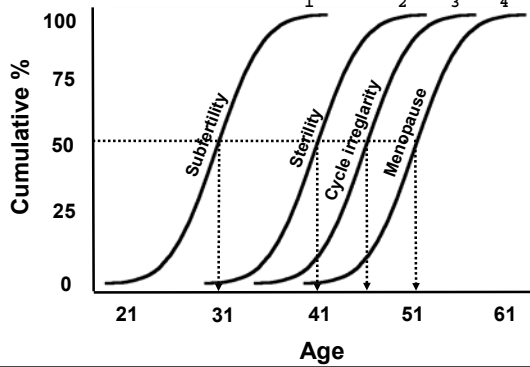
**Ovarian Reserve =
follicle number and oocyte quality**



- Age at menopause (51)
- Ovarian reserve tests
- Ovarian response in IVF

- Age at natural sterility (41)
- Age at start of subfertility (31)
- Ongoing pregnancy in IVF

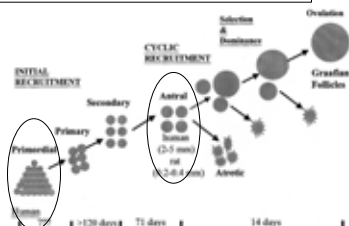
Variation in age at menopause and preceding reproductive events



Ovarian Reserve Tests: Quantity

- Mark the **size of the antral follicle cohort** that is continuously present in the ovaries
- This cohort is proportionally related the **primordial follicle pool**

Quality??



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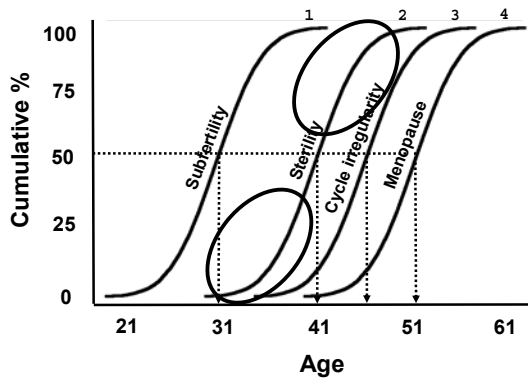
Aim of Ovarian Reserve assessment

To identify cases with

Severely diminished or with
Still adequate

ovarian reserve

Variation in age at menopause and preceding reproductive events



If diminished ovarian reserve for age..

Initiate treatment in time

- In subfertile couples with otherwise good prognosis

Adapt treatment in IVF/ICSI indicated couples

- hormonal stimulation
- type of stimulation protocol

Refuse treatment in IVF/ICSI indicated couples

- very poor chance of pregnancy (< 5% per cycle)

Apply embryoselection

- PGS

If still adequate ovarian reserve for age..

Allow treatment

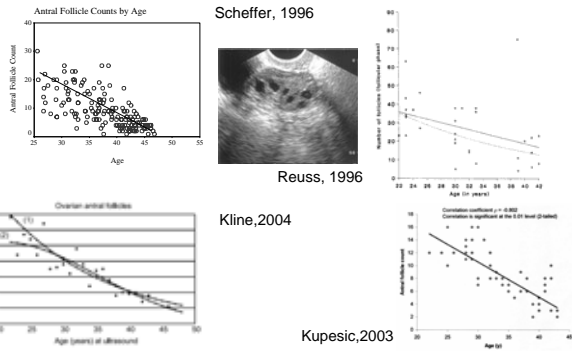
- in women over 40 years
- in poor responders

Questions

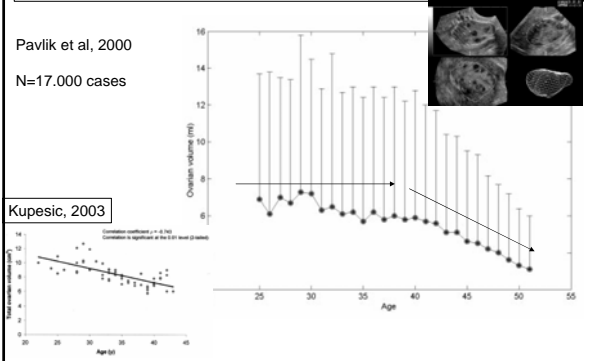
- What is Ovarian Reserve?
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AFC decline with female age

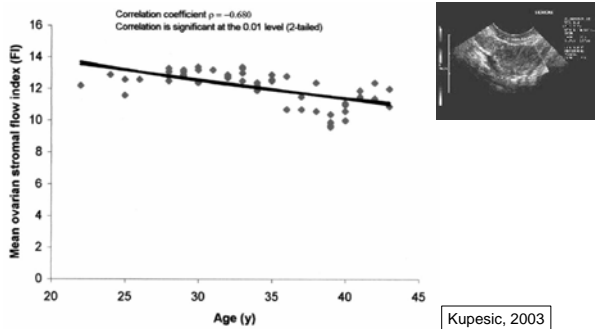


Ovarian Volume by female age



Ovarian Blood Flow by female age

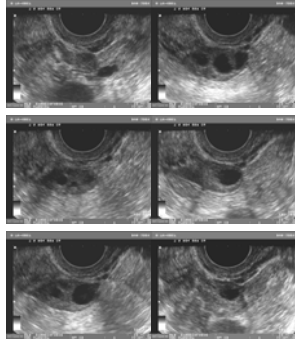
Vessel: PI, RI, PSV (Duplex Doppler)
Stroma vascularisation: VI, FI, VFI (Power Doppler)



Reproducibility of measurements

For OVVOL and FLOW measures hardly data

AFC few studies: adequate 3D?



2D real time versus 3D post hoc

n=81

Two observers



Technique	Observer 1	Observer 2	Observer 1 and 2
2D, mean (\pm 95% CI)	0.994 (0.987–0.997)	0.994 (0.988–0.997)	0.970 (0.945–0.984)
3D, mean (\pm 95% CI)	0.996 (0.993–0.998)	0.996 (0.992–0.998)	0.996 (0.993–0.998)
	NS	NS	$P < 0.01$

NS, not significant. Jayaprakasan, 2007

Time consumption:
2D: 1.3 minutes
3D: 4 minutes

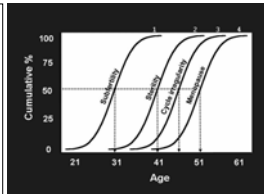
Relevant improvement??

Questions

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How to value ovarian reserve testing in cases with regular menstrual cycle ?

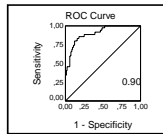
- Female Age
- Basal FSH, AMH, InhibinB
- Ultrasound AFC, Volume
- Challenge tests
- Maximal IVF stimulation



Test Accuracy

	nonPreg	Preg
Abn Test	A	B
Norm Test	C	D

Sensitivity, specificity, positive likelihood ratio for several cutoffs



Clinical value

Accuracy and.....

- Proportion of abnormal tests
- Pre test ----- post test probability of outcome
- False positive Rate

Meta-analysis

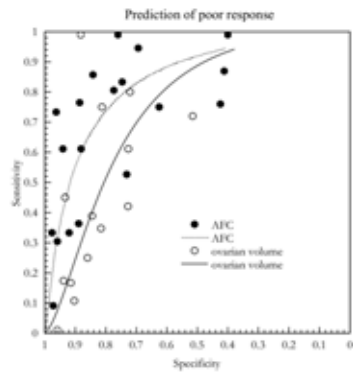
Broekmans et al, HRU 2006

AFC and Ovarian Volume: prediction poor response in IVF

Hendriks et al, 2007

Accuracy
AFC is good,
and better
than OVVOL

P=0.03

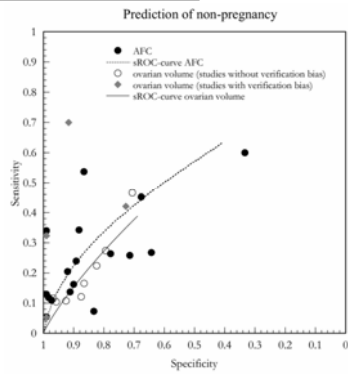


AFC and Ovarian Volume: prediction non-pregnancy in IVF

Hendriks et al, 2007

Both tests
equally poor

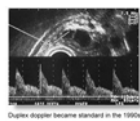
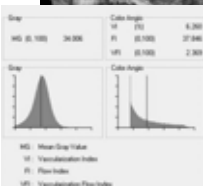
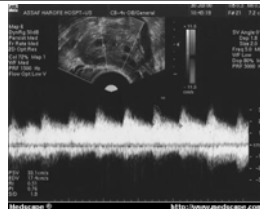
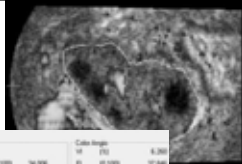
P=0.61



Ovarian Blood Flow

Vessel: PI, RI, PSV (Duplex Doppler)

Stroma vascularisation: VI, FI, VFI (Power Doppler)

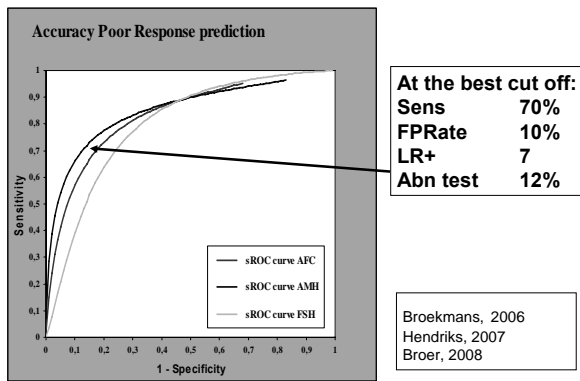


Duplex doppler became standard in the 1990s

Ovarian Blood Flow - studies

Study	Cases (n)	Timing	Method	Preg	Nonpreg	p	Cut Off	Sens	Spec
Ozturk	53	On agonist	PI uterine a	3.2	3.0	0.34	3.46	30%	95%
Ng	111	On agonist	VFI stroma	0.64	0.59	0.78			
Merce	65	On agonist	FI stroma	58.2	56.4	0.48			
Kupesic	56	On agonist	FI stroma	12.6	11.9	0.01	11	42%	96%
							13	85%	23%
Engmann	88	On agonist	PSV stromal a				10 cm/s	42%	86%
Engmann	105	Day 2-3-4	PSV uterine a	45 cm/s	44 cm/s	0.78			
			PI stromal a	0.87	0.92	0.65			
Popovic	145	On agonist	Stroma score						
Ng	193	On agonist	PSV stromal a						
Younis	32	Day 2-3-4	PSV stromal a						

Prediction of Poor Response: comparison



So,..... Poor Response prediction AFC

With abnormal test: what to do?

- Apply higher dose?
- Apply different stimulation approach?
- Refuse treatment

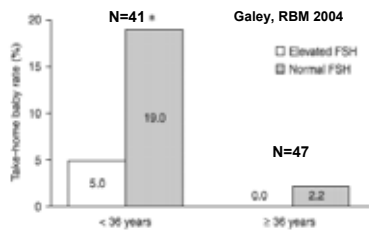
Predicted Poor Response Individualize dose FSH?

- **Yes:** 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).
- **No:** 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 IVF

The young (<37 years) poor responder with normal ovarian reserve test (basal FSH <12 IU/L) produces quite a normal pregnancy rate: 23% per cycle

(N=66/124 poor responders. Lashen HR 1999)



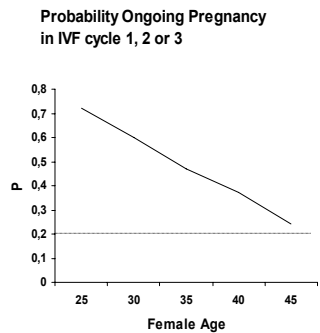
Prediction of Ongoing Pregnancy in three cumulative cycles IVF

Hendriks, RBM 2008

Prospective N=222

Multivariate analysis using age, FSH, AFC and Inhibin B

ONLY female age.....



Hendriks, RBM 2008

Expected Poor Responder Concept

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

- Female Age
- 1st cycle Poor Response type:

Expected = abnormal ORT (FSH AFC InhB)

Poor Response = ≤ 4 oocytes

Probability Ongoing Pregnancy in IVF cycle 2 or 3

Female Age	PR	NR	Exp PR	Unexp PR
25	0.35	0.65	0.15	0.55
30	0.25	0.55	0.15	0.45
35	0.18	0.45	0.15	0.35
40	0.12	0.35	0.15	0.25
45	0.08	0.25	0.15	0.18

Screen for still adequate OR in females over 40...??

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

75% allowed entry in program
Cumulative live birth in two cycles: 17%
Cost per child: 44.000 euro

Screen in women over 40...??

- Tsafirir, RBM online 2007
- Cumulative Delivery rate according to Response in IVF

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

Are ORTs prior to ART useful?

- 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,
 - Do IVF
 - ORTs to assess
 - First cycle poor response type
 - Expected response in females over 40
- before advice to stop

Apply repeated AFC??

TABLE 3

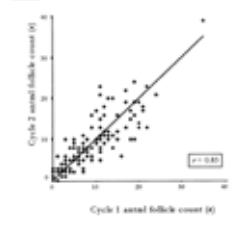
Logistic regression analysis for the prediction of poor response, expressed as odds ratios and area under the receiver operating characteristic curve (ROC_{AFC}) for age, infertility diagnosis, and various antral follicle count variables.

Variable	Odds ratio (95% CI)	P value	ROC _{AFC}
Univariate			
Age (per year)	1.02 (0.99-1.17)	.07	0.61
Infertility diagnosis	ns	<.005	0.71
Male	1.00	ns	ns
Tubal	1.96 (0.61-6.32)	.26	ns
Unexplained	6.86 (2.64-17.81)	<.005	ns
Cycle 1 antral follicle count (a)	0.70 (0.60-0.81)	<.005	0.87
Cycle 2 antral follicle count (a)	0.71 (0.61-0.82)	<.005	0.81
Mean antral follicle count (a)	0.67 (0.58-0.78)	<.005	0.87
Highest antral follicle count (a)	0.65 (0.58-0.73)	<.005	0.89
Lowest antral follicle count (a)	0.70 (0.60-0.81)	<.005	0.81
Multivariate			
Highest antral follicle count (a)	0.65 (0.58-0.73)	<.005	0.89

Note: CI = confidence intervals, ns = not applicable

Source: Repeated antral follicle counts. Fertil Steril 2004

FIGURE 1
Plot of the first antral follicle count against the second antral follicle count. The solid line represents equality of the two counts.

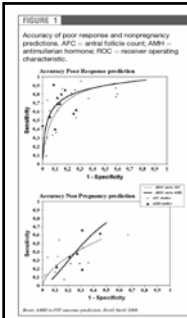


Source: Repeated antral follicle counts. Fertil Steril 2004

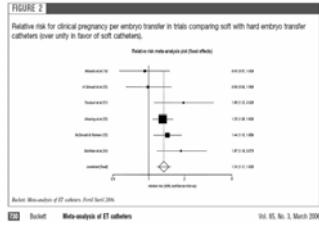
No

Conclusions

- AFC offers a good estimate of ovarian capacity but fails to predict pregnancy
- Routine AFC in IVF/ICSI populations is not to be advised
- AFC is of value in Specific conditions:
 - Poor responder typing**
 - Females over 40 years**



Impact study: stop OR tests or Soft catheters ??



Stop OR screening,
cost reduction 20 euro per IVF indicated couple

Stop using soft echogenic ET catheter,
cost reduction 21 euro per IVF treated couple

Your choice is.....
