eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

"Mild stimulation strategies in IVF"

SPECIAL INTEREST GROUPS
REPRODUCTIVE ENDOCRINOLOGY &
SAFETY AND QUALITY IN ART

3

28 June 2009
Amsterdam
The Netherlands

PRE-CONGRESS COURSE 3

Organised by the Special Interest Groups Reproductive Endocrinology, Safety and Quality in ART and Task Force on Mild Approaches in Assisted Reproduction

Table of contents

Program overview **Page 2**

Speakers' contributions

Mild ovarian stimulation for IVF: theory and practice – ***Bart Fauser (The Netherlands)*** **Page 4**

Ovarian stimulation and embryo quality: less is more? – ***Esther Baart (The Netherlands)*** **Page 14**

Natural cycle IVF -Is it effective and cost-effective - ***Geeta Nargund (United Kingdom)*** **Page 24**

Individualising ovarian stimulation for IVF - ***Anders Nyboe Andersen (Sweden)*** **Page 39**

Single embryo transfer: where are we? - ***Petra de Sutter (Belgium)*** **Page 62**

How can we reduce the burden of treatment? **- *Jacky Boivin (United Kingdom)*** **Page 79**

Panel discussion: The impact of milder stimulation upon indicators of benefit (efficacy, safety, time and costs, quality)

- Is there an optimal balance? - ***Christina Bergh (Sweden)*** **Page 94**
- Which patients benefit? - ***Karl Nygren (Sweden)*** **Page 98**

Notes **Page 101**

PRE-CONGRESS COURSE 3 - PROGRAM

Mild stimulation strategies in IVF

Organised by the Special Interest Groups Reproductive Endocrinology, Safety and Quality in ART and Task Force on Mild Approaches in Assisted Reproduction

Course co-ordinators: Nicholas Macklon (NL), Christina Bergh (Sweden) and Geeta Nargund (UK)

Course description: Milder strategies for ovarian stimulation in IVF are being increasingly advocated as a means of achieving satisfactory live birth rates while minimizing severe side effects such as multiple pregnancy, ovarian hyperstimulation syndrome and patient drop out from treatment. But is this hype or hope? This course, which is provided jointly by the SIGs Safety and Quality in ART and Reproductive Endocrinology, will provide participants with a state of the art overview of these new approaches, and by critically examining their risk and benefits compared with conventional stimulation strategies, will clarify their appropriate use in clinical practice. An update in single embryo transfer outcomes will be provided, and a panel discussion will engage speakers and delegates in the contentious issues around mild strategies in IVF.

Target audience: Clinicians, midwifes/nurses, biologists/embryologists working with reproductive medicine

08:45 - 09:00	Introduction - ***Nicholas Macklon (The Netherlands)***
09:00 - 09:30	Mild ovarian stimulation for IVF: theory and practice - ***Bart Fauser (The Netherlands)***
09:30 - 09:45	Discussion
09:45 - 10:15	Ovarian stimulation and embryo quality: less is more? - ***Esther Baart (The Netherlands)***
10:15 - 10:30	Discussion

10:30 - 11:00 **Coffee break**

11:00 - 11:30 Natural cycle IVF -Is it effective and cost-effective - ***Geeta Nargund (United Kingdom)***

11:30 - 11:45 Discussion

11:45 - 12:15 Individualising ovarian stimulation for IVF - ***Anders Nyboe Andersen (Sweden)***

12:15 - 12:30 Discussion

12:30 - 13:30 **Lunch**

13:30 - 14:00 Single embryo transfer: where are we? - ***Petra de Sutter (Belgium)***

14:00 - 14:15 Discussion

14:15 - 14:45 How can we reduce the burden of treatment? ***- Jacky Boivin (United Kingdom)***

14:45 - 15:00 Discussion

15:00 - 15:30 **Coffee break**

15:30 - 16:30 Panel discussion: The impact of milder stimulation upon indicators of benefit (efficacy, safety, time and costs, quality)

The following topics will be presented (5 minutes followed by panel discussion):

• Defining success in IVF - ***Bart Fauser (The Netherlands)***
• Cost-effectivity - ***Petra de Sutter (Belgium)***
• Is there an optimal balance? - ***Christina Bergh (Sweden)***
• Which patients benefit? - ***Karl Nygren (Sweden)***

16:30 - 16:45 Summary and conclusions - ***Nicholas Macklon (The Netherlands)***

16:45 - 17:00 Discussion

Mild ovarian stimulation for IVF;
- theory and practice

Prof.Dr. Bart CJM Fauser
University Medical Center,
Utrecht, The Netherlands

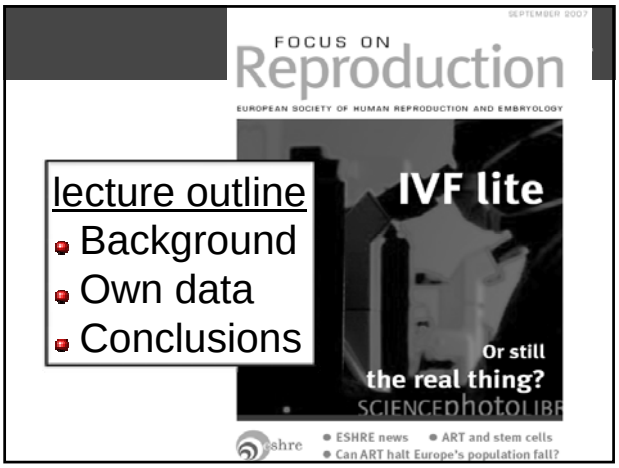
Fauser Conflict of interest statement

Grant support and fees from the following companies

- Andromed,
- Ardana,
- Ferring,
- Genovum,
- Glycotope,
- Merck Serono,
- Organon,
- Pantharei Bioscience,
- Philips,
- PregLem,
- Schering,
- Schering Plough,
- Serono,
- Wyeth.

Learning objectives

- To appreciate why understanding ovarian physiology is important for improving ovarian stimulation protocols
- To appreciate that GnRH antagonist co-treatment enables the development of simpler stimulation protocols closer to physiology
- To appreciate that failed implantation is still the major cause of failed IVF
- To appreciate that what we do today should be viewed in the context of future health of IVF children (Barker hypothesis)
- To understand that the current measure to define success in IVF has major shortcomings
- To appreciate that access to IVF is insufficient in the overwhelming majority of countries worldwide

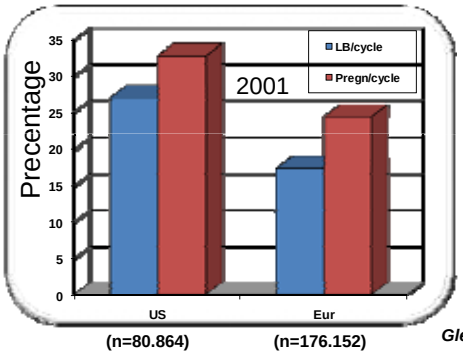


lecture outline

- Background
- Own data
- Conclusions

How successful is IVF ?

(isolated focus on outcomes per cycle)

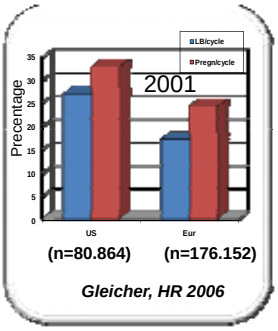


(n=80.864) (n=176.152)

Gleicher, HR 2006

How to define successful IVF

- Towards a more holistic approach -



(n=80.864) (n=176.152)

Gleicher, HR 2006

The issues

- Live births? (20 wks)
- Patients treated (age, indic., smoking)
- Multiples/fetal reduction?
- Complications? (OHSS)
- Side effects / long-term risks?
- Cryo results?
- Definition started cycle?
- Duration of cycle?
- Cost?
- Drop outs? (cumulative results)

The IVF paradox

Universitair Medisch Centrum Utrecht

Insufficient access to treatment

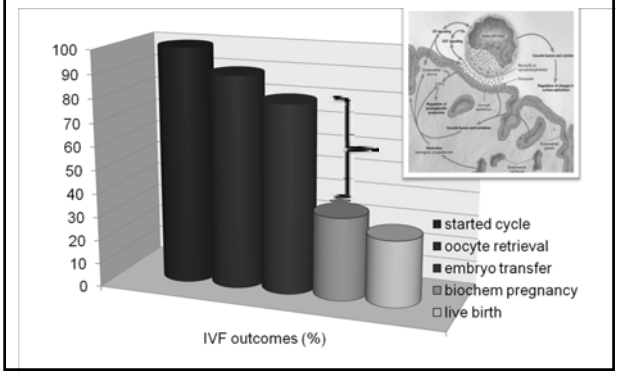
- Expensive
- No health insurance coverage

Tendency Overtreatment in Western societies

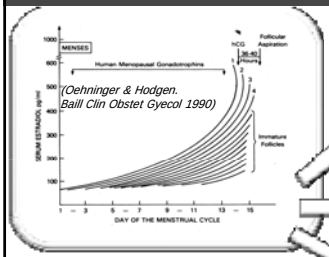
- Varying indications for treatment
- Commercial environment / consumer behaviour

> 70% of failed IVF = failed implantation

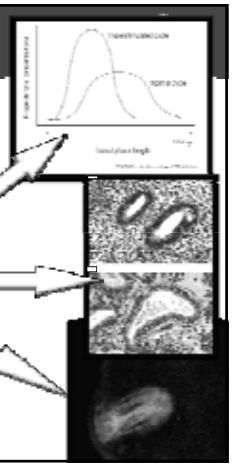
Universitair Medisch Centrum Utrecht



Superovulation strategy for in vitro fertilization



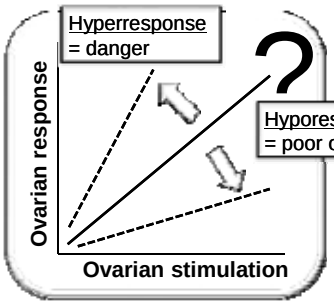
(Oehninger & Hodgen. Baill Clin Obstet Gyecol 1990)



Consequences for

- luteal phase endocrinology
- Endometrial receptivity
- Embryo aneuploidy

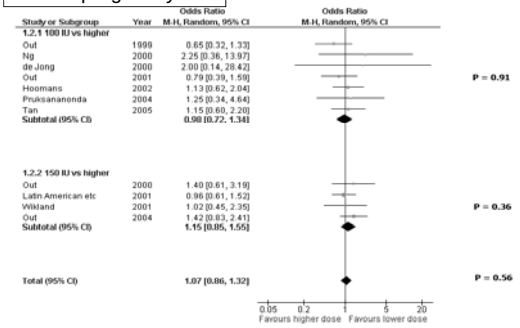
The need of more patient tailored ovarian stimulation for IVF



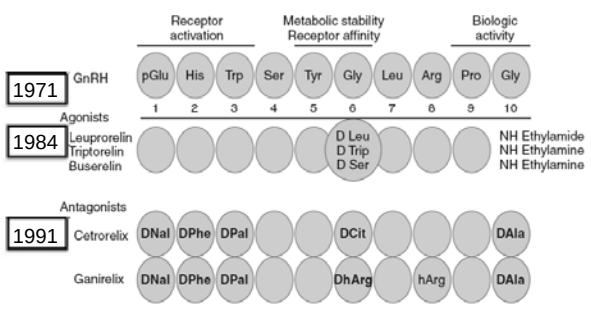
Individualization;
- female age
- BMI
- smoking
- AMH / AFC
- genetic markers

Ovarian stimulation for IVF
- meta analysis gonadotropin doses

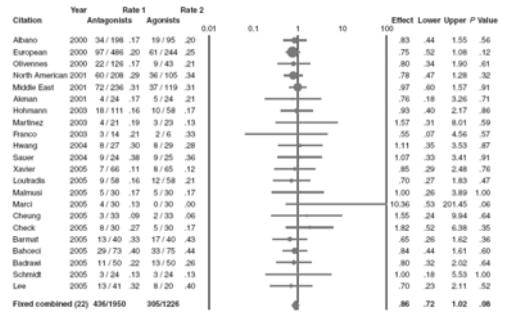
Clinical pregnancy rate (Sterrenburg, unpublished)



Native GnRH vs GnRH analogues



Meta-analysis GnRH agonist vs antagonist - *ongoing pregnancy rates*



Citation	Year	Rate 1 Antagonists		Rate 2 Agonists		Effect	Lower	Upper	P Value
Albano	2000	34 / 198	.17	19 / 95	.20	.83	.44	1.55	.56
European	2000	97 / 486	.20	61 / 244	.25	.75	.52	1.08	.12
Olivennes	2000	22 / 126	.17	9 / 43	.21	.80	.34	1.90	.61
North American	2001	60 / 208	.29	36 / 105	.34	.78	.47	1.28	.32
Middle East	2001	72 / 236	.31	37 / 119	.31	.97	.60	1.57	.91
Akman	2001	4 / 24	.17	5 / 24	.21	.76	.18	3.26	.71
Hohmann	2003	18 / 111	.16	10 / 58	.17	.93	.40	2.17	.86
Martinez	2003	4 / 21	.19	3 / 23	.13	1.57	.31	8.01	.59
Franco	2003	3 / 14	.21	2 / 6	.33	.55	.07	4.56	.57
Hwang	2004	8 / 27	.30	8 / 29	.28	1.11	.35	3.53	.87
Sauer	2004	9 / 24	.38	9 / 25	.36	1.07	.33	3.41	.91
Xavier	2005	7 / 66	.11	8 / 65	.12	.85	.29	2.48	.76
Loutradis	2005	9 / 58	.16	12 / 58	.21	.70	.27	1.83	.47
Malmusi	2005	5 / 30	.17	5 / 30	.17	1.00	.26	3.89	1.00
Marci	2005	4 / 30	.13	0 / 30	.00	10.36	.53	201.45	.06
Cheung	2005	3 / 33	.09	2 / 33	.06	1.55	.24	9.94	.64
Check	2005	8 / 30	.27	5 / 30	.17	1.82	.52	6.38	.35
Barmat	2005	13 / 40	.33	17 / 40	.43	.65	.26	1.62	.36
Bahceci	2005	29 / 73	.40	33 / 75	.44	.84	.44	1.61	.60
Badrawi	2005	11 / 50	.22	13 / 50	.26	.80	.32	2.02	.64
Schmidt	2005	3 / 24	.13	3 / 24	.13	1.00	.18	5.53	1.00
Lee	2005	13 / 41	.32	8 / 20	.40	.70	.23	2.11	.52
Fixed combined (22)		436/1950		305/1226		.86	.72	1.02	.08

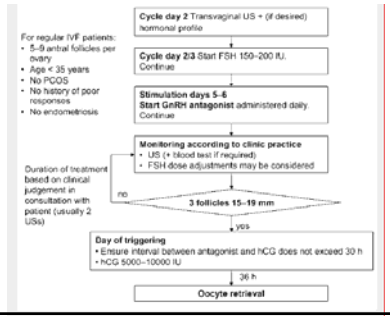
Kolibianakis, HRU 2006

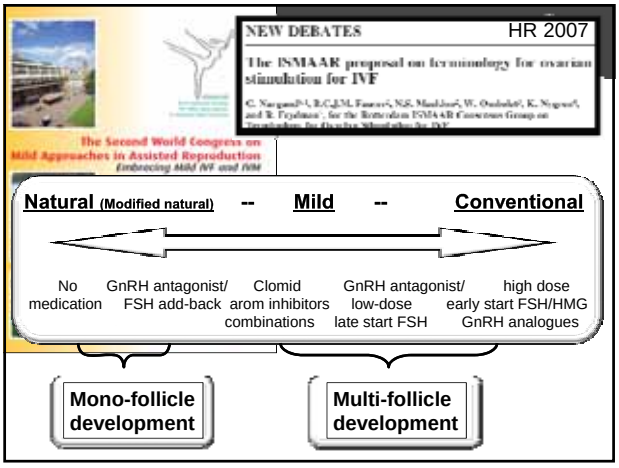
2009

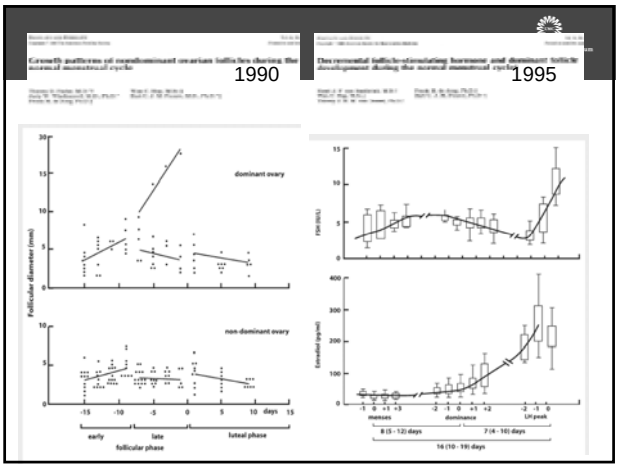
human reproduction OPINION

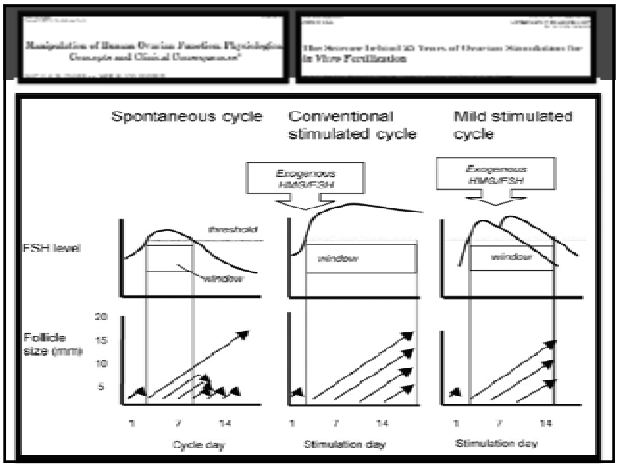
Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment

Paul Devroey[1,10], Mohamed Aboulghar[2], Juan Garcia-Velasco[3], Georg Griesinger[4], Peter Humaidan[5], Efstratios Kolibianakis[6], William Ledger[7], Candido Tomás[8], and Bart C.J.M. Fauser[9]

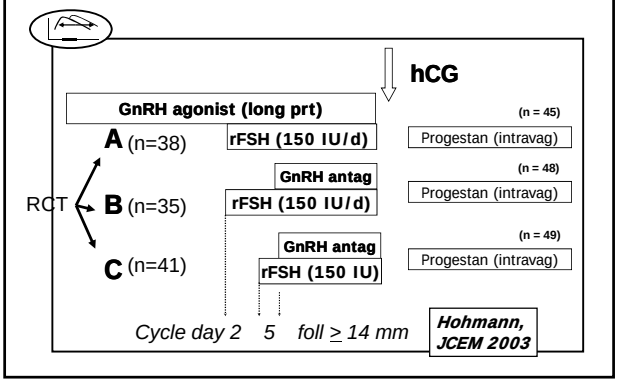


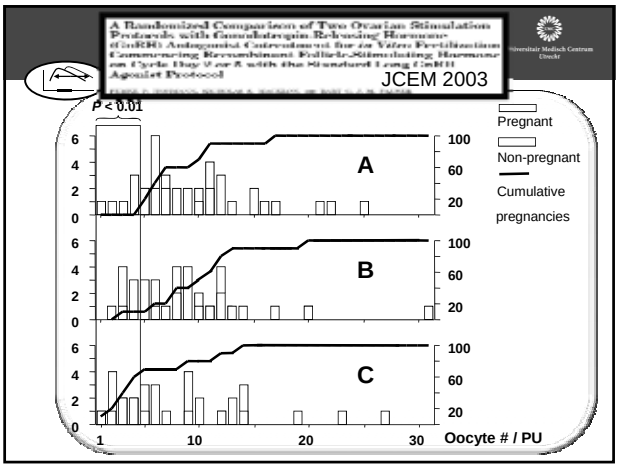






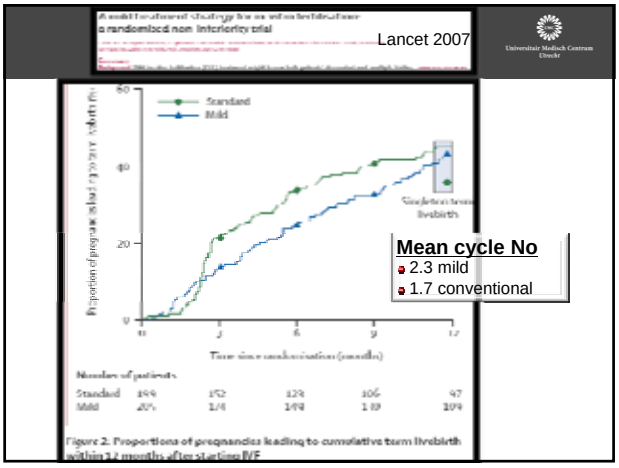
Mild Hyperstimulation for IVF: Study design





IVF study design issues

- Pregnancy rates as primary outcome ⇨ Health babies
- Outcomes per cycle ⇨ Per stared treatment
- Isolated focus on outcomes ⇨ Holistic approach (outcomes vs discomfort, complications, cost



Cycle specific characteristics

Universitair Medisch Centrum Utrecht

	Mild treatment (n=444)	Standard treatment (n=325)	p
Duration of ovarian stimulation (days)	[illegible]	[illegible]	<0·0001*
Duration of injections (days)	8·5 (2·7)	25·1 (6·8)	<0·0001*
Total dose of follicle stimulating hormone (IU)	[illegible]	[illegible]	<0·0001*
Cancellation of started cycle	80 (18·0%)	27 (8·3%)	<0·0001†
Number of oocytes per retrieval	[illegible]	[illegible]	<0·0001*
‡Number of embryos per retrieval	3·8 (2·7)	3·8 (2·6)	0·0002*
Number of cryopreserved embryos per fresh embryo transfer cycle	[illegible]	[illegible]	[illegible]
Continuing pregnancy per started cycle (fresh embryos)	78 (17·6%)	83 [illegible]	<0·0001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1·4%)	[illegible]	0·8†
Term livebirth per started cycle (fresh embryos)	70 [illegible]	73 [illegible]	[illegible]
Term livebirth per started cycle (cryopreserved embryos)	[illegible]	3 (0·9%)	0·8†
§Ovarian hyperstimulation syndrome	6 (1·4%)	12 (3·7%)	0·04†

Values are mean (SD) or number (%) of cycles. [illegible]

Table 2: Cycle-specific characteristics of [illegible] cycles finished within 1 year

Pregnancy outcomes

Universitair Medisch Centrum Utrecht

	Mild strategy		Standard strategy	
	Singleton	Multiple*	Singleton	Multiple
Livebirths (total)	91	1	76	25
Liveborn children	91	3	76	52†
Term livebirth (≥37 weeks' gestation)	86	0	69	17
Late preterm livebirth (32–37 weeks' gestation)	2	0	6	5
Early preterm livebirth (<32 weeks' gestation)	3	1	1	3
Birthweight (kg)‡	3·34 (0·79)	1·34	3·35 (0·79)	2·34 (0·73)

*One set of triplets were born in the mild treatment group after intrauterine insemination in a cycle that was cancelled because of monofollicular growth. †One twin pregnancy resulted in one intrauterine death and one livebirth. ‡Birthweight is mean (SD). For multiple pregnancies the mean birthweight of the twins or triplets was used to calculate the overall mean birthweight per treatment group. The difference in distribution of term, late preterm, and early preterm livebirths between the standard and mild treatment group is significant (p=0·04; χ^2 test with continuity correction).

Table 3: Pregnancy outcome after mild and standard IVF treatment

Patient distress and IVF

- conclusions own studies -

Universitair Medisch Centrum Utrecht

Effectiveness of a psychosocial counselling intervention for first-time IVF couples: a randomized controlled trial
HR 2005

The psychological impact of mild ovarian stimulation combined with single embryo transfer compared with conventional IVF
HR 2006

The psychological impact of IVF failure after one or more cycles of IVF with a mild versus standard treatment strategy
HR 2007

Low negative affect prior to treatment is associated with a decreased chance of live birth from a first IVF cycle
HR 2008

Conclusions:

Little perceived need for counselling
No difference 3 counselling sessions

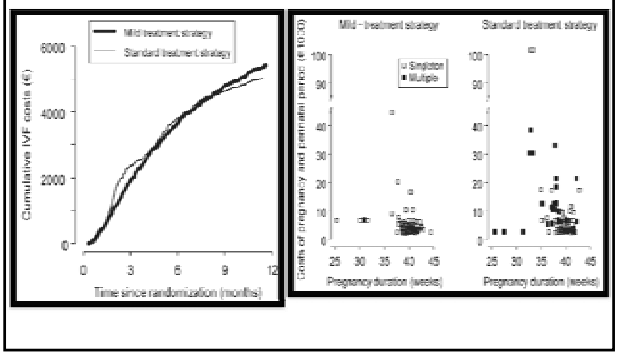
More physical and depressive symptoms during down regulation in conventional IVF

Failed IVF results in less depressive symptoms after mild IVF

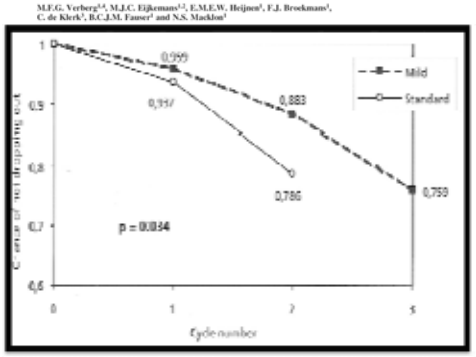
Complex relationship between initial psychol. parameters and IVF outcomes

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

HR 2008



Why do couples drop-out from IVF treatment? A prospective cohort study



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

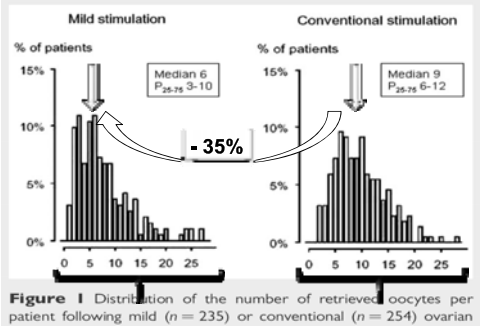
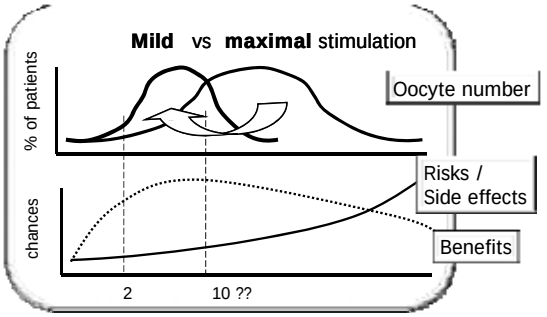


Figure 1 Distribution of the number of retrieved oocytes per patient following mild ($n = 235$) or conventional ($n = 254$) ovarian

Optimal oocyte number for IVF
- how to balance risks vs benefits -



(adapted from Nyboe Andersen)

In vitro fertilization
- the true balance -

Substitute outcome parameters

- Oocyte number
- Follicle number
- Embryo number
- Implantation rate
- Pregnancy rate/cyle

Healthy term live birth per treatment

risks / complications

patient discomfort

costs

Heijnen, HR 04

Collaborators in mild IVF studies

Rotterdam

- de Jong
- Hohmann
- Beckers
- Eijkemans

Utrecht

- Heijnen
- Baart
- Verberg
- Boomsma
- Teklenburg
- Sterrenburg

Ovarian stimulation and embryo quality: less is more?

Esther Baart, PhD

Department of Reproductive Medicine and Gynaecology, University Medical Center, Utrecht and Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Erasmus Medical Center, Rotterdam, The Netherlands

Conflict of interest

I have no conflict of interest to report

Learning Objectives

- Differences in oocyte quality exist in a cohort of oocytes retrieved after ovarian stimulation
- Embryo quality is not completely reflected by embryo morphology
- The ability of an oocyte/embryo to correctly segregate chromosomes is a quality indicator
- Mild stimulation may allow only the most mature follicles to develop, resulting in the retrieval of only the most competent oocytes
- Mild stimulation lowers the proportion of aneuploid embryos
- Further development of mild stimulation strategies is needed to optimize oocyte quality

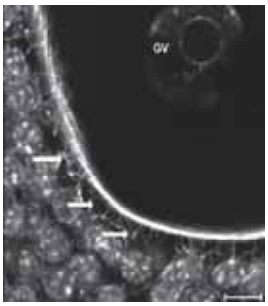
What is a good oocyte/ embryo?

- Competent to undergo fertilization
  - *Chromatin remodeling*
  - *DNA repair*
- Supports timely completion of cleavage divisions
- Reliably segregates chromosomes
  - *Spindle formation*
  - *Checkpoint functions*
- Activates the embryonic genome (8 cell stage)
  - *Chromatin remodeling*
  - *Establishment of genomic imprinting*

Oocyte growth and maturation

Cumulus cells 'feed' the oocyte

- Transzonal projections connect oocyte and cumulus cell
- TZP mediates transport of nutrients and small molecules (mRNAs?)
- Density is regulated by the oocyte
- Highly sensitive to FSH



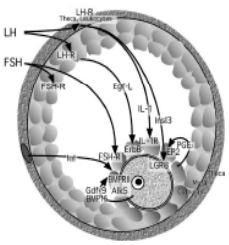
Hutt and Albertini, RBM online, 2007

Follicle and oocyte development are interlinked

Intra-follicular signaling between:

- Oocyte
- Cumulus granulosa cells
- Mural granulosa cells
- Theca cells

Proliferation
⇩⇧
Differentiation
⇩⇧
Luteinization

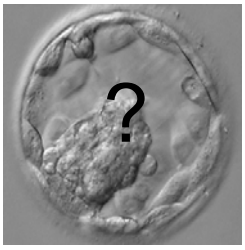


Russell and Robker, HRU, 2007

How to assess embryo quality?
- The classical approach -

- Morphology and development:
  - *Assessment of pronucleate embryos*
  - *Timing of cleavage*
  - *Assessment on day 3 after fertilization*
  - *Development to the blastocyst stage*
- Implantation potential, ongoing PR and live birth

The perfect embryo
(based on morphology and development)



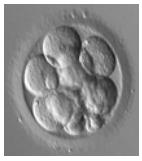
Papanikolaou et al., NEJM, 2006

Successful implantation after SET in 49% of patients ≤36 yrs

⇨ At least 50% of embryos are chromosomally abnormal

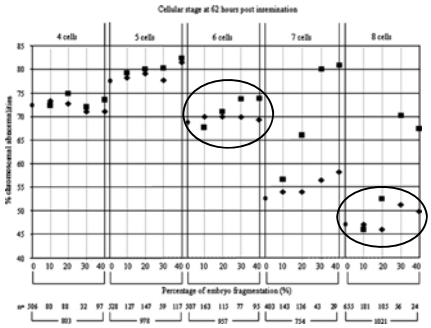
Day 3: cleavage stage and chromosome abnormalities

- 662 patients, 916 cycles
- Poor prognosis patients
- PGS on day 3
- XY,13, 14, 15, 16, 18, 21, 22
- Cleavage stage assessment



Magli et al., Fertil Steril, 2007

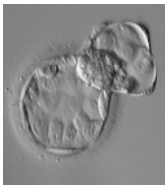
Day 3: fragmentation and cell number



Magli *et al.*, Fertil Steril 2007

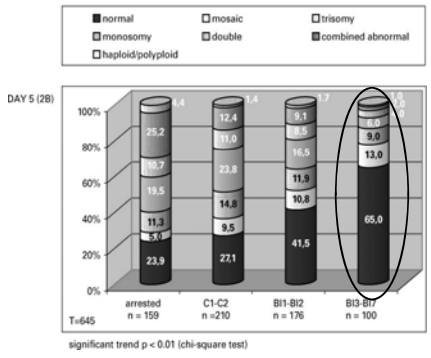
Development to the blastocyst stage and chromosomal abnormalities

- 148 patients, 148 cycles
- patients ≥37 years
- IVF and ICSI
- PGS on day 3, two cells
- XY, 13, 16, 18, 21, 22
- Assessment of blastocyst development



Staessen et al., Hum Reprod, 2004

FISH diagnosis on day 3 and development on day 5



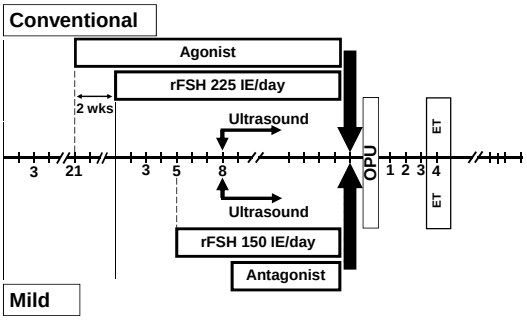
Staessen et al., Hum Reprod, 2004

Randomized comparison of two ovarian stimulation approaches

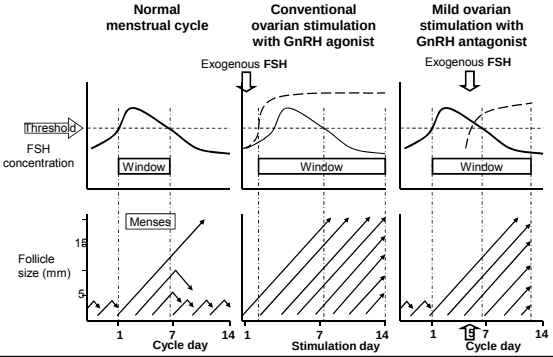
- Determine the incidence of aneuploidy and mosaicism in embryos from younger IVF patients
- Study the effect of ovarian stimulation on embryo aneuploidy
- Can PGS be used as an extra parameter to assess embryo quality?

Comparison of stimulation approaches

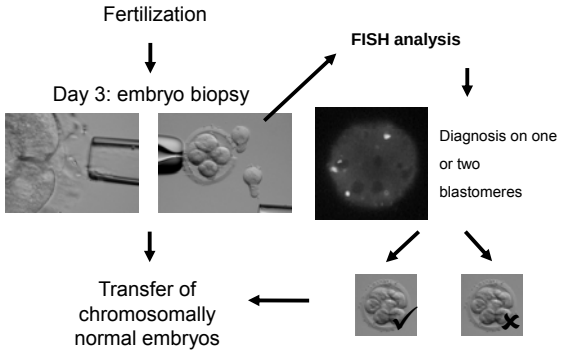
Randomization of 111 patients:



Ovarian stimulation and follicle development



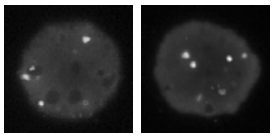
Preimplantation genetic screening



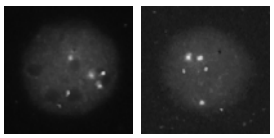
Fixation and analysis of blastomeres

Method using HCl/Tween and Methanol/Acetic acid

First round of FISH:
chromosomes
1, 7, 15, X & Y

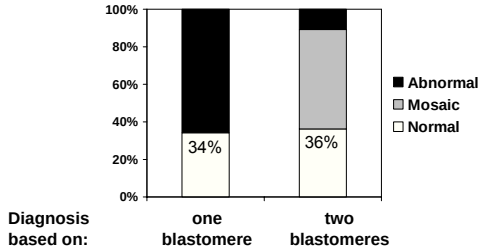


Second round of FISH:
chromosomes
13, 16, 18, 21, 22



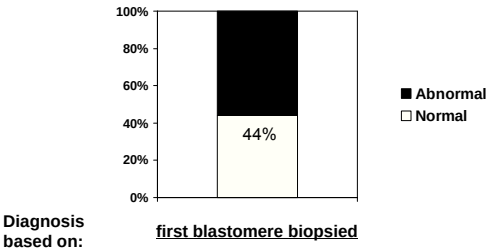
PGS Diagnosis in young IVF patients

Analysis of 265 embryos:

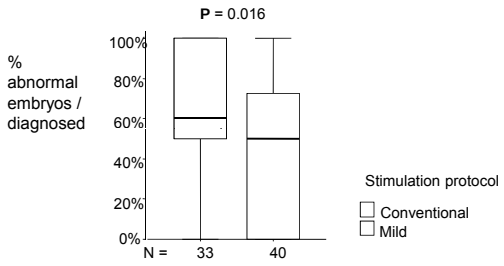


PGS Diagnosis for statistical analysis

Analysis of 265 embryos:



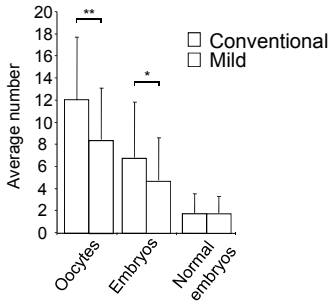
Lower aneuploidy rate after mild stimulation



Good quality embryo rate per patient:

35% 51% P= 0.04

Average number per patient



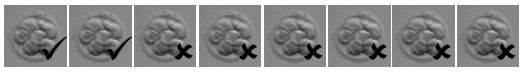
What could it mean to the embryologist?

Conventional ovarian stimulation:

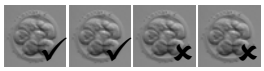
Mild ovarian stimulation:

What could it mean to the embryologist?

Conventional ovarian stimulation:



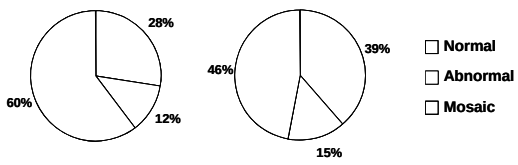
Mild ovarian stimulation:



Chromosomal mosaicism after analysis of two cells

Conventional stimulation
(98 embryos)

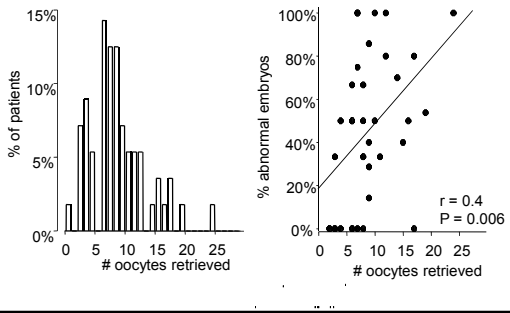
Mild stimulation
(96 embryos)



Rate of mosaic embryos per patient:

65% 37% P= 0.004

Mild stimulation and ovarian response



Conclusions

- Follicle development is correlated to oocyte quality
- The chromosome constitution provides an additional marker for oocyte/embryo quality
- Ovarian stimulation has an impact on embryo aneuploidy rates (chromosomal mosaicism)
- Ovarian stimulation should not aim at maximizing oocyte yield but optimizing oocyte quality

BIBLIOGRAPHY

- Baart EB, Martini E, Eijkemans MJ *et al.* 2007 Milder ovarian stimulation for *in-vitro* fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Human Reproduction* **22**, 980-988.
- Hutt KJ, Albertini DF 2007 An oocentric view of folliculogenesis and embryogenesis. *Reproductive BioMedicine Online* **14**, 758-764.
- Magli MC, Gianaroli L, Ferraretti AP *et al.* 2007 Embryo morphology and development are dependent on the chromosomal complement. *Fertility and Sterility* **87**, 534-541.
- Papanikolaou EG, Camus M, Kolibianakis EM *et al.* 2006 *In vitro* fertilization with single blastocyst-stage versus single cleavage-stage embryos. *New England Journal of Medicine* **354**, 1139-1146.

- Russell DL, Robker RL 2007 Molecular mechanisms of ovulation: co-ordination through the cumulus complex. *Human Reproduction Update* **13**, 289-312.
- Staessen C, Platteau P, Van Assche E *et al.* 2004 Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. *Human Reproduction* **19**, 2849-2858.

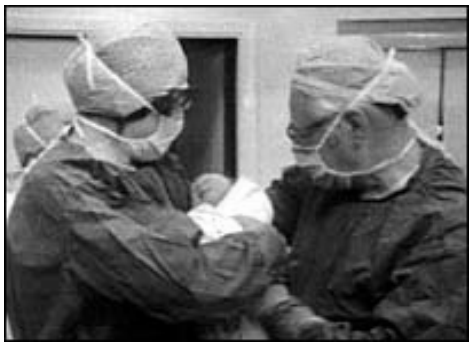
Natural cycle IVF :
Is it Effective and Cost-effective?

Geeta Nargund FRCOG
Head of Reproductive Medicine
St George's Hospital London
Chair, ESHRE Task Force " Mild ART "

Disclosures

None

BIRTH OF LOUISE BROWN:
25th July 1978



Learning Objectives

- Definition of Natural cycle IVF
- Terminology for Effectiveness & Cost-effectiveness
- Different forms of ovarian stimulation for IVF
- Indications for Natural cycle IVF
- Clinical management of Natural cycle IVF
- Methods used for modified Natural cycle IVF
- Relevant studies published on Natural cycle IVF
- Results & Cost-effectiveness of Natural cycle IVF
- Critical analysis and future indications for Natural cycle IVF

Natural cycle IVF

- Spontaneous cycle
- Single mature oocyte
- No medication used at any stage of cycle
- Monitoring with USS and or Hormone assay

Nargund et al: Human Reprod;2001;16:259-262

Effectiveness: The Definition

- Efficiency: doing things in the most economical way (good input to output ratio)
- Efficacy: getting things done, i.e. meeting targets
- Effectiveness: doing "right" things, i.e. setting right targets to achieve an overall goal (the *effect*)

Cost-Effectiveness

Cost-Effectiveness Analysis (CEA)

Is a form of **economic analysis** that compares the relative expenditure (costs) and outcomes (effects) of two or more courses of action.

Natural /Modified natural cycle IVF

- Cohort studies
- Cumulative data
- In selected population

1. **Poor responders**
2. **Failed implantation**
3. **Older women**
4. **Cancer risk group**

The ISMAAR proposal on Terminology for Ovarian Stimulation for IVF

Rotterdam consensus group on Terminology for ovarian stimulation for IVF

Nargund G , Fauser BCJM , Macklon NS , Ombelet W , Nygren K and Frydman R

Human Reproduction 2007;22(11) 2801-2804

For the ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF

Consensus on Terminology

Consistency is needed

- For clinical practice
- For research publications
- Patient understanding & communication
- For policy makers
- For public information

Terminology is focused on the meaning & conveyance of concepts

Definitions

Terminology	***Aim***	***Methodology***
Natural cycle IVF	*Single oocyte*	*No medication*
Modified Natural cycle IVF	*Single oocyte*	*hCG only* *Antagonist & FSH/HMG add-back*
Mild IVF	*2-7 oocytes*	*Low dose FSH/HMG, oral compounds & antagonist*
Conventional IVF	*≥8 oocytes*	*Agonist or antagonist conventional FSH/HMG dose*

Terminology

Recommended	**To replace**
Natural cycle IVF	*Unstimulated, Spontaneous cycle IVF*
Modified Natural cycle IVF	*Semi-natural, Controlled natural cycle IVF*
Mild IVF	*Soft, Minimal stimulation, 'Friendly' IVF*
Conventional IVF	*Standard, Routine IVF , Controlled Ovarian Hyperstimulation (COH) IVF*

Modified Natural cycle IVF

- Spontaneous cycle
- Exogenous hormones used

Scenarios:

1. hCG only
2. GnRH antagonist ±FSH add-back & hCG
3. Luteal support

- Low risk of cancellation
- Commonly used method of natural cycle IVF

Rongieres-Bertrand et al:Hum Reprod,1999;14:683—688
Nargund & Frydman: RBM Online,2007;14;550-552

Modified Natural cycle IVF

- More physiological

Follows the path of follicular growth

- Minimal cost
- Fits into a spontaneous cycle
- Less stressful
- No cancellation/LH surge with antagonist
- Effective alternative

Time for a re-think?

- Revival of natural cycle IVF
- Concept of modified natural cycle IVF
- Development of protocols for Mild IVF
- Concerns about conventional stimulation IVF

Conventional stimulation (downregulation & high stimulation) approaches:

- Complex /unphysiological/unnecessary/unpleasant
- Time consuming (up to 4-5 weeks)
- High costs (direct and indirect)
- Patient discomfort (prolonged injections)
- Menopausal symptoms, Headaches
- Supra-physiological steroid levels
- OHSS
- Thrombo-embolism
- Increase in chromosome abnormalities in oocytes & embryos
- Adverse endometrial conditions
- Long-term health consequences
- High drop-out rates (psychological burden)

Development of Superovulation IVF protocols

- To block premature LH surge
- To avoid cancellation of cycles
- To plan weekly schedules in clinics
- Due to relative inefficiency of single embryo transfer
- To allow multiple fresh embryo transfer

Why Now?

- Single Embryo Transfer
- Clinical availability of antagonists
- Advances in Endocrinology
- Latest Ultrasound Technology
- Improved Embryology
- Concerns about embryo & endometrial quality
- Cancer survivors requiring ART
- *"Cost"* of conventional IVF
- Increased demand in public health service

Natural/Modified natural cycle IVF:

Patient selection - Current practice

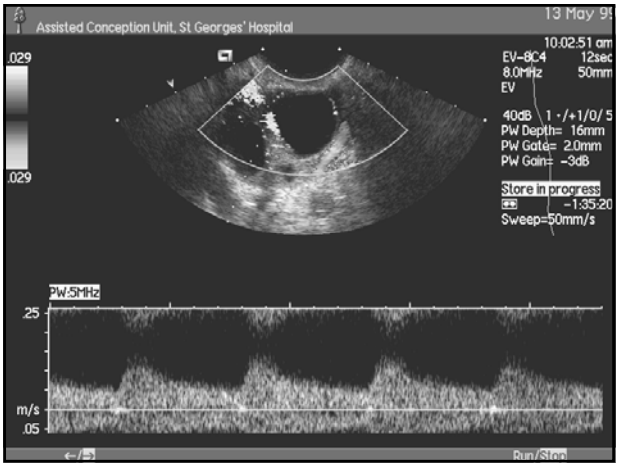
- In cancer patients & those with family H/O cancer
- Poor responders
- Older women
- Failed implantation
- With severe endometriosis
- For those who want to avoid drugs

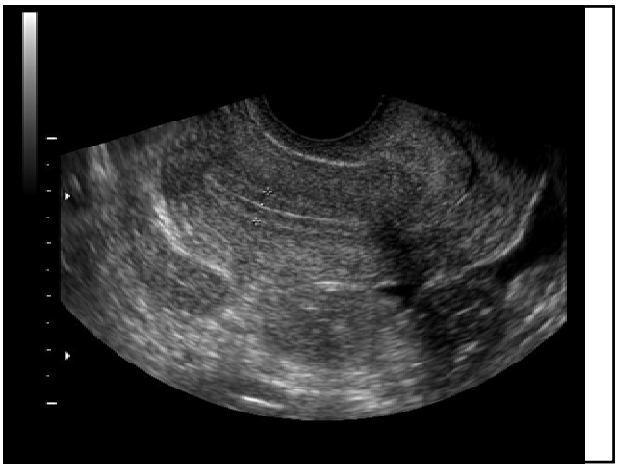
Monitoring & Optimisation of cycles

- Normal cycle length
- Follicular-Endometrial synchronisation
- Alternate ovulation
- Single ovary

Synchronising Follicular & Endometrial growth & maturity

- Growth of follicle &Thickness of endometrium (early scan)
- Volume & follicular blood flow and Endometrial morphology & blood flow
- Peri- ovulatory follicle, Endometrial morphology & cervical mucus





Revival of Natural cycle IVF

- 44 cycles
- 33 women (26-36 years)
- Single dose Cetrorelix & HMG (4.7±1.4 amps)
- 4 cycles cancelled
- 40 oocyte collections
- 10 cycles with no oocytes
- 22 embryo transfers
- 7 clinical pregnancies
- 32% clinical pregnancy per ET
- 17.5% clinical pregnancy per oocyte collection

Rongieres-Bertrand C et al Human Repro 1999:14 (3): 683-8

Natural Cycle IVF

Cumulative Conception & Live birth Rates:
Nargund et al Human Reprod 2001
-52 women &181 cycles (3.49 cycles/patient)
-Life table analysis
After 4 successive cycles of treatment
Cumulative probability of pregnancy -46%
Cumulative probability of Live birth -32%

Natural Cycle IVF

Nargund et al: Human Reprod 2001

Conclusions:

1. For maximum effectiveness, must be offered as a series of treatment cycles
2. Safer, less stressful and can be offered over consecutive cycles
3. Can be offered at ~23% of the cost of stimulated cycle

Natural cycle IVF : Cost Effectiveness Analysis

- **Daya et al: Human Reprod 1995**

  240 cycles: 12% clinical pregnancy/cycle

  Despite the high failure rate at each step in the process, natural cycles are more cost-effective than stimulated cycles which incur an incremental cost per live birth of $48,000. Natural cycles offer a low-cost alternative that may be more accessible to patients
- **Nargund et al: Human Reprod 2001**

  181 cycles: Cumulative LBR -32% (4 cycles)

  Natural cycle IVF can be offered at 23% cost of stimulated cycle

Modified Natural Cycle IVF

- *Feldman B et al: Gynae Endo 2001*
- *Nargund et al: Human Reprod 2001*
- *Ubaldi FM : RBM online 2005*

-Favourable in poor responders & failed implantation

-The use of antagonists did not change intrafollicular VEGF/Inhibin A levels

Natural cycle IVF:

In Poor Responders

- Prospective study
- 22 poor responders over 1 year
- 44 NCIVF and 55 SIVF cycles
- 82% had one oocyte collected
- 41% had atleast 1 cycle with ET
- 9% had a live birth

Results of NCIVF & SIVF comparable

Feldman et al: Gynae Endocrinology 2001

Semi-Natural IVF:

In Poor prognosis patients

- Prospective study -133 cycles
- Altered ovarian status & Implantation failure
- 66 patients (AOS -47; IF-19)
- OPU rate (81.2%;61.1%)
- Clinical pregnancy rate/OPU (15.4%;16.6%)

Castelo-Branco A et al:Gynae Obstet Biol Reprod: 2004

Modified Natural cycle IVF:

In Poor Responders

- 540 cycles
- Retrospective evaluation
- MNIVF vs Antagonist SIVF vs LongSIVF
- 52 vs 200 vs 288 cycles
- 1.4 vs 2.3 vs 2.5 oocytes
- 10% vs 14.3% vs 6.75% implantation
- 10.2% vs 7.4% vs 10.6% pregnancies

Elizur et al: Assist Reprod Genetics 2005

Natural cycle IVF:
In Poor Responders

- 294 patients & 500 consecutive cycles
- ≤ 35 : 36-39 : ≥40 years old
- 18.1% : 11.7% : 5.8% pregnancy/cycle
- 29.2% : 20.6% : 10.5% pregnancy/ET
- 31.7% : 20.3% : 10.5% pregnancy/pt

NCIVF is an effective treatment.

Schimberni et al: Fertil Steril 2008

Semi-Natural Cycle IVF

Pelinck MJ (Netherlands): Human Reprod 2005

-Late follicular start FSH/Antagonist
-50 patients/119 cycles (2.4 cycles/pt)
-52 Embryo Transfers
-17 ongoing pregnancies
-PR = 32.7%/ET
Cumulative ongoing pregnancy rate
-After 3 cycles: 34%
-Live Birth Rate per patient: 32%

Modified Natural cycle IVF:
Cumulative pregnancy rates

- 268 patients with sequential treatment
- MNC IVF followed by COS IVF
- Time to pregnancy -28.8 weeks
- 9 cycles of MNC followed by COSIVF
- Cumulative ongoing pregnancy 56.7%
- Cumulative LBR 50% per patient

Sequential treatment is patient-friendly,low-risk & has low twin pregnancy rate

Pellinck et al: Hum Reprod 2008

Natural /Modified Natural cycle IVF/ICSI:
In cancer risk women

- In BRCA1 & BRCA2 carriers
- H/O breast tumours
- Other oestrogen dependent tumours
- Prior to chemotherapy in other cancers

An effective & safe option

Hirt et al: Fertil steril 2008

Dor J : NCIVF abstracts :2006

Natural cycle IVF with IVM: A New approach?

- In ovulatory Normal & PCO women
- hCG 10,000 IU
- 3 women
- 3 pregnancies
- 2 live births

Chain RC et al : Fertil Steril 2004

- 350 cycles
- 262 women
- 15.2% ongoing pregnancy rate

Benkhalifa M et al:RBM Online 2009

Natural/Modified Natural cycle IVF: Patient opinions

Despite cancellations & lower success rates per cycle, women prefer:

- Natural selection
- Simplicity & short duration
- Treatment fitted in their spontaneous menstrual cycles
- No/Low hormone strategy
- No/Few injections
- No/Few side effects
- Fewer visits/blood tests
- No/Less interference with professional/social life

Hojaard et al,Hum Reprod 2001
Norman A & Nargund G (MSc Thesis) 2004
Pistorius EN et al ,Hum Fertil 2006
Sedbon E et al ,RBM Online 2006 (French data)
De clerk C et al ,Hum Reprod 2007
Verberg MF et al Hum Reprod 2008

What are the priorities for "results" of IVF?

For the Patient

- No side effects
- No OHSS
- Less interference
- Low cost
- No long-term concerns
- Healthy mother & Child

Safety and Comfort

For the Service &State

- Low Cost/Economic loss
- Social responsibility
- No multiple pregnancy
- No OHSS & future risks
- Healthy mother & child
- Suitable for developing & developed world

Quality NOT Quantity

Mild Vs Standard Strategy
Heijnen et al: Lancet 2007

Mild Strategy

- 444 cycles
- SET
- Term live birth rate 43.4%
- OHSS -1.4%
- Mean cycle -2.3

Standard Strategy

- 325 cycles
- DET
- Term live birth rate 44.7%
- OHSS – 3.7%
- Mean cycle – 1.7

Natural cycle IVF: Is it effective & cost-effective?

- Yes. For selected groups of patients

For a wider application using public purse:
Well designed, large scale, randomised, controlled trials are required using different methods of stimulation.

- Mild IVF would be an acceptable future strategy for wider application

References

1.Nargund G,Fauser BC,Macklon NS et al : Hum Reprod 2007;22(11) 2801-2804

2.Nargund G,Waterstone J,Bland J et al: Hum Reprod 2001;16(2) 259-262

3. Rongieres-Bertrand , Olivennes F, Righini C et al:Hum Reprod,1999;14:683—688

4.Nargund & Frydman: RBM Online,2007;14;550-552

References (continued)

5.Daya S,Gunby J,HughesEG et al:Hum Reprod 1995;10(7) 1919-1724

6.Feldman B,Seldman DS,Levron J et al:Gynaecol Endocrinol 2001;15(5) 328-334

7.Ubaldi FM,Rienzi L,Ferrero s et al:RBM Online 2005;10(2)235-246

8.Castelo-Branco A,Frydman N,Kadoch J et al:J Gynaecol Obstet Biol Reprod 2004;33(6)518-524

References (continued)

9.Elizur SE,Aslan D,ShulmanA et al:J Assist Reprod Genet 2005;22(2)75-79

10.Schimberni M,Morgia F,Colabianchi J et al :Fertil Steril 2008;9 (Epub ahead of print)

11.Pelinck MJ,Vogel NE,Hoek A et al:Hum Reprod 2005;20(3) 642-648

12.Pelinck MJ,Knol HM,Vogel NE et al;Huma Reprod 2008;23(8)1808-1814

References (Continued)

13. Hirt R,Davy C,Gulbert J et al:Fertil Steril 2008;90(4)1199
14. Dor J:Abstarct Book 2006;ISMAAR Congress (www.ismaar.org)
15. Chian RC,Buckett WH,Abdul JAK et al:Fertil Steril 2004;82(6)1675-1678
16. BenkhalifaM,Demirol A,Menezo Y et al:RBM Online 2009;18(1)29-36

References (continued)

17. Hojgaard A, Ingerslev HJ, Dinesen J et al: Hum Reprod 2001;16:1391–1396
18. Heijnen E, Marinus JC, De Klerk C, Polinder S et al:Lancet 2007;369:743–749.
19. Verberg MF,Macklon NS,Nargund G et al:Hum Reprod Update 2009;15(1) 13-29

Individualising ovarian stimulation for IVF

Anders Nyboe Andersen, Professor

The Fertility Clinic, Copenhagen University Hospital, Rigshospitalet, Denmark

Disclosure of conflicts of interest.
Have done RCT with: Merck Serono, Organon, Ferring, MediCult

Have received educational grants for ph.d students from
Merck Serono, Organon and Ferring

Learning objectives

- That a number of variables can be used to calculate/construct gonadotropin dosage nomograms
- That we may do controlled ovarian stimulation with a ”conventional”, ”mild” or **”appropriate” (individual)** approach
- That individually based dosage regiments do give a significantly more favourable oocyte distribution which may have clinical benefits.

P4

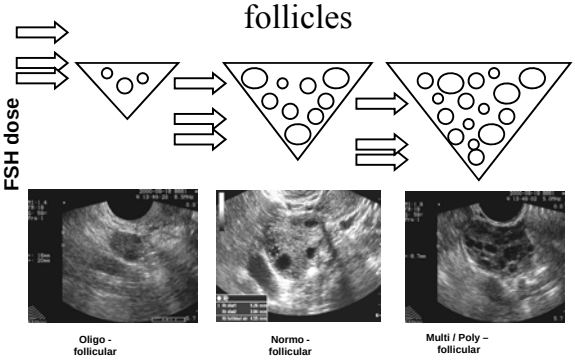
Ovarian stimulation with gonadotrophins What are our key concerns?

- Ovulation induction in anovulatory patients
  - Defining **threshold dose** that induces maturation of a single dominant follicle
- Controlled ovarian stimulation for IUI in ovulatory patients
  - Defining a **dose that is just above the threshold** in order to induce growth of two (or three) follicles
- Controlled ovarian stimulation for IVF
  - Defining the **appropriate dose** well above the threshold according to your target
    - Conventional IVF – long and short
    - Mild IVF

Slide 3

P4 What is our key concern?
to
What are our key concerns?
Li; 23/01/2008

The FSH dose and recruitable follicles

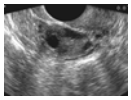


What determines the ovarian follicular response

The number of recruitable follicles
Their sensitivity to FSH
The dose of FSH
The bioavailability of FSH

The ovary holds the key to stimulation strategies

- **THE OVARY**
  - AFC
  - Volume



  Clinical
  - Age, reflects AF
  - Cycle length, reflects AF

  Endocrine
  - FSH, reflects AF and
  - AMH reflects preantral and small AF
  - (FSH receptor polymorphism)
- **BODY WEIGHT**
  - BMI - Bioavailability

Slide 4

P5 The FSH dose and the recruitable follicles
to
The FSH dose and recruitable follicles
Li; 23/01/2008

Slide 5

P7 What does ++++ refer to?
Li; 23/01/2008

Slide 6

P7 What does ++++ refer to?
Li; 23/01/2008

Controlled ovarian stimulation for Individualised FSH stimulation/

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

In brief….

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

Controlled ovarian stimulation for IVF/ICSI

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

Prospective studies – agonists

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

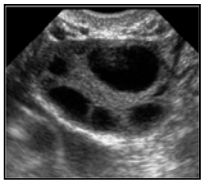
Prospective studies – antagonists

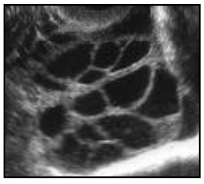
Ref	Age	Dose / IU	Nr. cycles	Oocytes (mean)	Pregn rate
Wikland 2001	20-39	150 vs. 225	60 vs. 60	9.1 vs 11*	NS
Out 2004	18-39	150 vs 200	131 vs. 126	10.3 vs 11.9	NS

*** p < 0.05**

Why individual stimulation?

"Unexpected" low response "Unexpected excessive response"





Variability of ovarian response

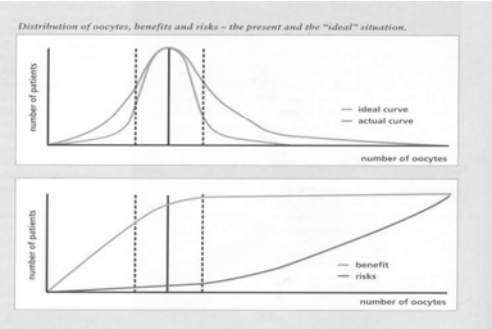
	100 IU	200 IU	Ref
Oocytes range	1-29	3-30	Out 1999
Oocytes range	1-30	1-40	Out 2001

Variability of ovarian response

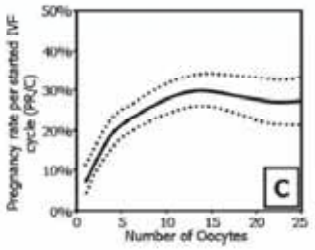
	150 IU	250 IU	Ref
Oocytes range	1-24	1-60	Out 2000
Oocytes range	1-31	1-35	Out 2001

Let's be honest:
'Controlled ovarian stimulation'
is quite often rather 'uncontrolled'

The concept



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



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

Harrison *et al.* 2001

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

Harrison *et al*. 2001- results

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

Response prediction study - suggestion of a FSH dosage nomogram

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

Predictive factors

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

Popovic-Todorovic *et al.* 2003

Significant predictors of number of retrieved oocytes in bivariate linear regression

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

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

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

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

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

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

rFSH dosage nomogram (1)

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

rFSH dosage nomogram (2)

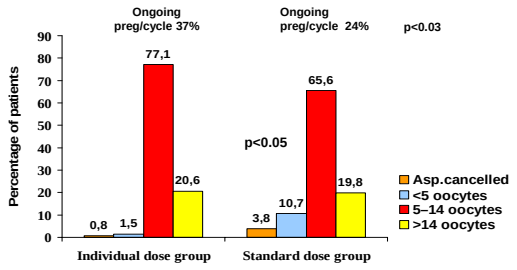
Age	*rFSH score IU/day*	*rFSH starting dose*
> 35	**20**	
30 - 35	**10**	
< 30	**0**	
Smoking habits/ cigarettes per day		***Score***
Non smoker	**0**	
≤ 10	**10**	
> 10	**20**	
Total rFSH score (sum of scores) same as dose IU/day		***Score***

Individual vs. standard rFSH dose RCT

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

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

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



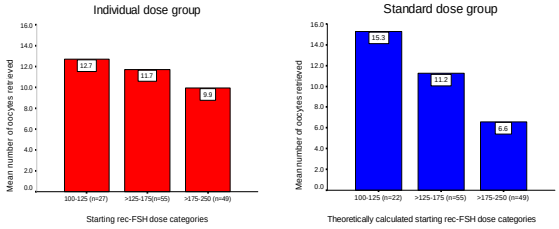
Popovic-Todorovic et al. Hum Reprod 2003; 18(11):2275–2282

Results

Oocyte distribution

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

Does the model predict the response?



P14

Conclusions on RCT

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

Risk charts to identify low and excessive responders among first cycle IVF/ICSI standard patients

Could it be that the parameters we use to identify the clinically relevant patient groups – low vs high responders – are different

A ”risk chart” may be another possibility to identify those patients where you decide to modify the ”standard dose” in your clinic.

Slide 29

P14 Normogram
to
Nomogram
Li; 23/01/2008

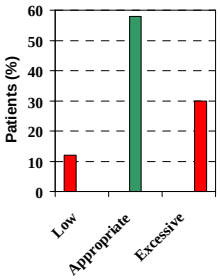
Material and Methods

- ”Standard” patients (n=276)
- 150 IU rFSH/day
- Low responders:
- < **8** follicles ≥11 mm
- Excessive responders:
- > **20** follicles ≥11 mm

- Logistic regression analysis
- 1000 bootstrap cross - validations

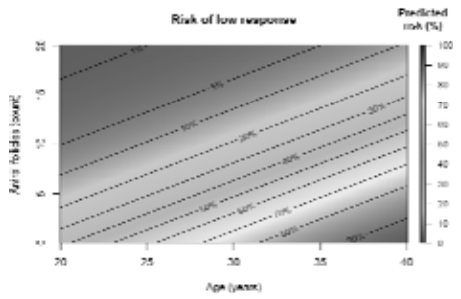
Ovarian response in 276 standard patients 150 iu/day- follicles

Follicles	16.8 ± 8.5 (1-53)
Low	33 (12)
Appropriate	160 (58)
Excessive	83 (30)

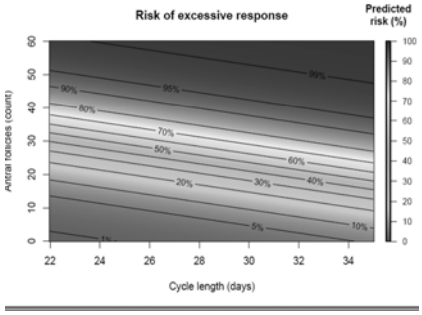


Freiesleben et al, submitted

Risk - low response



Risk – excessive response



Risk charts

- Risk charts allows clinicians to be guided on the percentage risk of either low or exccessive response and may be used as a guide to increase or decrease the standard dose used in the clinic

The Serono database study (CONSORT)

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

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

The Serono database study

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

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

Howles et al. Curr Med Res Opin 2006; 22(5):907–918
Olivennes et al., RBMONline, 2009, 18, 195-204

FSH dosing based on AMH

(Nelson *et al*., 2007 and 2009)

Determination of pragmatic clinical cut-offs of AMH levels

- <1.0 pmol/l
- 1 to <5.0 pmol/l
- 5.0 to <15 pmol/l
- 15 to <25 pmol/l

Table 1 Deployment of GnRH analogues and doses of follicle stimulating hormone in the groups categorized by anti-Müllerian hormone in the two centres

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

AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone.

AMH – as a single dosing parameter

- This was a non-controlled non-randomised study

1. It seems safe to dose aggressively with AMH < 5pmol/l
2. Dosing with 150 iu/day in patients with AMH > 15 pmol/l lead to 20/148 (14%) patients who were hospitalised due to OHSS

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

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

Nelson *et al.*, 2009
AMH category : 1- <5 pmol/l

	Centre 1 N=370	Centre 2 N=168	P value
Protocol	***Agonist + 375 IU***	***Antagonist + 300 IU***	
Patients	74 (20%)	61 (36.3%)	
Age(mean)	37.3	39.0	0.005
AMH (median)	2.6	3	0.4
Nr of oocytes	5 (3-7)	3 (1-4)	<0.001
Low oocyte yield n(%)	7/55 (12.7%)	20/56 (35.7%)	0.001
Freeze all n (%)	1 (1.4%)	0	1.0
Cancelled cycles n(%)	19 (25.7%)	5 (8.2%)	0.005
Clinical pregnancy rate per cycle n(%)	6 (8.1%)	9 (14.7%)	0.27

Nelson *et al.,* 2009 AMH category : 5 - <15 pmol/l

	Centre 1 N=370	Centre 2 N=168	P value
Protocol	***Agonist+ 225/300 IU***	***Agonist + 225/300 IU***	
Patients	128 (34.6%)	73 (43.4%)	
Age(mean)	35.1	37	<0.001
AMH (median)	9.2	8.7	0.93
Nr of oocytes	10 (7-15)	6 (4-10)	<0.001
Low oocyte yield n(%)	13 (10.1%)	0 (1.4%)	0.61
Freeze all n (%)	1 (1.4%)	0	0.04
Hospitalized for OHSS	3(2%)	1 (0%)	1.0
Cancelled cycles n(%)	3 (2.3%)	0 (8.2%)	1.0
Clinical pregnancy rate per cycle n(%)	29/125 (23.2%)	24 (32.9%)	0.13

Nelson *et al.,* 2009 AMH category : ≥15 pmol/l

	Centre 1 N=370	Centre 2 N=168	P value
Protocol	***Agonist + 150 IU***	***Antagonist + 150 IU***	
Patients	148 (40.1%)	34 (20.2%)	
Age(mean)	32.8	32	0.94
AMH (median)	22.4	25.8	0.018
Nr of oocytes	14 (10-19)	10 (8.5-13.5)	<0.001
Low oocyte yield n(%)	4/144 (2.8%)	1/33 (3.0%)	1.0
Freeze all n (%)	27 (18.2%)	0 (0%)	0.003
Hospitalized for OHSS	20 (13.9%)	0 (0%)	0.002
Cancelled cycles n(%)	4(2.7%)	1 (2.9%)	1.0
Clinical pregnancy rate per cycle n(%)	47 (31.8%)	21 (61.7%)	0.002

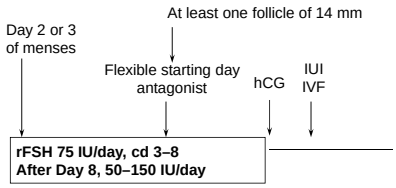
Prediction of an optimal ovarian response in ovulatory patients stimulated with low-dose rFSH and GnRH antagonist protocol

An integrated low-dose approach for IUI / IVF

Freiesleben et al.Reprod Biomed Online. 2008

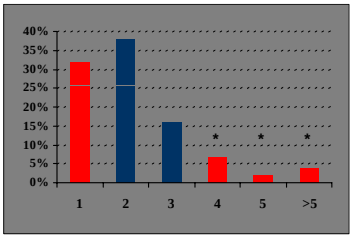
29

Treatment regimen



Number of follicles

Number of follicles ≥15 mm on the day of hCG



☐ Undesired ovarian response
☐ Desired ovarian response

*Converted to IVF

Predictors of the number of mature follicles (>15 mm)

- Simple linear regression:
  - Body weight p<0.005
  - BMI p<0.03
  - Ovarian volume p<0.04
  - AFC p<0.01
- Multiple linear regressions identified two independent predictors:
  - Body weight p<0.001
  - AFC p<0.004

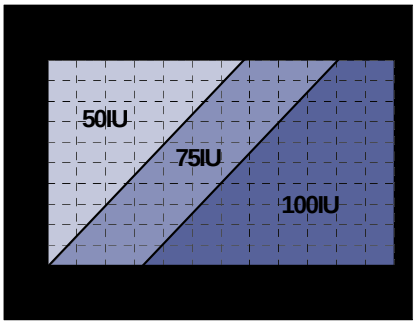
Slide 46

P9 Third bullet point amended (previously 9<superscript>1

Li; 23/01/2008

A rFSH dosing nomogram for IUI

based on the 2 independent variables: Body weight and AFC



A RCT with and FSH dosing in an antagonist protocol for IUI/IVF

- 258 Couples with unexplained, mild male factor, mild endometriosis
- Indication for IUI – first FSH cycle
- Randomised to
  1) Standard FSH (75 iu/day), n=113
  2) Individual (50 -100iu/day) according to nomogram, n=115

Freiesleben et al , Submitted

A RCT with and FSH dosing in an antagonist protocol for IUI/IVF

	Follicles > 14 mm		
	1	**2-3**	**> 3**
Individual	23%	70%*	7%
Standard	33%	56%*	11%

*difference 14.3 CI 2-26, P<0.05)

Ongoing preg/cycle Indiv: 20.4% vs Stand: 18.4%
Multiples: Indiv: 4.3 vs Stand: 23.8%

Freiesleben et al , Submitted

An integrated low-dose approach for IUI / IVF

What can be achieved with a low-dose ”integrated” IUI /IVF Protocol?

	Cycles	Live Preg/cycle	Twins	Triplets
IUI	344 (92%)	75/344 (22%)	9 (12%)	2 (2.7%)
IVF	31 (8%)	10/31 (32%)	1 (10%)	
All	**375**	**85/375 (23%)**	**10 (12%)**	**2 (2.3%)**

Final conclusion

- An estimated 50% of the world’s COS for ART are **first** cycles with uncertain responses.
- Considering the number of published papers on COS for IVF/ICSI, it is amazing that the knowledge we have on response predictive factors has only sporadically been **developed into clinically useful models** to guide us on the key issue of appropriate gonadotrophin dosing
- Dosing models based on simple clinical, sonographic and endocrine tests should be tested in RCTs
- We need these models for long and short protocols, and for conventional and mild stimulation – different targets.

References

Freiesleben et al. Reprod Biomed Online 2008: 17; 632-641.
Howles et al. Curr Med Res Opin 2006: 22; 907-918
Latin-American Puregon Study Group Fertil Steril 2001: 76; 950-956.
Nelson et al. Hum Reprod 2007: 22; 2414-2421
Nelson et al. Hum Reprod 2009: 24; 867-875
Olivennes et al. RBMONline 2009: 18; 195-204
Out et al. Hum Reprod 1999: 14; 622-627.
Out et al. Hum reprod 2001: 16; 1104-1109.
Out et al, Hum Reprod 2004: 19; 90-95
Popovic-Todorovic et al. Hum Reprod 2003: 18; 2275–2282
Popovic-Todorovic et al. Hum Reprod 2003: 18; 781–787
Van der Gaast et al. Reprod Biomed Online 2006: 13; 476-480.
Wikland et al. Hum Reprod 2001: 16; 1676-1681.

Single embryo transfer: where are we?

Prof. Dr. Petra De Sutter
Div. Reproductive Medicine, Dept Ob/Gyn
University Hospital Ghent / University Ghent

Disclosure

Institutional research and/or traveling grants have been received in 2009 by the following companies :

- Merck-Serono
- Ferring
- Cook

Learning objectives

After this lecture, participants should be able to

- Understand the risks and complications of multiple pregnancies
- Describe the patients who are twin prone and candidates for elective SET
- Understand the conclusions from randomized trials comparing SET with DET
- Have an idea of the worldwide application of the SET strategy to date
- Compare SET with DET from a health-economic perspective

Multiple embryo transfer to increase the chance for *a* (successful?) pregnancy

Table 1. Embryo number at transfer relative to multiple implantation, pregnancy rate, embryonic implantation, and abnormality rate

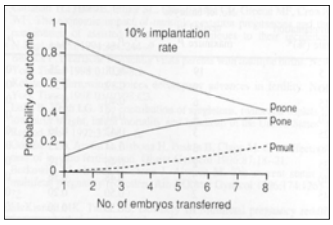
No. of embryos	No. of cycles	Single gestation (No.)	Twin gestation (No.)	Triplet gestation (No.)	Quadruplet gestation (No.)	Pregnancy rate per embryo transfer (%)	Multiple pregnancy rate (%)	Embryo implant	Infants with abnormalities	
									No.	%
1	227	22	0	0	0	9.7†	0	9.7†	0	0.0
2	402	97	17	0	0	28.4‡	15	16.3	3	2.3
3	661	164	74	10	0	37.5	34	17.2	6	1.8
4	832	207	84	32	6	30.5	36	14.9	15	2.7
5	47	15	5	1	0	40.4	33	11.1	2	7.8
6	4	1	1	0	0	50.0	50	12.5	0	0.0
Total/av.	2173	504	181	43	6	33.8	31.3	15.4	24	2.4

*$p < 0.00001$, significantly lower than all other embryo transfer groups.
†$p < 0.005$, significantly lower than three, four, five, and six embryo transfer groups.
‡$p < 0.05$, significantly lower than two, three, and four embryo transfer groups.

Elsner et al., Hum Reprod 1997

4

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 10% implantation rate



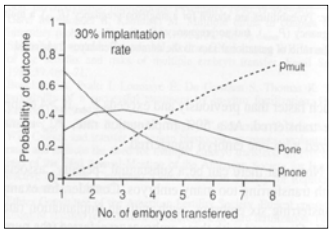
Martin and Welch, FS 1998

1 embryo transferred:
* P_{one}= 10%
* P_{mult} = 0%
* P_{none} = 90%

3 embryos transferred:
* P_{one} = 27.5%
* P_{mult} = 2.5%
* P_{none} = 70%

5

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 30% implantation rate



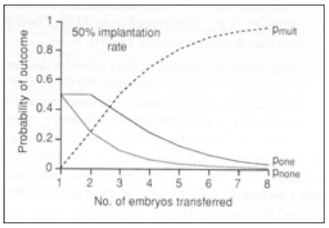
Martin and Welch, FS 1998

1 embryo transferred:
* P_{one}= 30%
* P_{mult} = 0%
* P_{none} = 70%

3 embryos transferred:
* P_{one} = 44%
* P_{mult} = 22%
* P_{none} = 34%

6

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 50% implantation rate



Martin and Welch, FS 1998

1 embryo transferred:
* P_{one}= 50%
* P_{mult} = 0%
* P_{none} = 50%

2 embryos transferred:
* P_{one} = 50%
* P_{mult} = 25%
* P_{none} = 25%

7

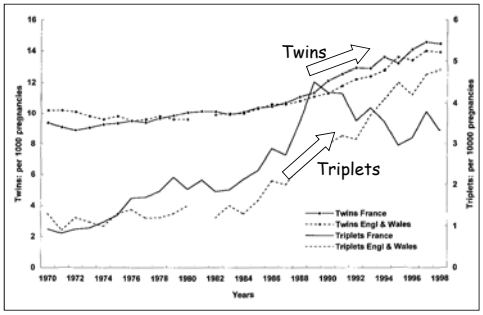
	IR(%)	n embr	P_{one}	P_{mult}
P_{none}	5	19	0.38	0.25	0.38
	10	9	0.39	0.23	0.39
	15	6	0.40	0.22	0.38
	20	4	0.41	0.18	0.41
	25	3	0.42	0.16	0.42
	30	3	0.44	0.22	0.34
	35	2	0.46	0.12	0.42
	40	2	0.48	0.16	0.36
One TQE	**40**	**1**	**0.40**	**0.00**	**0.60**
	45	2	0.50	0.20	0.30
	50	1	0.50	0.00	0.50

Pregnancy outcomes at various implantation rates if the number of embryos transferred is selected to maximize the P (singl. pregn.)[8]

The problem of multiple pregnancies

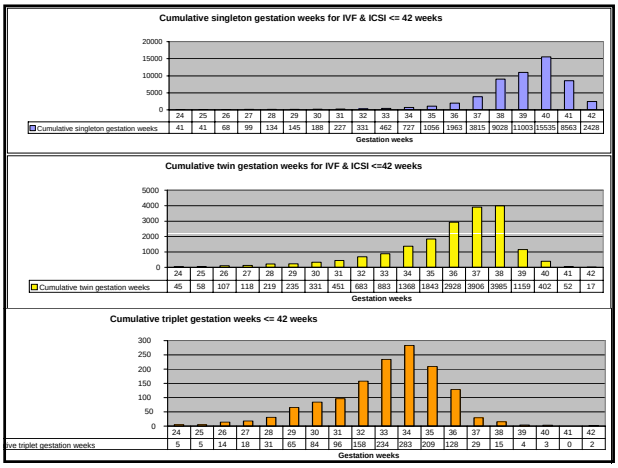
9

Twins and Triplets: England and Wales and France 1970-1998



Blondel & Kaminski 2002. Semin Perinatol 26:239-49.

10



Maternal Morbidity

Multiple (n=44,674) vs singleton pregnancy (n=165,188)	RR (95% CI)
Pre-eclampsia	2.8 (2.7-2.9)
Gestational diabetes	1.1 (1.9-1.2)
Myocardial infarction	**3.7 (2.3-5.8)**
Heart failure	**12.9 (2.7-62.3)**
Venous thromboembolism	**2.7 (2.0-3.5)**
Pulmonary oedema	**7.1 (4.5-11.3)**
Post partum haemorrhage	1.9 (1.8-1.9)
Caesarean delivery	2.2 (2.1-2.2)
Hysterectomy	2.3 (1.7-3.2)

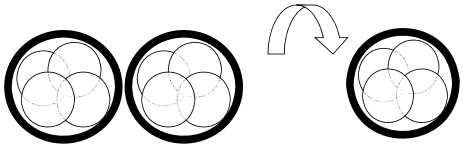
12

Walker et al, BJOG, 2004

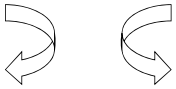
Elective single embryo transfer

13

Reducing the number of twin births



Single embryo transfer in <u>selected</u> cases



Twin-prone patient selection

Embryo selection

14

The pioneers

- Coetsier T, Dhont M. (Ghent) Avoiding multiple pregnancies in in-vitro fertilization: who's afraid of single embryo transfer? Hum Reprod 1998;13:2663-4. **<u>The concept</u>**
- Vilska S, Tiitinen A, Hydèn-Granskog C, Hovatta O. (Helsinki) Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth. Hum Reprod 1999;14:2392-5.
- In women with medical contraindications for MP (hemi-uterus, isthmic insufficiency, IDDM,…) **<u>The first clinical data</u>**

<u>Pregnancy rate</u>

- 74 elective SET 29.7% + FER = 47.3%
- 94 non-elective SET 20.2%
- 742 two-embryo transfers 29.4% 24% twins

15

Patient selection

Multivariate analysis of >2000 cycles: robot photo of SET-suitable patient

- **Female age** < 35-37 years of age
- **IVF cycle number** 1st and 2nd
- **No. of good quality embryos available** ≥ 2
- **Tubal factor infertility** (absent)

(Strandell et al., Hum Reprod, 2000)

Univariate and multivariate analysis of 661 cycles

+

- **IVF as method of fertilization**
- **No of 4-cell embryos on day 2**
- **FSH per oocyte retrieved**

(Thurin et al., Hum Reprod, 2005)

16

RCT: SET versus DET

in pts. <34y, 1st trial, at least two TQEs

Group	SET	DET
N cycles (transfers)	29	36
N postive HCG	18	28
N clinical pregnancies	14	26
N ongoing pregnancies	11	26
N multiplepregnancies	1 MZ	6
Conception rate (%)	18/29 (62.1%)	28/36 (77.8%)
CPR (%)	14/29 (48.3%)	26/36 (72.2%)
OPR (%)	11/29 (37.9%)	24/36 (66.7%)
MPR (%)	1/11 (9.1%)	6/24 (25%)
OIR (%)	11/29 (37.9%)	30.73 (41.7%)

Gerris J et al. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. Hum Reprod 1999;14:2581-7.

Fragment.	N bl D2	N bl D3	Implanted fraction (%)	N embryos
2	4	10	50.0	10
1	4	8	44.2	547
2	4	9	41.7	24
2	4	8	40.4	193
1	4	9	37.5	40
1	5	10	36.4	22
2	5	10	35.7	14
1	5	8	32.4	34
1	5	9	31.1	45
1	2	7	29.4	17
1	2	8	29.2	24
1	2	6	28.6	14
2	5	9	28.6	42
1	6	10	27.3	11
2	2	8	27.3	11
1	4	7	24.8	101
2	5	7	23.8	21
2	4	7	20.7	58
1	3	7	20.0	10
1	4	10	20.0	25

Embryo characterisation: Ranking of implantation potential of embryos with 1-to-1 documented outcome on the basis of day 2/3 morphology

The implantation potential of human embryos is not a categorical variable (top versus non-top = a useful simplification) but a continuous variable ranging between 0-50% for the "best" (= "least bad") embryos.

JUDICIOUS eSET IS LINKED TO RIGID EMBRYO SELECTION

Total: 1704 SETs of embryos, all without MNB's, at least 10 embryos in each group

Clinical results and the Belgian model

19

BELGIAN FUNDING REGULATION

- Six IVF/ICSI cycles (= oocyte harvests) funded in a life-time
- 1250 € per cycle for laboratory costs (gamete procurement and handling)
- Including cryocycles
- Up to the age of 43 years

Linked to a rational transfer strategy

≤ 36 years

1st attempt ever or 1st trial after previous IVF/ICSI-delivery: always one embryo;

2nd attempt: one embryo if of sufficient quality; two if of insufficient quality;

≥3rd attempt: max 2 embryos.

>36 - ≤39 years

1st and 2nd attempt: maximum 2 embryos;

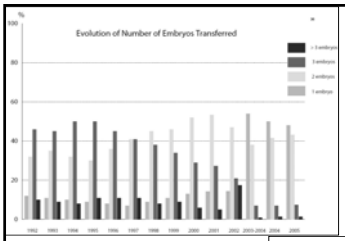
≥3rd attempt: max 3 embryos.

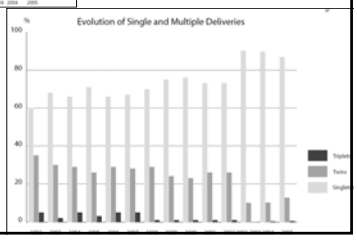
> 39 years

No maximum number of embryos to transfer is dictated

CRYOCYCLES: 1 or 2 embryos

20





Birthweight of singletons after assisted reproduction is higher after single- than after double-embryo transfer

Petra De Sutter[1,3]*, Ilse Delbaere[1]*, Jan Gerris[1], Hans Verstraelen[1], Sylvie Goetgeluk[2], Josiane Van der Elst[1], Marleen Temmerman[1] and Marc Dhont[1] Hum Reprod, 2006

Table II. Outcome parameters of SET and DET singleton pregnancies (gestational age, birthweight, preterm birth and l

	SET (n = 404)	DET (n = 431)	Adjusted P-value	Crude OR (CI)
Gestational age (days)	276.2 (±10.5)	273.4 (±15.0)	<0.01	
Birthweight (grams)	3324.6 (±509.7)	3204.3 (±617.5)	<0.01	
Preterm birth	6.2%	10.4%		1.77 (1.06–2.94)
Low birthweight	4.2%	11.6%		2.99 (1.69–5.27) (<2

Human Reproduction Vol.22, No.4 pp. 1073-1079, 2007 doi:10.1093/humrep/del492
Advance Access publication January 24, 2007

Obstetric and neonatal outcome after single embryo transfer

P.Poikkeus[1,3], M.Gissler[2], L.Unkila-Kallio[1], C.Hyden-Granskog[1] and A.Tiitinen[1]

[1]Department of Obstetrics and Gynaecology, Helsinki University Central Hospital and [2]National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland and

[3]To whom correspondence should be addressed at HYKS-instituutti huone 3009/Terkko, Haartmaninkatu 4, 00290 Helsinki, Finland. Tel: +358-50-3646 534, fax: +358-9-4717 5550; E-mail: piia.poikkeus@hus.fi

BACKGROUND: Single embryo transfer (SET) pregnancies practically lack vanishing twins and may be associated with improved neonatal outcome. Our objective was to compare the obstetric and neonatal outcome of SET singletons with the outcome of singletons following double embryo transfer (DET) and spontaneous conception. **METHODS:** A 7-year (1997–2003) cohort of fresh SET (n = 269) and DET (n = 230, including 25 vanishing twins) cycles resulting in singleton birth at Helsinki University Central Hospital, Finland, was linked to the Finnish Medical Birth Register and the obstetric and neonatal outcome data compared with that from 15 037 spontaneously conceived singleton pregnancies. **RESULTS:** The obstetric and neonatal outcome of the SET group was comparable to that in the DET group. Compared with the comparison cohort, gestational hypertension (P = 0.005), placenta praevia (P < 0.001), preterm contractions (P = 0.01) and maternal hospitalization (P < 0.001) was more typical of women in the SET group. After adjusting for age, parity and socio-economic status the SET pregnancies showed increased risks of Caesarean section [odds ratio (OR) 1.54 with 95% confidence interval (CI) 1.18–2.00], preterm birth (OR 2.85; 95% CI 1.96–4.16) and low birthweight (OR 2.01; 95% CI 1.19–3.99) compared with the comparison cohort. **CONCLUSIONS:** Our results indicate that subject- and infertility-related mechanisms other than the number of transferred embryos influence the neonatal outcome of singleton IVF pregnancies.

First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction

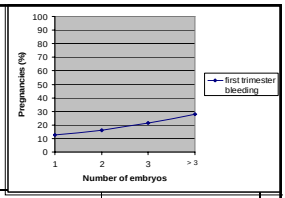
Petra De Sutter[1], Julie Bontinck, Valerie Schutysers, Josiane Van der Elst, Jan Gerris and Marc Dhont

Infertility Centre, University Hospital Gent, Gent, Belgium Hum Reprod 21; 1907-11, 2006

Patients	253 **with bleeding**	1179 **without bleeding**	
% 2nd T bleeding	12.3%	3.0%	4.56 (CI 2.76-7,56)
% 3rd T bleeding	5.1%	1.9%	2.85 (CI 1,42-5,73)
% P-PROM	7.6%	3,2%	2.44 (CI 1.83-4,31)
% Preterm contractions	13.9%	6.7%	2.27 (CI 1.48-3,47
% IUGR	3.2%	5,5%	0.57 (CI 0.270-1,21
% intrauterine death	0.8%	1.0%	0.78 (CI 0.17-3.48)
% Caesarean section	19%	19.4%	0.98 (CI 0.69-1,39)
Duration of pregnancy	272±17	275±14	P= 0.0092
% Preterm births	11.6%	7.4%	1.64 (CI 1.05-2.55)
% Very preterm births	2.4%	0.8%	3.05 (CI 1.12-8.31)
Birth weight (g)	3157±607	3272±559	P=0.0038
% low birth weight	8.8%	7.2%	1.24 (CI 0.76-2.02)
% very low birth weight	2.4%	0.7%	3.56 (CI 1.28-9.90)
% 1 min Apgar score <7	8.1%	8.0%	1.02 (CI 0.61-1.71)
% 5 min Apgar score <7	2.1%	2.6%	0.80 (CI 0.32-2.03)
% NICU admission	17.9%	11%	1.75 (CI 1.21-2.54)
% perinatal deaths	1.2%	1.4%	0.87 (CI 0.25-3.02)

Linear correlation between incidence 1st trimester bleeding and number of embryos transferred

Not only does eSET cause less twin-related morbidity and mortality but also healthier singletons



Embryos	Total Pregnant	1st trim. bleeding	Controls
1	208	26 (12.5%)	182 (87.5%)
2	795	129 (16.2%)	666 (83.8%)
3	347	75 (21.6%)	272 (78.4%)
> 3	82	23 (28.0%)	59 (72%)

25

Results of SET versus DET - Finland

Type of transfer	Transfers	CPR/ET	DR/ET	TPR/D
	N	n (%)	n (%)	n (%)
2 embryos	517	203 (40.0)	160 (30.9)	42/160 (26.2)
compulsory SET	94	17 (18.1)	13 (13.8)	1/13 (7.7)
elective SET	127	49 (38.6)	34 (26.8)	1/34 (2.9)

CPR=clinical pregnancy rate; ET=embryo transfer; DR=delivery rate; TPR=twin pregnancy rate; D=delivery

Tiitinen et al., Hum Reprod 2001; 16: 1140-1144

26

Cryo-augmentation effect after eSET

Type of ET	Transfers	PR	DR	Twins
	n	n (%)	n (%)	n (%)
Fresh ET	127	49 (38.6)	34 (26.8)	1 (2.9)
Frozen ET	129	39 (30.2)	32 (24.8)	4 (12.5)
1 embryo	46	8 (17.4)	5 (10.9)	0
2 embryos	83	31 (37.3)	27 (32.5)	4 (14.8)
CPR/patient		78 (62.4)	66 (52.8)	5 (7.6)

ET=embryo transfer; PR=pregnancy rate; DR=delivery rate; CPR=cumulative pregnancy rate

Tiitinen et al., Hum Reprod 2001; 16: 1140-1144

27

Cryopreservation

- When more eSET is performed, more embryos are available for cryopreservation
- Optimal standard of success = the cumulative OPR per oocyte harvest = fresh + frozen/thawed attempts
- The more eSET the better a centre
- The more cryocycles the better the centre

28

Swedish Experience: 1 + 1 cryo = 2

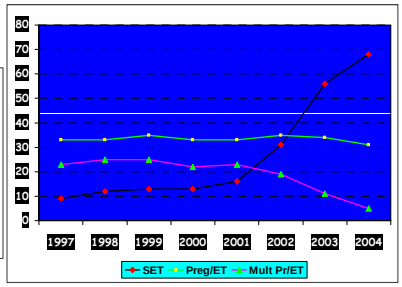
Thurin et al., N Engl J Med 2004; 351: 2440-2442.
Academic Hospital Göteborg and 10 other Scandinavian centres: RCT

·Fresh DET:

* 42.9% live birth rate
* 33% twins

·Fresh SET + 1 cryo-SET:

* 28.5%
* + cryo: 38.8%



% SET in Sweden

29

Dutch experience: 2 x 1 = 1 x 2

Lukassen et al., Hum Reprod 2005; 20: 702-708 - UMC Nijmegen

Table II. The cumulative outcome of fresh embryo transfers

Variable	SET (n = 54)			DET (n = 53)
	1st cycle	2nd cycle	Cumulative	
No. of subjects	54	40	54	53
No. of transfers	54	35[a]	[illegible]	[illegible]
Clinical pregnancy [n (%)]	20 (37)	10 (25)	(56)	(47)
Miscarriage [n (%)]	6 (11)	2 (5)	8 [illegible]	[illegible]
Ectopic pregnancy [n (%)]	0	0	0	[illegible]
Live birth [n (%)]	14 (26)	8 (20)	(41)	(36)
Singleton [n (%) of live births]	14 (100)	8 (100)	22 [illegible]	
Twin [n (%) of live births]	0	0	0	(37)
Perinatal death (n)	0	0	0	1
Preterm birth < 37 weeks [n (%)]	2 (14)	0	2[c] (10)	5[d] (20)
Low birthweight infants (<2500 g) [n (%)]	1 (7)	0	1[c] (5)	10[d] (40)

30

Human Reproduction Vol.22, No.6 pp. 1689–1694, 2007
Advance Access publication on April 5, 2007

eSET irrespective of the availability of a good-quality embryo in the first cycle only is not effective in reducing overall twin pregnancy rates

Anfke P.A.van Montfoort[1,5], Audrey A.A.Fiddelers[2], Jolande A. Land[3,4], Carmen D.Dirksen[2], Johan L.Severens[2], Joep P.M.Geraedts[3], Johannes L.H.Evers[1] and John C.M.Dumoulin[1]

INTRODUCTION: In several clinics, elective single-embryo transfer (eSET) is applied in a selected group of patients based on age and the availability of a good-quality embryo. Whether or not eSET can be applied irrespective of the presence of a good-quality embryo in the first cycle, to further reduce the twin pregnancy rate, remains to be elucidated. METHODS: In patients <38 years two transfer strategies were compared, which differed in the first cycle only: group A (n = 141) received eSET irrespective of the availability of a good-quality embryo, and group B (n = 174) received eSET when a good-quality embryo was available while otherwise they received double embryo transfer (DET; referred to as eSET/DET transfer policy). In any subsequent cycle, in both groups the eSET/DET transfer policy was applied. RESULTS: After completion of their IVF treatment (including a maximum of three fresh cycles and the transfer of frozen–thawed embryos), comparable cumulative live birth rates (62.4% in group A and 62.6% in group B) and twin pregnancy rates (10.1 versus 13.4%) were found. However, patients in group A required significantly more fresh (2.0 versus 1.8) and frozen (0.8 versus 0.5) cycles. CONCLUSIONS: The transfer of one embryo in the first cycle, irrespective of the availablity of a good-quality embryo, in all patients <38 years, is not an effective transfer policy for reducing the overall twin pregnancy rate.

31

Human Reproduction Vol.22, No.6 pp. 1689–1694, 2007
Advance Access publication on April 5, 2007

eSET irrespective of the availability of a good-quality embryo in the first cycle only is not effective in reducing overall twin pregnancy rates

Anfke P.A.van Montfoort[1,5], Audrey A.A.Fiddelers[2], Jolande A. Land[3,4], Carmen D.Dirksen[2], Johan L.Severens[2], Joep P.M.Geraedts[3], Johannes L.H.Evers[1] and John C.M.Dumoulin[1]

INTRODUCTION: In several clinics, elective single-embryo transfer (eSET) is applied in a selected group of patients based on age and the availability of a good-quality embryo. Whether or not eSET can be applied irrespective of the presence of a good-quality embryo in the first cycle, to further reduce the twin pregnancy rate, remains to be elucidated. METHODS: In patients <38 years two transfer strategies were compared, which differed in the first cycle only: group A (n = 141) received eSET irrespective of the availability of a good-quality embryo, and group B (n = 174) received eSET when a good-quality embryo was available while otherwise they received double embryo transfer (DET; referred to as eSET/DET transfer policy). In any subsequent cycle, in both groups the eSET/DET transfer policy was applied. RESULTS: After completion of their IVF treatment (including a maximum of three fresh cycles and the transfer of frozen–thawed embryos), comparable cumulative live birth rates (62.4% in group A and 62.6% in group B) and twin pregnancy rates (10.1 versus 13.4%) were found. However, patients in group A required significantly more fresh (2.0 versus 1.8) and frozen (0.8 versus 0.5) cycles. CONCLUSIONS: The transfer of one embryo in the first cycle, irrespective of the availablity of a good-quality embryo, in all patients <38 years, is not an effective transfer policy for reducing the overall twin pregnancy rate.

?

32

ER
ON
Gynécologie Obstétrique & Fertilité 36 (2008) 1158–1161
http://france.elsev

Trente-neuvième Journée thématique de la SFEF (Paris, 22 mai 2008)

Transfert monoembryonnaire : expérience du CHU de Rennes

Single-embryo transfer: Rennes' Hospital experience

D. Le Lannou *, M.-C. Laurent, J.-F. Griveau, E. Véron, F. Jaffré, G. Jouve, A. Gueho, K. Morcel

Transfert de deux embryons versus deux transferts d'un embryon chez des patientes de pronostic différent

	Moins bon pronostic (n = 63)		Très bon pronostic (n = 67)	
	1 embryon	2 embryons	1 embryon	2 embryons
Transfert frais	15 G (23 %)	20 G (32 %)	21 G (31 %)	27 G (40 %)
Transfert congelé	6 G (13,6 %)	–	7G (17 %)	–
Total	21 G (33 %)	20 G (32 %)	28 G (42 %)	27 G (40 %)

33

Gynécologie Obstétrique & Fertilité 36 (2008) 1158–1161

Trente-neuvième Journée thématique de la SFEF (P

Transfert monoembryonnaire : expéri

Single-embryo transfer: P

D. Le Lannou *, M.-C. La

DÉBAT

Contre l'obligation du transfert monoembryonnaire

Against the obligation of single-embryo transfer

P. Pierrat *, E. Lourdel, F. Cabry, N. Grenier, P. Sanguinet, L. Henry,

Transf… …des

…pronostic

…(67)

	…ns	1 embryon	2 embryons
Transfe…	…9 G (32 %)	21 G (31 %)	27 G (40 %)
Transfert	–	7G (17 %)	–
Total	…8 (33 %)	20 G (32 %)	28 G (42 %) 27 G (40 %)

34

USA

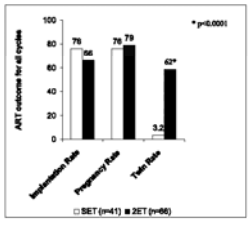
Elective single blastocyst transfer reduces twin rates without compromising pregnancy rates

Amy Criniti, M.D.,[a] Angela Thyer, M.D.,[b] Gregory Chow, M.D.,[a] Paul Lin, M.D.,[b] Nancy Klein, M.D.,[b] and Michael Soules, M.D.[b]

[a]University of Washington Fertility and Endocrine Center and [b]Seattle Reproductive Medicine, Seattle, Washington

FIGURE 1

Implantation rates, clinical pregnancy rates, and twinning rates for non-donor cycles that met criteria for single blastocyst transfer.



Criniti. Moving toward single blastocyst transfer. Fertil Steril 2005.

Conclusion(s): Single blastocyst transfer can be performed in good-prognosis patients without compromising pregnancy rates. Twin pregnancy rates can be significantly reduced with eSET. (Fertil Steril® 2005;84:1613–9 ©2005 by American Society for Reproductive Medicine.)

Australia

Elective transfer of single fresh blastocysts and later transfer of cryostored blastocysts reduces the twin pregnancy rate and can improve the in vitro fertilization live birth rate in younger women

Michael Henman, M.Med.Sc., James W. Catt, Ph.D., Tina Wood, B.Sc.(Agr.), Mark C. Bowman, M.B., Ph.D. C.R.E.I, Kylie A. de Boer, Ph.D., and Robert P. S. Jansen, M.D., C.R.E.I.

Sydney IVF, Sydney, New South Wales, Australia

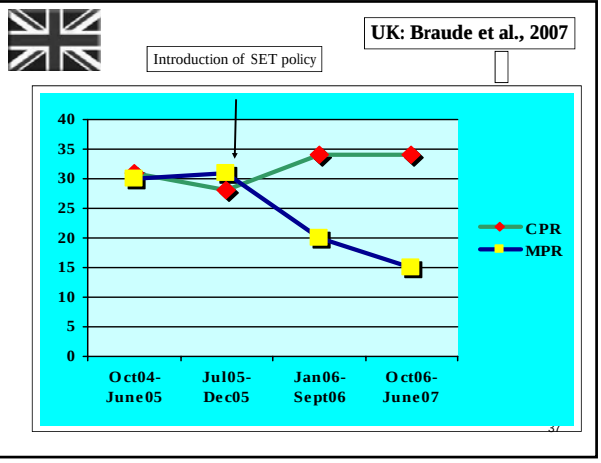
TABLE 1

Immediate clinical results from the fresh blastocyst transfers, comparing eSET with elective two-embryo transfer.

	One fresh blastocyst (eSET)	Two fresh blastocysts	χ^2
Transfer procedures	121	285	
Gestational sac–positive pregnancies	58 (48)	173 (61)	5.1 ($P<.025$)
Fetal heart–positive pregnancies	54 (45)	163 (57)	4.9 ($P<.03$)
Twin fetal hearts	1 (2)	72 (44)	
Fetal heart–positive implantations	55 (45)	236 (42)	ns
Fetal heart–positive fetal losses	4 (7.3)	27 (11.4)	0.43 (ns)
Loss of all fetuses before delivery	4 (7.4)	11 (6.8)	0.02 (ns)
Babies born alive	51	209	
Pregnancies ending with live birth	50	152	
Couples still without a baby	71 (59)	133 (47)	4.4 ($P=.035$)
Blastocysts in cryostorage	574	872	

Note: Numbers in parentheses are percentages.
ns = nonsignificant.

Henman. Elective single blastocyst transfer. Fertil Steril 2005.



Prerequisites for a particular centre to implement esET

- 1. Excellent results (the better the centre, the higher % of eSET)
- 2. Willingness to decrease a very high MP rate
- 3. Willingness to invest in optimization of a freeze/thaw programme
- 4. eSET must be compatible with specific societal circumstances in which the centre works

38

A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles *Hum Reprod 2004; 19 (4): 917-923*

J.Gerris[1,5], P.De Sutter[2], D.De Neubourg[1], E.Van Royen[1], J.Vander Elst[2], K.Mangelschots[1], M.Vercruyssen[1], P.Kok[2], M.Elseviers[3], L.Annemans[4], P.Pauwels[1] and M.Dhont[2]

- Prospective non-randomized multicenter study, comparing SET with DET in good prognosis patients
- 408 cycles - 367 transfers

	eSET	DET
N of transfers (44%)	201 (56%)	158
Clinical pregn rate	83/206 (40.3%)	65/161 (40.4%)
Live births	77/206 (37.4%)	59/161 (36.6%)
Singletons	77 (100%)	39 (66%)
Twins	-	20 (34%)

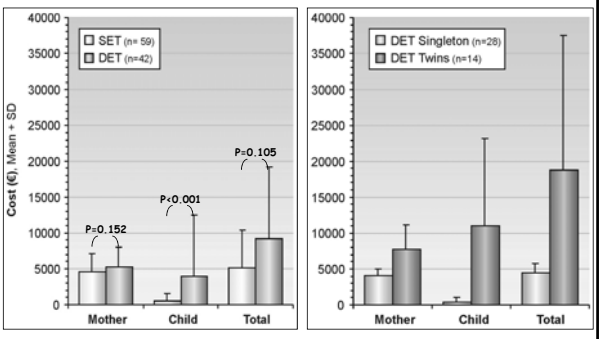
39

Real-life health-economic study

This prospective health economic study shows that eSET is equally effective as but ~50% cheaper than double embryo transfer in first IVF/ICSI cycles.

40

Health economic comparison SET/DET and singletons/twins in DET



41

Only cases with complete data included

De Sutter, P., Gerris, J. and Dhont, M. (2002) A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI. *Hum. Reprod.*, **17**, 2891–2896.

A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI: a sensitivity analysis

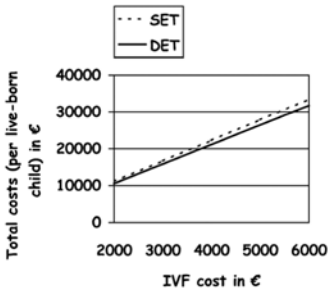


Figure 2. Correlation between IVF costs and total cost per live-born child for SET and DET, taking into account increases in neonatal care expenses, proportionally to IVF costs.

42

Cost-effectiveness analysis of different embryo transfer strategies in England

S Dixon,[a] F Faghih Nasiri,[b] WL Ledger,[c] EA Lenton,[d] A Duenas,[a] P Sutcliffe,[a] JB Chilcott[a]

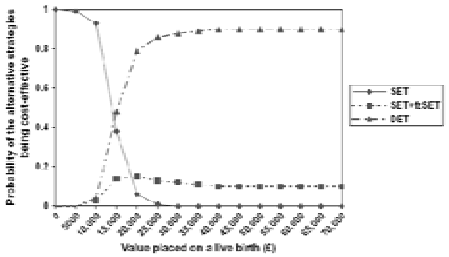


Figure 3. Cost-effectiveness acceptability curve for two embryo strategies including SET (age less than 30 years).

Human Reproduction Update, Vol.13, No.1 pp. 1–13, 2007

Economic evaluations of single- versus double-embryo transfer in IVF

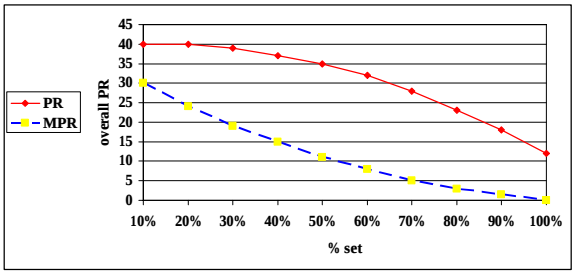
A.A.A. Fiddelers[1,4], J.L. Severens[1,3], C.D. Dirksen[1], J.C.M. Dumoulin[1], J.A. Land[2] and J.L.H. Evers[2]

		Costs (€)	Effects (%)	Costs per effect (€)	ICER (DET versus eSET)
Gerris *et al.* (2004)	eSET (one cycle)	7126	37.4	NR[a]	
	DET (one cycle)	11 039	36.6	NR[a]	NR[a]
Lukassen *et al.* (2005)	eSET (two cycles)	NR[a]	40.7	13 438	
	DET (one cycle)	NR[a]	35.8	13 680	NR[a]
Thurin *et al.* 2006[b]	eSET (one cycle)	9309	38.8	23 984	
	DET (one cycle)	12 318	42.9	28 712	71 940
Thurin *et al.* 2006[c]	eSET (one cycle)	10 905	38.8	NR[a]	
	DET (one cycle)	14 676	42.9	NR[a]	91 722
Fiddelers *et al.* (2006)	eSET (one cycle)	7334	20.8	35 260	
	DET (one cycle)	10 924	39.6	27 586	19 096

It can be concluded that DET is the most expensive strategy. DET is also most effective if performed in one fresh cycle. eSET is only preferred from a cost-effectiveness point of view when performed in good prognosis patients and when frozen/thawed cycles are included. If frozen/thawed cycles are excluded, the choice between eSET and DET depends on how much society is willing to pay for one extra successful pregnancy.

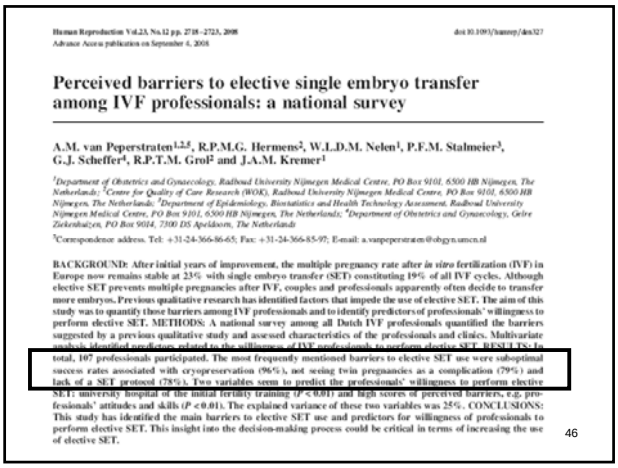
44

Conclusion: SET in whom and when?



? ? ?

45



Human Reproduction Vol.23, No.12 pp. 2718–2723, 2008 doi:10.1093/humrep/den327
Advance Access publication on September 4, 2008

Perceived barriers to elective single embryo transfer among IVF professionals: a national survey

A.M. van Peperstraten[1,2,5], R.P.M.G. Hermens[2], W.L.D.M. Nelen[1], P.F.M. Stalmeier[3], G.J. Scheffer[4], R.P.T.M. Grol[2] and J.A.M. Kremer[1]

[1]*Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands;* [2]*Centre for Quality of Care Research (WOK), Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands;* [3]*Department of Epidemiology, Biostatistics and Health Technology Assessment, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands;* [4]*Department of Obstetrics and Gynaecology, Gelre Ziekenhuizen, PO Box 9014, 7300 DS Apeldoorn, The Netherlands*

[5]Correspondence address. Tel: +31-24-366-86-65; Fax: +31-24-366-85-97; E-mail: a.vanpeperstraten@obgyn.umcn.nl

BACKGROUND: After initial years of improvement, the multiple pregnancy rate after *in vitro* fertilization (IVF) in Europe now remains stable at 23% with single embryo transfer (SET) constituting 19% of all IVF cycles. Although elective SET prevents multiple pregnancies after IVF, couples and professionals apparently often decide to transfer more embryos. Previous qualitative research has identified factors that impede the use of elective SET. The aim of this study was to quantify those barriers among IVF professionals and to identify predictors of professionals' willingness to perform elective SET. **METHODS:** A national survey among all Dutch IVF professionals quantified the barriers suggested by a previous qualitative study and assessed characteristics of the professionals and clinics. Multivariate analysis identified predictors related to the willingness of IVF professionals to perform elective SET. **RESULTS:** In total, 107 professionals participated. The most frequently mentioned barriers to elective SET use were suboptimal success rates associated with cryopreservation (96%), not seeing twin pregnancies as a complication (79%) and lack of a SET protocol (78%). Two variables seem to predict the professionals' willingness to perform elective SET: university hospital of the initial fertility training ($P < 0.01$) and high scores of perceived barriers, e.g. professionals' attitudes and skills ($P < 0.01$). The explained variance of these two variables was 25%. **CONCLUSIONS:** This study has identified the main barriers to elective SET use and predictors for willingness of professionals to perform elective SET. This insight into the decision-making process could be critical in terms of increasing the use of elective SET.

46

Thank you !

47

References

1: Wang YA, Sullivan EA, Healy DL, Black DA. Perinatal outcomes after assisted reproductive technology treatment in Australia and New Zealand: single versus double embryo transfer. Med J Aust. 2009 Mar 2;190(5):234-7.

2: Roberts SA, Fitzgerald CT, Brison DR. Modelling the impact of single embryo transfer in a national health service IVF programme.Hum Reprod. 2009 Jan;24(1):122-31.

3: Le Lannou D, Laurent MC, Griveau JF, Véron E, Jaffré F, Jouve G, Gueho A, Morcel K. [Single-embryo transfer: Rennes' Hospital experience] Gynecol Obstet Fertil. 2008 Nov;36(11):1158-61.

4: van Peperstraten AM, Hermens RP, Nelen WL, Stalmeier PF, Scheffer GJ, Grol RP, Kremer JA. Perceived barriers to elective single embryo transfer among IVF professionals: a national survey. Hum Reprod. 2008 Dec;23(12):2718-23.

5: Cutting R, Morroll D, Roberts SA, Pickering S, Rutherford A; BFS and ACE. Elective single embryo transfer: guidelines for practice British Fertility Society and Association of Clinical Embryologists. Hum Fertil (Camb). 2008 Sep;11(3):131-46.

6: Poikkeus P, Tiitinen A. Does single embryo transfer improve the obstetric and neonatal outcome of singleton pregnancy? Acta Obstet Gynecol Scand. 2008;87(9):888-92.

7: Delbaere I, Vansteelandt S, Gerris J, De Sutter P, De Bacquer D, Temmerman M. Human chorionic gonadotropin levels in early IVF/ICSI pregnancies are higher in singletons after single embryo transfer compared with singletons after double embryo transfer. Hum Reprod. 2008 Nov;23(11):2421-6.

8: Bhatt T, Baibergenova A. A comparison of the cost-effectiveness of in vitro fertilization strategies and stimulated intrauterine insemination in a Canadian health economic model. J Obstet Gynaecol Can. 2008 May;30(5):411-20.

9: Dixon S, Faghih Nasiri F, Ledger WL, Lenton EA, Duenas A, Sutcliffe P, Chilcott JB. Cost-effectiveness analysis of different embryo transfer strategies in England. BJOG. 2008 May;115(6):758-66.

10: van Montfoort AP, Fiddelers AA, Land JA, Dirksen CD, Severens JL, Geraedts JP, Evers JL, Dumoulin JC. eSET irrespective of the availability of a good-quality embryo in the first cycle only is not effective in reducing overall twin pregnancy rates. Hum Reprod. 2007 Jun;22(6):1669-74.

11: Poikkeus P, Gissler M, Unkila-Kallio L, Hyden-Granskog C, Tiitinen A. Obstetric and neonatal outcome after single embryo transfer. Hum Reprod. 2007 Apr;22(4):1073-9.

48

12: Fiddelers AA, Severens JL, Dirksen CD, Dumoulin JC, Land JA, Evers JL. Economic evaluations of single- versus double-embryo transfer in IVF Hum Reprod Update. 2007 Jan-Feb;13(1):5-13.
13: De Sutter P, Delbaere I, Gerris J, Verstraelen H, Goetgeluk S, Van der Elst J, Temmerman M, Dhont M. Birthweight of singletons after assisted reproduction is higher after single-than after double-embryo transfer. Hum Reprod. 2006 Oct;21(10):2633-7.
14: Fiddelers AA, van Montfoort AP, Dirksen CD, Dumoulin JC, Land JA, Dunselman GA, Janssen JM, Severens JL, Evers JL. Single versus double embryo transfer: cost-effectiveness analysis alongside a randomized clinical trial. Hum Reprod. 2006 Aug;21(8):2090-7.
15: De Sutter P, Bontinck J, Schutysers V, Van der Elst J, Gerris J, Dhont M. First-trimester bleeding and pregnancy outcome in singletons after assisted reproduction. Hum Reprod. 2006 Jul;21(7):1907-11.
16: van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GA, Land JA, Geraedts JP, Evers JL, Dumoulin JC. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. Hum Reprod. 2006 Feb;21(2):338-43.
17: Thurin A, Hardarson T, Hausken J, Jablonowska B, Lundin K, Pinborg A, Bergh C. Predictors of ongoing implantation in IVF in a good prognosis group of patients. Hum Reprod. 2005 Jul;20(7):1876-80.
18: Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EM, Scheenjes E, Kremer JA. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. Hum Reprod. 2005 Mar;20(3):702-8.
19: Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, Bergh C. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. N Engl J Med. 2004 Dec 2;351(23):2392-402.
20: van Montfoort AP, Dumoulin JC, Land JA, Coonen E, Derhaag JG, Evers JL. Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles. Hum Reprod. 2005 Feb;20(2):433-6.
21: Gerris JM. Single embryo transfer and IVF/ICSI outcome: a balanced appraisal. Hum Reprod Update. 2005 Mar-Apr;11(2):105-21.
22: Tiitinen A, Hydén-Granskog C, Gissler M. What is the most relevant standard of success in assisted reproduction?: The value of cryopreservation on cumulative pregnancy rates per single oocyte retrieval should not be forgotten. Hum Reprod. 2004 Nov;19(11):2439-41.

49

23: Gerris J, De Sutter P, De Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, Vercruyssen M, Kok P, Elseviers M, Annemans L, Pauwels P, Dhont M. A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Hum Reprod. 2004 Apr;19(4):917-23.
24: Söderström-Anttila V, Vilska S, Mäkinen S, Foudila T, Suikkari AM. Elective single embryo transfer yields good delivery rates in oocyte donation. Hum Reprod. 2003 Sep;18(9):1858-63.
25: De Sutter P, Van der Elst J, Coetsier T, Dhont M. Single embryo transfer and multiple pregnancy rate reduction in IVF/ICSI: a 5-year appraisal. Reprod Biomed Online. 2003 Jun;6(4):464-9.
26: De Sutter P, Gerris J, Dhont M. A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI: a sensitivity analysis. Hum Reprod. 2003 Jun;18(6):1361.
27: De Sutter P, Gerris J, Dhont M. A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI. Hum Reprod. 2002 Nov;17(11):2891-6.
28: Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Vercruyssen M, Barudy-Vasquez J, Valkenburg M, Ryckaert G. Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. Hum Reprod. 2002 Oct;17(10):2626-31.
29: Tiitinen A, Halttunen M, Härkki P, Vuoristo P, Hyden-Granskog C. Elective single embryo transfer: the value of cryopreservation. Hum Reprod. 2001 Jun;16(6):1140-4.
30: Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Van de Meerssche M, Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. Hum Reprod. 1999 Oct;14(10):2581-7.
31: Van Royen E, Mangelschots K, De Neubourg D, Valkenburg M, Van de Meerssche M, Ryckaert G, Eestermans W, Gerris J. Characterization of a top quality embryo, a step towards single-embryo transfer. Hum Reprod. 1999 Sep;14(9):2345-9.
32: Coetsier T, Dhont M. Avoiding multiple pregnancies in in-vitro fertilization: who's afraid of single embryo transfer? Hum Reprod. 1998 Oct;13(1O):2663-4.

50

How can we reduce the burden of treatment?

Jacky Boivin, Ph.D.
School of Psychology
Cardiff University

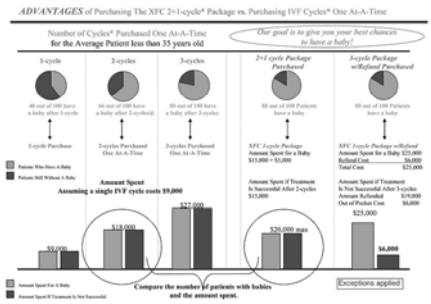
Disclosure

- ASRM, ESHRE and Merck-Serono jointly sponsored the FertiQoL project

Learning objectives

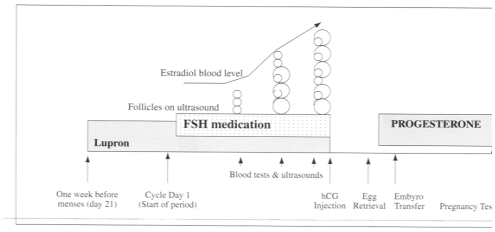
- Identify sources of burden in fertility treatment
- Describe psychosocial reactions during treatment and their impact on treatment outcome
- Learn general and treatment specific techniques to minimise the burden of treatment
  - Techniques for patients
  - Techniques for staff
- Gain knowledge on the effectiveness of general and treatment specific interventions on wellbeing and pregnancy rates

Causes of burden: Financial strain



www.ivfdoc.com

IVF/ICSI monitoring associated source of distress



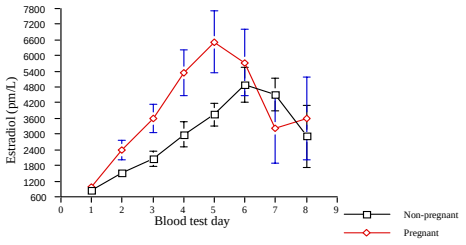
Standard Lupron – FSH Cycle

Before Cycle Start
- Start vitamins with folic acid (0.4 mg or 400 mcg).

Monitoring
- Typically started on FSH Treatment day 6-8.

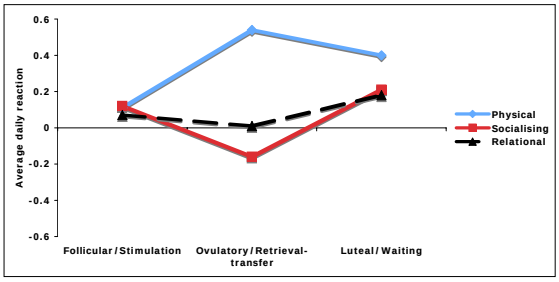
Day after Egg Retrieval
- Start progesterone for 14 da
- Stop progesterone only if pre

IVF pharmacology: Estradiol (pm/L) with hMG-stimulation



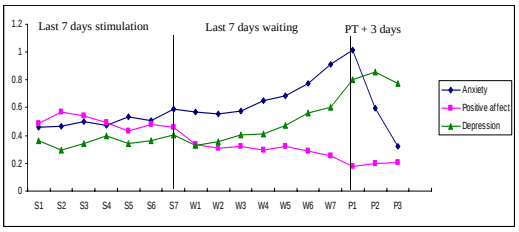
Boivin, doctoral dissertation, 1995

Causes of burden: physical and behavioral consequences



Boivin et al. Hum Reprod 1996 7

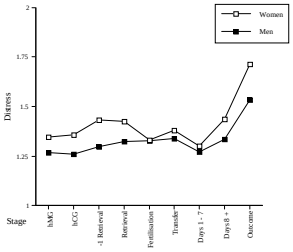
Causes of burden: uncertainty and harm



S = stimulation
W = waiting
P = Pregnancy test

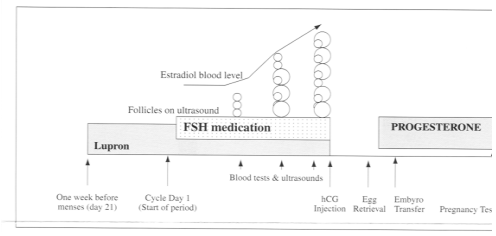
Boivin & Walker, ESRC, 1997 8

Partner distress during IVF



Boivin et al. Hum Reprod 1998 9

Causes of burden: Staff feedback & monitoring during IVF/ICSI



Standard Lupron – FSH Cycle

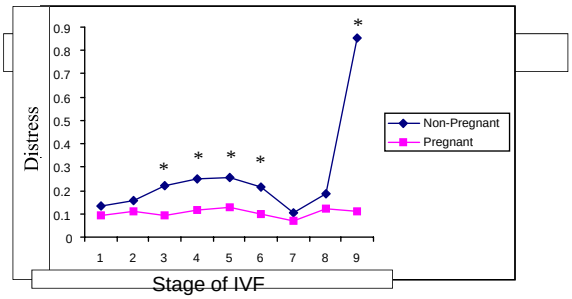
Before Cycle Start
- Start vitamins with folic acid (0.4 mg or 400 mcg).

Monitoring
- Typically started on FSH Treatment day 6-8.

Day after Egg Retrieval
- Start progesterone for 14 da
- Stop progesterone only if pre

10

Causes of burden: Negative feedback from staff

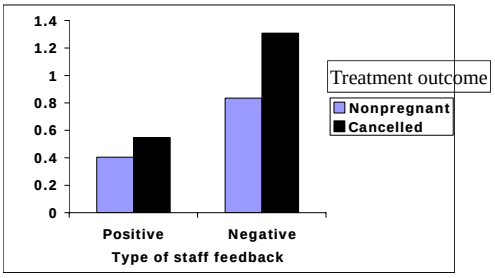


1=GnRH-a
2=hMG-only
3=hMG+scans*
4=hCG*
5=Retrieval*
6=Transfer*
7=Waiting(1)
8=Waiting(2)
9=Pregnancy test*

Boivin & Takefman, Fertil Steril, 1995

11

Impact of staff feedback on emotional distress during IVF



Prospective study: Women (N=97) monitored distress daily during stimulation and OR-ET. Women assigned to nonpregnant or cancelled group based on treatment eventual outcome (Boivin, Proceedings, 2000)

12

Causes of burden: Stressful organisational care

Investigation & Initial treatment → IVF/ICSI

% ending treatment

5.3% - 40%
Diagnosis, IUI, DI

Malcolm & Cummings, 2004: 16.9 - 39%
Gleicher et al, 1996: 25 - 40%
Goverde et al. 2000: 15 - 16%
Guerif et al. 2003: 5.3-25%

12.2% to 62%
IVF, ICSI, etc

Olivius et al. 2004: 53.8%
Goverde et al. 2000: 42%
Osmanagaglu et al. 1999: 25-40%
Smeenk et al, 2004: 12.2-18.3%
Schröder et al. 2004: 39-62%

13

CONTROVERSY: WHY COUPLES DISCONTINUE IVF TREATMENT

FERTILITY AND STERILITY®
Copyright ©2004 American Society for Reproductive Medicine
Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Why do couples discontinue in vitro fertilization treatment? A cohort study

Catharina Olivius, B.Sc.,* Barbro Friden, M.D., Ph.D.,* Gunilla Borg, R.N., B.S.,* and Christina Bergh, M.D., Ph.D.*
Sahlgrenska University Hospital, Göteborg, and Varberg Hospital, Varberg, Sweden

Reason	Percentage
Emotional distress & coping failure	**17%**
Stressful organisational care • **Assembly-line treatment** • **Never the same staff** • **Clinic disorganised**	**64.3%**
Poor patient-centered care • **Insufficient care of the man** • **Lack of empathy** • **Poor listening skills** • **Unkind treatment by staff**	**48%**

Other "psychological" reasons:
• balancing treatment & work commitment (Osmanagaoglu et al. 1999)
• distance from clinic (Malcolm et al. 2004)
• undergone agreed number of cycles (deVries et al. 1999)

14

Other psychological variables must be involved

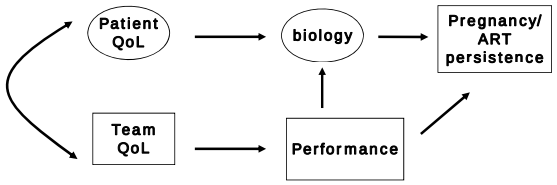
- "Psychologically too stressful" (Osmanagaoglu et al. 1999)
- "Psychological burden" (Olivius et al. 2004)
- "Psychological reasons" (Smeenk et al. 2004)
- "Emotional costs" (Hammarberg et al. 2001)
- "Reached limit" (Brew et al. 2001)
- "Emotional exhaustion" (Daniluk, 2001)

15

How can we reduce the burden of treatment?

16

Targets to reduce the burden of treatment



Boivin & Duff, in prep

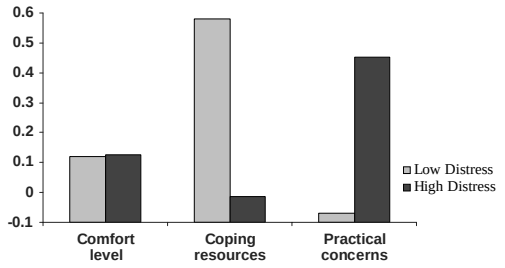
17

Intervention effects on all outcomes (■ = positive intervention; □ no intervention effect).

	1	2	3	4	5	6	7	8	9	10	11	12	13
Counselling													
• Holzle et al. 2002							□		□				
*• Strauss et al. 2002							□		□		■	■	□
*• Emery et al. 2001	□			□									□
• Christie & Morgan, 2000													
• McNaughton et al. 2000												■	
* Wischmann et al. 2001 -02							□		□		■		□
• Kemeter & Fiegl, 1999													
• Pengelly et al. 1995												■	
*• Connolly et al. 1993			□	□	□				□	□		■	
*• Liswood, 1995							□		□	□			
• Bents, 1991								■	■		■		
• Brandt & Zech, 1991													
*• Sarrel & deCherney, 1985													■
• Ellenberg & Koren, 1982													
• Bresnick & Taymor, 1979											■		
Focussed education program													
*• Tuschen-Caffier 1999									■			■	
• McQueeney et al. 1997	■							■			■	■	■
*• Stewart et al. 1992	■	■					■					■	
*• Takefman et al. 1990	□			□					□		■		□
*• Wallace 1984, 1985			□	■	□							■	□
• O'Moore et al. 1983				■									
Comprehensive educational													
*• Domar et al. 2000a, 2000b	□	□	□	■	■				■			■	
• Domar et al. 1990			■	■	■								
• Domar et al. 1992			□	■	■								
• Clark et al. 1995, 1998		■				■							

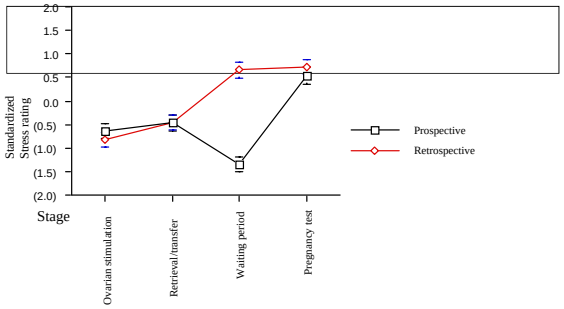
Table 1:Boivin,Soc Sci Med 2003

Most important reason for not using counselling



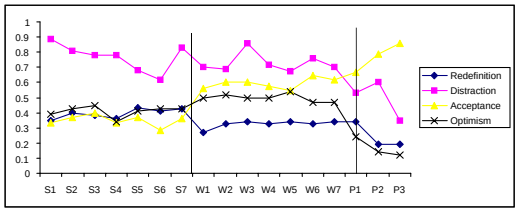
Boivin et al. Hum Reprod, 1999 19

Prospective versus retrospective accounts of distress during IVF



Boivin & Takefman, Fertil Steril, 1995 20

Capitalise on spontaneous coping efforts



Boivin & Walker, Proceedings, 1997 21

Brief coping interventions for the waiting period: The Positive Reappraisal Intervention Card

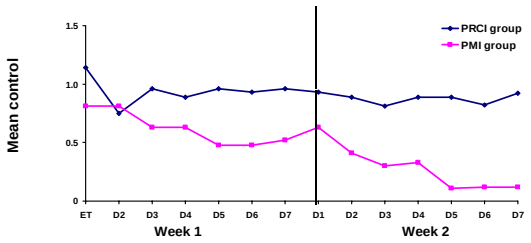
- Ten statements
  - Rationale explained to women
  - "prime" positive redefinition associated with positive adjustment
  - Instruction to read once in the morning, once in the evening and any other time needed

During this experience I will:
Try to do something that makes me feel good
See things positively
Look on the bright side of things
Make the best of the situation
Discover what is important in life
Focus on the positive aspects of the situation
Find something good in what is happening
Try to do something meaningful
Focus on the benefits and not just the difficulties
Learn from the experience

Lancastle and Boivin. *Hum Reprod* 2008.

22

Randomised Controlled (Pilot) Trial of Positive Reappraisal Coping Intervention

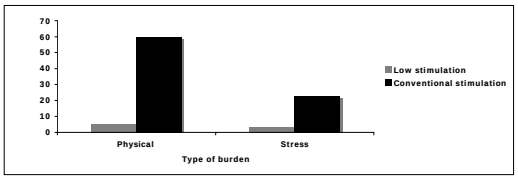


PRCI = positive reappraisal coping intervention; PMI = Control mood intervention; ET = embryo transfer.

Lancastle & Boivin. *Hum Reprod*, 2008; under review.

23

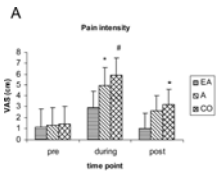
Use minimal stimulation protocols to reduce physical symptoms



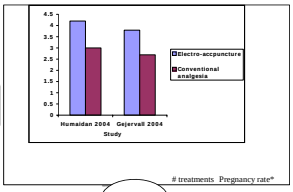
Hojgaard et al. Hum Reprod 2001

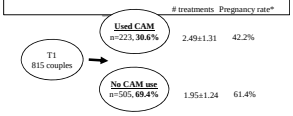
24

Role for complementary (CAM) interventions in reducing physical burden of treatment?



Sator-Katzenschlager, S. M. et al. Hum. Reprod. 2006 21:2114-2120

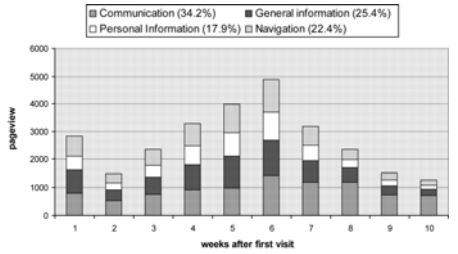




Boivin & Schmdit, Humn Reprod, in press, N=728 women
Prospective 12-month observational cohort study

25

Reduce burden by giving patients control over monitoring



The number of page-views per week after a patient/couple's first visit to the website

Tuil, W.S. et al. Hum. Reprod. 2006 21:2955-2959; doi:10.1093/humrep/del214

Human Reproduction

Online viewing behaviour

Table I. The usage of the PHR developed at Radboud University Nijmegen Medical Centre in terms of the number page-views per type of content during the patients first IVF/ICSI treatment cycle (n = 1150 patient couples).

Content type	Pageviews[1]	Average[2]	Mean[3]	SD[4]
Forum viewing[5]	366 175	318.4	44	632.1
Treatment information	60 838	52.9	42	46.2
Medical records	43 513	37.8	29	36.0
Day planner	25 453	22.1	7	34.0
Classroom[5]	22 155	19.3	2	57.9
Personalized prognosis	18 860	16.4	13	14.2
Downloadable documents	11 984	10.4	8	11.0
Forum posting[5]	11 774	10.2	0	26.7
Hospital information	9424	8.2	4	11.3
Frequently asked questions	7917	6.9	5	7.4
General information	7380	6.4	4	7.8
External hyperlinks	1211	1.1	0	1.8
Literature	1209	1.1	1	1.4
Website help	994	0.9	0	1.4
Total	588 887	512.1	191	801.3

Tuil, W.S. et al. Hum. Reprod. 2006 21:2955-2959; doi:10.1093/humrep/del214

27

Online support intervention

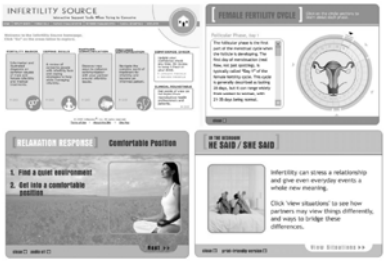


Figure 8: Infertility source web images

28

Cousineau et al. 2008

Optimizing IVF

1. Make IVF easier for patients
2. Stress Reduction
3. Invest in nurses
4. Focus on customer satisfaction
5. Improve communication
6. Develop IVF leadership
7. Improve documentation
8. Continual improvement
9. Data collection

Alper, Munich, 2004

29

Experiences of sonography nurses

Table 2. Factors causing difficulty when giving bad news: mean scores (ranked) and standard deviations ($N = 92$)

	M	SD
The patient is not expecting to hear bad news	3.65	1.07
Insufficient time to support the patient adequately	3.58	1.06
Pressure of being behind schedule for subsequent patients	3.41	1.18
Not knowing how the patient will react	3.12	1.13
Difficulty contacting the doctor to refer the patient on to	3.08	1.28
There is no chance to plan how to tell the patient	2.83	1.11
People accompanying the patient have different reactions which also have to be coped with	2.77	1.21
Colleagues are too busy to help with other appointments	2.76	1.22

Simpson & Bor, 2001

30

Interventions available to manage distressed patients

- Outburst (This is catastrophe!)
  - Don't take it personally, be patient, stay calm, listen & express empathy
- Freeze ("….")
  - Ask questions (what are you thinking?), share the silence, give them space and an opportunity to speak later
- Denial ("This isn't happening")
  - Empathise, repeat the facts, reinforce identity
- Plea ("just give me another chance")
  - Confirm the decision is final, focus on positive consequences
- Self-blamer ("I'm useless", "a failure")
  - Reinforce their identity, explain what else has contributed
- Attack ("It's your fault, your incompetent")

  Don't take it personally, remain calm, listen, don't answer back, empathise with the anger & disappointment

31

Emotional care can become a priority even in busy clinics

- Identify challenging situations
  - Administration, nursing, laboratory, physicians, etc
- Discuss different approaches to handling specific challenging situations
  - Identify strengths and limitations
  - Work out situational factors that impact on realistic implementation of different approaches
- Practice using different approaches and implement those best for you and the context

32

Impact of reducing burden

33

Improved quality of life during treatment

34

Available in 17 languages

FertiQoL International

Optional Treatment Module

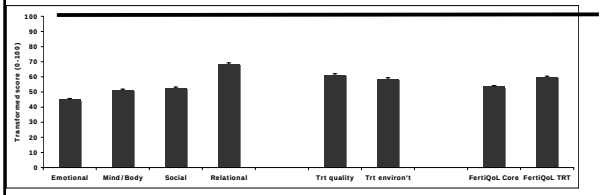
Have you started fertility treatment (this includes any medical consultation or intervention)? If Yes, then please respond to the following questions. For each question, kindly check (tick the box) for the response that most closely reflects how you think and feel. Relate your answers to your current thoughts and feelings. Some questions may relate to your private life, but they are necessary to adequately measure all aspects of your life.

	For each question, check the response that is closest to your current thoughts and feelings	Always	Very Often	Quite often	Seldom	Never
T1	Does infertility treatment negatively affect your mood?	☐	☐	☐	☐	☐
T2	Are the fertility medical services you would like available to you?	☐	☐	☐	☐	☐

	For each question, check the response that is closest to your current thoughts and feelings	An Extreme Amount	Very Much	A Moderate Amount	A Little	Not At All
T3	How complicated is dealing with the procedure and/ or administration of medication for your infertility treatment(s)?	☐	☐	☐	☐	☐
T4	Are you bothered by the effect of treatment on your daily or work-related activities?	☐	☐	☐	☐	☐
T5	Do you feel the fertility staff understand what you are going through?	☐	☐	☐	☐	☐
T6	Are you bothered by the physical side effects of fertility medications and treatment?	☐	☐	☐	☐	☐

	For each question, check the response that is closest to your current thoughts and feelings	Very Dissatisfied	Dissatisfied	Neither Satisfied nor Dissatisfied	Satisfied	Very Satisfied
T7	Are you satisfied with the quality of services available to you to address your emotional needs?	☐	☐	☐	☐	☐
T8	How would you rate the surgery and/or medical treatment(s) you have received?	☐	☐	☐	☐	☐
T9	How would you rate the quality of information you received about medication, surgery and/or medical treatment?	☐	☐	☐	☐	☐
T10	Are you satisfied with your interactions with fertility medical staff?	☐	☐	☐	☐	☐

Scope to improve quality of life during fertility treatment

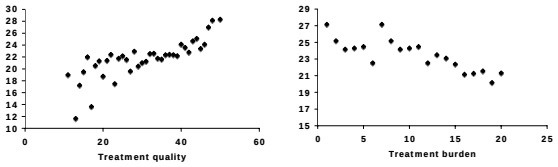


FertiQoL Core N=1230*; FertiQoL treatment* N =1050

FertiQoL validation sample

36

Increased treatment persistence

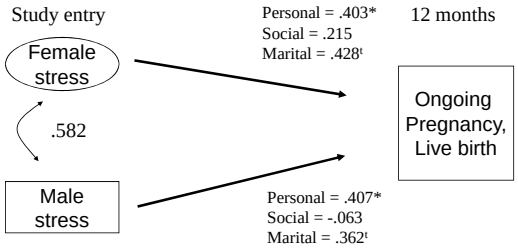


FertiQoL validation sample, n = 1027

Persistence = intention to persist with treatment

37

Reduced effect of distress on treatment outcome

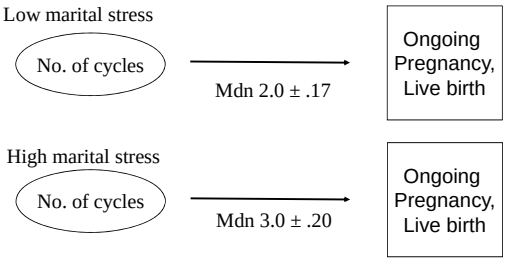


Discriminant *f*: $\chi 2(9)=21.4$, p=.01, N=818 couples
WGr: pooled-within group correlation with discriminant function (controlling for age, years infertile); * p < .05

38

Boivin & Schmidt, 2005a

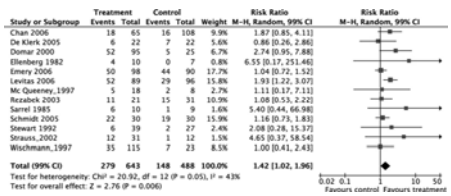
Couples may require fewer treatment cycles to conceive



Note. Cycle by marital stress interaction on live birth (B=.182 ± .08, Wald(1)=4.76, P < .05, OR=1.20; Model $\chi 2(F(3, 817)=27.03$, p < .001).

39

Effect of psychosocial interventions on pregnancy rates



Hammerli, K. et al. Hum Reprod Update 2009 0:dmp002v2-17; doi:10.1093/humupd/dmp002

Human Reproduction Update

Learning objectives

- Identify sources of burden in fertility treatment
- Describe reactions during treatment and their impact on treatment outcome
- Learn general and treatment specific techniques to minimise the burden of treatment
  - Techniques for patients
  - Techniques for staff
- Gain knowledge on the effectiveness of general and treatment specific interventions on wellbeing and pregnancy rates

41

Conclusion

- Psychosocial factors have an impact on ART
- Need to expand and diversify psychological services to meet needs of patients and staff

42

How can we reduce the burden of treatment?

Jacky Boivin, Ph.D.
School of Psychology
Cardiff University

Boivin@cardiff.ac.uk

Mild stimulation strategies in IVF

Is there an optimal balance?

Christina Bergh

ESHRE Amsterdam 2009

Is there an optimal balance?
(In the number of oocytes retrieved)

Benefits: Singleton live births

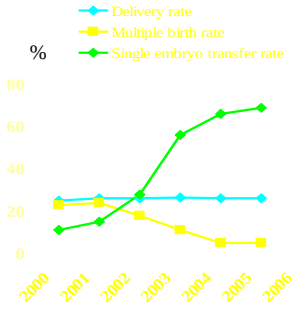
Risks: Complications (OHSS)

Is there an optimal balance? (In the number of embryos replaced)

Benefits: Singleton live births

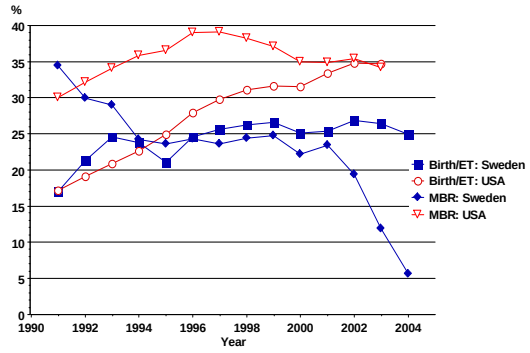
Risks: Complications (multiple births)

Delivery rate, multiple birth rate and single embryo transfer rate in Sweden 2000-2006

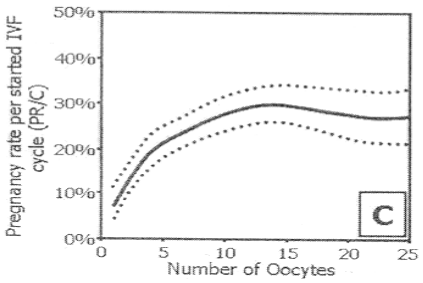


Karlström and Bergh, 2008

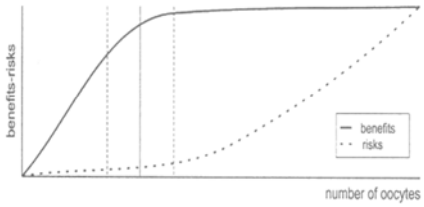
Birth per embryo transfer (%) and MBR in Sweden and USA



Karlström and Bergh, Hum Reprod 2007;22:2207-7. With permission from Oxford University Press



Reprinted from Van der Gast et al, RBMonline 2006;13:476-80, with permission from Reproductive Healthcare Ltc

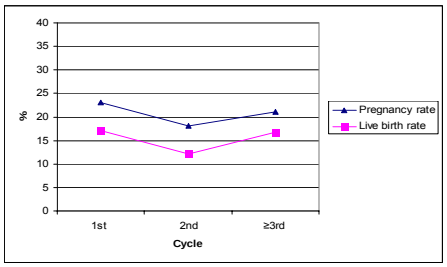


Popovic-Todorovic et al, Hum Reprod 2003;18:2275-82

With permission of Oxford University Press

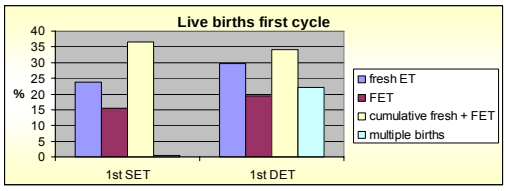
Live birth after 1st, 2nd or > 3rd cryopreservation SET from the same egg retrieval

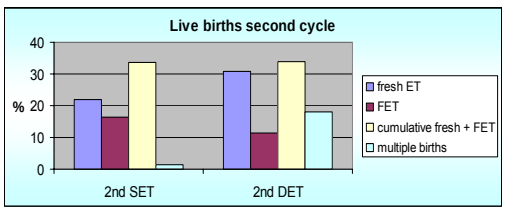
(371 women, 622 cryopreservation SETs)



Reprinted from Olivius C et al 2008 RBMonline 2008;17:676-83,

with permission from Reproductive Healthcare Ltc.





Lundin and Bergh, RBMonline 2007

Is there an optimal balance?
(In the number of oocytes retrieved)

10 oocytes !?

We don’t know!

RCT-ESHRE Task force on Mild stimulation

Which patients benefit?

Karl Nygren M.D., Ph.D.
EIM Past Chair
ICMART Chair
SQUART and TFMS member
(PCC 3, Amsterdam, 2009)

Conflict of interest

- None to declare, July 2009.

  Karl Nygren

Benefit?

- Benefit equals success ?
- Success rate equals pregnancy rate?
- No + No !

Benefit is the balance between effacay, safety, quality, cost and time.

What patients benefit, differs in different settings:

- Policy on the number of embryos/ET (SET)
- Patient characteristics (e.g. age)
- Clinic capacity
- Clinics finansial arrangements
- Re-imbursement policies
- Patient´s attitudes
- Doctor´s attitudes
- Effiacy reporting
- Safety reporting
- Quality reporting

Patient selection:

- Self selection
- Doctor´s selection

Patient self selection

- Avoidence of ”hormones”
- Natural
- Complications
- Cost
- Risk
- Previous experience

Doctor´s selection

- Matching SET
- Risk awareness, risk factors
- Cost awareness
- Patient´s individual prognosis on efficacy

Who can best decide on patient benefit?

Probably the well informed couple
(in agreement with their doctor)

So, which patients benefit?

- Younger rather than older
- High rather than low ovarian capacity
- IVF rather than ICSI
- Patients at increased risk for complications
- At clinics with a pro-SET policy
- At clinics where ”benefit” is understood
- The well informed patient

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES