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, Inhibin 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)

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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 poor response.

Predictive model	Sens	Spec	PPV	NPV	ROC AUC	Correct predictions (%)
Inhibin B	0.42	0.92	0.68	0.79	0.77	92 (77%)
FSH	0.44	0.93	0.73	0.80	0.84	94 (78%)
Antral follicle count	0.61	0.88	0.69	0.84	0.87	96 (80%)
FSH + inhibin B	0.58	0.94	0.81	0.84	0.89	100 (83%)
Antral follicle count + inhibin B	0.69	0.88	0.71	0.87	0.90	99 (83%)
Antral follicle count + FSH	0.72	0.93	0.81	0.89	0.90	104 (87%)
Antral follicle count + FSH + inhibin B	0.75	0.95	0.87	0.90	0.92	107 (89%)

Note: PPV = positive predictive value; NPV = negative predictive value; ROC AUC = area under the receiver operating characteristic curve.

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A systematic review of tests predicting ovarian reserve and IVF outcome

F.J.Broekmans[1], J.Kwee[2], D.J.Hendriks[1], B.W.Mol[3] and C.B.Lambalk[2,4]

Scientific papers analysed in the review

FSH
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.*, 1998; Sharif *et al.*, 1998;Bassil *et al.*, 1999; Hall *et al.*, 1999; Bancsi *et al.*, 2000;Chae *et al.*, 2000; Creus *et al.*, 2000; Fabregues *et al.*, 2000; Jinno*et al.*, 2000; Penarrubia *et al.*, 2000; Mikkelsen *et al.*, 2001; Nahum*et al.*, 2001; van der Stege and van der Linden, 2001; Esposito *e al.*,2002; Chuang *et al.*, 2003; Fiçicioglu *et al.*, 2003; Kwee *et al.*,2003; Yanushpolsky *et al.*, 2003; Akande *et al.*, 2004; Erdem *et al.*,2004.

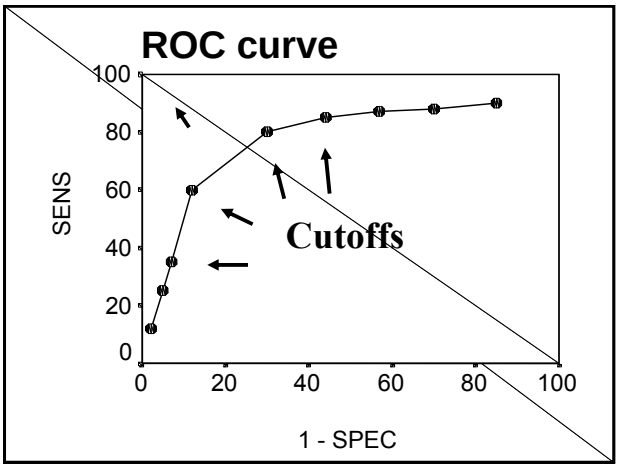
AMH:
van Rooij *et al.*,2002; Muttukrishna *et al.*, 2004

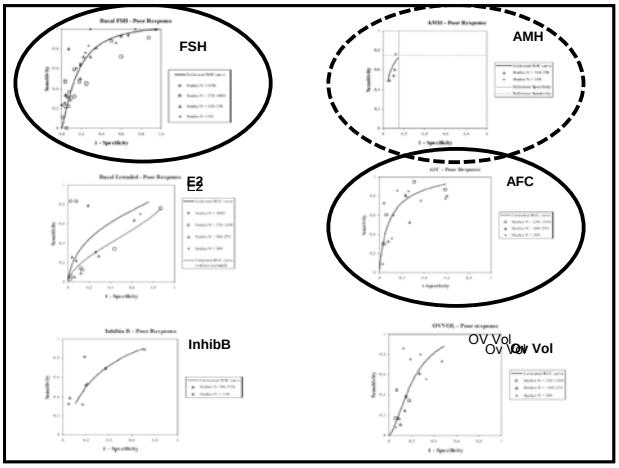
Inhibine B:
Balasch *et al.*, 1996; Seifer *et al.*, 1997;Hall *et al.*, 1999; Creus *et al.*, 2000; Fabregues *et al.*, 2000;Penarrubia *et al.*, 2000; Bancsi *et al.*, 2002a; Fiçicioglu *et al.*,2003; Erdem *et al.*, 2004

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

Antral Follicle 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.*, 2002a; Erdem *et al.*, 2002; Fisch and Sher, 2002;Fiçicioglu *et al.*, 2003; Frattarelli *et al.*, 2003; Jarvela *et al.*, 2003;Kupesic *et al.*, 2003; Yong *et al.*, 2003; Durmusoglu *et al.*, 2004.

Ovarian volume:
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

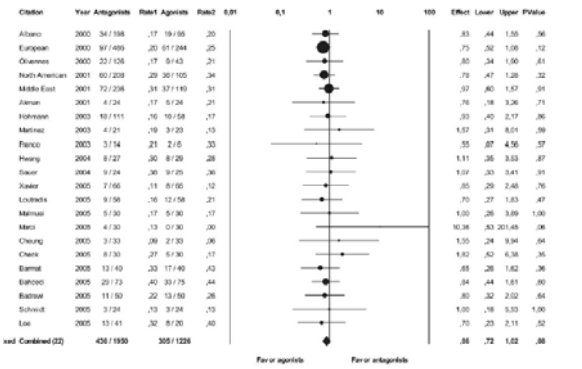
Choosing the GnRH analogs

- 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

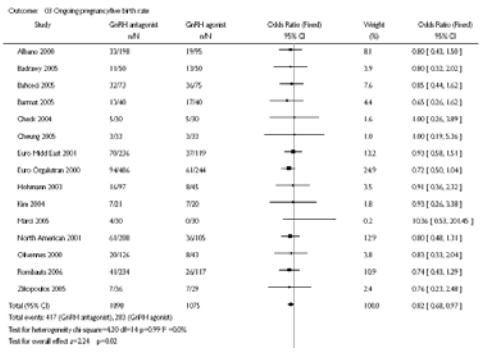
GnRH analogs exemple of remaining questions

- 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…



live birth in 12 studies using published data (Arce *et al.*, 2005). No significant difference was present in the probability of live birth between the two GnRH analogues [odds ratio (OR), 0.86; 95% confidence intervals (CI), 0.72 to 1.02]. This

Kolibianakis et al, Hum Reprod. Update 2006, ahead of print



Al Inany et al, Cochrane Database Syst Rev. 2006 Jul 19

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 **cancellation** 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 I. rFSH dosage nomogram

	FSH score IU/day	rFSH starting dose
Total number of follicles 10mm day 2–5		
<15	90	
15–25	60	
>25	50	
Total ovarian volume day 2–5		Score
<9 ml	90	
9–13 ml	60	
>13 ml	50	
Total Doppler score day 2–5		Score
2–3	30	
4	20	
5	10	
6	0	
Age (years)		Score
>35	20	
>30-≤35	10	
≤30	0	
Smoking habits; cigarettes/day		Score
>10	20	
≤10	10	
Non-smoker	0	
Total FSH score (sum of scores) same as dose IU/day		

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	0.249	0.044	< 0.001
Total Doppler score	1.295	0.396	0.001
Smoking status	3.840	0.748	0.015
Serum testosterone	1.457	0.769	0.060

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

Popovic-Todorovic et al 2003 a,b

The CONSORT study

Methodology

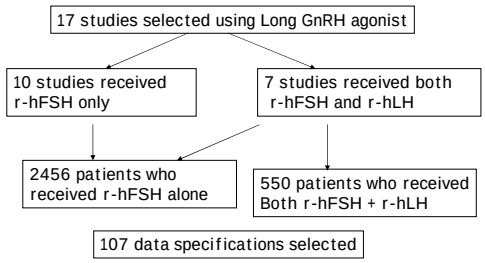
- Analysis of a large (>1300) 'homogeneous' ART patient database
  - < 35 years age
  - Rec-hFSH stimulation
- Select ovarian response **variables** which could define an optimal ovarian response
- Identify **predictive factors** of ovarian response
- Produce a model based upon the predictive factors that will improve the identification of the appropriate FSH starting dose
- Expert panel:
  Andrea Borini, Italy, Francois Olivennes, France, Geoffrey Trew, UK, Matts Wikland, Sweden, Fernando Zegers, Chile

Overview of patient database analysed

Overview of patient database analysed

Study Number	Year	Study Design	# of FSH Patients	# of LH Patients	Country (ies)	# of Centres	Age (yrs)
7648	1995-1996	Double-blind, double-dummy, randomised, multicentre, 2 parallel groups	205	0	Europe	9	20-38
9180A	1997-1998	Phase II, single centre, assessor blind, randomised, parallel groups	44	0	UK	1	18-38
9180B	1998	Phase II, single centre, assessor blind, randomised, parallel groups	44	0	UK	1	18-38
8839	1997-1999	Phase III, open, randomised, multicentre, parallel groups	85	42	Italy	5	18-38
9029	1997-1999	Estudio clinico multicéntrico, randomizado, controlado	46	23	Spain	11	18-38
9032	1997-1999	Estudio clinico en fase II/III, randomizado, comparativo, con grupo en paralelo	45	22	Spain	1	18-38
9318	1998	A randomised, prospective, double-blind study	114	54	Spain	6	18-37
9027	1998-1999	A prospective, multicentre, randomised, patient-blind, parallel group study	297	0	UK	4	18-39
9261	1998-1999	An open-label, randomised, multicentre, 2 parallel groups study	431	212	US	42	18-40
9640	1998-1999	A phase III, single centre, parallel, randomised open-label comparative study	140	70	UK	1	> 18
20421	1999	A pilot, single centre, open, randomised, parallel group study	51	0	Europe	1	18-38
20377	199-2000	An exploratory, multicentre, double-blind, randomised, parallel group study	145	0	Europe	5	20-38
21419	1999-2001	A prospective, randomised, assessor-blind, phase IV study	545	0	UK	1	18-39
20557	2000-2001	A phase III, multicentre, double-blind, randomised, parallel group study	166	0	Europe/US	3	18-38
21875	2000-2001	A multicentre, randomised, assessor blind, controlled, dose ratio finding phase II pilot study	169	127	Europe/Israel	15	38-42
21822	2000-2001	A phase II/III, single centre, open, randomised, comparative parallel group study	43	0	Sweden	1	18-38
21884	2000-2001	A phase III, multicentre, multinational, randomised, assessor-blind study	474	0	US/Argentina	32	18-39

Studies included in ART r-hFSH alfa Treatment Guidelines Project



Of these 107 data specifications there were identified:

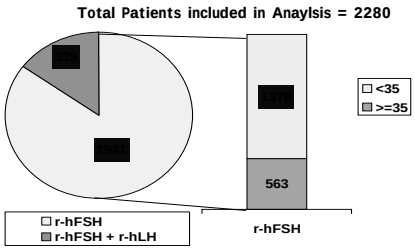
18 Predictive Factors and 25 Response Variables

'Wish List' of 18 Predictive Factors

- Age
- Weight
- BMI
- Smoking History
- Type of Infertility (Primary/Secondary)
- Duration of infertility
- Minimum Cycle Length
- Maximum Cycle Length
- Mean Cycle Length
- Previous ART treatment
- No. previous ART attempts
- Basal FSH
- Basal E2
- Basal Prolactin
- Basal LH
- Antral Follicle Count (< 11mm) at screening
- No. Follicles > 11mm at screening
- Mean Ovarian Volume

25 response variables have been included in the first analysis, including 7 embryo score evaluation parameters

Distribution of patients by Gonadotrophin treatment and age



Patient population selected for in-depth analysis
< 35 years treated with r-hFSH alfa alone

The CONSORT calculator


ORIGINAL ARTICLE

Predictive factors and a corresponding treatment algorithm for controlled ovarian stimulation in patients treated with recombinant human follicle stimulating hormone (follitropin alfa) during assisted reproduction technology (ART) procedures. An analysis of 1378 patients

C. M. Howles*, H. Saunders†, V. Alam‡ and P. Engrand§ on behalf of the FSH Treatment Guidelines Clinical Panel

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

Frequency of significant predictive factors for patients receiving r-hFSH alfa alone and < 35 yrs

Predictive Factors	Total Score for Predictive Factors (Maximum Score = 28)	
Age	9.5	3
Weight	4.5	
BMI	12	
Smoking History	6	2
Type of Infertility (P/S)	4	
Duration of Infertility (yrs)	2	
Minimum Cycle Length (days)	1	
Maximum Cycle Length (days)	4	
Mean Cycle Length (days)	4	
Previous ART (Y/N)	3	
Number of Previous ART	2.5	1
FSH Level at Screening (IU/L)	15.5	
Number of Follicles < 11mm at Screening	8.5	
Number of Follicles >= 11mm at Screening	3.5	4
Mean Ovarian Volume (cm3)	6	

+++The studies included did not had AMH measurements+++

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

The CONSORT calculator

$$Y \text{ (oocytes retrieved)} = \alpha + \beta_1 \text{AGE} + \beta_2 \text{AGE}^2 + \beta_3 \text{BMI} + \beta_4 \text{FSH} + \beta_5 \text{FOLL\_LT11} + \beta_6 \text{DOSE}$$

Therefore:

$$\text{DOSE} = (Y - (\alpha + \beta_1 \text{AGE} + \beta_2 \text{AGE}^2 + \beta_3 \text{BMI} + \beta_4 \text{FSH} + \beta_5 \text{FOLL\_LT11})) / \beta_6$$

Most important predictive factors:

1. Basal FSH
2. BMI
3. 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® 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®
  - 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
  - regular spontaneous ovulatory menstrual cycle 21–35 days in length
  - early follicular phase (days 2–4) serum levels of FSH (≤ 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^2

Patient flow

- 172 patients enrolled
- 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 oocytes 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

Patient flow

- Statistical plan required at least 5 patients/group for analysis
- 161 patients received an individualized starting dose between 75 IU and 225 IU (ITT population)

75 IU n=48	112.5 IU n=45	150 IU n=34	187.5 IU n=24	225 IU n=10	**n=161**

CONSORT ART study results: Demographics (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** (3.5)	**31.4** (2.3)	**32.2** (1.8)	**32.2** (1.8)	**33.3** (1.9)	**31.3** (2.9)
BMI, kg/m^2	**21.6** (2.7)	**22.3** (2.2)	**22.8** (2.7)	**23.1** (3.1)	**23.2** (2.3)	**22.4** (2.7)
Basal FSH, IU/L	**5.79** (1.4)	**6.57** (1.7)	**6.14** (1.3)	**7.34** (1.4)	**8.10** (2.0)	**6.46** (1.6)
Number of antral follicles	**13.4** (5.5)	**9.4** (4.3)	**7.8** (3.5)	**7.4** (3.8)	**8.2** (4.9)	**9.9** (5.1)

All values mean (SD)

Protocol deviations

- 48 patients had major protocol deviations
  - two populations analyzed:

Intent-to-treat (ITT) received at least one dose of study medication	**Per-protocol (PP)** fulfilled all protocol criteria without major deviation

- Main deviations were:
  - FSH dose increased (n=19; 12%)
  - allocated a dose based on variables inconsistent with the CRF data (n=14; 9%)
  - hCG administered when protocol criteria had not been met (n=13; 8%)
- PP Population:

75 IU n=29	112.5 IU n=31	150 IU n=26	187.5 IU n=19	225 IU n=8	**n=113**

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

CONSORT ART study results:
Treatment (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)
Total FSH dose, IU	**1102** (672)	**1287** (447)	**1632** (341)	**2044** (276)	**2573** (552)	**1498** (648)
FSH duration, days	**12.5** (4.4)	**11.0** (2.9)	**10.6** (1.8)	**11.0** (1.4)	**11.5** (2.4)	**11.4** (3.1)
Oocytes retrieved	**8.3** (4.5)	**9.6** (6.5)	**12.1** (6.4)	**12.7** (4.3)	**8.3** (3.8)	**10.3** (5.7)
No. cycles cancelled (%)	**12** (25.0)	**4** (8.9)	**4** (11.8)	**2** (8.3)	**2** (20.0)	**24** (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	**1.9** (0.9)	**1.8** (0.7)	**2.0** (0.8)	**2.0** (0.6)	**1.4** (1.1)	**1.9** (0.8)
% clinical pregnancies per cycle (N)	**31.3** (15)	**31.1** (14)	**35.3** (12)	**50.0** (12)	**20.0** (2)	**34.2** (55)
% multiple pregnancies (N)	**20.0** (3)	**14.3** (2)	**33.3** (4)	**25.0** (3)	**0.0** (0)	**21.8** (12)
% implantation rate	**36.5** (42.8)	**24.3** (35.0)	**28.2** (38.9)	**37.1** (40.5)	**11.9** (20.9)	**29.8** (38.5)

All values mean (SD) unless stated otherwise

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 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 readily available patient characteristics
- Provides individualized starting doses
  - 91% received a different dose compared with investigator's opinion
- Resulting in adequate oocyte yield and high clinical pregnancy rates

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).

CONSORT ART study results: Outcome (PP population)

	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	**1.8** (0.6)	**1.7** (0.8)	**2.1** (0.7)	**1.9** (0.6)	**1.4** (1.0)	**1.8** (0.7)
% clinical pregnancies per cycle (N)	**37.9** (11)	**32.3** (10)	**46.4** (12)	**63.2** (12)	**25.0** (2)	**41.6** (47)
% multiple pregnancies (N)	**18.2** (2)	**20.0** (2)	**33.3** (4)	**25.0** (3)	**0.0** (0)	**23.4** (11)
% implantation rate	**43.3** (44.1)	**22.0** (32.7)	**35.5** (40.6)	**45.4** (40.3)	**13.9** (22.2)	**33.7** (39.0)

All values mean (SD) unless stated otherwise

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