PRE-CONGRESS COURSE 7

Ovarian stimulation for ART: how to achieve efficacy and safety?

Special Interest Group Reproductive Endocrinology
London - UK, 7 July 2013

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Ovarian stimulation for ART: how to achieve efficacy and safety?

London, United Kingdom
7 July 2013

Organised by
The ESHRE Special Interest Group Reproductive Endocrinology

Contents

Course coordinators

Georg Griesinger (Germany)

Course description

Ovarian stimulation remains an essential part of ART. Inter-individual variation in ovarian response represents a significant clinical and economical challenge. Undoubtedly, there is a need to reliably predict ovarian response to stimulation, to tailor stimulation protocols optimizing the probability of pregnancy and keep at the same time the risks of complications and costs at a minimum.
Special emphasis needs to be given on how to avoid excessive response and predict the occurrence of ovarian hyperstimulation syndrome (OHSS), as well as on maximizing tolerability of treatment from a patient's perspective.
Topics to be covered include ovarian stimulation strategies; primary, secondary and tertiary prevention of OHSS; development of protocols for patients with diminished ovarian reserve; ovarian reserve testing and its practical implications; mild stimulation and financial implications; segmentation of IVF treatment; impact of ovarian stimulation on the endometrium; and emergency stimulation for oncofertility patients.

Target audience

Physicians and scientists in reproductive medicine

Scientific programme

Session 1: Cost implications of ovarian stimulation in expected normal responders
Chairman: Daniela Romualdi - Italy

09:00 - 09:15	Introduction and E-system voting
09:15 - 09:45	Conventional stimulation & cryopreservation of surplus oocytes or embryos is the most cost-effective treatment *Filippo Ubaldi - Italy*
09:45 - 10:15	Repetitive natural cycles or mild stimulation offer most benefit per € spent *Michael von Wolff - Germany*
10:15 - 10:30	E-system voting & Discussion

10:30 - 11:00 Coffee break

Session 2: Poor response to ovarian stimulation: three short sketches and a mini-debate
Chairman: Frank J. Broekmans - The Netherlands

11:00 - 11:15	Is the clinical impact of a poor response female age dependant? *Simone Broer - The Netherlands*
11:15 - 11:30	Is manipulating intra-ovarian androgen conditions effective in upgrading ovarian response? *Renato Fanchin - France*
11:30 - 11:45	Will application of stimulation dosages over 225 IU per day prevent a poor response? *Frank J. Broekmans - The Netherlands*
11:45 - 12:30	Mini - Debate: A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment
11:45 - 12:00	Pro *Petra De Sutter - Belgium*
12:00 - 12:15	Con *Pia Saldeen - Sweden*
12:15 - 12:30	E-system voting

12:30 - 13:30 Lunch

Session 3: Excessive response
Chairman: Georg Griesinger - Germany

13:30 - 13:40	Introduction and E-system voting
13:40 - 14:00	How should we stimulate patients with polycystic ovaries *Efstratios Kolibianakis - Greece*
14:00 - 15:00	Debate: Excessive ovarian response affects oocyte quality, endometrial receptivity and child health
14:00 - 14:22	Pro *Nicholas Macklon - United Kingdom*
14:22 - 14:44	Con *Karin Middelburg - The Netherlands*
14:45 - 15:00	E-system voting & Discussion

15:00 - 15:30 Coffee break

Session 4: Individualisation of ovarian stimulation: can it impact the outcome?
Chairman: Efstratios Kolibianakis - Greece

15:30 - 15:45	Introduction and E-system voting
15:45 - 16:15	Maximising success rates by stimulation individualization *Ernesto Sr. Bosch - Spain*
16:15 - 16:45	Individualisation of ovarian stimulation has little impact on outcome *Georg Griesinger - Germany*
16:45 - 17:00	E-system voting & Discussion

www.generaroma.it

g.en.e.r.a.

Valle Giulia Clinic, Rome, Italy

Conventional stimulation and cryopreservation of surplus oocytes or embryos is the most cost-effective treatment

Filippo Maria Ubaldi
M.D. M.Sc.

Outline / learning objectives

- Definition of poor and high responders
- Description of different stimulation protocols
- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions

Conflict of interest

I declare no conflict of interest

related to this presentation

Agenda

- Definition of poor and high responders
- Description of different stimulation protocols
- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions

Definition of poor and high responders

Consensus Building

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)***

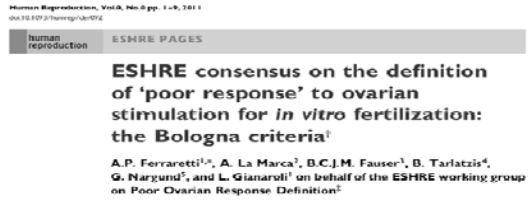
E2 <600, <3 oocytes ***(Marci 2005)***

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

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

Definition of poor and high responders

Consensus Building



Poor Ovarian Response definition

At least two of the following three features must be present:

(i) Advanced maternal age (≥40 years) or any other risk factor for POR;

(ii) A previous POR (≤3 oocytes with a conventional stimulation protocol);

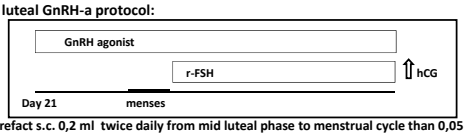
(iii) An abnormal ovarian reserve test (AFC 5–7 follicles or AMH 0.5–1.1 ng/ml)

Agenda

- Definition of poor and high responders
- Description of different stimulation protocols
- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions

Different stimulation protocols

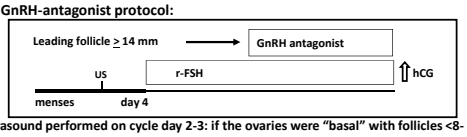
Long luteal GnRH-a protocol:



Suprefact s.c. 0,2 ml twice daily from mid luteal phase to menstrual cycle than 0,05 ml s.c. twice daily untill hCG

From cycle day 3, with "basal" ovaries, gonadotropins with a patient taylored dose

Mild GnRH-antagonist protocol:



Ultrasound performed on cycle day 2-3: if the ovaries were "basal" with follicles <8- 10 mm, ovarian stimulation was started on day 4 with a patient taylored dose.

GnRH-ant was started when the leading follicle was 14-15 mm with serum LH<10 IU/mL

Agenda

- Definition of poor and high responders
- Description of different stimulation protocols
- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions

Cost-effectiveness analysis

Heijnen et al., 2007; Polinder et al., 2008

A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial

Cost-effectiveness of a mild compared with a standard strategy for IVF: a randomized comparison using cumulative term live birth as the primary endpoint

STUDY DESIGN (patients < 38 yr old):

MILD STIMULATION + SINGLE EMBRYO TRANSFER (up to 4 cycles in 1 yr)

VS

CONVENTIONAL STIMULATION + DOUBLE EMBRYO TRANSFER (up to 3 cycles in 1 yr)

OUTCOMES: term live births after 1yr & costs* of the 2 strategies

COST-EFFECTIVENESS DEFINITION

$$\frac{\text{Difference in average costs}}{\text{difference in average effects between STANDARD and MILD}}$$

** Treatment costs (up to the outcome of the last IVF cycle) + antenatal, peripartum, postpartum care (until 6 weeks after delivery) [alternatively miscarriage or ectopic pregnancy costs were considered]*

Cost-effectiveness analysis

Heijnen et al., 2007

Lower rate of cancellation of the started cycles, higher ongoing pregnancy rate and term live birth rate (fresh cycles) through the standard stimulation protocol

No significant differences in depression, anxiety, physical discomfort and subjective sleep quality

Cost-effectiveness analysis

Polinder et al., 2008

Parameters

Table 1. Cost categories and data used in cost calculations.

Cost category	Parameter	Data collection volume of care			Unit estimate	
		CRF (physician)	Questionnaire patient	Questionnaire obst/gyn	Unit price (€)	Calculation method
Medication						
GnRH analogue[a]	Strategy	*			145/710[b]	Cost price
Recombinant FSH	Days	*			595/816[b]	Cost price
HMG/Pergoveris	Days	*			18[b]	Cost price
Technical procedures						
Oocyte retrieval	Strategy	*			596	Real costs
Laboratory procedures	Strategy	*			variable	Real costs
Embryo transfer	Strategy	*			253–267	Real costs
Immunal care						
Hospital (antenatal)	Days	*	*	*	488	Real costs
Hospital (general)	Days	*	*	*	330	Real costs
NICU/MCU[c]	Days	*	*	*	1170	Real costs
Physician	Visits	*	*	*	50/247	Charges
Ultrasound	Number	*		*	42	Charges
Prenatal screening				*	267	Charges
Other therapy	Number			*	Variable	Charges
Delivery	Category		*	*	Variable[d]	Literature
Paramedical care						
Obstetrician	Visits		*	*	75	Charges
General practitioner (inpatient)	Visits		*		20	Fees
General practitioner (home visit)	Visits		*		50	Fees
Social worker	Visits		*		34	Charges
Maternity nurse	Days		*		95.8	Charges
Non-medical costs						
Travel costs	Distance		*		0.11/km	Guideline
Absence from work	Days		*		29–40/h	Guideline

obst/gyn, obstetrician/gynaecology.
[a]GnRH antagonist for cost treatment and GnRH agonist for standard treatment.
[b]For the costs of medication, mean costs were used per couple.
[c]Embryo transfer for SET €751 and for double embryo transfer €760.
[c]Neonatal intensive care unit/medium care unit.
[d]Physician visits, costs for an inpatient visit at the IVF department are €20 and telephonically consults are €28.
[d]Delivery costs depend on delivery at home/in hospital, with or without complications, delivery with caesarean section (with or without complications).
Data used in the cost calculations.

Cost-effectiveness analysis

Polinder et al., 2008

Table III. Clinical outcomes and costs (€) within 12 months after randomization of 404 patients randomized for a mild or standard strategy in IVF, as a basis for the current health economic evaluation.

	Randomized (n)		P-value
	Mild (205) (mean ± SD)	Standard (199) (mean ± SD)	
Mean number of cycles within 1 year (n)	2.3	1.7	<0.001
Pregnancy within 1 year leading to term live birth (n)	86	86	NS
Cumulative term live birth rate from pregnancies within 1 year (%)[a]	43.4	44.7	NS
Multiple pregnancies leading to term live birth per randomized couple (%)	0	6.5	<0.001
Incidence of ovarian hyperstimulation syndrome (%)	1.4	3.7	0.04
Number of dropouts	36	32	NS
Costs of IVF treatment with 1 year			
Technical procedures	1083 ± 734	991 ± 594	NS
Intramural care	330 ± 201	370 ± 180	0.006
Medication	1626 ± 1056	1737 ± 1069	NS
Indirect costs[b]	1948 ± 2250	1740 ± 1845	NS
Costs of pregnancy and delivery from pregnancies within 1 year			
Medical costs	530 ± 984	1061 ± 2036	0.001
Delivery	449 ± 951	504 ± 854	NS
Costs of the neonatal period from pregnancies within 1 year			
Hospital admission mother	542 ± 375	1066 ± 1164	<0.001
Hospital admission child	342 ± 374	1653 ± 1337	<0.001
Maternity care	684 ± 498	593 ± 348	<0.001
Indirect costs[b] (pregnancy + neonatal)	379 ± 1177	802 ± 2270	NS
Total costs within 1 year	8014 ± 5408	10 745 ± 11 225	0.006

Source: Heijnen et al. (2007).
[a]The cumulative rates differ from the raw percentages, because the cumulative rates were calculated using the Kaplan–Meier method, accounting for censoring due to pregnancies within 1 year that did not lead to a term live birth.
[b]Indirect costs involve traffic costs and absence from work/sick leave.

The overall increase in costs is determined by summing up small differences (often not even significant) in indirect costs, intramural care or delivery care (almost double for the standard strategy), without conside-ring that the study design contemplates only SET in the mild stimulation protocol and double ET in the standard stimulation protocol. The latter obviously involves higher peripartum and postpartum care costs

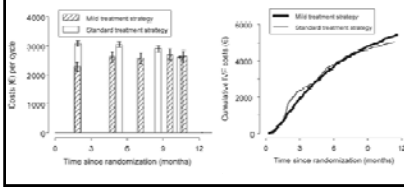
Cost-effectiveness analysis

Polinder et al., 2008

Table IV. Costs, effects and incremental cost-effectiveness ratio of patients randomized for a mild or standard strategy in IVF: results from base-case analysis and sensitivity analysis.

	Mild		Standard		Incremental C/E ratio[a]
	Mean total costs (€)	Effectiveness (%)	Mean total costs (€)	Effectiveness (%)	
Term live birth 12 months (base-case analysis)	8333	43.4	10 745	44.7	185 000
Live birth 12 months	8333	45.5	10 745	50.9	44 700
Term live birth all cycles[b]	10 033	53.6	12 657	51.8	Dominated
Live birth all cycles[b]	10 033	59.0	12 657	61.3	115 000
Term live born child 12 months	8333	43.4	10 745	53.2	24 600
Live born child 12 months	8333	46.0	10 745	63.9	13 500
Term live born child all cycles[b]	10 033	56.6	12 657	62.3	46 000
Live born child all cycles[b]	10 033	60.0	12 657	73.8	19 100

[a]C/E ratio, cost-effectiveness ratio.
[b]Analysis on all available treatment cycles, including cycles performed after the 12 months period, and including cycles in excess of the three or four cycles that were refunded.



The MILD STIMULATION effectiveness increases thanks to an higher number of cycles. BUT also to the costs

Cost-effectiveness analysis

Letter to the editor *(Craft and Hodgson)*

Correspondence

STUDY DESIGN:

Why did they compare MILD STIMULATION + SINGLE ET vs CONVENTIONAL STIMULATION + DOUBLE ET and not SINGLE ET for both the strategies?

STUDY DESIGN (2):

Why did they consider up to 4 cycles for the MILD STIMULATION group VS up to 3 cycles for the CONVENTIONAL STIMULATION group in a 12-month period and not up to 3 cycles in a 10-month period for both the strategies?

OUTCOME:

Is it fair for patients to achieve a lower live-birth rate with the mild stimulation protocol than with standard?

CONCLUSION:

Biological variance should be addressed before promoting mild stimulation protocol as a fixed philosophy. Age, basal FSH and antral follicle counts should be considered.

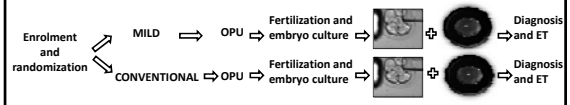
*Ian Craft, David Hodgson
margaret@lfc.org.uk
London Fertility Centre, Cozens House, 112a Harley Street, London W1G 7JH, UK

Correlation between euploidy and stimulation protocol Baart et al., 2007

Human Reproduction Vol.22, No.1 pp. 980–988, 2007
Advance Access publication January 4, 2007

Milder ovarian stimulation for *in-vitro* fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial

Esther B.Baart[1,2,5], Elena Martini[2], Marinus J.Eijkemans[3], Diane Van Opstal[4], Nicole G.M.Beckers[2], Arie Verhoeff[2], Nicolas S.Macklon[1] and Bart C.J.M.Fauser[1,2]



PRIMARY OUTCOME:
ovarian response & proportion of chromosomally-abnormal embryos/patient

SECONDARY OUTCOME:
proportion of fertilized oocytes, proportion of embryos with normal morphology & proportion of embryos biopsied and diagnosed

Correlation between euploidy and stimulation protocol Baart et al., 2007

Table III. Outcome after IVF and preimplantation genetic screening diagnosis following conventional or mild ovarian stimulation

	Conventional stimulation	Mild stimulation	*P**	Difference (95% CI)
IVF characteristics				
No. of patients	40	55[a]		
Oocytes retrieved (n)	12.1 ± 5.7	8.3 ± 4.7	<0.01	3.7 (1.6–5.9)
Fertilization rate (%)	57 ± 28	55 ± 30	0.81	1.5 (−10–13)
Embryos (2pn)	6.8 ± 3.0	4.7 ± 3.9	0.03	2.0 (0.2–3.9)
Good quality embryo rate[b] (%)	35 ± 29	51 ± 40	0.04	−17 (−32–1)
Diagnosis based on first cell biopsied[c]				
No. of patients	33	40		
Embryos diagnosed	4.8 ± 3.5	3.6 ± 2.7	0.10	1.2 (−0.2–2.7)
Percentage of embryos diagnosed (%)	40 ± 22	45 ± 21	0.38	−5 (−15–6)
Abnormal embryos/embryos diagnosed (%)	63 ± 28	45 ± 35	0.016	19 (4–34)
Diagnosis based on two cells				
No. of patients	30	38		
Abnormal embryos/embryos diagnosed (%)	73 ± 33	55 ± 42	0.045	19 (0.3–36)
Mosaic embryos/embryos diagnosed (%)	65 ± 37	37 ± 39	0.004	28 (10–47)
Clinical outcome measures				
Embryos/transfer	1.45 ± 0.51	1.46 ± 0.51		
Ongoing pregnancy rate/started cycle (%)	7/41 (17)	12/63 (19)		
Ongoing pregnancy rate/transfer (%)	7/38 (23)	12/35 (34)		

Data are expressed on a per patient basis and are presented as mean and SD, unless otherwise stated.
* *P*-values are from a two-sample t-test.
[a]One patient out of the 56 undergoing oocyte retrieval yielded no oocytes.
[b]Embryos with normal morphology were defined as embryos with timely development, <20% fragmentation, equally sized blastomeres and small or no irregularities observed in the cytoplasm.
[c]Diagnosis of normal or abnormal embryos was based on the FISH results of one cell. If two cells were available, the first cell biopsied was determined in retrospect and used for diagnosis. Rates were calculated first per patient and then averaged.
[d]Only embryos, whose two cells were available for diagnosis were taken into account. An embryo was considered abnormal if at least one of the two cells showed an abnormal result.

Correlation between euploidy and stimulation protocol Labarta et al., 2012

JCEM ONLINE
Advances in Genetics—Endocrine Research

Moderate Ovarian Stimulation Does Not Increase the Incidence of Human Embryo Chromosomal Abnormalities in *in Vitro* Fertilization Cycles

Elena Labarta, Ernesto Bosch, Pilar Alamá, Carmen Rubio, Lorena Rodrigo, and Antonio Pellicer

Department of Human Reproduction, Instituto Valenciano de Infertilidad, University of Valencia, 46015, Valencia, Spain

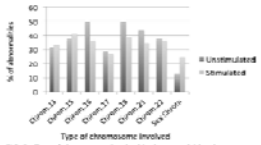


FIG. 3. Type of chromosome involved in the aneuploid embryos group. No statistically significant differences ($P > 0.05$) were observed in any of the analyzed chromosomes between the unstimulated and the stimulated cycle. Chrom., Chromosome.

Conclusions: Moderate ovarian stimulation in young normo-ovulatory women does not significantly increase the embryo aneuploidies rate in *in-vitro* fertilization derived human embryos as compared with an unstimulated cycle.

(*J Clin Endocrinol Metab* 97: E1987–E1994, 2012)

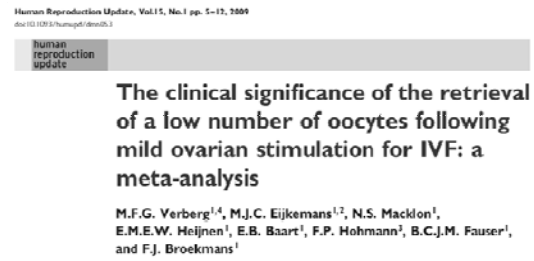
Correlation between euploidy and stimulation protocol

The scientific soundness of both studies is limited by the fact that 9chr FISH is an unappropriate strategy to perform PGS and that blastomere stage is subjected to a number of problems among which mosaicism is the most critical.

These results could then be misleading and the analysis might be better reconducted at the blastocyst strage through 24chr platforms (aCGH, qPCR, …)

Relationship between response to the stimulation and implantation rate

Verberg at al., 2009


Human Reproduction Update, Vol.15, No.1 pp. 5–12, 2009

human reproduction update

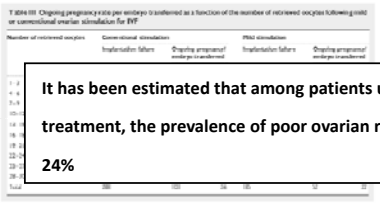
The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis

M.F.G. Verberg[1,4], M.J.C. Eijkemans[1,2], N.S. Macklon[1], E.M.E.W. Heijnen[1], E.B. Baart[1], F.P. Hohmann[2], B.C.J.M. Fauser[1], and F.J. Broekmans[1]

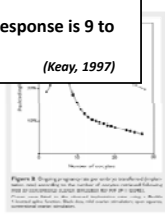
Meta-analysis of 3 RCTs comparing mild to conventional stimulation protocol

Relationship between response to the stimulation and implantation rate

Verberg at al., 2009

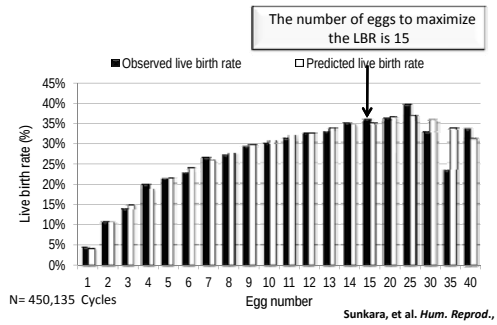


It has been estimated that among patients undergoing IVF treatment, the prevalence of poor ovarian response is 9 to 24% ***(Keay, 1997)***



MILD STIMULATION PROTOCOLS elicit better results in poor responders WHILE STANDARD STIMULATION PROTOCOLS elicit better results in good responders

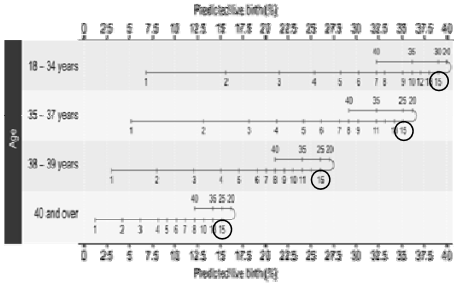
Number of oocytes needed to maximize live birth rate



N= 450,135 Cycles

Sunkara, et al. *Hum. Reprod.*, 2011

15 eggs in all patients population



Sunkara, et al. *Hum. Reprod.*, 2011

Agenda

- **Definition of poor and high responders**
- **Description of different stimulation protocols**
- **Literature review of comparisons between conventional stimulation and mild stimulation**
- **Retrospective analysis of our data**
- **Conclusions**

Retrospective analysis of our data

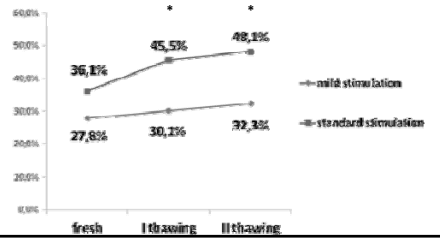
Good responders
Fresh cycles characteristics

	Antagonist	Long	
Cycles (N)	226	233	
Age (m±SD)	36.2±3.0	36.5±3.2	ns
Previous IVF cycle performed (m±SD)	1.7+0.2	1.6+0.4	ns
Baseline FSH (m±SD)	7.5±3.4	7.2±2.9	ns
Gonadotropins (m±SD)	1840.1±845.3	2074.4±928.7	P<0.001
Days of Stimulation (m±SD)	11.0±1.8	12.8±1.7	P<0.001
COC retrieved (m±SD)	8.6±5.3	12.6±5.7	P<0.001
Metaphase II (m±SD)	6.4±4.1	9.4±5.7	P<0.001
Vitrified oocytes (m±SD)	3.3±4.0	4.9±3.5	P<0.01
Obtained embryos (m±SD)	3.6±2.1	4.4±2.0	P<0.001
Top quality embryos (m±SD)	2.2±1.8	2.7±1.9	P<0.005
Vitrified embryos (m±SD)	1.1±1.6	1.7±1.7	P<0.005

Retrospective analysis of our data

Good responders
Cumulative ongoing PR/cycle

	Antagonist	Long	
Fresh cycles (%)	63/226 (27.8)	84/233 (36.1)	ns
I warming (%)	70/226 (30.1)	106/233 (45.5)	P=0.0015
II warming (%)	73/226 (32.3)	112/233 (48.1)	P<0.005



Conclusions

-**Mild protocols of stimulation are less expensive than standard stimulation ones, but need more cycles to reach a comparable outcome**

- **A putative influence of stimulation protocols on embryo euploidy is yet to be described through a reliable analysis method and an appropriate biopsy strategy**

- **The number of retrieved oocytes associated with the highest implantation rate in every category of patients is 15**

- **Standard protocols of stimulation for good responder patients seem to be more effective than mild ones, in particular when considering also embryo transfers carried out after thawing the delivery rate per started cycle becomes significantly higher with a standard stimulation protocol than with a mild one**

HIGHER COST-EFFECTIVENESS OF MILD STIMULATION PROTOCOLS IS YET TO BE PROPERLY DEMONSTRATED IN ORDER TO REACH A GENERALLY-ACCEPTED CONSENSUS AMONG PHYSICIANS

Repetitive natural cycles or mild stimulation protocols offer most benefit per spent

Prof. Michael von Wolff, MD

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

University Women`s Hospital
Department of Gynecological Endocrinology and Reproductive Medicine

I hereby confirm that we do not have

any commercial and financial

relationships related to this presentation

and its contents

Repetitive natural cycles or mild stimulation protocols offer most benefit per spent

Learning objectives:

- **What are natural cycle or mild stimulation protocols?**
- **What kind of benefits offer these kind of treatments?**
- **What does an optimized NC-protocol look like?**
- **What are the pregnancy rates one can expect?**
- **How long does the treatment take to achieve a pregnancy?**
- **How much does an optimized cycle cost the IVF-center?**
- **What are the costs per pregnancy?**

What are natural cycle or mild stimulation protocols?

Rotterdam ISMAAR (International Society for Mild Approaches in Assisted Reproduction) Consensus Group-Classification (Nargund et al., 2007):

Conventional IVF:

IVF with gonadotropin dosages to receive the highest possible number of oocytes with low risk of OHSS

Mild IVF:

Conventional stimulation IVF with low dosages of gonadotropins or clomifencitrate

Natural Cycle IVF:

~~**IVF without any stimulation**~~

Modified Natural Cycle IVF

Natural Cycle IVF with HCG to induce ovulation

Are we summarizing different therapies as one treatment?

Mild IVF and Natural Cycle-IVF (NC-IVF) are completely different techniques concerning:

- **Costs (In mild IVF but not in NC-IVF: expensive HMG/FSH)**
- **Downregulation (In mild IVF but not in NC-IVF: GnRHa or GnRHant)**
- **Aspiration (In mild IVF but not in NC-IVF: Aspiration with anaesthesia)**

Conclusion:
Mild IVF and NC-IVF are different techniques and can not be combined for a comparison with conventional IVF

To visualize the problem

You can not compare a Mercedes with both, a Golf and a Smart. You have to choose the car you want to compare the Mercedes with

Mercedes	Golf	Smart
		
= cIVF	= Mild IVF	= Modified NC-IVF

Definitions in this presentation

Therefore: Definitions used in this presentation:

- **Mercedes = cIVF: Conventional IVF with high dosages of HMG/FSH**
- **Smart = Mod. NC-IVF: Any IVF without HMG/FSH and without high dosages of CC, allowing repetitive, monthly IVF-cycles (i.e.: high dosages of CC frequently require a break of one month due to formation of ovarian cysts)**

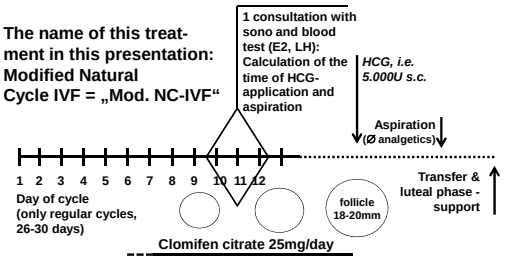
Another question: What does „benefit per spend“ mean?

A list of 10 possible benefits:

1. **Fewer consultations?**
2. **No injections?**
3. **Treatment without side effects?**
4. **Faster aspiration?**
5. **Aspiration without anaesthesia?**
6. **No complications such as OHSS?**
7. **No twins or triplets?**
8. **Lower costs per cycle?**
9. **Lower costs per pregnancy?**
10. **Pregnancy in the shortest possible treatment time?**

The „Smart"-treatment chosen for the comparison with the „Mercedes"-treatment:

The name of this treatment in this presentation: Modified Natural Cycle IVF = „Mod. NC-IVF"



von Wolff et al., submitted

Why Mod. NC-IVF and not NC-IVF?

Each patient, with a maximum of one previous cIVF received a NC-IVF cycle followed by a Mod. IVF-cycle

	NC-IVF	Mod. NC-IVF
Cycles (n)	55	49
Age (years)	35.1 (range: 21-42)	
Consultations before aspiration	1.1	1.1
Premature ovulations / cycle (%)	29	8
Transfers / cycle (%)	39	61
Clinical pregnancy rate / cycle (%)	12.4%	
Multiple pregnancies (%)	0	0

Conclusion: Mod. NC-IVF is much more efficient, resulting in much higher transfer rates / cycle

von Wolff et al., submitted

NC-IVF in previous studies

	Janssens et al., 2000	Polyzos et al., 2012	Roesner et al., 2012
Cycles (n)	75	390	591
Age (years)	22-38	37.3 ± 3.9	?
Consultations before aspiration	4?	4?	?
Premature ovulation (%)	19%	?	23%
Transfers (%)	47%	42%	31%
Clinical pregnancy rate / cycle (%)	9%	4.6% (low responder)	4.2%

Conclusion:
These data clearly demonstrate, that NC-IVF without modifications offer less benefits than Mod. NC-IVF

Benefit 1: fewer consultations?

	Cumulative pregnancy rate /initiated cycle(s)	Cumulative number of required consultations (n)[2]
cIVF 1 cycle without cryo cycles	30%[4]	5
cIVF 2 cycles without cryo cycles	51%[4]	3
1 cryo cycle following cIVF	20%[4]	3
cIVF plus 1 cryo cycle	44%[4]	8
Mod. NC-IVF, 1 cycle	12%	2.6
Mod. NC-IVF, 2 cycles	23%[5]	5.2
Mod. NC-IVF, 3 cycles	32%[5]	7.8
Mod. NC-IVF, 4 cycles	40%[5]	10.4
Mod. NC-IVF, 5 cycles	47%[5]	12.0

[2] Calculations are based on a transfer rate of 100% in cIVF and cryo cycles and 60% in NC-IVF.
[4] Approximated according to pregnancy rates in the ESHRE register (Ferraretti et al. 2012)
[5] Approximated according to pregnancy rates in Berne (12%, table 1): >1 cycle calculated: i.e. 2 cycles: 100-88[2]/100)

Conclusion: Mod. NC-IVF require around 40-50% more consultations / achieved pregnancy than cIVF

von Wolff et al., submitted

Benefit 2: No injections?

Mod. NC-IVF	cIVF
1 injection / cycle	**≥15 injections / cycle** **1-2 injections /day**
Injections to achieve a 50% cumulative pregnancy rate: 6 injections	**Injections to achieve a 50% cumulative pregnancy rate: ≥20-30 injections**

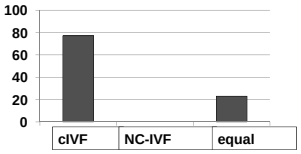
Conclusion:
Mod. NC-IVF require much fewer injections than cIVF

Benefit 3: Treatment without side effects?

Mod. NC-IVF	cIVF
No side effects	Dyscomfort due to low and high estrogen concen-trations

13 patients received both: Mod. NC-IVF and cIVF.

Question: Which kind of treatment did you find more unplesant until aspiration ?



Conclusion:
Mod. NC-IVF has less side effects than cIVF and women experience the time until aspiration less unpleasant

Benefit 4: Faster aspiration?

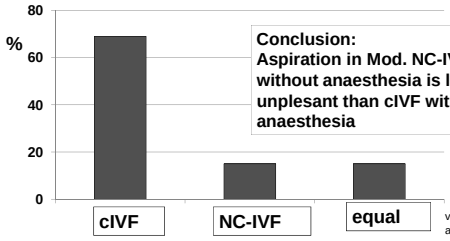
Mod. NC-IVF	cIVF
Aspiration time: 2 min. Patient is allowed to eat before aspiration	Aspiration time: ≥ 5 min. Patient is not allowed to eat anything beforehand Anaesthesia required

Conclusion:
Aspiration in Mod. NC-IVF is easier and faster than in cIVF

Benefit 5: Aspiration without anaesthesia and analgetics?

13 patients received both: an aspiration in cIVF with anaethesia and an aspiration in NC-IVF without any anaethesia and analgetics.

Question: Which kind of aspiration did you find more unplesant ?



Conclusion:
Aspiration in Mod. NC-IVF without anaesthesia is less unplesant than cIVF with anaesthesia

von Wolff et al., submitted

Benefit 6: No complications such as OHSS?

Mod. NC-IVF	cIVF
Berne: OHSS: 0%	Berne: •OHSS without hospitalisation: around 2% •OHSS III° requiring hospitalisation: around 1% (Antagonist protocols)

Conclusion:
Mod. NC-IVF is a therapy without any OHSS

Benefit 7: No twins and triplets?

Mod. NC-IVF	cIVF
Twins / pregnancy: Berne: <1% Janssens et al., 2000: ? Polyzos et al., 2012: ? Roesner et al., 2012: ?	Twins / pregnancy: Europe*: Twins: 21% / pregnancy

Conclusion:
Mod. NC-IVF is a therapy almost without any multiple pregnancies

*Ferraretti et al., 2012

Benefit 8: Lower costs per cycle?

	cIVF - 1 fresh cycle[1]	cIVF - 1 Cryo cycle following cIVF[2]	NC-IVF - 1 fresh cycle[3]
Total required consultations /cycle (n)[4]	5	3	3
Required labour - physician (min.)	105	60	75
Required labour - secretaries and nurses (min.)	90	45	60
Required labour - IVF-laboratory staff (min.)	250	120	195
Required medication (€)	1200,-	70,-	40,-
Required blood tests (E2, LH) (€)	60,-	0	35,-
Required consumables IVF-laboratory (€)[5]	184,-	191,-	179,-
Anaesthesia and postoperative care (€)	500,-	0	0
Total costs consumables, anaesthesia, blood tests	1744,-	261,-	254,-
Total labour (min.)	445	225	330
Total costs (€)[6]	2188,-	383,-	431,-

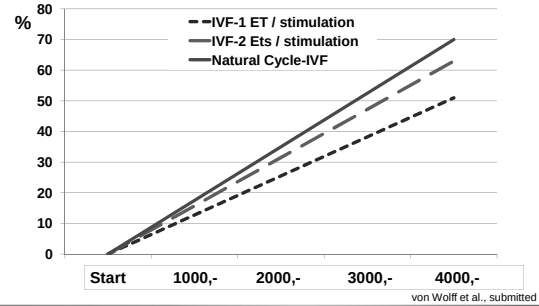
[1] cIVF including gonadotropins and GnRH agonists/antagonists
[2] Including cryopreservation by vitrification and cryo cycles with estrogen/progesterone supplementation
[3] NC-IVF with clomiphene citrate
[4] According to treatment protocol in Berne
[5] 1/3 of cycles fertilization by ICSI, 2/3 by insemination. Gas for incubators, laboratory equipment etc. not included
[6] Physician € 40,-/hour, secretaries & nurses: € 30,-/hour

Conclusion: Mod. NC-IVF is much cheaper per cycle than cIVF

von Wolff et al., submitted

Benefit 9: Lower costs per pregnancy?

Pregnancy rate per money spent



von Wolff et al., submitted

Benefit 10: Pregnancy in the shortest possible treatment time?

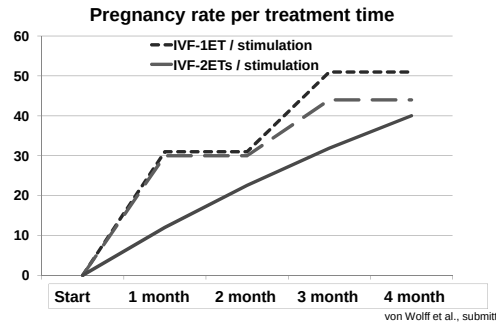
	Cumulative pregnancy rate /initiated cycle(s)	Cumulative required treatment time (month)[3]
cIVF 1 cycle without cryo cycles	30%[4]	1
cIVF 2 cycles without cryo cycles	51%[4]	3
1 cryo cycle following cIVF	20%[4]	1
cIVF plus 1 cryo cycle	44%[4]	3
NC-IVF, 1 cycle	12%	1
NC-IVF, 2 cycles	23%[5]	2
NC-IVF, 3 cycles	32%[5]	3
NC-IVF, 4 cycles	40%[5]	4
NC-IVF, 5 cycles	47%[5]	5

[3] Including a break of 1 month following a classical IVF-cycle (fresh transfer) and no break between NC-IVF-cycles
[4] Approximated according to pregnancy rates in the ESHRE register (Ferraretti et al. 2012)
[5] Approximated according to pregnancy rates in Berne (12%, table 1): >1 cycle calculated: i.e. 2 cycles: 100-88²/100)

Conclusion: Mod. NC-IVF require more time / achieved pregnancy than cIVF

von Wolff et al., submitted

Benefit 10: Pregnancy in the shortest possible treatment time?



von Wolff et al., submitted

In which catagory does Mod. NC-IVF offer more benefits*?

1. Fewer consultations/achieved pregnancy? **No**
2. No injections? **Yes**
3. Treatment without side effects? **Yes**
4. Faster aspiration? **Yes**
5. Aspiration without anaesthesia? **Yes**
6. No complications such as OHSS? **Yes**
7. No twins or triplets? **Yes**
8. Lower costs per cycle? **Yes**
9. Lower costs per achieved pregnancy? **Yes**
10. Pregnancy in the shortest possible treatment time? **No**

***** Mod. NC-IVF only in women with regular menstrual cycles.

Summary

- **NC-IVF require some modifications („Mod. NC-IVF“) and needs to be performed under optimized conditions to be a real alternative for conventional IVF („cIVF“)**
- **Mod. IVF can only effectively be performed in women with regular menstrual cycles**
- **Mod. NC-IVF provides many benefits in comparison to cIVF**
- **Costs per achieved pregnancy seem to be lower in Mod. NC-IVF**
- **Treatment time per achieved pregnancy seems to be higher in Mod. NC-IVF**
- **Mod. NC-IVF should not be performed in women around the age of 40 with a high ovarian reserve as treatment time is essential**

References

Ferraretti AP, Goossens V, de Mouzon J, Bhattacharya S, Castilla JA, Korsak V et al. European IVF-monitoring (EIM); Consortium for European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe: results generated from European registers by ESHRE. Hum Reprod. 2012;27:2571-84.

Janssens RM, Lambalk CB, Vermeiden JP, Schats R, Schoemaker J, Hum Reprod. In-vitro fertilization in a spontaneous cycle: easy, cheap and realistic. 2000 Feb;15(2):314-8.

Nargund G, Fauser BC, Macklon NS, Ombelet W, Nygren K, Frydman R, Rotterdam ISMAAR Consensus Group. The ISMAAR proposal on terminology for ovarian stimulation for IVF. Hum Reprod. 2007 Nov;22(11):2801-4. Epub 2007 Sep 12.

Polyzos NP, Blockeel C, Verpoest W, De Vos M, Stoop D, Vloeberghs V, Camus M, Devroey P, Tournaye H. Live birth rates following natural cycle IVF in women with poor response according to Bologna criteria. Hum Reprod. 2012 Dec;27(12):3481-6. doi: 10.1093/humrep/des318. Epub 2012 Aug 30.

Roesner S., Pflaumer U., Germeyer A., Montag M., Strowitzki T., Toth B. Natural Cycle IVF-evaluation in 591 cycles. Arch Gynecol Obstet. 2012 PO-Endo 04.15

Is the clinical impact of a poor response female age dependant?

Simone Broer, MD, PhD
Reproductive Medicine
University Medical Center Utrecht
The Netherlands

Conflicts of interest

No potential conflicts of interest

Learning objectives

- The influence of age on the pregnancy prospects for poor responders
- Integration of quality and quantity aspects for individualizing pregnancy prospects
- Predictive possibilities for pregnancy prospects of poor responders

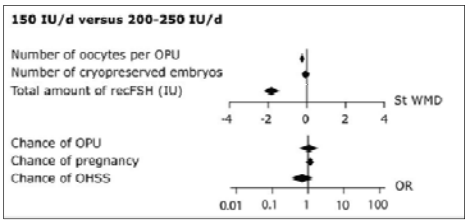
Overview

- Definitions
- Poor responders and pregnancy prospects
- Poor responders in age categories
- Quality aspects
- Prediction of prospects for poor responders
- Quantity vs quality
- Conclusions

Poor responders

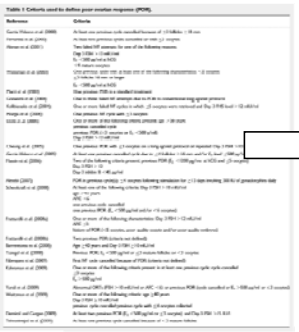
- Diminshed ovarian reserve / ovarian ageing?
- Sub Optimal stimulation?

Suboptimal exposure to gonadotrophins



Sterrenburg et al., HRU 2011

Poor ovarian response

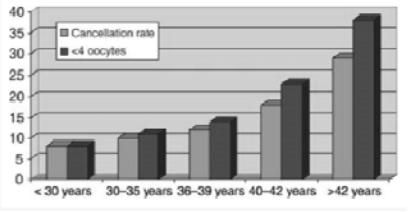


At least 2 of the 3 features must be present

1. Advanced maternal age (≥40) or any other risk factor for POR
2. A previous POR (≤3 oocytes) with conventional stimulation protocol
3. Abnormal ovarian reserve test

Ferraretti et al, ESHRE workshop, Hum Reprod 2011

Incidence of poor response



Percentage of poor responders increases with age

Ferraretti et al, ESHRE workshop, Hum Reprod 2011

Pregnancy rates in Poor vs Normal responders

Author	N	Poor responders	Normal responders	P-value
Biljan *et al.*	828	11.9%	29.4%	0.015
Hendriks *et al.*	222	7.6%	25.9%	0.001
Saldeen *et al.*	1803	9.0%	32.6%	<0.001
Sutter, de *et al.*	9644	17.0%	35.0%	<0.001
Timeva *et al.*	975	12.1%	27.8%	<0.05
Zhen *et al.*	472	14.8%	36.7%	<0.05
Pooled estimate	**14338**	**14.8%**	**34.5%**	

Oudendijk et al., HRU 2012

Pregnancy rates in Poor Responders Female Age categories

Author	N	Female age	p Value
		28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 >46	
Zhen *et al.*	472	18.5%	2.8%	p<0.001
Rooij, van *et al.*	47	13.0%	4.0%	
Biljan *et al.*	42	27.8%	4.2%	p>0.05
Saldeen *et al.*	290	14.0%	3.0%	
Inge *et al.*	39	27.1%	12.7%	
Sutter, de *et al.*	1280	23.0%	12.0%	p<0.0001
Galey-Fontaine *et al.*	163	14.6%	4.9%	p<0.04
Ulug *et al.*	290	19.5%	7.2%	1.5%	p<0.04
Hanoch *et al.*	143	19.3%	6.0%	6.5%	p=0.004
Yih *et al.*	4862	35%	21%	17%	11%	

Oudendijk et al., HRU 2012

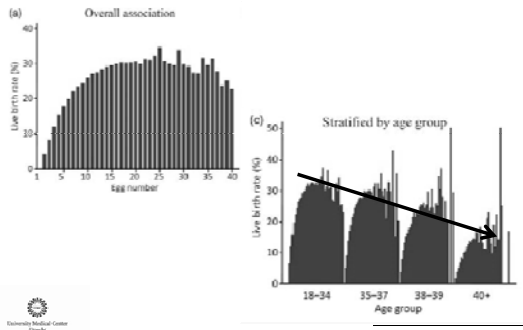
Pregnancy prospects per number of oocytes retrieved

Study	N	1	2	3	4	5	p Value
Baka *et al.*	96c	0.0%	15.2%	12.5%			p=0.41
Gaast, van der *et al.*	7422w	7.0%	11.5%	15.6%	18.6%	21.7%	–
Timeva *et al.*	975w	0.0%	10.8%	8.7%	11.5%	22%*	p<0.05
Ulug *et al.*	290c	2.3%	4.3%	11.5%	15.9%		p<0.05

N = number of women(w)/ cycles(c) included, PR= pregnancy rate,

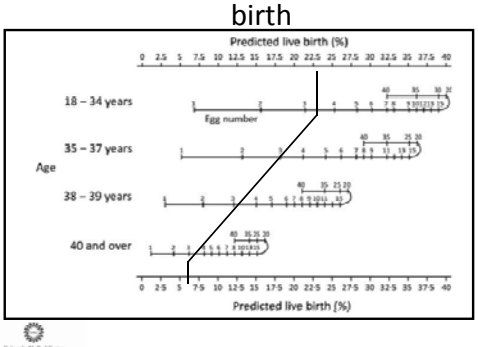
Oudendijk et al., HRU 2012

Live birth rate per number oocytes



Sunkara et al., HRU 2011

Nomogram for the prediction of live birth



Sunkara et al., HRU 2011

Quantity versus Quality?

OR

Are they related?

Miscarriage rates

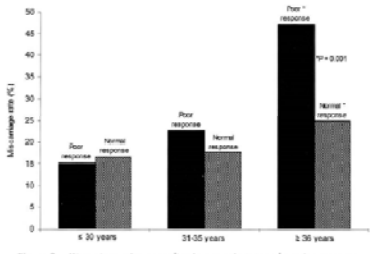


Figure 2 Miscarriage rates according to age category and ovarian response.

Haadsma et al., RBM online 2010

Trisomic pregnancy rates

Table I ORs of trisomic pregnancy associated with parameters of oocyte quantity, subfertility and lifestyle characteristics

	n	Cases[a] (n = 28; median (10th–90th percentile) or no. (%))	Controls[a] (n = 140; median (10th–90th percentile) or no. (%))	OR for trisomic pregnancy (95% CI)[b]	P-value
Parameters of oocyte quantity					
History of ovarian surgery before IVF cycle	168				
Yes		5 (17.9)	7 (5.7)	3.3 (1.0–10.5)	0.04
No		23 (82.1)	133 (94.3)	1.0 (reference)	—
Total number of oocytes retrieved in IVF cycle	168	6.5 (2–19)	8 (4–18)	1.0 (0.9–1.0)	0.32
Number of retrieved oocytes in categories	168				
1–4		9 (32.2)	17 (12.1)	3.7 (1.2–11.7)	0.03
5–8		8 (28.6)	57 (40.7)	0.9 (0.3–2.2)	0.76
≥9		11 (39.3)	66 (47.1)	1.0 (reference)	
Poor response in IVF cycle	168				
Yes (≤3 oocytes)		4 (14.3)	9 (6.4)	2.7 (0.7–10.7)	0.15
No (≥4 oocytes)		24 (85.7)	131 (93.6)	1.0 (reference)	

Haadsma et al, Hum Reprod 2010

Euploidy rates – day 3 embryo

Table 1 Embryonic euploidy rate per cycle and the proportion of women who had at least one euploid embryo following day-3 biopsy and array CGH.

No. of day-3 embryos	Oocyte donor	All women (age in years)			
		<35	35–39	40–42	>42
1–4					
Women (n)	3	27	43	60	24
Euploid embryos (%)	75.0	35.2	28.8	17.2	6.9
Women with ≥ 1 euploid embryo (n, %)	3 (100)	18 (66.7)	24 (55.8)	26 (43.3)	6 (25.0)
5–7					
Women (n)	9	48	98	39	16
Euploid embryos (%)	57.7	57.3	25.9	16.1	6.3
Women with ≥ 1 euploid embryo (n, %)	9 (100)	44 (91.7)	83 (84.7)	36 (51.0)	4 (25.0)
8–10					
Women (n)	6	42	71	40	17
Euploid embryos (%)	54.1	36.0	28.5	17.5	7.8
Women with ≥ 1 euploid embryo (n, %)	6 (100)	40 (95.2)	66 (93.0)	29 (72.5)	9 (52.9)
>10					
Women (n)	24	64	70	36	11
Euploid embryos (%)	42.7	44.7	32.4	15.6	14.8
Women with ≥ 1 euploid embryo (n, %)	24 (100)	64 (100)	68 (97.1)	30 (83.3)	10 (90.9)

Odds Ratio of at least one euploid embryo by female age

OR 0.79
(95%CI 0.75-0.85)

Odds Ratio of at least one euploid embryo by every additonal embryo available

OR 1.33
(95%CI 1.24-1.43)

Every year increase female age = decrease 2.4% euploidy rate

Cohort size not significantly associated with euploidy rate

Ata et al., RBM online 2012

Euploidy rates – blastocyts

Table 2 Blastocyst euploidy rate and the proportion of women who had at least one euploid blastocyst following day-5 biopsy and array CGH.

No. of blastocysts	Oocyte donor	All women (age in years)			
		<35	35–39	40–42	≥43
1–4					
Women (n)	7	13	28	28	8
Euploid embryos (%)	70.2	66.0	49.1	34.2	16.7
Women with ≥ 1 euploid embryo (n, %)	7 (100)	12 (92.3)	22 (78.6)	17 (60.7)	3 (37.5)
5–7					
Women (n)	4	15	26	16	3
Euploid embryos (%)	72.5	69.9	52.3	31.0	13.3
Women with ≥ 1 euploid embryo (n, %)	4 (100)	15 (100)	25 (97.2)	13 (81.3)	2 (66.7)
8–10					
Women (n)	4	12	15	7	2
Euploid embryos (%)	62.4	56.7	48.3	27.4	22.5
Women with ≥ 1 euploid embryo (n, %)	4 (100)	12 (100)	15 (100)	6 (85.7)	2 (100)
>10					
Women (n)	4	5	7	7	1
Euploid embryos (%)	68.7	51.3	51.4	40.9	16.7
Women with ≥ 1 euploid embryo (n, %)	4 (100)	5 (100)	7 (100)	7 (100)	1 (100)

Odds Ratio of at least one euploid embryo by female age

OR 0.82
(95%CI 0.70-0.94)

Odds Ratio of at least one euploid embryo by every additonal embryo available

OR 1.55
(95%CI 1.25-1.93)

Every year increase female age = decrease 2.9% euploidy rate

Cohort size not significantly associated with euploidy rate

Ata et al., RBM online 2012

Quality and female age

Table 5 Effect of females ageing on chromosome alignment in MII oocytes

Age of mice	No. of mice examined	No. of oocytes examined	Chromosome alignment	
			Normal (%)	Abnormal (%)
Young	10	70	59 (84.3)[a]	11 (15.7)[c]
Middle-aged	13	62	38 (61.3)[b]	24 (38.7)[d]
Aged	15	61	31 (50.7)[b]	30 (49.3)[d]

Chromosomal aneuploidy mostly due to non-disjunction and meiotic errors

Chromosomal aneuploidy is increased with female age

Long-Bo Cui et al., Zygote 2013

Quality and biological age

Table 2. Chromosome anomalies of 3.5-day embryos in CBA/Ca mice: variation according to maternal age and unilateral ovariectomy

Experimental group	Maternal age (days)	Total embryos analysed	Percent analysed	Chromosome analysis								Percent aneuploidy
				4 n	3 n	2 n/3 n	41	40	39	38	37	
ovx	63–91	67	29.0	–	–	–	–	59	8	–	–	11.9
Sham	63–91	66	27.7	–	1	–	–	61	4	–	–	6.1
ovx	154–182	75	29.2	–	1	–	3	60	10[1]	1	–	17.3
Sham	154–182	65	27.1	–	–	–	–	62	3[1,2]	–	–	4.6
ovx	245–280	41	28.1	2	–	1	3	35	7[1]	3	1	22.0
Sham	245–280	38	24.9	–	1	–	1	45	6	3	2	12.1
Sham	308–339	40	20.8	–	1	–	1	36	8[1,2]	–	–	19.0

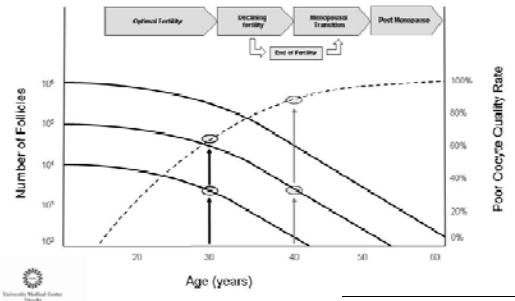
[1] Represents embryos in which two good analysable cells were found to have 39 chromosomes

Indepent of female age, aneuploidy occurs more often in mice who underwent ovariectomy.

Aneuploidy is related to biological age

Brook et al., Human Genetic 1984

Integration of quantity and quality



Broer, Academic PhD Thesis, 2011

Can we predict which poor responder will become pregnant?

Univariable Models	OR	95% CI	P-value
Patient characteristics			
Age	0.96	0.90-1.02	0.178
BMI	0.97	0.88-1.08	0.622
Duration of subfertility	0.82	0.68-0.99	0.039
Ovarian Reserve Tests			
FSH	1.04	0.97-1.11	0.322
AFC	1.06	0.99-1.14	0.092
AMH	1.28	1.04-1.59	0.020

	Ongoing Pregnancy Prediction		
Univariable models	AUC	95%CI	n=
Age	0.54	0.40-0.69	388
Duration of subfertility	0.51	0.32-0.69	250
AMH	0.57	0.38-0.75	166
Multivariable models	AUC	95%CI	n=
Age and AFC			
Age	0.55	0.36-0.74	223
Age & AFC	0.57	0.38-0.78	
Age and AMH			
Age	0.55	0.37-0.74	166
Age & AMH	0.57	0.38-0.75	

IPD-PROPR
Subgroup analysis of the IMPORT and EXPORT study

Dolleman, Broer et al., on behalf of the IMPORT & EXPORT study group, Manuscript in writing

Nomogram
Age and Number of Oocytes

Chances of ongoing pregnancies across number of oocytes categories

Age (years)	Number of oocytes: 1	2	3	4	5	>5
<31	22.2%	28.4%	12.6%	20.2%	15.3%	26.2%
95% CI	*7-5*	*13-51*	*5-30*	*9-40*	*6-33*	*18-37*
31-35	22.6%	28.9%	12.9%	20.6%	15.6%	26.6%
95% CI	*7-53*	*14-51*	*5-29*	*9-39*	*7-32*	*20-35*
36-38	19.3%	25.0%	10.9%	17.6%	13.2%	23.0%
95% CI	*6-48*	*11-47*	*4-26*	*8-35*	*5-29*	*16-32*
38-40	17.0%	22.0%	9.4%	15.4%	11.5%	20.3%
95% CI	*5-45*	*9-44*	*3-23*	*6-33*	*5-26*	*12-32*
>40	12.1%	16.0%	6.5%	10.9%	8.0%	14.6%
95% CI	*3-36*	*6-35*	*2-17*	*4-25*	*2-20*	*3-20*

Dolleman, Broer et al., on behalf of the IMPORT & EXPORT study group, Manuscript in writing

Nomogram of AFC and age

Percentage of ongoing pregnancies across AFC categories

Age (years)	Antral Follicle Count (2-10 mm follicles): <4	4-8	8-10	10-15	>15
<31	13.0%	16.2%	25.3%	17.3%	26.3%
95% CI	*4-39%*	5-45%	*7-61%*	*4-50%*	*5-70%*
31-35	7.85%	9.9%	15.9%	10.4%	16.6%
95% CI	*3-21%*	*4-23%*	*6-36%*	*3-28%*	*4-52%*
36-38	9.75%	12.3%	19.4%	12.9%	20.2%
95% CI	*4-23%*	*5-28%*	*7-43%*	*4-33%*	*5-57%*
38-40	13.5%	16.8%	25.8%	17.6%	26.8%
95% CI	*5-31%*	*7-37%*	*9-54%*	*5-46%*	*5-70%*
>40	7.7%	9.7%	15.6%	10.3%	16.3%
95% CI	*3-18%*	*4-23%*	*5-39%*	*3-31%*	*3-56%*

Dolleman, Broer et al., on behalf of the IMPORT & EXPORT study group, Manuscript in writing

Nomogram of AMH and Age

Percentage of ongoing pregnancies across AMH categories

		Antimullerian Hormone (ng/ml)				
		<0.4	0.4-0 .8	0.8-1.6	1.6-2.8	>2.8
Age (years)	<31	17.8%	19.9%	30.3%	25.6%	40.2%
	95% CI	*6-44%*	*7-44%*	*12-58%*	*7-62%*	*15-73%*
	31-35	13.8%	15.4%	24.2%	20.2%	33.0%
	95% CI	*5-34%*	*6-34%*	*12-43%*	*6-49%*	*11-65%*
	36-38	8.1%	9.2%	15.1%	12.3%	21.5%
	95% CI	*2-24%*	*3-24%*	*6-35%*	*3-39%*	*6-54%*
	38-40	15.8%	17.7%	27.3%	22.9%	36.7%
	95% CI	*5-41%*	*6-41%*	*11-53%*	*6-59%*	*10-75%*
	>40	8.0%	9.1%	14.9%	12.2%	21.3%
	95% CI	*2-23%*	*3-27%*	*5-37%*	*3-43%*	*5-57%*

Dolleman, Broer et al., on behalf of the IMPORT & EXPORT study group, Manuscript in writing

Answers...

Is the clinical impact of a poor response female age dependant?

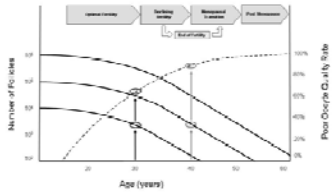
⇩

ABSOLUTELY!

Counseling poor responders

- Age
- Actual number of oocytes
- AMH/AFC prior

INDIVIDUALISE.....



Conclusions

- Poor response must be evaluated in the perspective of a womans age
- Poor responders have lower pregnancy rate/live birth rate compared to normal responders
- Age negatively influences the quality of the oocyte/embry and thereby the pregnancy prospects
- Still, age, actual number of oocytes, AFC and AMH can not predict non-pregnancy

  → but we can use them for counseling!

Acknowledgements

- Frank Broekmans
- Madeleine Dolleman
- Bart Fauser
- Jeroen van Disseldorp
- Ben Willem Mol
- Brent Opmeer
- Rene Eijkemans
- IMPORT study group
- EXPORT study group

References

- Oudendijk et al., The poor responder in IVF: is the prognosis always poor? A systematic review, Human Reproduction Update 2012;18(1):1-11
- Sterrenburg et al., Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis, Human Reproduction Update 2011;17(2):184-96
- Ferraretti et al., ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Human Reproduction 2011; ;26(7):1616-24
- Sunkara et al., Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles, Human Reproduction 2011;26(7):1768-74
- Haadsma et al., Miscarriage risk for IVF pregnancies in poor responders to ovarian hyperstimulation, RBM online 2010;20(2):191-200
- Haadsma et al., A reduced size of the ovarian follicle pool is associated with an increased risk of a trisomic pregnancy in IVF-treated women, Human Reproduction 2010;25(2):552-8
- Ata et al., Array CGH analysis shows that aneuploidy is not related to the number of embryos generated, RBM online 2012; 24(6):614-20
- Broer, Assessment of current and future ovarian reserve status, Academic Thesis, University Utrecht 2011
- Dolleman et al., Predicting Ongoing Pregnancy in Patients With a Poor Response to Ovarian Hyperstimulation in IVF treatment: an IPD meta-analysis, Manuscript in writing
- Long-Bo Cui, et al., The Kunmin mouse: as a model for age-related decline in female fertility in human. Zygote, 2013:1-10.
- Brook et al., Maternal ageing and eneuploid embryos – Evidence from the mouse that biological and not chronological age is the important influence. Human Genetics 1984;66:41-45

Is manipulating intra-ovarian androgen conditions effective in upgrading ovarian response?

Professor Renato Fanchin, MD, PhD

Head, Reproductive Medicine
Hôpital Antoine Béclère, University of Paris-Sud
INSERM U782
Clamart-France
renato.fanchin@abc.aphp.fr

Conflict of Interest

The presenter has no conflict of interest regarding the content of this course

Learning objectives

- Understanding why androgens are likely to be involved in the regulation of ovarian follicle growth
- Understanding what are the strategies that have been used to improving intra-ovarian androgen concentrations
- Awareness of main results of clinical approaches trying to enhance intra-ovarian androgen concentrations

Ovarian function defect

Clinically sizable features:

Less FSH-sensitive follicles

Inadequate response to FSH

Early follicle selection

Poor oocyte competence

Reduced likelihood of pregnancy

Proposed approaches

Increasing gonadotropin dose

Reducing GnRH agonist dose

Using GnRH antagonists

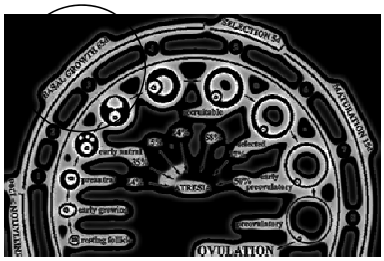
Administering growth hormone

Administering aspirin

Doing ICSI…

Management perspectives

Non-FSH strategies



Androgen hypothesis

Androgen hypothesis

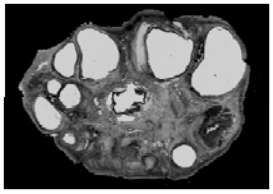
Erickson & Yen, Semin Reprod Endocrinol, 1984

Lobo, JCE&M, 1984

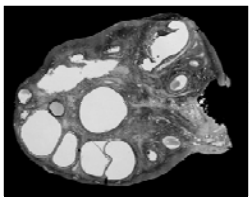
Kase et al, Acta Endocrinol, 1963

Futterweit & Deligdisch, JCE&M, 1986
Pache et al, Histopathology, 1991

Androgen hypothesis



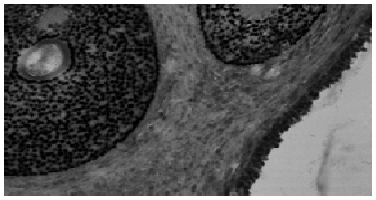
PCOS



Female-to-male transsexual

Androgen hypothesis

Specific immunostaining for androgen receptors in the ovary:

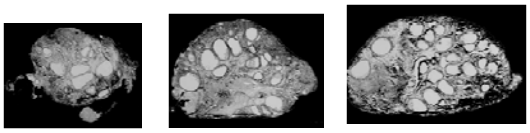


4.2-fold as high in immature as in preovulatory GCs

Hillier et al, Hum Reprod, 1997

Androgen hypothesis

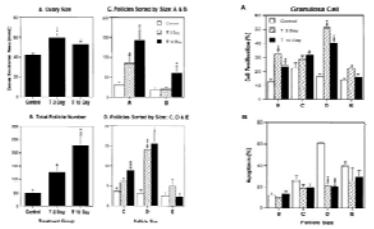
Control Day 3 Day 10



Increased folliculogenesis in androgen-treated rhesus monkeys

Vendola et al, J Clin Invest, 1998

Androgen hypothesis



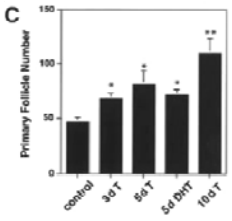
∇ folliculogenesis

∇ GC proliferation

© GC apoptosis

Vendola et al, J Clin Invest, 1998

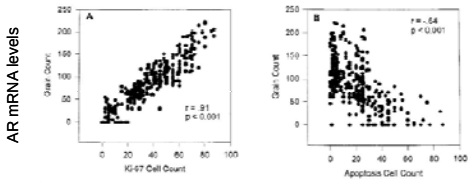
Androgen hypothesis



Androgens promote initial follicle recruitment in rhesus monkeys

Vendola et al, Biol Reprod, 1999

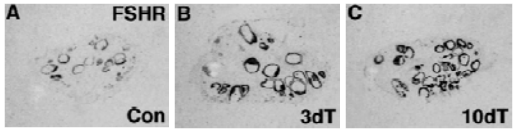
Androgen hypothesis



GC proliferation GC apoptosis

Weil et al, JCE&M, 1998

Androgen hypothesis



Increase in FSHR expression in androgen-treated rhesus monkeys

Weil et al, JCE&M, 1999

Androgen hypothesis

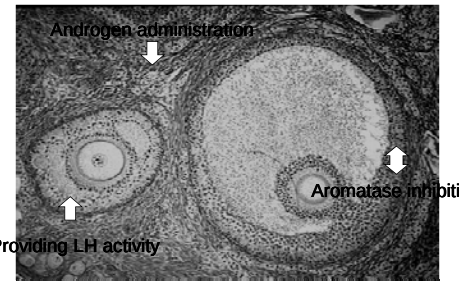
	Estradiol (pg/ml)	Inhibin B (pg/ml)	Testosterone (ng/ml)	Androstenedione (ng/ml)	LH (IU/l)	BMI (kg/m²)	Insulin (mIU/l)
FNPO							
2–5 mm	0.123 (NS)	−0.092 (NS)	0.266 (0.0001)	0.305 (0.0001)	0.166 (0.02)	0.036 (NS)	−0.116 (NS)
6–9 mm	−0.114 (NS)	0.228 (0.002)	−0.154 (0.03)	−0.064 (NS)	0.021 (NS)	−0.283 (0.0001)	−0.252 (0.0008)

Serum androgen levels correlated with small AFC in PCOS

Jonard et al, Hum Reprod, 2003

Enhancing androgen availability

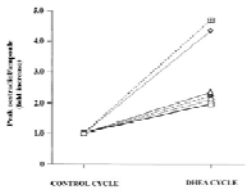
Finding the best way of ∇ ovarian androgen availability:



Androgen administration

Dehydroepiandrosterone

Androgen administration



2.9 ± 0.5-fold increase

6 “poor responders”

DHEA, 80 mg/day for 2 months

Casson et al, Hum Reprod, 2000

Androgen administration

Table I. Comparison of results of IVF before and after treatment with dehydroepiandrosterone (DHEA)

	Pre-DHEA	Post-DHEA	*P*-value
n	25	25	
Age (years)	38.9 ± 0.8	40.4 ± 0.8	–
Weeks of DHEA	–	17.6 ± 2.13	–
Cancellation	8/25 (32%)	1/25 (4.3%)	0.02
Peak estradiol (pmol/l)	3493 ± 312	4063 ± 389	Not significant
Oocytes	3.4 ± 0.5	4.4 ± 0.5	<0.05
Fertilized oocytes	1.4 ± 0.3	3.0 ± 0.5	<0.001
Percentage of fertilized oocytes	39	67	<0.001
Day 3 embryo blastomeres	3.8 ± 0.4	4.7 ± 0.5	0.01
Day 3 embryo grade	2.9 ± 0.1	3.4 ± 0.09	0.02
Cumulative embryo score per oocyte retrieved	8.4 ± 1.5	16.1 ± 1.6	0.001
Transferred embryos	1.8 ± 0.2	2.4 ± 0.3	0.005
Normal day 3 embryos	1.2 ± 0.2	2.2 ± 0.4	0.001

25 “poor responders”, DHEA, 75 mg/day for 4 months

Barad et al, Hum Reprod, 2006

Androgen administration

	Pre-DHEA					Post-DHEA			
Cases	Age (y)	FSH (mIU/mL)	LH (mIU/mL)	E_2 (pg/mL)	Amenorrhea (mo)	DHEA (d)	FSH (mIU/mL)	E_2	Last menstrual period	Outcome
1	37	102	45	27	9	63	18.9	62	15/09/06	C-section 18/03/07
2	36	112	52	18	12	91	12	58	06/04/07	27 wk gestation
3	35	40	84	30	6	45	12.5	56	10/07/07	14-wk gestation
4	38	30	30	35	12	65	19	48	18/07/07	7 wk missed abortion
5	40	45	34	22	13	180	14	59	28/07/07	11 wk gestation

5 “poor responders”, DHEA, 50-75 mg/day for 1-6 months

Mamas & Mamas, Fertil Steril, 2007

Androgen administration

62 “poor responders”

DHEA (75 mg/d) 16 wks (n=17)

No treatment (n=16)

RCT

Variables	DHEA (n = 26)	Control (n = 25)	P value
Mean E2* on hCG (pg/ml)	732 ± 337	917 ± 487	0.2
Mean E2 per retrieved oocyte (pg/ml)	239 ± 120	335 ± 150	0.35
Mean progesterone on hCG (ng/ml)	0.8 ± 0.6	0.7 ± 0.4	0.71
Endometrial thickness on hCG (mm)	10.5 ± 2.5	10.8 ± 2.8	0.74
Mean number of retrieved oocytes	2.2 ± 1.6	2.5 ± 2.4	0.65
Fertilisation rate (%)	58.5%	56.5%	0.43
Mean no. of embryo transfer	2.1 ± 1.0	2.2 ± 0.7	0.72
Mean scoring of leading embryo transfer	3.1 ± 0.5	3.1 ± 0.4	0.45
Clinical Pregnancy (%)	7 (26.9%)	3 (12.0%)	0.07
Live birth rate	6 (23.1%)	1 (4.0%)	0.05

2 COH cycles

Wiser et al, Hum Reprod, 2010

Androgen administration

	DHEA group (n = 9)	Placebo group (n = 12)	P value
Age (yr)	35.9 ± 3.26	33.4 ± 4.74	0.196[a]
BMI (kg/m^2)	21.4 ± 1.94	21.1 ± 4.08	0.961[a]
Duration of POI (months)	30 (2–81)	43 (6–132)	0.477[a]
FSH at diagnosis (IU/liter)	79.2 ± 35.1	61.8 ± 33.7	0.783[a]
Previous use of HRT	4/9 (44.0%)	11/12 (91.7%)	0.46[b]
Baseline serum levels			
AMH (ng/ml)	0 (0)	0 (0–0.13)	0.209[a]
FSH (IU/liter)	101.9 ± 49.8	91.6 ± 32.6	0.678[a]
Estradiol (pmol/liter)	89 (73–268)	73 (73–109)	0.300[a]
Testosterone (ng/ml)	0.27 ± 0.12	0.56 ± 0.37	0.698[a]
DHEA-S (μg/dl)	160.9 ± 68.7	157 ± 107	0.967[a]
SHBG (nmol/liter)	47.3 ± 16.8	50.6 ± 26.0	0.708[a]
IGF-1 (ng/ml)	145.4 ± 56.6	150.0 ± 60	0.611[a]
Baseline US/S findings AFC	0 (0–2)	0 (0–2)	0.327[a]
Total ovarian volume (cm^3)	1.50 (0–2.2)	1.51 (0.6–2.9)	0.413[a]
Follicles ≥10 mm	0	0	1.0[a]

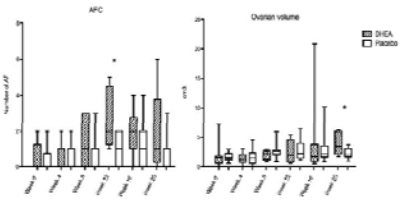
22 POF patients

DHEA (75 mg/d) 16 wks **(n=10)**

Placebo **(n=12)**

Yeung et al, J Clin End Metab, 2013

Androgen administration



22 POF patients

DHEA (75 mg/d) 16 wks **(n=10)**

Placebo **(n=12)**

Yeung et al, J Clin End Metab, 2013

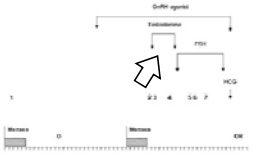
Androgen administration

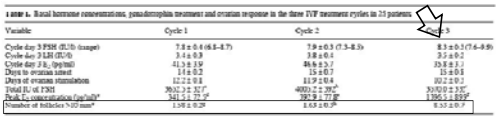
T patches

Androgen administration

25 “poor responders”

T patches (20 µg/d)
for 5 days





Balasch et al, Hum Reprod, 2006

Androgen administration

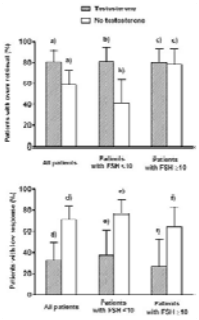
62 “poor responders”

T patches
(20 µg/d)
5 days

(n=31)

No
treatment

(n=31)



Fábregues et al, Hum Reprod, 2009

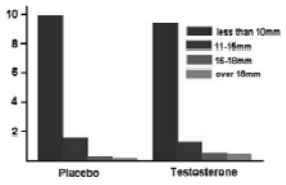
Androgen administration

12 women, aged 38-45 years

T patches
(2.5 mg/d)
12 days

Placebo

(Crossover study)



Sipe et al, Hum Reprod, 2009

Androgen administration

T gels

Androgen administration

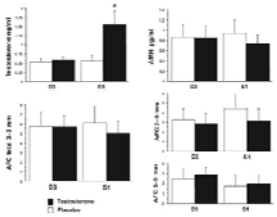
49 “poor responders”

T gel
(10 mg/d)
15-20 days

(n=24)

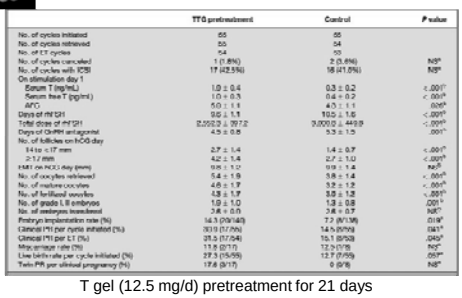
Placebo

(n=25)



Massin et al, Hum Reprod, 2006

Androgen administration



	TTG pretreatment	Control	P value
No. of cycles initiated	55	55	
No. of cycles retrieved	55	54	
No. of ET cycles	54	53	
No. of cycles canceled	1 (1.8%)	2 (3.8%)	NS*
No. of cycles with ICSI	17 (42.5%)	16 (41.0%)	NS*
On stimulation day 1			
Serum T (ng/mL)	1.0 ± 0.4	0.3 ± 0.2	<.001*
Serum free T (pg/mL)	1.0 ± 0.3	0.4 ± 0.2	<.001*
AFC	5.0 ± 1.4	4.7 ± 1.1	0.06*
Days of rhFSH	9.6 ± 1.1	10.5 ± 1.6	<.001*
Total dose of rhFSH	2,202.3 ± 297.2	3,000.0 ± 449.9	<.001*
Days of GnRH antagonist	4.5 ± 0.6	5.3 ± 1.5	.001*
No. of follicles on hCG day			
14 to <17 mm	2.7 ± 1.4	1.4 ± 0.7	<.001*
≥17 mm	4.2 ± 1.4	2.7 ± 1.0	<.001*
MRT on hCG day (mm)	18.1 ± 1.2	18.1 ± 1.4	NS*
No. of oocytes retrieved	5.4 ± 1.9	3.8 ± 1.4	<.001*
No. of mature oocytes	4.6 ± 1.7	3.2 ± 1.2	<.001*
No. of fertilized oocytes	4.3 ± 1.7	3.0 ± 1.2	<.001*
No. of grade I, II embryos	1.9 ± 1.0	1.3 ± 0.8	.001*
No. of embryos transferred	3.4 ± 0.5	3.4 ± 0.7	NS*
Embryo implantation rate (%)	14.3 (20/140)	7.2 (8/139)	0.04*
Clinical PR per cycle initiated (%)	30.9 (17/55)	14.5 (8/55)	0.03*
Clinical PR per ET (%)	31.5 (17/54)	15.1 (8/53)	.040*
Miscarriage rate (%)	11.8 (2/17)	12.5 (1/8)	NS*
Live birth rate per cycle initiated (%)	27.3 (15/55)	12.7 (7/55)	.057*
Twin PR per clinical pregnancy (%)	17.6 (3/17)	0 (0/8)	NS*

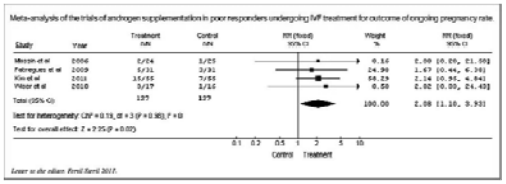
T gel (12.5 mg/d) pretreatment for 21 days

RCT, no placebo, no blinding

n=110 poor responders

Kim et al, Fertil Steril, 2011

Androgen administration

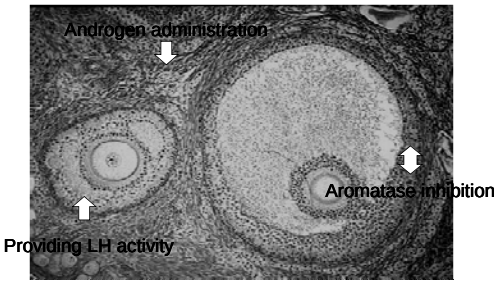


DHEA or T pretreatment x pregnancy rate in IVF-ET

Sunkara & Coomarasamy, Fertil Steril, 2011

Enhancing androgen availability

Finding the best way of ∇ ovarian androgen availability:



Aromatase inhibition

Variables	FSH only (20 cycles)	Letrozole + FSH (14 cycles)	P Value
Total FSH/cycle (IU)	1500 ± 708	616 ± 454	0001
Stimulation days/cycle	9 ± 3.42	6.57 ± 1.95	026
Day of hCG administration	11.6 ± 7.77	11.78 ± 0.979	NS
No. of mature follicles (>18 mm)	1.9 ± 0.6	3.5 ± 1.8	003
E2 on hCG day (pmol/L)	2471 ± 1113	1789 ± 898	NS
E2/mature follicle on hCG day (pmol/L)	1324 ± 493	629 ± 392	0001
Endometrial thickness on hCG day (mm)	0.89 ± 0.1	0.88 ± 0.09	NS
LH on hCG day (IU/L)	10.3 ± 4.5	16.7 ± 13.7	NS

12 "poor responders", 34 cycles

Letrozole (2.5 mg/d) for 5 days

Mitwally et al, Hum Reprod, 2006

Aromatase inhibition

	Letrozole (n = 71)	Control (n = 76)	P
No. of oocytes retrieved	6.1 ± 0.4	4.3 ± 0.3	.03
Fertilization rate (%)	66.2	63.3	.51
No. of embryos transferred	2 ± 0.1	2.3 ± 0.1	.00
PR/cycle	22.4	15.2	.39
PR/transfer	41.7	26.9	.36
Implantation rate	25	9.4	.009
Cycle cancellation due to low response	15.5	19.7	.82
Total cycle cancellation	43.7	44.7	.97
Miscarriage rate	20	7.7	.8
Multiple pregnancy rate (twins)	46.7	7.7	.04

147 "poor responders"

OCP + Letrozole (2.5 mg/d) during the first 5 days of FSH treatment

OCP + FSH treatment

Garcia-Velasco et al, Fertil Steril, 2005

Aromatase inhibition

Stimulation results.

Protocol	Gonadotropin dose, 75 IU ampules	Duration of stimulation, days	Peak E_2, pg/mL	Oocytes retrieved	% Metaphase II oocytes
AL	56.3 ± 9.9	9.9 ± 1.3	1,403 ± 965	12 ± 6	70 ± 20
ML	52.5 ± 13	10.1 ± 1.6	3,147 ± 1,189	13 ± 5.3	78 ± 15
P	NS	NS	<.05	NS	NS

Treatment outcome.

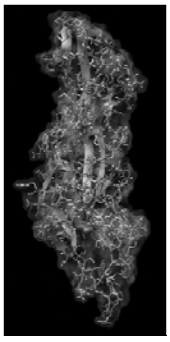
	Fertilization, %	Day 3 embryo score	Embryos transferred	Implantation rate, %	Ongoing pregnancy rate, %
AL	71	3.48 ± 0.27	3.5 ± 1.3	15	37
ML	73	3.47 ± 0.28	3.7 ± 1.3	21	52
P	NS	NS	NS	NS	<.05

Letrozole (2.5 mg/d) during the first 5 days of FSH (n=179)

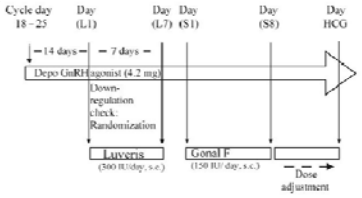
OCP + Micro-flare (n=355)

Schoolcraft et al, Fertil Steril, 2008

Providing LH activity



Providing LH activity



LH priming

Cédrin-Durnerin et al, Hum Reprod, 2008

Providing LH activity

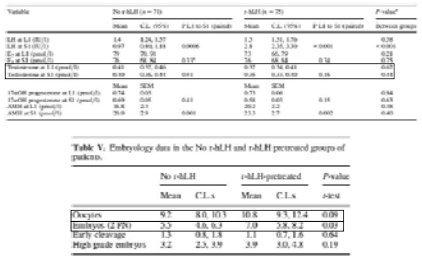


Table V. Embryology data in the No r-hLH and r-hLH pretreated groups of patients.

	No r-hLH		r-hLH-pretreated		*P*-value
	Mean	C.I.s	Mean	C.I.s	*t*-test
Oocytes	9.2	8.0, 10.3	10.8	9.3, 12.4	0.09
Embryos (2 PN)	3.2	3.0, 4.3	3.9	3.8, 5.2	0.05
Early cleavage	1.3	0.8, 1.8	1.1	0.7, 1.6	0.64
High grade embryos	3.2	2.3, 3.9	3.9	3.0, 4.8	0.19

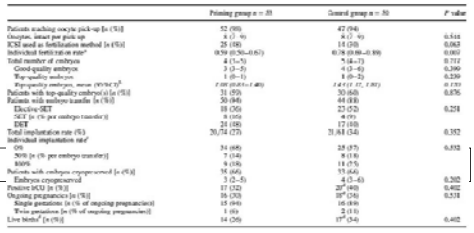
Cédrin-Durnerin et al, Hum Reprod, 2008

Providing LH activity

103 “normal” patients (androgen priming, n=53)

Lossl et al, Hum Reprod, 2008

Providing LH activity



103 “normal” patients (androgen priming, n=53)

Lossl et al, Hum Reprod, 2008

Providing LH activity

	Group 1 (r-FSH) n = 27	Group 2 (r-FSH+hCG) n = 19
E_2 on day 5 of FSH admin.	757.3 ± 175.8	720 ± 214.4
E_2 on day of hCG admin.	1643.5 ± 600.2	2125* ± 1190
E_2/follicle on day of hCG admin.	200 ± 98.9	229 ± 116.9
No. of follicles	8 ± 3	10 ± 3
No. of oocytes	7 ± 3	8 ± 3
Mature oocytes (%)	66.7 ± 17	78.9 ± 18
Fertilized oocytes (%)	87.3 ± 12.9	93 ± 13
Embryo quality (%)	47.6	85.3*
Endometrial quality (%)	46.4	61.3*
Pregnancy Rate (%)	51.8	46.5*

46 “normal” patients, one previous ICSI failure

hCG (200 IU/d) for 7 days after pituitary suppression (before FSH?)

Beretsos et al, Reprod Biol Endocrinol, 2009

Providing LH activity

	D1-hCG	Control	P value
Total oocytes / patient (mean ± SD)	11.0±5.2	11.2±5.0	0.9
MII oocytes / patient (mean ± SD)	8.5±4.2	8.9±4.0	0.6
Normally fertilized rate (%)	84%	81%	0.4
Cleavage rate (%)	81%	81%	1.0
Blastomeres on Day 3 (#/embryo; mean ± SD)	6.6±2.2	7.2±1.3*	<0.05
Top Quality Embryos on Day 3 (#; mean ± SD)	1.0±0.2*	0.5±0.5	<0.001

100 “normal” patients, one previous IVF-ET failure

hCG (250 µg) on day 1, FSH administration starting on day 3

Motta et al, J Assist Reprod Genet, 2009

Providing LH activity

	D1-hCG	Control	P value
Embryos transferred (mean ± SD)	3.5±1.1	3.6±1.1	0.7
Biochemical pregnancy/ET (%)	67*	41	0.02
On going pregnancy/ET (%)	64*	41	0.04
Implantation (%)	33*	21	0.03
Birth/ET(%)	47	34	0.2
Abortion/ET (%)	16	6	0.1
Multiples/pregnancies (%)	23	27	0.7

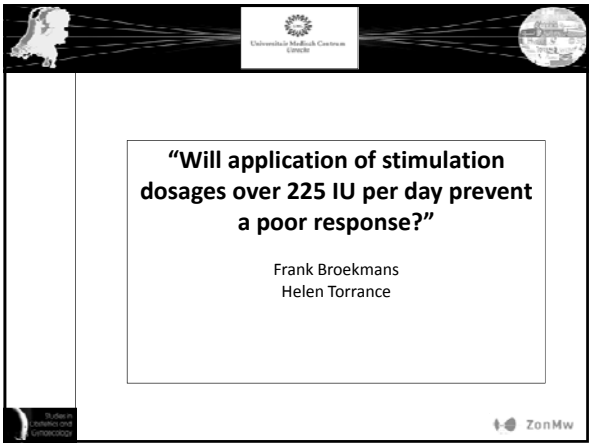
100 "normal" patients, one previous IVF-ET failure

hCG (20 µg) on day 1, FSH administration staring on day 3

Motta et al, J Assist Reprod Genet, 2009

Conclusions

1. Alleviating reproductive implications of ovarian aging constitutes one of the single most important challenges in reproductive medicine for the next years
2. Whereas the relationship between increased androgen availability and the bulk of growing follicles in the ovaries is likely, the best way to provide such an activity remains to be set
3. Recent trials indicate that androgen administration, in particular DHEA, are effective in increasing the number of ovarian follicles, but further RCT are needed to confirm and/or expand these first observations
4. In the light of these first results, and in the absence of other effective treatments, clinical use of androgens should be considered to enhance ovarian function in selected cases



Disclosures

Member external advisory board Merck Serono,
Member external advisory board Gideon Richter
Consultancy work MerckSharpDome
Educational activities Ferring BV
Consultancy work Roche

LEARNING OBJECTIVES

1. APPRECIATE KNOWLEDGE ON PHARMACODYNAMICS OF GONADOTROPIN OVARIAN STIMULATION
2. ACKNOWLEDGE EXPLANATIONS FOR POOR OVARIAN RESPONSE
3. ACCEPT THE CURRENT INABILITY TO ALTER FATE OF A POOR RESPONDER

Answer to Take Home

…the ovaries… are no oranges…

Agenda

Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

Definition

Operational:

≤3 oocytes with conventional stimulation protocol

And/or

Advanced maternal age (≥40) and/or Abnormal OvarianReserveTest

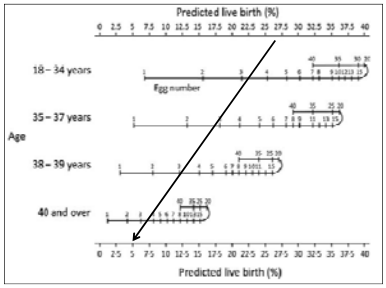
Ferraretti et al, Hum Reprod 2011

Agenda

Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

Significance



Sunkara
HFEA
N=400.000
HR 2011

Agenda

Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

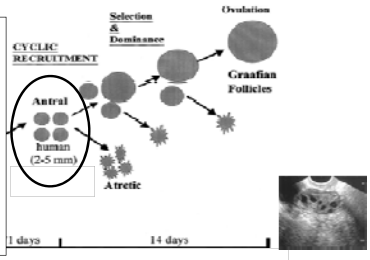
Causes - Folliculogenesis

Genetic variants FSH receptor

FSH underdosing

Small cohort

Variation

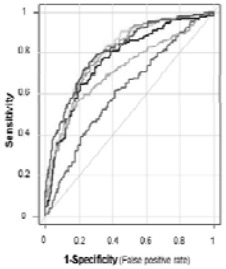


Agenda

Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

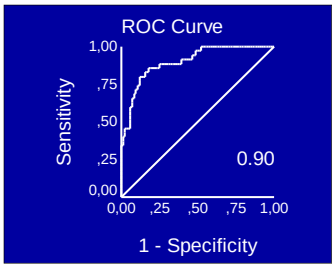
Forecasting



AUC age:	0.60 (0.57-0.64)
AUC age+FSH:	0.69 (0.66-0.72)
AUC age+AFC:	0.76 (0.72-0.80)
AUC age+AMH:	0.80 (0.76-0.84)
AUC AMH:	*0.81 (0.77-0.84)*
AUC age+AMH+AFC+FSH:	*0.81 (075-0.86)*

Broer, IMPORT
study, HRU 2012

Forecasting *poor response*



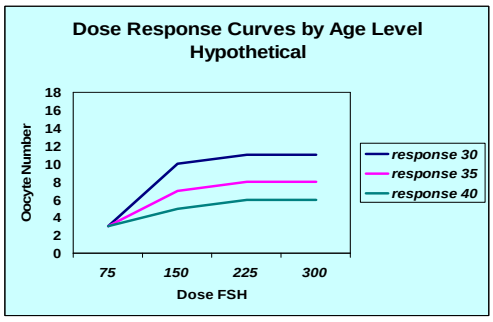
Predicting
…false negatives and positives..

Personalising
Can we increase the antral follicle number and egg yield

Agenda

Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

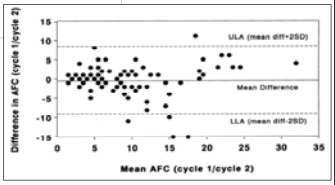


Ovarian Response to COS

It is the **cohort**

Not the FSH

And the **size** may vary…



Predicted Poor Response

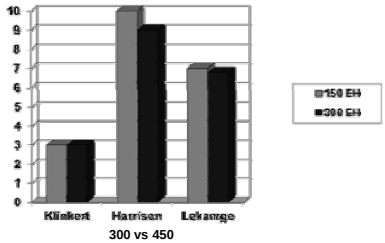
Klinkert et al Hum Rep 2005: n=52
- P: IVF patiënts with AFC < 5 (2-5mm)
- I: 300 IU FSH/day
- C: 150 IU FSH/day
- O: oocyte yield and ongoing pregnancy

Harrison et al Fertil & Steril 2001: n=170
- P: IVF/ICSI patiënts, with FSH > 8.5 U/L
- I: 300 IU FSH/day
- C: 150 IU FSH/day
- O: oocyte yield and ongoing pregnancy

Lekamge et al J Assist Repr Genet 2008: n=122
- P: IVF patiënts with AMH < 14 pmol/L + age < 36 year
- I: 300 IU FSH/day
- C: 150 IU FSH/day
- O: oocyte yield and ongoing pregnancy

Berkkanoglu et al Fertil & Steril: n= 119
- P: ICSI patients, with AFC <12, and FSH< 12U/l
- I: 450 and 600 IU FSH/day
- C: 300 IU FSH/day
- O: oocyte yield and ongoing pregnancy

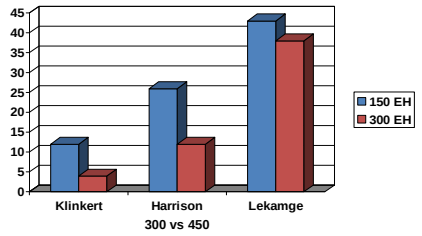
Oocyte Yield



300 vs 450

Higer FSH dose: no effect on number of oocytes

Ongoing Pregnancies



Higher FSH dose: no effect on outcome Pregnancy

Predicted Normal response

Jayaprakasan et al BJOG 2010: n=131

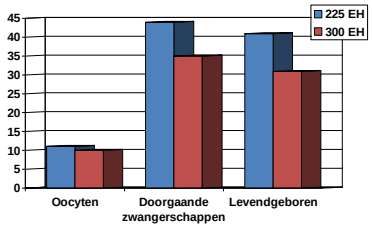
P: IVF/ICSI patiënts aged < 39 jaar, FSH < 12 and AFC 8-21

I: 300 IU/day

C: 225 IU/day

O: oöcyte number, ongoing pregnancy and live birth

Predicted Normal Response



Higher FSH dose:
no effect on Oocyte yield nor Ongoing pregnancies nor Live Birth

Actual poor response

Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in vitro fertilisation (IVF) (Review)

THE COCHRANE COLLABORATION®

There is insufficient evidence to use of any particular intervention to improve treatment outcomes in poor responders in IVF.

ONLY one RCT on FSH dose adjustment: 225 versus 450 DURING poor response cycle

Van Hoof *et al.* (1993)	Prospective randomized study (doubling hMG dose on day 5 of COH versus unchanged hMG dose)	<3 follicles and E_2 <400 pg/ml on day 5 of stimulation in previous cycle	225 IU/day i.m. hMG from day 3 for 5 days, increasing to 450 IU/day

Agenda

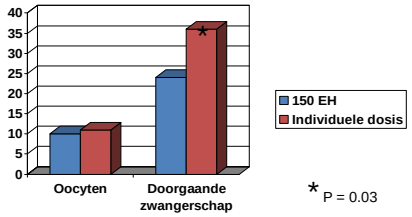
Poor Ovarian Response

- **Definition**
- **Significance**
- **Causes**
- **Forecasting**
- **Prevention– Dose adjustments**
- **Conclusions**

Conclusion

…the ovaries… are no oranges…even if squeezed

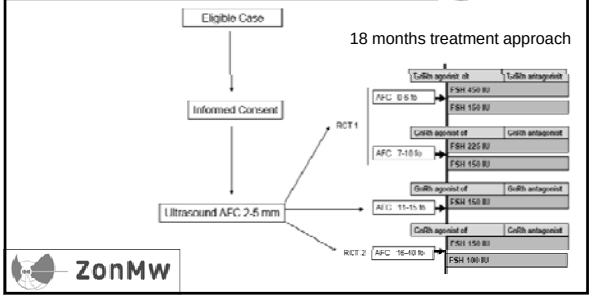
Still,…hope ? .. Popovic et al



Individualised dosing:
not more oocytes, BUT more ongoing pregnancies…

The OPTIMIST trial
OPTIM*isation of cost effectiveness through* ***I****ndividualised FSH* ***S****timulation dosages for IVF* ***T****reatment: a randomised trial.*
Dutch RM consortium

OPTIMIST



ZonMw

Conflict of Interest / Disclosure Statement

Prof. dr. F.J. Broekmans receives monetary compensation:

Member of the external advisory board for Merck Serono, The Netherlands

Member advisory board Roche, Switzerland

Consultancy work for Gedeon Richter, Belgium

Consultancy work for MSD, The Netherlands

Educational activities for Ferring BV, The Netherlands

Educational activities for MSD, The Netherlands

19-03-2013

Mini - Debate: A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment : PRO !

Petra De Sutter
Centre for Reproductive Medicine
University Hospital Gent

ESHRE – PCC London

Conflicts of interest

I have the following interests to declare (last three years):

- Institutional unrestricted research grants from Ferring and Merck-Serono
- Personal travel grants from Ferring, Merck-Serono, MSD
- Speaker allowances from Ferring, Ipsen
- Institutional training centre for Cook

Learning objectives

After this debate, the participants should be able to

- Understand the decision making process on whether or not to start/continue treatment
- Discuss the elements of importance in this decision making:
  - Medical indication for treatment
  - Health-economic aspects
  - Psychological / ethical aspects
  - Risks and complications

Introduction

ART: IVF and ICSI

Medical aspects: "indications for treatment"
Health economic aspects
Ethical/psychological aspects

When to start?
When to stop?

Different aspects may be conflicting

Non-medical aspects

- health-economic / financial arguments (1 cycle expectant management = 0 Euro <> 1 IUI cycle = 300 Euro <> 1 IVF cycle = 4000 Euro)
- Psychological / ethical arguments (willingness-to-pay, impatience, autonomy to decide)
- To be balanced against risks and complications (psychosocial burden, OHSS, multiple pregnancies, procedure-related risks?)

When not to allow further treatment to a poor responder after adequate FSH dosing?

When to stop?

(Starting or) continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

Financial burden?

If society pays: legitimate ethical reasons for watchdog position of physician! (5%/cycle = 42 yrs)

If patient pays: willingness-to-pay after realistic information about chances prevails

When to stop?

(Starting or) continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

Emotional burden ?

(+) Patient may want to continue/start treatment for Ψ reasons (even if chances are low)

(-) Patient may want to stop treatment for Ψ reasons (even if chances are high)

When to stop?

(Starting or) continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

Risks and complications ?

Even if patient pays and may have a "Ψ indication", IVF is not ethically defendable if chances of pregnancy are <1-2% = incidence of complications ! (age limit 45 years)

What with younger patients with poor prognosis?

Continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

If chances are < 5% per cycle ?

e.g. (very) poor responders, bad embryo quality, failed implanters > 6 cycles?

⇩

Oocyte donation

Conclusion

The decision when to start and when to stop ART should be taken after informed consent ("colloque singulier")

It should depend on available (medical) evidence of chances of pregnancy after expectant management <> non-IVF <> IVF treatment

It should be modulated by financial and emotional arguments

Decision to treat ≠ availability of reimbursement (fast IVF if reimbursement or no treatment if not reimbursed)

Emotional burden should be considered, both in the decision to treat and not to treat

A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment

Contra arguments

Pia Saldeen
MD, PhD

IVF-klinikenCuraÖresund
Malmö, Sweden

Disclosures

No conflict of interest within the topic presented in this lecture

Learning objectives

To understand why first time poor responders should be offered further IVF cycle/s

Poor response

- Prevalence 5.6-35.1% depending on the definition (Oudedijk et al, 2011)
- No universal consensus on definition until 2011
- 2011 ESHRE Bologna criteria: consensus on the definition of ´poor response´ (Ferraretti et al, 2011)
- Criteria based on risk factors, previous cycle and ovarian reserve test

Bologna criteria for poor ovarian response (POR)

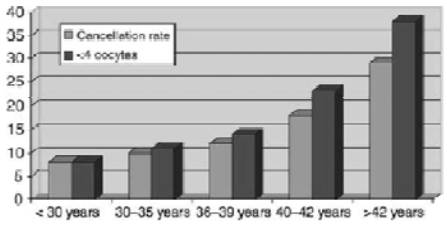
Two of the three criteria must be present

- ✓ Advanced maternal age (≥ 40) or other risk factor for POR
- ✓ Previous cycle with ≤ 3 oocytes with a conventional stimulation
- ✓ Abnormal ovarian reserve test (i.e AFC < 5-7 or AMH < 0.5-1.1 ng/ml)

Two episodes of POR after maximal stimulation in the abscence of advanced maternal age or abnormal ovarian reserve tests

Ferraretti *et al,* 2011

Prevalence of POR in relation to female age



Ferrarretti *et al*, 2011

The relationship between age and POR (cycles cancelled because of absent or low ovarian response or pick ups with ≤ 3 oocytes) in 3825 women undergoing the first IVF cycle in the Bologna S.I.S.Me.R unit and in the Modena University unit 2004-2009.

What is the problem with POR?

The prognosis
- Reduced pregnancy rates after IVF
- High cancellation rates

The prevalence

Economy
- High treatment costs per delivered child (high quantity of gonadotropins, reduced delivery rates)

Strategies
- No treatment strategy better than the other

Psychology
- High stress and burden on the patients
- Extensive counselling needed

Ethical issues
- Patient autonomy/preferences
- Potential conflicts

But..

- POR can be an occasional finding (Veleva et al, 2005)
- Not all POR have poor pregnancy prospects
- Even if reduced pregnancy prospects at a group level, women with POR do get pregnant and deliver after IVF.
- Since reduced pregnancy rates, reasonable to try more than one IVF cycle
- Cumulative ongoing pregnancy rates (3 cycles) of 11.5-19.0 % in expected poor responders (Veleva et al, 2005 and Hendriks et al, 2008).
- To reduce costs, natural cycle IVF might be an alternative

Natural cycle IVF in poor responders

- An alternative to conventional IVF or oocyte donation?
- Less expensive
- Lower treatment burden?
- As effective as ovarian hyperstimulation?

Natural-cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles

Mauro Schimberni, M.D.,* Francesco Morgia, B.S.,* Ida Colabianchi, M.D.,* Annalisa Gallorardo, M.D.,* Claudio Pisticelli, M.D.,* Pierluigi Giannini, M.D.,* Monica Montepini, B.S.,* and Marco Sbracia, M.D.†

* [illegible] † [illegible]

Fertil Steril, 2009

- 500 consecutive NC IVF cycles in poor responders (294 women)
- Inclusion criterias: ≤ 44 yrs, and if in previous cycle ≤ 1 follicle
- hCG 10 000 IU
- All ICSI
- Mean female age 39.3

Schimberni *et al*, 2009

PR per cycle and cumulative PR

Cycle #	PR/cycle	Cumulative PR	# of pregnancies
#1	9.5%		28
#2	9.7%	12.9%	10
#3	12.0%	15.0 %	6
#4	10.2%	16.3%	4
#5	7.1%	16.7%	1

49 pregnancies in 294 women

Schimberni *et al*, 2009
Data on poor responder-natural cycle IVF- and age

	ALL	≤ 35	36-39	≥ 40
# patients	294	60	69	165
# cycles	500	105	120	275
PR/cycle	9.8 %	18.1%	11.7%	5.8%
PR/patient	16.7 %	31.7%	20.3 %	9.7%

Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria

N.P. Polyzos*, C. Blockeel, W. Verpoest, M. De Vos, D. Stoop, Y. Vloeberghs. M. Camus. P. Devroey. and H. Tournaye

- Retrospective cohort trial
- 136 poor ovarian responders (Bologna criteria)
- 390 Natural cycle IVFs
- Mean age 37.3
- Mean # of previous cycles 3.8

Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria

N.P. Polyzos*, C. Blockeel, W. Verpoest, M. De Vos, D. Stoop, Y. Vloeberghs. M. Camus. P. Devroey. and H. Tournaye

	All	≤ 35	36-39	≥40
# cycles	390	122	168	100
Oocyte retrieval rate	74.6%	77.9%	73.2%	73.0%
ET rate	42.1%	47.5%	43.5%	33%
LBR/cycle	10/390 2.6%	3/122 2.5%	4/168 2.4%	3/100 3.0%
LBR/patient	7.4%	7.9%	7.4%	6.8 %

Although the best treatment for POR is oocyte donation..

A first cyle poor responder after adequate FSH dosing should be allowed further ART treatment, because…

- A single episode of POR can be an occasional finding
- Pregnancy prospects might vary within the group of poor responders
- Even a true poor responder can get pregnant and deliver after IVF
- If tubal factor or severe male factor, no other possibility than IVF
- Not all couples are willing to go for oocyte donation
- Patient autonomy and preferences should be respected
- Natural cycle IVF might be a cost-effective alternative to conventional IVF - results contradictory
- Further studies on the reproductive potential of Bologna criteria POR needed (after IVF with our without gonadotropin stimulation)

Further..

- The Bologna criteria was not set up to exclude poor prognosis patients from IVF
- Main purpose: research, homogenous population in future trials

References

- Ferraretti et al. ESHRE consensus on the definition of `poor repose´ to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011; 26:1616-1624.
- Hendriks et al. Expected poor ovarian response in predicting cumulative pregnancy rates: a powerful tool. RMB Online 2008;5:727-36.
- Klinkert et al. Expected poor responders on the basis of an antral follicle count to no benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial. Hum Reprod 2005;20:611-615.
- Klinkert et al. A poor response in the first in vitro fertilization cycle is not necessarily related to a poor prognosis in subsequent cycle. Fertil Steril 2004;81: 1247-53.
- Oudendijk et al. The poor responder in IVF: is the prognosis always poor? A systematic review. Hum Reprod Update 2012; 18:1-11
- Pandian et al. Intervention for ´poor responders´ to controlled ovarian hyperstimulation (OCH) in in-vitro ferrtlisation (IVF). Cochrane Database Syst Rev 2010 Jan 20;(1) CD 04379
- Polyzos et al. Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria. Hum Reprod 2012; 12:3481-3486.
- Saldeen et al. The probability of succesful IVF outcome after poor ovarian reponse. Acta Obstet Gynecol Scand 2007; 86:457-61.
- Schimberni et al. Natural-cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles. Fertil Steril 2009; 92:1297-1301.
- Veleva et a. An initial low response predicts poor outcome in in vitro fertilization/intracytoplasmic sperm injection despite improved ovarian response in consecutive cycles. Fertil Steril 2005; 83:1384-1390.

How should we stimulate patients with polycystic ovaries

Stratis Kolibianakis

MD MSc PhD

Assistant Professor

in Obstetrics Gynaecology and Assisted Reproduction

Unit for Human Reproduction

1st Department of Obstetrics and Gynaecology

Aristotle University of Thessaloniki, Greece

Disclosure

No commercial and/or financial relationships with manufacturers of pharmaceuticals, mentioned in this presentation

Invited speaker for MSD, Serono, Ferring

Learning objectives

By the end of this presentation it should be clear:

What is the most efficient way to stimulate patients with PCOS

What is the most safe way to stimulate patients with PCOS

Infertility treatment in PCOS

First line treatment:
life style changes
ovulation inducing agents
clomiphene citrate - insulin-sensitizing medications

No conception
gonadotrophin treatment
or
laparoscopic ovarian drilling

IVF

Ovarian stimulation for IVF in PCOS

Understimulation

Overstimulation

Ovarian hyperstimulation syndrome

odds ratio 6.8 (95%: 4.9-9.6)

Tummon et al 2005

Maternal mortality rates from OHSS

~3 deaths per 100 000 IVF cycles performed

Confidential Enquiry into Maternal and Child Health, 2007; Braat et al., 2010

Ovarian stimulation for IVF in PCOS

IVM

Metformin pretreatment

Gonadotrophin

Analog

Triggering signal

Segmentation

Ovarian stimulation for IVF in PCOS

IVM

Ovarian stimulation for IVF in PCOS

IVM

Ooocyte collection from the ovaries of women with PCOS in an unstimulated cycle

maturation in-vitro prior to insemination

Siristatidis et al 2011

Ovarian stimulation for IVF in PCOS

IVM

non-randomised comparisons of IVM and conventional ART

non-comparative case series

RCTs comparing IVM protocols

IVM is a feasible option for subfertile women with PCOS

Favorable maturation, fertilization, pregnancy, and live birth rates

Pregnancy complications, congenital anomalies, similar to those of conventional IVF

Siristatidis et al 2011

Ovarian stimulation for IVF in PCOS

IVM

No data from randomised trials to support recommendations for clinical practice at present

Until more evidence is available,

IVM may not be the preferred first line of treatment for subfertile women with PCOS

Siristatidis et al 2011

Ovarian stimulation for IVF in PCOS

Pretreatment with metformin?

Rationale: to improve IVF outcome

Reduction of intraovarian androgens, leading to an improvement in oocyte quality and fertilization

Reduction in OHSS rate

Ovarian stimulation for IVF in PCOS

Metformin

enhances insulin sensitivity

in the liver, where it inhibits hepatic glucose production,

in the peripheral tissue, where it increases glucose uptake and utilization into muscle tissue

reduces insulin resistance, insulin secretion and hyperinsulinaemia

Dunn and Peters, 1995

Ovarian stimulation for IVF in PCOS

Pretreatment with metformin

5 IVF trials

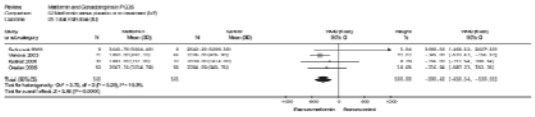
396 patients with PCOS

Metformin + IVF vs. IVF

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Less FSH required after metformin pretreatment



WMD = –290.4 IU

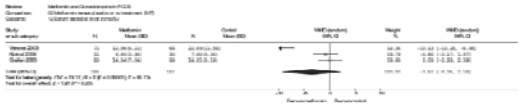
95% CI = –450.3 to –130.5

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Metformin pretreatment

E2 on the day of hCG



WMD = –3.5 nmol/l

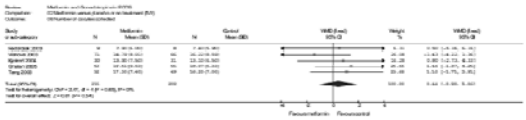
95% CI = –9.2 to +2.2

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Metformin pretreatment

COCs



WMD = +0.44

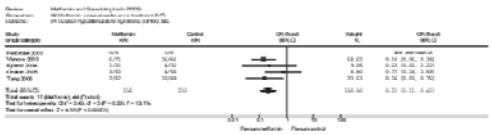
95% CI: –0.98 to +1.86

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Metformin pretreatment

OHSS rate



OR = 0.21

95% CI: 0.11– 0.41

RD = -12%

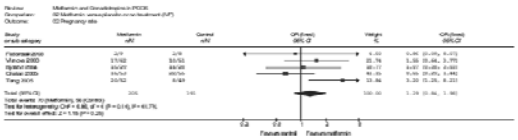
95 CI: -24 to 0.0

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Metformin pretreatment

Pregnancy rate



OR = 1.29

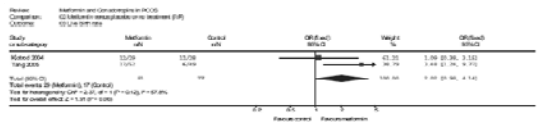
95% CI: 0.84 – 1.98

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Metformin pretreatment

Live birth rate



OR = 2.02

95%: CI = 0.98–4.14

Costello et al 2006

Ovarian stimulation for IVF in PCOS

Gonadotrophin of choice?

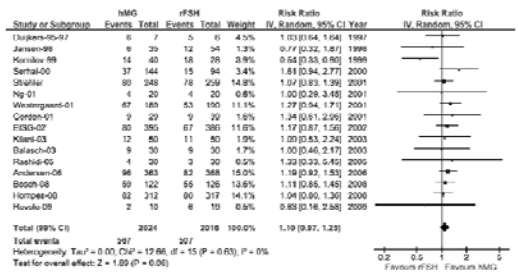
No comparative data
regarding the outcome of IVF in PCOS patients
stimulated with different gonadotrophin preparations

Data from ovulation induction cycles:
no outcome differences in the gonadotrophin preparations

Nugent et al., 2000; van Wely et al., 2003b

Ovarian stimulation for IVF

Pregnancy rate



hMG versus rhFSH

Adjusting for baseline conditions

RR =1.04

95% CI: 0.89 to 1.15

RD = 0.01

95% CI: - 0.02 to +0.04

Lehert 2010

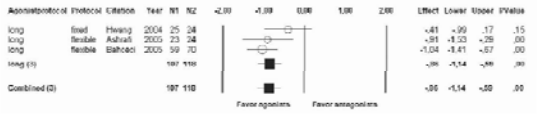
Ovarian stimulation for IVF in PCOS

Which analogue?

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

Duration of stimulation



SD = -0.86

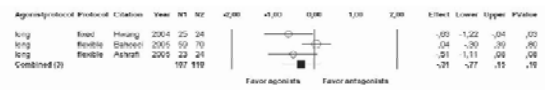
95% CI: -1.14 to -0.59

Griesinger 2006

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

Gonadotrophin consumption



SD = -0.31

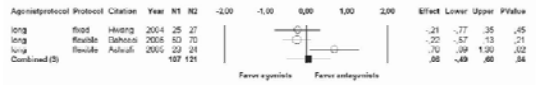
95% CI: -0.77 to +0.15

Griesinger 2006

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

COCs



SD = 0.6

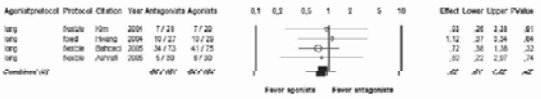
95% CI: -0.49 to +0.60

Griesinger 2006

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

Clinical pregnancy



OR = 0.82

95% CI: 0.51 to 1.32

Griesinger 2006

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

OHSS rate

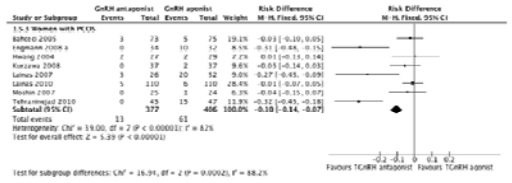
OR = 0.73

95% CI: 0.22 to 2.38

Griesinger 2006

OHSS per woman randomized Cochrane 2011

PCOS

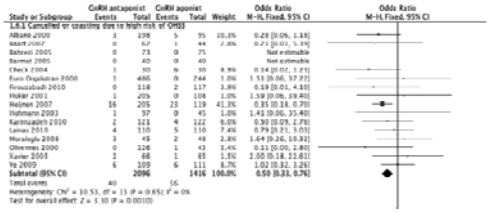


risk difference: -10%

95% CI: -14.0 to -7.0

Al-Inany et al 2011

Cancellation or coasting due to OHSS risk



Odds ratio: 0.50%

95% CI: 0.33 to 0.76

Al-Inany et al 2011

Ovarian stimulation for IVF in PCOS

Which triggering signal?

GnRHa-triggering of final oocyte maturation
in GnRH-ant protocols
in patients at risk
of developing OHSS

536 patients

Griesinger et al 2006

GnRHa-triggering of final oocyte maturation in GnRH-ant protocols
in patients at risk of developing OHSS.

Reference	Trial type	Oocyte source	Ovulation trigger	n	OHSS % (n)
Acevedo et al 2006	RCT	donors	GnRHa hCG	30	**0 (0/30)**
Bodri et al 2009	Retrospective	donors	GnRHa hCG	1046	**0 (0/1046)**
Griesinger et al 2007	Observational, High risk	own	GnRHa	20	**0 (0/20)**
Manzanares et al 2009	Retrospective case-control, high risk	own	GnRHa hCG : cancelled	42	**0 (0/42)**
Hernandez et al 2009	Retrospective	donors	GnRHa hCG	254	**0 (0/254)**
Orvieto et al 2006	Retrospective, high risk	own	GnRHa hCG	82	**0 (0/82)**
Shapiro et al 2007	Retrospective, high risk: agonist arm only	donors	GnRHa hCG	32	**0 (0/32)**
Sismanoglu et al 2009	RCT	donors	GnRHa hCG	44	**0 (0/44)**
Galindo et al 2009	RCT	donors	GnRHa hCG	106	**0 (0/106)**
Shahrokh et al 2010	RCT, high risk	own	GnRHa hCG	4	**0 (0/45)**

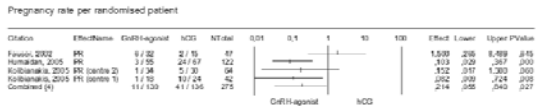
1660 patients

2196 patient : no severe OHSS

Why do we still use hCG for final oocyte maturation?

Why do we still use agonists for controlling endogenous LH?

Replacement of hCG by GnRH agonist



GnRH agonist can replace hCG for induction of final oocyte maturation but

luteal phase is insufficient and leads to a lower pregnancy rate

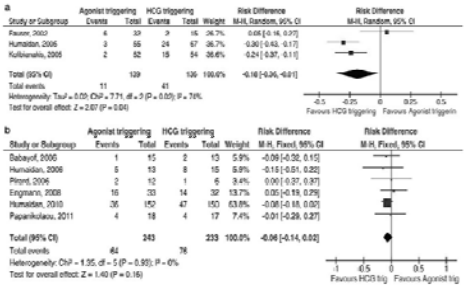
Griesinger et al Hum Reprod Update 2005

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

Standard LPS

Modified LPS

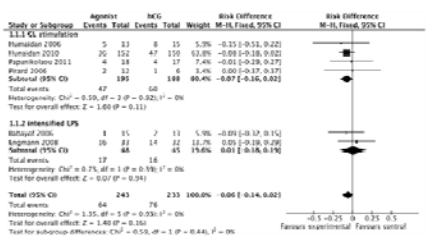


Ongoing pregnancy rate

Humaidan et al 2010

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

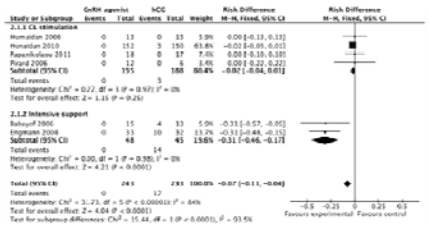


Ongoing pregnancy rate

Kolibianakis et al 2011

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients



OHSS rate

Ovarian stimulation for IVF in PCOS

IVF segmentation

Ovarian stimulation for IVF in PCOS

Elective cryopreservation of all pronuclear oocytes
after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS
Griesinger et al 2007

20 patients at increased risk of developing OHSS

defined as >20 follicles >10 mm or

E2 >4000 pg/ml at the time of induction of final oocyte maturation or

a history of cycle cancellation due to OHSS risk or

the development of severe OHSS in a previous cycle

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

	% (*n*)	95% CI
Biochemical PR/patient	5.3 (1/19)	0.9–24.6
Ongoing PR/patient*	36.8 (7/19)	19.1–59.0
Ongoing PR/first ET	31.6 (6/19)	15.4–54.0
Ongoing PR/ET	29.2 (7/24)	14.9–49.2

PR, pregnancy rate.
*Presented here is the cumulative pregnancy rate resulting from 24 ETs in 19 patients.

No patient developed signs or symptoms of clinically relevant OHSS II–III

0%, 95% CI: 0.0–16.1

Ovarian stimulation for IVF in PCOS

GnRH agonist for triggering final oocyte maturation

in patients with polycystic ovaries

Unit for Human Reproduction
Medical School, Aristotle University of Thessaloniki

Kolibianakis et al unpublished

Inclusion criteria

Indication for IVF

Presence of PCO ovaries (volume >10cm^3, >12 AF)

≥14 follicles ≥ 11mm on the day of triggering final oocyte maturation

Stimulation:

rec FSH 150-300 IU/day

Suppression of LH:

GnRH antagonist daily,

fixed day 5 or flexible after day 5

Criteria for triggering:

presence of ≥ 3 follicles of ≥ 17mm

Triggering:

triptorelin 0.2 mg

Kolibianakis et al unpublished

Fertilization method

ICSI, IVF, ICSI/IVF

Freezing at 2PN stage

Patients were instructed to report any symptoms associated with OHSS, in which case were examined at the clinic
Admission in the hospital was performed in case of severe OHSS

Thawing cycle:

Hormonal substitution with estrogen /progesterone

Transfer up to three embryos

Kolibianakis et al unpublished

Patient population

111patients

PCO ovaries : 111patients (100%)

PCOS :61patients (54.9%)

male factor was also present in 34 patients (no testicular sperm was used)

Age 32.4±4.8 years

BMI : 24.3 ± 5.6 Kg/m^2

Kolibianakis et al unpublished

Stimulation characteristics

Mean FSH starting dose:

171± 42 IU

Mean antagonist starting day

5.7 ± 1.4

Mean duration of stimulation

10.6 ± 2.5 days

Mean total dose of FSH required

1888± 655 IU

Kolibianakis et al unpublished

Hormonal values on the day of triggering final oocyte maturation

LH

2.3 ± 2.1IU/L

P

1.4 ± 0.7 ng/ml

E2

4107±1450 pg/ml

Follicles

26.1±8.4

Kolibianakis et al unpublished

Embryological data

COCs

19.5±10.3

Fertilization rate

54.9± 18.1%

2PN oocytes

10.1±5.6

Kolibianakis et al unpublished

OHSS

Severe OHSS:

0 patients

OHSS associated symptoms
(nausea, abdominal pain-distention, oliguria, feeling unwell):

0 patients

Duration of luteal phase

range: 5-10 days

Kolibianakis et al unpublished

Thawing cycles

2PN oocytes: **847**

Thawed embryos: **506**

Still frozen 2PN oocytes: **341**

FRET cycles :
158
mean: 1.4

Kolibianakis et al unpublished

Biochemical % 95%CI n	**Ongoing pregnancy** % 95%CI n	**Cumulative Ongoing pregnancy** % 95% CI
49.5 40.4- 58.7 55	**38.7%** 30.2- 48.0 43	**68.3%** 50.3-86.4

Conclusions

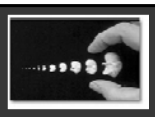
No association between the type of gonadotrophin used for ovarian stimulation and outcome differences can currently be supported in PCOS patients undergoing IVF

The use of GnRH antagonists as compared to GnRH agonists
in PCOS patients undergoing IVF is associated with
decreased duration of stimulation
decreased gonadotrophin consumption and
a similar probability of pregnancy

Conclusions

Pretreatment of PCOS patients with metformin does not appear to improve the probability of pregnancy after IVF

In PCOS patients, segmentation of ovarian stimulation
by replacement of hCG with GnRH agonist for triggering final oocyte maturation
appears to be an attractive option,
since it maintains the probability of pregnancy and
eliminates the occurrence of OHSS



University of Southampton School of Medicine

Excessive ovarian response affects oocyte quality, endometrial receptivity and child health

Nick Macklon
Professor of Obstetrics and Gynaecology, University of Southampton, UK
Director, Complete Fertility Centre Southampton

Visiting Professor, University of Copenhagen and University of Adelaide

complete FERTILITY CENTRE SOUTHAMPTON

Southampton NHS University Hospitals NHS Trust

University of Southampton School of Medicine

Conflicts of interest

- I have received consultancy and speaker fees from the following companies:

  Ferring, Organon, Schering Plough,MSD, Serono, Merck Serono, IBSA and Anecova.

2

University of Southampton School of Medicine

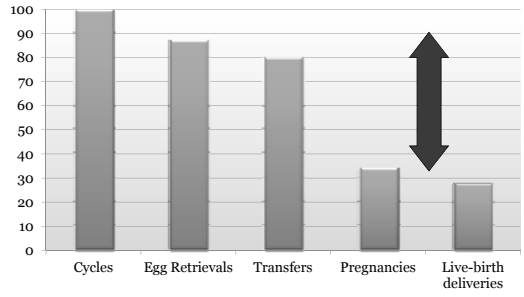
Learning Objectives

At the end of this debate I hope to have convinced the audience that:

- Excessive ovarian response affects oocyte quality, endometrial receptivity and child health
- We can ameliorate these effects.
- They should vote for the motion!

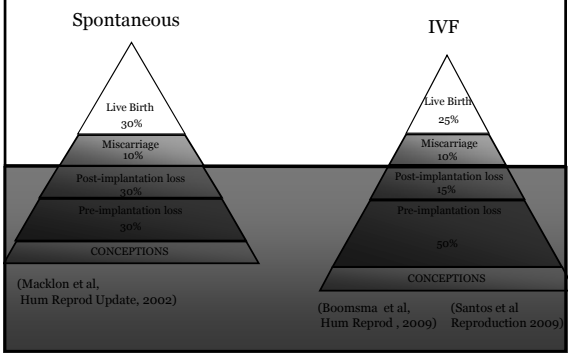
3

Implantation is rate limiting step in IVF



CDC

The Iceberg of pregnancy loss



(Macklon et al, Hum Reprod Update, 2002)

(Boomsma et al, Hum Reprod , 2009)

(Santos et al Reproduction 2009)

REPRODUCTION

REVIEW

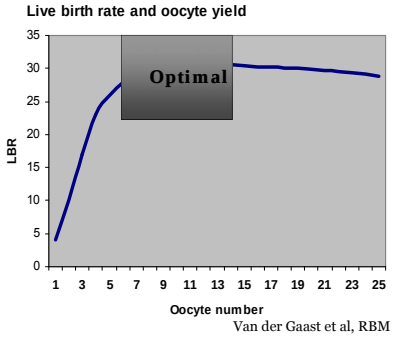
2010 139;234

The impact of ovarian stimulation for IVF on the developing embryo

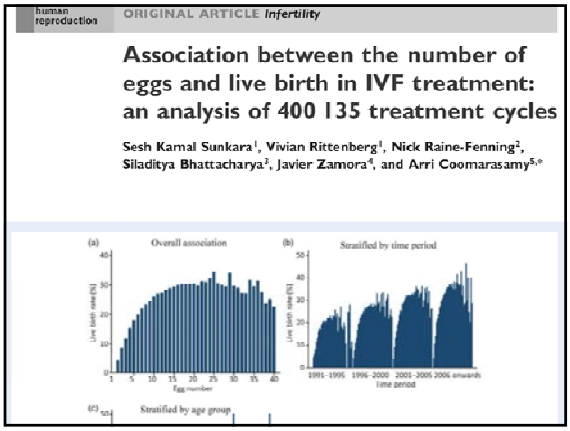
Margarida Avo Santos, Ewart W Kuijk and Nick S Macklon

University Medical Centre Utrecht, Reproductive Medicine and Gynaecology, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

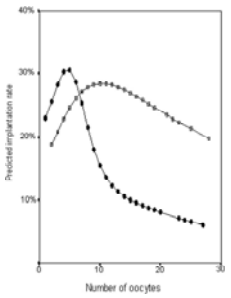
Optimal number of oocytes after long protocol?



Van der Gaast et al, RBM Online, 2006



Number of oocytes and implantation after a mild stimulation protocol



Meta-analysis of studies with late start rFSH (CD5) and flexible start GnRH antagonist.

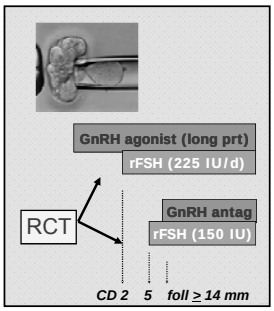
> 10 oocytes → decrease in chance on ongoing implantation

Conventional

Mild

Verberg et al Hum Rep Update 2009

Does mild stimulation reduce the rate of embryo aneuploidy?



2 blastomeres
10 chromosomes
- *1, 7, 15, X, and Y*
- *13, 16, 18, 21, 22*

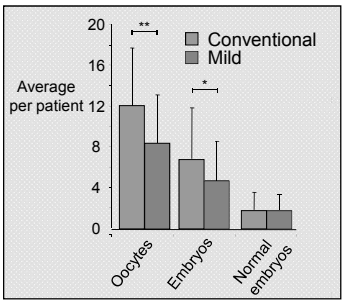
111 Patients
528 fertilized oocytes
302 embryos FISHed

Baart et al, Hum Reprod 2007

10

Milder ovarian stimulation for *in-vitro* fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial HR 2007

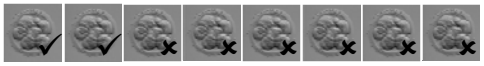
Esther B Baart[1,2,5], Elena Martini[2], Marlènes J Eijkemans[3], Diane Van Opstal[4], Nicole G M Beckers[1], Arie Verhoeff[4], Nicolas S Macklon[1] and Bart C J M Fauser[1,7]



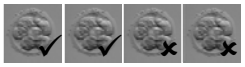
11

Mild Stimulation: helping the embryologist select.

Conventional ovarian stimulation



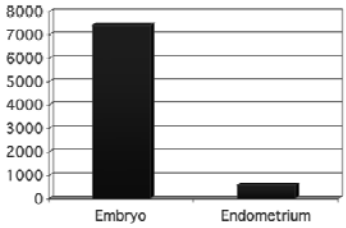
Mild stimulation



12

What about the endometrium?

Pubmed cited IVF papers

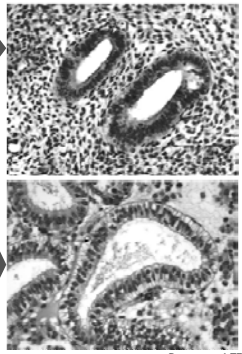


Ovarian stimulation damages the endometrium

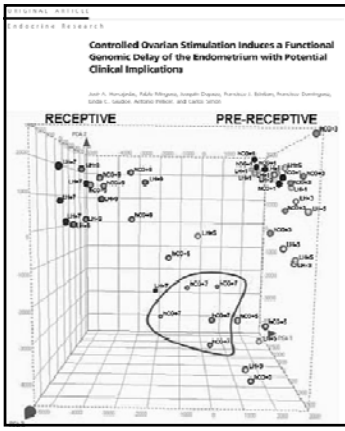
Natural cycle, day of ovulation

When advanced >3 days
NO IMPLANTATION
Kolibianakis, *et al.*
Fertil Steril, 2002.

Stimulated cycle, day of OPU
Secretory features present:
Subnuclear vacuoles displacing nucleus



Devroey, *et al.* TEM. 2004;15:84.



25 natural cycles

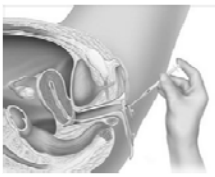
25 stimulated cycles

Biopsies on day
1
3
5
7
after LH rise/hCG

J Clin Endocrinol Metab. 93:4500-4510, 2008.

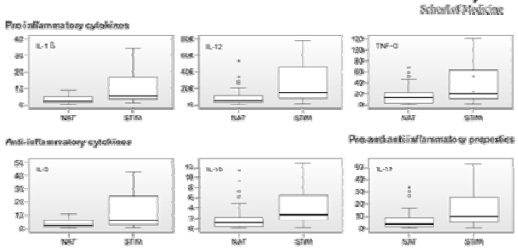
What does the embryo see?

- Endometrial secretions
- Can be safely carried out prior to Embryo Transfer[1,2]
- Demonstrates molecular fingerprint for implantation[2]



1. Van der Gaast, *et al.* 2003.
2. Boomsma, *et al.* 2008.

Ovarian stimulation on intra-uterine cytokine profile



Multivariable analysis in 203 patients showed significant relations between the number of oocytes retrieved and secretion concentrations of IL-12, Dkk-1 (positive) and VEGF, IL-15 (negative).

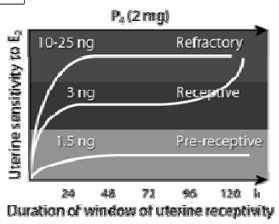
Boomsma, *et al. Fertil Steril.* 2010.

IVF and the Endometrium

Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation

Wen-ge Ma*, Haengseok Song†, Sanjoy K. Das, Bibhash C. Paria, and Sudhansu K. Dey†

A scheme depicting modulation of the window of receptivity in the P4-primed uterus in response to changing estrogen levels. This scheme shows that estrogen at low threshold level extends the window of uterine receptivity for implantation, but higher levels rapidly close this window, transforming the uterus into a refractory state.

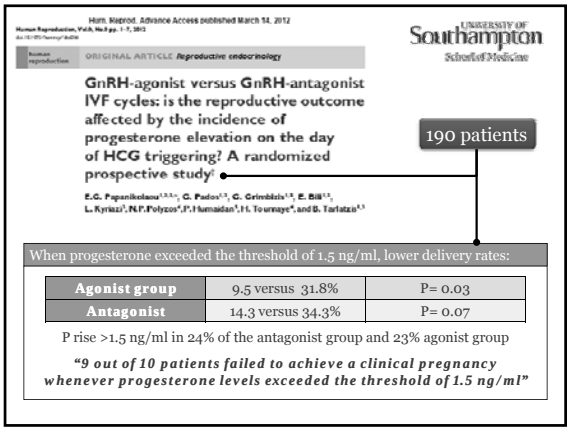


What about impact of high Progesterone levels?

Most recent meta-analysis in GnRH antagonist cycles (n=585)

- Patients with progesterone elevation
  - higher serum estradiol levels on the day of hCG (p=0.008)
  - more COCs retrieved (+2.9, 95% CI +1.5 to +4.4, p < 0.001)
- Progesterone elevation on the day of hCG administration was associated with a significantly decreased probability of clinical pregnancy per cycle (-9%, 95% CI -17 to -2, p>0.005)
- In conclusion, in patients treated with GnRH antagonists and gonadotrophins, progesterone elevation on the day of hCG administration is significantly associated with a lower probability of clinical pregnancy

Kolibianakis, *et al. Curr Pharm Biotech.* 2012.



Hum. Reprod. Advance Access published March 14, 2012

ORIGINAL ARTICLE *Reproductive endocrinology*

GnRH-agonist versus GnRH-antagonist IVF cycles: is the reproductive outcome affected by the incidence of progesterone elevation on the day of HCG triggering? A randomized prospective study

E.G. Papanikolaou, G. Pados, C. Grimbizis, E. Bili, L. Kyrgiazi, N.P. Polyzos, P. Humaidan, H. Tournaye, and B. Tarlatzis

University of Southampton School of Medicine

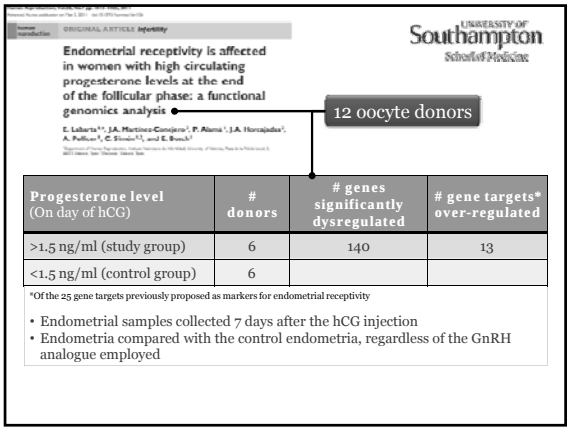
190 patients

When progesterone exceeded the threshold of 1.5 ng/ml, lower delivery rates:

Agonist group	9.5 versus 31.8%	P= 0.03
Antagonist	14.3 versus 34.3%	P= 0.07

P rise >1.5 ng/ml in 24% of the antagonist group and 23% agonist group

"9 out of 10 patients failed to achieve a clinical pregnancy whenever progesterone levels exceeded the threshold of 1.5 ng/ml"



ORIGINAL ARTICLE *Infertility*

Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis

E. Labarta, J.A. Martínez-Conejero, P. Alamá, J.A. Horcajadas, A. Pellicer, C. Simón, and E. Bosch

University of Southampton School of Medicine

12 oocyte donors

Progesterone level (On day of hCG)	**# donors**	**# genes significantly dysregulated**	**# gene targets* over-regulated**
>1.5 ng/ml (study group)	6	140	13
<1.5 ng/ml (control group)	6		

*Of the 25 gene targets previously proposed as markers for endometrial receptivity

- Endometrial samples collected 7 days after the hCG injection
- Endometria compared with the control endometria, regardless of the GnRH analogue employed

University of Southampton School of Medicine

Ovarian stimulation makes babies smaller by disrupting the endometrium

The endometrium and the baby

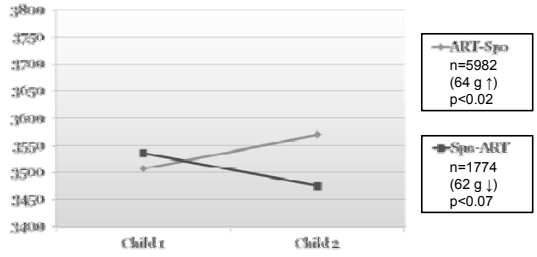
- Perinatal outcome of singleton siblings born after Assisted Reproductive Technology and spontaneous conception

  Danish National Sibling-Cohort study

AIM: Separate the effects of the maternal characteristics and the effects of infertility

Henningsen AA, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN

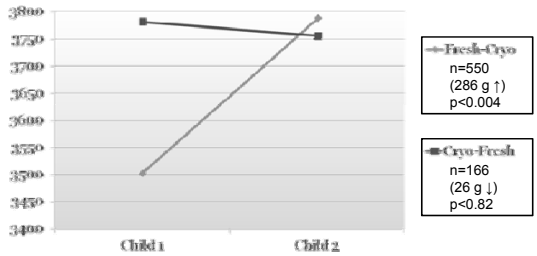
Birthweight (g), adjusted*



*maternal age, parity, year of birth, sex

IVF procedure or Ovarian Stimulation?

Cryo: Birthweight (g), adj.*



*maternal age, parity, year of birth, sex

What can we do to ameliorate the impact of ovarian stimulation on the endometrium?

Does milder stimulation reduce estradiol and progesterone levels at the end of the follicular phase?

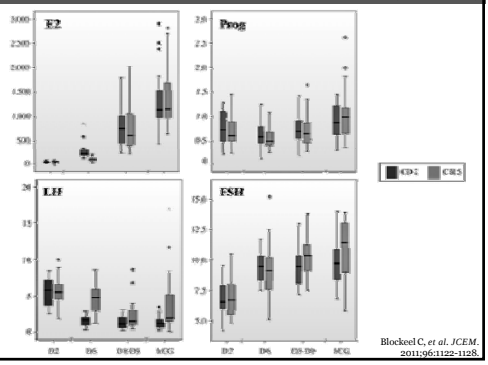
Follicular Phase Endocrine Characteristics during Ovarian Stimulation and GnRH Antagonist Cotreatment for IVF: RCT Comparing recFSH Initiated on Cycle Day 2 or 5

Christophe Blockeel,* Monique D. Sterrenburg,* Frank J. Broekmans, Marinus J. C. Eijkemans, Johan Smitz, Paul Devroey, and Bart C. J. M. Fauser

Centre for Reproductive Medicine (C.B., J.S., P.D.), Universitair Ziekenhuis Brussel, 1090 Brussels, Belgium; Department of Reproductive Medicine and Gynecology (M.D.S., F.J.B., M.J.C.E., B.C.J.M.F.) and Julius Centre for Health Sciences and Primary Care (M.J.C.E.), University Medical Centre Utrecht, 3508 GA Utrecht, The Netherlands

Blockeel C, *et al. JCEM*. 2011;96:1122-1128

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM



Blockeel C, *et al. JCEM*. 2011;96:1122-1128

'There is an alternative' I said to Jean. 'We could try freezing human embryos, and keep them in store until the effects of the fertility drugs have faded away and their menstrual cycles were back to normal. The womb would then be receptive, and capable of sustaining the growth of the fetus'

The idea suddenly excited me. We could provide the mother with a whole family spaced in the way she wished, just thawing out each embryo when desired.

R.G Edwards 1976
A Matter of Life. The Story of IVF
2nd edition 2011, Impression Publishing

Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis

- Three trials accounting for 633 cycles in women aged 27–33 years
- Mostly high responders

Characteristics of the clinical trial included in the review.

Study ID	Patients (Fresh/FET)	Age, y (Fresh/FET)	Duration of trial	Day of embryo transfer	Outcome
Aflatoonian et al. (24)	374 (187/187) High responders	28.1 ± 3.5/27.3 ± 4.4	February 2007–February 2009	Day 2	Ongoing pregnancy Implantation Clinical pregnancy Miscarriage rate
Shapiro et al. (18)	147 (67/78) Normal responders	32.9 ± 3.7/33.0 ± 3.8	October 2007–October 2010	Day 5 (blastocyst)	Ongoing pregnancy Implantation Clinical pregnancy Early pregnancy loss
Shapiro et al. (25)	122 (62/60) High responders	31.4 ± 3.7/30.6 ± 3.7	July 2007–July 2010	Day 5 (blastocyst)	Ongoing pregnancy Implantation Clinical pregnancy Early pregnancy loss

Roque. Elective frozen-thawed embryo transfer. *Fertil Steril* 2012.

Meta-analysis results

Study or Subgroup	Frozen-Thawed Events	Frozen-Thawed Total	Fresh Events	Fresh Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ongoing Pregnancy						
Aflatoonian 2010	73	187	52	187	46.0%	1.4 [1.05, 1.88]
Shapiro 2011 – Normal	39	70	27	67	24.4%	1.38 [0.97, 1.98]
Shapiro 2011 – High	38	60	34	62	29.6%	1.15 [0.86, 1.55]
Total (95% CI)		**317**		**316**	**100.0%**	**1.32 [1.10, 1.590**
Total events	150		113			
Heterogeneity: Chi² = 1.03, df =2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 3.00 (P = 0.003)						
Clinical Pregnancy						
Aflatoonian 2010	78	187	58	187	47.9%	1.34 [1.02, 1.77]
Shapiro 2011 – Normal	42	70	29	67	24.5%	1.37 [0.99, 1.94]
Shapiro 2011 – High	39	60	34	62	27.6%	1.19 [0.88, 1.59
Total (95% CI)		**317**		**316**		**1.31 [1.10, 1.56]**
Total events	159		121			
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.04 (P = 0.002)						
Miscarriage						
Aflatoonian 2010	5	187	6	187	33.2%	0.83 [0.26, 2.68]
Shapiro 2011 – Normal	6	70	7	67	39.6%	0.82 [0.29, 2.32]
Shapiro 2011 – High	4	60	5	62	27.2%	0.83 [0.23, 2.93]
Total (95% CI)		**317**		**316**	**100.0%**	**0.83 [0.43, 1.60]**
Total events	15		18			

Risk Ratio M-H, Fixed, 95%CI

Roque. Elective frozen-thawed embryo transfer. *Fertil Steril*, 2012.

Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

Eleven studies met the inclusion criteria

- Singleton pregnancies after the transfer of frozen thawed embryos were associated with better perinatal outcomes compared with those after fresh IVF embryos

Lower relative risks (RR) and 95% confidence intervals (CI) after FET for:

	RR	95% CI
antepartum haemorrhage	0.67	0.55–0.81
preterm birth	0.84	0.78–0.90
small for gestational age	0.45	0.30–0.66
low birth weight	0.69	0.62–0.76
perinatal mortality	0.68	0.48–0.96

Conclusions

- Despite embryo selection, implantation rates after IVF are lower than after spontaneous conceptions
- Mild stimulation probably does not improve embryo quality; it just 'selects the best'.
- Ovarian stimulation disrupts the endometrium and intra-uterine environment
- No clinical intervention yet shown to ameliorate this.

Conclusions: Freeze all frees all.

- Doctor free to stimulate ovaries without disrupting endometrium
- Women free of OHSS risk

Embryos free to implant in more physiological environment

Babies free of impact of ovarian stimulation on development

The way ahead…

Stimulate with gonadotropins
in order to obtain 10-15 oocytes

Freeze all embryos and
transfer in FET cycle

Further Reading

Santos MA, Kuijk EW, Macklon NS. The impact of ovarian stimulation for IVF on the developing embryoReproduction. 2010 Jan;139(1):23-34

.Macklon NS, Stouffer RL, Giudice LC, Fauser BC. The science behind 25 years of ovarian stimulation for in vitro fertilization Endocrine Rev. 2006 Apr;27(2):170-207

Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Syste fertilizationmatic review and meta-analysis. Hum Reprod Update. 19(2):87-104 2013

38

Excessive ovarian response affects oocyte quality, endometrial receptivity and child health

K.J. Middelburg, P. Schendelaar, J. Seggers, M.L. Haadsma, M.J. Heineman, A.F. Bos, M. Hadders-Algra

Excessive ovarian response affects oocyte quality, endometrial receptivity and child health

So does potentially any form of Assisted Reproductive Technology.

The statement is therefore potentially misleading so I am against it.

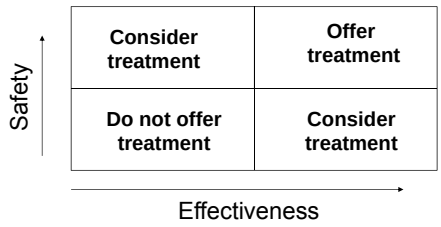
Disclosure statement

Nothing to disclose

None of the members of the research group have any commercial and/or financial relationship with manufacturers of pharmaceuticals, laboratory supplies and/or medical devices.

Conditions for treatment

Conditions for treatment



Outline

Conditions for treatment: Effectiveness & Safety

- Safety of ART
  - Perinatal outcome
  - Long term follow-up

  } Potential mechanisms that may influence outcome
- Effectiveness of ART
  - Unexplained subfertility

Conclusions and reflections

Learning objectives

- What is known on safety of ART?
  - Perinatal outcome
  - Long term follow-up
- What mechanisms may influence outcome following ART?
- What is known on effectiveness of ART?
  - Indications

Perinatal outcome of singletons born following ART

Outcome	% ART/C	n ART/C	RR / OR (95%CI)	Ref
Preterm birth < 37 wks	11% / 6% 12% / 5%	5361 / 7038 12114 / 410690	RR 2.04 (1.80–2.32) OR 1.95 (1.73–2.20)	A B
Birth weight < 2500 g	11% / 6% 10% / 4%	5361 / 7038 10096 / 195342	RR 1.70 (1.50–1.92) OR 1.77 (1.40–2.22)	A B
Ceasarean section	26% / 18%	5084 / 6616	RR 1.54 (1.44–1.66)	A
Admission NICU	17% / 12%	4428 / 5621	RR 1.27 (1.16-1.40)	A
Perinatal mortality	1.2 % / 0.8 % 2.0 % / 0.7 %	4582 / 5641 5199 / 192993	RR 1.68 (1.11-2.55) OR 2.19 (1.61-2,98)	A B

A: Helmerhorst et al 2004; B: Jackson et al, 2004

Birth defects in children born following ART

Outcome	% ART/C	n ART/C	RR / OR (95%CI)
All birth defects	7% / 5%*	92671 / 3870760	RR 1.32 (1.24– 1.42)
Major birth defects	3% / 2%*	92671 / 3870760	RR 1.42 (1.29-1.56)

* Risks are subject to population background risk

Hansen et al, 2013

Impact

5 Millionth IVF Baby Born This Year

05 Jul 2012 Click to Print

Experts estimate that around now, approximately **5 million babies have been born as a result of assisted reproduction technologies - namely IVF and ICSF.** The first test tube baby was born in July 1978, in England, her name was Louise Brown. These data were presented yesterday at the 28th Meeting of the European Society of Human Reproduction and Embryology (ESHRE), Istanbul, Turkey.

Experts from ICMART (International Committee for Monitoring Assisted Reproductive Technologies) worked out the figure of 5 million babies from the number of IVF and ICSI treatment cycles recorded around the world up to 2008 - they then estimate what the additional numbers probably have been since then.

The presenters yesterday said that up to the end of last year, the total number of births was about 4.6 million, and this year the total will be around 5 million.

Dr David Adamson, chairman of ICMART, said:

"It means that this technology has been highly successful in treating infertile patients. Millions of families with children have been created, thereby reducing the burden of infertility.

"The technology has improved greatly over the years to increase pregnancy rates. The babies are as healthy as those from other infertile patients who conceive spontaneously. The technology is available globally in many different cultures. The major barriers to access are economic, and societal in some situations. With these accomplishments as a foundation, and with prevention of Professor Robert Edwards as a Nobel Laureate,

1% of 5.000.000 = 50.000

Potential mechanisms that may underlie poorer outcome

1) Patient factors related to subfertility

2) Early fetal losses

3) Aspects of the ART procedure
   a) Laboratory procedures involved in ART
   b) Ovarian stimulation

Patient factors related to subfertility

- Increased risk of obstetrical complications
  - Preeclampsia, antepartum haemorrhage, caesarean section
- Increased risk of adverse perinatal outcome
  - Preterm birth, low birth weight, perinatal death

Outcome	n TTP >1y	n TTP < 1y	RR / OR (95%CI)
Preterm birth < 37 wks	7585	57818	OR 1.35 (1.22-1.50)

Draper et al, 1999; Thomson et al, 2005; Pandian et al, 2001; Pinborg et al, 2013

Early fetal losses

- ~10% of ART-singletons originate from twin pregnancies

Outcome	Early fetal loss	Controls	RR / OR (95%CI)
Preterm birth < 37 wks	1727	19808	OR 1.73 (1.54-1.94)
Birth weight < 2500 g	1727	19808	OR 2.09 (1.82-2.39)
SGA	642	5237	OR 1.50 (1.03-2.20)

Luke et al, 2009; Pinborg et al, 2007; Pinborg et al, 2013

Laboratory procedures involved in ART

- Large-offspring syndrome in livestock, reduced birth weight in mice
- Animal studies not confounded by subfertility
- Culture conditions may lead to disturbed genomic imprinting

Young et al, 1998, Ceelen and Vermeiden, 2001; Dumoulin et al, 2010

Laboratory procedures involved in ART

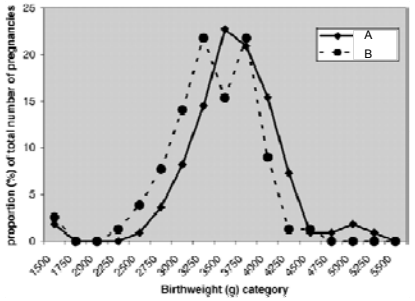
Human Reproduction, Vol.25, No.3 pp. 605–612, 2010

human reproduction ORIGINAL ARTICLE *Embryology*

Effect of *in vitro* culture of human embryos on birthweight of newborns

John C. Dumoulin[1,2,6], Jolande A. Land[3], Aafke P. Van Montfoort[1,2], Ewka C. Nelissen[1,2], Edith Coonen[1,2], Josien G. Derhaag[1,2], Inge L. Schreurs[1], Gerard A. Dunselman[1,2], Arnold D. Kester[4], Joep P. Geraedts[2,5], and Johannes L. Evers[1,2]

Birthweight distributions of live born singletons resulting from embryo culture in either A or B sequential media. The graph depicts the percentage of newborns per birthweight category.



Dumoulin J C et al. Hum. Reprod. 2010;25:605-612

human reproduction

Laboratory procedures involved in ART

Human Reproduction, Vol.28, No.3 pp. 828–834, 2013
Advanced Access publication on December 11, 2012 doi:10.1093/humrep/des410

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Does long *in vitro* culture promote large for gestational age babies?

S. Mäkinen[1], V. Söderström-Anttila[1], J. Vainio[2], A.-M. Suikkari[1], and T. Tuuri[1,*]

[1]Family Federation of Finland, Fertility Clinic Helsinki, Fredrikinkatu 47, 00100 Helsinki, Finland [2]Faculty of Biological Sciences, University of Helsinki, 00014 University of Helsinki, Finland

*Correspondence address. Tel: +358-9-6161221; E-mail: dmo.tuuri@vaestoliitto.fi

Increase in birthweight with longer time in culture

Table III Crude and AORs for SGA and LGA babies after Day 3 and Days 5–6 transfers (Day 2 as a reference group).

	SGA		LGA	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
D2	1	1	1	1
D3	1.12 (0.63–2.00)	1.00 (0.54–1.85)	1.25 (0.71–2.21)	1.18 (0.66–2.11)
D5–6	0.28 (0.07–1.15)	0.25 (0.06–1.12)	2.23 (1.17–4.26)	2.22 (1.14–4.34)

AORs were obtained after stratification for fertilization method, age of mother, mother's BMI, main course of infertility, parity, gender of newborn, gestational age and embryo culture period.

Table IV Absolute and gender and gestational age adjusted mean birthweights (SD scores) according to the embryo culture period (with 95% CI).

	Total	Day 2	Day 3	Day 5–6
n	10079	871	1139	69
Mean weight (g) (SD)	3492 (565)	3489 (568)	3450 (567)	3612 (521)
Mean SD score	−0.021	−0.057[a]	0.005[b]	0.380[a,b]
95% CI	−0.08 to 0.04	−0.13 to 0.01	−0.17 to 0.18	0.09–0.67

[a]P = 0.004 between Day 2 and Days 5–6.
[b]P = 0.05 between Day 3 and Days 5–6.

Mäkinen et al, 2013

Ovarian stimulation

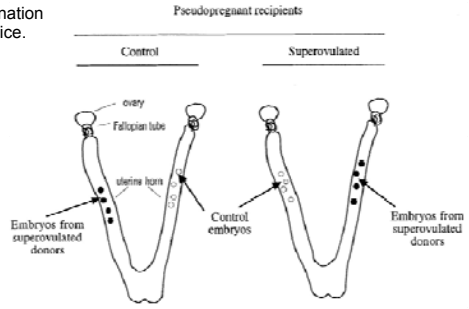
Possible explanations

- Loss of natural selection of the dominant oocyte, resulting in reduced oocyte quality
- Impaired endometrial receptivity due to supraphysiological estradiol levels

Ertzeid and Storeng, 2001; van der Auwera and d'Hooghe, 2001

Ovarian stimulation

- Embryo donation model in mice.



Ertzeid G , and Storeng R Hum. Reprod. 2001;16:221-225

human reproduction

Ovarian stimulation

- Higher percentage of blastocysts on day 4 in control mice (61% vs. 41%; P < 0.001)
- Reduction of implantation rate of superovulated embryos in control mice (12% vs 25%; P 0.001)

→ Reduced embryo developmental capacity

- Higher implantation rate of control embryos in control recipients than in superovulated recipients (25% vs. 7%; p = 0.0001)
- Lower birth weight in superovulated recipients than in control recipients (0.51g vs. 0.72g; P = 0.006)

→Reduced endometrial receptivity

Ertzeid and Storeng, 2001

Ovarian stimulation

Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

Abha Maheshwari, M.D.,[a] Shilpi Pandey, M.R.C.O.G.,[b] Ashalatha Shetty, M.D.,[b] Mark Hamilton, M.D.,[b] and Siladitya Bhattacharya, M.D.[a]

[a] Reproductive Medicine, Division of Applied Health Sciences, University of Aberdeen, and [b] Assisted Reproduction Unit, Aberdeen Maternity Hospital, Aberdeen, United Kingdom

Ovarian stimulation

TABLE 3

Overall table for effect and sensitivity analysis (frozen vs. fresh IVF/ICSI pregnancies).

Outcome	No. of frozen vs. fresh IVF/ICSI conceptions	Overall effect (RR, 95% CI) fixed effect	Heterogeneity (I^2)	Subgroup analysis (matched cohort) (calculated only if there was a statistical difference)	Risk difference (calculated only if there was a statistical difference)
Small for gestational age	1,933 vs. 3,141	0.45 (0.30–0.66)	22%	NA	−0.02 (−0.03, −0.01)
Birth weight <2,500 g	8,536 vs. 25,800	0.69 (0.62–0.76)	28%	0.59 (0.45–0.78)	−0.03 (−0.03, −0.02)
Birth weight <1,500 g	3,552 vs. 16,469	0.72 (0.50–1.04)	0	NA	NA
Delivery at <37 weeks	10,017 vs. 27,686	0.84 (0.78–0.90)[b]	74%	0.72 (0.63–0.82)	−0.02 (−0.03, −0.01)
Delivery at <32 weeks	3,050 vs. 13,630	0.73 (0.50–1.08)	11%	0.76 (0.44–1.33)	−0.00 (−0.01–0.00)
APH	3,875 vs. 7,000	0.67 (0.55–0.81)	0	NA	−0.02 (−0.02, −0.01)
Congenital anomalies	3,152 vs. 6,308	1.05 (0.81–1.35)	47%	0.88 (0.63–1.24)	NA
Cesarean section	5,435 vs. 16,740	1.10 (1.05–1.15)	18%	1.12 (1.06–1.18)	0.03 (0.01, −0.05)
Transfer to NICU	3,552 vs. 16,469	1.00 (0.92–1.08)	69%	0.86 (0.72–1.03)	NA
Perinatal mortality	5,546 vs. 17,424	0.68 (0.48–0.96)	0	0.64 (0.43–0.97)	−0.00 (−0.01, −0.00)

Note: APH = antepartum hemorrhage; CASP = critical appraisal skills program; CI = confidence interval; NA = not available; NICU = neonatal intensive care unit; RR = relative risk.
[b] Sensitivity analysis performed only if there was a mixture of good and poor quality studies.
[b] Random effect model −0.86 (0.72–1.03).

Maheshwari. Frozen versus fresh ET. Fertil Steril 2012.

Maheswari et al. 2012

Long term consequences of poorer perinatal outcome

- Developmental Origins of Health and Disease
- Association birthweight and risk of chronic disease including coronary heart disease, hypertension, stroke, and type 2 diabetes in later life
  - ➢ Lower birth weight → higher risk
- Environmental influences acting during early development shape disease risk in later life
- Early environment in assisted reproduction

Barker 1990; Godfrey et al, 2007; Gluckman et al, 2008

Editorial

Manipulating Nature

Might There Be a Cardiovascular Price to Pay for the Miracle of Assisted Conception?

David S. Celermajer, MB, BS, PhD, DSc

Assisted reproductive technologies (ARTs) have brought the miracle of childbirth to literally hundreds of thousands of adults who would otherwise not have conceived children; indeed, it is now estimated that 1% to 3% of all births in many developed nations involve ARTs.[1] The first ART birth, however, was not until 1978, and so even the oldest such offspring are only now entering young adult life. Will they have the same health outcomes as those babies conceived "naturally"?

Article see p 1890

There have been some health problems documented after ART. In studies to date, ART has been consistently associated with multiple births and low birth weight in offspring[2]; these factors may in turn be linked to long-term cardiovascular risk.[3] Data from meta-analyses have also suggested an in ART children aged 8 to 18 years compared with naturally conceived children, which suggests these as potential mechanisms of late cardiovascular risk.[6]

Can environmental exposures so early in life actually alter vascular phenotype and risk? In 1992, we first demonstrated arterial abnormalities (systemic endothelial dysfunction) in high-risk children as young as 8 years of age.[7] We found similar early vascular functional abnormalities in the pulmonary circulation in high-risk children with congenital heart disease.[8] In 1997, Napoli et al[9] found aortic lipid deposition in fetuses of hypercholesterolemic mothers, and in 2005, we[10] found increased aortic wall thickness in growth-restricted newborns in the first days of life, which implicates fetal events in the modification of potential vascular risk. The present data from Scherrer et al[5] suggest that even the environment of the embryo might alter cardiovascular risk

Cardiovascular risk in ART-children

Age	n ART/ n controls	Bp ART	Bp controls	p- value	Reference
8	150/ 147	100/60	95/55	P < 0.001	Belva et al, 2007
8-18	225 / 225	109/61	105/59	P< 0.001	Ceelen et al, 2008
4-14	106 / 68	SDS +0.3/+0.7	SDS -0.3/+0.2	P< 0.001	Sakka et al, 2010
14	217/ 223	♀ 109/64 ♂ 113/ 64	♀ 111/66 ♂ 116/65	ns	Belva et al, 2012
11-12	65 / 57	113/ 70 FMD: 6.7 PWV: 7.8 m/s CIMT: 410 µm Pap: 39 mmHg	113/70 FMD: 8.6 PWV: 6.5 m/s CIMT: 370 µm Pap: 30 mmHg	ns P < 0.0001 p < 0.001 p < 0.0001 p < 0.0001	Scherrer et al, 2012*

* Measures for vascular function: FMD = flow-mediated dilation of the brachial artery, PWV = pulse-wave velocity, CIMD = carotid intima-media thickness, Pap = pulmonary artery pressure

Cerebral palsy in ART-children

Human Reproduction, Vol.25, No.8 pp. 2115–2122, 2010
Advanced Access publication on June 16, 2010 doi:10.1093/humrep/deq070

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Multiplicity and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: a population-based cohort study

D. Hvidtjørn[1,*], J. Grove[1], D. Schendel[2], C. Sværke[1], L.A. Schieve[2], P. Uldall[3,4], E. Ernst[5], B. Jacobsson[6], and P. Thorsen[1]

[1]Institute of Public Health, Department of Epidemiology, University of Aarhus, 8000 Århus, Denmark [2]Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, 30333 Atlanta, GA, USA [3]National Institute of Public Health, Copenhagen, Denmark [4]Pediatric Clinic, Rigshospitalet, University Hospital of Copenhagen, Denmark [5]Reproductive Laboratory, Skejby University Hospital, 8200 Århus, Denmark [6]Perinatal Center, Department of Obstetrics and Gynecology, Institute for the Health of Women and Children, The Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

Table III Risk of CP in children born after assisted conception and IVF and OI separately compared with NC children, hazard risk ratios (HRR) and 95% CI.

	Assisted conception	IVF	OI
Crude	1.90 (1.57–2.31)	2.34 (1.81–3.01)	1.55 (1.17–2.06)
Basic*	1.72 (1.39–2.12)	2.09 (1.51–2.65)	1.47 (1.09–1.97)
Basic* and multiplicity	1.12 (0.88–1.41)	1.07 (0.78–1.47)	1.13 (0.83–1.53)
Basic* and GA	0.96 (0.77–1.19)	0.90 (0.68–1.20)	1.01 (0.74–1.36)
Basic* and multiplicity and GA	0.96 (0.76–1.22)	0.91 (0.66–1.24)	1.01 (0.74–1.37)
Twins and more**	0.96 (0.78–1.22)	0.99 (0.78–1.27)	1.00 (0.78–1.28)
GA weeks: 20–27***	32.63 (23.36–45.59)	30.91 (21.63–44.16)	34.18 (23.98–48.73)
GA weeks: 28–31***	33.12 (27.42–40.00)	35.01 (29.60–43.31)	32.57 (26.73–39.69)
GA weeks: 32–36***	4.44 (3.71–5.31)	4.39 (3.64–5.28)	4.47 (3.72–5.38)
GA weeks: 37–41	reference	reference	reference
GA weeks: 42+***	1.58 (0.90–1.49)	1.19 (0.92–1.53)	1.17 (0.91–1.50)
In strata of multiplicity			
Singletons, crude	1.31 (0.99–1.72)	1.44 (0.93–2.21)	1.24 (0.87–1.76)
Twins and more, crude	1.19 (0.85–1.67)	1.22 (0.83–1.78)	1.13 (0.68–1.88)
Singletons, basic*	1.21 (0.90–1.62)	1.21 (0.75–1.94)	1.21 (0.84–1.74)
Twins and more, basic*	1.04 (0.71–1.53)	1.07 (0.69–1.65)	1.00 (0.57–1.74)

*Multiple analysis including sex, maternal age, education, smoking and parity.
**Twins and more compared with singletons and controlled for assisted conception, sex, maternal age, education, smoking, GA and parity.
***Strata of GA compared with term born children (GA 37–41) and controlled for assisted conception, sex, maternal age, education, smoking, multiplicity and parity.

Hvidtjørn et al. 2010

Neurodevelopmental outcome of singletons born following ART

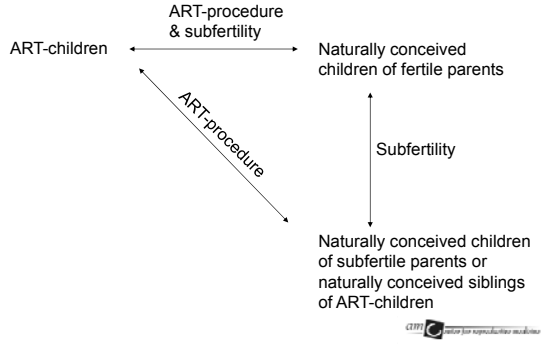
Outcome	Results
Neuromotor development	ART- children ≈ naturally conceived
Cognition	ART- children ≈ naturally conceived
Behaviour	ART- children ≈ naturally conceived

Pertinent conclusions precluded due to:

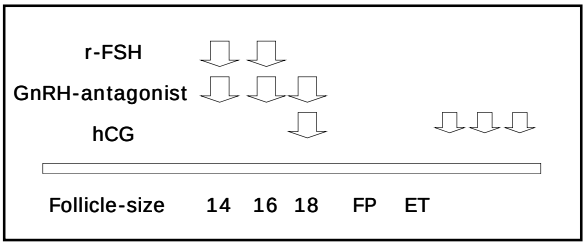
- Limited methodological quality of controlled studies, problems with attrition, blinding, power
- Meta-analyses not possible due to large variety in age of testing and neurodevelopmental tests used
- Data on long term follow-up limited

Middelburg et al. 2008

Effects of ART and subfertility

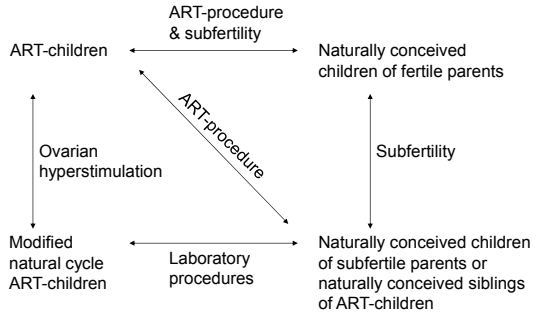


ART in the Modified Natural Cycle



Pelinck et al. 2007

Effect of Ovarian Hyperstimulation



Ovarian hyperstimulation and neurodevelopment

Age	n COH/ MNC	Measure	Outcome	OR(95%CI)
3 mo	68 / 56	Abnormal GM's*	44% / 32%	1.49 (0.70; 3.18)
18 mo	66 / 56	Complex MND**	11% / 9%	1.30 (0.38; 4.42)
2 y	66 / 56	Complex MND**	5% / 2%	1.92 (0.52; 7.10)
				Mean difference (95% CI)
18 mo	66 / 56	Movement variation***	92 / 95	- 1.0 (-1.8; -0.2)

Measured with * General Movements, ** Hempel Neurological examination, and *** Infant Motor Profile

Middelburg et al. 2009, Middelburg et al. 2010, Schendelaar et al 2011, Schendelaar et al 2013

Ovarian hyperstimulation and mental development and behaviour

Age	n COH/ MNC	Measure	Outcome	Mean difference (95% CI)
2 y	66 / 56	Mental development*	98 / 101*	-1.9 (-6.6; 2.9)
2 y	66 / 55	Behaviour**	46 / 47**	-1.1 (-4.4; 2.2)

Measured with * BSID II, MDI, and **Child behaviour check list, Total problems scale

Jongbloed- Pereboom et al, 2011

Ovarian hyperstimulation and birth defects

Age	n COH/ MNC	Measure	Outcome	OR (95% CI)
2 y	66 / 56	Minor anomalies*	50% / 54%	1.13 (0.52–2.47)
2y	66 / 56	Clinically relevant abnormalities*	11% / 4%	2.97 (0.49-18.21)

* Dysmorfic features according to Merks et al.

Seggers et al, 2012

Conclusions on safety of ART

Perinatal outcome

- Increased risk of preterm birth & low birth weight
- Uncertainty concerning the mechanism that underlies poorer perinatal outcome:
  - Patient factors related to subfertility
  - Early fetal losses
  - Ovarian hyperstimulation
  - Laboratory procedures involved in ART

Conclusions on safety of ART

Long term follow-up

- Concern about cardiovascular risk in ART children
- Neurodevelopmental outcome reassuring, but
  - Increased risk of cerebral palsy and neurodevelopmental disorders in ART children mediated by a higher rate of preterm birth
  - Long term follow-up limited and neurodevelopmental disorders may emerge as children grow older

→ Safety is not guaranteed yet

Outline

Conditions for treatment: Effectiveness & Safety

- Safety of ART
  - Perinatal outcome
  - Long term follow-up

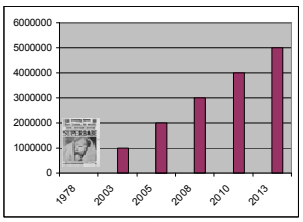
  } Potential mechanisms that may influence outcome
- Effectiveness of ART
  - Unexplained subfertility

Conclusions and reflections

Indications

<u>1990</u>
- 50% tubal pathology
- 20% male factor
- 15% unexplained subfertility
- 15% other

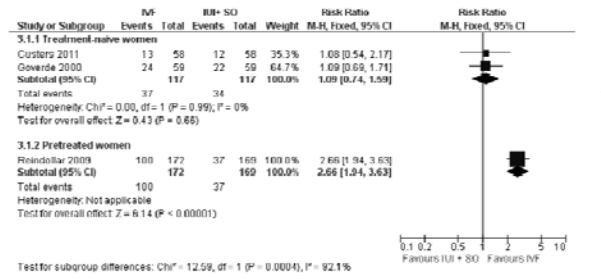
<u>2010</u>
- 10% tubal pathology
- 35% male factor
- 25% unexplained subfertility
- 30% other



Annual reports AMC/VUmc

ART in unexplained subfertility

Figure 5. Forest plot of comparison: 3 in vitro fertilisation (IVF) versus intrauterine insemination plus ovarian stimulation (IUI+SO), outcome: 3.1 live birth rate per woman.



Pandian et al. 2012,

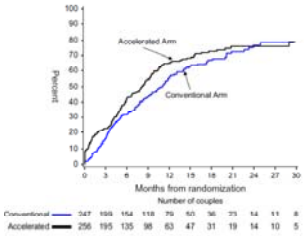
IVF vs. SO+IUI

A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial

Richard H. Reindollar, M.D.,[a] Meredith M. Regan, Sc.D.,[b] Peter J. Neumann, Sc.D.,[c] Bat-Sheva Levine, M.D.,[c] Kim L. Thornton, M.D.,[d] Michael M. Alper, M.D.,[d] and Marlene B. Goldman, Sc.D.[e]

[a] Department of Obstetrics and Gynecology, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [b] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [c] Center for the Evaluation of Value and Risk in Health, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [d] Department of Obstetrics, Gynecology and Reproductive Biology, Division of Reproductive Endocrinology and Infertility, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Boston IVF, Waltham, Massachusetts; and [e] Departments of Obstetrics and Gynecology and Community and Family Medicine, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

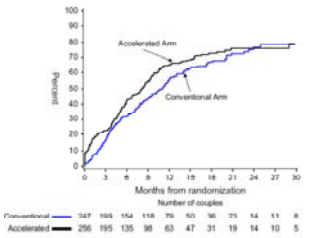
IVF vs. SO+IUI



Time Period (m)	Hazard Ratio	95% CI		P-value
≤ 3	1.52	1.02	2.28	0.04
> 3 to 11	1.40	1.03	1.90	0.03
> 11	0.60	0.34	1.06	0.08

Reindollar et al, 2010

IVF vs SO+IUI

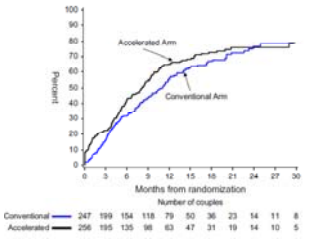


Kaplan-Meier Estimates of Cumulative Incidence of Pregnancy Leading to Delivery of a Live Born, According to Treatment Arm. HR = 1.251 (95% CI, 1.00 to 1.56; log rank P = 0.0452). Analysis also used a piecewise Cox proportional hazards model, overall P = 0.0057. Out of 106 couples who had their IUI prior to the date of randomization (but before pregnancy could be determined), 15 (3/50 conventional and 12/56 accelerated) became pregnant. Additionally, 4 couples in the accelerated arm became pregnant before initiating their first treatment cycle. These couples are shown as achieving pregnancy on day of randomization.

Reindollar et al, 2010

In vitro fertilisation for unexplained subfertility (Review)

Pandian Z, Bhattacharya S, Vale L, Templeton A



Out of 106 couples who had their IUI prior to the date of randomization (but before pregnancy could be determined), 15 (3/50 conventional and 12/56 accelerated) became pregnant.

Reindollar et al, 2010, Pandian et al, 2012

Conclusions on effectiveness of ART

- For the majority of indications of ART we are unsure on the effectiveness
- No comparative studies in unexplained, mild male?

Impact

5 Millionth IVF Baby Born This Year

05 Jul 2012 Click to Print

Experts estimate that around now, approximately **5 million babies have been born as a result of assisted reproduction technologies - namely IVF and ICSI**. The first test tube baby was born in July 1978, in England, her name was Louise Brown. These facts were presented yesterday at the 28th Meeting of the European Society of Human Reproduction and Embryology (ESHRE), Istanbul, Turkey.

Experts from ICMART (International Committee for Monitoring Assisted Reproductive Technologies) worked out the figure of 5 million babies from the number of IVF and ICSI treatment cycles recorded around the world up to 2008 - they then estimate what the additional numbers probably have been since then.

The presenters yesterday said that up to the end of last year, the total number of births was about 4.6 million, and this year the total will be around 5 million.

Dr David Adamson, chairman of ICMART, said:

> "It means that this technology has been highly successful in treating infertile patients. Millions of families with children have been created, thereby reducing the burden of infertility.
>
> "The technology has improved greatly over the years to increase pregnancy rates. The babies are as healthy as those from other infertile patients who conceive spontaneously. The technology is available globally in many different cultures. The major barriers to access are economic, and societal in some situations. With these accomplishments as a foundation, and with prevention of Professor Robert Edwards as a Nobel Laureate,

Conditions for treatment

Consider treatment	Offer treatment
Do not offer treatment	Consider treatment

Safety ↑

Effectiveness →

ARE THESE CONDITIONS FULFILLED??

Conditions for treatment

Unexplained subfertility? Mild male? Endometriosis? Poor ovarian reserve?

	Tubal pathology Severe male
	Anovulation

Safety ↑

Effectiveness →

References

- Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990 ;301:1111
- Belva F, Henriet S, Liebaers I, Van Steirteghem A, Celestin-Westreich S, Bonduelle M. Medical outcome of 8-year-old singleton ICSI children (born >or=32 weeks' gestation) and a spontaneously conceived comparison group. Hum Reprod. 2007;22:506-15.
- Belva F, Roelants M, De Schepper J, Roseboom TJ, Bonduelle M, Devroey P, Painter RC. Blood pressure in ICSI-conceived adolescents. Hum Reprod. 2012 Oct;27(10):3100-8
- Ceelen M, Vermeiden JP. Health of human and livestock conceived by assisted reproduction. Twin Res 2001; 4: 412-6.
- Ceelen M, van Weissenbruch MM, Vermeiden JP, van Leeuwen FE, Delemarre-van de Waal HA. Cardiometabolic differences in children born after in vitro fertilization: follow-up study. J Clin Endocrinol Metab. 2008 May;93(5):1682-8.
- Celermajer DS. Manipulating nature: Might there be a cardiovascular price to pay for the miracle of assisted conception? Circulation. 2012;125:1832-4
- Dumoulin JC, Land JA, Van Montfoort AP, Nelissen EC, Coonen E, Derhaag JG, Schreurs IL, Dunselman GA, Kester AD, Geraedts JP, Evers JL. Effect of in vitro culture of human embryos on birthweight of newborns. Hum Reprod. 2010;25:605-12.
- Draper ES, Kurinczuk JJ, Abrams KR, Clarke M. Assessment of separate contributions to perinatal mortality of infertility history and treatment: a case-control analysis. Lancet 1999; 353: 1746-9.
- Ertzeid G, Storeng R. The impact of ovarian stimulation on implantation and fetal development in mice. *Hum Reprod* 2001; 16: 221-5.
- Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA. Epigenetic mechanisms and the mismatch concept of the developmental origins of health and disease. Pediatr Res. 2007;61:5R-10R.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61-73.

References

- Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. Hum Reprod Update. 2013 [Epub ahead of print]
- Helmerhorst FM, Perquin DAM, Donker D and Keirse MJNC. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004; 328, 261-265.
- Hvidtjørn D, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis. Arch Pediatr Adolesc Med. 2009;163:72-83.
- Jackson RA, Gibson KA, Wu YW and Croughan MS Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103, 551-563.
- Jongbloed-Pereboom M, Middelburg KJ, Heineman MJ, Bos AF, Haadsma ML, Hadders-Algra M. The impact of IVF/ICSI on parental well-being and anxiety 1 year after childbirth. Hum Reprod. 2012;27:2389-95
- Luke B, Brown MB, Grainger DA, Stern JE, Klein N, Cedars MI; SART Writing Group. The effect of early fetal losses on singleton assisted-conception pregnancy outcomes. Fertil Steril. 2009;91:2578-85
- Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril. 2012;98:368-77
- Mäkinen S, Söderström-Anttila V, Vainio J, Suikkari AM, Tuuri T. Does long in vitro culture promote large for gestational age babies? Hum Reprod. 2013;28:828-34
- Middelburg KJ, Heineman MJ, Bos AF, Hadders-Algra M. Neuromotor, cognitive, language and behavioural outcome in children born following IVF or ICSI–a systematic review. Hum Reprod Update 2008; 14, 219-231.

References

- Middelburg KJ, Heineman MJ, Bos AF et al. The Groningen ART cohort study: ovarian hyperstimulation and the in vitro procedure do not affect neurological outcome in infancy. Hum Reprod 2009; 24: 3119-26.
- Middelburg KJ, Haadsma ML, Heineman MJ, Bos AF, Hadders-Algra M. Ovarian hyperstimulation and the in vitro fertilization procedure do not influence early neuromotor development; a history of subfertility does. Fertil Steril 2010; 93: 544-53.
- Pandian Z, Bhattacharya S, Templeton A. Review of unexplained infertility and obstetric outcome: a 10 year review. Hum Reprod 2001; 16: 2593-7.
- Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2012;4:CD003357.
- Pelinck MJ, Vogel NE, Arts EG et al. Cumulative pregnancy rates after a maximum of nine cycles of modified natural cycle IVF and analysis of patient drop-out: a cohort study. Hum Reprod 2007; 22: 2463-70.
- Pinborg A, Lidegaard O, la Cour Freiesleben N, Andersen AN. Vanishing twins: a predictor of small-for-gestational age in IVF singletons. Hum Reprod 2007; 22: 2707-14.
- Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update. 2013;19:87-104
- Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010;94:888-99.
- Sakka SD, Loutradis D, Kanaka-Gantenbein C, Margeli A, Papastamataki M, Papassotiriou I, Chrousos GP. Absence of insulin resistance and low-grade inflammation despite early metabolic syndrome manifestations in children born after in vitro fertilization. Fertil Steril. 2010;94:1693-9

References

- Schendelaar P, Middelburg KJ, Bos AF, Heineman MJ, Jongbloed-Pereboom M, Hadders-Algra M. The Groningen ART cohort study: the effects of ovarian hyperstimulation and the IVF laboratory procedures on neurological condition at 2 years. Hum Reprod. 2011;26:703-12.
- Schendelaar P, Heineman KR, Heineman MJ, Jongbloed-Pereboom M, La Bastide-Van Gemert S, Middelburg KJ, Van den Heuvel ER, Hadders-Algra M. Movement variation in infants born following IVF/ICSI with and without ovarian hyperstimulation. Early Hum Dev. 2013;89:507-13
- Scherrer U, Rimoldi SF, Rexhaj E, Stuber T, Duplain H, Garcin S, de Marchi SF, Nicod P, Germond M, Allemann Y, Sartori C. Systemic and pulmonary vascular dysfunction in children conceived by assisted reproductive technologies. Circulation. 2012;125:1890-6.
- Seggers J, Haadsma ML, Bos AF, Heineman MJ, Keating P, Middelburg KJ, van Hoften JC, Veenstra-Knol HE, Kok JH, Cobben JM, Hadders-Algra M. Dysmorphic features in 2-year-old IVF/ICSI offspring. Early Hum Dev. 2012;88:823-9.
- Thomson F, Shanbhag S, Templeton A, Bhattacharya S. Obstetric outcome in women with subfertility. BJOG 2005; 112: 632-7.
- Van der Auwera I, D'Hooghe T. Superovulation of female mice delays embryonic and fetal development. Hum Reprod 2001; 16: 1237-43.
- Young LE, Fernandes K, McEvoy TG et al. Epigenetic change in IGF2R is associated with fetal overgrowth after sheep embryo culture. Nat Genet 2001; 27: 153-4.

Suggested presentations

- **Sunday 7 July; Pre-congress course 6: High standard psychosocial care in your clinic; how to implement new guidelines**
  11:00 - 11:30: Patients' and professionals' barriers and facilitators of tailored expectant management
  Noortje Van Den Boogaard - The Netherlands

- **Monday 8 July; Session 07: Female infertility: new developments**
  11:00 - 11:15: Preliminary comparative effectiveness of IVF with single embryo transfer or IVF in the modified natural cycle and IUI with hyperstimulation; a randomized trial (INeS trial)
  Alexandra Bensdorp, The Netherlands

- **Tuesday 9 July; Session 29: Ovarian stimulation**
  11:00 - 11:15: Continued treatment with clomiphene citrate in subfertile women with World Health Organization type II anovulation who are not pregnant after six ovulatory cycles
  Nienke Weiss, The Netherlands

- ***Tuesday 9 July; Session 45: Clinical female infertility***
  15:15 - 15:30; An economic analysis comparing IVF with a single embryo transfer and IVF with a modified natural cycle to IUI with hyperstimulation (the INeS trial)
  Raïssa Tjon-Kon-Fat, The Netherlands

Maximising success rates by stimulation individualization

Dr. Ernesto Bosch
Medical Director Human Reproduction Unit
Instituto Valenciano de Infertilidad
Valencia. Spain

Disclosure of Potential Conflicts of Interest

Dr. E. Bosch declares having received honoraria during the last 36 months for consultancy, participating in advisory boards and lectures including services in speakers bureaus by MSD, Merck-Serono and Ferring pharmaceuticals

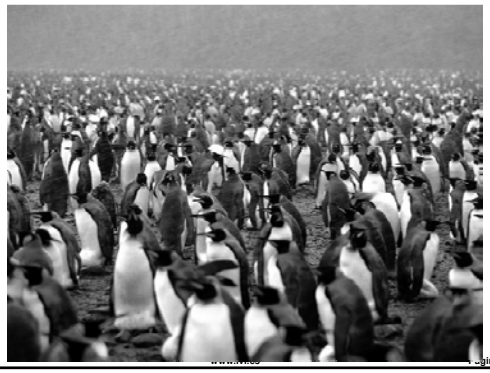
Primary:

- Understand the advantages of individualizing ovarian stimulation for optimizing IVF outcome

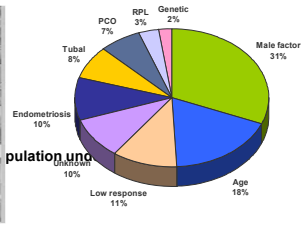
Secondary:

- Recognize the heterogeneity of population undergoing IVF
- Identify advantages and pitfalls of serum AMH
- Anticipate situations that may impact on ovarian response
- Consider the role of other ovarian response biomarkers
- Guidelines for choosing the personalized ovarian stimulation protocol

Patients are not all the same



Heterogeneity of population undergoing COS for IVF



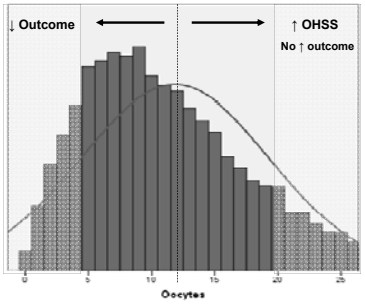
Heterogeneity of population undergoing COS for IVF

	≤ 35		36-40		> 40	
BMI	< 25	≥ 25	< 25	≥ 25	< 25	≥ 25
Normo ovulatory	31.9%	5.6%	19.3 %	4.1%	7.0 %	1.8%
Anovulation/PCO	4.5 %	2.5%	1.4 %	0.9%	0.06 %	0.04%
Low responders	4.4 %	0.7%	3.6 %	0.6%	0.34 %	0.06%
Endometriosis	5.7 %	0.4%	2.7 %	0.2%	0.18 %	0.02%

Bosch & Ezcurra, Reprod Biol Endocrinol. (2011) 21;9:82.

Heterogeneity of ovarian response to COS for IVF

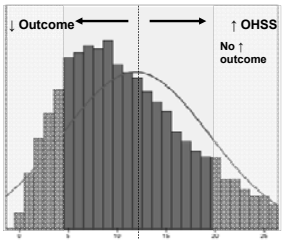
(n=4727; 12.1 ± 7.5 oocytes; Age 34.5 ± 4.1)



PÁG.7 www.ivi.es Página 7

Maximising success rates by stimulation individualization

iCOS



PÁG.8 www

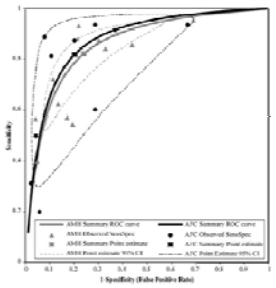
Maximising success rates by stimulation individualization

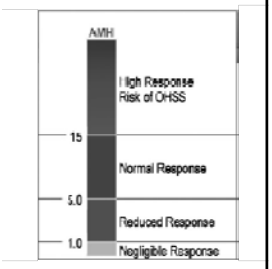
Taylor made for perfect individualization

1st step for success: Take the exact measurements

PÁG.9 www.ivi.es Página 9

Maximising success rates by stimulation individualization

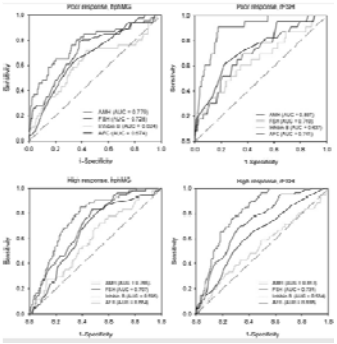




Broer et al, Fertil Steril (2009), 91: 705-14

Nelson et al, Hum Reprod (2009), 24: 867-75

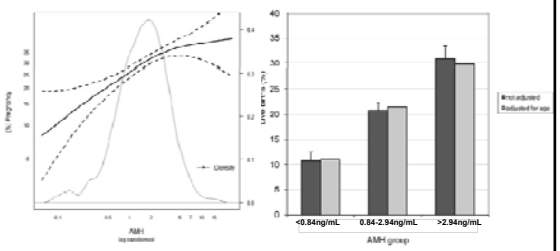
Maximising success rates by stimulation individualization



Arce et al, Fertil Steril (2013), Feb. 5 (Epub ahead of print)

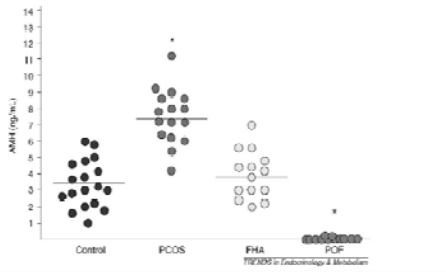
Maximising success rates by stimulation individualization

Antimüllerian Hormone Levels Are Strongly Associated With Live-Birth Rates After Assisted Reproduction



Brodin et al, JCEM (2013), 98: 1107-1114

Maximising success rates by stimulation individualization

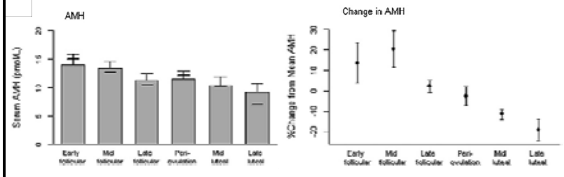


La Marca et al (2009) Hum Reprod 24: 2264-75

..Not everything is what it seems…

Maximising success rates by stimulation individualization

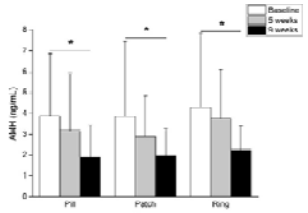
Variation in antimüllerian hormone concentration during the menstrual cycle may change the clinical classification of the ovarian response



Hadlow et al. Fertil Steril (2013), Feb. 21 (Epub ahead of print)

Maximising success rates by stimulation individualization

Antimüllerian hormone levels decrease in women using combined contraception independently of administration route

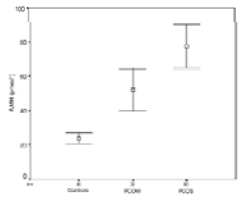


Kalio et al. Fertil Steril (2012), Dec. 20 (Epub ahead of print)

The relationship of AMH with PCO mprphology and PCO syndrome: A prospective cohort study

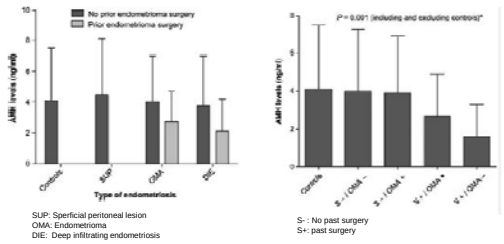
	n	Age	BMI	FSH (IU/l)	LH (IU/l)	AMH (pmol/l)
Controls	90	32.5 (3.3)	24.8 (2.6)	6.3 (2.0)	4.9 (3.0)	23.6 (15.0)
PCOM	35	32.1 (4.2)	24.7 (2.6)	5.6 (1.4)	5.3 (3.0)	52.2* (35.0)
PCOS	90	31.6 (4.4)	24.9 (2.4)	5.1* (1.4)	8.8* (5.2)	77.6***(61.0)

AMH, anti Müllerian hormone; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.
*P < 0.001 versus controls.
**P < 0.05 versus PCOM.



Homburg et al. Hum Reprod (2013), 28:1077-1083

In women with endometriosis anti-Müllerian hormone levels are decreased only in those with previous endometrioma surgery



SUP: Sperficial peritoneal lesion
OMA: Endometrioma
DIE: Deep infiltrating endometriosis

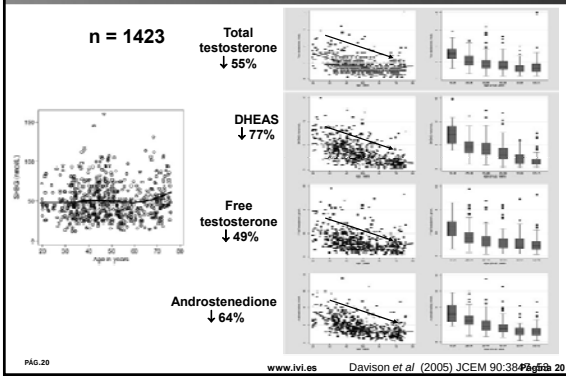
S- : No past surgery
S+: past surgery

Streuli et al. Hum Reprod (2012), 27:3294-3302

❿ Impact of different factors on ovarian response, regardless of ovarian reserve

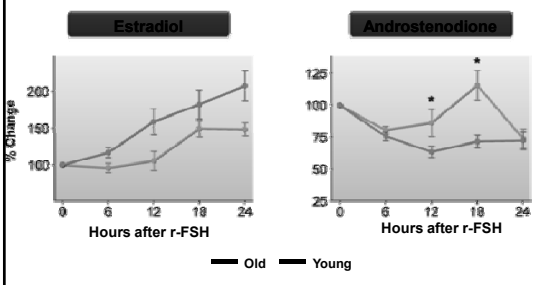
- ❖ Age
- ❖ Basal androgen levels
- ❖ Basal gonadotrophyn levels
- ❖ BMI
- ❖ Hyperinsulism
- ❖ Hyperprolactinemia
- ❖ Gonadotrpoyn receptor polymorfisms

Ovarian ageing: Endocrine features



Davison *et al* (2005) JCEM 90:3847–53

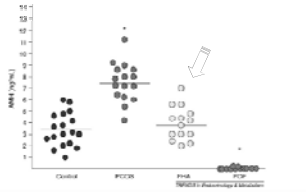
Ovarian ageing: Endocrine features



Welt *et al* (2006) Hum Reprod;21:2189–93

Hypothalamic-pituitary failure: Endocrine features

- ↓ E2 levels (sometimes below detection level)
- FSH and LH < 1.2 IU/L (consider when FSH < 5 IU/L)
- Variable response to pulsatile GnRH
- Normal Inhibin-B
- AMH within normal limits



La Marca et al (2009) Hum Reprod 24: 2264-75

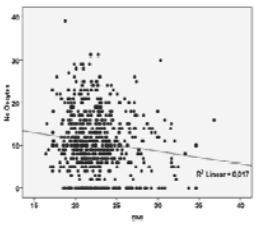
Hypothalamic-pituitary failure: Ovarian stimulation management

150 FSH +	Fols > 10 mm	E2 (pg/ml) / fol > 15 mm	Endometrial thickness (mm)	% hCG
0 LH	0-1	28 ± 8	3 - 4	0
25 LH	1-2	106 ± 59	3 - 4	60
75 LH	4-5	267 ± 54	7 - 8	75
225 LH	3-4	472 ± 213	7 - 8	85

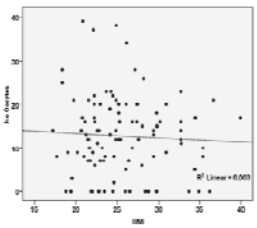
The European Recombinant Human LH Study Group (1998), JCEM 83: 1507-14

Different impact of BMI on ovarian response in PCO than no PCO women

≤ 35 yo; Initial dose=225 IU; No PCO



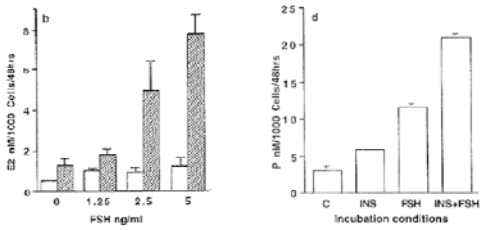
≤ 35 yo; Initial dose=225 IU; PCO



Bosch et al (Unpublished data)

Hypothalamic-pituitary dysfunction_PCO: Endocrine features

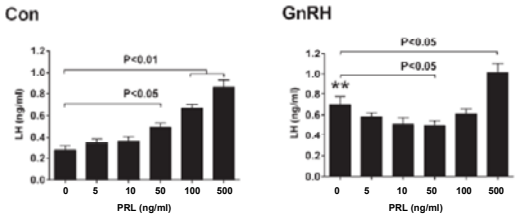
Modulation by insulin of gonadotrophins action



Willis et al, (1996), JCEM 81: 302-309

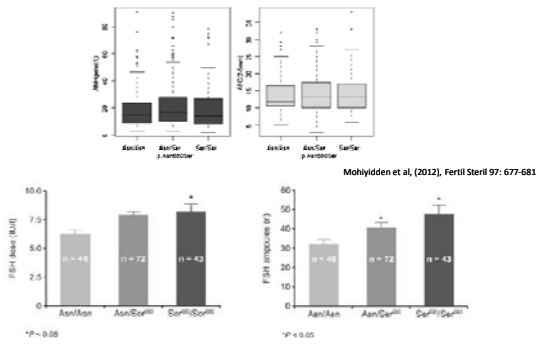
Hyperprolactinemia: Endocrine features

Effects of PRL on basal and GnRH-stimulated LH release



Hodson et al, (2010) Biol Reprod 83; 1046-55

FSH receptor polimorphisms



Mohiyiddeen et al, (2012), Fertil Steril 97: 677-681

Alviggi, Humaidan and Ezcurra, (2012). Reprod Biol Endocrinol 10: 118

LH receptor polimorphisms

Suboptimal response to GnRHa long protocol is associated with a common LH polymorphism

	Group A (n = 22)	P-value A versus B	Group B (n = 15)	P-value B versus C	Group C (n = 23)	P-value A versus C
No. of v-βLH carriers (%)[a]	7 (31.8)	NS	1 (6.7)	NS	0	<0.05
Suppressed LH	0.85 ± 0.3	NS	1.2 ± 0.4	NS	1.6 ± 1.7	<0.05
Starting FSH dose (IU)	201.1 ± 34.9	NS	196.0 ± 36.7	NS	192.4 ± 37.2	NS
Duration of stimulation (days)	13.7 ± 1.0	<0.05	11.1 ± 1.4	NS	11.3 ± 1.1	<0.05
No. of rhFSH ampoules	51.9 ± 6.3	<0.001	34.0 ± 5.5	<0.001	18.9 ± 3.1	<0.001
Day 5 oestradiol concentration (pg/ml)	104.3 ± 85.6	NS	248.3 ± 173.7	NS	346.2 ± 250.6	0.067
Day 8 LH concentration (IU/l)	0.8 ± 0.2	NS	1.02 ± 0.21	0.08	1.7 ± 1.7	<0.05
Day 8 oestradiol concentration (pg/ml)	636.0 ± 314.9	NS	987.4 ± 379.5	NS	1549.7 ± 1110.6	NS
Oestradiol at HCG day (pg/ml)	1561.0 ± 556.2	<0.05	2725.9 ± 794.4	NS	2856.1 ± 739.7	<0.05
No. of oocytes retrieved	7.3 ± 1.5	<0.05	11.7 ± 2.4	<0.05	14.7 ± 4.1	<0.001
Implantation rate[b] (%)	11.1		12.8		14.5	
No. of pregnancies[b] (%)	7 (31.8)		6 (40.0)		10 (43.5)	
No. of abortions (%)	2 (9.1)		1 (6.7)		1 (4.3)	
No. of ongoing pregnancies[b] (%)	5 (22.7)		5 (33.3)		9 (39.1)	

Alviggi et al RBMOnline (2009);18: 9–14

Endocrine evaluation of infertile patients before COS for IVF

- **Minimal**
  - AMH
  - FSH
  - E2
- **Recommended**
  - LH
  - PRL
  - TSH, T3, T4
- **Consider depending on the case**
  - Total Te
  - SHBG
  - Insulin
  - FSH/LH Polimorfisms

COS: Decision-making

- Type of gonadotrophin suppression
- Dose of FSH
- Administration of LH activity (LH, hMG, hCG)
- Choice of alternative protocols

GnRH agonists vs GnRH antagonists

Gonadotrophin-releasing hormone antagonists for assisted reproductive technology (Review)

THE COCHRANE COLLABORATION®

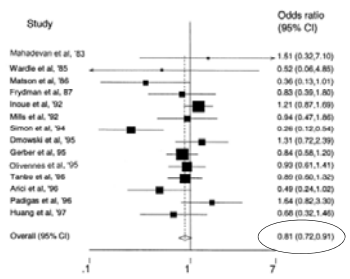
45 RCT (n=7511)

Live birth: OR=0.86 (0.69-1.08)

OHSS: OR=0.43 (0.33-0.57)

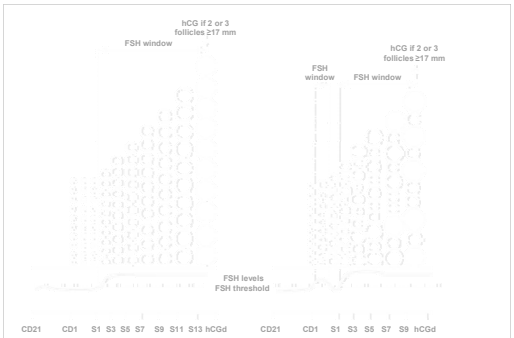
Al Inany et al (2011) Cochrane Database Syst Rev

GnRH agonists vs GnRH antagonists in Endometriosis



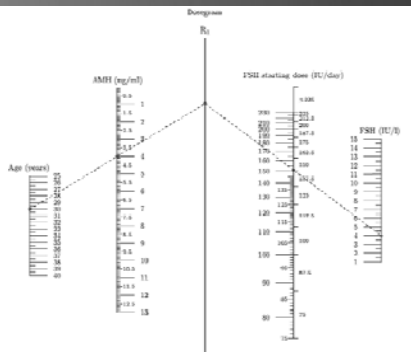
Barnhart et al (2002) Fertil Steril 77: 1148-55

GnRH agonist versus GnRH antagonist: Follicular growth dynamics



Huirne et al. (2007) Hum Reprod; 22: 2483-90

Normogram for individualizing FSH dose according to markers of ovarian reserve



PÁG.34

www.ivi.es La Marca et al (2012) BJOG 119: 11 Página 34

LH supplementation in unselected population

Among patients treated with FSH and GnRH analogues for *in vitro* fertilization, is the addition of recombinant LH associated with the probability of live birth? A systematic review and meta-analysis

Study	FSH + LH (n/N)	FSH (n/N)	OR, fixed (95% CI)	Weight (%)	OR, fixed (95% CI)
Agonist					
Sills 1999	3/13	10/17		10	0.21 [0.04, 1.05]
Balasch 2001	0/16	1/14		2.32	0.27 [0.01, 7.25]
Humaidan 2004	39/116	31/115		31	1.37 [0.78, 2.41]
Fabregues 2006	24/60	25/60		22.5	0.93 [0.45, 1.93]
Tarlatzis 2006	6/55	10/59		12.9	0.6 [0.2, 1.78]
Subtotal (95% CI)	72/260	77/265		78.72	0.94 [0.64, 1.39]
Antagonist					
Sauer 2004	9/25	10/24		9.8	0.79 [0.25, 2.49]
Griesinger 2005	8/62	9/65		11.48	0.92 [0.33, 2.56]
Subtotal (95% CI)	17/87	19/89		21.28	0.86 [0.4, 1.85]
Total (95% CI)	89/347	96/354		100	**0.92 [0.65, 1.31]**

0.01 0.1 1 10 100

Favours r-hFSH *Favours r-hFSH + r-hLH*

PÁG.35

www.ivi.es Kolibianakis, et al. (2007) *Hum Reprod Update*;13 Página 35

LH supplementation in poor responders

Review: Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles

Comparison: rLH and rFSH versus rFSH alone for COH in GnRH agonist dowregulated IVF/CSI cycles in poor responders

Outcome: Ongoing pregnancy per woman randomised

Study or subgroup	rLH and rFSH n/N	rFSH alone n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Barrenetxea 2006	8/36	7/36		25.7%	1.18 [0.38,3.70]
DePlacido 2005	19/65	13/65		43.5%	1.65 [0.74,3.71]
Ferraretti 2004	22/54	11/54		30.8%	2.69 [1.14,6.33]
Total (95%CI)	155	155		100.0%	1.85 [1.10,3.11]

Total events: 49 (rLH andr FSH), 31 (rFSH alone)
Heterogeneity: Chi²=1.40, df=2 (P=0.50); I²=0.0%
Test for overall effect: Z=2.32 (P=0.020)

0.1 0.2 0.5 1 2 5 10

Favours r-hFSH *Favours r-hFSH + r-hLH*

PÁG.36

www.ivi.es Mochtar MH (2007), Cochrane Database Página 36 2.

Total serum Te as a biomarker of LH need for COS

Ongoing pregnancy rate per started cycle transfer according to androgen levels

	FSH	FSH+LH	RR (95% CI)	p
Te ≤0.45 ng/mL	33.1 (25.4-41.7)	44.4 (36.1-53.2)	1.34 (0.98-1.85)	0.06
Te >0.45 ng/mL	50.0 (37.5-62.5)	40.0 (28.6-52.6)	0.80 (0.53-1.20)	0.28
DHEAS ≤156 mcg/L	32.4 (24.3-41.7)	38.2 (29.6-47.5)	1.18 (0.82-1.69)	0.37
DHEAS >156 mcg/L	47.3 (36.3-58.5)	43.4% (32.9-54.6)	0.92 (0.65-1.30)	0.63
Δ_4 ≤1.90 ng/mL	39.1 (30.5-48.4)	46.0 (37.1-55.2)	1.18 (0.87-1.60)	0.30
Δ_4 >1.90 ng/mL	40.3 (29.7-51.8)	47.9 (36.9-59.2)	1.19 (0.82-1.72)	0.35

Bosch et al (2011), ESHRE.

Choice of alternative protocols

Choices for COS according to possible combinations of GnRH analogs and stimulation drugs

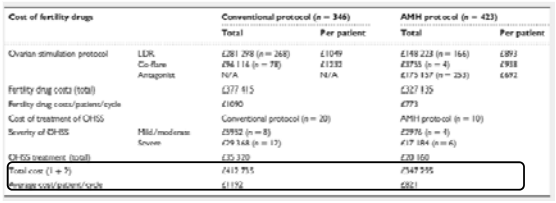
	GnRH agonist			GnRH antagonist			No GnRH analogue	
	Long	Short	Microflare	Standard	Mild	Modified natural	Mini	Natural
FSH								
HMG								
FSH+LH								
Others: Clomiphene Letrozole Testosterone Estrogens								

AMH tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF

Clinical outcomes	Conventional protocol (n = 346)	AMH-tailored protocol (n = 422)	Unadjusted P-value*	Adjusted P-value*
Cancelled cycles due to				
Poor response	14 (4.0%)	14 (3.3%)	0.75	0.37
Elective freeze all	0	3 (0.7%)	0.26	0.066
Other reasons	4 (1.2%)	4 (0.9%)	1	0.80
Number (SD) of oocytes	12.4 ± 7.8	10.6 ± 6.9	0.008*	0.007*
OHSS leading to				
Cycle cancellation and/or freeze all	24 (6.9%)	10 (2.3%)	0.002	0.004
Hospital admission	10 (2.9%)	5 (1.2%)	0.12	0.15
Fertilisation				
Incidence of failed fertilisation	27 (7.8%)	19 (4.5%)	0.066	0.11
Absence of normal embryos	4 (1.2%)	3 (0.7%)	0.71	0.54
Embryo transfer				
Women who had embryo transfer (based on outcome data)	273 (78.9%)	370 (87.5%)	0.002	0.003
Pregnancy				
Pregnancy per cycle started	62 (17.9%)	117 (27.7%)	0.002	0.002
Live births per cycle started	55 (15.9%)	101 (23.9%)	0.002	0.003
Twin births per cycle started	9 (2.6%)	20 (4.7%)	0.12	0.15
Live birth per IVF	50.1%	59.8%	0.048	0.053

Yates et al (2011) Hum Reprod 26: 2353-2362

AMH tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF



Cost of fertility drugs		Conventional protocol (n = 346)		AMH protocol (n = 423)	
		Total	Per patient	Total	Per patient
Ovarian stimulation protocol	LDR	£281 298 (n = 268)	£1049	£148 228 (n = 166)	£893
	Co-flare	£94 114 (n = 78)	£1333	£3755 (n = 4)	£938
	Antagonist	N/A	N/A	£175 137 (n = 253)	£692
Fertility drug costs (total)		£377 415		£327 120	
Fertility drug costs/patient/cycle		£1090		£773	
Cost of treatment of OHSS		Conventional protocol (n = 20)		AMH protocol (n = 10)	
Severity of OHSS	Mild/moderate	£5952 (n = 8)		£5976 (n = 4)	
	Severe	£29 568 (n = 12)		£17 184 (n = 6)	
OHSS treatment (total)		£35 520		£23 160	
Total cost (1 + 2)		£413 935		£347 595	
Average cost/patient/cycle		£1192		£821	

Yates et al (2011) Hum Reprod 26: 2353-2362

Conclusions and reflections (I)

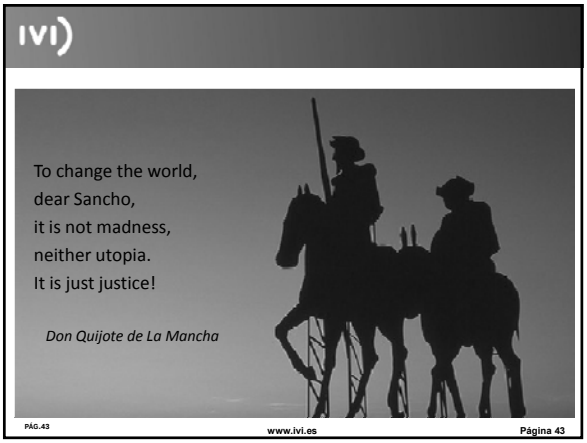
Reproductive medicine is not different than the rest of medical areas. Despite its clear and crucial benefits, the way to personalized medicine and customized therapy is still very large, with several barriers to overpass.

On one side, the pharmaceutical industry promotes a block buster model, focused on developing and marketing drugs for as broad a patient group as possible, while discourages the development of therapies aimed at smaller subpopulations and the diagnostic tests that can identify them.

Conclusions and reflections (II)

On the other side, the regulatory agencies cause too many resources to be devoted to phase-three clinical trials, and too few to monitoring and assessment after a particular drug has been approved.

On the top of that, clinicians' daily practice is still based too often in a trial and error methodology, despite the availability of fine diagnostic tests that could help for a more personalized prescription of drugs and procedures.


To change the world,
dear Sancho,
it is not madness,
neither utopia.
It is just justice!
Don Quijote de La Mancha
PÁG.43
www.ivi.es
Página 43

Individualisation of ovarian stimulation has little impact on outcome

Georg Griesinger
University of Lübeck, Germany

Conflict of interest disclosure

within the last 36 months

- Consultancy: Glycotope, MSD, Merck-Serono
- Invited speaker: Merck-Serono, MSD, Ferring
- Participated in industry funded research: IBSA, Glycotope, MSD

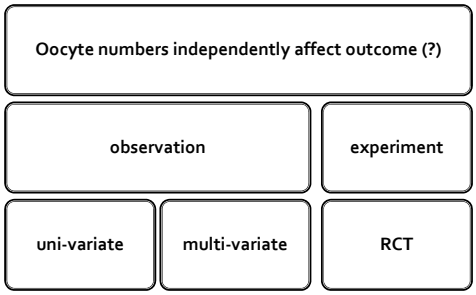
Learning objectives

- Understand the assocation between oocyte numbers and outcome
- Understand promises and limits of prediction of ovarian response
- Understand natural occuring variation in ovarian response and how this affects outcome

Definitions

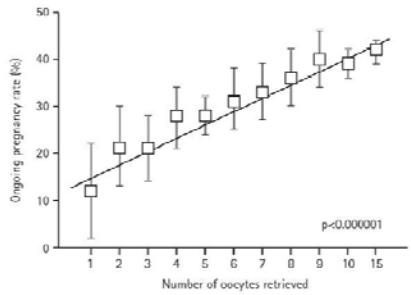
- Individualisation: discriminating the individual from the generic group
- Ovarian stimulation: retrieving multiple oocytes for IVF
- Outcome: live birth or cumulative live birth

What is the underlying assumption to individualisation?



Observations

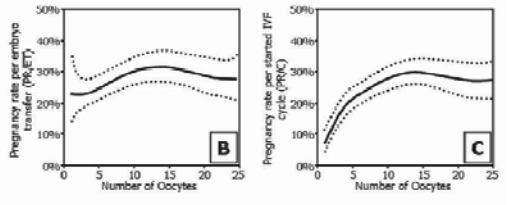
The association of oocyte numbers with outcome – a UNIVARIATE analysis



Bosch & Ezcurra, Reprod Biol Endocrinol. 2011; 9: 82.0

The association of oocyte numbers with outcome – a MULITVARIATE analysis

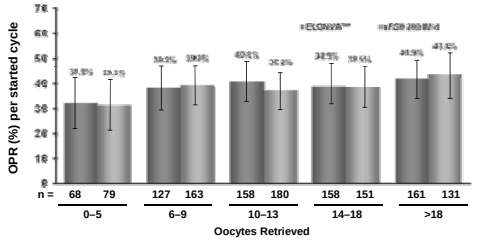
Adjustement for: age, fecundity, cause of infertility, FSH dosage, type of luteal support, no. of embryos transferred



Van der Gaast et al., RBMonline 2009

The association of oocyte numbers with outcome – a UNIVARIATE analysis

Engage trial, n ~1500 patients, <36 yrs



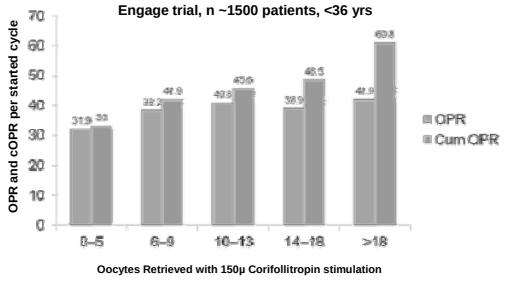
Fatemi, Doody, Griesinger et al. Hum Reprod 2012

The association of oocyte numbers with outcome – a MULITVARIATE analysis

Factors in the multi-variate model	Oocyte categories	Odds ratio for ongoing pregnancy
Oocytes	0-5 vs. 10-13	0.87 (0.59-1.30)
	6-9 vs. 10-13	1.04 (0.74-1.44)
	14-18 vs. 10-13	1.02 (0.74-1.42)
	>18 vs. 10-13	1.17 (0.84-1.63)
Age	Per year increase	0.96 (0.92-0.99)
Cycle day FSH start (d2 vs. d3)	Day 3 vs. day 2	1.21 (0.97-1.51)
Region (NA vs. Europe)	NA vs. EUR	1.96 (1.56-2.46)
Progesterone on day of hCG	>1.5 vs. ≤1.5 ng/mL	0.46 (0.30-0.70)

Fatemi, Doody, Griesinger et al. Hum Reprod 2012

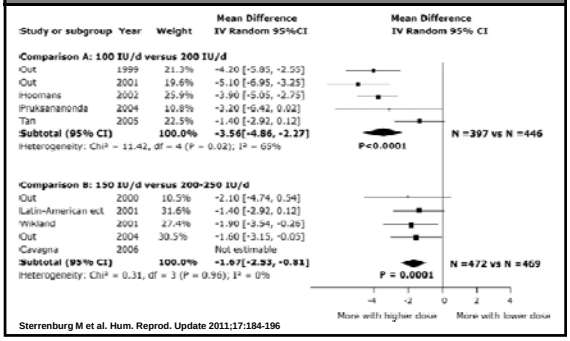
The association of oocyte numbers with cumulative outcome – univariate



Data on file, courtesy of MSD

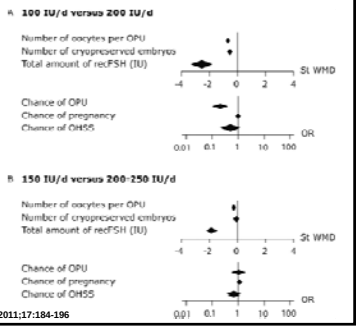
Experiments

low vs. high dose of FSH: effect on no. of oocytes (n=1,976 patients)



Sterrenburg M et al. Hum. Reprod. Update 2011;17:184-196

low vs. high dose of FSH: outcomes (n=1,976)



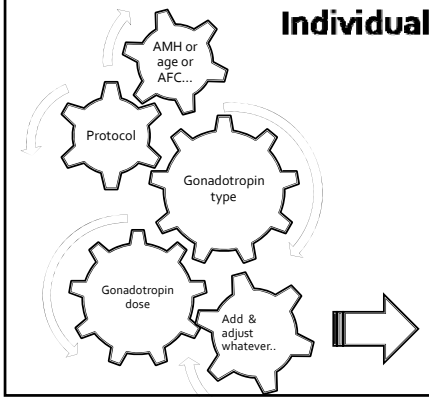
Sterrenburg M et al. Hum. Reprod. Update 2011;17:184-196

Are oocyte numbers and pregnancy chance related?

Best estimate from multivariate analyses and RCTs:

The relationship between oocyte numbers and pregnancy chance appears to be weak (as long as there are sufficient oocytes for an embryo transfer to happen)

Individualisation?

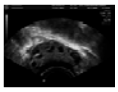
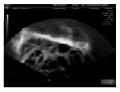


Live birth?
Cancellation?
Safety?
Tolerability?

Individualisation: two issue

- Variation! („the play of chance")
- predict → individualize → alter outcome ?

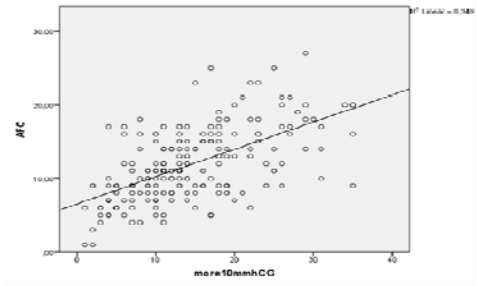
Variation!

1. 
   Number of FSH sensitive follicles
   → Stimulation
2. 
   Number of pre-ovulatory follicles

but: inter-individual variation
and intra-individual variation

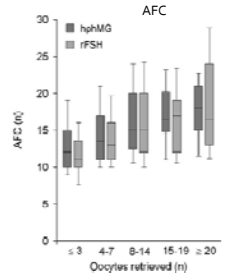
3. Oocyte retrievel rate per follicle — Variation!
4. Fertilisation rate — Variation!
5. Good quality embryo formation — Variation!

Inter-individual variation in ovarian response: AFC by pre-ovulatory follicles

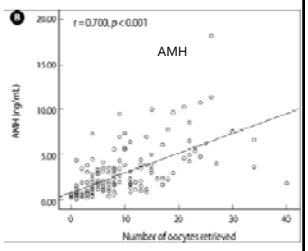


All patients on the same protocol, no adaption allowed; Luebeck IVF, data on file

Inter-individual variation in ovarian response

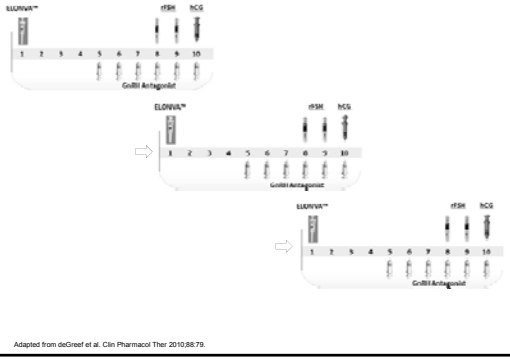


Arce et al., Fertil Steril 2013



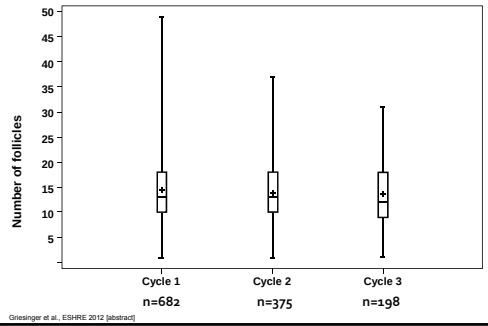
Lee et al., ECERM 2012

Intra-individual variation



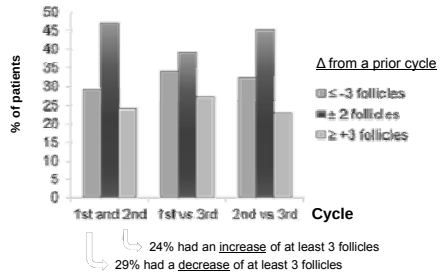
Adapted from deGreef et al. Clin Pharmacol Ther 2010;88:79.

Trust trial: repetitive stimulation in the same protocol



Griesinger et al., ESHRE 2012 [abstract]

Differences in Number of Follicles Between Cycles for Subjects Who Underwent Three Cycles



24% had an increase of at least 3 follicles
29% had a decrease of at least 3 follicles

Griesinger et al., ESHRE 2012 [abstract]

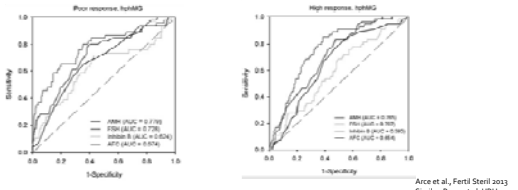
There Is Considerable Inter-cycle Variation in Ovarian Response

- For women with a normal response (6-<18 follicles), in the first cycle the probability to switch to a low (0-<6 follicles) or high ovarian response (>18 follicles) in the second cycle was 19%.
- The probability for those with a low or high ovarian response in the first cycle to switch to a normal response in the second cycle was 39%.

Griesinger et al., ESHRE 2012 [abstract]

predict → individualize → alter outcome ?

- Prediction: mostly on extremes of response



Arce et al., Fertil Steril 2013
Similar: Broer et al. HRU 2012

...will create many false positives and false negatives (because of variation!)

predict → individualize → alter outcome ?

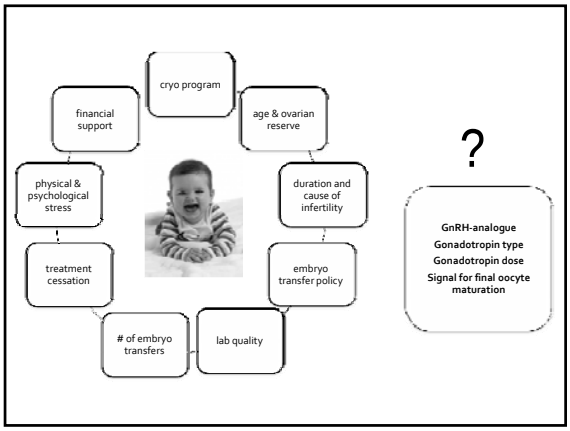
- Individualize (to avoid extremes)

1. avoid poor response:
   → give higher FSH doses (concept failed!?)
   → create more FSH sensitive follicles (how?)

2. avoid hyper response:
   → allow only a part of the FSH-sensitive follicles to grow (?)

Proven concept: Individualisation to prevent OHSS

- Predict risk by number of growing follicles
- Replace hCG by Agonist trigger
- Freeze all embryos



Conclusion

- Oocyte numbers and pregnancy rate have only a weak association
- There is enormous variation in ovarian response (as well as down-stream events), making response prediction (and even more so outcome prediction) a difficult task
- No measure has been found to increase the number of follicles in poor responders and no measure has been shown to be effective in avoiding excessive response (e.g. in patients with a high number of similarily FSH-sensitive follicles)

Thank you very much for your attention!

griesing@uni-luebeck.de

You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis
  12-13 September 2013 - Prague, Czech Republic
- Female genital tract congenital malformations: new insights in an old problem
  27-28 September 2013 - Thessaloniki, Greece
- Introducing new techniques into the lab
  4-5 October 2013 - Barcelona, Spain
- Polycystic ovary syndrome: A new look at an old subject
  25-26 October 2013 - Rome, Italy
- Infections from conception to birth: role of ART
  7-8 November 2013 - Berlin, Germany
- Endoscopy in reproductive medicine
  20-22 November 2013 - Leuven, Belgium
- From early implantation to later in life
  28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency
  6-7 December 2013 - Utrecht, The Netherlands

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES