eshre

SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Patient-centered fertility care

Special Interest Group Group Safety and Quality
& the Task Force Developing Countries and Infertility

10

27 June 2010
Rome, Italy

PRE-CONGRESS COURSE 10 – Table of contents

Patient-centered Fertility Care

Organised by the Special Interest Group Safety and Quality in ART and the Task Forces Mild Approaches in Assisted Reproduction and Developing Countries and Infertility

ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

ESHRE was founded in 1985 and its M**ission Statement** is to:

- promote interest in, and understanding of, reproductive science and medicine.
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform politicians and policy makers in Europe.
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance

Executive Committee 2009/2011

Chairman	Luca Gianaroli	Italy
Chairman Elect	Anna Veiga	Spain
Past Chairman	Joep Geraedts	Netherlands
	Jean François Guérin	France
	Timur Gürgan	Turkey
	Ursula Eichenlaub-Ritter	Germany
	Antonis Makrigiannakis	Greece
	Miodrag Stojkovic	Serbia
	Anne-Maria Suikkari	Finland
	Carlos Plancha	Portugal
	Françoise Shenfield	United Kingdom
	Etienne Van den Abbeel	Belgium
	Heidi Van Ranst	Belgium
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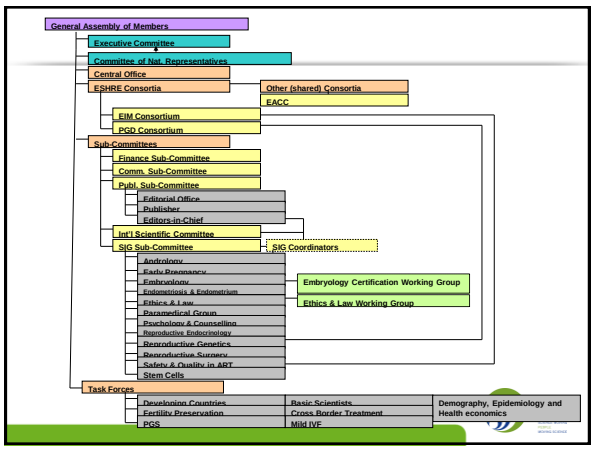

ESHRE Activities – Annual Meeting

- One of the most important events in reproductive science and medicine
- Steady increase in terms of attendance and of scientific recognition

Track record:

ESHRE 2008 – Barcelona: 7559 participants
ESHRE 2009 – Amsterdam: 8132 participants

Future meetings:

ESHRE 2010 – Rome, 27-30 June 2010
ESHRE 2011 – Stockholm, 3-6 July 2011

ESHRE Activities – Scientific Journals

Human Reproduction with impact factor 3.773

Human Reproduction Update with impact factor 7.590

Molecular Human Reproduction with impact factor 2.537

ESHRE Activities – Campus and Data Collection

- Educational Activities / Workshops
  - Meetings on dedicated topics are organised across Europe
  - Organised by the Special Interest Groups
  - Visit: www.eshre.eu under CALENDAR
- Data collection and monitoring
  - EIM data collection
  - PGD data collection
  - Cross border reproductive care survey

ESHRE Activities - Other

- Embryology Certification
- Guidelines & position papers
- News magazine “Focus on Reproduction”
- Web services:
  - RSS feeds for news in reproductive medicine / science
  - Find a member
  - ESHRE Community

ESHRE Membership (1/3)

- ESHRE represents over 5,300 members (infertility specialists, embryologists, geneticists, stem cell scientists, developmental biologists, technicians and nurses)
- Overall, the membership is distributed over 114 different countries, with 50% of members from Europe (EU). 11% come from the US, India and Australia.

ESHRE Membership (2/3)

	1 yr	3 yrs
Ordinary Member	€ 60	€ 180
Paramedical Member*	€ 30	€ 90
Student Member**	€ 30	N.A.

*Paramedical membership applies to support personnel working in a routine environment such as nurses and lab technicians.
**Student membership applies to undergraduate, graduate and medical students, residents and post-doctoral research trainees.

ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

Annual Meeting	Ordinary	€ 480	(€ 720)
	Students/Paramedicals	€ 240	(€ 360)
Workshops	All members	€150	(€ 200)

2) Reduced subscription fees to all ESHRE journals – e.g. for Human Reproduction €191 (€ 573!)

3) ESHRE monthly e-newsletter

4) News Magazine "Focus on Reproduction" (3 issues p. a.)

5) Active participation in the Society's policy-making

Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

- Andrology
- Early Pregnancy
- Embryology
- Endometriosis / Endometrium
- Ethics & Law
- Safety & Quality in ART
- Psychology & Counselling
- Reproductive Genetics
- Reproductive Surgery
- Stem Cells
- Reproductive Endocrinology

Task Forces

A task force is a unit established to work on a single defined task / activity

- Fertility Preservation in Severe Diseases
- Developing Countries and Infertility
- Cross Border Reproductive Care
- Reproduction and Society
- Basic Reproductive Science
- Fertility and Viral Diseases
- Management of Infertility Units
- PGS
- EU Tissues and Cells Directive

Annual Meeting

Rome, Italy 27 June to 30 June 2010

Pre-congress courses (27 June):

- PCC 1: Cross-border reproductive care: information and reflection
- PCC 2: From gametes to embryo: genetics and developmental biology
- PCC 3: New developments in the diagnosis and management of early pregnancy complications
- PCC 4: Basic course on environment and human male reproduction
- PCC 5: The lost art of ovulation induction
- PCC 6: Endometriosis: How new technologies may help
- PCC 7: NOTES and single access surgery
- PCC 8: Stem cells in reproductive medicine
- PCC 9: Current developments and their impact on counselling
- PCC 10: Patient-centred fertility care
- PCC 11: Fertility preservation in cancer disease
- PCC 12: ESHRE journals course for authors

Annual Meeting – Scientific Programme (1/2)

Rome, Italy 27 June to 30 June 2010

- Molecular timing in reproduction
- Rise and decline of the male
- Pluripotency
- Preventing maternal death
- Use and abuse of sperm in ART
- Live surgery
- Emerging technologies in the ART laboratory
- Debate: *Multiple natural cycle IVF versus single stimulated cycle and freezing*

Annual Meeting – Scientific Programme (2/2)

- Fertility preservation
- Congenital malformations
- ESHRE guidelines
- Data from the PGD Consortium
- European IVF Monitoring 2007
- Debate: *Selection of male/female gametes*
- Third party reproduction in the United States
- Debate: *Alternative Medicine, patients feeling in control?*
- Historical lecture: "Catholicism and human reproduction"

Certificate of attendance

1/ Please fill out the evaluation form during the campus

2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu

3/ You need to enter the results of the evaluation form online

4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website

5/ After the campus you will receive an email from ESHRE with the instructions

6/ You will have TWO WEEKS to print your certificate of attendance

Contact

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PRE-CONGRESS COURSE 10 - Programme

Patient-centered Fertility Care

Organised by the Special Interest Group Safety and Quality in ART and the Task Forces Mild Approaches in Assisted Reproduction and Developing Countries and Infertility

Course coordinators: Geeta Nargund (United Kingdom), Jan Kremer (The Netherlands) and Willem Ombelet (Belgium)

Course description: It is our aim to provide an overview of different methods and effective strategies to increase patient satisfaction with fertility care. Methods to improve our understanding of determinants of patient satisfaction will be highlighted as well as possible methods to achieve acceptable live birth rates while minimizing side effects. Strategies to increase accessibility to infertility services in developing countries will be described.

Target audience: Clinicians, psychologists, biologists, embryologists, counsellors, midwives, nurses and other paramedicals working in the field of reproductive medicine.

Scientific programme:

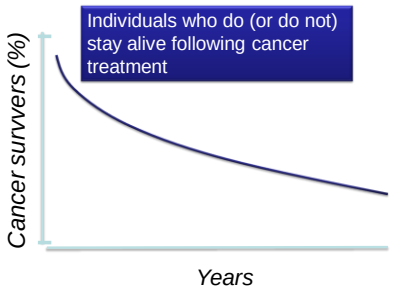
09:00 – 09:30	Why do couples drop out from infertility treatment? - **Bart Fauser (The Netherlands)**
09.30 – 09:45	Discussion
09.45 – 10:15	Mild stimulation protocols for IVF: an update - **Geeta Nargund (United Kingdom)**
10:15 – 10:30	Discussion
10:30 – 11:00	Coffee break
11:00 – 11:30	Coming soon to your clinic: patient-centered high-quality care - **Jan Kremer (The Netherlands)**
11:30 – 11:45	Discussion
11:45 – 12:15	Lifestyle factors and infertility - **Nick Macklon (United Kingdom)**
12:15 – 12:30	Discussion
12:30 – 13:30	Lunch
13:30 – 14:00	Infertility-related stress in men and women - **Jacky Boivin (United Kingdom)**
14:00 – 14:15	Discussion
14:15 – 14:45	Patient-friendly ART: the patients view **– Clare Lewis-Jones (United Kingdom)**
14:45 – 15:00	Discussion
15:00 – 15:30	Coffee break
15:30 – 16:00	Accessible and affordable infertility services in developing countries - **Willem Ombelet (Belgium)**
16:00 – 16:15	Discussion
16:15 – 16:45	IVF in developing countries: Principles, procedures and protocols **– Jonathan Van Blerkom (USA)**

16:45 – 17:00 Discussion
17:00 Conclusion

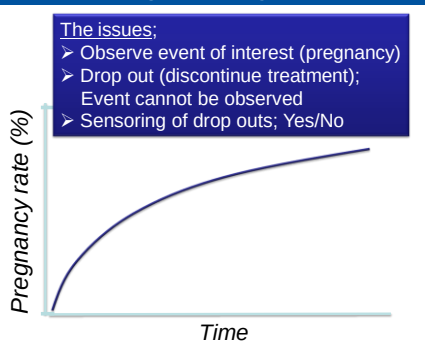
ovarian stimulation for IVF;
- drop outs

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

Life table analysis



Cumulative pregnancy rate following infertility treatment



Cumulative pregnancy rate

(proportional hazard, Kaplan Meier, live table analysis)

Drop out

Per cycle analysis

Optimistic;
assume normal pregnancy chance in drop outs

Pessimistic;
assume no pregnancy chance

Pregnancy rate (%)

Time

ORIGINAL ARTICLE

N Engl J Med 2009;360:236-43.

Cumulative Live-Birth Rates after In Vitro Fertilization

Beth A. Malizia, M.D., Michele R. Hacker, Sc.D., M.S.P.H., and Alan S. Penzias, M.D.

Optimistic = patients who did not return had same chance of pregnancy

Conservative = patients who did not return had no chance of pregnancy

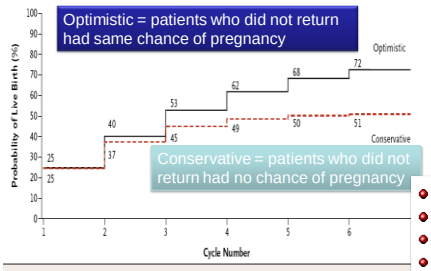


Figure 1. Kaplan–Meier Curves for Optimistic and Conservative Cumulative Live-Birth Rates among 6164 Women.

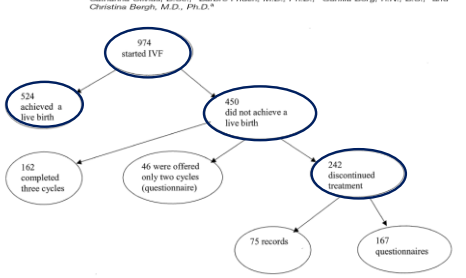
- retrospective
- uncontrolled
- 2000-2005
- 6,164 patients
- 14,248 cycles

CONTROVERSY: WHY COUPLES DISCONTINUE IVF TREATMENT

FERTILITY AND STERILITY® VOL. 82, NO. 2, FEBRUARY 2004

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

Catharina Olivius, B.Sc.,[a] Barbro Friden, M.D., Ph.D.,[b] Gunilla Borg, R.N., B.S.,[a] and Christina Bergh, M.D., Ph.D.[a]



Why discontinue IVF ? (Olivius, F&S 2004)

reasons	percentage
Psychological burder	26
Poor prognosis	25
Spontaneous pregnancy	19
Physical burden	6
Serious disease	2
Other reasons	7

Study Design:
974 started IVF,
450 no live birth,
242 discontinued (25%); questionnaire

Comments from 143 patients about care in IVF clinic

Type of comment	Example	n (%)
Emotional and stressful reaction due to infertility	Couldn't cope, need a psychologist	**25 (17%)**
Organisational problems	Poor organisation, insufficient care, never same people	**37 (26%)**
Poor ability to handle psychological distress	Doctors and nurses didn't listen, no empathy	**43 (30%)**
Lack of autonomy during treatment	Assembly line, stressful, need more information	**60 (42%)**

Olivius, FS 2004

Other psychological reasons for IVF discontinuation

Reasons	Reference
Balancing treatment and work committment	Osamangaoglu'99
Distance from clinic	Malcolm'04
Undergone agreed number of cycles	De Vries'99

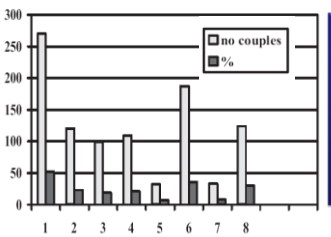
What is the most accurate estimate of pregnancy rates in IVF dropouts?

T.E.M. Verhagen[1,3], J.C.M. Dumoulin[1], J.L.H. Evers[1] and J.A. Land[1,2]

Research question	• Impact of loss to follow-up on cumulative pregnancy rates • Pregnancy rate of drop outs between no vs same probability
Study design	Retrospective, 588 couples starting IVF
Results	Cycle based CPR (3 cycles) - 63-71% as treated - 65% completed Real time CPR (9 months) - 54-59% as treated - 55% completed
Conclusions	Accurate estimate for PR in drop outs = 14%

Reasons for discontinuation of IVF treatment: a questionnaire study

M.Rajkhowa[1,3], A.Mcconnell[1] and G.E.Thomas[2]



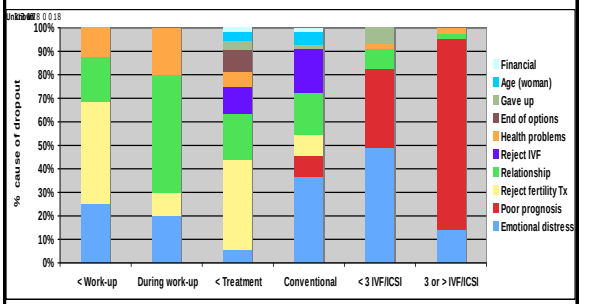
1=pregnant
2=lack of success
3=lack of NHS funds
4=personal finance
5=medical/other advice
6=psychological stress
7=discomfort
8=other

Reasons for Dropout in Infertility Treatment

U. Van den Broeck[a] L. Holvoet[a] P. Enzlin[b] E. Bakelants[a] K. Demyttenaere[c] T. D'Hooghe[a]

Drop-out reasons according to degree of impact (n=142)	
Psychological burden	6.0
Physical burden	4.5
Women's age	3.6
Relationship burden	3.4
Perceived lack of staff empathy	3.5
Alternatives for child wish	2.4
Financial burden	2.2
Negative impact on social contacts	2.1
Perceived lack of staff expertise	1.8

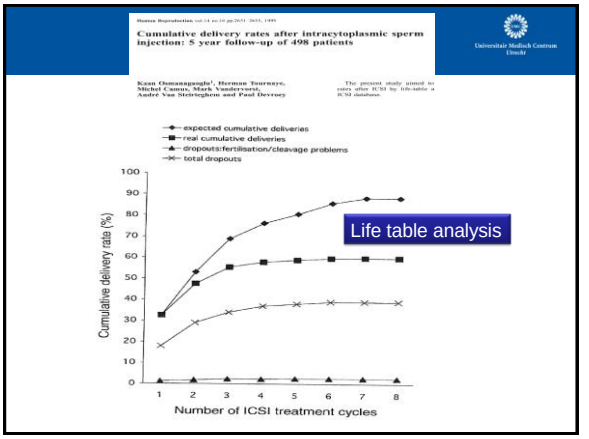
To minimise dropout need to know causes stress (when)



Brandes et al. HRU, 2009

Incidence of drop-out

Incidence	reference
25 %	Osmanagaoglu, 1999
25 %	Olivius, 2004
17 %	Verberg, 2008
18 %	Brandes, 2009



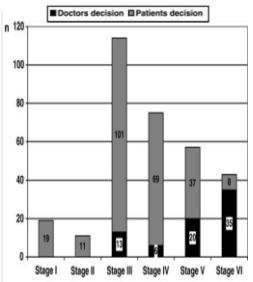
A qualitative study of women's decision-making at the end of IVF treatment

V.L.Peddie[1,3], E.van Teijlingen[2] and S.Bhattacharya[1]

Objective	Examine patients perspective of decision making
Methods	Semi-structured interviews in 25 women who decided to end treatment
Results	➢ Women experience difficulty in accepting infertility remains unresolved ➢ Felt that they started with unrealistic expectations ➢ Felt vulnerable by pressure of media and society ➢ Decision to stop offered way out of emotional distress ➢ Had to address issues they previously avoided
Conclusion	Psychological preparation of couples who decide to end IVF should improve

When and why do subfertile couples discontinue their fertility care? A longitudinal cohort study in a secondary care subfertility population

M. Brandes[1,3], J.O.M. van der Steen[1], S.B. Bokdam[1], C.J.C.M. Hamilton[1], J.P. de Bruin[1], W.L.D.M. Nelen[2], and J.A.M. Kremer[2]



Discontinue infertility work-up, or treatment (n=319)

Stages:

I = before work-up started
II = during work-up
III = after work-up
IV= during/after conventional fertility treatment
V = stopped before 3rd IVF cycle

When and why do subfertile couples discontinue their fertility care? A longitudinal cohort study in a secondary care subfertility population

M. Brandes[1,3], J.O.M. van der Steen[1], S.B. Bokdam[2], C.J.C.M. Hamilton[1], J.P. de Bruin[1], W.L.D.M. Nelen[2], and J.A.M. Kremer[2]

Reasons IVF discontinuation (n=319)	%
Emotional distress	49
Poor prognosis (doctor's refusal)	33
Relationship problems	8.8
No faith in treatment	7.0
Health problems	1.8

A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment F&S 2010

Alice D. Domar, Ph.D., Kristin Smith, Lisa Conboy, Sc.D., Marie Iannone, M.S., and Michael Alper, M.D.

Objective	Why insured patients drop out of IVF in the USA ?
Design	Women < 40 yrs, private clinic, insured, not pregnant, who did not return
Results	**39% of termination due to stress** - toll on couples relationship - too anxious or depressed **Suggestion for patient support** - written information on how to deal with psychological stress - easy access to psychologist or social worker
Conclusions	US patients similar reasons for terminating IVF compared to Europe and Australia

Questions concerning drop outs

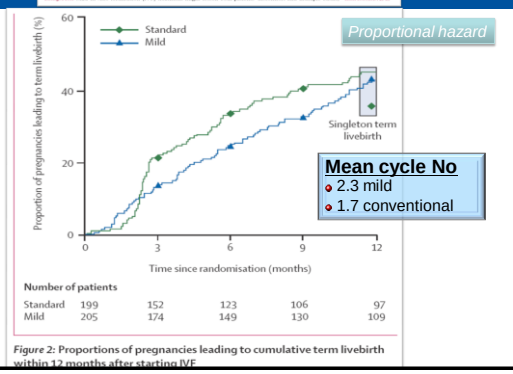
- Frequency of discontinuation of treatment in other areas in medicine?
- Balance IVF outcomes per cycle versus per treatment strategy paradigm
- Balance burden of treatment versus efficacy
- Introduce support by social worker / psychologist
- Implement concept of hostmanship in team

IVF study design issues

How to define success	Conventional context	Current context
Measure of success	Pregnancy rate	Healthy babies
Relevant denominator	Per cycle	Per started treatment (given period of time)
Success context	Isolated focus on success	Holistic approach involving success in relation to discomfort, stress, complications and cost

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

Lancet 2007



Mean cycle No
- 2.3 mild
- 1.7 conventional

Figure 2: Proportions of pregnancies leading to cumulative term livebirth within 12 months after starting IVF

Cycle specific characteristics

	Mild treatment (n=444)	Standard treatment (n=325)	p
Duration of ovarian stimulation (days)	8·3 (2·2)	11·5 (3)	<0·0001*
Duration of injections (days)	8·5 (2·7)	25·3 (6·8)	<0·0001*
Total dose of follicle stimulating hormone (IU)	1307 (529)	1922 (758)	<0·0001*
Cancellation of started cycle	80 (18·0%)	27 (8·3%)	<0·0001†
Number of oocytes per retrieval	6·9 (4·6)	8·5 (4·3)	<0·0001*
‡Number of embryos per retrieval	2·8 (2·7)	3·8 (2·9)	0·0002*
Number of cryopreserved embryos per fresh emby transfer cycle	0·8 (1·3)	0·6 (1·0)	0·04*
Continuing pregnancy per started cycle (fresh embryos)	78 (17·6%)	93 (28·6%)	<0·0001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1·4%)	4 (1·2%)	0·8†
Term livebirth per started cycle (fresh embryos)	70 (15·8%)	78 (24·0%)	0·003†
Term livebirth per started cycle (cryopreserved embryos)	49 (11·1%)	3 (0·9%)	0·8†
§Ovarian hyperstimulation syndrome	6 (1·4%)	12 (3·7%)	0·04†

Values are mean (SD) or number (%) of cycles. *t test for difference or †Pearson χ^2 test for difference. ‡Embryos suitable for embryo transfer. §Mild, moderate, and severe ovarian hyperstimulation syndrome.

Table 2: Cycle-specific characteristics of IVF cycles finished within 1 year

Patient distress and IVF
- conclusions own studies -

Conclusions:

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

Little perceived need for counselling
No difference 3 counselling sessions

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

More physical and depressive symptoms during down regulation in conventional IVF

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

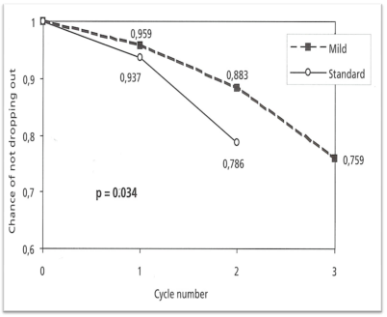
Failed IVF results in less depressive symptoms after mild IVF

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

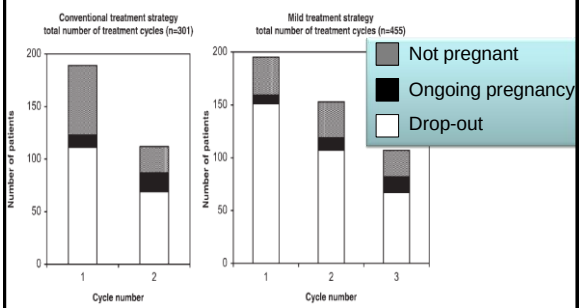
Complex relationship between initial psychol. parameters and IVF outcomes

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

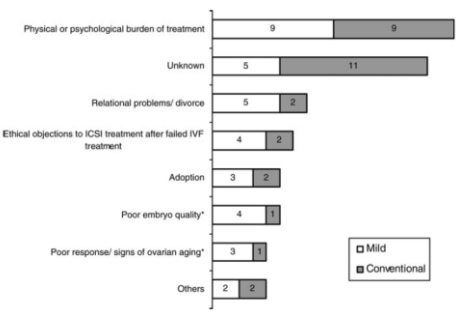
M.F.G. Verberg[1,4], M.J.C. Eijkemans[1,2], E.M.E.W. Heijnen[1], F.J. Broekmans[1], C. de Klerk[3], B.C.J.M. Fauser[1] and N.S. Macklon[1]



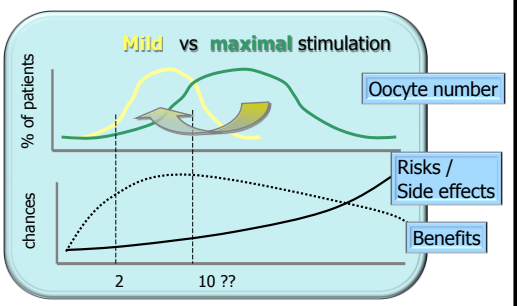
Outcome per IVF treatment cycle according to treatment strategy (Verberg HR'08)



Causes for drop-out from IVF (Verberg HR'08)

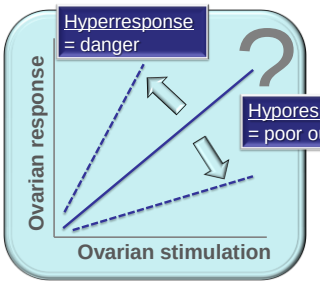


Optimal oocyte number for IVF
- how to balance risks vs benefits -



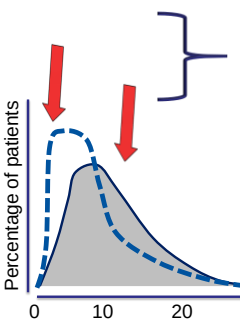
(adapted from Nyboe Andersen)

The need for more patient tailored ovarian stimulation for IVF



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

Transition from mild stimulation to mild response



- reduced response
- more homogeneous response

But
- higher cancellation rate
- some too high response

Individualized mild stimulation approaches

Drop outs in IVF
- summary

Definition	Event of interest cannot be observed
Frequency	Up to 30%
Statistical handling	Assume no, normal, or intermediate chance of pregnancy
Causes	• Stress, marital difficulty, family, work • Discomfort, side effects, complications • Poor prognosis, counselling by doctor • Money

Mild stimulation protocols for IVF: An update

Geeta Nargund FRCOG

Lead Consultant,Department of Reproductive Medicine
St George's Hospital, London

President
International Society for Mild Approaches in Assisted Reproduction (ISMAAR) –Registered Charity 1123677
www.ismaar.org

Learning Objectives

- To outline the terminology for mild stimulation protocols for IVF
- To discuss different protocols for mild stimulation
- To discuss basic physiology of follicular maturation
- To present scientific evidence for Natural & Mild IVF
- To outline the problems with conventional IVF
- To discuss the benefits of Mild/Natural IVF
- To evaluate monitoring methods for Mild/Natural IVF
- To highlight safety & cost-effectiveness of mild approaches in ART

Mild stimulation strategies for IVF

- Natural cycle
- Modified natural cycle
- Mild
  -Clomid + hCG
  -Clomid +FSH/HMG ± antagonist +hCG
  -Day 5 start FSH+antagonist+hCG
  -FSH + 200iu hCG +antagonist +hCG
- Low dose hCG/agonist for trigger (↓ OHSS)
- Natural cycle with IVM

Aims of IVF stimulation protocols

- Cost
- Visits
- Monitoring
- Side effects & Risks
- Complications (OHSS)
- Discomfort
- Disturbance to everyday life
- Stress
- Long-term effects & risks

Increase simplicity ,affordability ,Safety ,Comfort and Success

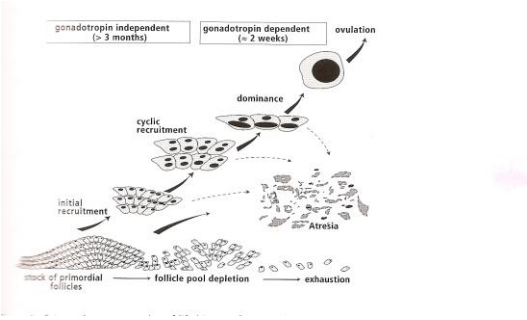
Conventional stimulation (downregulation & high stimulation) approaches:

- 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
- Concrn about increase in chromosome abnormalities in oocytes & embryos
- Adverse endometrial conditions
- Long-term health consequences
- High drop-out rates (psychological burden)

Mild IVF :Why Now?

- **Clinical availability of antagonists**
- **Advances in Endocrinology**
- **Latest Ultrasound Technology**
- **Improved Embryology**
- **Elective Single Embryo Transfer**
- **Fertile women having stimulation for ICSI (male factor only)**
- **Safety & comfort of oocyte donors**
- **Concerns about embryo & endometrial quality**
- ***"Cost"* of conventional IVF**
- **Cancer survivors requiring ART**
- **Increased demand in public health service**

Life history of ovarian follicles



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 Reprod: 1-4,September 2007

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

ISMAAR 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*

Modified Natural cycle & Mild IVF – Protocols

Modified natural cycle IVF
- Indomethacin 50mg tds
- Antagonist ± HMG/FSH
- hCG 5k or 10k
- Flushing or no flushing
- Luteal support –hCG or progesterone

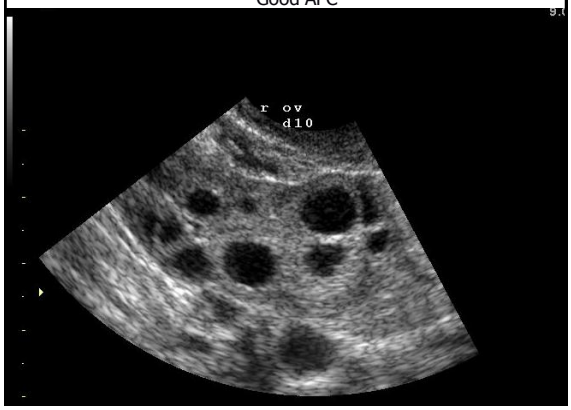
Mild IVF
- Clomiphene alone +hCG
- Day 2 Clomiphene + HMG or rFSH+hCG or Gn RH agonist
- Day 5 FSH + antagonist
- FSH +Low dose hCG+antagonist
- Luteal support hCG or Progesterone

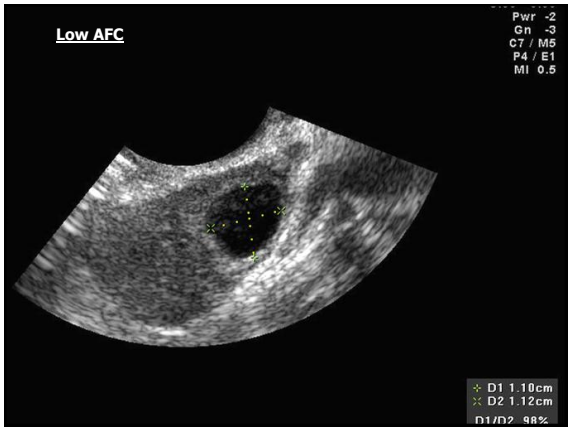
Ultrasound alone is effective for monitoring :Cochrane review 2008

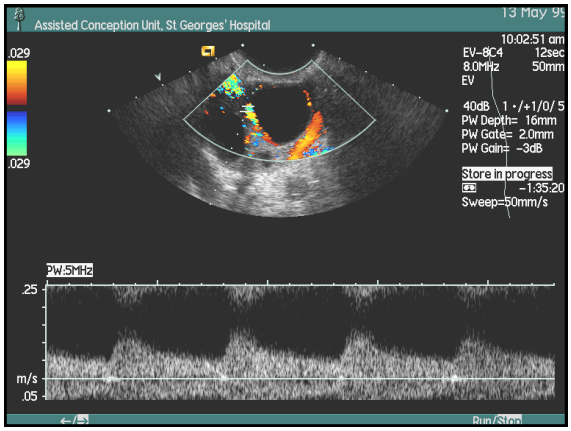
Pre-IVF assessment

- Ovarian reserve assessment (AFC)
- Identifying risks for over-response (PCO, ↓BMI)
- Monitoring a spontaneous cycle & its length (for natural cycle IVF)
- Planning mild IVF
- Optimisation of hCG dose
- Availability of facility and expertise

Good AFC




Low AFC
Pwr -2
Gn -3
C7 / M5
P4 / E1
MI 0.5
D1 1.10cm
D2 1.12cm


Assisted Conception Unit, St Georges' Hospital
13 May 95
10:02:51 am
EV-8C4 12sec
8.0MHz 50mm
EV
40dB 1 •/+1/0/ 5
PW Depth= 16mm
PW Gate= 2.0mm
PW Gain= -3dB
Store in progress
-1:35:20
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PW.5MHz
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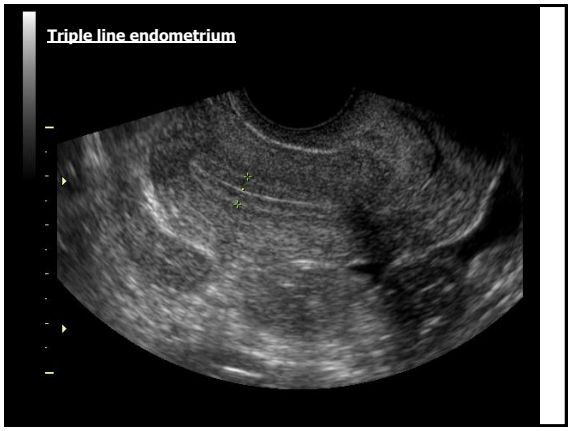

Triple line endometrium

AMH & inhibin B in relation to follicle diameter in small antral follicles

- AMH & inhibin B in follicles 3-12mm
- AMH 1124±158ng/ml in 3mm follicles
- AMH 392±98ng/ml in 12mm follicles (P<0.0005)
- inhibin B 57±10ng/ml in 3mm follicles
- Inhibin B 142±10ng/ml in 12 mm follicles
- Intrafollicular AMH progressively ↓ with ↑ follicle diameter
- Intrafollicular inhibin B ↑ with ↑ follicle diameter
- AMH,inhibin B are important for follicle selection

Andersen A, Schmidt KT,Kristensen SG et al: Hum Reprod March 2010

Prediction of high ovarian response: AMH vs small AFC (2-6 mm)

- Prospective study
- 159 patients
- Basal AMH & small AFC measured
- AMH & small AFC have same predictive value for high response
- Sensitivity & specificity -89% & 92% (small AFC)
- Sensitivity & specificity – 93% & 78% (AMH)

Aflatoonian A, Oskouian H, Ahmadi S and Oskouian L:
J Assist Reprod Genet 2009 26 (6); 319-25

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/Modified natural cycle IVF:

Patient selection - Current practice

- Young women with blocked tubes
- In cancer patients & those with family H/O cancer
- Poor responders
- Older women
- Failed implantation
- For those who want to avoid drugs

Monitoring & Optimisation of cycles

- Normal cycle length
- Follicular-Endometrial synchronisation
- Timing egg collection
- Luteal support

Medication used to prevent LH surge/ ovulation in modified natural cycles

- Indomethacin (50mg TDS)
- Antagonist (2-3 days)
- Indomethacin + Antagonist

Natural Cycle IVF

Cumulative Conception & Live birth Rates:
Nargund et al Human Reprod 2001
-181 cycles
82% had eggs collected with 70% fertilisation rate
24%/ET pregnancies : 16.7%/ET LBR
-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

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

Semi-Natural Cycle IVF

For Poor responders/Low ovarian reserve/Failed implantation

1. Castlo-Branco,Frydman (France) 2004
133 cycles/16.6% pregnancy/oocyte collection

2. Elizur S 2005 -540 cycles-Agonist/Antagonist/Natural IVF
10.6%/6.75%/10.2% pregnancy/cycle

Semi-Natural Cycle is a feasible alternative

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%

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

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
- Severe endometriosis

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

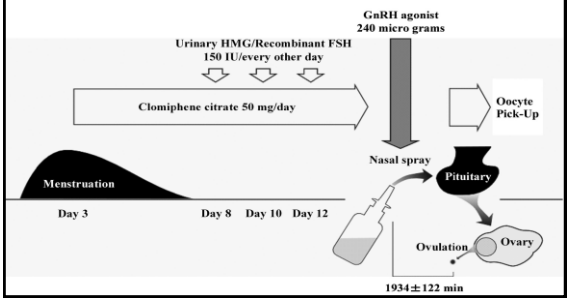
Despite cancellations & lower success rates per cycle, women prefer:

- 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

Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study

Teramoto S & Kato O:RBM Online 2007



Teramoto & Kato: RBM Online 2007

Age	27-29	30-32	33-35	36-38	39-41	42-44	45-47	Total
cycles	107	3335	6286	8465	10688	9732	4767	44345
ETs	499	1460	2671	3279	3447	2522	1011	14889
LBR/ Cycle (%)	14.6	13.5	10.5	7.4	3.1	1.0	0.1	5.2

Characteristics of randomized controlled trials involving ovarian stimulation with clomiphene citrate for IVF

Study	Inclusion criteria	Study protocol	Control stimulation protocol	Main outcome
MacDougall et al. (1994)	Patients 38 years with .1 year of infertility, spontaneous ovulatory regular cycles and normal semen analysis	CC 100 mg, from Days 2–6, hCG when the leading follicle was 17 mm (n ¼ 16)	Natural cycle IVF with hCG when the leading follicle was 17 mm (n ¼ 14)	Cancellation rate 0 versus 71%. Ongoing pregnancy rate 13 versus 0% (NS)
Dhont et al. (1995)	Patients with no previous IVF attempts. Treatment included IVF-ET, ZIFT and GIFT	OAC pretreatment, CC 100 mg for 5 Days and (150) subsequent HMG (n ¼ 151)	OAC pretreatment, long acting GnRH agonist and (300 IU) HMG (n ¼ 152)	Cancellation rate 20.5 versus 2.6%. Ongoing pregnancy rate 24.5 versus 36.8% (P ¼ 0.02)
Ingerslev et al. (2001)	Couples with no previous IVF attempts under 35 years with ICSI indication, tubal factor or idiopathic infertility	CC 100 mg, from Days 3–7 and hCG when the leading follicle was 20 mm (68 patients, 111 cycles)	Natural cycle IVF with hCG when the leading follicle was 17 mm (64 patients, 114 cycles)	Cycles resulting in embryo transfer 53.2 versus 25.4%. Ongoing pregnancy rate (per cycle) 18.0versus 3.5% (P , 0.001)
Fiedler et al. (2001) (abstract)	Random selected normal cycling women	100 mg CC CD 5–9, from Day 9 additional 150 IU HMG or FSH. GnRH antagonist from Day 10 (n ¼ 295)	100 mg CC CD 5–9, from Day 9 additional 150 IU HMG or FSH (n ¼ 291)	Ongoing pregnancy rate 23 versus 21% (NS)
Weigert et al. (2002)	Women with no previous IVF cycles, between 20 and 39 years, with normal ovulatory cycles with tubal, male factor or unexplained infertility	OAC pretreatment. CC 100 mg for 5 days in combination with 225 IU of rFSH and 75 IU of rLH on alternate days (n ¼ 154)	Long GnRH suppression and 150 IU rFSH (n ¼ 140)	Ongoing pregnancy rate 35 versus 29% (NS)
Engel et al. (2003)	Healthy female partners of infertile couples, between 18 and 39 years, with regular cycle length. No more than three previous IVF cycles or basal FSH .10 IU/l	Single dose GnRH antagonist protocol. CC 100 mg CD 2–6 of 3–7, CD 6 start 150 IU rFSH (n ¼ 5)	Single dose GnRH antagonist protocol. CC 100 mg CD 2–6 of 3–7, CD 6 start 150 IU HMG (n ¼ 5)	Live birth rate 40 versus 20% (NS)
Lin et al. (2006)	Couples with male-factor infertility who were about to undergo their first ICSI cycle	CC/HMG. Cetrorelix protocol (n ¼ 60)	buserelin long protocol (n ¼ 60)	Pregnancy rate 41.7 versus 40% (NS)

The number of included cycles is equal to the number of included patients unless stated otherwise. Outcomes were significantly different unless stated otherwise.

A Simplified COS protocol for IVF in low resource setting

- Clomiphene 100mg/day day 3-7
- The first ovarian sonography at cycle day 10-12 depending on cycle length
- No antagonists are used
- A single urinary LH at the time when the patient is going to trigger ovulation, that is when the leading follicle is ≥17 mm.
- If urinary LH is positive the retrieval is advanced one day.
- A single dose of hCG 5000 iu is used to trigger ovulation.
- Oocyte retrieval is done irrespective of follicle number.
- No luteal support is given

Andersen et al –Manuscript in preparation

Characteristics of randomized controlled trials involving mild 'late start' ovarian stimulation for IVF treatment.

Study	Inclusion criteria	Study protocol	Control stimulation protocol	Main outcome
De Jong et al. (2000)	Normo-ovulatory patients with a regular indication for IVF	From CD 5 ovarian stimulation with 100 IU/day FSH. GnRH antagonist from CD 8 or from leading foll 13 mm. No luteal support was provided (n ¼ 8)	From CD 5 ovarian stimulation with 150 IU/day FSH. GnRH antagonist from CD 8 or from leading foll 13 mm. No luteal support was provided (n ¼ 7)	Multiple follicle development 63 versus 100%. Ongoing pregnancy rate 25 versus 14% (NS)
Hohmann et al. (2003)	Normo-ovulatory patients with a regular indication for IVF (or IVF/ICSI)	Fixed FSH doses 150 IU/day from CD 5, GnRH antagonist from leading foll 14 mm (n ¼ 45)	1. Fixed FSH doses 150 IU/day from CD 2, GnRH antagonist from leading foll 14 mm (n ¼ 48). 2: Long GnRH agonist protocol, fixed FSH doses after 2 weeks 150 IU/day (n ¼ 49)	Ongoing pregnancy rate 16 versus 17% (1.) versus 18% (2.) (NS)
Heijnen et al. (2007)	Regular cycling patients, below 38 years, BMI 19–29	Fixed FSH doses 150 IU/day from CD 5, GnRH antagonist from leading foll 14 mm. Combined with single embryo transfer (205 patients, 444 cycles)	Long GnRH agonist protocol, fixed FSH doses after 2 weeks 150 IU/day (199 patients, 325 cycles)	Ongoing pregnancy rate per year of treatment 47 versus 51% (NS)
Baart et al. (2007)	Regular cycling patients, below 38 years, BMI 19–29. Sperm count .5 million/ml. First cycles	Fixed FSH doses 150 IU/day from CD 5, GnRH antagonist from leading foll 14 mm (n ¼ 55)	Long GnRH agonist protocol, fixed FSH doses after 2 weeks 225 IU/day (n ¼ 40)	Proportionally less chromosomal abnormal embryos were obtained after mild ovarian stimulation

The number of included cycles is equal to the number of included patients unless stated otherwise. Outcomes were significantly different unless stated otherwise.

Mild Vs Standard Strategy
Heijnen et al: Lancet 2007

Mild Strategy	Standard Strategy
• 444 cycles	• 325 cycles
• SET	• DET
• Term live birth rate 43.4%	• Term live birth rate 44.7%
• OHSS -1.4%	• OHSS – 3.7%
• Mean cycle -2.3	• Mean cycle – 1.7
D5 150iu FSH +antagonist	*Long protocol+225FSH*

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:

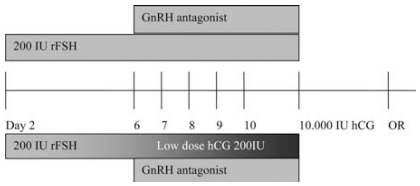
Mild+ SET Vs Std +DET (205 cycles Vs 199 cycles)

- Over 1 year (4 Mild vs 3 Std cycles)
- Cost of IVF - €8337 Vs 10,745
- 6 vs 16 preterm livebirths (<37weeks)
- Obs/postnatal cost/preg -€1947 vs 4136
- Incremental cost-effectiveness ratio/extra pregnancy-Term livebirth €185k

Polinder et al: Human Reprod 2007

Can 200IU hCG replace FSH in IVF cycles?

Blockeel,De Vos & Verpoest et al:HR Oct 2009



Can 200 IU hCG replace FSH in IVF Cycles?

Blockeel,De Vos,Verpoest et al HR 2009

rFSH Group (35)

- No with +ve hCG -19
- Positive hCG /cycle- 55%
- Positive hCG/ET-66%
- Live birth/cycle-29%
- Live birth/retrieval-31%
- Live birth/ET -35%

Low-dose hCG (35)

- No with +ve hCG -17
- Positive hCG/cycle-49%
- Positive hCG/ET-63%
- Live birth/cycle-37%
- Live birth/Retrieval-45%
- Live birth/ET-48%

Low-dose hCG is useful in the prevention of OHSS

Nargund G et al RBM Online 2007

- Women at risk of severe OHSS (PCO/PCOS)
- High ovarian volume & more than 40 follicles
- High vascularity & serum E2 levels
- Low-dose hCG at 2500 iu may be useful in preventing OHSS
- Low-dose hCG does not seem to adversely affect the pregnancy rate of IVF cycles
- The current minimum dose of hCG could be reduced from 5000 iu to 2500 iu
- Further large randomised studies are required

Conclusions

- Minimal effective dose of stimulation based on BMI, age & ovarian reserve to be used in the first cycle
- Options regarding no/mild stimulation to be offered as appropriate
- Counselling regarding safety ,comfort & success rates & closure essential
- Mild stimulation combined with eSET can help to reduce risks, cost and to increase safety and accessibility of ART
- Natural/Modified Natural cycle are useful in women with H/O poor ovarian response, failed implantation & those at cancer risk
- Mild IVF with oral compounds ± minimal amounts of gonadotrophins is useful in low resource settings
- Further prospective randomised studies are needed

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UMC St Radboud

Coming soon to your clinic: Patient Centered ART

Prof. dr. Jan A.M. Kremer, gynaecologist
Head of the IVF centre Nijmegen

Radboud University Medical Centre Nijmegen

Rome, June 27th, 2010

UMC St Radboud

Learning objectives

- Know the definition of patient centeredness
- Know the different dimensions of patient centeredness
- Learn more about the relationship between EBM and PCM
- Learn how to measure patient centeredness
- Know the possibilities of web 2.0 tools to facilitate patient centeredness

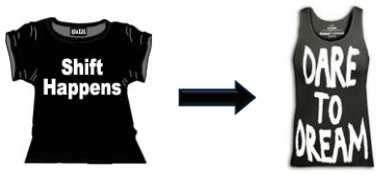
UMC St Radboud

Matrix analysis by patients (2001)

	POLICY	ORGANIZATION	PEOPLE
TECHNIQUE	Goals	Tasks	Expertness
	More attention patients needs	*Shorter lines*	*More social skills*
POLITICS	Influence	Decisions	Autonomy
	Better tuning	*More clearness*	*Empowerment patient*
CULTURE	Climate	Collaboration	Attitude
	Safer atmosphere	*Better collaboration*	*More compassion*

UMC St Radboud

From paradigm shift tot dream



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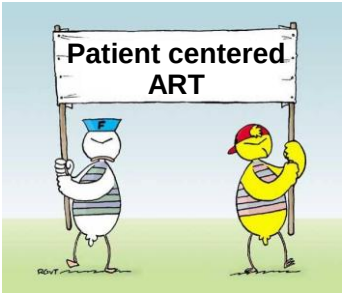

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Is patient centered ART the same as patient friendly ART?

- Patient-friendly ART is a wrong term; do not use it
  - *False attractiveness*: too positive, ART and infertility is not friendly
  - *No clear definition*: could be used for any less invasive form of ART
  - *Commercial incentives*: can be used to prevent drop-outs and to increase the turnover of cycles and medication
- "Patient-centered ART" is much better!

UMC St Radboud

What is patient centered ART?

More than just being nice to patients

Patient centeredness ≠ patient satisfaction

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What is patient centeredness?

- Focus on patient's experiences and needs
- Institute of Medicine, 2001:

  Being respectful of (and responsive to) individual patient preferences, needs and values; and ensuring that patient values guide all clinical decisions.

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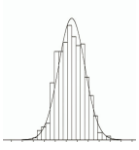
Dimensions of quality of care

1. Safety
2. Effectiveness
3. Timeliness
4. Efficiency
5. Equity of access
6. **Patient centeredness**



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Dimensions of patient centeredness

1. Access to care
2. Respect for patient's values, preferences, needs
3. Coordination and integration of care
4. Information, communication and education
5. Physical comfort
6. Emotional support and alleviation of fear and anxiety
7. Involvement of partner, family and friends
8. Transition and continuity

picker INSTITUTE *through the patient's eyes*

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Human Reproduction Update Advance Access published March 11, 2010
Human Reproduction Update, Vol.00, No.0 pp. 1–21, 2010
doi:10.1093/humupd/dmq004

human reproduction update

The patients' perspective on fertility care: a systematic review

E.A.F. Dancet [1,2,3], W.L.D.M. Nelen [2], W. Sermeus [3], L. De Leeuw [3], J.A.M. Kremer [2], and T.M. D'Hooghe [1,*]

[1]Leuven University Hospital, Leuven University Fertility Centre, Herestraat 49, 3000 Leuven, Belgium [2]Department of Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands [3]Catholic University Leuven, Centre for Health Services & Nursing Research, Kapucijnenvoer 35, 3000 Leuven, Belgium

*Correspondence address. E-mail: thomas.dhooghe@uzleuven.be

Submitted on September 21, 2009; resubmitted on December 21, 2009; accepted on January 28, 2010

CONCLUSIONS: Fertility patients have 'human needs' besides their need for medical care.

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Patient Centered Medicine
versus
Evidence based Medicine

- Two popular and relevant paradigms in medicine
- They focus on different aspects of medical care
  - **EBM**: positivistic biomedical perspective
  - **PCM**: humanistic bio-psychosocial perspective

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Is EBM patient-centered?

- Yes, at the first glance, it offers patients high quality care
- No, EBM is disease-oriented and not patient-oriented:
  - In RCT's patient characteristics are often seen as disturbing factors
  - Clinics are filled with patients who are not eligible for inclusion
  - EBM is about groups and not about individuals
  - Does not focus on the unique patient in your clinic with her own needs, expectations and characteristics

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Is PCM evidence-based?

- PCM is not firmly rooted in empirical evidence, because it is a fuzzy global concept:
  - Different connotations for different people
  - Core-elements are clear, but the periphery is vague
  - It is a container-concept
  - It is difficult to measure

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Bridging the gap is the challenge

EBM

PCM

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How to measure patient centeredness?

- Not easy, because of the fuzzy concept
- Focus groups, interviews, qualitative studies (e.g. storytellers) and questionnaires
- Use standardized and validated tests, if available (scientific use, benchmarking)
- Measure experiences and not satisfaction
- Focus on the eight dimensions of PCM

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1. How to measure access to care

- Evaluation of waiting time for the first visit after referral
- Evaluation of waiting time for ovum pickup

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2. How to measure respect for patient's values and needs

- For instance by questionnaires based on qualitative focus groups

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3. How to measure coordination

Subfertile couples' negative experiences with intrauterine insemination care

Esther C. Haagen, M.D.,[a,b] Rosella P. Hermens, Ph.D.,[b] Willianne L. Nelen, Ph.D.,[a,b] Didi D. Braat, Ph.D.,[a] Jan A. Kremer, Ph.D.,[a] and Richard P. Grol, Ph.D.[b]

[a] Department of Obstetrics and Gynecology, and [b] Centre for Quality of Care Research, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Objective: To identify subfertile couples' experiences with specific aspects of intrauterine insemination (IUI) care and to determine which patient and hospital characteristics affect their experiences.
Design: Cross-sectional survey with written questionnaires.
Setting: One large tertiary hospital and nine medium-sized hospitals, including both teaching and nonteaching centers, in the southeast of the Netherlands.
Patient(s): One thousand seventy-nine subfertile couples who underwent IUI treatment between April 2000 and August 2002.
Result(s): The response rate was 71%. Many subfertile couples have had negative experiences with IUI care, particularly regarding the doctor's attitude and coordination of care. Among several patient and hospital characteristics that significantly predicted these negative experiences, the main predictors were no ongoing pregnancy and high education level.
Conclusion(s): From the perspective of subfertile couples, several aspects of IUI care are in serious need of improvement, particularly care aspects regarding the doctor's attitude and coordination of care. These findings are an important incentive for developing tailored interventions that address the reported deficits in IUI care to meet subfertile couples' needs better. (Fertil Steril® 2008;89:809–16. ©2008 by American Society for Reproduc-

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4. How to measure information, communication and education

- Measure guideline based indicators on information provision

Variation in subfertility care measured by guideline-based performance indicators

S.M. Mourad[1,2], W.L.D.M. Nelen[1], R.P.M.G. Hermens[3], L.F. Banesi[3], D.D.M. Braat[1], G.A. Zielhuis[4], R.P.T.M. Grol[3] and J.A.M. Kremer[1,3]

- Measure the experienced and actual knowledge of patients

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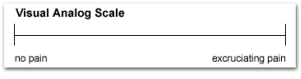
5. How to measure physical comfort?

- Pain scores on visual analog scales (VAS) after the ovum pickup



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6. How to measure emotional support and alleviation of fear?

- Measure experiences of patients by fine-tuned questionnaires
- Standardized questionnaires
  - State and Trait Anxiety Inventory' (STAI), *Spielberger 1983*
  - Beck Depression Index (BDI) *Beck 1997*

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Integrated methods to measure patient centeredness

- CAHPS (Consumer Assessment of Healthcare Providers and Systems), AHRQ *www.cahps.ahrq.gov*
- CQ index (Consumer Quality Index), NIVEL http://www.nivel.nl/cqi

cahps® Surveys and Tools To Advance Patient-Centered Care

nivel

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Group interviews with patients

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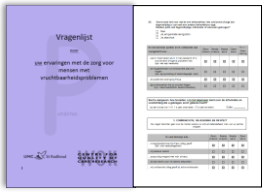
Next step: questionnaire



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Feedback to the clinics

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Patient Centeredness Europe (PC Europe)

Thomas D'Hooghe
&
Eline Dancet
Leuven

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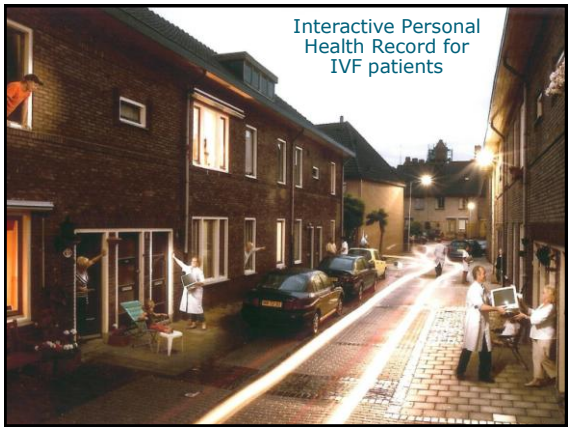
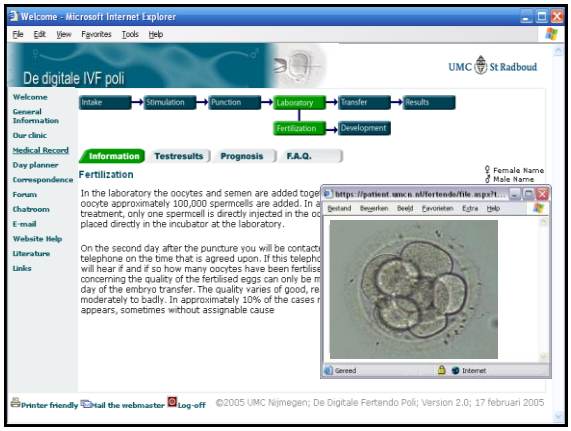
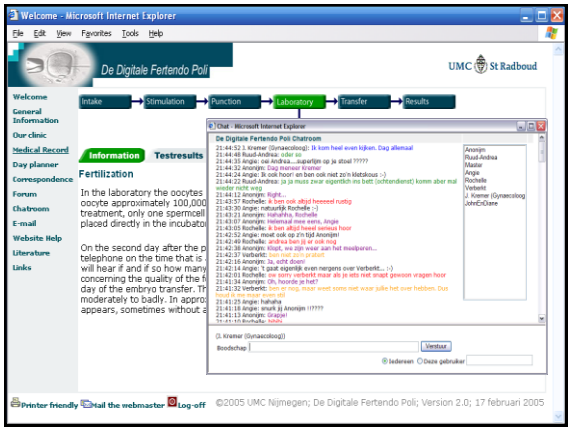
Examples of patient centered PhD projects in Nijmegen

- Shared decision making in SET or DET *(A. v. Peperstraten)*
- Implementation of clinical guidelines via patients *(S.Mourad)*
- Stress reduction by online cognitive therapy *(J. Dapperen)*
- Patient participation in guidelines by wiki's *(E. den Breejen)*
- Patient participation in leaflets by wiki's *(T. van de Belt)*
- Evaluation of patient centered Fertility community *(A. Aarts)*
- Measuring patient centeredness, CQ NL *(I. van Empel)*
- Measuring patient centeredness, PC Europe *(E. Dancet)*
- Interactive Personal Health Record *(W. Tuil)*






Welcome - Microsoft Internet Explorer
De Digitale Fertendo Poli
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Stimulation
Punction
Laboratory
Transfer
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Information
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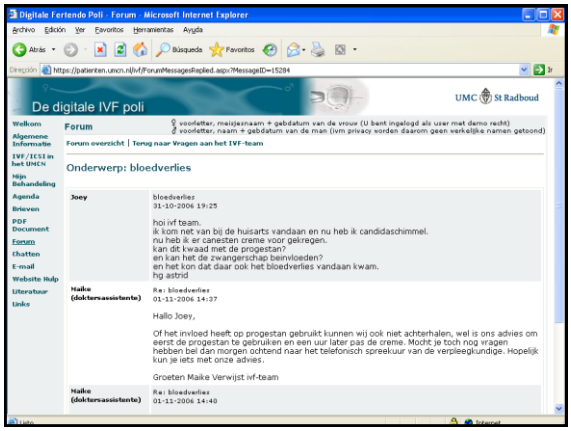
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Forum
Onderwerp: bloedverlies


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Coming soon to your clinic:
Patient Centered ART

UNIVERSITY OF Southampton
School of Medicine

Lifestyle factors and infertility

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

UNIVERSITY OF Southampton
School of Medicine

Disclosures

- I have received research funding and speaker and consultancy fees from:
- Schering Plough, MSD, Merck Serono, Ferring, Anecova

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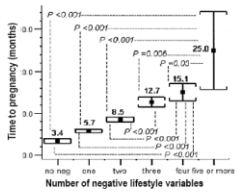
Learning Objectives

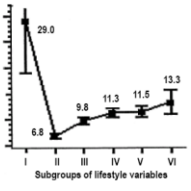
To understand:

- How does lifestyle impact on fertility?
- How does lifestyle impact the embryo?
- What can we do about it?

Negative lifestyle and fertility

(Hassan and Killick Fertility and Sterility 81:384, 2004)





Negative factors include:

1. Women's smoking >15 cigarettes/day
2. Men's smoking >15 cigarettes/day
3. Men's alcohol >20 units/week
4. Women's coffee/tea intake>7 cups/day
5. Women's weight >70 kg
6. Social deprivation score >60
7. Women's age >35 years, and/or partners' age >45 years at the time of discontinuing contraception

Women's BMI in kg/m2 were:

(I) 19
(II) 19–24
(III) 25–29
(IV) 30–34
(V) 35–39
(VI) 39

Your patient…

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- 35 years old
- Gravida 0

- PCOS
- Body mass index: 37
- Smokes
- Not taking folate supplements

Impact of obesity of clinical, hormonal and metabolic features of PCOS

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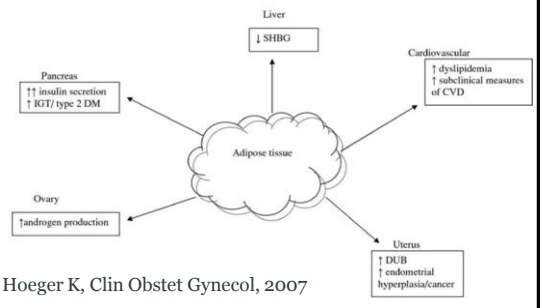

Hoeger K, Clin Obstet Gynecol, 2007

Endocrine Impact of Obesity

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- Obesity associated with increased insulin resistance
- High serum insulin may drive increased androgen production
- Insulin resistance associated with suppression of SHBG

Women with PCOS and obesity have higher T4 than PCOS alone

Peripubertal obesity associated with 2 fold increase in T4 levels

Hoeger K, Clin Obstet Gynecol, 2007

Obesity and reproduction – bad synergies

Prior to pregnancy

Increases length of time to pregnancy, menstrual disorders, more drugs needed

Early pregnancy

Miscarriage, fetal anomalies

During pregnancy

Increased gestational diabetes, high blood pressure, PET, DVT, instrumental and operative delivery

Postpartum

Haemorrhage, infection, DVT

After pregnancy

Increases diabetes mellitus, high blood pressure, endometrial cancer, cardiovascular disease, musculoskeletal problems

Human Reproduction Update, Vol.12, No.6 pp. 673–683, 2006
Advance Access publication August 4, 2006
doi:10.1093/humupd/dml056

A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome

C.M.Boomsma[1,7], M.J.C.Eijkemans[2], E.G.Hughes[3], G.H.A.Visser[4], B.C.J.M.Fauser[5] and N.S.Macklon[6]

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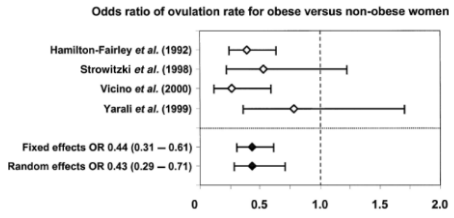
Meta-analysis: 720 women with PCOS vs 4505 controls

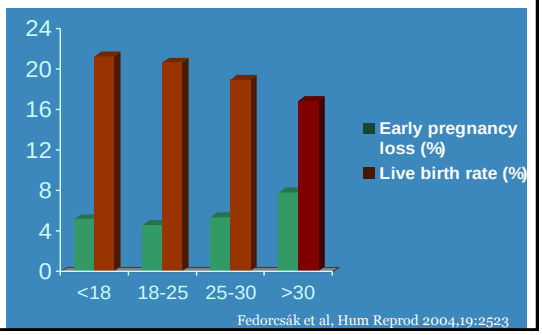
	OR	95% CI
Gestational Diabetes:	2.94	1.70-5.08
Pregnancy induced hypertension:	3.67	1.98-6.81
pre-eclampsia	3.47	1.95-6.17
Pre-term birth	1.75	1.16-2.62
Peri-natal mortality	3.07	1.03-9.21

Ovulatory infertility and Obesity



Mulders et al. Hum Reprod Update 2003

What is the impact of obesity on IVF/ICSI outcomes ?



Fedorcsák et al, Hum Reprod 2004,19:2523

Smoking and infertility

Smoking and infertility

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Approximately 30% of reproductive age women and 35% of reproductive age men in the United States smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent but are not generally appreciated. (Fertil Steril® 2006;86(Suppl 4):S172–7. ©2006 by American Society for Reproductive Medicine.)

'13% of infertility is due to smoking'

Smoking and Infertility

Human Reproduction Vol.20, No.7 pp. 1867–1875, 2005 doi:10.1093/humrep/deh498
Advance Access publication April 7, 2005

Effects of subfertility cause, smoking and body weight on the success rate of IVF

A.M.E.Lintsen[1,7], P.C.M.Pasker-de Jong[2], E.J.de Boer[3], C.W.Burger[4], C.A.M.Jansen[5], D.D.M.Braat[1] and F.E.van Leeuwen[6] on behalf of the OMEGA project group

- **8000 women**
- **Effect of smoking on IVF outcomes:**

Smoking makes your ovaries 10 years older

Smoking and IVF success

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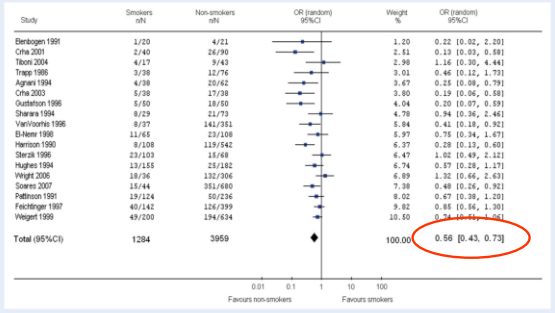
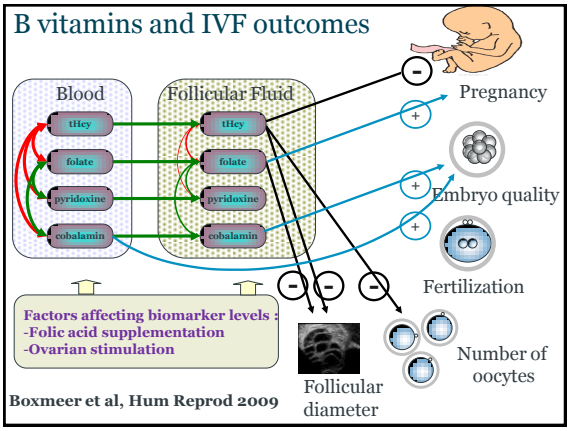


Figure 2 Odds ratio of clinical pregnancy rate per cycle.
Total events: 236 (smokers), 1303 (non-smokers). Test for heterogeneity: $\chi^2 = 33.27$, df = 17 ($P = 0.01$), $I^2 = 48.9\%$. Test for overall effect: $z = 4.26$ ($P < 0.0001$).

B vitamins and IVF outcomes



Boxmeer et al, Hum Reprod 2009

Lifestyle and the embryo

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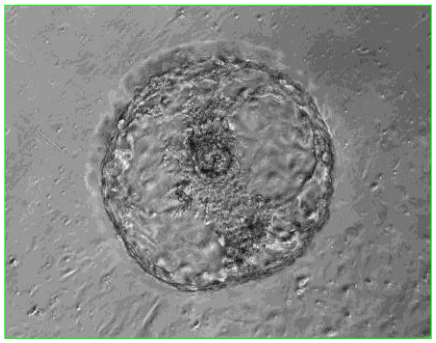
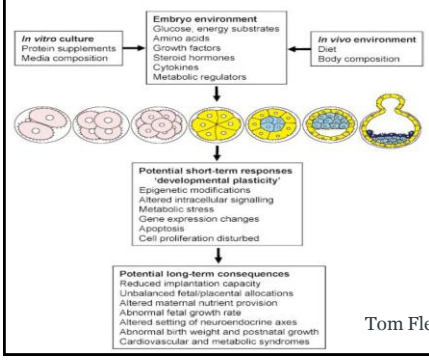


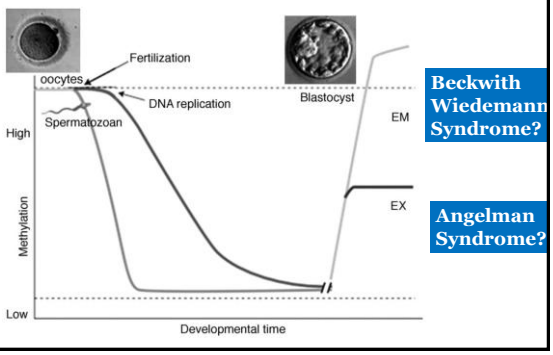
The embryo and it's future

University of Southampton School of Medicine



Tom Fleming 2005

Preimplantation demethylation and remethylation



Beckwith Wiedemann Syndrome?

Angelman Syndrome?

Mice made obese pre-pregnancy

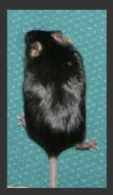
Low Fat Diet
"Healthy"

Nutrition Facts
Servings Per Mouse

Amount Per Serving	2.4g/day
Total Fat	6%
Cholesterol	0%
Total Carbohydrate	65%
Dietary Fibre	9%
Sugars	34%
Protein	19%

Vitamin A 1.2%
Calcium 0.46% Iron 85mg/kg

- Muesli, skim milk
- Fruit salad + yoghurt
- Beef salad + multigrain roll



High Fat Diet
"Unhealthy, Western-Style"

Nutrition Facts
Servings Per Mouse

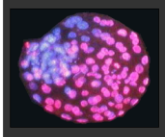
Amount Per Serving	4.5g/day
Total Fat	21%
Cholesterol	0.15%
Total Carbohydrate	50%
Dietary Fibre	9%
Sugars	34%
Protein	19%

Vitamin A 1.2%
Calcium 0.46% Iron 85mg/kg

- Bacon + eggs
- Big Mac + Mars Bar
- Fish & chips

Slide courtesy of R Norman

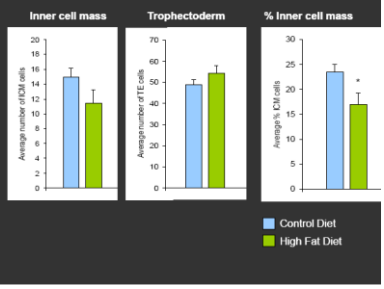
Early embryo development- cell allocation



"Differential stain"

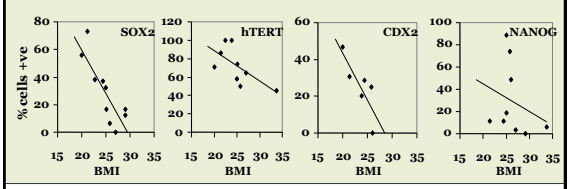
Trophectoderm
Placenta

Inner cell mass
Fetus



Slide courtesy of R Norman

Maternal BMI affects early embryo phenotype



Relationship between embryonic potency protein marker expression and maternal BMI

Eckert et al, 2007

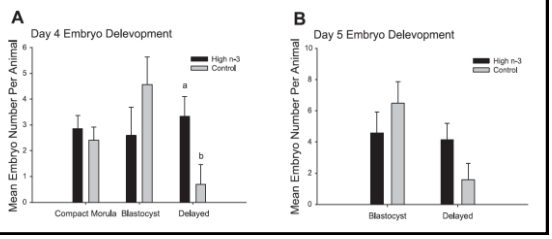
Am J Physiol Endocrinol Metab 294: E425–E434, 2008.
First published December 11, 2007; doi:10.1152/ajpendo.00406.2007.

Maternal supply of omega-3 polyunsaturated fatty acids alter mechanisms involved in oocyte and early embryo development in the mouse

Sarah L. Wakefield,[1] Michelle Lane,[1] Samantha J. Schulz,[1] Michelle L. Hebart,[2] Jeremy G. Thompson,[1] and Megan Mitchell[1]

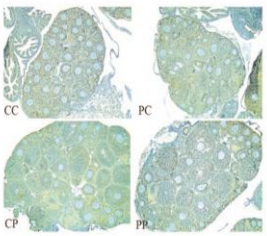
[1]Discipline of Obstetrics and Gynaecology, School of Paediatrics and Reproductive Health, and [2]Discipline of Agricultural and Animal Science, School of Agriculture and Wine, The University of Adelaide, Adelaide, Australia

Submitted 28 June 2007; accepted in final form 4 December 2007



Maternal exposure to polycyclic aromatic hydrocarbons diminishes murine ovarian reserve via induction of *Harakiri*

Andrea Jurisicova,[1,2] Asako Taniuchi,[1] Han Li,[1] Yuan Shang,[1] Monica Antenos,[3] Jacqui Detmar,[1] Jing Xu,[1] Tina Matikainen,[4] Adalberto Benito Hernández,[5] Gabriel Nunez,[6] and Robert F. Casper[1]



Exposed ovaries: Follicles depleted by two thirds

Xenotransplanted human ovary: Same effect

J. Clin. Invest. **117**:3971–3978 (2007)

So what can we do about it?

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Why Bother?

TABLE 1. Clinical Impact of Lifestyle Management in PCOS

Clinical Characteristics	Findings
Menstrual frequency	Consistently improved in all studies
Ovulation	Small studies suggest improvement in rates of ovulation
Pregnancy	Uncontrolled data suggests improvement in rate of pregnancy. No data on pregnancy complications
Hirsutism/androgens	Decreases in free testosterone consistently seen but hirsutism not studied
Glucose tolerance	Improvements in the general population studies, no data specifically in PCOS
Cardiovascular risk	Improvements in lipids in a few studies, small studies suggest improvement in subclinical disease

Hoeger K, Clin Obstet Gynecol, 2007

Diet or Exercise- or both?

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ORIGINAL ARTICLE
Endocrine Care

The Effect of a Hypocaloric Diet with and without Exercise Training on Body Composition, Cardiometabolic Risk Profile, and Reproductive Function in Overweight and Obese Women with Polycystic Ovary Syndrome

Rebecca L. Thomson, Jonathan D. Buckley, Manny Noakes, Peter M. Clifton, Robert J. Norman,

Patients and Intervention: Ninety-four overweight and obese women with PCOS (age 29.3 ± 0.7 yr; body mass index 36.1 ± 0.5 kg/m^2) were randomized to diet only (DO; n = 30), diet and aerobic exercise (DA; n = 31), or diet and combined aerobic-resistance exercise (DC; n = 33).

Conclusion: In overweight and obese women with PCOS, the addition of aerobic or combined aerobic-resistance exercise to an energy-restricted diet improved body composition but had no additional effect on improvements in cardiometabolic, hormonal, and reproductive outcomes relative to diet alone. (*J Clin Endocrinol Metab* 93: 3373–3380, 2008)

Which diet?

Dietary Composition in Restoring Reproductive and Metabolic Physiology in Overweight Women with Polycystic Ovary Syndrome

L. J. MORAN, M. NOAKES, P. M. CLIFTON, L. TOMLINSON, AND R. J. NORMAN

Reproductive Medicine Unit, Department of Obstetrics and Gynecology, University of Adelaide, Queen Elizabeth Hospital (L.J.M., L.T., R.J.N.), Woodville, South Australia 5011, Australia; and CSIRO Health Sciences and Nutrition (L.J.M., M.N., P.M.C.), Adelaide, South Australia 5000, Australia

•12 week energy restriction diet
•Randomised to high or low protein diet

RESULTS
-Both interventions improved cyclicity, lipid profile
-Mean weightloss 7.5%
-LP diet : HDLs decreased 10%
: FAI increased 44%

CONCLUSIONS:
Both diets work!
High protein diet may have slight advantages

University of Southampton
School of Medicine

Moment of caution…

Effect of a very-low-calorie diet on in vitro fertilization outcomes

A low-calorie diet in a group of overweight or obese patients for a short period before and during IVF results in variable tolerance to the dietary regime and an unsatisfactory IVF outcome. (Fertil Steril® 2006;86:227–9. ©2006 by American Society for Reproductive Medicine.)

10 women, 18-40 years, BMI >28, indication for IVF

Diet from day14 or day 21 of previous cycle to day of OPU

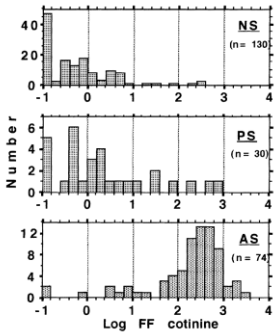
4 patients withdrew
Mean duration of diet: 27-41 days
Weight loss: 5.3-8.2 kg (mean 6.3% of body weight)
3 patients : total fertilization failure

Tsegareli et al 2006 Fertil Steril

Diet and Fertility: where are we now?

- Calories more important than dietary composition
- Short term restriction may be all that is needed
- But beware of ketotic diets for fertility
- No real evidence of benefit of Glycaemic Index diets

Nicotine in the oocyte follicle



Zenzes et al, 2005

Diet and IVF outcome?

ARTICLE IN PRESS

The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/ intracytoplasmic sperm injection treatment increases the chance of pregnancy

Marijana Vujkovic, B.Sc.,[a] Jeanne H. de Vries, Ph.D.,[a] Jan Lindemans, Ph.D.,[b] Nick S. Macklon, Ph.D.,[a,b,c] Peter J. van der Spek, Ph.D.,[d] Eric A. P. Steegers, Ph.D.,[a] and Régine P. M. Steegers-Theunissen, Ph.D.[a,e,f]

Fertil Steril 2010

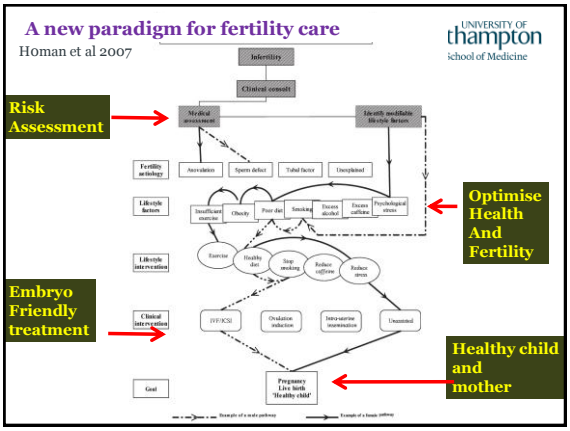
- 161 women undergoing IVF/ICSI
- Validated dietary questionnaire

DIET:	'Health conscious'	'Mediterranean'
Blood Folate	+	+
Blood Vit B6		+
Follicle Vit B6		+
Chance of pregnancy		+ OR 1.4 (1.0-1.9)

A new paradigm for fertility care

Homan et al 2007

UNIVERSITY OF thampton
School of Medicine



CONCLUSIONS

UNIVERSITY OF Southampton
School of Medicine

1. Larger RCTS needed to assess impact of interventions.
2. MORE EMPHASIS ON PREVENTION:
   Focus on lifestyle and diet in adolescent girls
3. Build lifestyle interventions into reproductive treatment pathway
4. Invest effort and money into lifestyle programs

ESHRE Campus

Winchester, UK
May 13-14 2011

UNIVERSITY OF Southampton
School of Medicine

'The embryo as a patient'

University of Southampton School of Medicine

Further reading

- Hassan and Killick(2004) Fertil Steril 81,384
- Boomsma et al, (2006) Hum Rep Update 12, 673
- Boxmeer et al (2008) Hum Rep 23, 2570
- Watkins et al (2008) Semin Reprod Med 26, 175
- Homan et al (2007) Hum Rep Update 13, 209
- Macklon et al (eds) (2009) Textbook of Periconceptional Medicine

Infertility-related stress in men and women

Jacky Boivin, PhD, CPsychol

School of Psychology
Cardiff

Conflict of interest

- Research funding from Merck-Serono S.A. in collaboration with the Economic and Social Research Council on the international survey of contemporary reproductive decision-making in 18 countries www.startingfamilies.com
- Consultancy work with Schering-Plough on reducing the burden of treatment

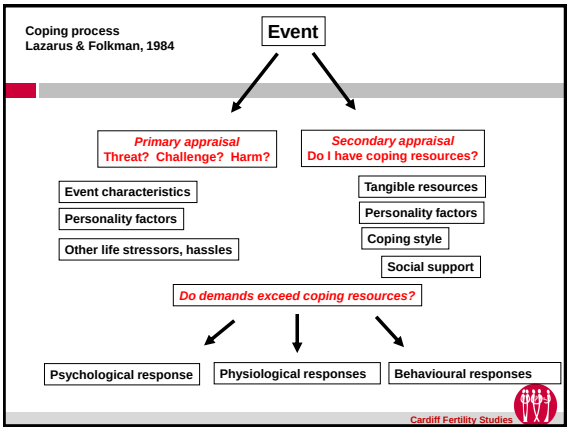
Learning objectives

- Learn proportion of psychosocial research on stress
- Describe domains of investigation in psychosocial stress research
- Identify factors that contribute to stress during treatment
- Describe the quality of research on anxiety and depression related to outcome of ART
- Understand the impact of stress [anxiety] on ART single cycle of ART

What is stress?

- *Response*
  - Psychological and physical phenomena
- *Stimulus*
  - aspects of the environment that increase demands upon or disorganise the individual
- *Transactional*
  - relationship between the person and the environment

Cardiff Fertility Studies



Cardiff Fertility Studies

Stress in ART

- Chronic stressor due to threat of childlessness
- Acute stressor due to fertility treatment and its many unfamiliar procedures, side-effects and psychological demands
- Inconsistent findings
  - Designs do not take account of how psychobiological relationship would manifest
  - Transient effect most likely
  - Timing of psychological assessment
  - Failure of treatment due to several problems
  - Heterogeneous patient population

Cardiff Fertility Studies

Comprehensive review & meta-analysis of stress research

- Is pre-treatment emotional distress associated with outcome after a cycle of ART?

With Emily Griffiths & Christos Venetis

Cardiff Fertility Studies

Search strategy

- An exhaustive search of bibliographic databases and manual search of reference lists on seven databases
  - PubMed, PsycINFO/PsychNET, ISI Web of Knowledge and Web of Science
  - 1985 to April 2009 [update April 2010]
  - contact 28 authors to obtain unpublished work (including unpublished dissertations), additional data or clarification
  - No limit on language

Cardiff Fertility Studies

Inclusion criteria

- Women*
- ART cycle (IVF, ICSI GIFT)
- Prospective study with psychological assessment prior to Day 5 of stimulation
- 'Stress' measured as anxiety/depression
- Measure of treatment outcome
  - Preclinical, clinical or live birth

*Male data used only for topics report due to insufficient data on ART outcome

Cardiff Fertility Studies

Exclusion criteria

- ART with donated gametes
- RCTs evaluating psychological interventions
- Multiple cycles of ART
- Multiple publication
  - included team study with greatest sample size and relevant data

Data extraction

- Extracted by EG & JB
- All studies evaluated with Newcastle-Ottawa Quality Scales

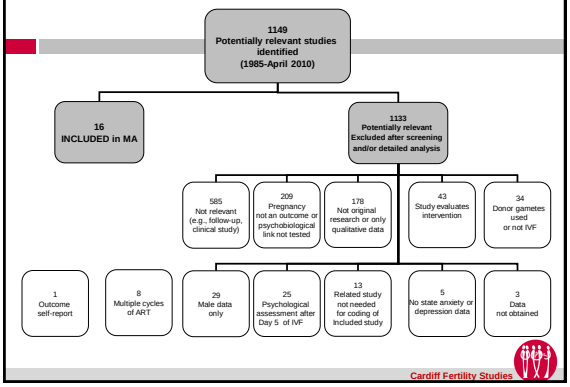
Analysis

- Standardised mean difference (Hedges g, adjusted for small sample) [primary outcome]
  - Pregnant and non-pregnant groups compared on the pre-treatment anxiety/depressions scores
  - One effect size per study, priority on anxiety
- Fixed effects model (random with heterogeneity)
- Q and I^2 reported
- Sub-group & sensitivity analysis
- Small study bias evaluated
  - Funnel plot
  - Egger's test
- Review Manager & Stata

Results

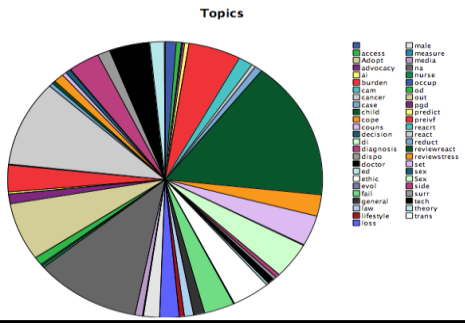
Cardiff Fertility Studies

Study decision flow chart for stress studies



Cardiff Fertility Studies

Topics addressed in 'stress' studies



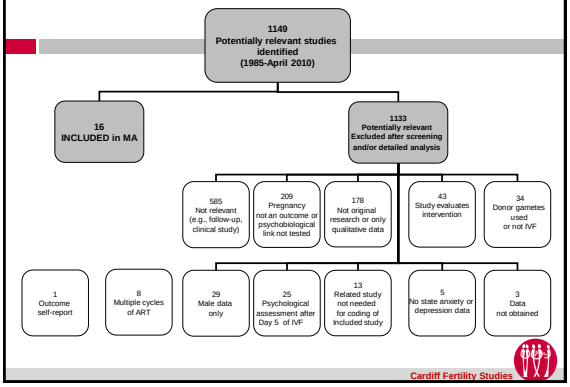
Popular topics (> 10%)

- Follow-up of children with ART (16.2%, n=187))
- Reactions during ART (10.1%, n=116)
- Effect of ART outcome (6.8%, n=78)
- Treatment burden (5.4%, n=62)

- Irrelevant studies (10.9%)

Sources of burden for men and women

Study decision flow chart for stress studies



Characteristics of included studies (n=16)

- age range 29.7 to 36.8 years
- duration of infertility range 3.2 to 7.8 years
- 14/16 studies sampled women with previous experience of using ART

- Day 5 to 2.8 months pre-IVF
- 25% assessed outcome 14+ days after ET
- 43.8% non-pregnant group included cancelled cycles

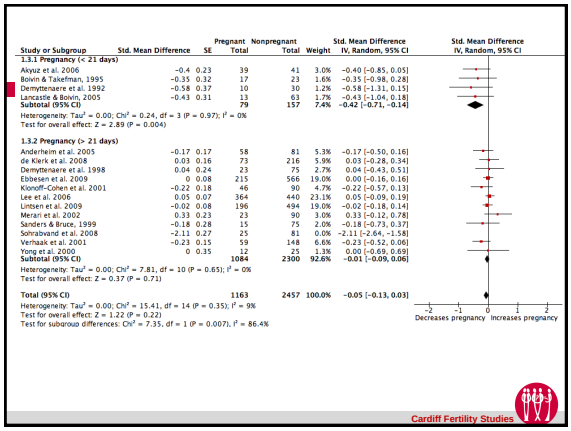
Quality assessment dimensions

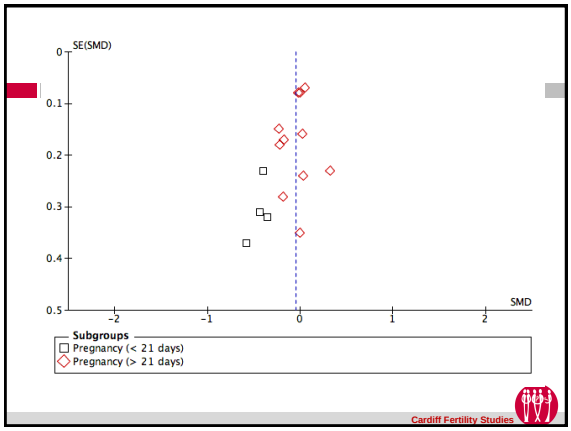
- **Sample representativeness:**
  - * = most (> 80%) eligible patients were invited and most (> 80%) agreed to participate or sample size > 500.
- **Ascertainment of distress**:
  - * = Distress assessed with standard, reliable and valid tool.
- **Comparability on confounders**:
  - ** = Pregnant and non-pregnant groups equivalent on age, previous ART experience, parity and duration of infertility; * = Equivalent on at least two confounders
- **Outcome and follow-up:**
  - * = Completion rate (CR, agreed/analysed) for patients undergoing ART[&] ≥ 80%. [&]Not all patients initially seen start ART **Other bias:**
  - * No other bias that could affect measurement of distress, outcome or their association.

Quality assessment

Table 1 Selected quality assessment criteria from Newcastle-Ottawa Quality Assessment Scale (Cohort studies)

Study Country	Representativeness of sample	Ascertainment of distress	Comparability on confounders	Outcome & follow-up	Other bias	Quality rating
Akyuz 2006, [abstract]		*		*		2
Anderheim 2005	*			*	*	3
Boivin 1995		*	**	*		4
Demytenaere 1992		*	No report	*	*	3
Demytenaere 1998		*	**	*	*	5
Ebbesen 2009	*	*	*	*	*	5
de Klerk 2008		*	*			2
Klonoff-Cohen 2001		*	*	*	*	4
Lancastle 2005	*	*	*		*	4
Lee 2006 [abstract]	*	*		Not reported	*	3
Lintsen 2009	*	*	*	*	*	5
Merari 2002		*	**	*	*	5
Sanders 1999		*	No evidence	*	*	3
Sohrabvand 2009			**	*		3
Verhaak 2001	*	*	*	*	*	5
Yong 2000			**	*		3





Conclusion

- Presence of emotional strain in ART well-established
  - Explanatory research now needed on sources of burden
  - Moderator analyses
- Stress effects unlikely to affect ART outcome on single cycle
  - Definitive good quality study on early and late pregnancy effects not yet done
  - Effect in high-risk group needs to be explored
- Less descriptive and more explanatory research required
- Coping interventions nevertheless required for effects on other end-points - quality of life and treatment burden

Bibliography

- Verhaak CM,.Smeenk JMJ,.Evers AWM, Kremer JAM, Kraaimaat FW, Braat DDM. Women's emotional adjustment to IVF: a systematic review of 25 years of research. Hum Reprod Update. 2007;13(1):27–36
- Lintsen AME, Verhaak CM, Eijkemans MJC, Smeen JMJ, Braat DDM. Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment. Hum Reprod. 2009;1(1):1-7
- Lancastle D, Boivin J. Feasibility, acceptability and benefits of a self-administered positive reappraisal coping intervention (PRCI) card for medical waiting periods. Hum Reprod 2008;23:2299–2307

Infertility related stress in men and women

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Cardiff Fertility Studies Research Group

School of Psychology

Cardiff University

School of Psychology

CARDIFF UNIVERSITY

PRIFYSGOL CAERDYDD

ESHRE, Rome, 2010

Commercial Relationships / Potential Conflict of Interest

- Infertility Network UK operate a corporate partnership scheme which offers different levels of partnership and allows companies to sponsor the charity's activities enabling the charity and corporate organisations to make an active and visible commitment to the development of high quality patient support and care. In the UK the Assn. of British Pharmaceutical Industries do not permit such companies to advertise their products to patients directly nor would I N UK agree to as we must remain independent.
- Accordingly both I N UK and our current corporate partners, Ferring Pharmaceuticals, Merck Serono, Merck Sharp Dohme, and Casmed do not publicise their product to our members/beneficiaries

Patient-friendly ART: the patients view

Clare Lewis-Jones MBE
Chair – Fertility Europe
And
Chief Executive
Infertility Network UK

Learning Objectives

- An understanding of the need for information, support, empathy, and honesty from clinics
- What clinics can do to help patients and provide patient-centered care
- The role and importance of patient organizations' as a partner with clinics in improving the patient journey and experience
- The importance of emotional support and counselling for couples going through fertility treatment

Topics to be covered

- What do we mean by “patient centered” or “patient friendly”?
- Do different patients interpret “patient-friendly” in different ways?
- The safety and efficacy of treatment in relation to patients autonomy.
- Some examples of this.
- Just what is the “bottom line” for patients in relation to patient-friendly care?
- How ART clinics might address patients concerns.
- How patient organisations can help

Definition of “Patient Centered Care” The Institute of Medicine

“Care that is respectful of and responsive to individual patient preferences and needs and that is guided by patient values”

The King’s Fund

“Patient centered care is multi-dimensional; it encompasses all aspects of how services are delivered to patients”

- Institute of Medicine offers this list:
  - Compassion, empathy and responsiveness to needs, values and expressed preferences
  - Co-ordination and integration
  - Information, communication and education
  - Physical comfort
  - Emotional support, relieving fear and anxiety
  - Involvement of family and friends

Results of a survey performed by the National infertility Awareness Campaign in 1997 on the emotional and financial impact of infertility

Tearfulness	97%
Depression	94%
Anger	84%
Loss of sex drive	80%
Inadequacy	72%
Guilt / Shame	62%
Envy/jealousy of pregnant women	2%
Sadness	2%
Helplessness	1%
Despair	1%

Suggestions as to why patients feel these emotions

ANGER -
With themselves.
With Society.
With the NHS.
With the clinic

SHAME -
Why me ?
Why us?
I'm letting my partner down.
I'm letting my doctors down.

FRUSTRATION
Everything seems to take so long
Why aren't I pregnant yet?
Why did the treatment fail - again?

DENIAL

But there has never been a history of this in my family
What the hell am I/are we doing here?

FEAR

What will happen?
Who will I see and why?
What questions will we be asked?
Will we know the answers?

ISOLATION

Nobody understands
My brothers/sisters/friends all have children
Too private/personal to talk to people about

DEPRESSION

Especially as the months & years go by

And at the end of all that???

TIRED!

Loss of confidence

Lack of self-esteem

All of the emotions discussed are exhausting

The effects of sub-fertility on relationships

And what about the impact of infertility on relationships?

- Relationship unchanged 35%
- Relationship improved 28%
- Relationship worsened/strained 31%
- Strained initially, now improved 2%

The emotional impact cannot be under-estimated

One in five respondents to the NIAC survey indicated they had experienced suicidal thoughts whilst going through infertility


Daily Mail, Thursday, February 4, 1999

The wife who could not face life without children

The patients' perspective on fertility care: a systematic review

E.A.F. Dancet et al 2010

- Results:
  - "Overall, fertility patients want to be treated like human beings with a need for: medical skills, respect, coordination, accessibility, information, comfort, support, partner involvement and a good attitude of and relationship with fertility clinic staff"

"Patient-friendly" procedures

- What does "patient-friendly" mean to patients?
  - Less drugs?
    - Natural or Mild IVF
  - Less painful procedures?
    - Injections
  - Fewer visits to the clinic?
    - "IVF in 2 weeks"

And/or?

- Clinic friendliness/understanding/time
- Safety versus success?
  - eSET
- Honest appraisal of a couples chance of success?
  - Based on evidence available from scientific studies
- Cost of treatment?
  - Equity of access

Do different patients interpret "patient-friendly" in different ways?

- Given the various hurdles patients encounter during a treatment cycle – some of which are more patient-centered than others.
  - Some couples want to produce as many eggs as possible as they feel this gives them a better chance of success
  - Some women will perhaps feel that the egg collection was painful – some won't
  - I would imagine most men would say surgical sperm retrieval as painful and not patient friendly! Whilst others would see it as just something they just have to get through.

Are patients really concerned about whether the treatment is "patient-friendly"?

- Or are they simply thankful that at least someone is willing to help them have a baby – no matter what that treatment entails in terms of safety/pain.
- Of course, this doesn't mean to say that those providing the treatment – and patient organisations such as members of Fertility Europe - shouldn't consider this aspect of fertility treatment

Or is it another aspect of care?

- Information – both medical and psychosocial
- Supportive attitude from the clinic/medical staff

"Patients' attitudes to medical and psychosocial aspects of care in fertility clinics: findings from the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme"
L. Schmidt et al 2003

- 2250 patients responded – 80% response rate
  - Vast majority considered a high level of medical information and patient-centered care as important
  - Fewer felt that professional psychosocial services were important and/or had the intention to use these services
  - Main predictor of perceived importance in patient-centered care and professional psychosocial services was high infertility related stress in the marital, personal and social domain

Conclusions

- A supportive attitude from medical staff and the provision of both medical and psychosocial information and support should be integral aspects of medical care in fertility clinics.
- Although only a minority of the participants perceived professional psychosocial services as important, they should be available for patients whose infertility causes them much strain, especially for patients whose marital relationship suffered much because of infertility

L. Schmidt et al 2003

With apologies to UK clinics…

- Results of complaints received by the Human Fertilisation & Embryology Authority 2007/08
  - Attitude 1
  - Response 1
  - Incident 2
  - Consent 3
  - Finance & Administration 7
  - **Information 8**
  - Other 8
  - **Consultation inc. clinical treatment 30**

Information

- Conflicting information regarding sperm donation
- Overwhelming quantity of information
- Insufficient information regarding failed/abandoned cycles
- Lack of information and lack of staff concern
- Incorrect and lack of information

Consultation and Clinical treatment

- Concern about type of treatment offered
- Insufficient information regarding donor anonymity
- Donor details requested 5 months late
- Poor treatment
- Centre did not act in best interests of patients
- After care following treatment
- Doctor didn't know patient and provided incorrect information

Recurrent theme

- Matches closely the issues raised by patients in general feedback to the HFEA
- In particular the quality and timeliness of information and emotional support received

Discussion

- Complaints remain low in relation to number of treatments per year – are patients nervous of complaining?
- Rushed consultation and a lack of understanding or empathy and failing to listen to patients is a common complaint about consultation with clinicians
- Complaints also arise because of differences in diagnosis when patients change to another clinic
- Lack of clarity and information for patients about costs – hidden extras e.g. scans/blood tests

Safety and efficacy of treatment in relation to patient autonomy

- Health risks to patient and to potential child
- Willingness to take that risk if it has the remotest possibility of achieving their deep-rooted desire to have a child?
- Willingness to take further risks after failed treatment?

There are many potential risks for patients and potential child from fertility treatment

- OHSS
- Ovarian cancer
- Surgical risks
- Risks of multiple pregnancies
- Ectopic pregnancy
- Heterotopic pregnancy
- Risk of miscarriage
- Psychological and emotional risks
  - Depression
  - Hormonal changes during a cycle of treatment
  - Strain on relationship

Why aren't patients more worried?

- Perhaps the right question we should ask is:
- Why are patients seemingly so willing to take risks, accept patient-unfriendly treatment, forego patient autonomy?

Because they desperately want to have a baby!

❑They want to achieve something that seems to come so easily to the vast majority

❑The thought of facing a life without children – of "involuntary childlessness – is unbearable

Fears of remaining childless

- The following were fears described by a member of More to Life on one of our forums:
  - *Getting old and having no one.*
  - *Getting ill and having no one to care.*
  - *Never moving on from this and living life to the full!*
  - *Having lots of regrets for not trying harder to have a child one way or another.*
  - *Having no one phone me - i.e. a daughter or a son - to say "hi mum".*

Patient-friendly procedures v. Success rates

- eSET
  - Reducing risk of conceiving a multiple pregnancy thus more "patient-friendly" in terms of safety
  - Reducing chances of conceiving – even slightly – is not considered "patient-friendly" by many patients – certainly currently in the UK.
  - Currently causing enormous anger amongst many patients in the UK

The funding of fertility treatment affects patients views in relation to patient autonomy and patient friendly treatment

- In the UK it is estimated that approx 70-80% of IVF takes place in the private sector
- Poor NHS funding leading to "Treatment by Postcode" or "Treatment by bank balance"
- Feel they need to take these risks – particularly if they can only afford to pay for one cycle of treatment
- If a patient is paying for their treatment should they have more say in that treatment?

Loss of patient autonomy

"I am one of the vast, vast majority who has paid for my own treatment (it's cost me about £25k to get this far) and I resent a government (who have taken money for each of these cycles in the form of the HFEA fee) decreasing my chances of success in this way.
By all means publicise the risks more (like the warnings on cigarette packages) but do not take away the right to choose"

Ovarian stimulation v. risk of OHSS

- Rarely OHSS can be life threatening and fatalities have been reported
- Yet…..

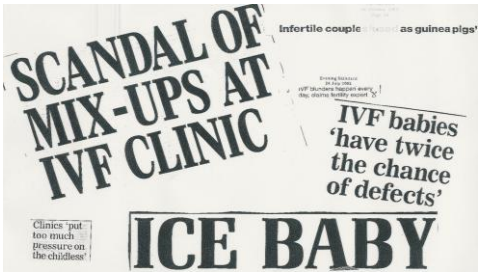
A patient's response for feedback

"For me I never felt (not sure if I was a bit naïve) there were many risks to it, apart from the obvious one of how would we personally deal with the potential failure of a cycle, which was a huge one. I never felt at risk with the procedures or drugs as such. Although on my last go (3rd attempt) I was flagged up as at risk of OHSS which was worrying. I also had a couple of passing out episodes on this cycle at egg collection which was quite daunting. I never really thought too much about the risks of multiple births either. To be honest I think the subject was skimmed upon at the clinic, but to be fair I could have asked for more info too!"

When surveyed in 2006, what services & information did I N UK members want?

- More on complementary therapies
- Food & Nutrition Advice
- NHS Funding issues
- More liaison with clinics
- An A-Z in layman's terms
- More on male infertility
- More on volunteering
- More organised chats
- Local units and events regionally
- Information on causes
- Suggestions for coping with treatments
- Support during pregnancy
- **NOTHING ABOUT INFORMATION ON PATIENT-FRIENDLY/CENTERED TREATMENTS OR RISKS**

Wouldn't You Have Fears?



How Can Clinics Help "Get It Right" for the Patients?

- Information

  •Give patients written information on all aspects of their investigations/treatment right the way through their time at the clinic in a range of languages/formats
  - Costed treatment plans
  - Information evenings

How Can Clinics Help "Get It Right" for the Patients?

- Communication
  - Ensure patients know who to contact if they have questions/concerns
  - Access to a counsellor - within the clinic and externally

How Can Clinics Help "Get It Right" for the Patients?

- Awareness
  - Think about how you give the patients their results – especially if negative obviously
  - Does the patient appear to be being impatient? Be aware that this might be the one and only IVF attempt they could afford
  - Remember - patients are trying to achieve possibly the most important thing in a couples lives

Environment

- Allocate area / space where patients can go for privacy
- Avoid using same waiting room as ante-natal clinic
- If not possible, then remove posters / literature which may upset or offend

Counselling

- Should be available at ALL clinics
- Should be available at all stages of treatment - i.E. Before, during and after
- Basic training in counselling for ALL clinic staff
- Leaflet explaining benefits of counselling and how to access it given to all patients

Time

- The most expensive thing of all, but almost the most important

How Can Patient Organisations Help?

☎Access to personal experiences
☎Access to good information
☎Self-help
☎Mutual help
☎Removes the feelings of isolation

Does Belonging to I N UK Help With the Management of Your Treatment?

– Yes	126
– No/not sure/sometimes	12

And in relation to SET?

- Some of the patients' views reviewed by the Expert Group on Multiple Births after IVF made it clear that "maintaining pregnancy rates" may be viewed differently by patients and clinicians

"We will need additional thawed embryo transfers costing more money; more time off work; more trips to the hospital; more invasive treatment/consultations; more upset"

Patient's opinions on what clinics should/could do or improve on to help patients

- The risks of multiples should definitely be explained better
- Advice from the clinic needs to be clear and not force the decision on the patient blaming everyone else! i.e. it is being forced on me
- Clinicians need to believe in this policy in a very real way – i.e. follow it through – not blame others but be fully behind SET

Information which needs to get out there to patients.

- What is the problem with having twins or more?
- Will single embryo transfer halve my chances of becoming pregnant?
- At what point in their treatment / assessment would they be informed of a SET or DET?

Information which needs to get out there to patients.

- Will clinics differ in their risk assessment and hence decision-making?
- Isn't SET all about the Government trying to save money?
- How the embryologist knows which is the best embryo to choose? (standard standards!)

Questions health professionals may have to ask themselves or may get asked by patients and – most importantly – ALL, have the same answers to…

- In other words – consistency
- Why should I recommend single embryo transfer?
- Won't SET mean that NHS patients are disadvantaged and private patients will incur increased costs
- What criteria do you use to select patients to be offered SET?

What information do patients need?

- Clinics to be consistent
- Clinics to have standardised information
- Clinics to be honest
- Clinics to be strong
- Clinics to be supportive
- Clinics not be to divisive or blaming others

An idea "borrowed" from the American Fertility Association

Infertility Risk Assessment

Women: Know Your Fertility Risks

Learn about some risks for infertility and what you might do to preserve your own ability to conceive a child.

Infertility is a disease that affects about 6 million American couples, roughly 10 percent of the reproductive age population. It's not just a female problem - men and women contribute about equally to the cause. Being aware of some risks for infertility may help you avoid a struggle when it comes time to try to get pregnant.

If you have any risk factors for infertility or have tried to conceive for one year without success, talk to your doctor.

Idea!
Leaflet about the
"Patient-friendly" fertility treatment
and Patient Autonomy? ESHRE?

"Creating a Family"

Creating a Family Is Central to the Life Plans of Most People. The Desire to Have Children Comes From Within the Individual. It Is a Conscious and Unconscious Complex Phenomena. Not Everyone Desires a Child With the Same Intensity and Not Everyone Will Actualise It. Nonetheless, It Is First and Foremost an Individual Issue.

References

1. "Patients' attitudes to medical and psychosocial aspects of care in fertility clinics: findings from the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme. Hum. Reprod. 2003 Mar; 18(3): 628-37.
2. "The patients' perspective on fertility care: a systematic review" Human Reproduction Update, Vol.00, No.0 pp 1-21, 2010

Thank you

Thank you

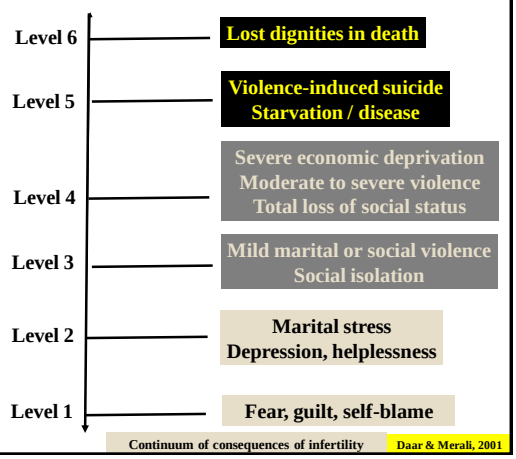
Accessible and affordable infertility services in developing countries

Willem Ombelet
Coordinator ESHRE Special Task Force on
"Developing countries and infertility"

ESHRE - PCC 10
Rome, 27-06-10

Conflict of Interest

There are no commercial relationships or other activities that might be perceived as a potential conflict of interest



Third World
=
overpopulation

1st priority
=
Education
Family-planning

ART =
ethical issue

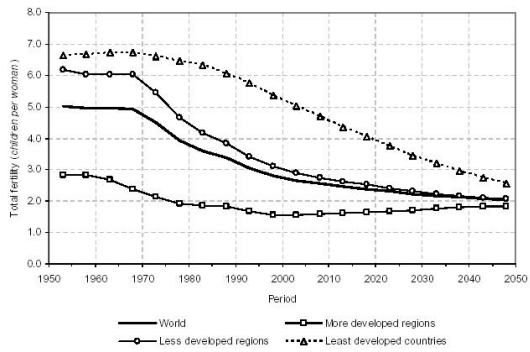
Limited budget

ART = expensive

Task n° 1
=
Prevention
Education

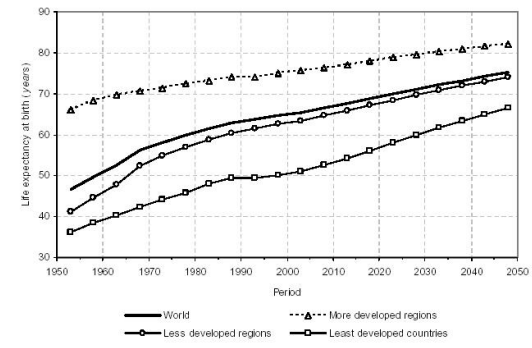
More important priorities:
HIV, tbc, malaria,
vaccinations …

Limited or no interest for infertility
in developing countries

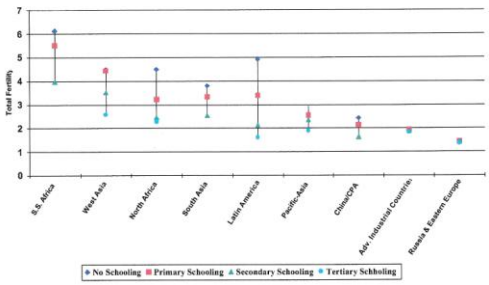


Global life expectance in developing countries

2000-2005: 51 yrs → 2045-2050: 67 yrs



Education !!!



Strategies to simplify ART

One-day diagnostic phase

Natural cycle / Clomiphene citrate / Low dose hMG or rec FSH

Monitoring : (only) ultrasound

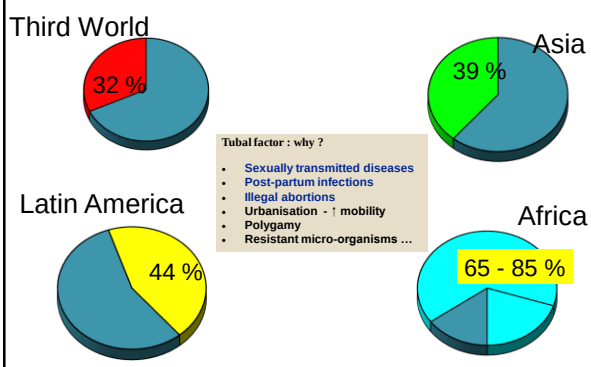
Clinical part: material

Single (Double) Embryo Transfer / Day 1 transfer

Laboratory – technics

Laboratory - material

Infection-related tubal factor



Ethics, social, legal, counselling

Affordable IVF for developing countries

Willem Ombelet started his career in infertility and IVF in 1984 in Pretoria, South Africa. Since 1987 he has been working in the Department of Obstetrics and Gynaecology in the St Jans Hospital of Genk, Belgium. He is the founder of the Genk Institute for Fertility Technology and Chairman of four 'Andrology in the Nineties' meetings. In 1998 he obtained his PhD degree at the University of Leuven. His thesis was entitled 'The value of sperm morphology and other semen parameters in diagnosis and treatment of human subfertility'. He became Head of the Department in 1999 and was the President of the Flemish Society of Obstetrics and Gynaecology from 2001 until 2004. Dr Ombelet is the co-ordinator of the ESHRE Special Task Force 'Developing countries and infertility'.

Dr Willem Ombelet

Willem Ombelet[1,3,*], Rudi Campo[2]
[1]Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk; [2]Leuven Institute for Fertility and Embryology, Leuven, Belgium; [3]Chairman of the Scientific Committee of the Flemish Society of Obstetrics and Gynaecology
*Correspondence: e-mail: willem.ombelet@telenet.be

Assisted reproduction is needed

Fertility on a shoestring

IVF isn't something most Westerners associate with Africa. But low-cost methods are urgently needed to treat the misery of infertility rampant on the continent, says **Helen Pilcher**.

Make it

SIMPLE
EFFICIENT
SAFE
AFFORDABLE

Problem of accessibility

- **Population : 1.000.000**
  - **100.000** — 10% Cohabiting woman (18 - 44 year)
    - 90% fertile
    - 10% infertile — **10.000**
      - 50% conservative
      - 50% seek infertility care — **5000**
        - 40% Pregnant without IVF (Spt, Non-IVF, after surgery,....)
        - 60% IVF selection — **3000**
          - 50% Need IVF — **1500**
          - 50% Refuse IVF

Assumed need for IVF / ICSI
=
1500 / year / million
Fauser et al, Hum Reprod Update, 8, 1, 2002

Nigeria
> 190 000 cycles per year

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4 Working Groups (WG)

- The one-day diagnostic phase — R Campo
- Ovarian stimulation for IUI & IVF/ICSI — AN Andersen
- Laboratory phase for IUI & IVF/ICSI — J Van Blerkom
- Fundraising — H Sallam

5 Study Groups (SG)

- Reproductive health education, prevention & awareness — G Serour
- Burden of disease & cost-effectiveness — D Habbema
- Training courses — I Cooke
- Intravaginal // intrauterine culturing — R Frydman
- Differences in ethics / law / religion / level of care — F van Balen

Level 1 – 3 clinics – action mode

(H Sallam – Monograph HR)

Level 1 basic infertility exploration
treatment options: up to IUI

Level 2 + diagnostic laparoscopy
treatment options: up to IVF

Level 3 + operative endoscopy
treatment options: ICSI & cryopreservation

Level 4 + ??

1. Equipping the clinics
2. Training the staff
3. Educating the public
4. Running the services

Developing countries & infertility

Health Care Centres

Family planning
Mother care
Infertility diagnosis
Infertility treatment

Accessible ART services

Diagnostic phase

Ovarian stimulation

Lab phase

One-day clinic (diagnosis)

Female — questionnaire — Male

Female	Male
Clinical examination Blood sample: Hb, Hep B, Hep C, HIV cervical smear TB-testing Hystero-salpingography Vaginal ultrasound PCT if regular cycle & easy access to centre Optional: mini-hysteroscopy	Clinical examination Blood sample: Hep B, Hep C, HIV TB-testing Semen examination: fresh sample Count & motility a + b After washing: IMC (& morphology)

Natural cycle IVF
systematic review – 1800 cycles

- Complication rate (MPR & OHSS) : almost zero
- Much cheaper
- ET per cycle: 45.5 %
- Ongoing pregnancy rate per cycle: 7.2 %
- Ongoing pregnancy rate per transfer: 15.8 %

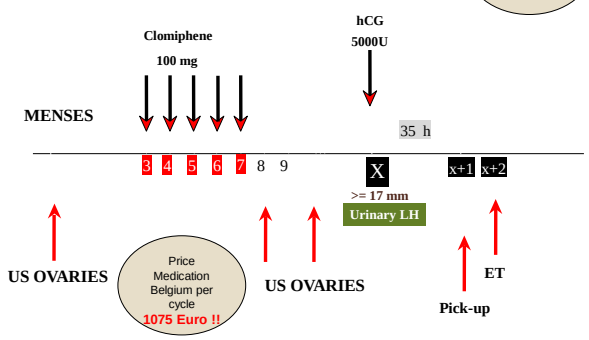
Reason: premature LH rise / ovulation

→ need for randomized controlled trials

Pelinck et al., HR Update, 8, 129, 2002

Modified IVF protocol

Price Medication 13 Euro



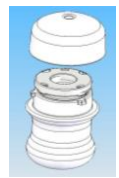
Monitoring ART treatment

IUI	max 2 US no biochemical testing
IVF	max 2 or 3 US no biochemical testing 1 x urinary LH

INVOcell

Ranoux & Frydman

INNER CHAMBER



OUTER RIGID SHELL

Action Plan – Objective & background

(J Van Blerkom)

- Minimalist approach – back to basics
- Avoid needless complex instrumentation / reagents ..
- Simple incubation system – single temperature (37°)
  - Battery
  - Warm water baths
- Non-CO_2 based culture conditions
  - Less oocytes / embryos
  - 24 – 36 culturing
- Culture medium: simple // for 1 – 2 days
- Looking for pronuclear characteristics / mononucleation / blastomere symmetry

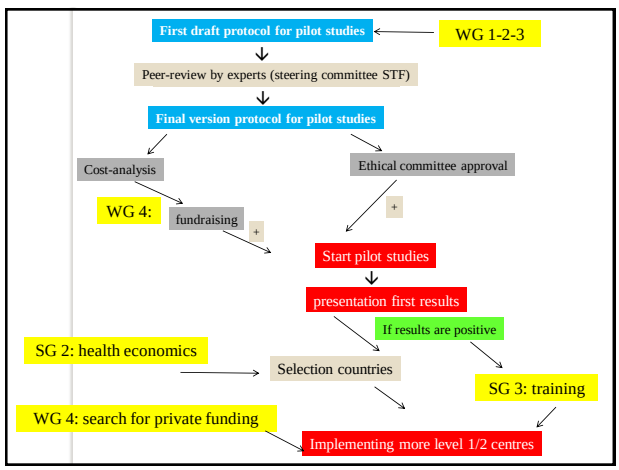
Pilot-projects for LC-IVF

Suggested countries / centres

Egypt	Alexandria, Cairo
SS-Africa	Nairobi, Kampala
South Africa	Pretoria
Indonesia	
Paraguay	Ascuncion
…	

Selection of patients / methods

- Only childless women
- Age limits: Women: > 18 & < 35 yrs
  Male: < 55 yrs
- only IVF (no ICSI)
- SET or DET



Training courses
(ESHRE, IFFS)

- different packages (level 1 – 3)
- Manual & protocols for each level
- train the trainees
  - Diagnostic phase (ISMAAR, EAGE ...)
  - Clinical aspects IUI & IVF cycles
  - Laboratory phase IUI & IVF/ICSI

Funding the project

ESHRE
- training courses / website / secretarial support

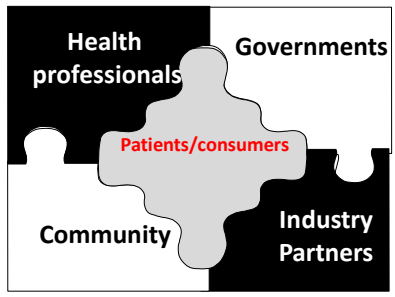
The Walking Egg Project npo
- secretarial support - project manager
- funding – campaigns (affordable art)

WHO
- Leaflets
- Implementing infertility services

Other foundations // NGOs
Governments
EC - United Nations
African World Bank …

World Community Statements

1. "Men and woman of full age, without any limitation due to race, nationality or religion, have the right to marry and to raise a family". This statement was adopted 60 years ago at the 1948 UN Universal Declaration of Human Rights and can't be misunderstood: it implies the right to access to fertility treatments when couples are unable to have children.
2. At the United Nations International Conference on Population and Development in Cairo in 1994 the following statement was made "Reproductive health therefore implies that people have the capability to reproduce and the freedom to decide if, when and how often to do so … and to have the information and the means to do so …"
3. United Nations Millennium Declaration, signed in September 2000 : "Achieve, by 2015, universal access to reproductive health".
4. In 2001, on the occasion of a WHO meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction" in Geneva, a call for the integration of infertility into existing sexual and reproductive health care programmes in developing countries was made.
5. In 2004 the World Health Assembly proposed five core statements, including "the provision of high-quality services for family-planning, including infertility services".
6. At the World Summit in 2005, the largest-ever gathering of world leaders called for achieving these goals by the year 2015.
7. At the Oslo Ministerial Declaration in 2007 health was recognised as one of the most important long-term foreign policy issues by the Ministers of Foreign Affairs of Brazil, France, Indonesia, Norway, Senegal, South Africa, and Thailand. "The well functioning health systems that are needed to reduce maternal newborn and child mortality and to combat HIV/AIDS, tuberculosis and malaria will also help countries to cope with other major health concerns such as sexual and reproductive health ...


Health professionals
Governments
Patients/consumers
Community
Industry Partners

Developing Platforms for Providing Low Cost IVF In Developing Countries: Challenges, Platforms, Prospects

Jonathan Van Blerkom
Department of Molecular Cellular and Developmental Biology, University of Colorado, Boulder, Colorado

Colorado Reproductive Endocrinology
Rose Medical Center, Denver, Colorado

ESHRE 2010

Challenges:

Each location presents unique problems: logistics--CO2, N2, availability of products, equipment maintenance and repair, technologists, patient compliance and acceptability of certain protocols, such as intravaginal culture.

The STF program is designed to be adaptable and adapted to each location, and to minimize manipulations, yet provide the ability to assess oocyte and embryo characteristics up to the 4-cell stage in accordance with the recent ALPHA/ESHRE guidelines on assessment.

Platforms:

C02-based incubation: where CO2 is available, conventional IVF in tubes with incubation in portable units with long term battery backup built in.

One-Step Method: IVF performed in the transfer catheter, which will virtually eliminate the need for manipulation. Low sperm numbers (about 200), in low Volume (30ul) with separate 5 ul column of hyaluronidase to enzymatically assist cumulus and coronal cell removal.

Intravaginal (INVOcell): may be used in certain locations

Protocols:

Simplified medium to support fertilization and development to 2-to4-cell stage, with maternal serum supplementation (25%) supplying protein, amino acids, and labile ingredients, etc.

Standard plasma protein availability, when necessary.

Medium is designed to have a long shelf life and to be reconstituted on site, as needed.

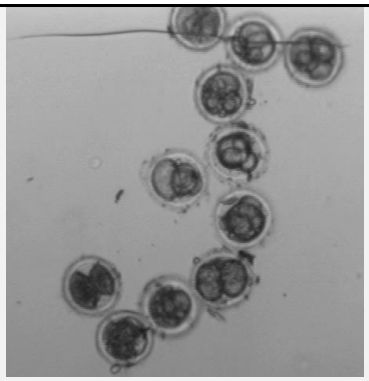
IVF in one-step catheter format or in tubes.

Training:

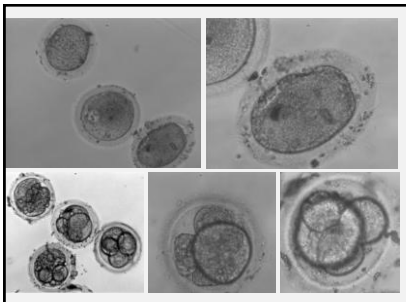
Task-oriented, image-recognition for sperm Numbers.

Each unit has set of fixed oocytes and early embryos

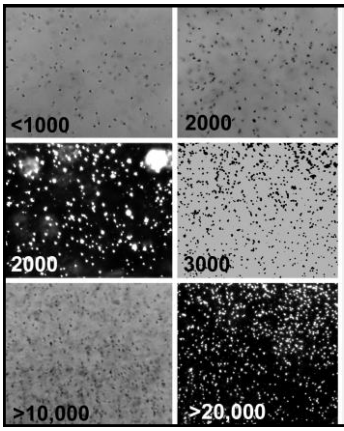
Permanent in-house reference of normal and abnormal specimens, which can be used for training and acquisition of manipulation skills for denudation, handling and transfer, where appropriate.



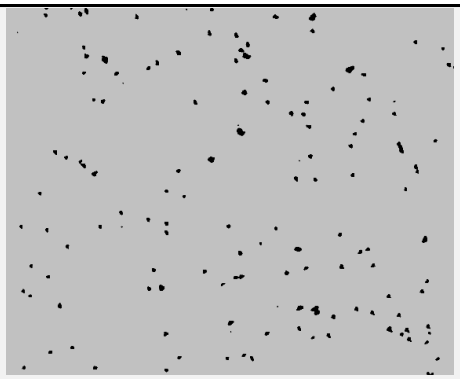
Typical early Embryo Reference Set



photographic examples from set for continual display/reference



typical photographic reference set for insemination



typical sperm density for catheter IVF

Prospects and Achievable Goals :

adaptability is essential
minimization of invasive steps
rapid acquisition of essential and specific skills
followed by ongoing education in embryology

evolution of protocols from experience leading to continual simplification without impairing outcome

commercial partners

training centers with unified and progressive curriculum (Alexandria)

Mark your calendar for the upcoming ESHRE campus workshops!

- **Basic Genetics for ART Practitioners**
  organised by the SIG Reproductive Genetics
  16 April 2010 - Porto, Portugal

- **Array technologies to apprehend developmental competence and endometrial receptivity: limits and possibilities**
  organised by the Task Force Basic Science in Reproduction
  22 April 2010 - Brussels, Belgium

- **The management of infertility – training workshop for junior doctors, paramedicals and embryologists**
  organised by the SIG Reproductive Endocrinology, SIG Embryology and the Paramedical Group
  26-27 May 2010 - Kiev, Ukraine

- **Preimplantation genetic diagnosis: a celebration of 20 years**
  organised by the SIG Reproductive Genetics
  1 July 2010 - Rome, Italy

- **EIM 10 years' celebration meeting**
  organised by the European IVF Monitoring Consortium
  11 September 2010 - Munich, Germany

- **The determinants of a successful pregnancy**
  organised by the SIGS Reproductive Surgery, Early Pregnancy and Reproductive Endocrinology
  24-25 September 2010 - Dubrovnik, Croatia

- **Basic training workshop for paramedics working in reproductive health**
  organised by the Paramedical Group
  6-8 October 2010 - Valencia, Spain

- **Forgotten knowledge about gamete physiology and its impact on embryo quality**
  organised by the SIG Embryology
  9-10 October 2010 - Lisbon, Portugal

www.eshre.eu
(see "Calendar")

Contact us at **info@eshre.eu**

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Keep an eye on our calendar section for more information on

Upcoming events

- **Female and male surgery in human reproductive medicine**
  8-9 October 2010 - Treviso, Italy
- **Promoting excellence in clinical research: from idea to publication**
  5-6 November 2010 - Thessaloniki, Greece
- **"Update on pluripotent stem cells (hESC and iPS)" and hands on course on "Derivation and culture of pluripotent stem cells"**
  8-12 November 2010 - Valencia, Spain
- **Women's health aspects of PCOS (excluding infertility)**
  18 November 2010 - Amsterdam, The Netherlands
- **Endoscopy in reproductive medicine**
  24-26 November 2010 - Leuven, Belgium
- **Fertility and Cancer**
  25-26 November 2010 - Bologna, Italy
- **The maternal-embryonic interface**
  2-3 December 2010 - Valencia, Spain
- **GnHR agonist for triggering of final oocyte maturation – time for a paradigm shift**
  3 December 2010 - Madrid, Spain
- **Raising competence in psychosocial care**
  3-4 December 2010 - Amsterdam, The Netherlands

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(see "Calendar")

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