Personalizing ovarian stimulation for IVF

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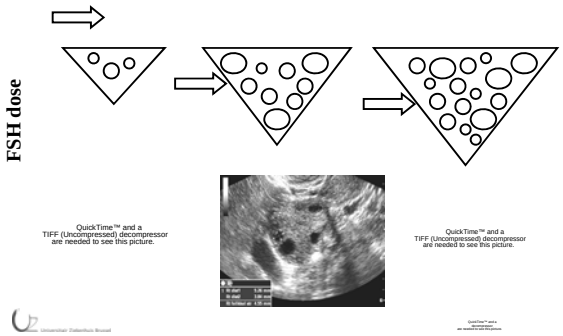
Controlled ovarian stimulation for IVF/ICSI

- Defining the appropriate dose well above the threshold according to your target
  - Conventional IVF – long and short
  - Mild IVF

In brief....

- FSH threshold
- What is the optimal starting FSH dose?
- Predictive factors and models
- Personalizing the FSH dose?
- Personalizing the protocol and the FSH dose?
- Future prospects

The threshold concept



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Controlled ovarian stimulation for IVF/ICSI

- The concept of a standard dose for a standard patient
- 'Standard' patient
  - → Below 40 years of age
  - → Regular menstrual cycle between 21–35 days
  - → Two ovaries
  - → Normal basal FSH level
- 'Standard' dose
  - → Range from 100–250 IU/day

Prospective studies – agonists

Ref	Age	Dose / IU	Nr. cycles	Oocytes (mean)	Pregn rate
Out 2001	18-37	100 vs. 200	91 vs. 88	5.7 vs 12	NS
Out 2000	18 -39	150 vs. 250	67 vs. 71	9.1 vs. 10.6	NS
Out 1999	18-39	100 vs. 200	101 vs. 98	6.2 vs. 10.6	NS
Lat Am 2001	30-39	150 vs. 250	201 vs. 203	8.9 vs. 10.2	NS
Yong 2003	23-41	150 vs. 225	60 vs. 63	6.3 vs 8.3	NS

Prospective studies – antagonists

Ref	Age	Dose / IU	Nr. cycles	Oocytes (mean)	Pregn rate
Wikland 2001	20-39	150 vs. 225	60 vs. 60	9.1 vs 11*	NS
Out 2004	18-39	150 vs 200	131 vs. 126	10.3 vs 11.9	NS

*** p < 0.05**

Variability of ovarian response

	100 IU	200 IU	Ref
Oocytes range	1-29	3-30	Out 1999
Oocytes range	1-30	1-40	Out 2001

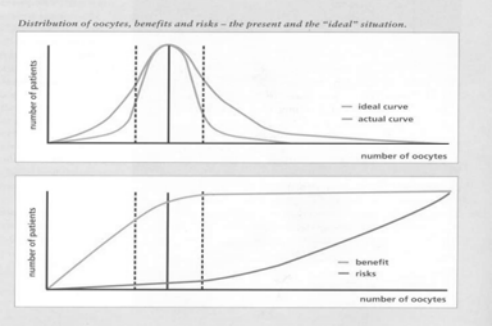
Variability of ovarian response

	150 IU	250 IU	Ref
Oocytes range	1-24	1-60	Out 2000
Oocytes range	1-31	1-35	Out 2001

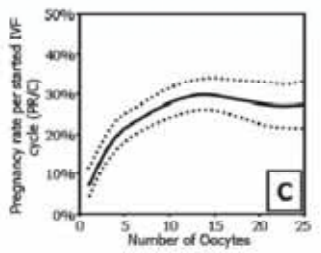
Controlled ovarian stimulation for IVF/ICSI

How controlled is it?

The concept



The number of retrieved oocytes in relation to pregnancy rate per started IVF cycle



Van der Gaast et al. Reprod Biomed Online 2006; 13(4):476–480

THE OVARY

- Holds the key to all stimulation strategies
- The number of recruitable follicles, their sensitivity to FSH and the bioavailability of FSH

The ovary

- Sonographical parameters
  - → AFC
  - → Volume
- Clinical
  - → Age reflects AFC
  - → Cycle length reflects AFC
  - → Body weight bioavailability
- Endocrine
  - → FSH reflects AFC
  - → FSH receptor polymorhism
  - → AMH reflects AFC

Predictive factors and models

- Bancsi *et al*. (2002) AFC+inhibin B+FSH
- Popovic Todorovic *et al*. (2003) age+AFC+ ovarian volume+ovarian stromal blood flow (Power Doppler score) +smoking
- Van Rooij *et al*. (2002) AMH+inhibin B+FSH
- Hendriks *et al*. (2005) FSH+AFC

Harrison *et al.* 2001

- First RCT attempting to individualize the dose according to the basal FSH level (n=345)
- Basal FSH < 8.5 IU/l randomized to receive 150 or 200 IU/day (146 vs. 151)
- Basal FSH > 8.5 IU/l randomized to receive 300 or 400 IU/day (24 vs. 24)
- Outcome measures – efficacy of gonadotropin therapy
  - → Doses adjustments on day 5 of stimulation
  - → Duration of stimulation
  - → Total dosage of FSH

Harrison *et al*. 2001- results

Characteristic	Group 1		Group 2	
Starting dose **Starting number**	**150 IU** **n=126**	**200 IU** **n=133**	**300 IU** **n=20**	**400 IU** **n= 17**
Oocytes retrieved				
Median	10	11	9	9
Range	3-27	3-32	3-26	1-19
Nr. of pregnancies per transfer (%)	29(26)	31(27)	2(12)	2(14)

Response prediction study - suggestion of a FSH dosage nomogram

- **145 1st IVF/ICSI cycle "standard" patients**
- **Down regulation with long protocol**
- **Starting dose of rFSH of 150 IU/day during the first week of treatment**

Predictive factors

- **Age**
- **Weight**
- **BMI**
- **Smoking habits**
- **Cycle length**
- **AFC**
- **Total ovarian volume**
- **Power Doppler (score allocation)**
- **Endocrine markers : FSH, LH, estradiol, testosterone, inhibin B**

Popovic-Todorovic et al. Hum Reprod 2003;18(4):781–787

Significant predictors of number of retrieved oocytes in bivariate linear regression

	Regression coefficient	Adjusted R^2	P value
Age	**0.182**	**0.026**	**0.030**
Cycle length	**0.244**	**0.053**	**0.003**
Smoking status	**0.226**	**0.044**	**0.007**
Serum FSH	**0.188**	**0.029**	**0.024**
Serum LH	**0.174**	**0.023**	**0.038**
Inhibin B	**0.195**	**0.031**	**0.020**
Ovarian volume	**0.376**	**0.136**	**<0.001**
AFC	**0.554**	**0.302**	**<0.001**
Total Doppler score	**0.476**	**0.221**	**<0.001**

Popovic-Todorovic et al. Hum Reprod 2003; 18(4):781–787

Significant predictors of number of retrieved oocytes in backward stepwise regression analysis

Variable	Standardised coefficient B	P value
Total number of antral follicles	0.424	<0.001
Total Doppler score	0.247	0.001
Smoking status	0.163	0.015

Model accounts for 38% variability of the number of retrieved oocytes

Popovic-Todorovic et al. Hum Reprod 2003; 18(4):781–787

rFSH dosage nomogram (1)

Total number of antral follicles < 10mm day 2-5	***rFSH score IU/day***	***rFSH starting dose***
< 15	90	
15 - 25	60	
> 25	50	
Total ovarian volume day 2-5		***Score***
< 9 ml	90	
9 -13ml	60	
>13ml	50	
Total Doppler score day 2-5		***Score***
2	30	
3 - 4	20	
5	10	
6	0	

rFSH dosage nomogram (2)

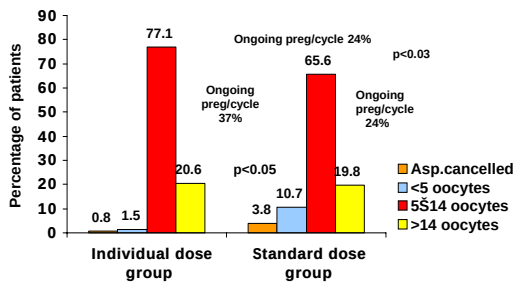
Age	*rFSH score IU/day*	*rFSH starting dose*
> 35	20	
30 - 35	10	
< 30	0	
Smoking habits/ cigarettes per day		***Score***
Non smoker	0	
≤ 10	10	
> 10	20	
Total rFSH score (sum of scores) same as dose IU/day		***Score***

Individual vs. standard rFSH dose RCT

- 232 1st IVF/ICSI treatment cycle standard patients
- Long agonist protocol
- Individual rFSH dose based on nomogram range 100-250 IU/day vs. standard dose of 150 IU/day
- Study end-points
  - → **To test whether rFSH dosage nomogram predicts the ovarian response**
  - → **To test whether use of the nomogram to dose the patients gives clinical benefits in relation to a more appropriate ovarian response, defined as retrieval of between 5-14 oocytes**

Popovic-Todorovic et al. Hum Reprod 2003; 18(11):2275–2282

Oocyte distribution in 262 patients
Standard dose versus individual dose based on nomogram model



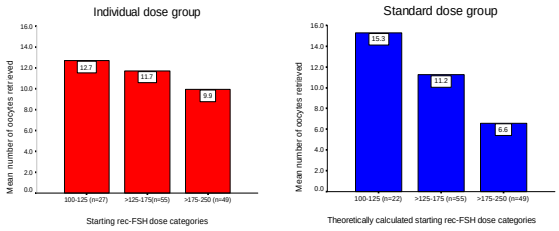
Popovic-Todorovic et al. Hum Reprod 2003; 18(11):2275–2282

Results

Oocyte distribution

	Individual dose group n=131	Standard dose group n=131	P value
<5 oocytes	**2**	**14**	**0.002**
5-14 oocytes	**101**	**86**	**0.04**
>14 oocytes	**27**	**26**	**NS**

Does the model predict the response?



Conclusions

- The use of the dosage nomogram predicted the ovarian response
- Individual dosage regimen in a well-defined ‘standard’ patient population increased the proportion of appropriate ovarian responses
- A higher ongoing pregnancy rate was observed in the individual dose group

Klinkert *et al.* 2005

- RCT 150 IU vs. 300 IU
- Low responders (<5 antral follicles)
- N=52, 28 pts > 40 years,24 pts < 41 years
- Basal FSH > 15 IU/l
- 150 IU group, dose doubled if there was no response, day 7 E_2 < 200 pmol/l or day 10 E_2 < 500 pmol/l.
- No dose adjustments in 300 IU group

Klinkert *et al*. 2005- results

- No difference in the median nr. of oocytes in 150 vs. 300 IU groups 3 vs. 3
- Cancellation rate 19 vs. 23%
- Ongoing pregnancy rate low, 8 vs. 4%

The Serono database study

- Predictive factors and a corresponding treatment algorithm for COS in patients with rFSH during ART procedures
- An analysis of 1378 patients (<35 years)
- Pooling of 11 trials
- Four factors remained significant during backward stepwise regression:
  - → Basal FSH
  - → BMI
  - → Age
  - → AFC

Howles et al. Curr Med Res Opin 2006; 22(5):907–918

The Serono Database study

- A dosing nomogram was developed, based on a weighed use of these four factors
- A computer model was developed to suggest FSH doses, based on clinical decisions and a target of stimulation of 11 oocytes
- In an uncontrolled clinical study the following distribution was found:

Dose IU/day	75	112	150	187	225
n	48	45	34	24	10
Oocytes	8.3	9.6	12.1	12.7	8.3

Howles et al. Curr Med Res Opin 2006; 22(5):907–918
Trew G. Presentation Serono Company Symposium. ESHRE 2007

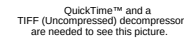
AMH - single predictive marker of ovarian response?

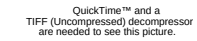
- AMH can be measured independently of the day of the menstrual cycle (La Marca *et al*., 2007).
- AMH has the same level of accuracy and clinical value for the prediction of poor ovarian response as has antral follicle count (Broer *et al*., 2008).
- AMH has at least the same level of accuracy and clinical value for the prediction of poor response and nonpregnancy as AFC (Broekmans *et al*., 2008)

Nelson *et al*., 2007

- Determination of pragmatic clinical cut-offs of AMH levels
  - → <1.0 pmol/l
  - → 1 to <5.0 pmol/l
  - → 5.0 to <15 pmol/l
  - → 15 to <25 pmol/l
- For identification of women at risk of an excessive response, an AMH 15 pmol/l had 88.0% sensitivity and 76.9% specificity, 77.8% women were identified correctly, positive likelihood ratio 3.8 and a negative likelihood ratio of 0.15.

Is one predictive factor sufficient?





Nelson *et al.*, 2009 - dosing and treatment strategies

Table I Deployment of GnRH analogues and doses of follicle stimulating hormone in the groups categorized by anti-Müllerian hormone in the two centres

AMH group (pmol/l)	Centre 1		Centre 2	
	FSH daily dose	GnRH analogue	FSH daily dose	GnRH analogue
<1.0	375	Antagonist	(Modified natural cycle)	(Antagonist)
1.0 to <5	375	Agonist	300	Antagonist
5.0 to <15	225	Agonist	225	Agonist
≥15.0	150	Agonist	150	Antagonist

Nelson *et al.*, 2009 - results Centre 1

Table III Patient characteristics and controlled ovarian stimulation details relative to anti-Müllerian hormone category for Centre 1

AMH category	1 to <5 pmol/l	5 to <15 pmol/l	≥15 pmol/l
Protocol	Agonist + 375 IU	Agonist + 225 IU	Agonist + 150 IU
Patients (n) % of cohort	74 (20%)	126 (34.6%)	148 (40%)
Age (years)	37.3 (34.6–39.3)	35.1 (32.7–37.3)	32.8 (28.8–36.2)
BMI (kg/m^2)	23.9 ± 7.5	23.8 ± 5.6	24.1 ± 5.6
AMH (median (IQR))	2.6 (1.8–3.7)	9.2 (6.8–11.9)	22.4 (18.3–29.9)
Duration of stimulation (days (IQR))	14 (13–15)	14 (13–15)	13 (12–14)
Number of oocytes collected	5 (3–7)	10 (7–15)	14 (10–19)
Number of oocytes fertilized	3 (2–4)	6 (3–9)	7 (5–11)
Low oocyte yield n (%)	7/55 (12.7%)	3 (2.3%)	4 /144 (2.8%)
Freeze all n (%)	1 (1.4%)	13 (10.1%)	27 (18.2%)
Hospitalized for OHSS	0 (0%)	3 (2%)	20 (13.9%)
Cancelled cycle n (%)	19 (25.7%)	3 (2.3%)	4 (2.7%)
Clinical pregnancy per cycle n (%)	6 (8.1%)	29/125 (23.2%)	47 (31.8%)
Clinical pregnancy per OR n (%)	6/55 (10.9%)	29/112 (25.9%)	47/144 (32.6%)
Clinical pregnancy per embryo transfer n (%)	6/54 (11.1%)	128 (34.6%)	47/117 (40.1%)

BMI, body mass index, OHSS, ovarian hyperstimulation syndrome. Values are either absolute numbers, median (inter-quartile range) or mean ± standard deviation. Outcome percentages calculated per cycle started, rates per oocyte retrieval (OR) and embryo transfer also provided.

Nelson *et al.*, 2009 - results Centre 2

Table IV Patient characteristics and controlled ovarian stimulation details relative to anti-Müllerian hormone category for Centre 2

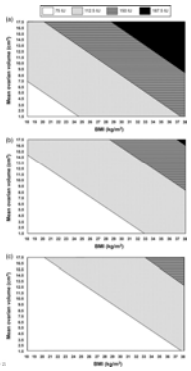
AMH category:	1 to <5 pmol/l		5 to <15 pmol/l		≥15 pmol/l	
Protocol:	Antagonist + 300 IU	*P**	Agonist + 225/300 IU	*P**	Antagonist + 150 IU	*P**
Patients (*n*) % of cohort	61 (36.3%)		73 (43.4%)		34 (20.2%)	
Age (years)	39.0 (32.0–41.0)	0.005	37 (34–39.5)	<0.001	32.0 (30.0–35.2)	0.94
BMI (kg/m^2)	24.6 ± 4.9	0.57	24.2 ± 3.7	0.63	23.6 ± 3.3	0.59
AMH (median [IQR])	3.0 (2.0–3.8)	0.40	8.7 (7.2–11.4)	0.93	25.8 (23.6–34.9)	0.018
Duration of stimulation (days [IQR])	10 (8–11)	<0.001	11 (10–12)	<0.001	9 (8–11)	<0.001
Number of oocytes collected	3 (1–4)	<0.001	6 (4–10)	<0.001	10 (8.5–13.5)	<0.001
Number of oocytes fertilized	2 (1–4)	0.10	4 (3–6)	0.027	6 (4–8)	0.009
Low oocyte yield *n* (%)	20/56 (35.7%)	<0.001	1 (1.4%)	0.61	1/33 (3.0%)	1.0
Freeze all *n* (%)	0 (0%)	1.0	0 (0%)	0.04	0 (0%)	0.003
Hospitalized for OHSS	0 (0%)	1.0	1 (0%)	1.0	0 (0%)	0.021
Cancelled cycle *n* (%)	5 (8.2%)	0.005	0 (0%)	1.0	1 (2.9%)	1.0
Clinical pregnancy per cycle *n* (%)	9 (14.7%)	0.27	24 (32.9%)	0.13	21 (61.7%)	0.002
Clinical pregnancy per OR *n* (%)	9/56 (16.1%)	0.58	24/73 (32.9%)	0.18	21/33 (63.6%)	0.001
Clinical pregnancy per embryo transfer *n* (%)	9/48 (18.7%)	0.40	24/71 (33.8%)	0.31	21/33 (63.6%)	0.019

BMI, body mass index; OHSS, ovarian hyperstimulation syndrome. Values are either absolute numbers, median (inter-quartile range) or mean ± standard deviation. Outcome percentages calculated per cycle started, rates per oocyte retrieval (OR) and embryo transfer also provided. *P**: comparison with data from Centre 1.

The present situation

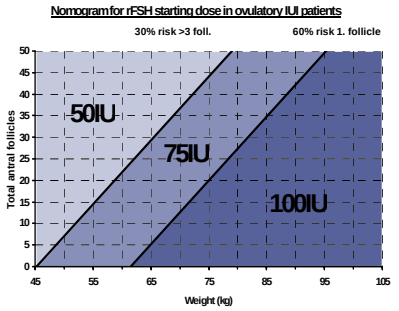
- Despite accumulation of data on predictive factors of ovarian response there is a lack of clinically applicable dosing models
- Simple dosing models are being developed for ovulation induction and ovarian stimulation for IUI

Nyboe Andersen *et al.*, 2008



Nomograms for prediction of individual FSH threshold dose in anovulatory patients undergoing ovulation induction with FSH preparations, according to menstrual cycle history, BMI and mean ovarian volume

rFSH dosing nomogram for IUI based on two variables: AFC and body weight



Freiesleben NL *et al*., 2008

Single or few predictive factors?

- Meta-analysis of Verhagen *et al*. (2008) showed that the performance of multivariate models in the prediction of poor ovarian response after IVF is comparable with that of AFC.
- AFC may be considered as the test of first choice in the assessment of diminished ovarian reserve.
- Future models for the prediction of poor response and pregnancy should incorporate the AFC.

Conclusion

- Considering the amount of research conducted on predictive factors of ovarian response to COS, it is striking that there is a lack of clinically useful models to guide us on the key issue of appropriate gonadotrophin dosing
- Dosing models based on simple clinical, sonographic and endocrine tests should be tested in RCTs
- These models need to be developed for long and short protocols, and for conventional and mild stimulation