# Individualized versus standard stimulation

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### Predictors of ovarian response

- Ovarian response:
  - Condition the incidence of cancellation
  - Play an important role in pregnancy rates
- The use of ovarian response predictors could help us to individualize treatment protocols
- Predictors can
  - Avoid poor response and OHSS,
  - Avoid cancellation
  - Individualize treatment
  - Choose the starting dose of gonadotrophins

# Predictors for ovarian response in ART fall into 3 main categories

1. Clinical:

Age, Cause of infertility,BMI

(eg Templeton & Morris, 1998; Hohmann et al 2001, Salha et al 2001)

2. Ultrasound:

.

 Number of antral follicles, Doppler score (resistance), Ovarian volume

(eg Lass et al 1997; Fratterelli et al 2000; Popovic Todorovic et al 2003; Hansen et al 2003; Scheffer et al 1999; 2003; Van Rooij 2002; Bancsi 2003, 2004, Hendriks 2005)

3. Hormone levels

 Basal FSH, I nhibin B, oestradiol, AMH
 (eg Toner et al 1991; Scott 1989,1996; Fratterelli et al 2000 Abdallah & Thum 2004; Eldar-Geva 2002; Fanchin 2003; Bancsi 2002, 2003, Visser 2005, Hendriks 2005)

#### FERTILITY AND STERILITY\* FOL. 77, NO. 2. FERELART 2007 Daysigt ODICAMERA Solds to deposit the back to Publical by David Samo In. Problem to David Samo In.

doi:10.1093/hummedides/034

Predictors of poor ovarian response in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve

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#### TABLE 3 Performances of several logistic models for the prediction of poor response at a cut-off point of 0.50 for the probability of oor response. edictive model Sen PPV NPV ROC AUC Co ect predic Inhibin B FSH Aurnal (oblicle count FSH + inhibin B Aurnal (oblicle count + inhibin B Aurnal (oblicle count + FSH Aurnal (oblicle count + FSH Aurnal (oblicle count + FSH + inhibin B Nove PPV = positive predictive value, NPV 92 (77%) 94 (78%) 96 (80%) 100 (83%) 99 (83%) 104 (87%) 107 (89%) 0.42 0.44 0.61 0.58 0.69 0.72 0.75 0.92 0.93 0.88 0.94 0.88 0.93 0.95 0.68 0.73 0.69 0.81 0.71 0.81 0.79 0.80 0.84 0.84 0.87 0.89 0.77 0.84 0.87 0.89 0.90 0.90 0.92 negative p e value; ROC AUC unde er oper

Human Reproduction Update, Vol.12, No.6 pp. 685–718, 2006 Advance Access publication August 4, 2006

A systematic review of tests predicting ovarian reserve and IVF outcome

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#### Scientific papers analysed in the review

**ESH** Scott *et al.*, 1989; Padilla *et al.*, 1990; Toner *et al.*, 1991; Khalifa *et al.*, 1992;Chan *et al.*, 1993; Ebrahim *et al.*, 1993; Fanchin *et al.*, 1994;Huyser *et al.*, 1995; Licciardi *et al.*, 1995; Smotrich *et al.*, 1995;Balasch *et al.*, 1996; Csemiczky *et al.*, 1996; Martin *et al.*, 1996;Pruksananonda *et al.*, 1996; Gurgan *et al.*, 1997; Chang *et al.*, 1998a; Evers *et al.*, 1998; Ranieri *et al.*, 1995; Shaff *et al.*, 1996;Balssil *et al.*, 1999; Hall *et al.*, 1999;Ba: *et al.*, 2000; Chea *et al.*, 2000; Creus *et al.*, 2000; Fabregues *et al.*, 2000; Jinno*et al.*, 2000; Penarrubia *et al.*, 2000; Mikkelsen *et al.*, 2000; 2001; Nahumet *al.*, 2001; van der Stege and van der Linden, 2001; Esposito *et al.*, 2002; Chuang *et al.*, 2003; Fiçicioglu *et al.*, 2003; Kwee *et al.*, 2003; Yanushpolsky *et al.*, 2003; Akande *et al.*, 2004; Ardum *et al.*, 2004. 2004, Er don, et al., AMH: van Rooij *et al.*,2002; Muttukrishna *et al.*, 2004

van Rooij *et al.*,2002; Muttukrishna *et al.*, 2004 <u>Inhibine B:</u> Balasch *et al.*, 1996; Seifer *et al.*, 1997;Hall *et al.*, 1999; Creus *et al.*, 2000; Fabregues *et al.*, 2000;Penarrubia *et al.*, 2000; Bancsi *et al.*, 2002a; Fiçicioglu *et al.*,2003; Erdem *et al.*, 2004

Estradioi: Licciardi *et al.*, 1995; Smotrich *et al.*,1995; Evers *et al.*, 1998; Vazquez *et al.*, 1998; Hall *et al.*, 1999;Frattarelli *et al.*, 2000; Penarrubi *et al.*, 2000; Phophong *et al.*,2000; Mikkelsen *et al.*, 2001; Ranieri *et al.*, 2001; Bancsi *et al.*,2002a.

2001: Ranieri *et al.*, 2001; Bancsi *et al.*,2002a. Antral Follice Count: Chang *et al.*,1998b; Frattarelli *et al.*, 2000; Ng *et al.*, 2000; Sharara andMcClamrock, 2000; Hsieh *et al.*, 2001; Nahum *et al.*, 2001;Bancsi *et al.*, 2002; Erdem *et al.*, 2002; Fisch and Sher. 2002; Fisch 2003; Frattarelli *et al.*, 2003; Jarvela *et al.*, 2003; Kupesic *et al.*, 2003; Yong *et al.*, 2003; Durmusoglu *et al.*, 2004. <u>Ovarian volume</u>: Syrop *et al.*, 1995; Lass *et al.*, 1997b;Frattarelli *et al.*, 2000; Schild *et al.*, 2001; Bancsi *et al.*, 2002a;Jarvela *et al.*, 2003; Kupesic *et al.*, 2003; Erdem *et al.*, 2004.









# **Ovarian response**

- Ovarian response depends on:
  - The FSH-sensitive follicle cohort
  - The type of stimulation regimen used
     Agonist
    - Antagonist
    - •No analogs
  - The dose of gonadotrophin

#### Choosing the GnRH analogs

- The GnRH analogs is often chosen according to habits or to global charateristics of patients (poor responders, PCOS, normo-responders).
- No reliable study is available on choosing the analogs on accepted individual predictors
- The different regimens:
  - GnRH-a long depot, GnRH-a long daily (follicular or luteal start), short, micro-flare
  - GnRH-anta single or multiple dose

have not even been compared in large prospective randomized studies

# GnRH analogs exemple of remaining questions

- How to choose between
  - Follicular or luteal start in GnRH-a long protocol used in normo responders?
  - GnRH-a depot versus GnRH-a daily started in follicular phase in normoresponders
  - GnRH-a daily luteal start or flare short protocol in poor responders?
  - GnRH-a flare or micro-flare in poor responders
  - GnRH-anta or short protocols in poor responders
  - GnRH-anta or long protocol in PCOS
  - Double suppression or long protocol in PCOS
  - Etc...





saay	GoRH antagorist n/N	GnPH agorist n/N	Odds Ratio (Fired) 95% Cl	(%)	Colds Ratio (Fired) 95% Cl
Albano 2000	33/198	1995		81	080[043.150]
Badrawy 2005	1150	13/50		3.9	080[032.202]
Bahoed 2005	32/73	3475	-	7.6	085[044,162]
Barrot 2005	13/40	12140		4.4	0.65 [ 0.26, 1.62 ]
Check 2004	5.00	\$/90		1.6	100[026,389]
Cheung 2005	3/33	3/93		1.0	100[019.536]
Euro Midd East 2001	70/236	377119	-	132	033[058,151]
Euro Orgalutran 2000	94466	61/244	-	249	072[050.104]
Hohmann 2003	16/97	845		35	091 [036, 232]
Kim 2004	7/21	7/20	_	1.8	053[026.338]
Marci 2005	430	0/90		0.2	1036 [ 0.53, 20145 ]
North American 2001	64/208	36/105	-	12.9	080[048,131]
Olvernes 2000	20/126	843		3.8	083[033,204]
Rombauts 2006	41/234	26/117	-	109	074[043,129]
Ziliopositos 2005	7/36	7/29		2.4	076[023.248]
Total (15% Cb) Total events: 417 (Gn/94 anta Test for heterogeneity chi sgo Test for overall effect 2=224	1890 gonist), 203 (GrF04 agonist) are=4.20 dl=14 p=0.99 P = p=0.02	1075 ) -00%	•	106.0	082[048.097]



# Choosing the starting dose

- The starting dose of gonadotrophins in COH for IVF is often chosen based on empirical feelings
- There is a need to better predict the patient's response to FSH stimulation to:
  - ➤ Avoid <u>cancellation</u> due to poor response
  - > Avoid OHSS related to high response
  - Obtain an adequate ovarian response to obtain the highest possible quality of embryo (DET, SET)

			Table IV. Significant predictors of number of retrieved oocytes in backward stepwise regression analysis			
			Variable	Regression coefficient	Standard error	P-value
		(	Total number of antral follicles Total Doppler score Smoking status Serum testosterone	0.249 295 840 1.457	0.044 0.396 0.748 0.769	< 0.001 0.001 0.015 0.060
Table I. rFSH dosage normogram			Model accounts for 38% variability	ty of the numb	er of retrieved oocy	vtes.
Total number of follicles 10mm day 2-5	FSH score IU/day	rFSH starting dose				
<15	90					
15-25	60					
>25 Total overian volume dev 2-5	50	Score				
<9 ml	90	ocure .				
9-13 ml	60					
>13 ml	50					
Total Doppler score day 2-5		Score				
2-3	30					
4	10					
6						
Age (years)		Score				
>35	20					
>30-<35	10					
<30	0					
Smoking habits; cigarettes/day		Score				
>10	20					
<10 Non-smolar	10					
Total ESH come (spec of control)	0					
same as dose IU/day						
			Popovic-Todor	ovic et a	1 2003 a,b	



# The CONSORT study

# Methodology

 Analysis of a large (>1300) 'homogeneous' ART patient database
 - < 35 years age</li>

- Rec-hFSH stimulation
- Select ovarian response <u>variables</u> which could define an optimal ovarian response
- I dentify <u>predictive factors</u> of ovarian response
- Produce a model based upon the predictive factors that will improve the identification of the appropriate FSH starting dose
- Expert panel: Andrea Borini, I taly, Francois Olivennes, France, Geoffrey Trew, UK, Matts Wikland, Sweden, Fernando Zegers, Chile

Overview of patient database analysed

Overview of	of	patient	database	anal	vsed
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Openation         Openation of the second secon	Study	Vear	Study Darian	# of FSH Patients	# of LH Patients	Country (ier)	# of Contror	A an (ver)
7648         1995.196         miniscentre, 2 parallel group, instance, and a second bind, randomised, parallel group, p		i cai	Double-blind double-dummy randomized	Taticats	Taticats	Country (its)	centres	Age (J13)
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Pase II, single centre, assesser blind, randomised,         Pase III, single centre, assesser blind, randomised,         Pase III, open, randomised, multicentre, parallel         Pase III, open, randomised, multicentre, parallel         Pase III, open, randomised,         Pase IIII, randomised,         Pase IIIII, randomised,         Pase IIIIII, randomised,         Pase IIIIII, randomised,         Pase IIIIII, randomised,         Pase IIIII, randomised, patratel         Pase IIIII, randomised, patratel         Pase IIIII, randomised, patratel         Pase IIII, randomised, patratel         Pase IIIII, randomised, patratel         Pase IIIIII, randomised, patratel         Pase IIIII, randomis	9180.4	1997-1998	parallel groups	44	0	UK	1	18-38
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	21884	2000-2001	assessor-blind study	474	0	US/Argentina	32	18-39





















# Incorporation of predictive factors into a model to define FSH starting dose

#### The CONSORT calculator

Y (oocytes retrieved) =  $\alpha + \beta_1 AGE + \beta_2 AGE^2 + \beta_3 BMI + \beta_4 FSH + \beta_5 FOLL_LT11 + \beta_6 DOSE$ Therefore:

DOSE = (Y - ( $\alpha$  +  $\beta_1$  AGE +  $\beta_2$  AGE <sup>2</sup> +  $\beta_3$  BMI +  $\beta_4$  FSH +  $\beta_5$  FOLL\_LT11)) /  $\beta_6$ 

Most important predictive factors:

- 1. Basal FSH
- 2. BMI
- з. Age
- 4. Antral follicle count

Howles et al. Curr Med Res Opin 2006;22:907-916

# **Prospective study design**

- Phase IV, open-label, in 18 centres worldwide
- GnRH agonist daily (long protocol)
- r-hFSH treatment (GONAL-f<sup>®</sup> pen)
  - fixed daily dose according to the CONSORT calculator (allocated using IVRS)
  - $-\,$  dose only to be reduced if risk of OHSS
- Set criteria for r-hCG triggering with a single sc 250 mcg injection of Ovidrel<sup>®</sup>
  - at least one follicle ≥18mm and 2 follicles ≥16mm
    IVRS = interactive voice response system

### Inclusion and exclusion criteria

- Inclusion criteria:
  - between 18 and <35 years</li>
  - regular spontaneous ovulatory menstrual cycle 21-35 days in length
  - early follicular phase (days 2-4) serum levels of FSH ( $\leq 12IU/L$ ) and  $E_2$  within centre's local normal range
  - both ovaries present
- Exclusion criteria:
  - previous poor response in two ART cycles (defined as <5 mature follicles and/or <3 oocytes collected)
  - previous over response (>24 oocytes)
  - BMI >30 kg/m<sup>2</sup>

### **Patient flow**

172 patients enrolled 

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- 166 received individualized dosing between 37.5 IU and 300 IU
  - 1 randomized to 37.5 IU prior to protocol amendment for minimum dose of 75 IU
    - withdrawn due to failed stimulation – 4 were allocated doses >225 IU

      - 2 randomized to 262.5 IU
         →1 had 5 occytes retrieved
         →1 withdrawn due to failure of DR
      - 2 randomized to 300 IU
        - →1 had 9 oocytes retrieved
          →1 had 12 oocytes retrieved
- 161 patients analyzed



Bonnographilice (ITT)							
	75 IU	112.5 IU	150 IU	187.5 IU	225 IU	All	
n	48	45	34	24	10	161	
Age, years	29.1 ( <del>3.5)</del>	<b>31.4</b> (2.3)	<b>32.2</b> (1.8)	<u>32.2</u> (1.8)	<b>33.3</b> (1.9)	<b>31.3</b> (2.9)	
BMI, kg/m <sup>2</sup>	<b>21.6</b> (2.7)	<b>22.3</b> (2.2)	<b>22.8</b> (2.7)	<b>23.1</b> (3.1)	<b>23.2</b> (2.3)	<b>22.4</b> (2.7)	
Basal FSH, IU/L	5.79 ( <del>1.4)</del>	<b>6.57</b> (1.7)	<b>6.14</b> (1.3)	7.34 (1.4)	<b>8:10</b> (2.0)	<b>6.46</b> (1.6)	
Number of antral	13.4 (5.5)	9.4 (4.3)	7.8	(3.8)	8.2	<b>9.9</b>	





# We are not very good at choosing the right dose for a patient

- Most patients (76%) received a dose lower than what would have been recommended by the investigator
- Only 9% received the same dose
- 15% received a higher dose than recommended by the investigator

<b>CONSORT ART study results:</b>
Treatment (ITT population)

	75 IU	112.5 IU	150 IU	187.5 IU	225 IU	All
	(n=48)	(n=45)	(n=34)	(n=24)	(n=10)	(n=161)
Total FSH	<b>1102</b>	<b>1287</b>	<b>1632</b>	<b>2044</b>	<b>2573</b>	<b>1498</b>
dose, IU	(672)	(447)	(341)	(276)	(552)	(648)
FSH duration, days	<b>12.5</b> (4.4)	<b>11.0</b> (2.9)	<b>10.6</b> (1.8)	<b>11.0</b> (1.4)	<b>11.5</b> (2.4)	<b>11.4</b> (3.1)
Oocytes retrieved	<b>8.3</b> (4.5)	<b>9.6</b> (6.5)	<b>12.1</b> (6.4)	<b>12.7</b> (4.3)	<b>8.3</b> (3.8)	<b>10.3</b> (5.7)
No. cycles	<b>12</b> (25.0)	<b>4</b>	<b>4</b>	<b>2</b>	<b>2</b>	<b>24</b>
cancelled (%)		(8.9)	(11.8)	(8.3)	(20.0)	(14.9)

All values mean (SD) unless stated otherwise



CONSORT ART study results:
Outcome (ITT population)

	75 IU (n=48)	112.5 IU (n=45)	150 IU (n=34)	187.5 IU (n=24)	225 IU (n=10)	All (n=161)
Embryos transferred	<b>1.9</b> (0.9)	<b>1.8</b> (0.7)	<b>2.0</b> (0.8)	<b>2.0</b> (0.6)	<b>1.4</b> (1.1)	<b>1.9</b> (0.8)
% clinical pregnancies per cycle (N)	<b>31.3</b> (15)	<b>31.1</b> (14)	<b>35.3</b> (12)	<b>50.0</b> (12)	<b>20.0</b> (2)	<b>34.2</b> (55)
% multiple pregnancies (N)	<b>20.0</b> (3)	<b>14.3</b> (2)	<b>33.3</b> (4)	<b>25.0</b> (3)	<b>0.0</b> (0)	<b>21.8</b> (12)
% implantation rate	<b>36.5</b> (42.8)	<b>24.3</b> (35.0)	<b>28.2</b> (38.9)	<b>37.1</b> (40.5)	<b>11.9</b> (20.9)	<b>29.8</b> (38.5)

Implantation rate = number of gestational sacs/total number of embryos transferred by patient



# Safety: OHSS reported (ITT population)

	75 IU (n=48)	112.5 IU (n=45)	150 IU (n=34)	187.5 IU (n=24)	225 IU (n=10)	All (n=161)
Moderate	1	2	1	2	1	7 (5.9%)
Severe	1			1		2 (1.7%)

- 2 patients reported mild OHSS during stimulation
- Both cases of severe OHSS associated with pregnancy

# What's the future of the CONSORT calculator?

- The next step is to compare the calculator to the experience-based choice of the starting dose.
- Lowest starting dose 112.5 IU

   More data required to understand
   abarcetration of patients who reapend to 75 UL
  - characteristics of patients who respond to 75 IU
- More work to develop suitable tool for — women >35 years of age
  - antagonist protocols

#### Summary

- Internationally validated FSH starting dose calculator
- The input variables utilize <u>readily available</u> patient characteristics
- Provides individualized starting doses 91% received a different dose compared with investigator's opinion
- Resulting in adequate oocyte yield and <u>high</u> <u>clinical pregnancy rates</u>

# CONCLUSION

- Individual predictors have been demonstrated to be reliable in prediction of ovarian response
- They have not been used to determine the choice of the regimen to propose on an individual basis (which analog, which protocol)
- They have been rarely used to choose the gonadotrophin starting dose.
- The CONSORT calculator appears to be an interesting tool to propose an individual starting dose.
- The dose selected by CONSORT was different than the one chosen by the clinician in 91% of the cases
- It superiority to the experience based choice remain to be demonstrated in terms of outcome (PR, OHSS).





	75 IU (n=29)	112.5 IU (n=31)	150 IU (n=26)	187.5 IU (n=19)	225 IU (n=8)	All (n=113)
Embryos transferred	<b>1.8</b> (0.6)	<b>1.7</b> (0.8)	<b>2.1</b> (0.7)	<b>1.9</b> (0.6)	<b>1.4</b> (1.0)	<b>1.8</b> (0.7)
% clinical pregnancies per cycle (N)	<b>37.9</b> (11)	<b>32.3</b> (10)	<b>46.4</b> (12)	<b>63.2</b> (12)	<b>25.0</b> (2)	<b>41.6</b> (47)
% multiple pregnancies (N)	<b>18.2</b> (2)	<b>20.0</b> (2)	<b>33.3</b> (4)	<b>25.0</b> (3)	<b>0.0</b> (0)	<b>23.4</b> (11)
% implantation rate	<b>43.3</b> (44.1)	<b>22.0</b> (32.7)	<b>35.5</b> (40.6)	<b>45.4</b> (40.3)	<b>13.9</b> (22.2)	<b>33.7</b> (39.0)

Implantation rate = number of gestational sacs/total number of embryos transferred by patient



# 75 IU group responses (PP population)

- Cycle cancelled due to inadequate response in 7/29 patients (24.1%)
- No identifying patient variable found