



**Dipartimento di Scienze Ginecologiche,
Ostetriche e della Riproduzione**

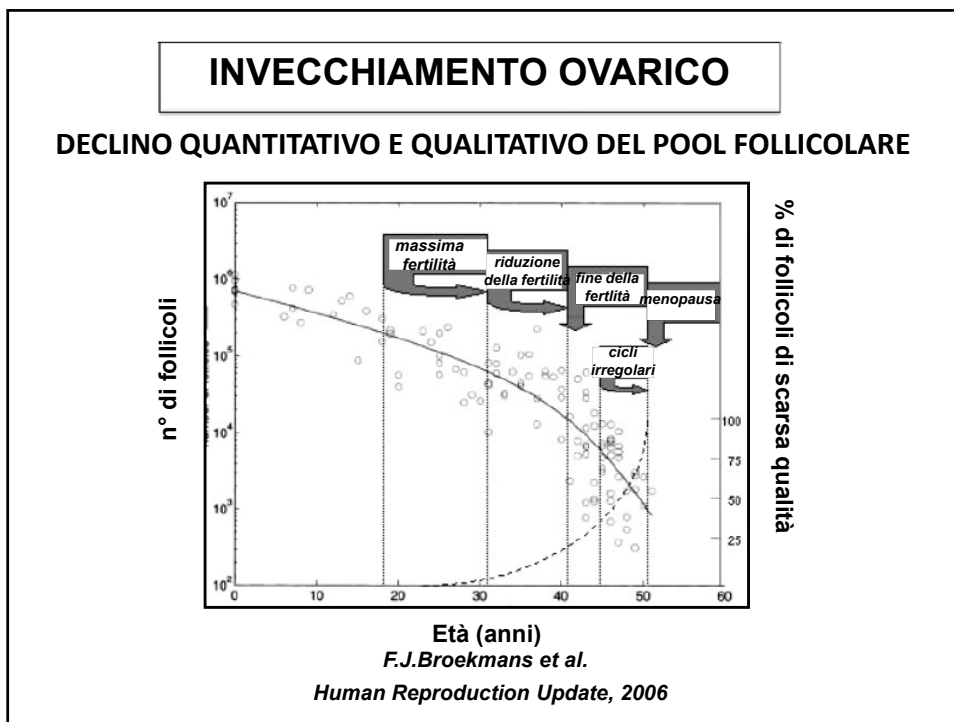
**MARKERS DELL'ETÀ OVARICA
E FERTILITÀ**

N. Colacurci
Sorrento, 14 Aprile 2010

**MARKERS DELL'ETÀ OVARICA
E FERTILITÀ**

**Cosa conosciamo
dell'invecchiamento
ovarico?**

**Perchè valutare la
riserva ovarica?**




INVECCHIAMENTO OVARICO

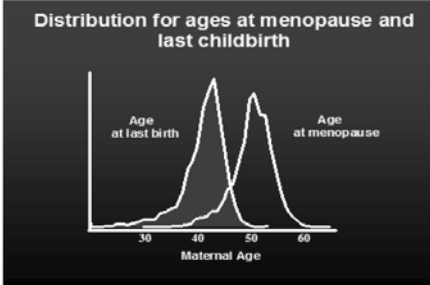
DATA DI NASCITA.....

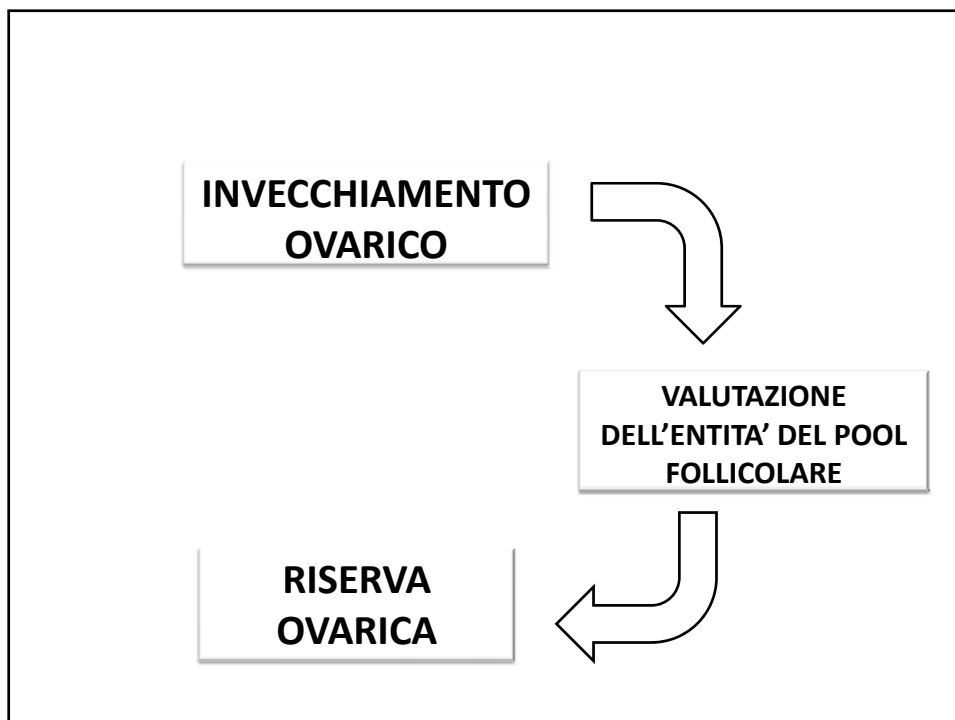
come valutarlo?

.....TROPPO SEMPLICE!



VARIAZIONI DELL'ETÀ DELLA MENOPAUSA E DELLA STORIA RIPRODUTTIVA





Perchè valutare la Riserva ovarica ?

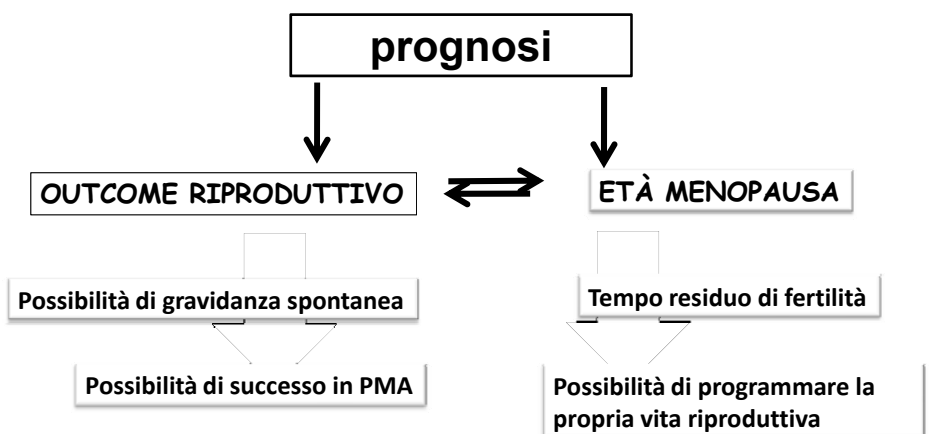
Counselling e scelta protocolli di induzione pre PMA

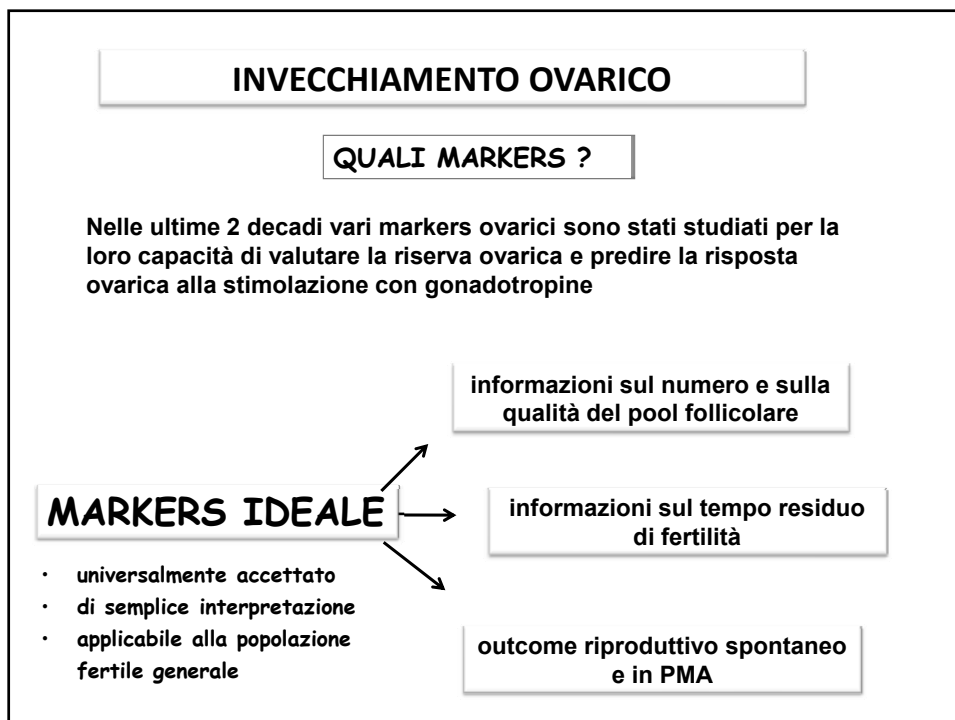
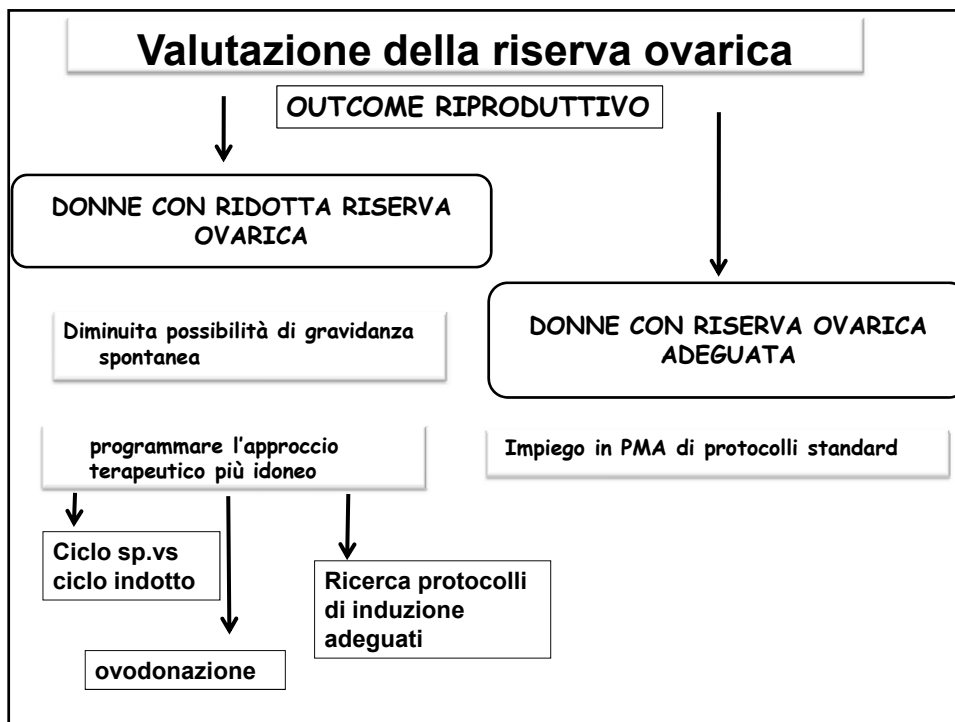
Valutazione capacità riproduttiva dopo trattamenti antineoplastici in eta' giovanile

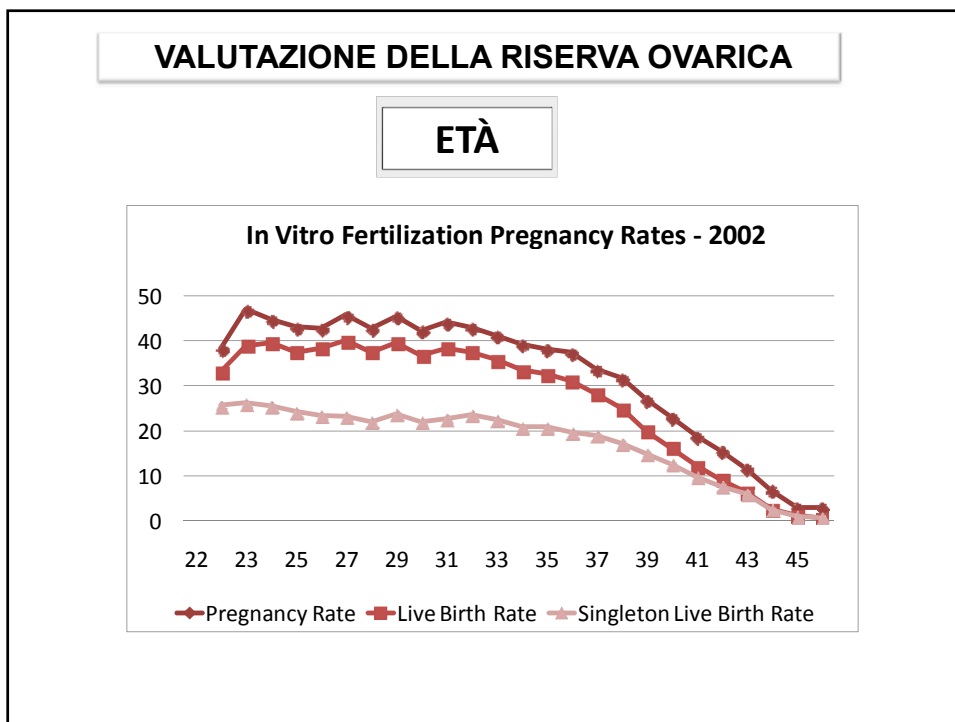
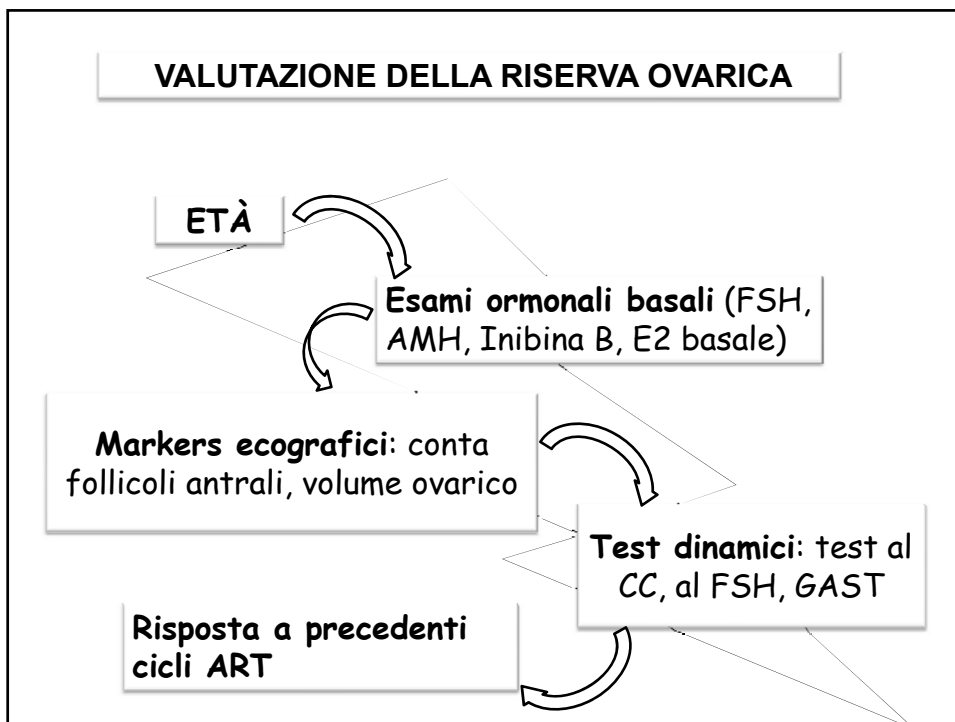
Timing riproduttivo

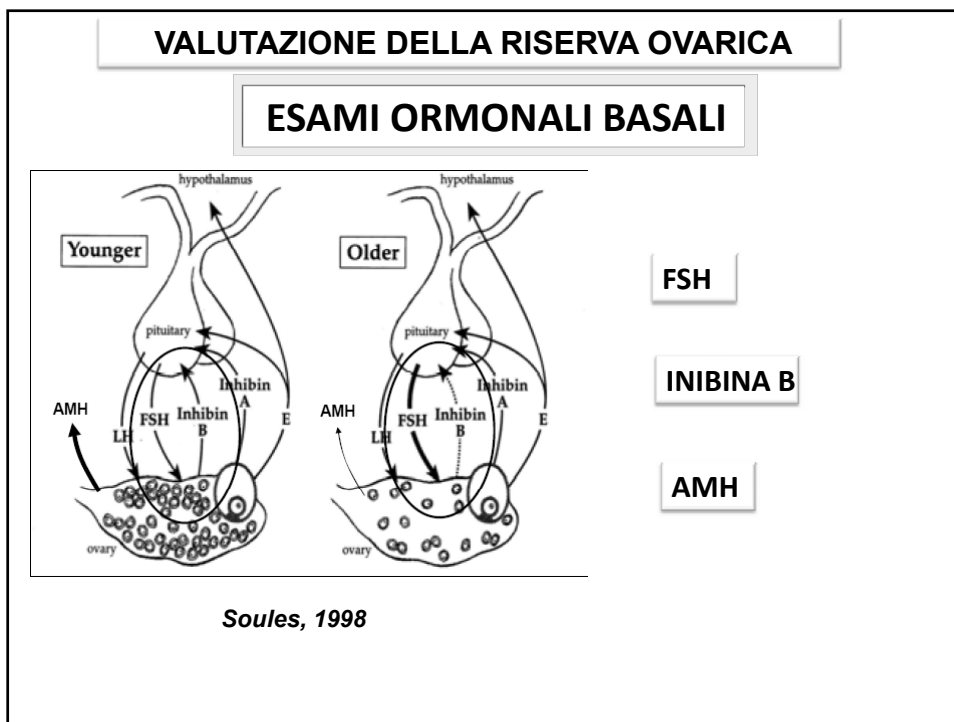
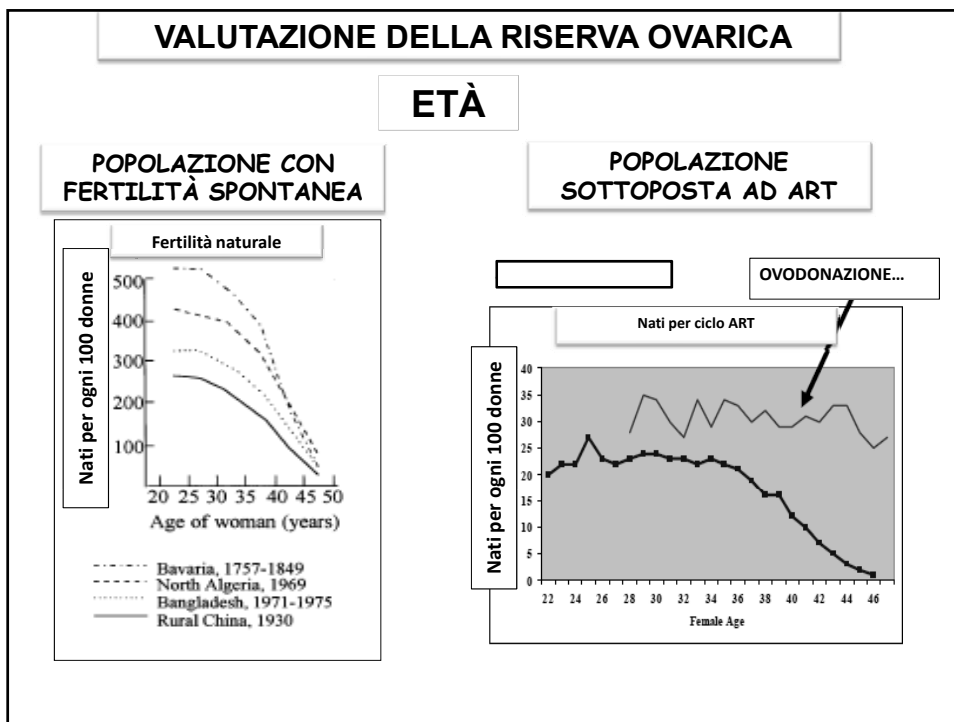
Desiderio personale

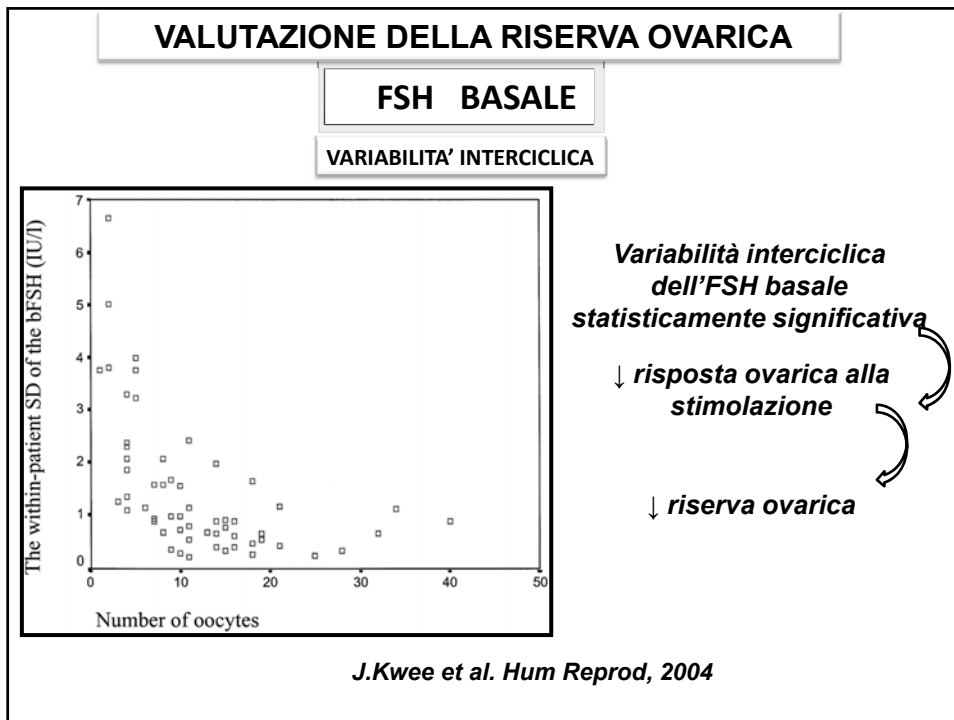
Valutazione della riserva ovarica











VALUTAZIONE DELLA RISERVA OVARICA

FSH BASALE :quale cut-off ?

	FSH ≤10 IU/l	FSH ≥10 ≤15 IU/l	FSH ≥ 15 IU/l
	Group A	Group B	Group C
Basal FSH level (IU/l)	7.0±1.5 (1.65–9.96)	12.0±1.6 (10–14.7)	28.2±18.5 (15–85)
Duration of stimulation (days)	8.0±2.6 (4–25)	8.2±2.0 (6–14)	9.6±3.6 (5–19) ^a
The required gonadotropin doses until oocyte retrieval (ampoules)	24.3±8.0 (8–76)	26.1±6.0 (18–41)	30.6±10.7 (17–59) ^b
Number of retrieved oocytes	8.7±6.1 (0–33)	5.5±6.4 (0–32) ^c	2.2±2.0 (1–8) ^d
Oocyte retrieval rate (%)	99.3	92.3	100
Number of fertilized oocytes	4.6±3.9 (0–20)	4.0±6.2 (0–32)	1.4±2.0 (0–8) ^d
Fertilization rate (%)	90.1	91.7	85.7

FSH ≥ 15 UI/l

RIDUZIONE DELLA RISPOSTA OVARICA IN COH IN MODO STATISTICAMENTE SIGNIFICATIVO

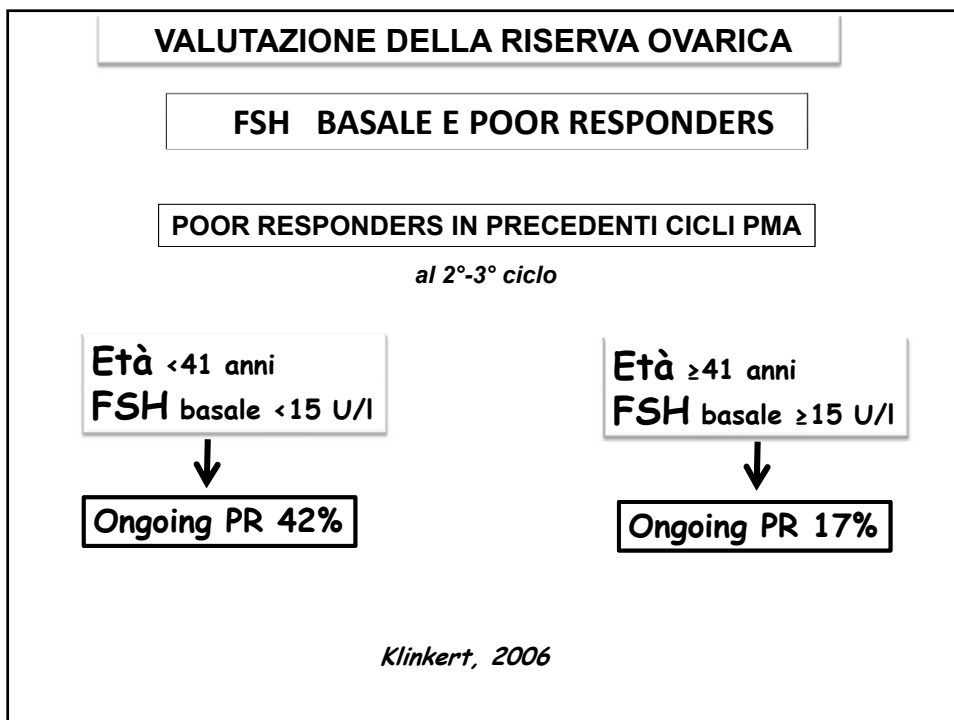
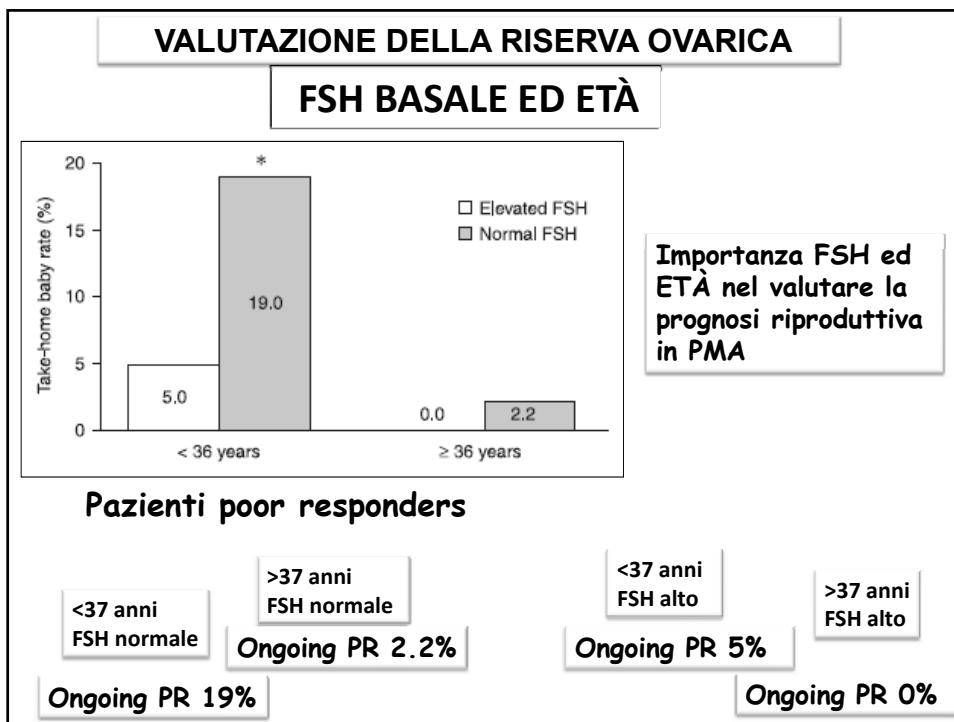
↓ n° ovociti recuperati

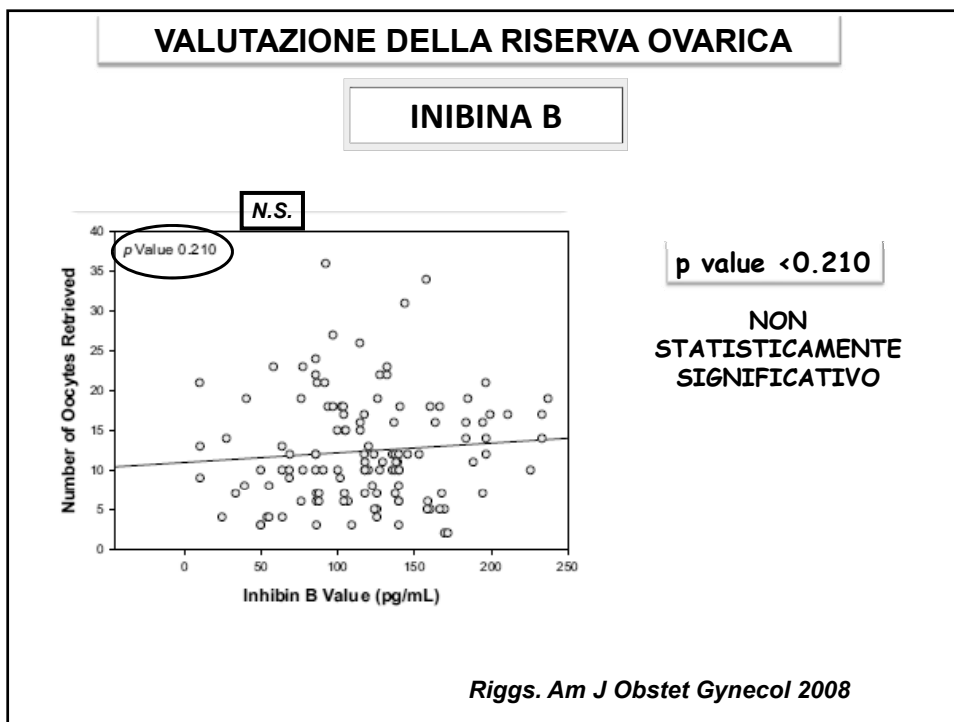
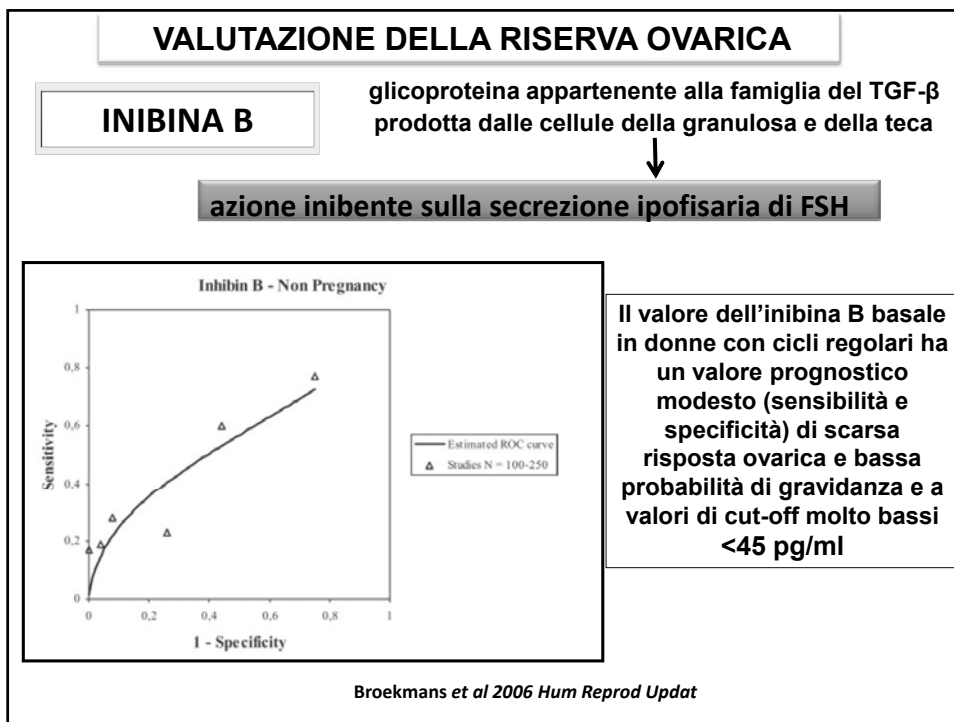
↓ n° ovociti fertilizzati

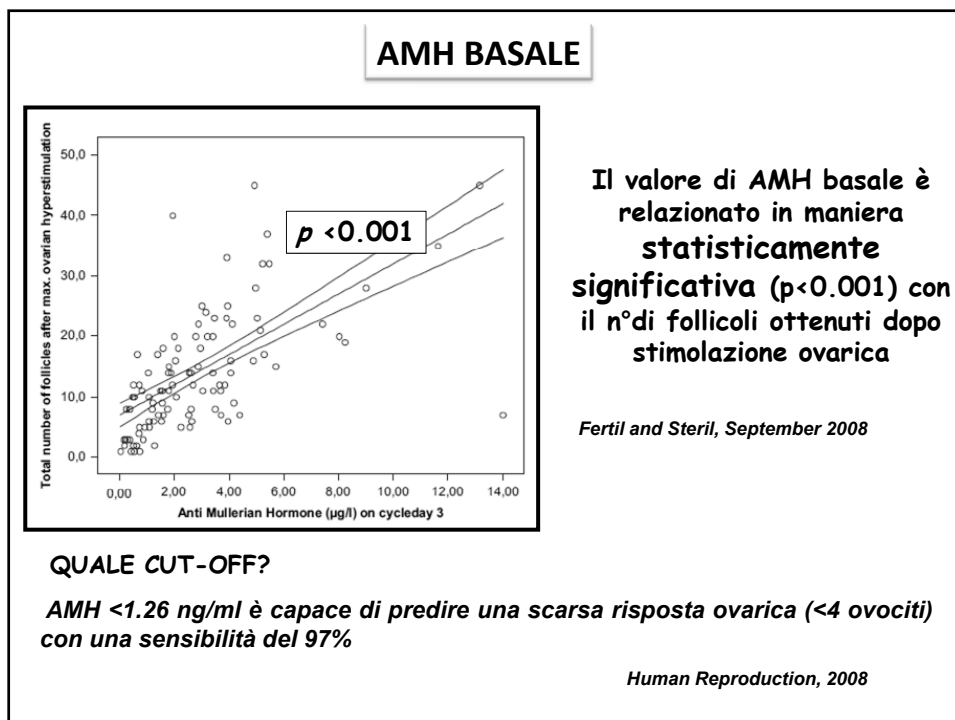
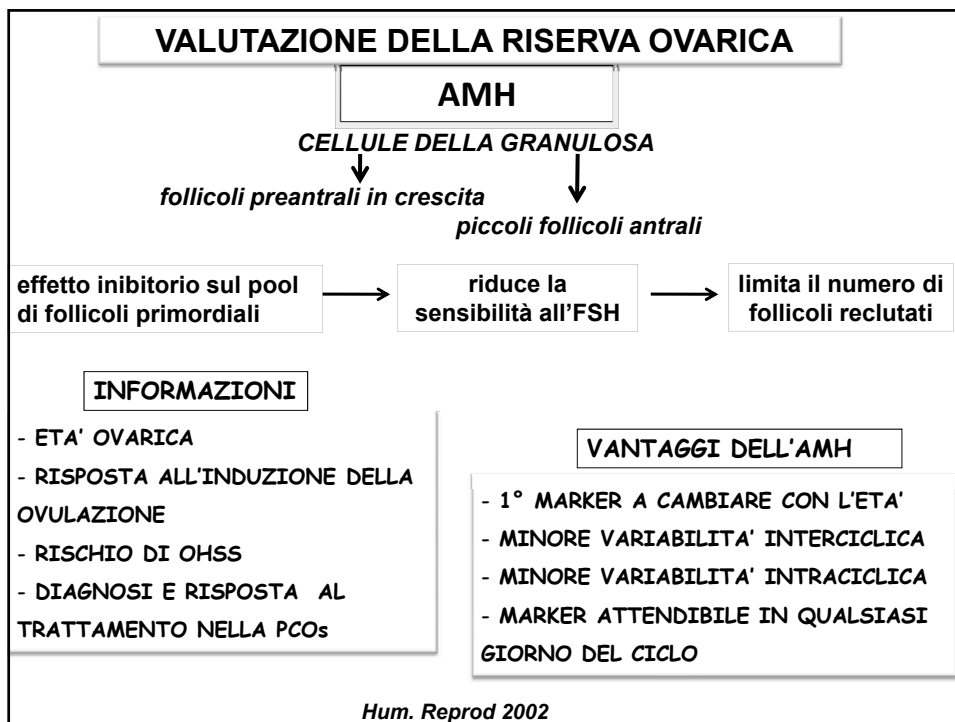
p < 0.001

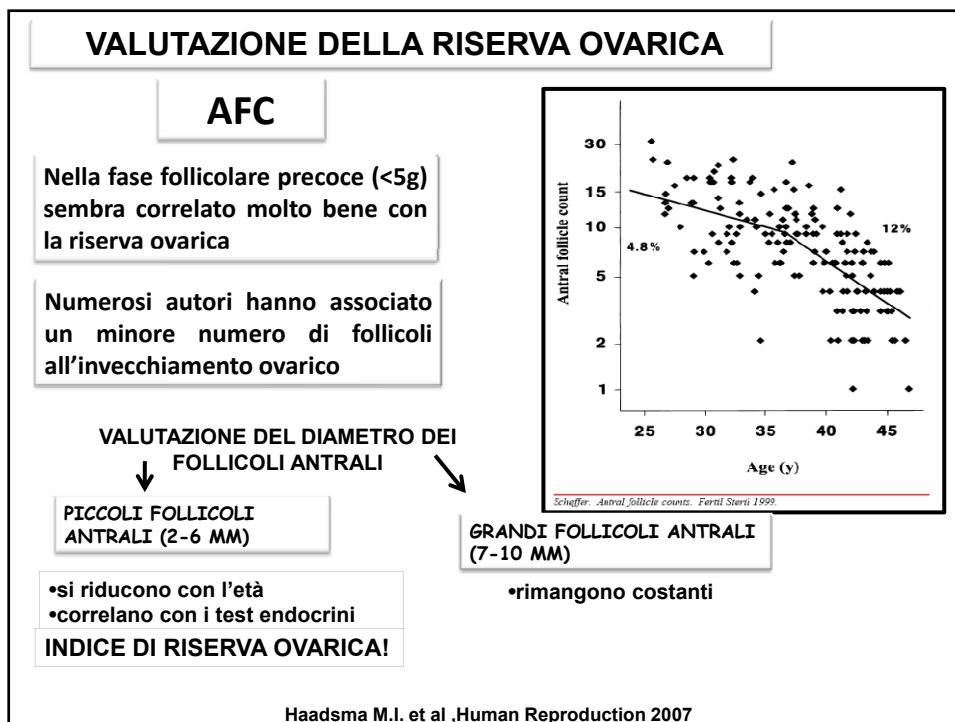
J Assist Reprod Genet (2008) 25:73–77
DOI 10.1007/s10815-007-9195-9

Values are mean±SD
Parentheses are ranges
^a A vs C, p<0.05
^b A vs C, p<0.01
^c A vs B, p<0.05
^d A vs C, p<0.001
^e B vs C, p<0.05





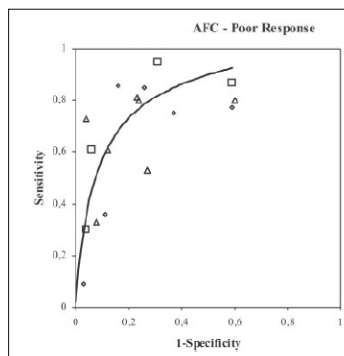




VALUTAZIONE DELLA RISERVA OVARICA

AFC

Author	Cycles (n)	AFC threshold value (n)	Prediction of poor response	
			Sensitivity	Specificity
Chang <i>et al.</i>	149	<3	0.73	0.96
Ng <i>et al.</i>	128	<4	0.33	0.92
		<6	0.80	0.76
		<9	0.80	0.40
Frattonelli <i>et al.</i> (2000)	278	<10	0.87	0.41
Sharara <i>et al.</i>	127	<4	0.53	0.73
Hsieh <i>et al.</i>	372	<3	0.61	0.94
Nahum <i>et al.</i>	272	<6	0.95	0.69
Bancsi <i>et al.</i>	120	<4	0.61	0.88
		<6	0.81	0.77
Frattonelli <i>et al.</i> (2003)	267	<4	0.30	0.96
Jarvelä <i>et al.</i>	45	<4	0.86	0.84
Yong <i>et al.</i>	47	<4	0.09	0.97
		<6	0.36	0.89
Fiçicioğlu <i>et al.</i>	58	<7	0.77	0.41
Erdem <i>et al.</i>	32	logistic model	0.75	0.63
Dumussoğlu <i>et al.</i>	91	<6.5	0.85	0.74



**UN CUT-OFF <5 di
PICCOLI FOLLICOLI
ANTRALI E' CONSIDERATO
UN TEST ATTENDIBILE DI
RISERVA OVARICA**

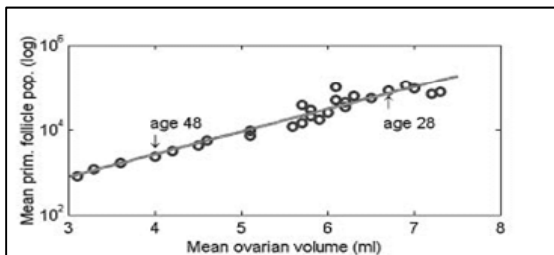
F.J.Broekmans et al. Hum Reprod Update, 2006

VALUTAZIONE DELLA RISERVA OVARICA

VOLUME OVARICO

La misurazione ecografica del volume ovarico è considerata un buon marker predittivo nei trattamenti di infertilità e un precoce e specifico indicatore dell'invecchiamento ovarico

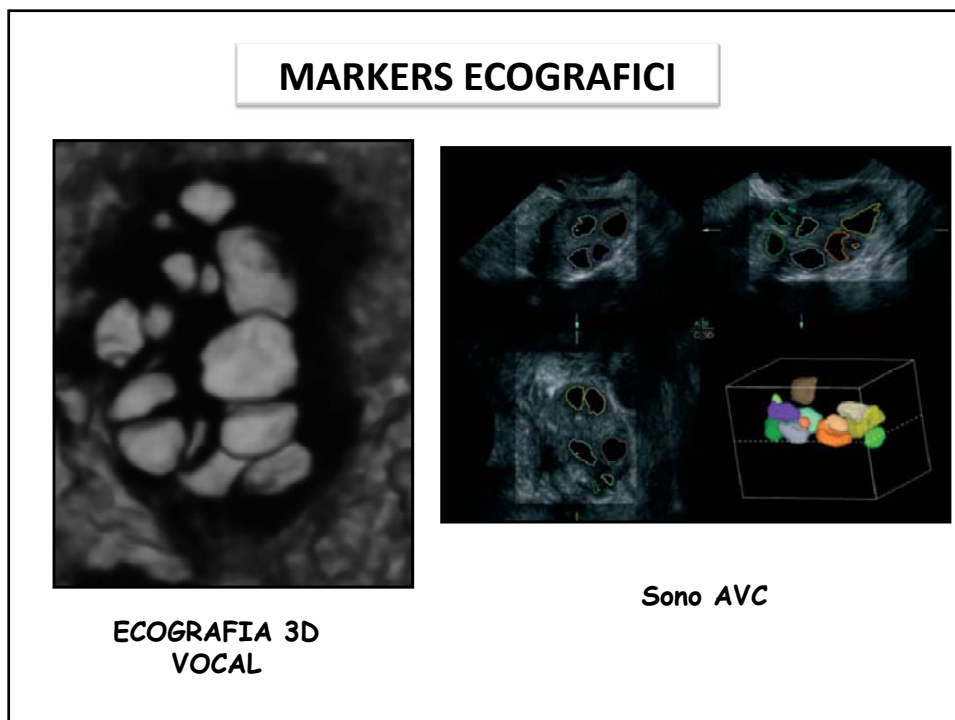
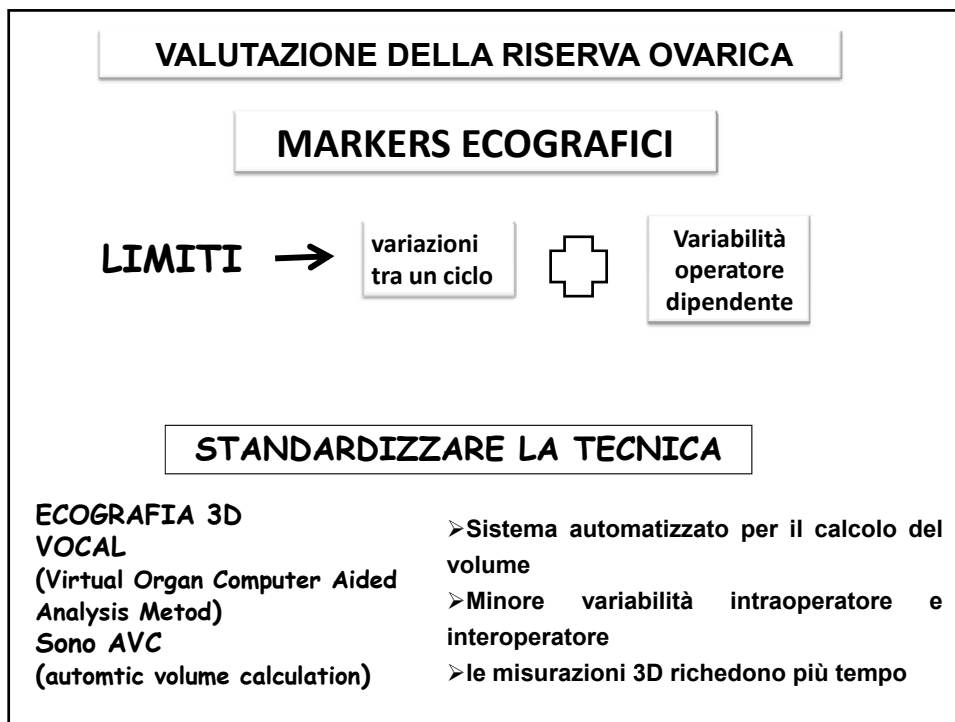
**IL VOLUME OVARICO PUÒ ESSERE UN PARAMETRO
INDIRETTO DEL NUMERO DEL POOL RESIDUO DI
FOLLICOLI ANTRALI**



6,6 ml	< 30 aa
6,1 ml	30-39 aa
4,8 ml	40-49 aa
2,6 ml	50-59 aa
2,1 ml	> 60 aa

Pavlik et al 2000



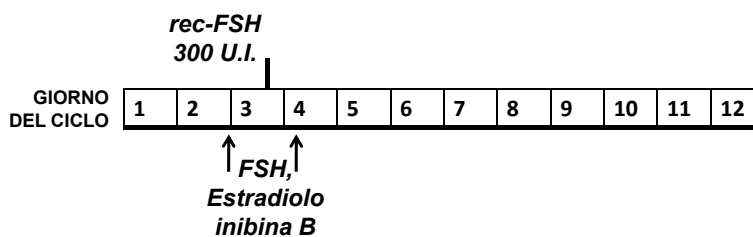


TEST AL CLOMIFENE CITRATO

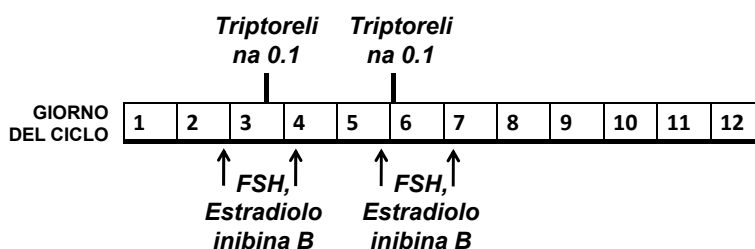
	Normal responders (n = 31)	poor responders (n = 25)	p value
Age (y)	33 ± 5.8	36.9 ± 4.8	<0.01
Day 3 FSH (mIU/mL)	6.2 ± 1.5	10.6 ± 3.6	<0.001
Day 3 E ₂ (pg/mL)	55.8 ± 38.6	65.3 ± 49.7	NS ^a
Day 3 inhibin (pg/mL)	98.6 ± 44.9	49.2 ± 35.2	<0.001
Day 10 FSH (mIU/ mL)	7.0 ± 1.4	13.2 ± 6.3	<0.001
Day 10 E ₂ (pg/mL)	451.7 ± 323.7	352.1 ± 273.0	NS ^a
Day 10 Inhibin (pg/ml)	309.2 ± 186.0	104.2 ± 57.0	<0.001
Mean ovarian volume (cm ³)	4.0 ± 1.5	2.5 ± 1.2	<0.001
Mean follicle count	4.7 ± 2.2	2.3 ± 1.5	<0.001

M Erdem, et al., J Assisted Reprod and Genetics, 2004

EFORT-Exogenous FSH ovarian reserve test



GAST-GnRH Agonist Stimulation Tests



TEST DINAMICI

LIMITI

- NECESSARIO INTERVENTO MEDICO
- LA PAZIENTE DEVE RECARSI PIU' VOLTE IN OSPEDALE
- SCARSA COMPLIANCE DELLE PAZIENTI (devono assumere farmaci a casa)

uso limitato nella pratica clinica!

VALUTAZIONE DELLA RISERVA OVARICA

MARKERS BASALI CONFRONTO

Characteristics of poor vs. normal responders.

Parameter	Poor responders (n = 29)	Normal responders (n = 81)	P
Age at baseline (y)	35.3 ± 3.0	33.5 ± 4.0	.029
CD3			
FSH (IU/L)	12.0 ± 11.5	6.6 ± 1.8	<.001
E ₂ (pmol/L)	124.1 ± 54.1	138.4 ± 156.5	.632
Inhibin B (ng/L)	76.0 ± 47.4	93.1 ± 43.0	.077
AMH (µg/L)	1.48 ± 2.59	3.53 ± 2.46	<.001

I PIÙ ATTENDIBILI MARKERS DI RISERVA OVARICA

FSH

AMH

Kwee. Fertil Steril 2008

VALUTAZIONE DELLA RISERVA OVARICA

MARKERS BASALI E ECOGRAFICI A CONFRONTO

	Continuous data vs. threshold value	Sensitivity	Specificity	Positive likelihood ratio	Predictive ability (ROC analysis)	Ref. no.
FSH ^a	Continuous	0.51-0.63	0.81	2.68	0.77	(15, 21, 22, 28)
	>10 mIU/mL	0.26-0.87	0.60-0.97	0.9-21.8	NA	
	>12 mIU/mL	0.24	1.00	0.24	NA	
CCCT ^b	Days 3/10 \geq 10 mIU/mL	0.69	0.88	5.75	0.81	(15, 21)
	Day 10 >10	0.65	0.87	5.0	NA	
	Day 10 >15	0.35	0.96	8.1	NA	
Inhibin B	Continuous	0.52-0.69	0.63-0.80	1.93-3.45	0.71	(15, 21, 22, 28)
	40 pg/mL	0.87	0.49-0.64	1.7-2.42	NA	
	<45 pg/mL	0.33-0.53	0.79-0.95	1.57-10.6	NA	
	<53.8 pg/mL	0.39	0.94	6.5	NA	
AMH	Continuous	NR	NR	NR	0.92	(15, 21, 26, 28)
	<0.1 ng/mL	0.49-0.76	0.88-0.94	4.08-12.6	NA	
	<0.2 ng/mL	0.54-0.87	0.64-0.90	2.45-5.7	NA	
	0.25 ng/mL	0.91	0.91	10.1	NA	
	<0.3 ng/mL	0.60	0.89	5.6	NA	
Ovarian volume	Continuous	0.81	0.81	4.26	0.82	(21)
	<2.98 cm ³	0.08-0.75	0.81-0.94	1.30-3.95	NA	
	<7 cm ³	0.39-0.55	0.67-0.85	1.67-2.51	NA	
	<8.6 cm ³	0.61	0.73	2.23	NA	
AFC	Continuous	0.75	0.63	2.03	0.78-0.80	(15, 21, 26-28)
	<4 antrals	0.09-0.86	0.84-0.97	3.3-5.4	NA	
	\leq 4 antrals	0.30-0.89	0.39-0.96	1.45	NA	
	<6 antrals	0.36-0.81	0.77-0.89	1.57-7.4	NA	

Sun. New approach to ovarian reserve testing
Fertil Steril 2008.

AMH > AFC, FSH > Inhibin B

VALUTAZIONE COMBINATA DI PIÙ MARKER preferibile a quella di un singolo marker con specifico cut-off

Author	Cycles (n)	Test Model	Prediction of poor response	
			Sensitivity	Specificity
Balasch <i>et al.</i>	120	Age + FSH	0.53	0.81
		Age + inhibin B	0.59	0.67
		Inhibin B + FSH	0.57	0.69
		Age + FSH + inhibin B	0.39	0.89
Fabregues <i>et al.</i>	80	FSH + Inhibin B	0.42	0.86
Ranieri <i>et al.</i>	177	FSH + GAST	0.97	0.55
Creus <i>et al.</i>	120	Age + FSH	0.83	0.77
		Age + inhibin B	0.74	0.50
		FSH + inhibin B	0.77	0.73
Bancsi <i>et al.</i>	120	Age + FSH + inhibin B	0.83	0.77
		FSH + inhibin B	0.58	0.94
		AFC + inhibin B	0.69	0.88
		AFC + FSH	0.72	0.93
Van Rooij <i>et al.</i>	119	AFC + inhibin B + FSH	0.75	0.95
		AMH + inhibin B + FSH	0.69	0.91
Muttukrishna <i>et al.</i>	69	FSH + inhibin B + AMH	0.63	0.83
Erdem <i>et al.</i>	32	CCCT + age	0.81	0.69
		CCCT + age + OVVOL + AFC	0.81	0.75
Durmusoglu <i>et al.</i>	91	Age + AFC	0.52	0.88

*Human
Reproduction
Update, Vol.12,
No.6 pp. 685-718,
2006*

CONCLUSIONI

**Sospetto anamnestico o clinico
di poor responder**

**VALUTAZIONE DELLA
RISERVA OVARICA**

Scelta del protocollo PMA

PROTOCOLLI PROPOSTI IN PMA PER IL TRATTAMENTO DELLE POOR RESPONDERS

Intervention proposed	Number of eligible RCTs	Pregnancy	Secondary outcomes	
			Significant effect detected	No significant effect detected
GnRH antagonist versus long GnRH agonist protocol	1	No statistically significant difference in ongoing pregnancy rates	Significantly shorter duration and less ampoules of gonadotropins required and significantly more COCs retrieved in the GnRH antagonist group	
Combination of clomiphene citrate with rFSH in a flexible GnRH antagonist protocol versus long GnRH agonist protocol	1	No statistically significant difference in pregnancy rates	Significantly less ampoules of gonadotropins required for ovarian stimulation and more COCs retrieved when clomiphene citrate with rFSH in a flexible GnRH antagonist protocol was used	
GnRH antagonist versus short GnRH agonist	3	No statistically significant difference in clinical pregnancy rates	Significantly less COCs retrieved in the GnRH antagonist group	No significant differences in the duration and the number of gonadotropin ampoules required.
Natural cycle IVF versus long GnRH-a	1	No statistically significant difference in clinical pregnancy rates		
Stop versus non-stop long GnRH-a protocol	2	No statistically significant difference in clinical pregnancy rates		No significant differences in the duration, the number of gonadotropin ampoules required and COCs retrieved
rFSH versus uFSH	1	No statistically significant difference in pregnancy rates	Significantly shorter duration and less ampoules of gonadotropins required, as well as significantly more COCs retrieved in the rFSH group	

Kyrou. Poor responders and pregnancy. Fertil Steril 2009.