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CLINICA VALLE GIULIA, Rome

Modified natural cycles: the Italian experience

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Poor ovarian Response ESHRE Campus symposium

Bologna 19-20 March 2010

Introduction

Ovarian superovulation is of paramount importance to obtain a good reproductive outcome

goals of the ovarian stimulation

selection of the correct stimulation protocol

In poor responders the induction of a multifollicular response is a challenge and a frustrating problem

Introduction

It has been estimated that among patients undergoing IVF treatment, the prevalence of poor ovarian response is 9 to 24%

(Keay, 1997)

Introduction

The lack of a uniform definition of poor responders makes it difficult to compare treatment outcomes and develop and assess protocols for prevention and management ***(Surrey 2000; Kailasam 2004; Franco 2006)***

FSH >10, E2 <900, <5 mature oocytes ***(Akman 2001)***

Age >37, FSH >9 ***(De Placido 2006)***

<4 oocytes when >300 IU FSH for >14 d. ***(Malmusi 2005)***

E2 <600, <3 oocytes ***(Marci 2005)***

FSH >10, <3 mature follicles ***(Cheung 2005)***

E2 <850, <4 follicles >15 mm ***(Schmidt 2005)***

Introduction

… after having had failed a previous standard COH

(Schachter 2001)

Woman who fails to produce an adequate number of mature follicles (generally <3 follicles <17mm) as a consequence of which a suboptimal number of oocytes can be retrieved

The Cochrane Library Issue 3 2007

Management of poor responders

- ✓ **High doses of gonadotrophins**
- ✓ **Addition of GH**
- ✓ **Luteal GnRH-a and its cessation at menses**
- ✓ **GnRH-a flare-up**
- ✓ **GnRH antagonists**
- ✓ **Natural cycle**
- ✓ **Novel proposals**

Natural cycle IVF

Advantages

- ✓ Simplicity, lighter treatment
- ✓ No anesthesia (no hospital stay)
- ✓ No multiple pregnancies
- ✓ No OHSS
- ✓ Reduced financial, social and emotional costs
- ✓ Consecutive cycles possible

Disadvantages

- ✓ Premature ovulation (10-40%)
- ✓ No oocyte (5-15%)
- ✓ Difficult scheduling
- ✓ Absence of transfer (50%)
- ✓ One embryo
- ✓ Lower pregnancy rates

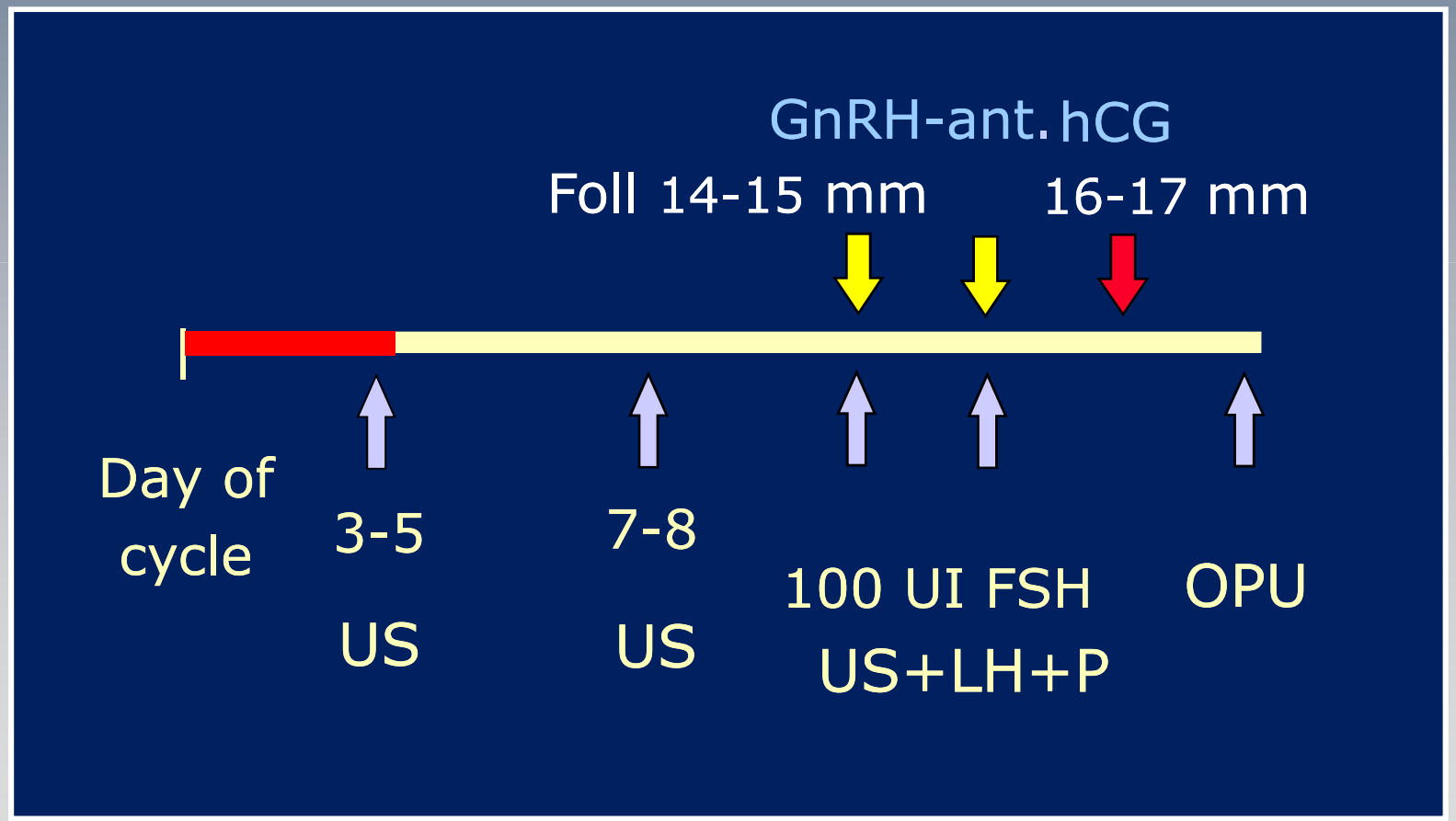
Natural cycle IVF

Premature LH surge and

spontaneous ovulation

30-60% of cycles

Natural cycle IVF with minimal stimulation



Poor responders and stimulation protocols

- ⇧ days of stimulation
- ⇧ amount of daily gonadotropins
- ⇧ amount of total gonadotropins
- ⇧ physical and emotional stress
- ⇩ follicular recruitment
- ⇩ oocytes retrieved

~~Advantages of COH~~

- ~~⇧ follicular recruitment~~
- ~~⇧ oocytes retrieved~~
- ~~⇧ number of embryos~~
- ~~⇧ pregnancy rates~~

Natural cycle in poor responders

Author	Study design	Patients	Cycles	Preg. rates/ET
Lindheim 1997	prospective with historical control	30	35	33,4%
Bassil 1999	prospective with historical control	11	16	18,6%
Feldman 2001	prospective with historical control	22	44	20,1%
Morgia 2004	prospective	59	114	14,9%
Elizur 2005	retrospective		52	14,3%
Schimberni 2009	retrospective	294	500	17,1%

Natural vs stimulated cycles

Morgia, Fertil Steril 2004	Natural cycles	COH mini-flare	P
Cycles	114	101	
Age (mean±SD)	38,9±3,4	39,1±4,1	-
Cycles with ET (%)	41,2	68,3	ns
No. embryos/ET	1,0	1,8±0,4	ns
Preg.rate/cycle	6,1	6,9	ns
Preg.rate/ET	14,9	10,1	ns
Implantation rate	14,9	5,5	0,05

	Modified natural cycles	FSH+GnRH-ant	Long GnRH-a	
Cycles	52	200	288	
No. oocytes	1,4	2,3	2,5	<0,05
Preg.rate/ET	14,3	10,2	10,6	ns
Implantation rate	10,0	6,7	7,4	ns

Elizur, J Assist Reprod Genet 2005

Natural cycles with minimal stimulation

- ✓ **962 consecutive "natural" cycles of any patient's age and high basal FSH serum level**
- ✓ **Follicle ≥14 mm → GnRH-antagonist 0,25 mm sc every 24 hours+75-150 IU gonadotropins → hCG administration**

Overall results

Started cycles	962
Patients	533
Cycle/patient (mean±SD)	1,8
Age (mean±SD)	39,0±3,9
Basal FSH (mIU/mL) (mean±SD)	14,6±5,6

Ubaldi et al., RBM Online 2007

Natural cycles with minimal stimulation

Overall results

Cancelled cycles prior to oocyte retrieval (%)	129/962 (13,4)
Cycles with no egg retrieved (%)	147/833 (17,6)
Cycles with egg retrieved (%)	686/962 (71,3)
2PN Fertilization rate (%)	557/679 (82,0)
N. of ET/started cycles (%)	524/962 (54,4)

Ubaldi et al., RBM Online 2007

Natural cycles with minimal stimulation

Overall results

N. of ET/started cycles (%)	524/962 (54,4)
Pregnancy rate/ cycle (%)	95/962 (9,9)
Pregnancy rate/ patient (%)	95/533 (17,8)
Pregnancy rate/ OPU (%)	95/833 (11,4)
Pregnacy rate/ ET (%)	95/524 (18,1)
Implantation rate (%)	97/547 (17,7)

Ubaldi et al., RBM Online 2007

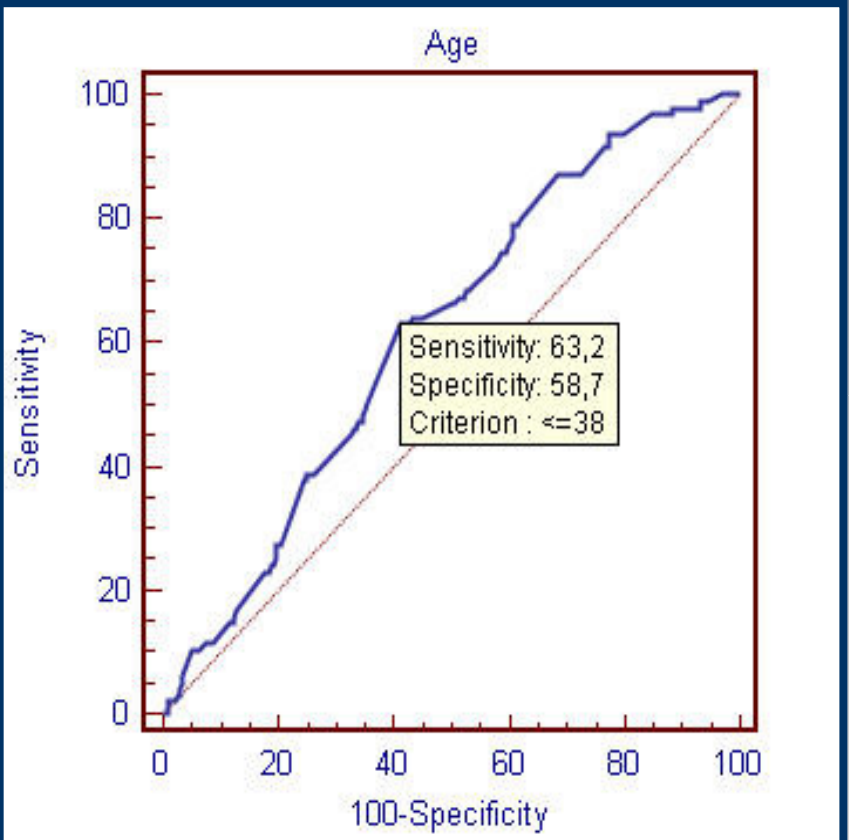
ROC curve analysis (age and pregnancy, cycles with ET)

Variable	Age
Classification variable	Preg

Positive group	
Preg	= 1
Sample size	95
Negative group	
Preg	= 0
Sample size	421

Disease prevalence (%)	unknown

Area under the ROC curve	0,617
Standard error	0,030
95% Confidence interval	0,573 to 0,659
Significance level P (Area=0.5)	0,0001



<=37,8333	49,47	39,1 - 59,9	64,85	60,1 - 69,4	1,41	0,78
<=37,9167	50,53	40,1 - 60,9	64,37	59,6 - 68,9	1,42	0,77
<=38 *	63,16	52,6 - 72,8	58,67	53,8 - 63,4	1,53	0,63
<=38,5	63,16	52,6 - 72,8	57,24	52,4 - 62,0	1,48	0,64
<=38,5833	64,21	53,7 - 73,8	56,53	51,6 - 61,3	1,48	0,63

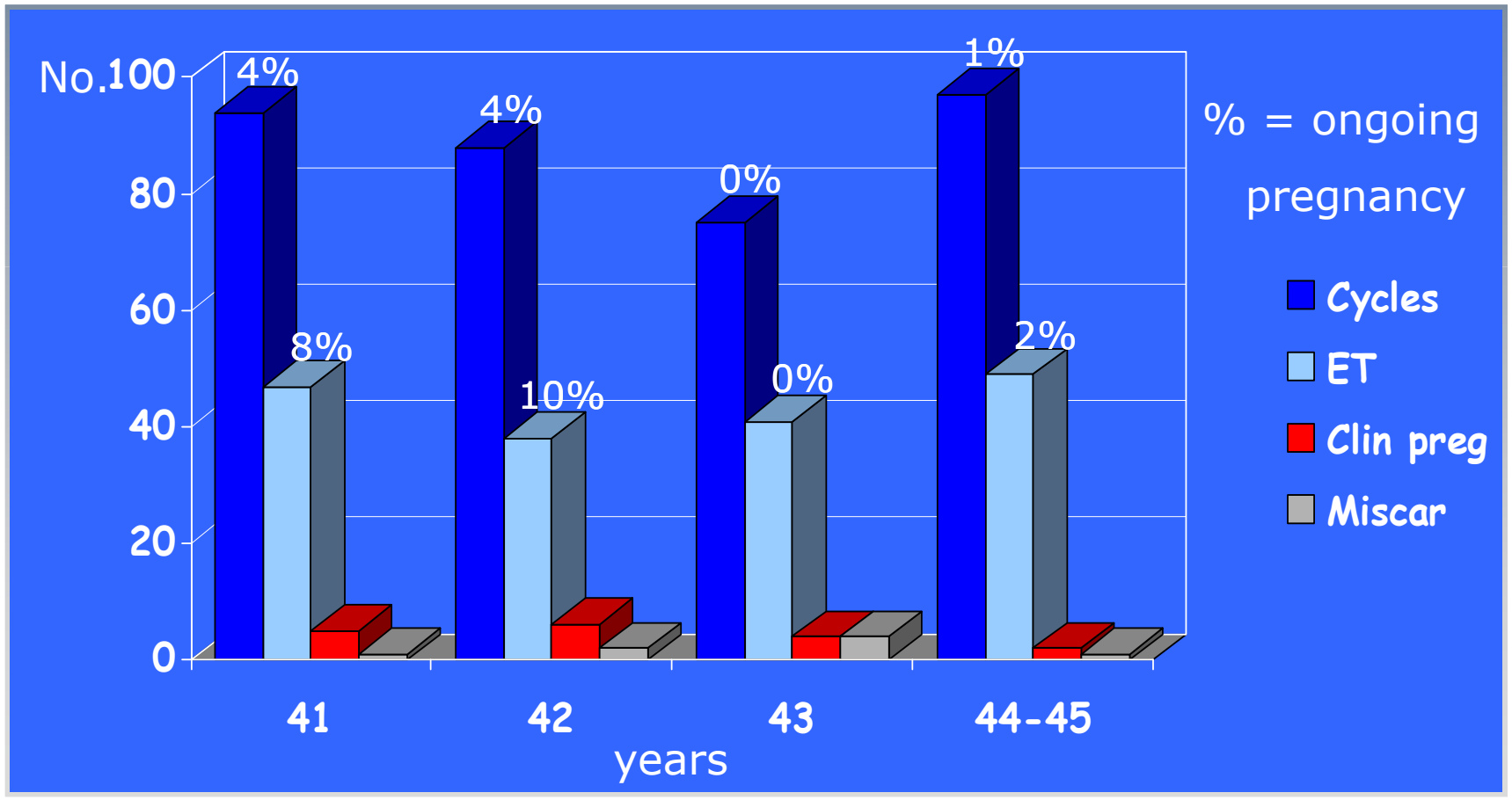
Natural cycles with minimal stimulation

Overall clinical results

	≤38 y	>38 y	P
N. of cycles	452	510	
N. of oocyte retrievals	380	453	
N. of embryo transfers	258/452 (57,0)	266/510 (52,1)	0,1
N. of clinical pregnancies	61	34	
Preg. rate/initiated cycle (%)	61/452 (13,5)	34/510 (6,6)	<0,001
Pregnacy rate/ET (%)	61/258 (23,6)	34/266 (12,8)	0,002
Implantation rate (%)	63/272 (23,1)	34/275 (12,4)	<0,001
Abortion rate	14/61 (22,9)	14/34 (41,1)	0,1

Ubaldi et al., RBM Online 2007

Clinical outcome in older patients



Multiple regression analysis (pregnancy all)

Age and FSH

Dependent Y	Preg
Method	Enter

Sample size	524
Coefficient of determination R^2	0,0337
R^2-adjusted	0,0300
Multiple correlation coefficient	0,1835
Residual standard deviation	0,3798

Regression Equation

Independent variables	Coefficient	Std.Error	t	P
(Constant)	0,76562			
Age	-0,01164	0,00443	-2,630	0,0088
FSH	-0,00998	0,00389	-2,568	0,0105

Analysis of Variance

Source	DF	Sum of Squares	Mean Square
Regression	2	2,6182	1,3091
Residual	521	75,1585	0,1443

F-Ratio	9,0748
Significance level	P<0,001

Zero order correlation coefficients

Variable	r
Age	-0,146
FSH	-0,144

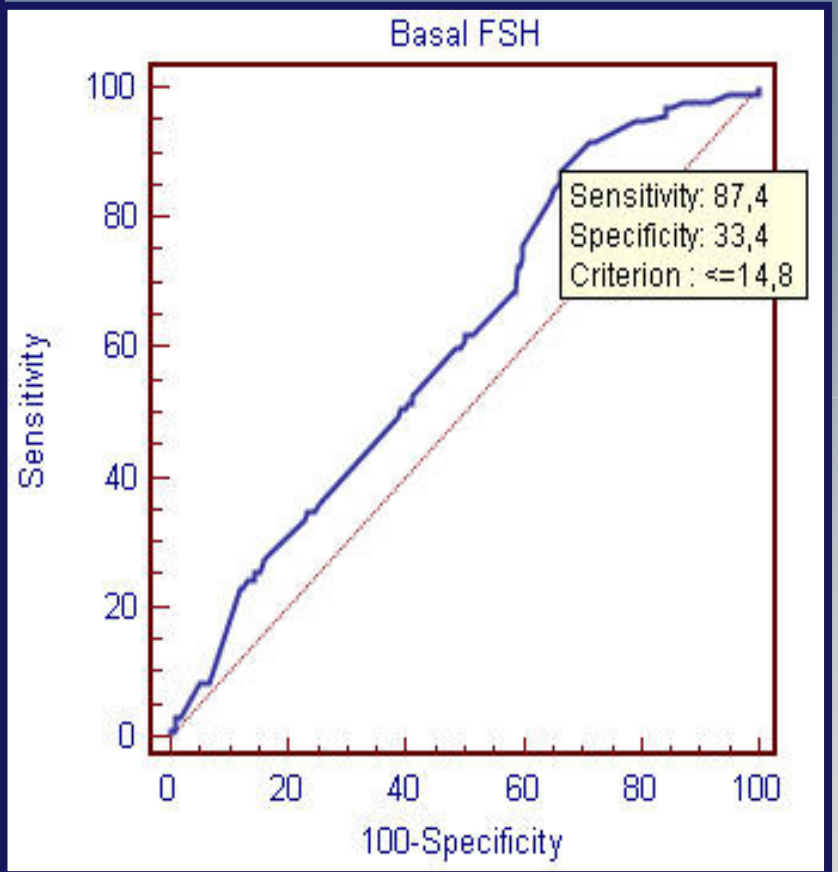
ROC curve analysis (FSH and pregnancy, cycles with ET)

Variable	Basal_FSH Basal FSH
Classification variable	Preg

Positive group	
Preg	= 1
Sample size	95
Negative group	
Preg	= 0
Sample size	419

Disease prevalence (%)	unknown

Area under the ROC curve	0,608
Standard error	0,030
95% Confidence interval	0,565 to 0,651
Significance level P (Area=0.5)	0,0004



<=14,3	85,26	76,5 - 91,7	33,65	29,1 - 38,4	1,29	0,44
<=14,6	86,32	77,7 - 92,5	33,65	29,1 - 38,4	1,30	0,41
<=14,8 *	87,37	79,0 - 93,3	33,41	28,9 - 38,2	1,31	0,38
<=15	91,58	84,1 - 96,3	28,64	24,4 - 33,2	1,28	0,29
<=15,9	91,58	84,1 - 96,3	27,68	23,5 - 32,2	1,27	0,30

Natural cycles: age and FSH

FSH IU/L	<12	12-15	16-19	≥20
≤39 y	34/132 (25,7)	21/83 (25,3)	4/31 (12,9)	1/17 (5,8)
>39 y	16/93 (17,2)	16/89 (17,9)	2/48 (4,1)	1/29 (3,4)
All ages	50/225 (22,4)	37/172 (21,5)	6/79 (7,5)	2/46 (4,3)

FSH IU/L	<15	16-19	≥20	
≤39 y	55/215 (25,5)[a]	4/31 (12,9)[b]	1/17 (5,8)[b]	a – b: P=0,1
>39 y	32/182 (17,5)[c]	2/48 (4,1)[d]	1/29 (3,4)[d]	c – d: P=0,03
All ages	87/397 (21,9)[e]	6/79 (7,5)[f]	2/46 (4,3)[f]	e – f: P<0,01

Ubaldi et al., RBM Online 2007

Age and FSH

FERTILITY AND STERILITY®
VOL. 81, NO. 6, JUNE 2004

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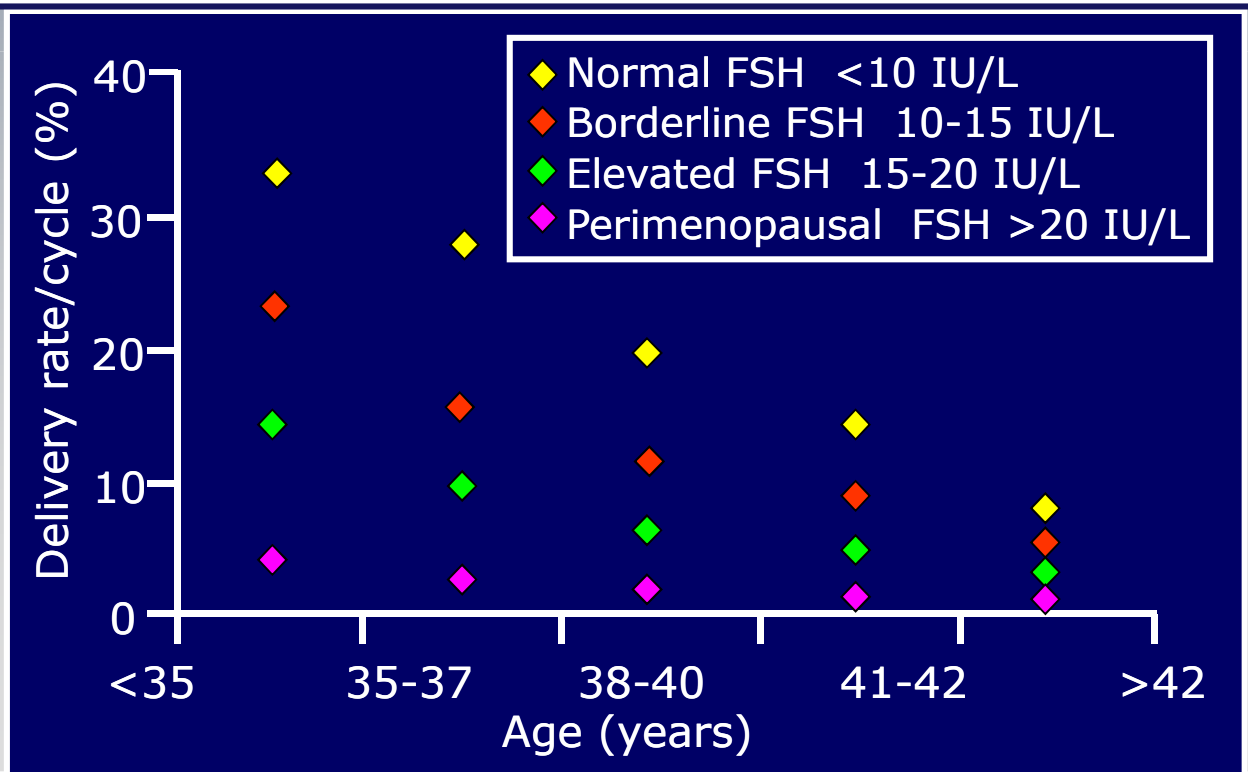
Modest follicle-stimulating hormone elevations in younger women: warn but don't disqualify

James P. Toner, M.D., Ph.D.



FSH and clinical results

Results: natural cycles with minimal stimulation

Cycles	78
Patients	32
Age (mean±sd)	39,4±1,7
Basal FSH (mean±sd)	21,9±1,9
GnRH antagonist (ampoules)	2,7±1,6
Embryo transfers (%)	19/78 (24,6)
Pregnancy rate/ET	0/19

Kolibianakis et al., Hum Reprod 2004

When FSH exceeded 20 mIU/mL there is a clear fall in ongoing pregnancy rate

van Rooij et al., Fertil Steril 2004

Correlation: embryo quality, age and FSH

Variable Y	Type_A_embryo
Variable X	Preg

Sample size	524
Correlation coefficient r	0,1711
Significance level	P=0,0001
95% Confidence interval for r	0,0867 to 0,2530

Variable Y	Type_A_embryo
Variable X	Age

Sample size	524
Correlation coefficient r	-0,0826
Significance level	P=0,0587
95% Confidence interval for r	-0,1671 to 0,0030

Variable Y	Type_A_embryo
Variable X	FSH

Sample size	524
Correlation coefficient r	-0,0724
Significance level	P=0,0977
95% Confidence interval for r	-0,1571 to 0,0133

Prospective study with historical control

Aim

To compare the results of conventionally stimulated cycles vs natural IVF cycles with minimal stimul. in poor responders

Materials and Methods

From Jan. 2004 to Dec. 2005, 106 poor responder patients whose treatment was cancelled for no ovarian response or failed to conceive or deliver during a previous ICSI attempt, underwent 106 natural ICSI cycles with minimal stimulation

Ubaldi et al Hum Reprod suppl 1 2007

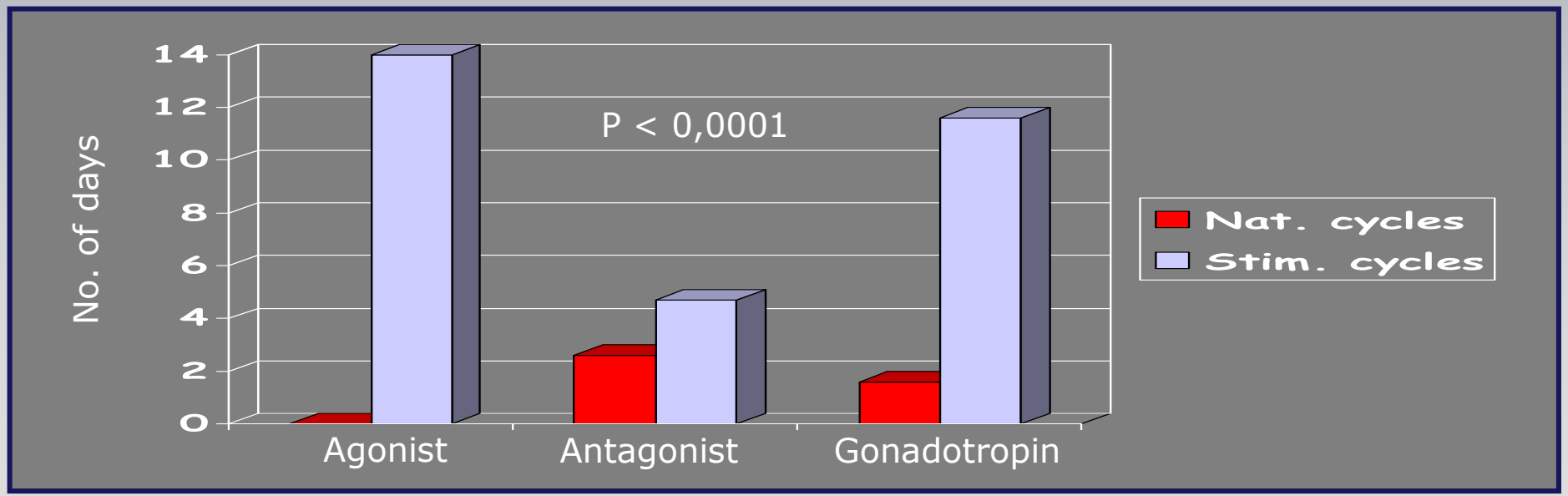
Prospective study with historical control

	Stimulated cycles	"Natural cycles"	
Started cycles	**106**	**106**	
Age (mean+SD)	**39,4±3,5**	**39,7±3,3**	**ns**
Basal FSH (mIU/mL)	**14,3±3,9**	**14,7±4,0**	**ns**
Stimulation protocols			
Minimal stimulation	**0**	**106**	
Flare-up protocol	**34**	**0**	
Long protocol	**15**	**0**	
FSH+Antag	**57**	**0**	

Ubaldi et al Hum Reprod suppl 1 2007

Prospective study with historical control

	Stimulated cycles	"Natural cycles"	P
IU of FSH used (mean±SD)	3874,86±1193,90	188,64±128,32	<0,0001
Days of agonist (mean±SD)	14,5±7,1	0	
Days of antagonist (mean±SD)	4,7±1,2	2,6±0,6	<0,0001
Days of gonadotropin (mean±SD)	11,6±2,4	1,6±0,6	<0,0001



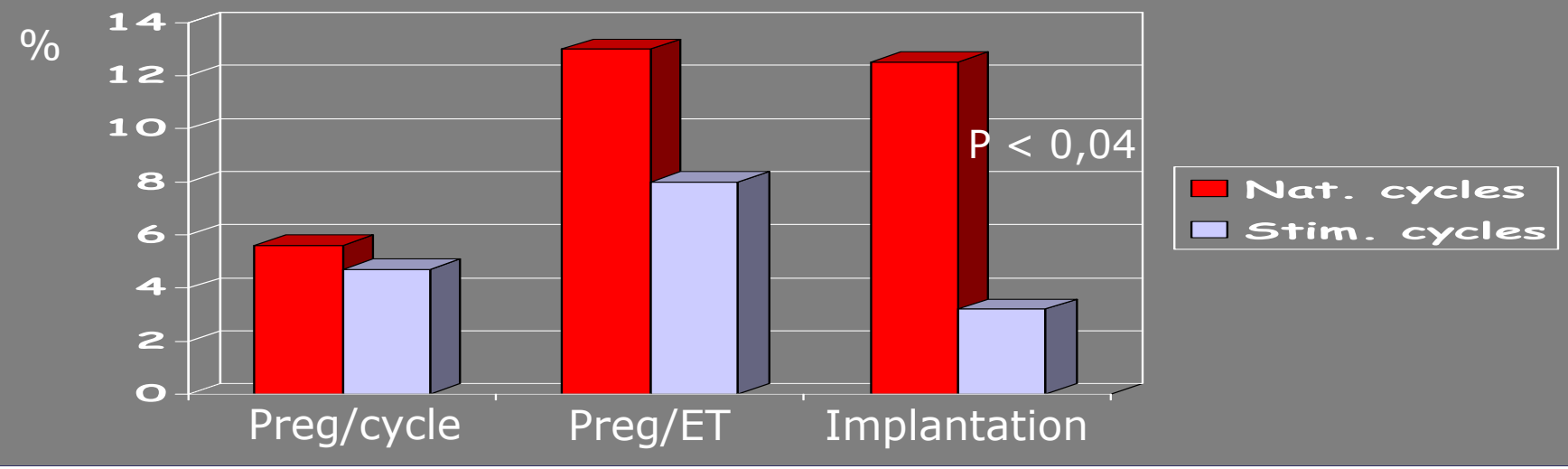
Prospective study with historical control

	Stimulated cycles	"Natural cycles"	P
No. follicles >15mm (mean±SD)	2,5±1,0	1,1±0,3	<0,0001
No. of cancelled cycles (%)	11/106 (10,3)	13/106 (12,6)	0,8
No. of OPU/started cycles (%)	95/106 (89,6)	93/106 (87,7)	0,8
Cycles with no egg retrieved (%)	9 (9,5)	25 (26,8)	0,03
Oocytes retrieved (mean±SD)	203 (2,1±1,0)	70 (0,7±0,5)	<0,0001
MII oocytes (%)	177/202 (87,6)	66/70 (94,2)	0,1
2PN fertilization (%)	136/177 (76,8)	50/66 (75,7)	0,9
Type A embryos (%)	53/136 (38,9)	25/50 (50%)	0,2

Ubaldi et al Hum Reprod suppl 1 2007

Prospective study with historical control

	Stimulated cycles	"Natural cycles"	P
Embryo transfer rate (%)	62/106 (58,5)	46/106 (43,3)	0,03
No. embryos transf. (mean±SD)	125 (1,3±1,1)	48 (0,5±0,5)	<0,0001
Clinical pregnancy rate/cycle (%)	5/106 (4,7)	6/106 (5,6)	1
Clinical pregnancy rate/ET (%)	5/62 (8)	6/46 (13)	0,5
Implantation rate (%)	4/125 (3,2)	6/48 (12,5)	0,04
No. of ectopic pregnancies	1	0	
No. of miscarriages	4	1	



Natural cycles with minimal stimulation

	"Natural cycles"	GnRH-a+FSH
Total costs/cycle (Euro)	1.550	6.050
FSH	120	4.300
Analogs	130	50
Hormonal dosages	50	100
Clinical and lab costs	1.250	1.600

Costs in our institution adjusted for reductions from incomplete cycles resulting from cancellations or failure at various stage prior to ET

Total costs/pregnancy (Euro)	12.300	72.050

Ubaldi et al, Hum Reprod, Supp 1, 2004

Conclusions

It is a valid alternative in poor responders: ⇨ there is less monitoring, less discomfort from OPU (no even local anesthesia) and quicker recovery period after OPU allowing patients to undergo repeated cycles

It has higher failure rate at each step in the process than stimulated cycles although the use of GnRH-ant. A very good councelling is mandatory although it is an easy and cost effective approach

Age is the best predictor of success. When FSH is >20 IU/L the success rate is extremely poor

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