eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Optimising the IVF protocol

and the use of experimental and adjunctive therapies

Special Interest Group Reproductive Endocrinology

7

1 July 2012
Istanbul, Turkey

Optimising the IVF protocol and the use of experimental and adjunctive therapies

Istanbul, Turkey
1 July 2012

Organised by
the Special Interest Group Reproductive Endocrinology

Contents

Course coordinator, teaching aims, course description and target audience **Page 5**

Programme **Page 7**

Speakers' contributions

Selecting COS protocols based on response prediction – **Marco Gaudoin (United Kingdom)** **Page 9**

What is a poor response and how should it be managed? – **Efstratios Kolibianakis (Greece)** **Page 18**

Strategies to prevent and manage OHSS – **Georg Griesinger (Germany)** **Page 45**

Evidence based approach to recurrent implantation failure – **Tarek El- Touky (United Kingdom)** **Page 61**

What is the role of aspirin, heparin, steroids & vitamins in IVF? – **Luciano Nardo (United Kingdom)** **Page 92**

Current evidence for alternative therapies in IVF – **Elisabet Stener-Victorin (Sweden)** **Page 112**

How can psychology and counselling help optimising treatment? – **Jacky Boivin (United Kingdom)** **Page 123**

Improving the health of the child born after IVF: implications on the peri-implanation period and for stimulation protocol selection – **Nick Macklon (United Kingdom)** **Page 137**

Upcoming ESHRE Campus Courses **Page 152**

Notes **Page 153**

Course coordinator

Georg Griesinger (Germany)

Teaching aims and course description

An evidence-based appraisal of treatment regimens for IVF and the role of experimental and adjunctive therapies.

Course description

To cover the full range of IVF regimens and how best to select and individualise depending upon patient characteristics, including strategies to reduce the risk of complications such as OHSS. To discuss evidence based management options for poor response, including growth hormone and DHEA supplementation, as well as the conundrum of implantation failure and recommendation for its management. To evaluate the current role for adjunctive therapies, such as aspirin, heparin, steroids, vitramins, acupuncture and homeopathy. To define the place for psychology, counselling and peri-conceptional care in optimising treatment and child health.

Target audience

Reproductive physicians and nurses

Scientific programme

Chair: Georg Griesinger (Germany)

09.00-09.10	Introduction – **Georg Griesinger (Germany)**
09.10-09.40	Selecting COS protocols based on response prediction – **Marco Gaudoin (United Kingdom)**
09.40-09.50	Discussion
09.50-10.20	What is a poor response and how should it be managed? – **Efstratios Kolibianakis (Greece)**
10.20-10.30	Discussion
10.30-11.00	Coffee break

Chair: Frank Broekmans (The Netherlands)

11.00-11.30	Strategies to prevent and manage OHSS – **Georg Griesinger (Germany)**
11.30-11.40	Discussion
11.40-12.15	Evidence based approach to recurrent implantation failure – **Tarek El- Touky (United Kingdom)**
12.15-12.30	Discussion
12.30-13.30	Lunch

Chair: Stratis Koblianakis (Greece)

13.30-14.00	What is the role of aspirin, heparin, steroids & vitamins in IVF? – **Luciano Nardo (United Kingdom)**
14.00-14.15	Discussion
14.15-14.45	Current evidence for alternative therapies in IVF – **Elisabet Stener-Victorin (Sweden)**
14.45-15.00	Discussion
15.00-15.30	Coffee break

Chair: Daniella Romualdi (Italy)

15.30-16.00	How can psychology and counselling help optimising treatment? – **Jacky Boivin (United Kingdom)**
16.00-16.15	Discussion
16.15-17.15	Improving the health of the child born after IVF: implications on the peri-implanation period and for stimulation protocol selection – **Nick Macklon (United Kingdom)**
17.15-17.30	Discussion
17.30	Panel Discussion, all speakers
18.00	Close

Selecting COS protocols based on response prediction

Marco Gaudoin
(MBChB, MD, FRCOG)
Consultant Gynaecologist
Medical Director, *GCRM*

ESHRE, Istanbul, July 2012

University of Glasgow

Learning objectives

- ovarian response predictors
- *why* it is valuable to predict the response
- *which* protocols
- *when* to use them

Acknowledgements
- ESHRE
- Prof. Richard Fleming
- Prof. Scott Nelson
- No conflicts of interest

University of Glasgow

Predictors of ovarian response

- age
- PCOS: Dale et al, 1991
- obesity: Shah et al, 2011
- genetic: FSH-receptor SNPs, Wunsch et al, 2007
- ovarian reserve tests: AFC, AMH
- past performance

University of Glasgow

GnRH-agonist "long" protocol

- since 1980's Fleming et al, 1982
- "one-size-fits-all"
  - –can use it for *all* women
- it works
- *"Why bother?"*

University of Glasgow

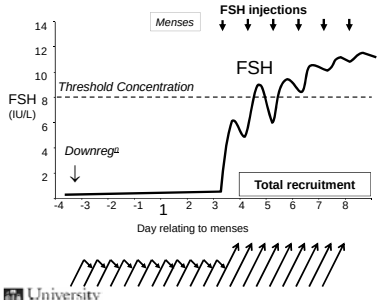
GnRH-agonist "long" protocol

- menopausal symptoms
- ↓ovarian reserve → long stim^{n}
- ↑ovarian reserve → OHSS
  - hosp^{n} costs
  - → death
  - ↓^{d} obstetric outcome

Courbiere et al, 2011

University of Glasgow

Why does the "long" protocol → OHSS?



Total recruitment: lead, medium, small cohorts: equivalent size → ↑egg yield → OHSS

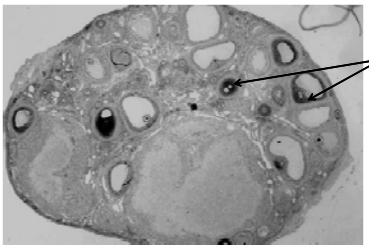
University of Glasgow

Anti-Müllerian Hormone

AMH

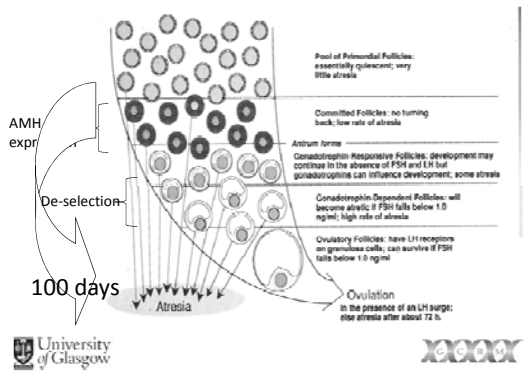
University of Glasgow

AMH expression



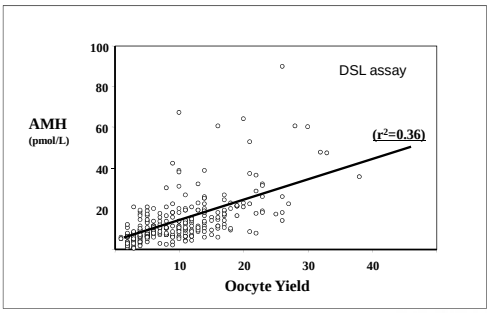
AMH in pre-antral and early antral follicles

University of Glasgow



University of Glasgow

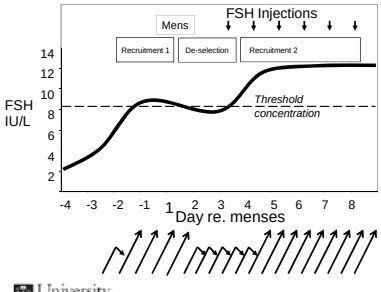
AMH and oocyte yield ("long protocol")



Nelson et al, 2007

Why does antagonist control yield fewer eggs?

Biology of follicular recruitment/selection



Endogenous *initial* recruitment → smaller *lead cohort* → *fewer eggs*

the *same* person responds *differently* to *different* protocols

…also *different* people respond *differently* to the *same* protocol

a) "normal" responders (low OHSS risk)
b) low responders
c) high responders (high OHSS risk)

University of Glasgow

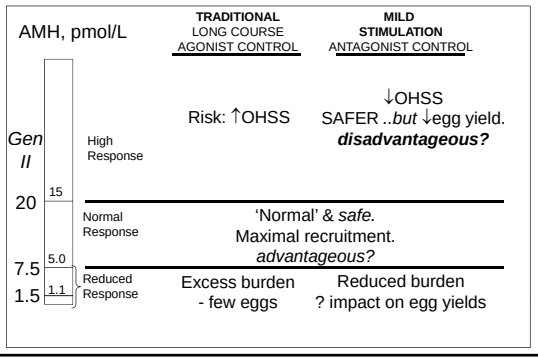
Individualization of R_x

Alternative stimulation regimes for:

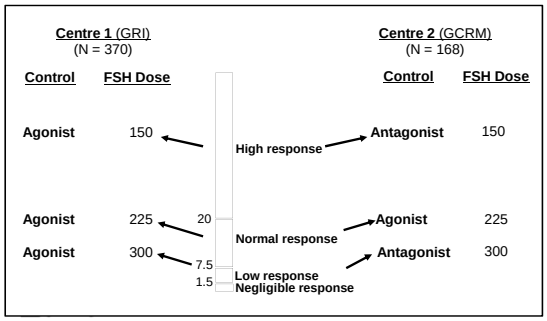
- … poor ovarian reserve (↓AMH)
- … high ovarian reserve (↑AMH)
- …amended further for BMI

University of Glasgow

Issues of Ovarian Stimulation

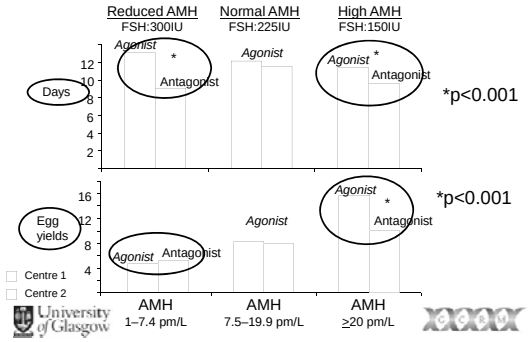


Prospective evaluation of AMH-based strategies in COS



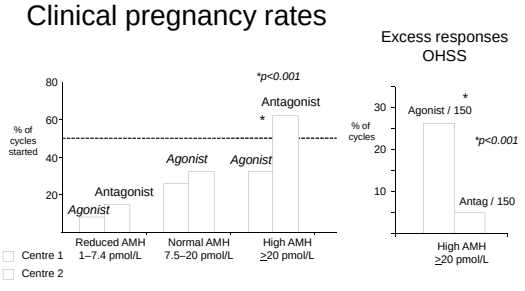
Nelson et al, 2009

Days FSH stimulation and egg yields



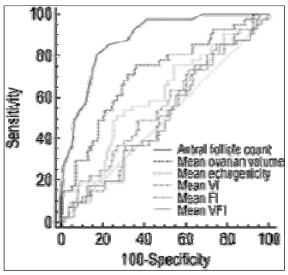
Nelson et al, 2009

Clinical pregnancy rates



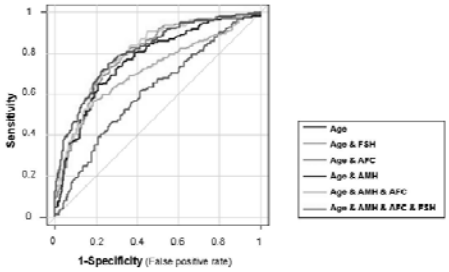
Nelson et al, 2009

AFC: Oocyte yield prediction



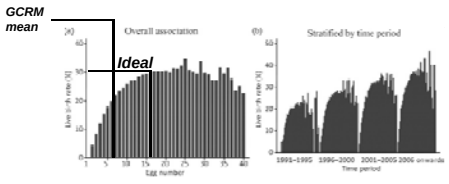
3-D computerised technology

Jayaprakasan et al, 2008



- predictive ability of AFC and AMH are similar
- effectively measure closely-related phenomena

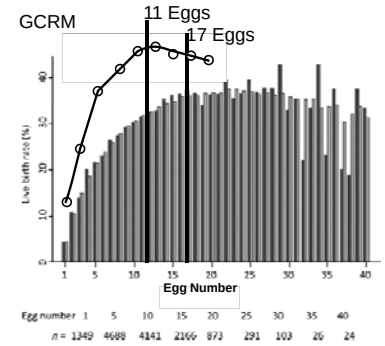
Are more eggs better?



- > 400,000 R_x cycles
- *"ideal"* egg yield c. **15-20** eggs.
- NB. *all age groups*
- *AMH-based programme: mean egg yield is 50% of "ideal"*

University of Glasgow

Sunkara et al, 2011.



Curve shifted: max. achieved at *lower* egg numbers - ? ***potential*** egg yield *versus* ***actual*** egg yield

University of Glasgow

AMH-dictated strategic approach

Primary observations

High responders (150 IU daily)	**Antagonist strategy** • '**normalized**' egg yields • **superior** safety profile • **higher** fresh CPR
Normal responders	Use **GnRH agonist** • Negligible failure of OPU or over-stimulation
Reduced responders	**Antagonist strategy** • reduced treatment burden **High dose FSH** • no clinical benefit • greater cost

University of Glasgow

Nelson et al, 2009

Selecting COS protocols based on response prediction

- predict ovarian response
  - age, past response, BMI, AFC, AMH, etc.

Aims:

1. high ovarian reserve: avoid OHSS
2. low ovarian reserve: reduce R_x burden

University of Glasgow

Selecting COS protocols based on response prediction

- understanding physiology:
  - can formulate different R_x protocols
- further refinement:
  - GnRHa trigger (Humaidan et al, 2011)
  - low ovarian reserve: adjuvant R_x/protocols
- → achieve stated aims
- ..and *optimise* pregnancy rates

University of Glasgow

References

- Courbiere et al, *Fertil Steril.* **2011**; 95(5):1629-32
- Dale et al, *Hum Reprod.* **1991**; 6(2): 238-41
- Fleming et al, *BJOG* **1982**; 80: 80-83
- Humaidan et al, *Hum Reprod Update* **2011**; 17(4): 510-24
- Jayaprakasan et al. *Hum Reprod* **2008;** 23(7): 1538-44
- Nelson et al, *Hum Reprod.* **2007**; 22(9): 2414-21
- Nelson et al, *Hum. Reprod* **2009**; 24: 867–875
- Shah et al, *Obstet Gynecol*. **2011**; 118(1): 63-70
- Sunkara et al, *Hum. Reprod* **2011;** 26(7):1768-74
- Wunsch et al *Ann Endocrinol (Paris).* **2007**; 68(2-3): 160-6

University of Glasgow

What is a poor response and how should it be managed?

Stratis Kolibianakis

MD MSc PhD

Assistant Professor

in Obstetrics Gynaecology and Assisted Reproduction

Unit for Human Reproduction
1st Department of Obstetrics and Gynaecology
Aristotle University of Thessaloniki, Greece

Disclosure

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

Invited speaker for MSD, Serono, Ferring

Learning objectives

By the end of this presentation it should be clear:

What is a poor ovarian response

How effective are the various strategies
used to manage poor ovarian response

What is poor ovarian response?

Multiple definitions of poor ovarian response

Ferraretti et al 2011

Definition of poor ovarian response

Bologna 2011

two out of three

(i) Advanced maternal age

(≥40 years) or any other risk factor for POR

(ii) A previous POR

(≤3 oocytes with a conventional stimulation protocol)

(iii) An abnormal ovarian reserve test

(i.e. AFC: 5–7 follicles or AMH: 0.5–1.1 ng/ml)

Ferraretti et al 2011

Management of poor responders

Problems with the existing literature

Treatment of "poor responders" has been attempted with various methods in retrospective, prospective studies using comparative and non-comparative designs

Most studies are underpowered and single and thus useful conclusions are difficult to be drawn

There is a need for an evidenced based approach in the problem of treatment of poor responders

Systematic reviews and meta-analyses

Kyrou et al., 2009 HRU

Bosdou et al., 2011 HRU

Interventions to enhance IVF outcome in poor responders

Addition of:

Growth hormone (GH) or GH-releasing factor (GHRF)

Pyridostigmine

Aspirin

L-arginin

Interventions to enhance IVF outcome in poor responders

- GnRH antagonist protocol versus

GnRH – agonist protocols

No pituitary suppression

Natural cycle

- Modifications of ovarian stimulation
- Intracytoplasmic sperm injection
- Day 2 versus day 3 embryo transfer

Interventions to enhance IVF outcome in poor responders

Androgens and/or androgen-modulating agents

Pretreatment with transdermal testosterone

Pretreatment with DHEA

Addition of aromatase inhibitors

Addition of recombinant luteinizing hormone (rLH)

Addition of hCG during ovarian stimulation

Addition of Growth Hormone (GH) or GH-releasing factor (GHRF)

GH enhances:

gonadotrophin effects on granulosa cells

Lanzone et al., 1992

GHRF enhances:

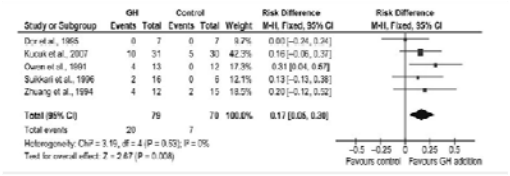
gonadotrophin-induced steroidogenesis

cyclic adenosine monophosphate formation (cAMP)

Doldi et al., 1996

Addition of GH

Live birth



RD = +17 %

95% CI: +5 to +30

Kolibianakis et al 2009 HRU

Addition of GHRF

- Single study - Howles et al., 1999
- Addition of GHRF versus no addition

Live birth rate: 5.2% versus 4.0%

RD = +1.2%

95% CI: -5.3 to +8.1

Addition of GH or GHRF

Conclusions

GH Addition:

Beneficial effect on the probability of live birth in poor responders

GHRF Addition:

No beneficial effect in poor responders

Addition of Pyridostigmine

- Acetylcholinesterase inhibitor
- Increase GH secretion by enhancing the action of acetylcholine

Delitala et al., 1988

Addition of Pyridostigmine

- Relevant study: Kim et al ., 1999 - 70 patients
- GnRH agonists and gonadotrophins
- Definition of poor response :
- < 3 oocytes retrieved and/or a minimum requirement of 50 ampoules of gonadotrophins in a previous failed IVF attempt
- Outcome: ongoing pregnancy / delivery rate

Addition of Pyridostigmine

Addition of pyridostigmine versus no addition:

Ongoing pregnancy/delivery rate:
8.6% versus 22.9%

RD = -14.3%
95% CI: -31.4 to +3.2

Kim et al ., 1999

Addition of Pyridostigmine

Conclusions

Addition of pyridostigmine

does not appear to improve the ongoing pregnancy / delivery rate in poor responders undergoing IVF

Addition of aspirin

Beneficial effect of the addition of low-dose aspirin in:

patients with low uterine blood flow undergoing thawed ET

Wada et al., 1994

oocytes donation recipients with a thin endometrium

Weckstein et al., 1997

Target of aspirin

impaired ovarian blood flow

Battaglia et al ., 2000

Addition of aspirin

- Relevant study: Lok et al., 2004 - 60 patients
- GnRH-agonists/HMG
- Definition of poor response:

recruitment of < 3 mature follicles (≥17mm) in previous IVF attempt or presence of repeated high basal levels of FSH (>10IU/L)

- Outcome : clinical pregnancy rate

Addition of aspirin

Addition of aspirin versus placebo

Clinical pregnancy rate:

3.33% versus 6.77%

RD = -3.33%

95% CI: -18.24 to +10.85

Lok et al., 2004

Addition of aspirin

Conclusions

A beneficial effect of low-dose aspirin
in poor responders undergoing IVF
is not currently supported

Addition of L-arginine

- L-arginine is involved in the formation of Nitric oxide (NO)

either by a calcium dependent or a cytokine-inducible NO synthatase

Moncada et al., 1991

NO, is an intra and intercellular modulator
that plays a role in follicular maturation and ovulation

Anteby et al., 1996

Addition of L-arginine

- Relevant study: Battaglia et al.,1999 - 34 patients
- Flare-up GnRH-agonist/pure FSH
- Definition of poor response:

at least one previous cycle cancellation due to E2<1100 pmol/l

and/or < 3 follicles recruited by day 8 in a previous IVF cycle

Outcome : COCs, pregnancy rate

Addition of L-arginine

Addition of L-arginine versus placebo

COCs: 4.1 ± 1.9 versus 1.6 ± 0.5

WMD = +2.5

95% CI: +1.53 to +3.47

Pregnancy rate : 17.6% versus 0%

RD = +17.6%

95% CI: -4.1 to +41.0

Battaglia et al.,1999

Addition of L-arginine

Conclusions

Addition of L-arginine in poor responders undergoing IVF:

Increase in the number of oocytes retrieved

No beneficial effect on pregnancy rate

Modification of the long GnRH agonist protocol

Different dosages of GnRH agonist

Different protocols for GnRH agonist administration

Modification of the Long GnRH agonist protocol

Relevant study: Dirnfeld et al., 1999 63 patients	Relevant study: Garcia-Velasco et al., 2000 70 patients
Standard long luteal protocol versus a stop agonist long protocol	Standard long luteal protocol versus a stop agonist long protocol
Stop agonist protocol: Administration of GnRH-agonist initiated in the midluteal phase and stopped upon adequate down-regulation	Stop agonist protocol: Administration of GnRH-agonist initiated in midluteal phase and stopped with the onset of menses

Modification of the Long GnRH agonist protocol

▣ Dirnfeld et al.,1999	Garcia-Velasco et al., 2000
Definition of poor response: ≤ 4 mature oocytes retrieved in at least one previous IVF cycle and/or a previous low response to COH as evidenced by a peak E2 level of<2.000 pmol/L	Definition of poor response: <3 follicles ≥18mm in diameter in a previous IVF attempt and presence of basal FSH concentration <12 IU/L
Outcome : ongoing pregnancy rate	Outcome : pregnancy rate

Modification of the Long GnRH agonist protocol

Dirnfeld et al., 1999	Garcia-Velasco et al., 2000
Ongoing pregnancy rate : 5.0% versus 2.6% Rate difference = +2.4% 95% CI: -9.1 to +14	Pregnancy rate : 13.9% versus 17.6% Rate difference = -3.7% 95% CI: -21.4 to +13.7

Modification of the Long GnRH agonist protocol

Conclusions

The use of the "stop" protocol described

does not appear to enhance the probability of pregnancy

over the conventional long protocol

Short versus long protocol

Short protocol:

Promotes follicular growth by taking advantage of the flare-up effect of GnRH-agonist on pituitary gonadotrophin release

Long protocol:

Results in a more coordinated follicular growth

Short versus long protocol

Relevant study: Weissman et al., 2003 - 60 patients

Short protocol:

a high dose of GnRH-agonist for 4 days, followed by standard GnRH-agonist dose

Long protocol:

a standard GnRH-agonist dose was used until pituitary down-regulation, followed by halving the GnRH-agonist dose

Definition of poor response :

presence of < 5 oocytes retrieved or <3 follicles of ≥ 16mm developed on the day of cycle cancellation, or serum E2 level < 500pg/ml on the day of hCG administration

Outcome: clinical pregnancy rate

Short versus long protocol

Clinical pregnancy rate: 3.4% versus 22.6% p=0.053

RD = -19.2%

95% CI: +0.35 to -38.6

- Weissman et al ., 2003

Short versus long protocol

Conclusions

Short and long agonist protocol did not yield significantly different results in poor responders undergoing IVF

GnRH antagonist versus GnRH agonists

GnRH antagonist are not administered during the stage of follicular recruitment and thus suppression of endogenous gonadotrophin secretion is not present at that time in contrast to GnRH agonists

Craft et al., 1999

GnRH antagonist versus GnRH agonists

Griesinger et al 2006

Relevant studies: 8 - 575 patients

2 studies→ long agonist protocol

6 studies → flare-up protocol

Definition of poor response:

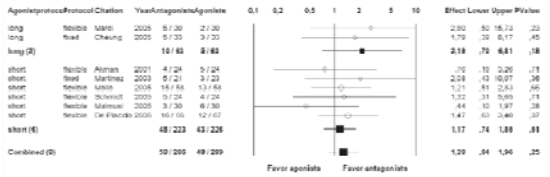
In the majority of studies → "inappropriate ovarian response" during a previous stimulated cycle

Only in two studies → age of the patients and the basal FSH concentrations were used as criteria

Outcome: clinical pregnancy rate, COCs

GnRH antagonist versus GnRH agonists

pregnancy rate



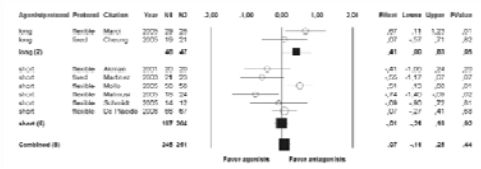
OR = 1.28

95% CI: 0.84 -1.96

Griesinger et al 2006

GnRH antagonist versus GnRH agonists

COCs



SDF = +0.07

95 % CI: -0.11 to +0.25

Griesinger et al 2006

GnRH antagonist versus GnRH agonists

Conclusions

No difference in pregnancy rates appears to exist

between GnRH agonists and GnRH antagonists

in poor responder patients

GnRH antagonists versus no pituitary suppression

- Relevant study: Akman et al., 2000 - 40 patients
- GnRH-antagonists/FSH+HMG versus FSH+HMG
- Definition of poor response:

at least two previous IVF attempts with low response due to:
baseline FSH >15mIU/ml or E2 on the day of HCG < 500pg/ml,
or < 4 oocytes retrieved

- Outcome : ongoing pregnancy rate

GnRH antagonists versus no pituitary suppression

Clinical pregnancy rate:

20.0% versus 6.2%

RD = +13.8%

95% CI: +39.5 to -11.8

GnRH antagonists versus no pituitary suppression

Conclusions

The addition of GnRH antagonists to ovarian stimulation

does not appear to increase significantly

the probability of pregnancy

in poor responder patients undergoing IVF

Short agonist versus natural cycle

The use of natural cycle IVF in poor responder patients

as alternative to ovarian stimulation:

→ less invasive

→ less costly

Short agonist versus natural cycle

- Relevant study: Morgia et al., 2004 - 129 patients
- natural cycle versus a short agonist protocol
- Definition of poor response:
  retrieval of <3 oocytes in a previous attempt
  or cancellation of the cycle because of no follicular development
- Outcome : pregnancy rate

Short agonist versus natural cycle

Natural cycle versus short agonist protocol

Pregnancy rate:
6.1% versus 6.9%
RD = -0.8%
95% CI: -8.2 to +6.2

Short agonist versus natural cycle

Conclusions

No significant difference in pregnancy rates
between natural cycle and short agonist protocol
in poor responders undergoing IVF

Modifications of ovarian stimulation

- High versus standard dose of FSH
- High versus decremental dose of FSH

Modifications of ovarian stimulation

Cedrin-Durnerin et al., 2000	**Klinkert et al., 2005**
96 patients	52 patients
high FSH fixed dose 450 IU versus a decremental dose 300 - 150 IU in a short mini-dose GnRH-a protocol	higher FSH starting dose 150 IU versus 300 IU during a long GnRH agonist protocol
Definition of poor response: retrieval of <5 oocytes in a previous cycle or elevated baseline FSH or E2 levels on CD 3	Definition of poor response: retrieval of <4 oocytes or < 3 follicles developed on the day of cycle cancellation
Outcome: pregnancy rate	Outcome: ongoing pregnancy rate

Modifications of ovarian stimulation

Decremental group versus high fixed dose group

Pregnancy rate:

6.25% versus 8.33%

RD = -2.08%

95% CI: -14.03 to +9.64

150 IU of FSH versus 300 IU of FSH

Ongoing pregnancy rate:

7.69% versus 3.85%

RD = +3.84%

95% CI: -12.19 to +20.60

Modifications of ovarian stimulation

Conclusions

A high fixed-dose gonadotrophin regimen

does not improve the probability of pregnancy

in poor responders

Modifications of ovarian stimulation

Initiation of FSH during the luteal phase

The antral follicles are present in late follicular phase of the ovarian cycle
and initiation of their further development occurs
under the action of the premenstrual FSH rise

Gougeon et al., 1996

Earlier administration of FSH might ↑ the number of recruited follicles
by opening the recruitment window
in the late luteal phase of the preceding cycle

Modifications of ovarian stimulation

Initiation of FSH during the luteal phase

- Relevant study: Rombauts et al., 1998 - 40 patients
- Initiation FSH during the luteal phase
- Definition of poor response:
  retrieval of 3 to 6 oocytes in the last FSH stimulated cycle
- Outcome : COCs

Modifications of ovarian stimulation

Initiation of FSH during the luteal phase

Number of oocytes retrieved

Initiation in the luteal phase versus standard FSH initiation

median: 4.5 - range: 2-12

versus

median: 6 - range: 1-10

Modifications of ovarian stimulation

Initiation of FSH during the luteal phase

The administration of FSH in the luteal phase

has no beneficial effect on the total number of oocytes retrieved

in poor responders

Intracytoplasmic sperm injection

Available evidence is not able to demonstrate

whether ICSI is more efficacious than conventional IVF

in poor responder patients

Van Steirteghem 1993

Intracytoplasmic sperm injection

- Relevant study: Moreno et al., 1998 - 104 patients
- Long GnRH-agonist protocol/HMG+FSH
- Fertization method: ICSI or IVF
- Definition of poor response:
  retrieval of <6 oocytes in a previous cycle
- Outcome: pregnancy rate

Intracytoplasmic sperm injection

IVF versus ICSI

Pregnancy rate :

17.3% versus 21.1%

RD = -3.8%

95% CI: -18.9 to +11. 4

Intracytoplasmic sperm injection

Conclusions

Pregnancy rates in poor responders

are not dependent on the fertilization method

- **Day 2 versus day 3 embryo transfer**

Because of concerns regarding the impact of in vitro culture conditions to the limited number of developing embryos in poor responders, it has been proposed that shortening the duration of embryo culture might be associated with an improvement in pregnancy rates by increasing the number of embryos available for transfer

- **Day 2 versus day 3 embryo transfer**

Relevant study: Bahceci et al., 2006 RCT - 281 patients

Long or short GnRH agonist protocol/rFSH

Definition of poor response:
<5 follicles > 13 mm at the end of stimulation

Primary outcome:
Pregnancy rate

- **Day 2 versus day 3 embryo transfer**

Ongoing pregnancy

Day 2 versus day 3 group

27.7% versus 16.3%

RD = +11.4%

95% CI: +1.6 to +21.0

Embryos transferred

Day 2 versus day 3 group

2.0 ± 0.8 versus 1.7 ± 0.8 embryos

RD = +0.30

95%CI: +0.11 to +0.49

- **Day 2 versus day 3 embryo transfer**

Conclusions

Shortening the duration of embryo culture is associated
with an improvement in pregnancy rates
probably by increasing the number of embryos available for transfer

Use of androgens or androgen modulating agents

for poor responders

Interest in androgen

Accumulation of androgens
in the micro milieu of the primate ovary,
plays a critical role in early follicular development and granulosa cell proliferation

Weil et al., 1998

Androgen excess
has been shown to stimulate early stages of follicular growth

Vendola et al., 1998; 1999, Weil et al., 1998

Increase the number of pre-antral and antral follicles

Hillier et al., 1997; Weil et al., 1998, 1999

Interest in androgen

↑ intraovarian concentration of androgens ↓

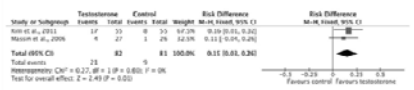
↑ FSH receptor expression in granulosa cells ↓

↑ Responsiveness of ovaries to FSH

Hillier and De Zwart, 1981; Harlow et al., 1986; Vendola et al., 1998; Weil et al., 1998

Addition of testosterone

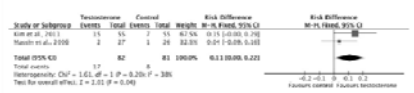
Clinical pregnancy



RD = 15%

95% CI: +3 to +26

Live birth



RD = 11%

95% CI: 0 to +22

Bosdou et al 2011

Addition of Testosterone

Duration of ovarian stimulation

WMD = -0.8 days95% CI: -1.3 to -0.3

Total dose of gonadotrophins required

WMD = -446.2 IUs

95% CI: -600.9 to -291.5

Number of COCs retrieved

WMD = +1.5 COCs

95% CI: +0.9 to +2.1

Bosdou et al 2011

Testosterone

Conclusions

Transdermal testosterone pretreatment
in poor responders undergoing ovarian stimulation for IVF

is associated with

reduced duration of gonadotrophins stimulation
reduced total dose of gonadotrophins required
increased number of COCs retrieved
+15% increase in the probability of clinical pregnancy
+11% increase in the probability of live birth

DHEA pretreatment

Clinical pregnancy rate
RD = +11%
95% CI: -15 to +37%

Single study
Wiser et al 2010
33 women

Live birth rate
RD = +11%
95% CI: -10 to +33%

COCs retrieved
WMD = -1.0
95% CI: -2.23 to +0.23

Wiser et al., 2010

Bosdou et al 2011

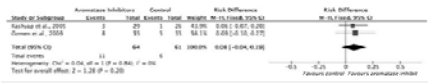
DHEA

Conclusions

It cannot be supported that DHEA pretreatment of poor responders
can increase clinical pregnancy rates, live birth rates
or the number of COCs retrieved

Aromatase inhibitors

Clinical pregnancy rate



RD = +8%

95% CI: -4.0 to +19.0%

Aromatase inhibitors

Total dose of gonadotrophins required for ovarian stimulation

WMD = -870 IUs

95% CI: -1110.2 to -629.8

COCs retrieved

WMD = +0.10

95% CI: -0.60 to +0.80

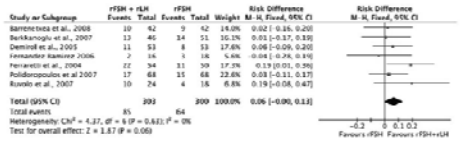
Aromatase inhibitors

Conclusions

Clinical pregnancy rates,
the total dose of gonadotrophins required for ovarian stimulation
and the number of COCs retrieved
are not associated with the addition of aromatase inhibitors
during ovarian stimulation of poor responders

rLH addition

Clinical pregnancy rate



RD = 6%

95% CI: -0.3 to +13%

rLH addition

Total dose of FSH required for ovarian stimulationWMD

= -272.85 IUs

95% CI: -600.52 to +54.83

Duration of ovarian stimulation

WMD = -0.31 days

95% CI: -0.66 to +0.04

COCs retrieved

WMD = -0.04

95% CI: -0.61 to + 0.54

rLH addition

Conclusions

A statistically significant association between rLH addition and achievement of clinical pregnancy in poor responders cannot not be confirmed

The same is true for the duration of stimulation, the total dose of gonadotrophins and the number of COCs retrieved

hCG addition

Single study, Berkkanoglu et al., 2007 - 99 women

Clinical pregnancy rate

RD = -5%

95% CI: -20 to +10%

Total dose of gonadotrophins required

WMD = -552.10 IUs

95% CI: -1035.16 to -69.04

Duration of ovarian stimulation

WMD = -1.00 days

95% CI: -1.71 to -0.29

hCG

Conclusions

The total dose of gonadotrophins required for ovarian stimulation and the duration of stimulation

were decreased when hCG was added during ovarian stimulation

Clinical pregnancy rates, however, were not significantly different

Conclusions

The management of poor responders still represents a challenge for the clinician, which is further complicated by the variations in the definition of poor ovarian response

With the exception of GH co-administration, addition of transdermal testosterone and shortening of the duration of embryo culture, none of the examined approaches currently appears to be beneficial

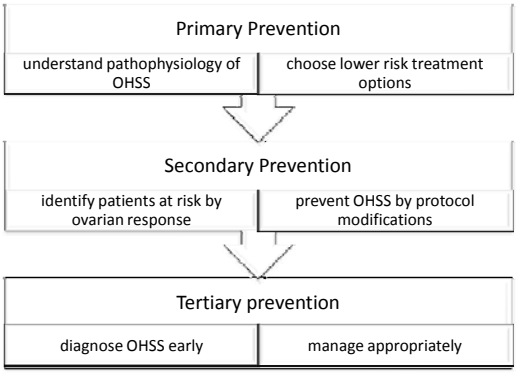
Due to the low incidence of poor ovarian response, evaluation of the interventions proposed is usually performed in single, underpowered studies, which might not allow the detection of the true effect of an intervention

Conflicts of interest

	Company
Honorarium, grants, travel cost reimbursement	IBSA, Ferring, Merck Serono, Kade Besins, MSD, Glycotope

Strategies to prevent and manage OHSS

Prof. Dr. Georg Griesinger
Universtiy of Lübeck, Germany



OHSS classification

„clinically relevant“ OHSS

OHSS Requiring hospitalisation

WHO grade III

Golan,1989 grade IV-V

Navot,1992 ‚severe‘ ‚critical‘

Rizk, 1999 grade B,C

What is the incidence of OHSS at your center?

OHSS incidence

country	source	incidence	comment
England	HFEA 2008	0.25%	rough estimate for severe OHSS
Finnland	Klemetti et al., Hum Reprod 2005	0.9%	Register linkage study; hospitalized because of OHSS
Europe	Mouzon et al., Reprod 2012	o.7%	No definition of severity
Germany	DIR Annual report 2010	0.23%	Severe OHSS

→ ascertainment bias likely

→ differences in definition

Perioperative and post-operative complications of transvaginal ultrasound-guided oocyte retrieval: prospective study of >1000 oocyte retrievals

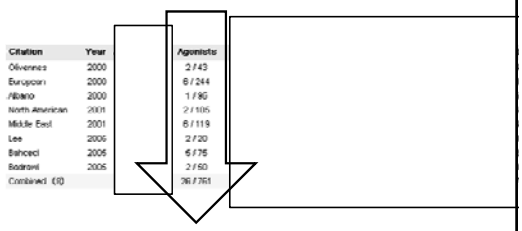
A.K.Ludwig[1], M.Glawatz, G.Griesinger, K.Diedrich and M.Ludwig

Table IV. Complications and hospitalizations occurring within 2 months of oocyte retrieval

	Prospective data	Retrospective data
OHSS III	2.7% (28/1038)	5.4% (5/93)

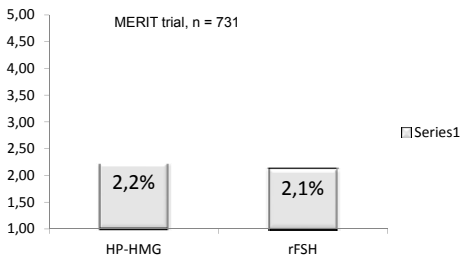
Hum Reprod. 2006 Dec;21(12):3235-40

OHSS requiring hospitalisation after long agonist stimulation



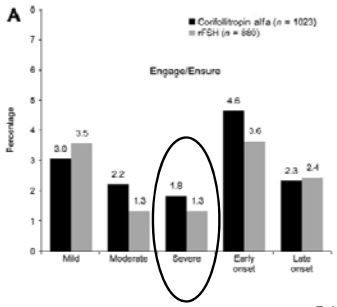
Kolibianakis et al., Hum Reprod Update 2006

Severe OHSS after long agonist stimulation



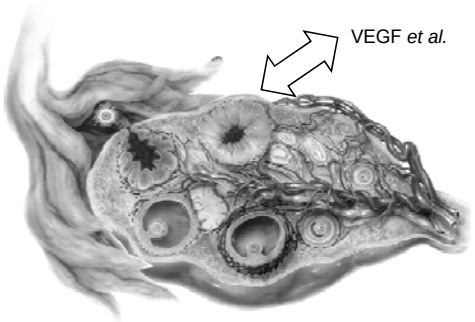
Nyboe- Andersen et al., Hum Reprod 2006

Severe OHSS after antagonist stimulation



Tarlatzis, Griesinger et al. RBMonline 2011

What causes OHSS?

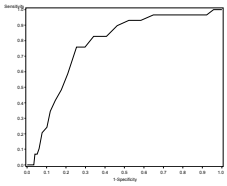


Can we reliably predict all OHSS cases?

Figure 1. ROC curve for severe OHSS

Severe OHSS prediction based on number of follicles (antagonist)

Combined analysis of ENGAGE, ENSURE & TRUST trial data
n = 2493



≥ 19 follicles >10mm:
sensitivity = 74%
specificity = 75%

99.5% of the patients with a follicle count lower than 19 were indeed not at risk of developing severe OHSS

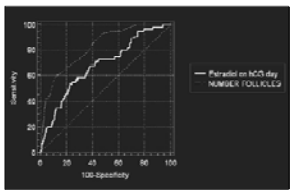
ROC for severe OHSS, AUC=0.779

Mannaerts, Witjes, Griesinger, ESHRE 2012

Figure 1. ROC curve for severe OHSS

Severe OHSS prediction based on number of follicles (antagonist)

single centre retrospective analysis
n = 1801

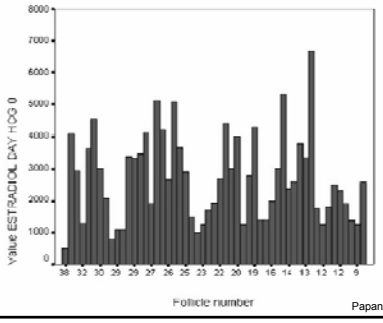


18 follicles >10 mm or E2 > 5,000 pg/l:
sensitivity = 83%
specificity = 84%

5/53 CASES OF SEVERE OHSS STILL MISSED WITH THESE CRITERIA

Papanicolaou et al., Fertil Steril 2006

Estradiol levels and follicle number in patients with severe OHSS



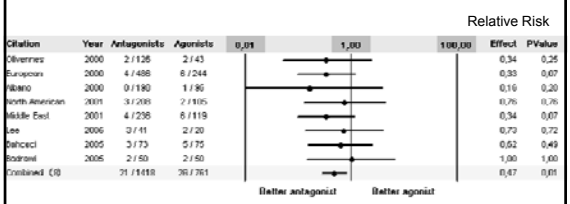
Papanicolaou et al., Fertil Steril 2006

Primary prevention

Primary Prevention

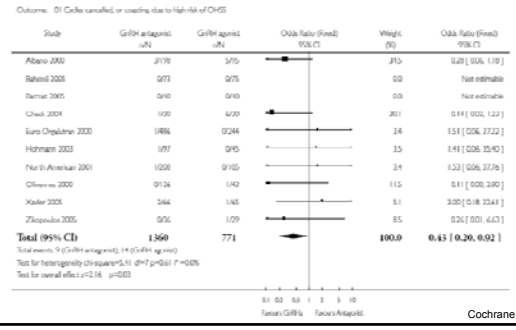
Stimulation	
➢ mild stimulation	➢ efficacy ? OHSS ↓
➢ natural cycle IVF	➢ efficacy ? OHSS Ø
➢ In-vitro maturation	➢ efficacy ? OHSS Ø
➢ GnRH-antagonist instead of long GnRH-agonist	➢ efficacy ↔ OHSS ↓

Primary prevention: OHSS III° requiring hospitalisation - Agonist vs. Antagonist



Kolibianakis et al., Hum Reprod Update 2006

Primary prevention: cycles cancelled or coasted in agonist vs. antagonist



Cochrane 2006

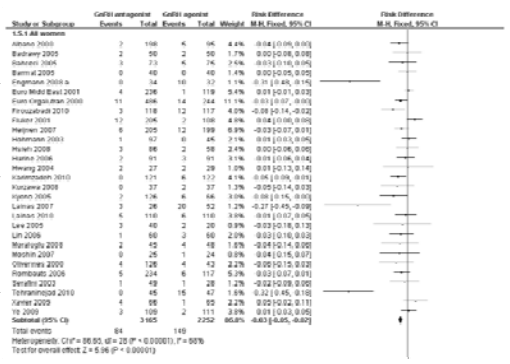
OHSS: Antagonist vs. Agonist

	Cochrane 2006[1]	**Kolibianakis[2]**
Risk of severe OHSS	OR 0.61 (95% CI –0.42, 0.89; *P*=0.01)	RR 0.46 (95% CI 0.26, 0.82; *P*=0.01)
Interventions to prevent OHSS	OR 0.44 (95% CI 0.21, 0.93; *P*=0.03)	

→ Relative Risk of severe OHSS is approniximately half with antagonist!

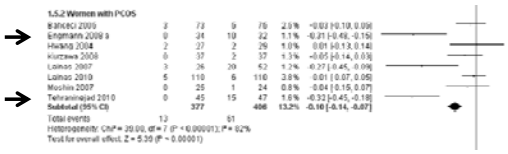
*1. Al-Inany et al. *Cochrane Database Syst Rev*. 2006;3:CD001750
2. Kolibianakis et al. *Hum Reprod Update*. 2006;12:651.

Cochrane 2011 antagonist vs. agonist, outcome: severe OHSS



→ co-intervention: GnRH-agonist trigger, different FSH doses, use of CC etc

Cochrane 2011 antagonist vs. agonist
Outcome: severe OHSS in **PCOS patients**



→ co-intervention: GnRH-agonist trigger, different FSH doses, use of CC etc

Secondary Prevention

stimulation	
➢ cycle cancellation	✔
➢ freeze all embryos	✔
➢ avoiding hCG for luteal phase support	✔
➢ coasting	
➢ intravenous albuming	
➢ early unilateral follicular aspiration	
➢ GnRH-agonist trigger instead of hCG	
➢ hCG dose reduction	
➢ Metformin co-treatment for PCOS	
➢ Dopamin agonist	

Secondary prevention: what does not work

- Intravenous albumin
  - (Youssef et al., 2011; Venetis et al., 2011)
- Earyl follicle aspiration
  - (Schröder et al., 2003; Egbase 1998)
- Using rhCG instead of uhCG
  - (Youssef et al., 2011)
- Using one type of FSH versus another
  - (van Wely et al., 2011)

Secondary prevention: coasting

Cochrane review 2011: only 4 RCTs

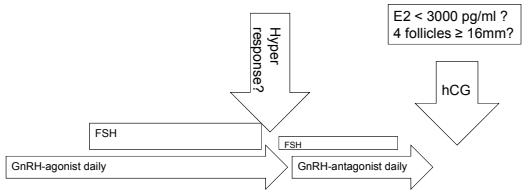
outcome	odds ratio
moderate and severe OHSS	0.53, 95% CI: 0.23 to 1.23
live birth	0.48, 95% CI: 0.14 to 1.62
clin pregnancy rate	0.69, 95% CI: 0.44 to 1.08

AUTHORS' CONCLUSIONS: There was no evidence to suggest a benefit of using coasting to prevent OHSS compared with no coasting or other interventions.

ALTERNATIVE CONCLUSION: Insufficient sample sizes to draw a conclusion really, reduction in OHSS likely, but at the cost of reduction in pregnancy chance

D'Angelo, Cochrane 2011

new concept: coasting with antagonist in long agonist protocol



Gustofson et al., Hum Reprod 2006
Gustofson et al., Fertil Steril 2006

Novel concepts in Coasting

Antagonist Coasting: RCT: 192 patients

	Antagonist coasting	Conventional coasting
Days of coasting	1.74 ± 0.91	2.82 ± 0.97
No of oocytes	16.5 ± 7.6	14.06 ± 5.2
No of embryos	2.87 ± 1.2	2.21 ± 1.1
Clinical pregnancy (N.S.)	55.32%	47.92%
No OHSS in both study groups		

Aboulghar et al., RBMonline 2007

Reduction of the hCG dose

- What is the minimally effective dose?

10.000 √
5.000 √ } equally effective, at least if bodyweight <80kg (Wikland et al., 2005; Stelling et al., 2003)
2.500 ?
<2.500 ?

- Will a lower dose help prevent OHSS?

10.000 vs. 5.000 vs. 2.500 IU hCG

- RCT, n= 80 PCOS ,GnRH-antagonist stimulation

	10,000 IU (n = 28),	**5,000 IU (n = 26)**	**2,500 IU (n = 26)**
Fertilisation rate	52.8%	65.4%	55.6%
Ongoing pregnancy rate	26.9% (7 of 26),	30.8% (8 of 26)	34.8% (8 of 23),
Early-onset OHSS III°	3.5% (1 of 28)	3.8% (1 of 26)	0%

Kolibianakis et al., 2007

Low-dose hCG triggering

- Retrospective study, n=94 cycles
- E2 > 2,500 - 4,000 pg/mL → 5000 IU
- E2 >4000 → 3300 IU

	5,000 IU (n=47)	**3,300 IU (n = 47)**
Ongoing pregnancy rate	50.0%	43.5%
Moderate OHSS	2.1%	10.6%
Severe OHSS	0%	4.2%

Schmidt et al., Fertil Steril 2007

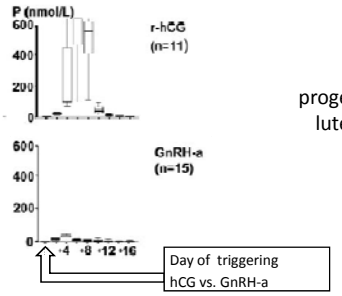
Dose-response: hCG and OHSS

	250µg rhCG	500µg rhCG	10,000 IU uhCG
serum P day 6–7 after hCG (nmol/L)	133	163	147
Oocytes retrieved	13.6	14.6	13.7
OHSS III°	3.2%	9.0%	3.1%

Differences between groups are not statistically significant

Chang et al., Fertil Steril 2001

Secondary prevention: GnRH-agonist triggering



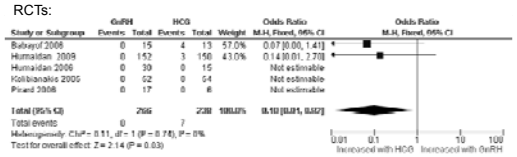
progesteron in the luteal phase

Day of triggering hCG vs. GnRH-a

Beckers et al., Hum Reprod 2003

OHSS incidence after Agonist trigger

RCTs:



Youssef M, Griesinger G et al., Cochrane Review. Hum Reprod 2009;24, Supplement: 1241 – 1530

Observational studies:

- >2000 OHSS risk patients
- > 30 studies

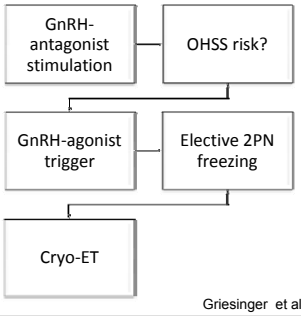
→ One early-onset, one late-onset OHSS

Update: Griesinger,et al, RBM online 2006

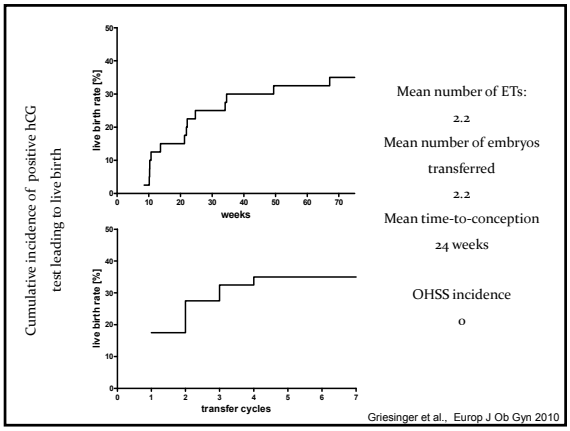
Developmental potential of oocytes after Agonist triggering

- Oocye donation: good PRs
  - Acevedo et al., Fertil Steril 2006
  - Shapiro et al., 2007
  - Bodri et al., Fertil Steril 2008
  - Hernandez et al., Fertil Steril 2009
- Frozen-thawed cycles: good PRs
  - Eldar-Geva et al., RBMonline 2006
  - Griesinger et al., Fertil Steril 2007
  - Griesinger et al., Hum Reprod 2007
  - Manzanres et al., Fertil Steril 2009
  - Griesinger et al., Eur J Ob Reprod Biol 2010

OHSS prevention: ‚freeze all'

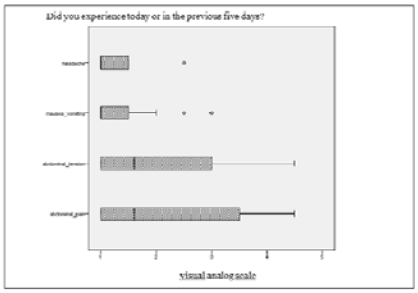


Griesinger et al., Hum Reprod 2007



Griesinger et al., Europ J Ob Gyn 2010

Tolerability: cohort of 30 patients, mean COCs: 17.0±8.5



Griesinger *et al.*, RBMonline 2011

German Multi-centric study

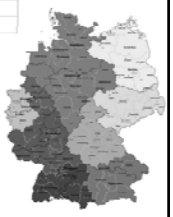
Ovarian Hyperstimulation Syndrome (OHSS) Prevention With Agonist

This study has been completed.

First Received: February 2, 2009 Last Updated: July 27, 2010 History of Changes

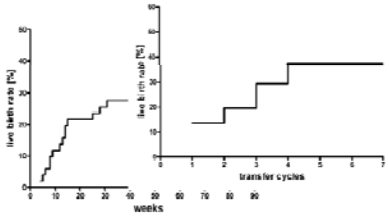
Sponsor:	University of Schleswig-Holstein
Information provided by:	University of Schleswig-Holstein
ClinicalTrials.gov Identifier:	NCT00835523

- study centres:
  Lübeck,
  Würzburg, Erlangen
  Augsburg, Düsseldorf



Live birth rate after agonist triggering (n=51 patients)

COCs retrieved: 20.3 (± 9.7)



[one early-onset case of OHSS]

Griesinger *et al.*, Fertil Steril 2011

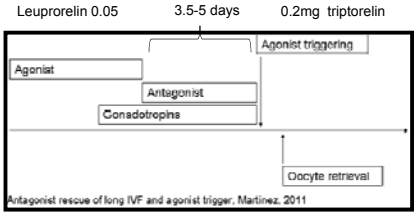
Agonist trigger & ‚freeze-all'

- Efficacious
- Safe
- Current best option if hyperresponse occurs

Agonist triggering: alternative options

- High-dosed luteal phase support with progesterone and E_2
  - (Engmann et al., 2008)
- Low-dose hCG at time of oocyte pick-up
  - (Humaidan et al., 2009; 2011)
- recLH
  - (Papanikolaou et al., 2011)

„Agonist rescue protocol": Agonist trigger after antagonist coasting



case series, n = 3
1/3 patients had no oocyte retrieved

Does Metformin reduce the risk of OHSS?

- Yes: RCT on 120 PCOS patients;
  RR for OHSS 0.28 (95% CI: 0.11-0.67)
  – (Palomba et al., Hum Reprod 2011)
- No: RCT on 134 women with ovulatory PCO
  OHSS incidence 8.7% vs. 7.7%
  – (Swanton et al., Hum Reprod 2011)

Does cabergoline 0.5mg/day reduce the risk of OHSS?

Cochrane review 2012: two placebo-controlled RCTs, n = 230 pats

outcome	odds ratio
Moderate OHSS	OR 0.38, 95% CI: 0.19 to 0.78
Severe OHSS	OR 0.77, 95% CI: 0.24 to 2.45
clin pregnancy rate	OR 0.94, 95% CI: 0.56 to 1.59
miscarriage rate	OR 0.31, 95% CI: 0.03 to 3.07

Tang et al., Cochrane 2012

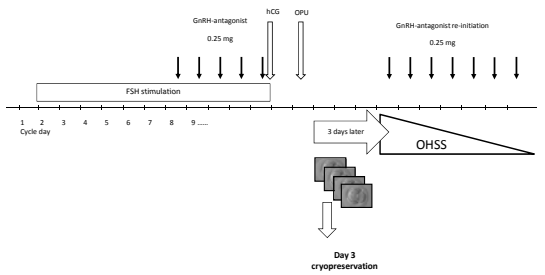
alternatively: Quinagolide 50µg/day (Busso et al., Hum Reprod 2010)

Tertiary prevention = treatment

- Hospitalisation if severe OHSS
- Maintain diuresis
- Anticoagulation
- Ascites drainage
- (cabergoline 0.5mg/d)

ESHRE OHSS guidelines

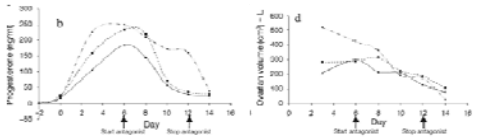
Tertiary prevention: luteal phase antagonist administration



adapted from Lainas et al. RBMonline 2007

Tertiary prevention: luteal phase antagonist administration

- Report on three cases: 31, 36, 48 COCs
- Blastocyst freezing



Lainas et al. RBMonline 2008

Thank you!

griesing@uni-luebeck.de

Recurrent implantation failure: Evidence-based approach

Tarek El-Toukhy,
Consultant and Senior Lecturer in Reproductive Medicine
Guy's and St. Thomas' Hospital
King's College London

Guy's and St Thomas' NHS

Conflict of Interest

NON

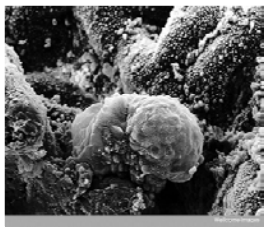
Guy's and St Thomas' NHS

Objectives

- To understand definition and prevalence of RIF
- To review the various causes of RIF
- To identify the best-available evidence in management of RIF

Structure of the talk

- Definition
- Prevalence
- Management
- Conclusion



Standardisation of the definition

Short communications

Towards better quality research in recurrent implantation failure: standardizing its definition is the first step

Before such trials can be conducted, ~~clinicians must agree~~ and standardize the definition of RIF first, as this will help the process of collection and analysis of data from different studies in order to shape scientific consensus.

Definition of RIF

- Absence of implantation (gestational sac seen on scan) after three embryo transfer cycles
- ~~Absence of implantation after replacin~~g ~~10 or more good quality embryo~~s

Important questions

– 28 year vs 42 year old?

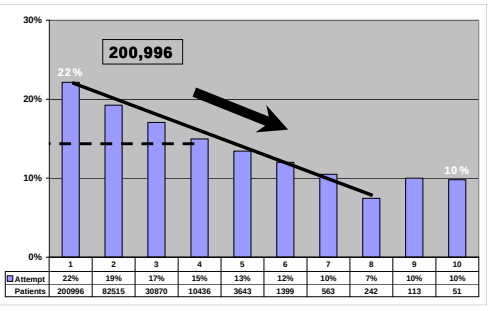
– Fresh vs frozen?

– Number replaced per transfer?

– Good quality Vs. poor quality embryos?

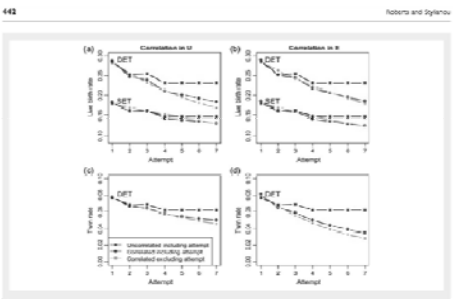
Highly inefficient in humans

LBR per attempt (All ages)
HFEA **1991 – 2006**



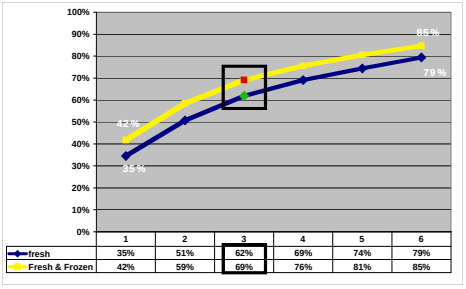
	1	2	3	4	5	6	7	8	9	10
Attempt	22%	19%	17%	15%	13%	12%	10%	7%	10%	10%
Patients	200996	82515	30870	10436	3643	1399	563	242	113	51

Prediction Model



Hum Reprod 2012

Cumulative LBR Age < 35 first attempt with freezing



	1	2	3	4	5	6
fresh	35%	51%	62%	69%	74%	79%
Fresh & Frozen	42%	59%	69%	76%	81%	85%

Challenges of RIF

Devastating event to couples

Formidable clinical challenge

BFS 2008

Challenges in Management

- Pressure to do/change something
- Heterogeneous/multi-factoria

- Limited evidence for interventions

Predictors of implantation

- Age
- Ovarian reserve
- Embryo and endometrial quality
- Success rate of clinic

Donoso et al, 2007

Do we expect all patients to have a pregnancy after a maximum of three cycles?

Management of expectations

Investigations of RIF

Who?

↓

Why?

↓

How?

Why investigate?

" to diagnose a pathology which is amenable to an evidence-based and effective treatment"

Rinehart, 2007

Pragmatic classification of RIF

- Expected RIF
- Unexpected RIF

Expected RIF

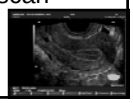
- Advanced maternal age
- Reduced ovarian reserve
- Poor quality embryos
- Atrophic endometrium

Do we need to investigate further?

Unexpected RIF

- Young age
- Adequate ovarian reserve
- Good quality embryos
- No pelvic pathology on routine scan

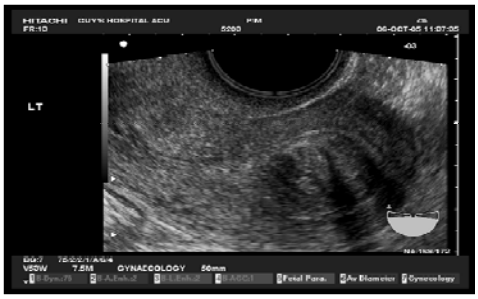
Investigate

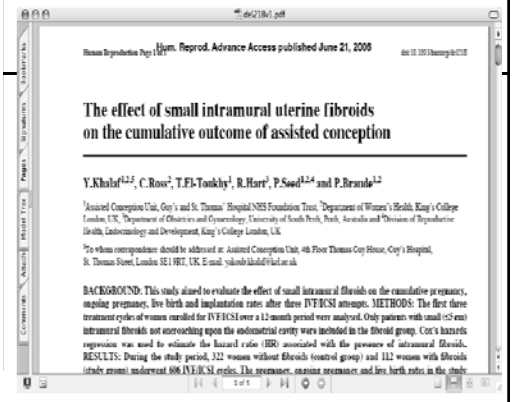


1. Detailed Imaging

- TVS
- HyCoSy
- 3D scan
- HSG

A - Uterine fibroids





Hum. Reprod. Advance Access published June 21, 2008

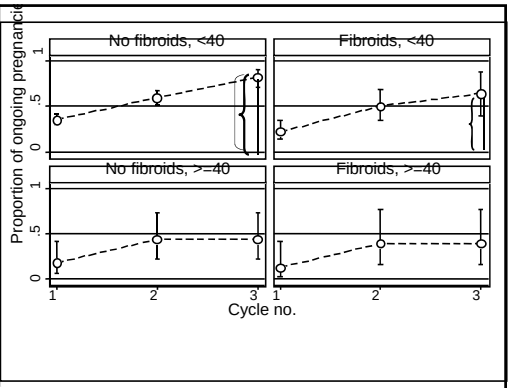
The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception

Y.Khalaf[1,2,5], C.Ross[2], T.El-Toukhy[1], R.Harr[3], P.Sood[1,2,4] and P.Braude[1,2]

[1]Assisted Conception Unit, Guy's and St. Thomas' Hospital NHS Foundation Trust, [2]Department of Women's Health, King's College London, UK, [3]Department of Obstetrics and Gynaecology, University of South Perth, Perth, Australia and [4]Division of Reproductive Health, Endocrinology and Development, King's College London, UK

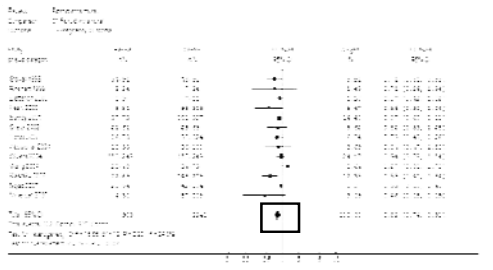
[5]To whom correspondence should be addressed at: Assisted Conception Unit, 6th Floor Thomas Guy House, Guy's Hospital, St. Thomas Street, London SE1 9RT, UK. E-mail: yakoub.khalaf@kcl.ac.uk

BACKGROUND: This study aimed to evaluate the effect of small intramural fibroids on the cumulative pregnancy, ongoing pregnancy, live birth and implantation rates after three IVF/ICSI attempts. METHODS: The first three treatment cycles of women enrolled for IVF/ICSI over a 12-month period were analysed. Only patients with small (≤5 cm) intramural fibroids not encroaching upon the endometrial cavity were included in the fibroid group. Cox's hazards regression was used to estimate the hazard ratio (HR) associated with the presence of intramural fibroids. RESULTS: During the study period, 322 women without fibroids (control group) and 112 women with fibroids (study group) underwent 606 IVF/ICSI cycles. The spontaneous, ongoing spontaneous and live birth rates in the study



Difference between groups is significant (P = 0.017)

Effect of small I/M fibroids on IVF outcome



Hum Reprod 2009

Effect of fibroids removal

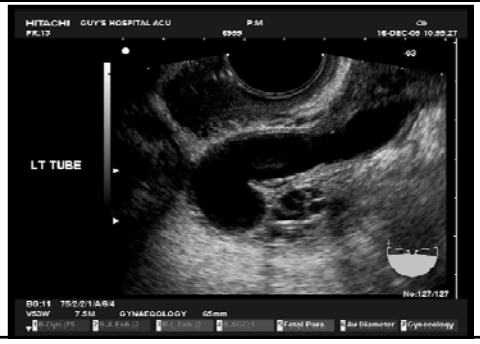
BULLETTI *et al.*: EFFECT OF MYOMA REMOVAL ON IVF 87

TABLE 2. Effect of surgical removal of myomas on IVF success rates

	Cumulative pregnancy rate *N* (% cases)	Delivery rate *N* (% cases)	Abortion rate *N* (% pregnancies)
Group A	28 (34)	21 (25)	8 (7)
Group B	13 (15)	10 (12)	3(4)
P	<.05	<.05	Not significant

Note: Group A included patients who underwent IVF after surgical removal of their myomas ($N = 84$). Group B included patients who underwent IVF without surgical removal of their myomas ($N = 84$). Subjects with fibroids were those who had one to more than five fibroids subserosal and intramural with at least one larger than 5 cm in diameter.

B - Hydrosalpinges



Effect of untreated hydrosalpinx

Table VI. Meta-analysis Of 14 studies

Outcome criteria	Group with hydrosalpinx (%)	Group without hydrosalpinx (%)	Odds ratio	Confidence interval
Pregnancy rate	19.67	31.2	0.64	0.56–0.74[a]
Implantation rate	8.53	13.68	0.63	0.55–0.72[a]
Delivery rate	13.4	23.44	0.58	0.49–0.69[a]
Early pregnancy loss rate	43.65	31.11	1.72	1.34–2.20[a]

[a]Odds ratio significantly different from 1 ($P < 0.05$)

Camus et al, 1999

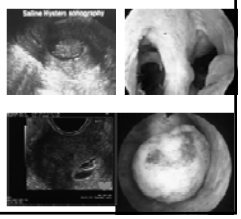
Effect of removal of hydrosalpinx

- Odds of pregnancy = 1.75 (1.1-2.9)
- Odds of ongoing pregnancy = 2.13 (1.2-3.7)
- Embryo implantation = 1.34 (0.9-2.1)
- Ectopic pregnancy=0.42 (0.1-2.1)
- Miscarriage=0.49 (0.2-1.5)

Cochrane review
Johnson et al. 2002

2. Outpatient hysteroscopy

- After 2 or more failed cycles 15-40% of patients will have an intra-cavitary lesion
(Olivera et al., 2003; Levi Setti, 2004; Urman, 2005)
- Polyps
- Adhesions
- Small fibroids
- Septae
- infection or hyperplasia



Hysteroscopy before IVF

Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis

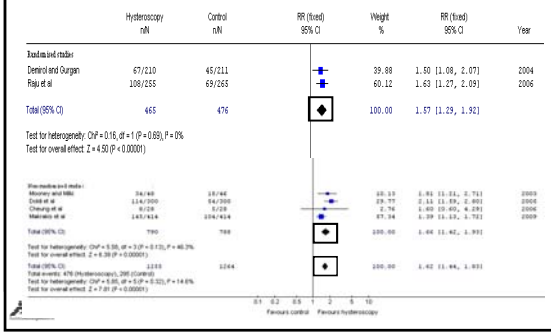
Pooling the results of five studies showed benefit from outpatient hysteroscopy in improving pregnancy rate in the subsequent IVF cycle (RR = 1.75, 95% CI 1.51–2.03)

RBM Online - Vol 16. No 5. 2008 712-719

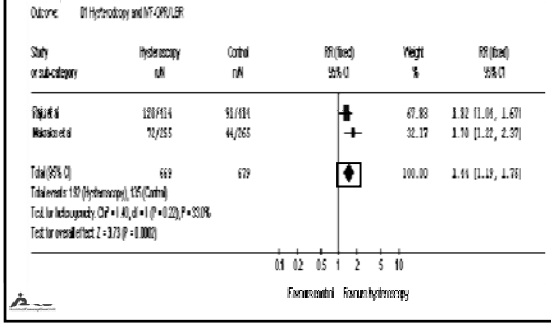
Updated Evidence

- Randomised Trials (2)
- Prospective observational data (4)

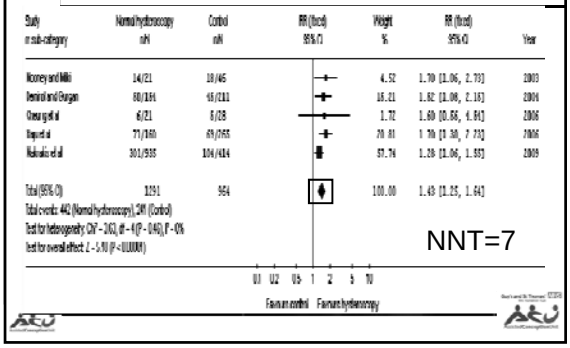
Updated Meta-analysis: CPR



Updated Meta-analysis: LBR



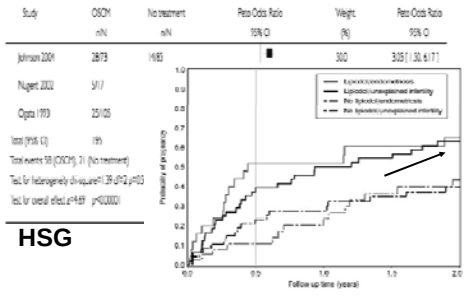
Normal hysteroscopy



Summary of literature

- **CPR/LBR could be improved by up to 50%**
- **Small NNT**
- **No complications reported**
- **Consistent results across all 6 studies**

Therapeutic effect of a diagnostic test?



HSG

Biological explanation

- **Identification/Correction of uterine pathology**
- **Facilitate future transfers**
  (CX dil., direction and depth)
  (Groutz et al., 2007, F&S; Pabuccu et al., 2005, JMIG)
- **Endometrial injury / stimulation**
  (Barash et al, 2003; Raziel et al, 2007; Zhou et al., 2008 – all F&S)

Cervical dilatation has a positive impact on the outcome of IVF in randomly assigned cases having two previous difficult embryo transfers

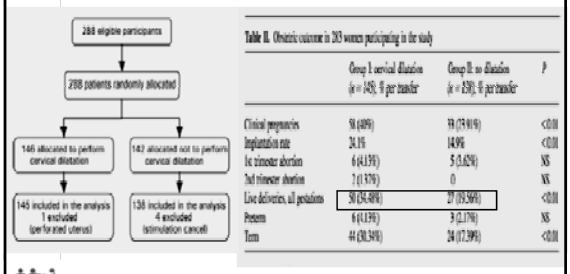


Table II. Obstetric outcome in 283 women participating in the study

	Group I cervical dilatation (n = 145); % per transfer	Group II, no dilatation (n = 138); % per transfer	P
Clinical pregnancies	58 (40%)	33 (23.91%)	<0.01
Implantation rate	24.1%	14.9%	<0.01
Ist trimester abortion	6 (4.13%)	5 (3.62%)	NS
2nd trimester abortion	2 (1.37%)	0	NS
Live deliveries, all gestations	50 (34.48%)	27 (19.56%)	<0.01
Preterm	6 (4.13%)	3 (2.17%)	NS
Term	44 (30.34%)	24 (17.39%)	<0.01

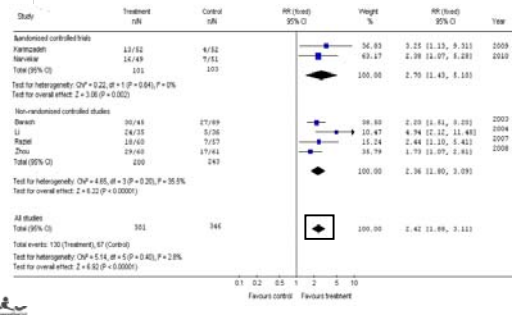
Prapas et al, 2004 HR

Endometrial injury: CPR

	Type of study	Scratch group	Control group	P-value
Barash 03	Observational	67%	30%	<0.001
Li 07	Observational	69%	14%	0.01
Raziel 07	Observational	30%	12%	0.03
Zhou 08	Observational	48%	28%	0.01
Karimzadeh 09	RCT	27%	9%	0.02
Narvekar 10	RCT	33%	14%	<0.01

OR = 2.4 (95% CI 1.9-3.1)

Endometrial injury: CPR

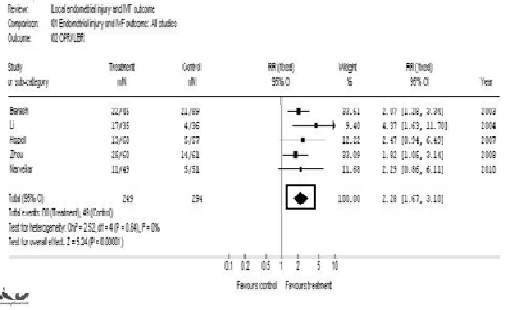


Endometrial injury: LBR

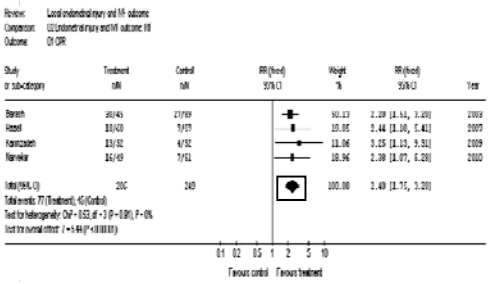
	Type of study	Scratch group	Control group	P-value
Barash 03	Observational	49%	24%	0.02
Li 07	Observational	48%	11%	0.01
Raziel 07	Observational	22%	7%	0.07
Zhou 08	Observational	42%	23%	0.01
Narvekar 10	RCT	23%	10%	0.03

OR – 3.0 (95% CI 1.9-4.6)

Endometrial injury: LBR



Endometrial injury: RIF



Biological explanation

- Release of cytokines and growth factors (LIF, IL-6 and 11, EGF) promoting endometrial development
- Alternation in endometrial gene expression (Laminin œ 4, Integrin œ 6, MMP1), which play key roles in implantation
- Delay endometrial maturation, thus promoting synchronisation with embryo stage

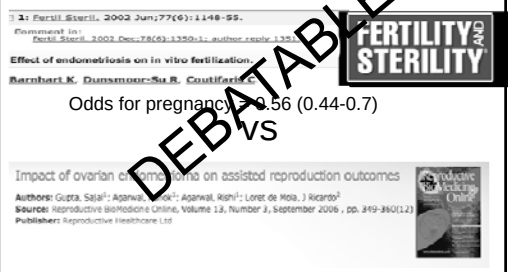
backward development

3. Laparoscopy

To diagnose and treat endometriosis

Does endometriosis reduce implantation rate?

Does endometriosis reduce IVF outcome?



DEBATABLE

Odds for pregnancy = 0.56 (0.44-0.7)

VS

Odds for clinical pregnancy = 1.07 (0.6-1.9)

Does surgical treatment of endometriosis improve IVF outcome?

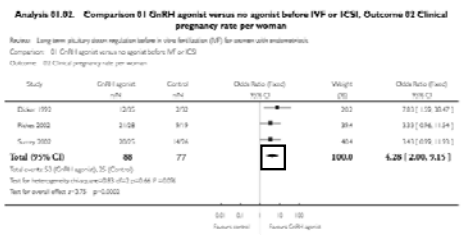
- One RCT - 99 women
  Impl rate = 16.5% vs 18.5%
  Preg rate = 34% vs 38%
  (Demirol et al, 2006)
- Three non-randomised controlled studies - 400 women No improvement in impl or preg rate
  (Pabuccu et al, 2004; Wong, 2004 and Garcia-Velasco et al., 2004)

Does medical treatment of endometriosis improve IVF outcome?

Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Review)

Sallam HN, Garcia-Velasco JA, Dias S, Arici A

Medical treatment of endometriosis improves IVF outcome



None of 165 women included had RIF

Should we offer laparoscopy?

- No benefit from surgical treatment of endometriosis
- Benefit from medical treatment has not been examined in RIF patients

VALUE IS DOUBTFUL

4. Karyotype analysis

To detect chromosomal aberrations

- Translocations
- Inversions or deletions
- X-chromosome mosaicism

Is the risk increased after RIF?

- Incidence in infertile population = 3-7%

  (Scholtes et al, 1998; Clementini et al, 2005; Riccaboni et al, 2008)

- Incidence in couples with RIF = 3-15%

  (Stern et al, 1999; Tarlatzis, 2000; Raziel et al, 2002)

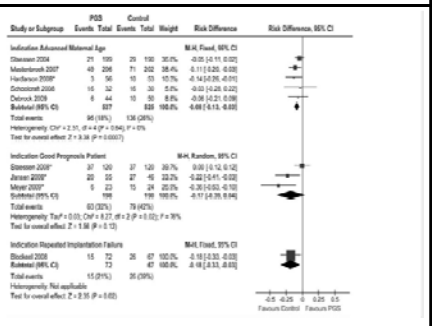
Incidence varies depending on cause of infertility and number of failed attempts

Should we offer PGD / PGS?

- PGD in RIF carrying specific translocations = No studies

- PGS for sporadic aneuploidies = one RCT (n=19) → no benefit (Werlin et al., 2003)

Aneuploidy screening Meta-analysis



PGS in RIF

RCT of PGS in patients with RIF

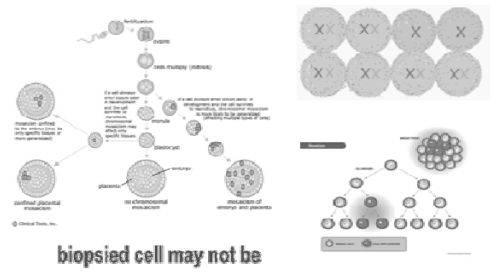
Blockeel C et al. Reprod Biomed Online. 2008; 17: 848-854

139 patients underwent ovarian stimulation and PGS was performed in 72 patients. Analysis of chromosomes X, Y, 13, 16, 18, 21 and 22 was carried out using FISH

There was no difference between the study and control groups in implantation (21.4% vs 25.3%) and clinical pregnancy rates (25.0% vs 40.3%)

PGS does not improve IVF outcome in women with RIF

High rates of Mosaicism



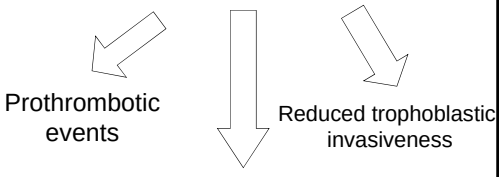
biopsied cell may not be representative

5-Immune testing

To detect immunological dysfunction

Immunological dysfunction

Breakdown of phospholipid adhesion molecules in trophoblast



Di Simone, 2000; Quenby, 2005

Main types of tests

- Anti-phospholipid antibodies
- Anti-thyroid antibodies
- Thrombophilic disorders
- Peripheral NK cell testing

1-Anti-phospholipid antibodies

1: Fertil Steril. 2000 Feb;73(2):330-3.

Comment in:
Fertil Steril. 2000 Sep;74(3):611-3.

Antiphospholipid antibodies and in vitro fertilization success: a meta-analysis.

Hornstein MD, Davis OK, Massey JB, Paulson RJ, Collins JA.

Relationship between APA status and IVF outcome

No effect of APA status on live birth rates in IVF

Authors	APA positive: live birth/total (%)	APA negative: live birth/total (%)
Birdsall et al., 1996	13/36 (36.1)	52/204 (25.5)
Denis et al., 1997	260/470 (55.3)	184/323 (57.0)
El-Roeiy et al., 1987	0/10 (0.0)	3/16 (18.8)
Gleicher et al., 1994	16/67 (23.9)	6/38 (15.8)
Kowalik et al., 1997	36/78 (46.2)	196/447 (43.8)
Totals	325/661 (49.2)	441/1,028 (42.9)

Hornstein. In vitro fertilization success. Fertil Steril 2000.

QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

Anti-phospholipid antibodies against phosphatidylinositol, and phosphatidylserine are more significant in reproductive failure than antibodies against cardiolipin only.

Ukova-Gallova Z, Krauz V, Novakova P, Milichovska L, Micanova Z, Bibkova K, Sucha R, Turek J, Balvin M, Rokyta Z.

Tested for 7 types of APA using ELISA

1073 after 1 failed IVF cycle
853 after RIF
627 after RM
412 after diagnostic lap
391 fertile controls

⇒ 50% positive in RIF (P<0.01)

Am J Reprod Imm, 2005

2-Anti-thyroid antibodies

- Is their prevalence increased in RIF vs infertile controls?

  YES (22-52%)

  Birkenfeld, 1994 HR
  Geva, 1995 HR
  Bussen, 2000 HR
  Bellver, 2008 HR

- Do they reduce success rate of IVF?

  Contradictory data

  2 studies = yes
  Geva, 1996 HR
  Kim, 1998 AJRI

  2 studies = no
  Kutteh, 1999 HR
  Negro, 2007 J Endocrinol Invest

Treatment of anti-thyroid antibodies

Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study

Roberto Negro[1,4], Tiziana Mangieri[2], Lamberto Coppola[2], Giovanni Presicce[2], Eugenio Caroli Casavola[2], Riccardo Ghemondi[2], Giancarlo Locorotondo[2], Paolo Caroli[3], Antonio Pezzarossa[3], Davide Dazzi[3] and Haslinda Hassan[4]

86 +ve for Anti-TPA

43 had T4 — 16 LB = 37%

43 had placebo — 10 LB = 23%

NS

Under-powered study - 340 are required

3-Thrombophilia Markers

- FVL mutation
- Prothrombin mutation
- MTHFR mutation
- Protein S, Protein C and anti-thrombin III deficiency

Thrombophilia Markers

- Conflicting evidence in relation to RIF
- Five studies (n=600) showed higher prevalence of one or more marker in women with RIF Grandome, 2001 FS - Azem, 2004 HR - Coulam, 2006 RBM - Qublan, 2006 HR - Bellever, 2008 HR
- One study (n=396) showed no difference in prevalence

Martinelli, 2003 Haematol

RIF and Thrombophilia

Low-molecular-weight heparin in the treatment of recurrent IVF–ET failure and thrombophilia: A prospective randomized placebo-controlled trial

Table II. Treatment characteristics and reproductive outcome.

	Group A (N = 42)	Group B (N = 41)	p-value
Day 3 FSH (IU/l)	6.1 ± 3.1	6.1 ± 3.3	NS
Days of stimulation	13.8 ± 4.1	13.3 ± 4.2	NS
No. of hMG ampoules	34.5 ± 6.3	34.2 ± 6.1	NS
No of oocytes retrieved	11.3 ± 3.2	11.2 ± 3.1	NS
– Metaphase II oocytes (%)	(93)	(92)	NS
Fertilization rate (%)	(73.1)	(73.3)	NS
No. of day 3 embryos	(8.3)	(8.1)	NS
Grade of embryos			
- Good (%)	(54)	(62)	NS
- Fair (%)	(26)	(25)	NS
- Poor (%)	(20)	(24)	NS
No. of embryos transferred	(3.3)	(3.2)	NS
Implantation rate* (%)	20/130 (15.4)	8/131 (6.1)	<0.001
Pregnancy rate (%)	13/42 (31)	4/41 (9.8)	<0.05
Multiple pregnancy rate (%)	3/13 (23.1)	1/4 (25)	NS
Abortion rate (%)	1/13 (7.7)	2/4 (50)	<0.05
ECTP** rate (%)	2/13 (15.4)	0	NS
Live birth rate (%)	10/42 (23.8)	1/41 (2.4)	<0.01

Use of Heparin in RIF

Human Reproduction Update, Vol.14, No.6 pp. 623–645, 2008

The potential role of heparin in assisted conception

Scott M. Nelson[1,3] and Ian A. Greer[2]

[1]Reproductive and Maternal Medicine, Division of Developmental Medicine, University of Glasgow, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow G31 ER, UK [2]Hull York Medical School, University of York, Heslington, York YO10 5DD, UK

[3]Correspondence address. Tel: +44-141-211-6705; Fax: +44-141-552-0853; E-mail: s.nelson@clinmed.gla.ac.uk

BACKGROUND: Heparan sulphates play key roles in conception and early pregnancy events. The role of heparin, a structural analogue, and its application to assisted conception, is largely unknown. METHODS: Relevant studies were identified by searching PubMed 1966–November 2007 and Google Scholar without limitations. Sensitive search strategies were combined with relevant medical subject headings and text words. RESULTS: The similarities of heparin and heparan, the haemostatic changes induced by ovarian stimulation and the risk of thrombosis, the contribution of thrombophilia to pregnancy and infertility outcomes, early embryo–maternal dialogue and how these various aspects of assisted conception may be modified by heparin are reviewed. CONCLUSIONS: Heparin can alter the haemostatic response to controlled ovarian stimulation and modify the risk of thrombosis. It can also modulate many of the fundamental physiological processes required for blastocyst apposition, adherence and implantation and as well as trophoblast differentiation and invasion due to its similarities with heparan sulphates and has the potential to improve pregnancy rates and outcomes.

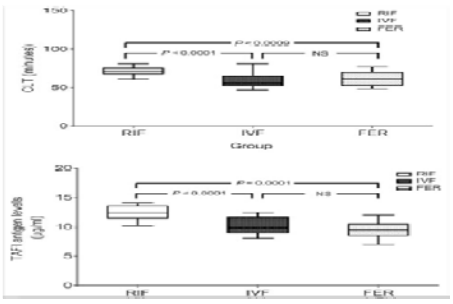
Heparin and RIF

1792 couples

42% (563/1344) vs **27%** (122/448) P<0.001

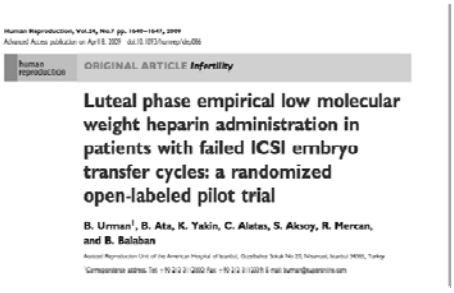
Nelson and Greer, HRU 2008

Reduced Fibrinolytic activity in RIF



Martinez-Zamora et al., 2011

Empirical Heparin and RIF



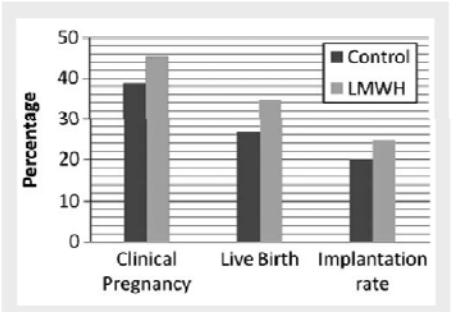
Human Reproduction, Vol.24, No.7 pp. 1640–1647, 2009

human reproduction ORIGINAL ARTICLE *Infertility*

Luteal phase empirical low molecular weight heparin administration in patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot trial

B. Urman[1], B. Ata, K. Yakin, C. Alatas, S. Aksoy, R. Mercan, and B. Balaban

Empirical Heparin and RIF



Empirical Heparin and RIF

Table II Overall outcomes

	LMWH	Control	Absolute difference, 95% CI	P-value
Clinical pregnancy (%)	39/75 (52.0)	29/75 (38.7)	0.0%, −9.8% to +21.8%	0.41
Multiple pregnancy (%) (twins, triplets, quadruplets)	12/39 (30.8) (9.1.2)	10/29 (34.5) (8.2.0)	0.0%, −22.8% to +24.4%	0.94
Implantation	24.5%	19.8%	4.7%, −4.7% to +14.1%	0.33
Ongoing pregnancy[2] (%) (>20 weeks)	36/75 (48.0)	26/75 (34.7)	13.3%, 0.5% to +24.9%	0.05
Live birth[3] (%)	36/75 (48.0)	26/75 (34.7)	13.3%, −0.7% to +27.3%	0.07

Table III Outcome in high-order (≥3) RIF

	LMWH	Control	Absolute difference, 95% CI	P-value
Clinical pregnancy	15/37 (40.5)	15/34 (44.1)	−3.6%, −25.0% to +17.8%	0.87
Multiple pregnancy (%) (twins, triplets, quadruplets)	6/15 (37.5) (5.1.0)	6/13 (30.8) (3.3.0)	6.7%, −20.3% to +40.3%	0.99
Implantation	21.4%	16.0%	5.4%, −7.9% to +18.9%	0.41
Ongoing pregnancy[2] (>20 weeks)	14/37 (37.8)	9/34 (26.5)	11.3%, −9.1% to +31.5%	0.29
Live birth[3]	12/37 (32.4)	8/34 (23.5)	8.9%, −11.5% to +29.3%	0.40

4-Peripheral NK cell testing

- NK level = not useful

  Gilman-Sachs, 1999; Thum, 2005
- NK subtypes = CD16+ and CD69+ appear to be increased in RIF

  Gilman-Sachs, 1999; Ntrivalas, 2001; Coulam and Roussev, 2003; Thum, 2004; Ntrivalas, 2005; Fukui, 206; Thum, 2007
- NK cytotoxicity assay = evidence suggests association with RIF

  Fukui, 1999; Ng, 2002; Coulam and Roussev, 2003; Fukui, 2006; Fukui, 2008

Evidence base

Testing of peripheral blood NK cells could be useful …….

- Small studies (<50)
- Test timing and normal ranges are not standardised
- Difficult to interpret by non-specialists
- Significance of results is not clear

6- Immune suppression

- Intravenous Immunoglobulin (IVIG)
- Steroids
- TNF-a blocking agents

IVIG and RIF

Meta-analysis of published trials showed that IVIG significantly improves the live birth rate in couples with unexplained RIF

NNT = 6

Clark et al, AJRI 2006; 23: 1-13

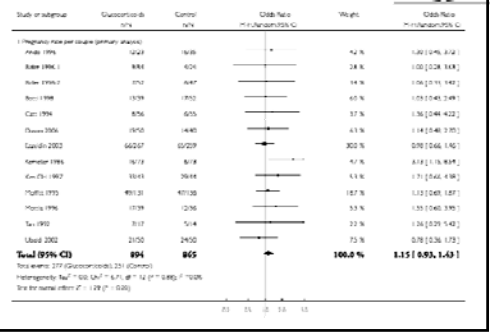
But… included 2 unpublished datasets

Not all studies were RCTs

Cost and potential side effects

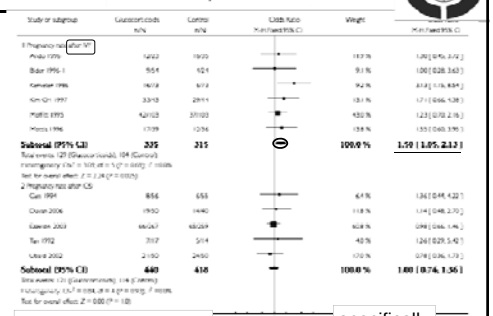
Peri-implantation glucocorticoid administration for assisted reproductive technology cycles (Review)

Boomsma CM, Keay SD, Macklon NS



Peri-implantation glucocorticoid administration for assisted reproductive technology cycles (Review)

Boomsma CM, Keay SD, Macklon NS



RIF was not examined specifically

ORIGINAL ARTICLE

Am J Reprod Immunol.

Treatment with Adalimumab (Humira®) and Intravenous Immunoglobulin Improves Pregnancy Rates in Women Undergoing IVF

Edward C. Winger[1], Jane L. Reed[1], Sherif Ashoush[2], Sapna Ahuja[2], Tarek El-Toukhy[2], Mohamed Taranissi[2]

Immune findings					
TNF-α/IL-10	41.5 ± 8.5	36.2 ± 7.1	40.0 ± 7.1	33.3 ± 3.6	0.02
IFNγ/ IL-10	16.8 ± 8.1	11.0 ± 4.0	11.8 ± 4.1	7.0 ± 5.1	0.001
NK 50:1 cytotoxicity, %	16.9 ± 6.4	15.6 ± 6.9	11.8 ± 2.9	11.9 ± 2.4	0.14
CD56+, %	7.5 ± 4.7	10.4 ± 7.1	4.0 ± 1.8	5.6 ± 2.1	0.012
CD16+/CD56+, %	10.6 ± 8.2	11.3 ± 6.5	10.0 ± 7.5	7.2 ± 2.3	0.79
Success rates					
Implantation rate (No. gestational sacs per embryo transferred)	59% (50/85)	47% (21/45)	31% (4/13)	0% (0/9)	0.0007**
Clinical pregnancy rate (First visit activity per IVF cycle)	85% (34/40)	67% (14/21)	44% (4/9)	0% (0/4)	0.0004**
Live birth rate	73% (30/41)	52% (12/23)	50% (3/6)	0% (0/2)	0.001**

All patients demonstrate pre-conceptional Th1/Th2 ratio elevation (TNF-α/IL-10 > 30.6 and/or IFNγ/IL-10 > 20.9), age <38 years and good IVF response at time of cycle (≥5 Day 3 embryos ≥6 cells).

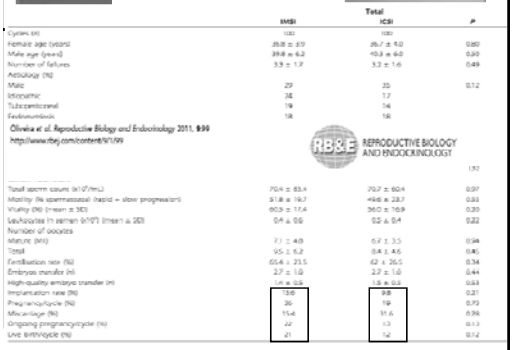
7- Use of IMSI

IMSI versus ICSI outcome: a meta-analysis
Souza Setti et al ,
RBMOnline Oct 2010

- No difference in fertilization rate
- Improved IR (OR = 2.72; 95%CI 1.50-4.95)
- Improved PR (OR = 3.12; 95% CI 1.55-6.26)
- Decreased miscarriage rate (OR = 0.42; 95% CI 0.23-0.78)

Conclusion: More randomized controlled trials are needed to confirm these results

IMSI in RIF



8- Blastocyst Transfer

Cleavage stage versus blastocyst stage embryo transfer in assisted conception (Review)
2007

Comparison 1. Live birth rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth per couple	9	1144	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [1.05, 1.74]
2 Live birth per couple: grouped by number of embryos transferred	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 equal number of embryos transferred	5	920	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.07, 1.85]

Only in good prognosis patients

9 - Assisted Hatching in RIF

- 1:

Effect of laser zona pellucida opening on clinical outcome of assisted reproduction technology in patients with recurrent implantation failure

Valojerdi et al Fertil Steril 2008; 90(1):84-91.

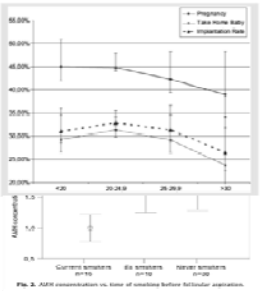
A randomized study of 796 patients with RIF

RESULTS: The clinical pregnancy and implantation rates were similar in the test and control groups.

CONCLUSION: Laser-assisted hatching had no effect in patients with recurrent implantation failure

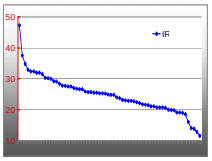
10 - Lifestyle adjustment

- Optimisation of BM
- Smoking cessation

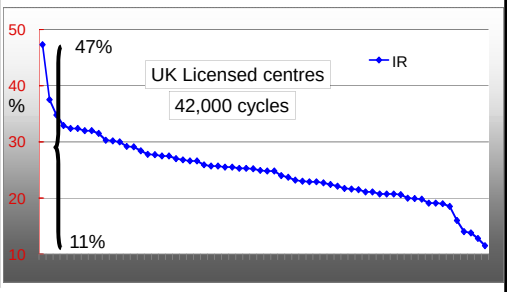


11 - Re-evaluation of treatment protocols

- Stimulation protocols
- Monitoring protocols
- Laboratory protocols
- Embryo transfer policies



Implantation rate in women <35



(HFEA, 2005 data)

Management Algorithm

Conclusion

- RIF is multi-factorial and management should be individualised
- Unexplained category should be recognised and dealt with prior to further treatment
- Few investigations and interventions are evidence based
- Management of expectations is important

“Knowledge is power”

“Half of what we know is untrue. The problem is that we do not know which half!”

F Bacon

Role of adjuvants in IVF

Luciano G. Nardo MD MRCOG
Director, Consultant Gynaecologist
Subspecialist in Reproductive Medicine & Surgery
GyneHealth – Conceive International
Manchester, UK

GyneHealth *Inspiring women's health*

Conflict of interest

Shareholder/Director: GyneHealth
Shareholder/Director: Conceive International
Shareholder/Director: Concepta
Consultancy agreements:
- Ethicon
- Merck Serono
- Ferring
- Cook

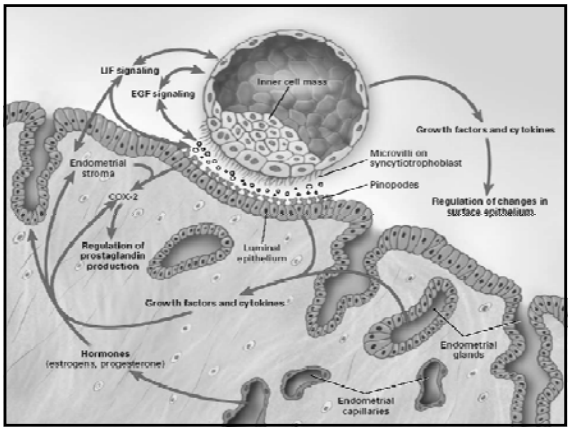
GyneHealth *Inspiring women's health*

Learning objectives

- Be aware of embryo-endometrium cross-talk
- Be aware of the available adjuvants in IVF
- Be aware of the physiological mechanisms of action of each adjuvant
- Be aware of the limitations of each adjuvant
- Be able to recommend evidence-based medical adjuvants

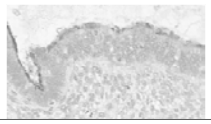
GyneHealth *Inspiring women's health*

Gyne Health
Inspiring women 's health



Treatment strategies

- Embryo
- Endometrium

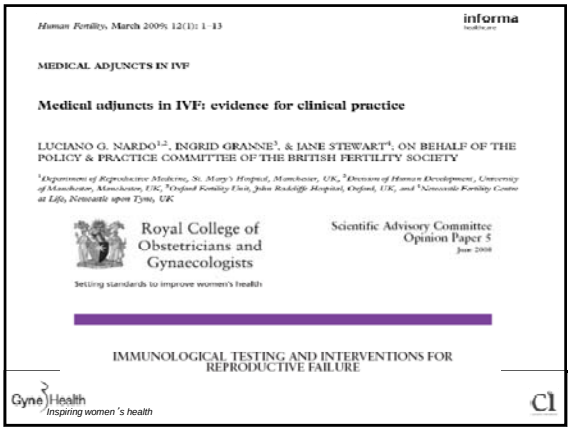


Gyne Health
Inspiring women 's health

Adjuvants in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- Uterine relaxants
- Aspirin
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol

Gyne Health
Inspiring women 's health



Gyne Health
Inspiring women 's health

Medical adjuncts in IVF

- **Immune therapies (IVIg, TNF-alpha, Intralipid)**
- Steroids
- Vasodilators
- Uterine relaxants
- Aspirin
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health
Inspiring women 's health

Intravenous immunoglobulins

The mode of action is far from being fully understood

Raised peripheral NK cells	*Coulam & Goodman, Early Preg 2000*
Positive antithyroid antibodies	*Sher et al., AJRI 1998*
Positive antiphospholipid antibodies	*Sher et al., AJRI 1998*
Shared human leucocyte antigens	*Elram et al., RBM Online 2005*

Gyne Health *Inspiring women's health*

Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial.

***Fertility and Sterility* 2000; 74:1108-1113.**

51 couples with repeated unexplained IVF failure

Treatment with IVIg (500mg/kg) or equivalent volume of normal saline

First infusion on the day of embryo transfer and second infusion was given 4 weeks later if clinical pregnancy confirmed

Live birth rates were 15% in the study group and 12% in the placebo group

IVIg failed to improve the live birth rate in couples with repeated unexplained IVF failure

Gyne Health *Inspiring women's health*

Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulins (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF).

***J Ass Reprod Genet* 2006; 23:1-13.**

Meta-analysis of published RCTs and cohort-controlled trials evaluating IVIg in IVF failure patients

Updated with two unpublished data sets *(still unpublished!)*

2 quoted RCT did not refer to RIF

NNT = 6 women for 1 additional live birth *(? calculation method)*

IVIg treatment significantly increase the live birth rate in couples with repeated unexplained IVF failure

Gyne Health *Inspiring women's health*

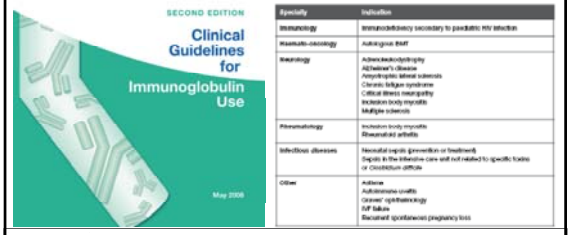
Risks and adverse effects of IVIg treatment

- Anaphylaxis
- Headache, malaise, flushing, fever, nausea, tachycardia
- Renal failure, aseptic meningitis, thromboembolic events, haemolytic anaemia

Sherer et al., Pharmacology 2001

Katzet al., Autoimm Rev 2007

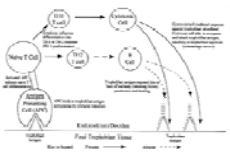
Gyne Health *Inspiring women's health*



Gyne Health *Inspiring women's health*

Tumour Necrosis Factor-alpha

The mode of action is NOT fully understood



Th1 bias — *Kwak-Kim et al., Hum Reprod 2003*

Increased TNF-alpha:IL-4 ratio — *Kalu et al., AJRI 2008*

Association TNF-alpha – NK cells — *Thum et al., AJRI 2007*

Gyne Health *Inspiring women's health*

Tumour Necrosis Factor-alpha

No correlation between serum levels of TNF-alpha and IVF outcome

Fasouliotis et al., *Hum Reprod* 2004
Thum et al., *AJRI* 2007

Correlation between TNF alpha/IL 10 elevation and risk of IVF failure

Immunotherapy (Adalimumab and IVIg) reduces this ration and improves significantly implantation rate

Winger et al., *AJRI* 2011

Gyne Health
Inspiring women 's health

Tumour Necrosis Factor-alpha

Pre-conception TNF-alpha inhibitor does not appear to increase the birth defect rate in women undergoing IVF

Winger et al., *AJRI* 2011

Risks and adverse effects

- Granulomatous disease
- Lymphoma
- Demyelinating disease

Gyne Health
Inspiring women 's health

Intralipid

20% intravenous fat emulsion made up of egg yolks, soyal oil and water used as a source of fat and calories in parental nutrition

Helps to potentiate the immune system

Is not expensive and easy to administer

Gyne Health
Inspiring women 's health

Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- **Steroids**
- Vasodilators
- Uterine relaxants
- Aspirin
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health *Inspiring women 's health*

Steroids

- Alter cytokine production
- Decrease uNK cells
- Modulate autoantibodies expression

Gyne Health *Inspiring women 's health*

Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database Systematic Review: CD005996, 2007*.

Truly RCTs - to investigate whether glucocorticoids treatment improve clinical outcomes in IVF/ICSI, compared to placebo or no glucocorticoids

1966 to June 2006

1759 couples

Primary outcome: live birth rate

Secondary outcomes: ongoing pregnancy rate and pregnancy rate

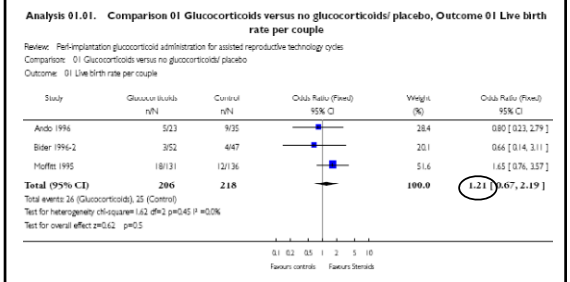
Gyne Health *Inspiring women 's health*

Live birth rate and ongoing pregnancy rate were reported only in 3 trials and analytical pooling showed **no significant difference** (OR 1.21, 95% CI 0.67-2.19, and OR 1.15, 95% CI 0.76-1.75)

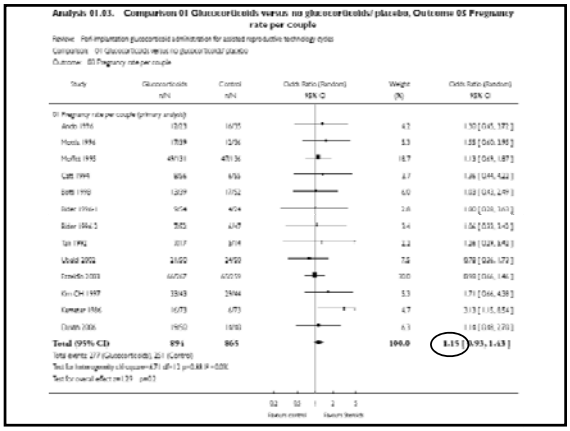
Pregnancy rate was reported in 13 trials and analytical pooling showed **no significant difference** (OR 1.15, 95% CI 0.93-1.43)

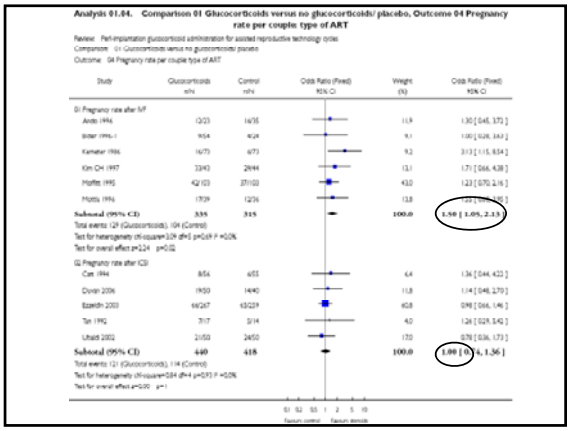
A subgroup analysis of 6 trials (650 subjects) undergoing conventional IVF alone showed a **significantly higher pregnancy rate** (OR 1.5, 95% CI 1.05-2.13)

Gyne Health
Inspiring women 's health



Gyne Health
Inspiring women 's health





Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database Systematic Review: CD005996, 2007*.

Authors' conclusions

Overall, there is no clear evidence that administration of peri-implantation glucocorticoids in ART cycles significantly improves clinical outcome. The use of glucocorticoids in women undergoing IVF (rather than ICSI) was associated with an improvement in pregnancy rates of borderline statistical significance. These findings are limited to the routine use of glucocorticoids and cannot be extrapolated to women with auto-antibodies, unexplained infertility or recurrent implantation failure. Further well designed randomised studies are required to elucidate the possible role of this therapy in well defined patient groups.

Gyne Health
Inspiring women 's health

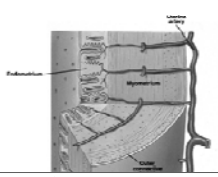
Medical adjuncts in IVF

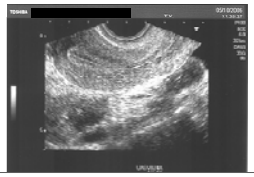
- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- **Vasodilators**
- Uterine relaxants
- Aspirin
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health
Inspiring women 's health

Vasodilators

To enhance endometrial vascularity and development





Gyne Health *Inspiring women 's health*

Nitroglycerine (NTG) *Ohl et al., Hum Reprod 2002*

RCT - IVF patients with implantation failure

No difference in treatment response, implantation rate, pregnancy rate, live birth rate

Sildenafil citrate *Check et al., Clin Exp Obstet Gynecol 2004*

Quasi-randomised trial - IVF patients failing to attain an ET ≥ 8mm

Neither endometrial thickness nor blood supply improved after sildenafil therapy

Gyne Health *Inspiring women 's health*

Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- **Uterine relaxants**
- Aspirin
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health *Inspiring women 's health*

Uterine relaxants

There may be an increased uterine activity in IVF as opposed to natural cycles

Lesny et al., Hum Reprod Update 1998

Adverse uterine contractility may occur at the time of embryo transfer

Morizaki et al., AJOG 1989

Gyne Health
Inspiring women's health

- **Nitroglycerine**
- **Beta2-adrenergic antagonists (ritodrine and terbutaline)**
- **Progesterone**

Observational studies showing no benefits

Gyne Health
Inspiring women's health

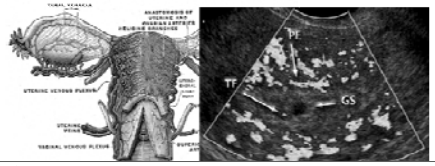
Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- Uterine relaxants
- **Aspirin**
- Heparin
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health
Inspiring women's health

Aspirin

Administration induces a shift from thromboxane A_2 to prostacyclin, leading to vasodilatation and increased peripheral blood supply



Gyne Health
Inspiring women's health

Low-dose Aspirin and Pregnancy

- Aspirin decreases the incidence of pre-eclampsia and preterm labour in high-risk women, when started in the second trimester

  The CLASP Study, 1994

- Aspirin and heparin are beneficial for women with recurrent miscarriage and APL syndrome

  Kutteh, 1996; Tulppala *et al*., 1997

Gyne Health
Inspiring women's health

Human Reproduction Update, pp. 1–8, 2007 doi:10.1093/humupd/dmm005

Low-dose aspirin for *in vitro* fertilization: a systematic review and meta-analysis

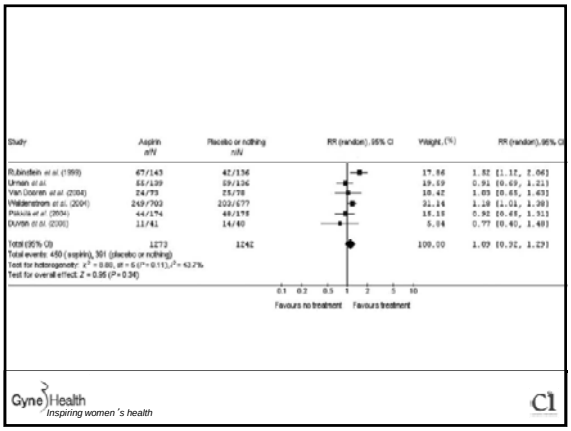
T.A.Gelbaya[1], M.Kyrgiou[2], T.C.Li[3], C.Stern[4] and L.G.Nardo[5,6]

Truly RCTs - to determine the effect of low-dose aspirin versus placebo or no treatment on the likelihood of clinical outcomes in IVF/ICSI cycles

Jan 1980 to March 2006
6 trials, 2515 cycles

Primary outcome: Clinical pregnancy rate

Gyne Health
Inspiring women's health



Gyne Health
Inspiring women's health

Live birth rate was reported only in 2 trials and analytical pooling showed **no significant difference** (OR 1.08, 95% CI 0.83-1.40)

Low-dose aspirin did not have any effect in poor responders (Lok *et al*., 2004) and in recipients of donated oocytes (Weckstein *et al*., 1997)

Gyne Health
Inspiring women's health

Another meta-analysis on the use of aspirin in IVF cycles reached the same conclusions

Khairy et al., Fertil Steril 2007; 88:822-831

RCT – adjuvant therapy with low-dose aspirin and prednisolone does not improve uterine blood flow, implantation and pregnancy rates

Revelli et al., Fertil Steril [epub ahead of print]

Yet, a meta-analytical pooling showed different results

Ruopp et al., Fertil Steril 2008; 90:71-76

Gyne Health
Inspiring women's health

Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- Uterine relaxants
- Aspirin
- **Heparin**
- Growth hormone / DHEA / Testosterone
- Oestradiol supplementation

Gyne Health *Inspiring women's health*

Heparin

Coagulation disorders could interfere with the different stages of embryo implantation

Chamley et al., 1998

Activation of the coagulation cascade and impairment of fibrinolysis occur during controlled ovarian stimulation and are more pronounced in women with OHSS

Rogolino et al., 2003

Gyne Health *Inspiring women's health*

In the literature

A few heterogenous clinical studies investigating the role of heparin in women with acquired thrombophilia undergoing IVF

No differences in implantation and pregnancy rates in APA positive women treated with heparin and aspirin

Schenk et al., 1996; *Kutteh et al., 1997*

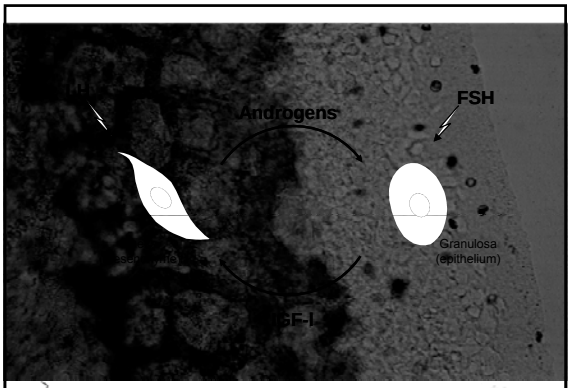
Double-blind cross-over RCT including 143 autoantibody positive women who had ≥ 10 failed ET cycles showed no differences in implantation and pregnancy rates between the treatment and placebo groups

Stern et al., 2003

Gyne Health *Inspiring women's health*

Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- Uterine relaxants
- Aspirin
- Heparin
- **Growth hormone / DHEA / Testosterone**
- Oestradiol supplementation



Growth hormone

Cochrane review of 9 trials (401 subjects) demonstrated that in patients with no history of poor response GH therapy did NOT affect live birth rate, whilst in poor responders the benefit just reached statistical significance

Harper et al., 2003

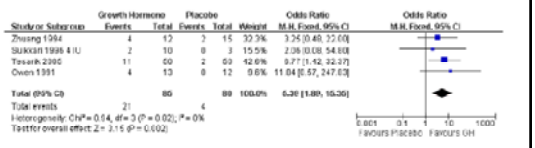
In 2004, NICE recommended NOT to use GH treatment due to the limited evidence and the lack of significant improvements in pregnancy rates

Growth hormone for in vitro fertilization (Review)

Duffy JMN, Ahmad G, Mohiyiddeen L, Nardo LG, Watson A

THE COCHRANE COLLABORATION

Figure 9. Forest plot of comparison: 2 Growth hormone versus placebo: Poor responder as defined by the study, outcome: 2.1 Live birth rate per woman randomised.



Gyne Health
Inspiring women 's health

DHEA

25mg TDS in women with reduced ovarian reserve improves significantly AMH levels and ovarian reserve. The benefits appear to be in parallel with longer DHEA use and is more pronounced in younger women

Gleicher et al., *Reprod Biomed Online* 2010

75 mg OD in poor responders undergoing IVF improves embryo quality and live birth rate – RCT

Wiser et al., *Hum Reprod* 2010

4-12 weeks course of treatment reduces embryo aneuploidy as shown by PGS studies

Gleicher et al., *Reprod Biol Endocrinol* 2010

Gyne Health
Inspiring women 's health

Human Reproduction Vol.21, No.7 pp. 1884–1893, 2006
Advance Access publication March 3, 2006

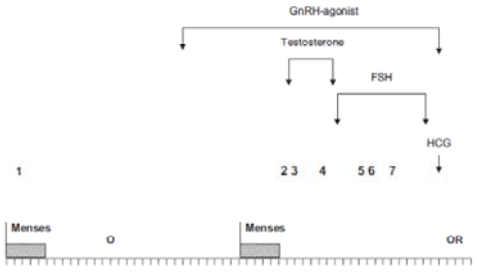
Pretreatment with transdermal testosterone may improve ovarian response to gonadotrophins in poor-responder IVF patients with normal basal concentrations of FSH

Juan Balasch[1,3], Francisco Fábregues[1], Joana Peñarrubia[1], Francisco Carmona[1], Roser Casamitjana[2], Montserrat Creus[1], Dolors Manau[1], Gemma Casals[1] and Juan A.Vanrell[1]

[1]Institut Clinic of Gynecology, Obstetrics and Neonatology and [2]Hormonal Laboratory, Hospital Clinic-Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain

[3]To whom correspondence should be addressed at: Institut Clinic of Gynecology, Obstetrics and Neonatology, Hospital Clinic-Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), C/Casanova 143, 08036-Barcelona, Spain. E-mail: jbalasch@ub.edu

BACKGROUND: Treatment of poor-responder patients to controlled ovarian stimulation for assisted reproduction, who have normal basal FSH concentrations, is one of the most difficult challenges in reproductive medicine. This study investigated the usefulness of testosterone pretreatment in such patients. METHODS: Prospective, therapeutic, self-controlled clinical trial including 25 consecutive infertile patients who had a background of the first and second IVF treatment cycle cancellations due to poor follicular response, in spite of vigorous gonadotrophin ovarian stimulation and having normal basal FSH levels. In the third IVF attempt, all patients received transdermal testosterone treatment (20 μg/kg per day) during the 5 days preceding gonadotrophin treatment. RESULTS: Twenty patients (80%) showed an increase of over fivefold in the number of recruited follicles, produced 5.8 ± 0.4 (mean ± SEM) oocytes, received two or three embryos and achieved a clinical pregnancy rate of 30% per oocyte retrieval. There were 20% cancelled cycles. CONCLUSION: Pretreatment with transdermal testosterone may be a useful approach for women known to be low responders on the basis of a poor response to controlled ovarian stimulation but having normal basal FSH concentrations.



Gyne Health
Inspiring women 's health

Table II. Oocyte retrieval and outcome of IVF in the testosterone supplemented cycle in 25 patients

Variable	Result
Cancelled cycles [*n* (%)]	5 (20)
Patients with HCG and ovum retrieval	20 (80)
Number of follicles punctured[a] (mean ± SEM)	8.5 ± 0.7
Number of oocytes retrieved[a] (mean ± SEM)	5.8 ± 0.4
Number of metaphase II oocytes[a] (mean ± SEM)	4.6 ± 0.4
Number of fertilized oocytes[a] (mean ± SEM)	3.8 ± 0.4
Number of embryos per patient[a] (mean ± SEM)	3.5 ± 0.3
Number of patients with embryo transfer[b]	20
Number of embryos per replacement[a] (mean ± SEM)	2.7 ± 0.1
High quality embryos replaced[a] (mean ± SEM)	1.75 ± 0.2
Implantation rate (%)[b]	16.6
Clinical pregnancies	
Number	6
Per started cycle (%)	24
Per oocyte retrieval (%)	30
Per embryo transfer (%)	30
Twins [*n* (%)]	3 (50)
Miscarriages [*n* (%)]	1 (16.6)

Gyne Health
Inspiring women 's health

Human Reproduction Vol.21, No.5 pp. 1204–1213, 2006 doi:10.1093/humrep/del481
Advance Access publication February 13, 2006

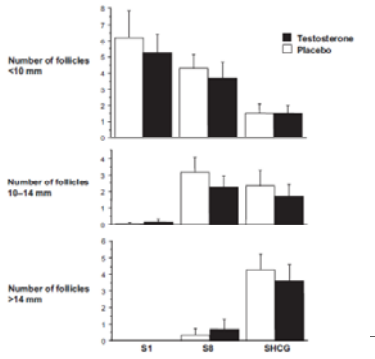
Effects of transdermal testosterone application on the ovarian response to FSH in poor responders undergoing assisted reproduction technique—a prospective, randomized, double-blind study

N.Massin[1], I.Cedrin-Durnerin[1], C.Coussieu[2], J.Galey-Fontaine[1], J.P.Wolf[3] and J.-N.Hugues[1,4]

[1]Reproductive Medicine Unit, Jean Verdier Hospital, University Paris XIII, Bondy, [2]Department of Hormonal Biochemistry, Hotel Dieu Hospital, Paris and [3]Department of Reproductive Biology, Jean Verdier Hospital, University Paris XIII, Bondy, France

[4]To whom correspondence should be addressed at: Reproductive Medicine Unit, Jean Verdier Hospital, Avenue du 14 juillet, 93143 Bondy Cedex, France. E-mail: jean-noel.hugues@jvr.ap-hop-paris.fr

BACKGROUND: In primates, androgens can play a synergistic role with FSH in promoting the early follicular recruitment, which is critical in assisted reproduction technique programmes. **OBJECTIVE:** To assess whether poor responders can benefit from androgen application. **METHODS:** Inclusion criteria were a previous poor ovarian response to controlled ovarian stimulation and a decreased hormonal ovarian reserve. Selected women were randomized to receive either transdermal application of testosterone ($n = 24$) or placebo ($n = 25$) gel for 15 days before FSH treatment for a second IVF cycle. Similar GnRH analogue and equivalent FSH daily doses were used in both cycles. The primary outcome was the total number of oocytes retrieved. **RESULTS:** Testosterone gel application resulted in a significant increase in plasma testosterone levels but did not significantly improve the antral follicle count. Furthermore, after gel application, the main parameters of the ovarian response (numbers of pre-ovulatory follicles, total and mature oocytes and embryos) did not significantly differ between testosterone and placebo-treated patients. **CONCLUSION:** No significant beneficial effects of androgen administration on the ovarian response to FSH could be demonstrated. However, subsequent clinical trials are needed to determine whether an optimal dose and/or a longer duration of testosterone administration may be helpful.



Gyne Health
Inspiring women 's health

Medical adjuncts in IVF

- Immune therapies (IVIg, TNF-alpha, Intralipid)
- Steroids
- Vasodilators
- Uterine relaxants
- Aspirin
- Heparin
- Growth hormone
- **Oestradiol supplementation**

Gyne Health
Inspiring women 's health

Oestradiol supplementation

Oestradiol is essential for endometrial priming and is responsible for proliferation of uterine surface epithelium, glands, stroma and blood vessels

Oestradiol levels are affected by the stimulation protocols

Gyne Health
Inspiring women 's health

The use of estradiol for luteal phase support in in vitro fertilization/intracytoplasmic sperm injection cycles: A systematic review and meta-analysis

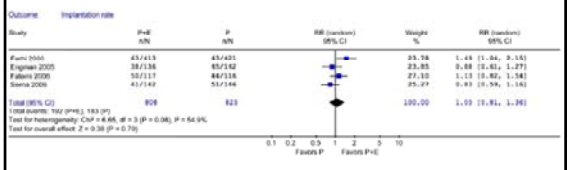
Tarek A. Gelbaya, M.D.,[a] Maria Kyrgiou, M.D.,[b] Ioanna Tsoumpou, M.B.ChB.,[c] and Luciano G. Nardo, M.D.[a,]*

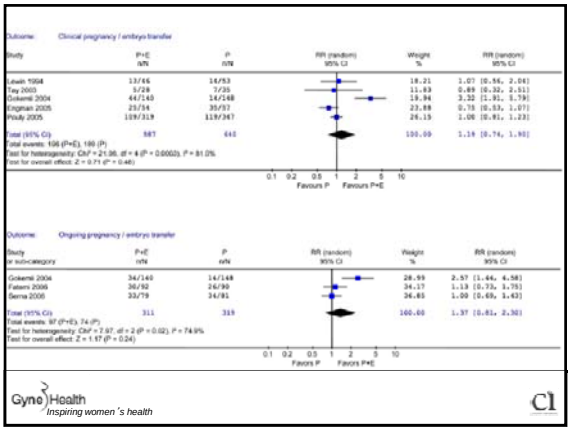
[a] Department of Reproductive Medicine, St. Mary's Hospital, Central Manchester and Manchester Children's University Hospitals, Manchester; [b] Department of Obstetrics and Gynaecology, Lancashire Teaching Hospitals, Preston; and [c] Department of Obstetrics and Gynaecology, Royal Lancaster Hospital, Lancaster, United Kingdom

10 RCTs comparing E_2 and Prog versus Prog alone

1993 – 2007

- Implantation rate
- Clinical pregnancy rate
- Ongoing pregnancy rate





Conclusions

- Current evidence for adjuvants in routine IVF is still weak
- Further studies are required
- When unproven therapeutic approaches are prescribed, patients should be made aware of the lack of evidence for clinical benefits and the potential risks, if any

Current evidence for alternative therapies in IVF

Elisabet Stener-Victorin

Institute of Neuroscience and Physiology, Department of Physiology, Sahlgrenska Academy, Göteborg University, Sweden *and*

Department of Obstetrics and Gynecology at the First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150040, China

The Sahlgrenska Academy

Disclosure

- Nothing to disclose

The Sahlgrenska Academy

Learning objectives

1. Rational for acupuncture during IVF
2. How does acupuncture affect endometrial circulation?
3. Acupuncture as pain relief during oocyte aspiration
4. Efficacy of acupuncture during embryo transfer

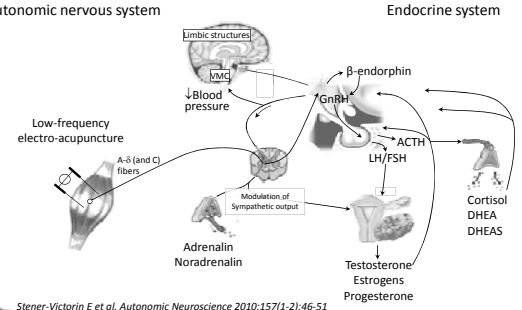
The Sahlgrenska Academy

Why acupuncture during in-vitro fertilization?

Acupuncture Physiology

Autonomic nervous system

Endocrine system



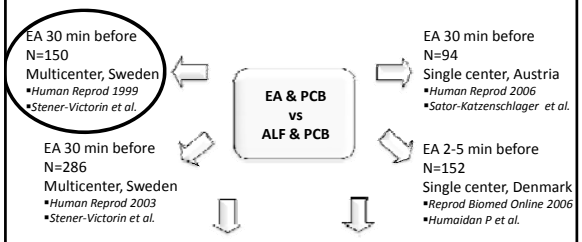
Stener-Victorin E et al. Autonomic Neuroscience 2010;157(1-2):46-51

How did it start?


Repeated electroacupuncture (EA) treatments→ Increase uterine artery blood flow

- EA treatments during 4 weeks (8 treatments) prior oocyte aspiration/ET reduce the blood flow impedance (PI) in the uterine arteries to normal levels at the time of ET
  - *Stener-Victorin et al. Human Reproduction, 1996; 11: 1314 – 1317*
  - *Ming H et al. Taiwan J Obstet and Gynecology 2009; 48: 148-151*
- **No effect on live birth rate!!**

Acupuncture as pain relief during oocyte aspiration



Efficacy of Acupuncture during Embryo Transfer

What is known?

There are at least 11 RCTs investigating the efficacy of acupuncture during ET

- Three found benefit of acupuncture relative to control
  - *Paulus WE, et al Fertility and Sterility 77, 721-724 (2002)*
  - *Dieterle S, et al Fertil Steril 85, 1347-1351 (2006)*
  - *Westergaard LG, et al. Fertil Steril 85, 1341-1346 (2006)*
- Six found no difference
  - *Moy I, et al. Fertil Steril 95:583-587 (2011)*
  - *Andersen D, et al. Reprod Biomed Online 21, 366-372 (2010)*
  - *Domar AD, et al. Fertil Steril 91:723-726(2009)*
  - *Smith C, et al. Fertil Steril 85, 1352-1358 (2006)*
  - *Benson M, et al. Fertility and Sterility Suppl, 135 (2006)*
  - *Paulus W, et al. Abstract of the 19th Annual Meeting of the ESHRE, Spain, O-052 (2003)*
- Two found a benefit of control relative to acupuncture
  - *So EW, et al. Hum Reprod 24:341-348 (2009)*
  - *Moy I, et al Fertil Steril 95: 583-587(2011)*

Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy

Wolfgang E. Paulus, M.D.,* Mingmin Zhang, M.D.,* Erwin Strehler, M.D.,* Imam El-Danasouri, Ph.D.,* and Karl Sterzik, M.D.*
Christian Gynecologic Institute, Ulm, Germany

n=160

ACU (n=80)
Acupuncture 25 min before and after ET – de qi 2 times
Before: PC6,SP8,LR3, GV20, ST29
After: ST36, SP6, 10, LI4
Auricular: Shenmen, Zhigong, Neifenmi, Naodian

Control (n=80)
ET without acupuncture
Remained lying still 25 min after ET

Results
- Pregnancy rate: **↑ ACU (34/80) 42.5% vs controls (21/80) 26.3%**

Conclusion(s)
- Acupuncture seems to be a useful tool for improving pregnancy rate after ART

Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial

Fertility and Sterility® Vol. 85, No. 5, May 2006

Lars G. Westergaard, M.D., Ph.D.,* Qunhui Mao, M.D.,* Marianne Krogslund,* Yoon Sundvold,* Susan Lenz, M.D., Ph.D.,* and Jørgen Grinsted, M.D., Ph.D.*
*Fertility Clinic, Triangelen, Hellerup, †Holistic Acupuncture Clinic, Frederiksberg C, and ‡Sundhed Acupuncture ApS, Vanlø, Denmark

n=273

ACU 1 (n=95)
Acupuncture 25 min before and after ET – de qi 2 times
Before: PC6,SP8,LR3, GV20, ST29
After: ST36, SP6, 10, LI4

ACU 2 (n=91)
Acupuncture 25 min before and after ET – de qi 2 times
Before: PC6,SP8,LR3, GV20, ST29
After: ST36, SP6, 10, LI4
2 days after ET: GV20, CV3, ST29, 36, SP6, 10, LI4

Control (n=87)
ET without acupuncture
Remained lying still 1 h after ET

Result(s)
- Clinical pregnancy rate**: ↑ ACU 1 (37/95) 39% vs. Control (21/87) 26%**
- Ongoing pregnancy rate: **↑ ACU 1 (34/95) 36% vs. control (19/87) 22%**

Conclusion(s)
- Acupuncture on the day of ET significantly improves the reproductive outcome of IVF/ICSI, compared with no acupuncture. Repeating acupuncture on ET day 2 provided no additional beneficial effect

Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer

Caroline Smith, Ph.D.,[a] Meaghan Coyle, B.Hlth.Sc. (Acup.),[b] and Robert J. Norman, M.D.[c,d]
[a]School of Health Science, The University of South Australia; [b]Department of Obstetrics and Gynecology, The University of Adelaide; [c]Research Centre for Reproductive Health, The Queen Elizabeth Hospital, University of Adelaide; and [d]Repromed, Adelaide, South Australia, Australia

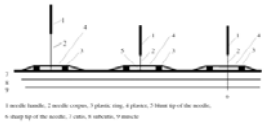
Fertility and Sterility® Vol. 85, No. 5, May 2006

n=228

ACU (n=110)
3 acupuncture, 25 min, 1) on day 9 of stimulation injections, 2) before and 3) after ET – de qi 2 times
Point selection: According to TCM based on Paulus et al. 2002 except LI4 and GV20

Sham ACU (n=118)
3 acupuncture, 25 min, 1) on day 9 of stimulation injections, 2) before and 3) after ET – de qi 2 times
Point selection: Close to but not on the real acupoints.
Streitberger placebo needle.

Problems with heterogeneity in Acupuncture Trials



Kleinheinz and Streitberger, Lancet 1998

Sham control has not been demonstrated to be inert →
Rather two different acupuncture techniques that are used →
Power calculation has to be based on this assumption

Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer

Caroline Smith, Ph.D.,[a] Meaghan Coyle, B.Hlth.Sc. (Acup.),[b] and Robert J. Norman, M.D.[c,d]
[a]School of Health Science, The University of South Australia; [b]Department of Obstetrics and Gynecology, The University of Adelaide; [c]Research Centre for Reproductive Health, The Queen Elizabeth Hospital, University of Adelaide; and [d]Repromed, Adelaide, South Australia, Australia

Fertility and Sterility® Vol. 85, No. 5, May 2006

n=228

ACU (n=110)
3 acupuncture, 25 min, 1) on day 9 of stimulation injections, 2) before and 3) after ET – de qi 2 times
Point selection: According to TCM based on Paulus et al. 2002 except LI4 and GV20

Sham ACU (n=118)
3 acupuncture, 25 min, 1) on day 9 of stimulation injections, 2) before and 3) after ET – de qi 2 times
Point selection: Close to but not on the real acupoints.
Streitberger placebo needle.

Result(s)

- Pregnancy rate: **ACU 31% vs sham ACU23%** → odds of achieving a pregnancy were 1.5 higher in the ACU but did not differ significantly from the sham ACU group

Conclusion(s)

- No significant difference in the pregnancy rate between groups; however, a smaller treatment effect can not be excluded.
- Our results suggest that acupuncture was safe for women undergoing ET

Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study

Fertility and Sterility® Vol. 85, No. 5, May 2006

Stefan Ebrecht, M.D.,[a] Guo Ying, M.D.,[a,b] Wolfgang Hentzmann, M.D.,[a] and Andreas Neuer, M.D.[a]

[a]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Witten/Herdecke, Dortmund, Germany; and [b]Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

n=225

ACU (n=116)
2 acupuncture, 30 min, 1) after ET 2) again 3 days later
After ET: CV3, 6, ST 29, PC6, SP8 and 10
3 days later: LI4, ST36, SP6, KI3, LR3
Auricular: See Paulus et al. 2002

Sham ACU (n=109)
2 acupuncture, 30 min, 1) after ET 2) again 3 days later
After ET: TE9, 12, GB31, 32, 34
3 days later: Same as above
Auricular: Different from Paulus et al Placebo treatment designed not to influence fertility

Result(s)
- Clinical pregnancy rate: ↑ **ACU 33.6% vs sham ACU 15.6%**
- Ongoing pregnancy rate: ↑ **ACU 28.4% vs sham ACU 13.8%**

Conclusion(s)
- Luteal-phase acupuncture has a positive effect on the outcome of IVF/ICSI

The Sahlgrenska Academy

ASRM 2007

O-106

ACUPUNCTURE LOWERS PREGNANCY RATES WHEN PERFORMED BEFORE AND AFTER EMBRYO TRANSFER. L. B. Craig, A. R. Criniti, K. R. Hansen, L. A. Marshall, M. R. Soules. Reproductive Endocrinology & Infertility, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Seattle Reproductive Medicine, Seattle, WA; Pacific Northwest Fertility & IVF Specialists, Seattle, WA.

n = 107

- Positive pregnancy test ↑ **control group (36/46) 78.3%** than the **acupuncture group (25/48) 52.1%**
- Clinical pregnancy rate ↑ **control group 69.6%** than in the **acupuncture group 43.8%**

In contrast to previous reports, acupuncture before and after embryo transfer was associated with lower biochemical and clinical pregnancy rates when compared to the control group.

The value of acupuncture in pateints undergoing IVF needs to be further examined before recommending it to patients.

The Sahlgrenska Academy

A randomized double blind comparison of real and placebo acupuncture in IVF treatment

Emily Wing See So, Ernest Hung Yu Ng[1], Yu Yeuk Wong, Estella Yee Lan Lau, William Shu Biu Yeung and Pak Chung Ho

Department of Obstetrics and Gynaecology, The University of Hong Kong, Hong Kong Special Administrative Region, Pokfulam Road, Hong Kong, People's Republic of China

n=370

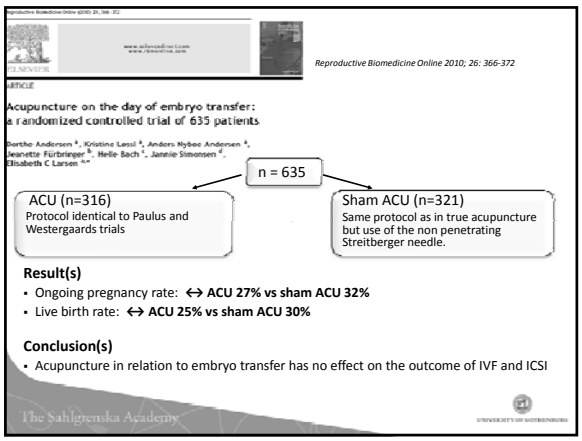
ACU (n=185)
During 25 min before ET: PC6, SP8, LR3, GV20, ST29
During 25 min after ET: ST36, SP6, 10, LI4
Stimulation: De Qi 2 times

Placebo ACU (n=185)
Same protocol as in true acupuncture but use of the non penetrating Streitberger needle

Result(s)
- Overall pregnancy rate: ↑ **placebo ACU 55.1% vs ACU 43.8%**
- No difference in live birth rate
- Reduction in endometrial and subendometrial vascularity, cortisol and anxiety level in both groups

Conclusion(s)
- Placebo acupuncture was associated with a significantly higher overall pregnancy rate when compared with real acupuncture. Placebo acupuncture may not be inert.

The Sahlgrenska Academy



Why acupuncture during embryo transfer?

Is there any rational?

The Sahlgrenska Academy

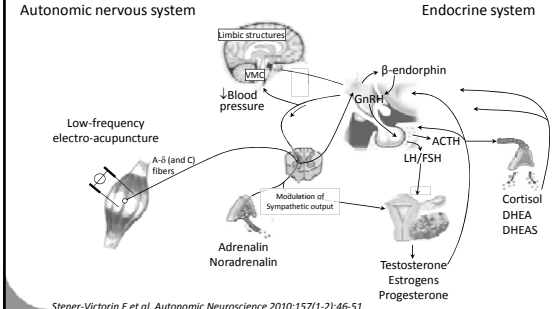
To date, there are few trial investigating possible mechanisms of action of acupuncture *or* presenting a rational of how/why acupuncture may improve IVF outcome when given before and after ET

The Sahlgrenska Academy

Acupuncture Physiology

Autonomic nervous system

Endocrine system



Stener-Victorin E et al. Autonomic Neuroscience 2010;157(1-2):46-51

The Sahlgrenska Academy

Number of treatments?

Cumulative effects of repeated treatment

Repeated acupuncture treatments → gradually enhance neuroendocrine and autonomic effects

- 6 - 12

- *Bossut et al. 1991*
- *Carlsson et al 2000*
- *Dyrehag et al 1997*
- *Johansson et al 2011*
- *List et al. 1992*
- *Lundeberg et al. 1988, 1993*
- *Stener-Victorin et al. 1996, 2000, 2002, 2008*

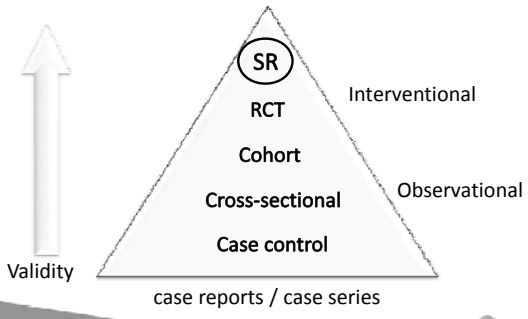
1 – 3 treatments = no treatment!

The Sahlgrenska Academy

What evidence exist for acupuncture during ET?

The Sahlgrenska Academy

Hierarchy of major study designs



The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

BMJ

RESEARCH

Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis

Systematic review

A systematic review and meta-analysis of acupuncture in *in vitro* fertilisation

Acupuncture and assisted conception (Review)

THE COCHRANE COLLABORATION®

2008: Concluded that acupuncture increases clinical pregnancy and live birth rate

2008: Found a pooled benefit on the clinical pregnancy

Concluded that acupunture increase live birth rate but not clinical pregnancy

Updated Cochrane → no effect

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

Acupuncture during ET??

- Does acupuncture enhance success rate of IVF treatment when performed around the time of ET?
  - According to the most recent systematic reviews/meta-analyses and after inclusion of the latest studies → acupuncture does ***NOT*** improve live birth rate
- What level of evidence is required by clinicians to incorporate a particular intervention into clinical practice?
  - Systematic reviews/meta-analyses → highest level available evidence
  - **However,** conclusions of a systematic review is dependent upon the quality of its component studies: e.g.
    - **Are included studies small?**
    - **Are they heterogenous?**

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

Does acupuncture improve IVF outcome?

How should such trial be performed?

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

Changes in serum cortisol and prolactin associated with acupuncture during controlled ovarian hyperstimulation in women undergoing in vitro fertilization–embryo transfer treatment

Paul C. Magarelli, M.D.,[a] Diane K. Cridennda, L.Ac.,[b] and Mel Cohen, Ph.D.[a]

[a]Reproductive Medicine and Fertility Centers and [b]East Woods Acupuncture, Colorado Springs, Colorado

Combination of acupuncture before and during ET (11 treatments)

- Beneficial regulation of cortisol and prolactin by acupuncture during hormonal stimulation of the IVF treatment → same pattern as normal fertile cycle dynamics
  - *Magarelli et al Fertil Steril. 2009 Dec;92(6):1870-9.*

TABLE 2

Stress hormones: Reproductive outcomes data.

	Ac (n = 34)	Control (n = 33)	P
Pregnancy rate (+hCG)	18 (53)	14 (41)	<.05
Clinical pregnancy rate (+fetal heart beat [FHB]), %	51	37	<.05
Miscarriages	0 (0)	2 (6)	<.05
Ectopic pregnancies	1 (3)	3 (8)	NS
Birth per pregnancy	17 (94)	9 (64)	<.05
Multiple births	2 (11)	5 (33)	<.05

Note: Data are presented as n (%) unless otherwise specified. NS = not significant (P>.05). All patients are IVF patients who underwent IVF medication stimulation, egg retrieval, and ET. N = 67.

Magarelli. Changes in cortisol and PRL with acupuncture. Fertil Steril 2009.

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG

What is needed?

- Optimize treatment protocols (combine acupuncture before and during ET) → efficacy trials may establish whether acupuncture ***can work*** under ideal circumstances

Conclusion

- No evidence that acupuncture improve live birth rate during IVF
- No evidence for adverse effects of acupuncture
- Need of a large RCT with optimized protocol with combined acupuncture before and during ET

The Sahlgrenska Academy

UNIVERSITY OF GOTHENBURG


Thank you!

How can psychology and counselling help optimise treatment?

Jacky Boivin, PhD, CPsychol

School of Psychology
Cardiff

Conflict of interest (past three years)

- Speaker fees, honorarium and/or research funding from Merck-Serono S.A.

Learning objectives

- Discover that developments in medicine impact practice of psychology & counselling
- Recognise need for greater involvement of medical staff in delivery of psychosocial care
- Describe the Integrated Psychosocial Approach to Infertility Care (IPA Care)
- Describe tools and techniques available to medical staff to tackle burden of treatment and evaluate their impact on treatment trajectory

History and evolution

Psyche → Infertility

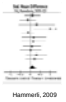
Year	% unexplained	% range
< 1960	34.0	(Sandler, 1955)
1960 - 1969	21.84	11.2 - 58.0
1970 - 1979	16.13	10.0 - 27.0
1980 - 1982	12.1	5.8 - 19.4
Templeton et al. 1982		

Infertility → Psyche

Monitoring

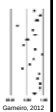
Assessment
Follow-up

Evaluation



Hammerli, 2009

Compliance



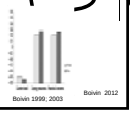
Gameiro, 2012

1940 — 1977 — 1978 — 2003 — 2012

Karl Menninger — Helen Deutch

"Infertility as a psychic conflict salling under a gynaecological flag" Menninger, 1943

Barbara Eck Menning Advocacy movement — Mahlstedt 195 "Working through" & grief & loss therapies



Boivin 1999; 2003

Boivin 2012

Human Reproduction, Vol.27, No.4 pp. 941–950, 2012
Advanced Access publication on January 18, 2012 doi:10.1093/humrep/der457

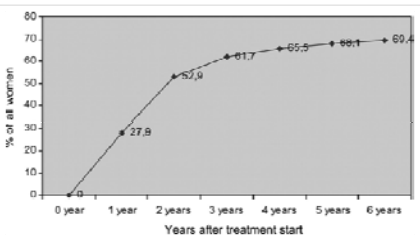
human reproduction OPINION

Tackling burden in ART: an integrated approach for medical staff

Jacky Boivin[1,*], Alice D. Domar[2], Daniel B. Shapiro[3], Tewes H. Wischmann[4], Bart C.J.M. Fauser[5], and Christianne Verhaak[6]

Compliance in ART

Fertility treatment is successful…

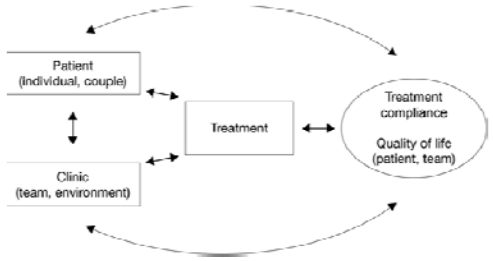


Cumulative percentage of the initial cohort in the 1338 women (study population I) with at least one delivery after 5 years of follow-up based on complete follow-up data from the National Medical Birth Register

Pinborg, A. et al. Hum. Reprod. 2009: Danish sample

Cardiff Fertility Studies

Integrated approach showing reciprocal influences among patient, clinic and treatment in influencing treatment continuation and quality of life.



Boivin J et al. Hum. Reprod. 2012;27:941-950

human reproduction

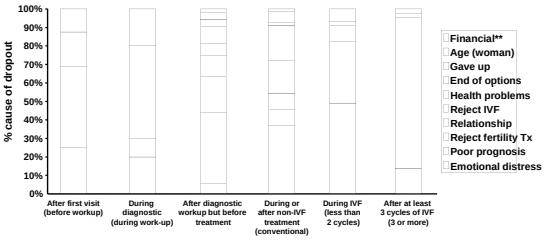
Tackling burden in ART: an integrated approach for medical staff

Table I
Factors cited by patients as contributing to their decision to end treatment

Patient (individual, couple)	Clinic (team, environment)	Treatment
Fear and negative treatment attitudes	Sub-optimal organizational care	Physical burden
Unfavourable attitudes to treatment (e.g. fear about health of baby, perceiving treatment to be unnatural, perceived costs)	Stressful care (disorganized, assembly-line treatment, different staff on clinic visits)	Worry about physical burden, physical symptoms and discomfort
Values (ethical, moral) and preferences incompatible with treatment	Insufficient information on alternatives, inadequate co-ordination	Injection protocols and adherence to treatment
Idiosyncratic barriers	Depersonalization (poor coordinated follow-up, results at work and without partner present)	Cycle monitoring
Psychological and emotional factors		Disruption of work and daily activities
Pre-ART psychological profile	Lack of continuity of care and negative doctor attitudes	Worry about cost
Difficulty in tolerating negative emotions for extended time periods	Overly bureaucratic procedures	Handling of poor prognosis
Uncertainty	Negative staff-patient interactions	Loss of hope for success (cycle number dependent)
Strain of repeated ART cycles	Lack of empathy, poor listening skills, insufficient care of the man, insufficient time for questions	
Relational strain		
Fear that ART will negatively impact relationship		
Perceived and actual asymmetry in treatment focus between partners (particularly prevalent in early phases of medical involvement)		

Boivin et al: Tackling Burden in ART. Humn Reprod, 2012

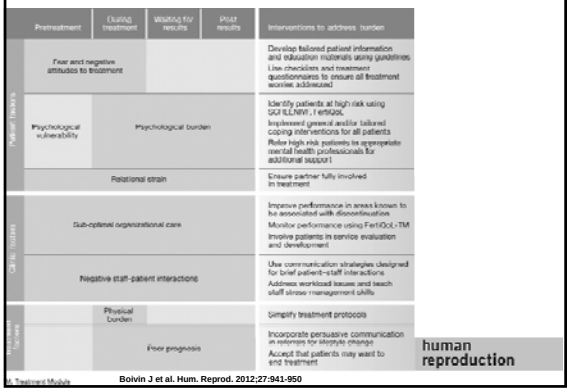
Psychosocial issues differ across stages of treatment



Brandes et al. *Hum Reprod.* 2009;24:3127,
consecutive cohort of 1391 patients
**IVF subsidised by national health service, which would reduce its impact

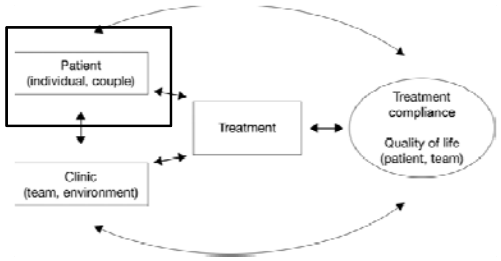
Cardiff Fertility Studies

Interventions differ across stages of treatment



Boivin J et al. Hum. Reprod. 2012;27:941-950

Integrated approach showing reciprocal influences among patient, clinic and treatment in influencing treatment continuation and quality of life.



Boivin J et al. Hum. Reprod. 2012;27:941-950

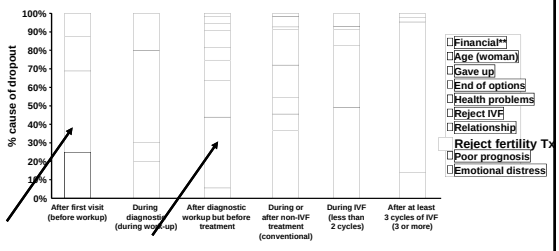
human reproduction

Patient factors

- **Fear and negative attitudes to treatment**
  - Education (pre-treatment, treatment changeover)
- **Psychological vulnerability & ability to withstand demands of treatment**
  - High-risk referral (pre-treatment), coping interventions (throughout)
- **Relational strain**
  - High-risk referral (pre-treatment); decisional-support (treatment change-over)

Cardiff Fertility Studies

Psychosocial issues differ across stages of treatment



Brandes et al. *Hum Reprod.* 2009;24:3127,
consecutive cohort of 1391 patients
**IVF subsidised by national health service, which would reduce its impact

Cardiff Fertility Studies

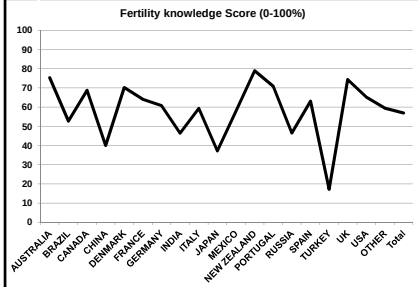
Education/Information

- **Educate & dispel myths**
  - Use standardised checklist (overall), specific treatments of common erroneous beliefs & misconceptions
  - Be honest about treatment demands
- **Know common moral and ethical objections**
- **Provide decisional support**
  - Deliberation tools

Boivin J et al. Hum. Reprod. 2012;27:941-950

Cardiff Fertility Studies

Fertility knowledge internationally

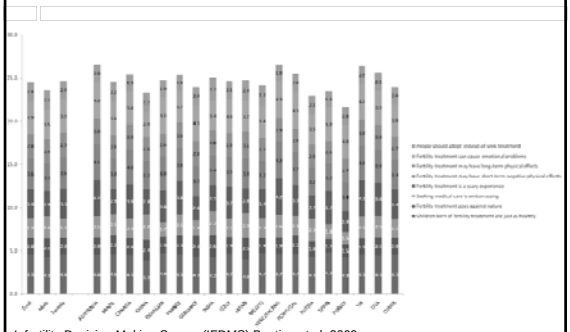


13 fertility items:
Risks, facts &myths

International Fertility Decision-Making Survey (N=10, 045),18 countries
Bunting et al. (under review)

Cardiff Fertility Studies

Common treatment beliefs

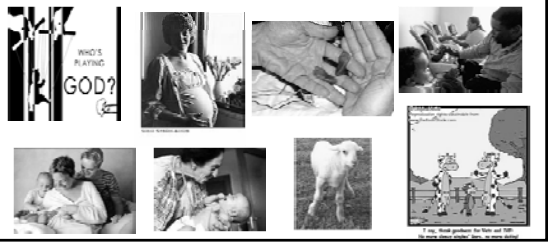


Infertility Decision-Making Survey (IFDMS) Bunting et al. 2009

Vol 10. No 3. 2005 310-319 Reproductive BioMedicine Online: www.rbmonline.com/Article/1529 on web 13 January 2005

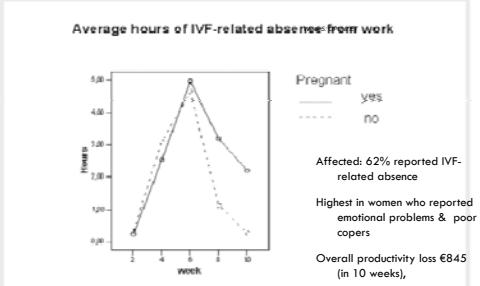
Ethics, legal, social, counselling

Assisted reproductive practice: religious perspectives



Treatment factors: Impact daily life

Figure 1 The pattern of IVF-related absence from work during 10 weeks following the start of treatment with gonadotrophin-releasing hormone injections

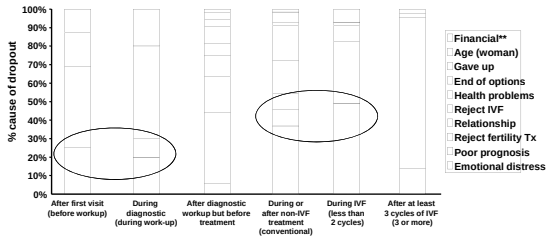


- Affected: 62% reported IVF-related absence
- Highest in women who reported emotional problems & poor copers
- Overall productivity loss €845 (in 10 weeks),

Bouwmans et al. 2008; Acta Obstet Gynecol Scand; N=384 women, daily diaries

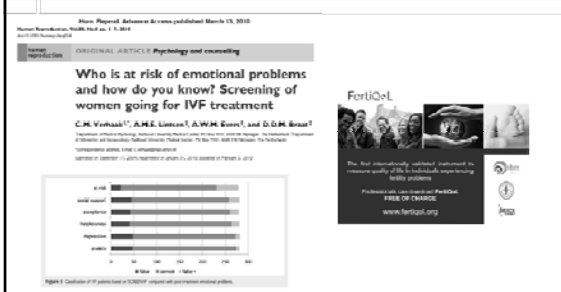
Use pre-treatment standardised checklists

Emotional distress

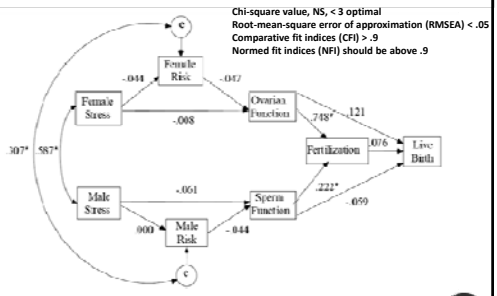


Brandes et al. *Hum Reprod.* 2009;24:3127,
consecutive cohort of 1391 patients
**IVF subsidised by national health service, which would reduce its impact

Identify & refer people at risk

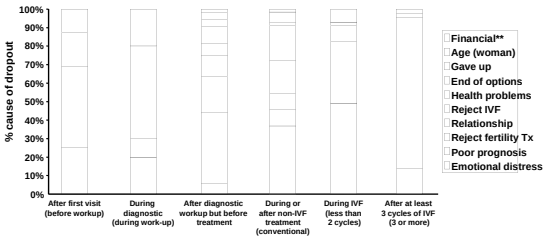


Shared toxic environments: His & her stress, lifestyle and biology



χ2 (15, N = 264) = 34.66, p = .003, RMSEA = .07, CFI = .94, NFI = .91. Values are path

Psychosocial issues differ across stages of treatment



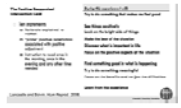
Brandes et al. *Hum Reprod.* 2009;24:3127, consecutive cohort of 1391 patients
**IVF subsidised by national health service, which would reduce its impact

Top factor that makes working with patients difficult?

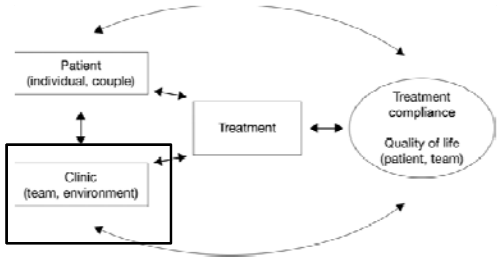
Boivin et al in prep: Survey ESHRE members, N=527

Implement cost- & time- effective psychosocial interventions

- Brief coping interventions (e.g., Positive Reappraisal Coping Intervention)
- Referral to online support websites, advocacy groups, telephone counselling
- Support bibliographies



Integrated approach showing reciprocal influences among patient, clinic and treatment in influencing treatment continuation and quality of life.



Boivin J et al. Hum. Reprod. 2012;27:941-950

human reproduction

Clinic Factors

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 [1,4]

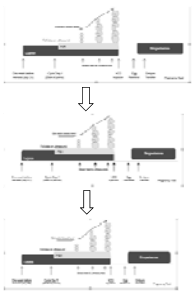
[1]Leuven University Hospital, Leuven University Fertility Centre, Herestraat 49, 3000 Leuven, Belgium [2]Department of Obstetrics and Gynecology, Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands [3]Catholic University Leuven, Centre for Health 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 20, 2010

Consensus among studies that following are important & problematic domains

Patient report of important, problematic domains in fertility clinics



- **Improve Access to care**
  - Waiting (referral, treatment, waiting room), freq of appointments, cost, distance
- **Improve Coordination and integration of care**
  - Organizational aspects (e.g., ease of arranging times, different specialists)
  - Technical aspects (e.g., comprehensive treatment & testing possible in one location, quality of information
- **Streamline care via Continuity and transition**
  - Continuity of care with fertility staff, attitude office staff
- **Cover Information, communication and education**
  … on alternatives, helping themselves, plan for future, emotional aspects
- **Address needs for emotional support and alleviation of fear and anxiety**
  Contact with prior patients
- **Identify threats to Physical comfort**
  Accommodation of clinic, separate clinic (from pregnant groups)

Dancet, 2010 HRU, N=51 studies

Aarts et al. 2011 Hum Rep
N=875 patients

FertiQoL predicts perceived patient-centredness:

- accessibility
- communication
- respect for values
- continuity
- autonomy
- competence

FertiQoL translations

Professional translations
Verified by fertility experts in local setting

See www.fertiqol.org for 23 languages: Korean, Vietnamese, Japanese in progress

Clinic procedures that make a difference

Clinic factors

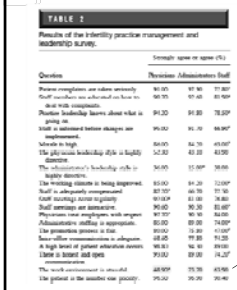


TABLE 2

Results of the infertility practice management and leadership survey.

Question	Strongly agree or agree (%)		
	Physicians	Administrators	Staff
Patient complaints are taken seriously	90.0%	97.9%	77.8%*
Staff members are informed on how to deal with complaints.	90.5%	97.6%	81.9%*
Practice leadership knows about what is going on	94.2%	94.8%	78.5%*
Staff is informed before changes are implemented.	95.0%	91.7%	66.9%*
Morale is high	64.0%	84.7%	49.0%*
The physician leadership style is highly directive	52.8%	43.1%	43.9%
The administrator's leadership style is highly directive.	56.0%	15.9%*	38.6%
The working climate is being improved.	85.0%	94.2%	72.0%*
Staff is adequately compensated	87.5%*	66.7%	77.9%
Staff meetings occur regularly	90.0%*	61.1%	38.8%
Staff earnings are normative.	90.0%	90.3%	81.6%*
Physicians treat employees with respect	97.5%*	90.3%	84.0%
Administrative staffing is appropriate.	85.0%	89.0%	74.0%*
The promotion process is fair.	80.0%	75.8%	47.0%*
Inter-office communication is adequate.	68.0%	77.8%	91.2%
A high level of patient education occurs	90.5%	96.9%	89.0%
There is honest and open communication	90.0%	89.0%	74.2%*
The work environment is stressful	48.9%*	73.7%	63.9%
The patient is the number one priority.	95.0%	95.9%	90.4%

% agree/strongly agree:
"Work environment is stressful"

Physician: 48.9
Administrator: 73.7
Staff: 63.9

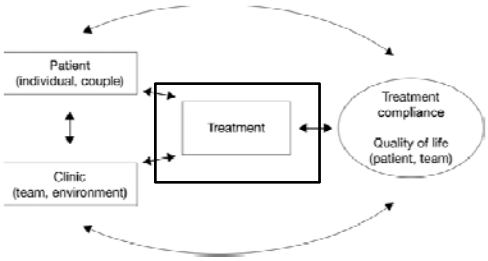
N=112 ART centres in USA
Gerson et al. 2004 Fertil Steril

Top factor that makes your work stressful?

Boivin et al in prep: Survey ESHRE members, N=527

Training opportunities for staff

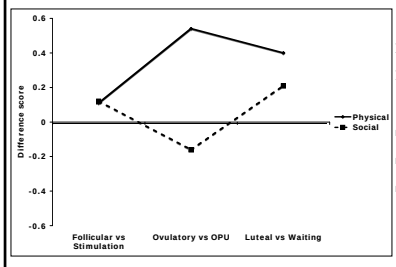
Integrated approach showing reciprocal influences among patient, clinic and treatment in influencing treatment continuation and quality of life.



Boivin J et al. Hum. Reprod. 2012;27:941-950

human reproduction

Treatment factors: Physical effects

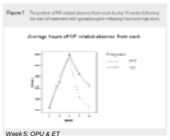


Discontinuation for Physical symptoms

- 3.7% Verhagen et al. 2008
- 6.5% Moini et al. 2009
- 36% van den Broeck 2009

Boivin et al. *Hum Reprod*. 1996. N=23 Canadian women
Physical and social reactions in IVF versus menstrual cycle without treatment
(daily monitoring, prospective)

Impacts on daily life



Week 5: OPU & ET

Table II Absence from work (in hours) and costs of productivity losses (in 2006 €) during IVF/ICSI treatment*

Main reason of IVF-related absence from work*	Mean hours IVF-related absence from work (SD)	Mean costs IVF-related absence from work (SD)
Physical problems (27%)	42.0 (54.0)	1077 (1375)
Emotional problems (6.1%)	40.8 (41.0)	1049 (1041)
Physical and emotional problems (1.66%)	40.7 (36.9)	1044 (938)
Visits to the IVF centre (50.4%)	10.0 (17.0)	261 (458)
All women with paid work	28 (37.8)	806 (985)

*From first artificial treatment (first day of gonadotrophin administered) until 10 weeks thereafter.
**6.7% of all women with paid work reported IVF-related absence from work.

9.5 hours, SD=40 (other health)

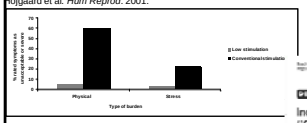
N=384 women, daily diaries

- Affected: 62% reported IVF-related absence from work & 19% absence for other health reasons
- Absence highest in women who reported emotional problems & poorer copers
- Overall productivity loss €845 (in 10 weeks), 68% due to IVF/ICSI (€596) … in women with emotional problems loss was €1063

Bouwmans et al. 2008; Acta Obstet Gynecol Scand

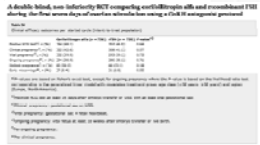
Effect of changing stimulation protocols

Hojgaard et al. *Hum Reprod*. 2001.



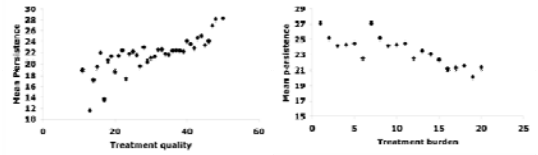
DEBATE Open Access

Individualised controlled ovarian stimulation (ICOS): maximising success rates for assisted reproductive technology patients



Devroey et al ENGAGE trial, Hum Reprod; Hum. Reprod. 2009;24(12): 3063-72.

Increased Treatment compliance



FertiQoL validation sample, n = 1027
Persistence = intention to persist with treatment
Boivin et al. 2011 Hum Reprod

Conclusion

- Medical developments impact on practice of psychology and how it can optimise patient experience
- The Integrated Approach to Fertility Care seeks to take account of all person, clinic and treatment factors that impact treatment compliance & quality of life in fertility clinics
- Matching interventions to sources of burden is likely to be essential
- Research on causes of burden and interventions is required

Bibliography

Boivin J, Domar A, Shapiro D, Wischmann T, Fauser B, Verhaak C. Tackling burden in ART: an integrated approach for medical staff. Hum Reprod. 2012;27(4):941-950.

Boivin, J, Takefman, J, Braverman, A. Development and preliminary validation of the fertility quality of life (FertiQoL) tool (2011). Human Reproduction, 26(8), 2084–2091.

Lancastle D, Boivin J (2008). Feasibility, acceptability and benefits of a self-administered positive reappraisal coping intervention (PRCI) card for medical waiting periods. Human Reproduction, 23, 2299–2307

E.A.F. Dancet, W.L.D.M. Nelen, W. Sermeus, L. De Leeuw, J.A.M. Kremer and T.M. D'Hooghe. The patients' perspective on fertility care: a systematic review. Human Reproduction Update. 2010;16 (5):467-8

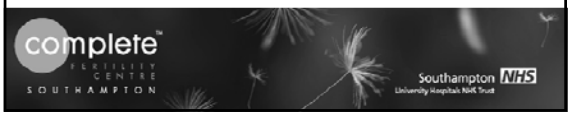
How can psychology & counselling help optimise treatment?

Jacky Boivin, PhD, Cpsychol
boivin@cardiff.ac.uk

School of Psychology
Cardiff

Improving the health of the child after IVF.

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



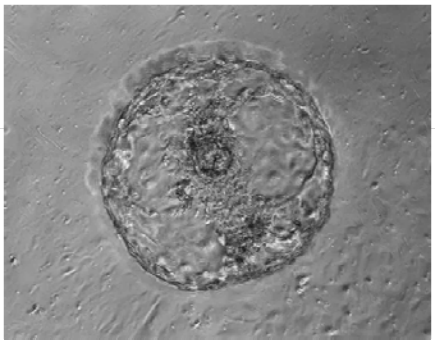
I have no conflict of interests in relation to the content of this lecture.

Learning Objectives

At the end of this lecture the delegate should be able to:

1. Outline the Developmental Origins of Health concept.
2. Undertand the impact of ovarian stimulation on the embryo
3. Describe factors affecting growth after IVF
4. Outline key periconceptional determinants of longterm health.
5. Describe the embryo selection hypthesis, and its implications for interventions aimed at improving implantation.

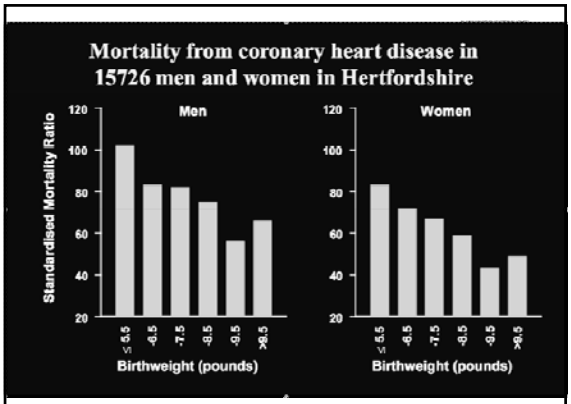
***Our* Patient**



DOHaD Concept of Programming

Malnutrition and other adverse environmental exposures during development alter gene expression and programme the body's structures and functions for life.

Adverse exposures also result in slow growth and small body size.



Developmental Origins of Disease

Maternal Body constitution/nutrition level

↓

'Plasticity' in the embryo developmental program

↓

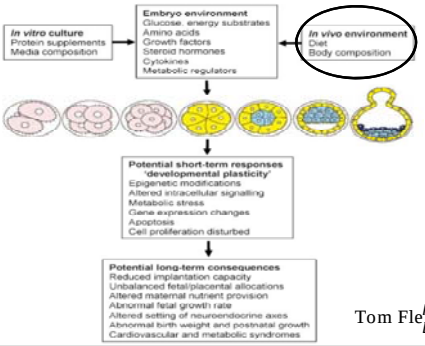
Matches growth and physiology to prevailing conditions

↓

If prenatal environment differ from postnatal:
inappropriate responses

Managing your patient

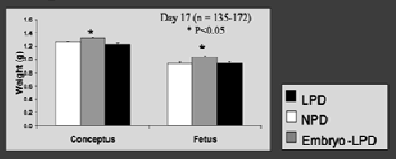
University of Southampton School of Medicine

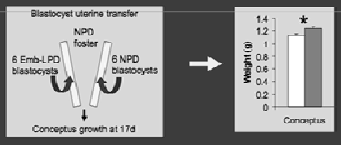


Tom Fleming 2005

Fleming et al Biol Reprod. 2004

When do responses to maternal diet occur?



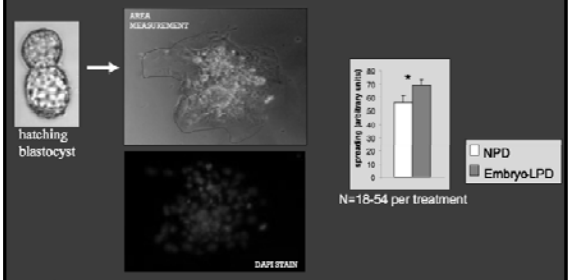


Increased perinatal growth in Emb-LPD conceptuses is detectable in late gestation, a response induced by the blastocyst stage independent of later maternal environment

Courtesy of Tom Fleming

Watkins et al. (2008) BOR 78:299

Response by trophectoderm to maternal Emb-LPD treatment: increased invasiveness



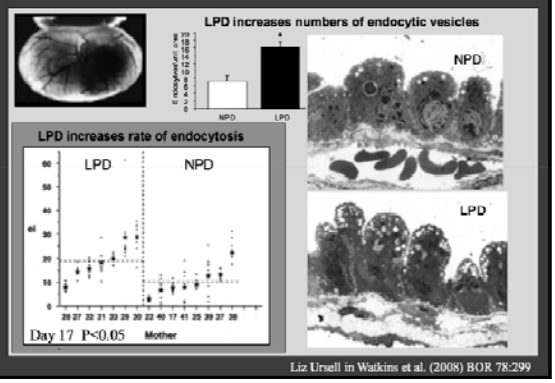
hatching blastocyst

N=18-54 per treatment

Emb-LPD response:
- increased trophectoderm proliferation and invasiveness
- increased placental efficiency?

Judith Eckert, Liz Burt

Maternal LPD induces responses in the visceral yolk sac

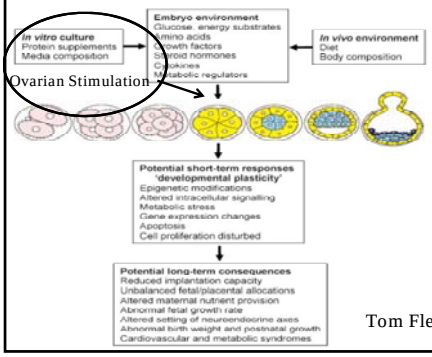


Liz Ursell in Watkins et al. (2008) BOR 78:299

University of Southampton School of Medicine

IVF

Managing your patient

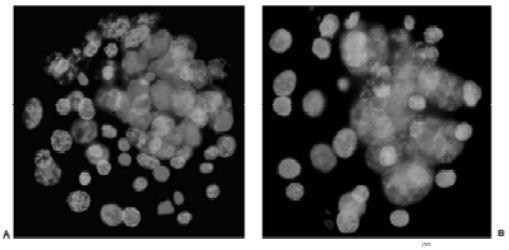


Tom Fleming 2005

Fleming et al Biol Reprod. 2004

Differential blastocyst development

IN- VIVO **IN- VITRO**

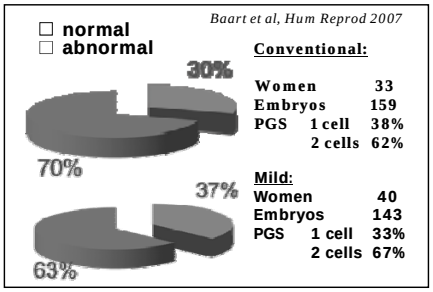


Higher number of trophectoderm cells
Faster embryo development

Giritharan et al, 2006

Percentage of aneuploid embryos following mild vs conventional ovarian stimulation for IVF

Baart et al, Hum Reprod 2007



Conventional:

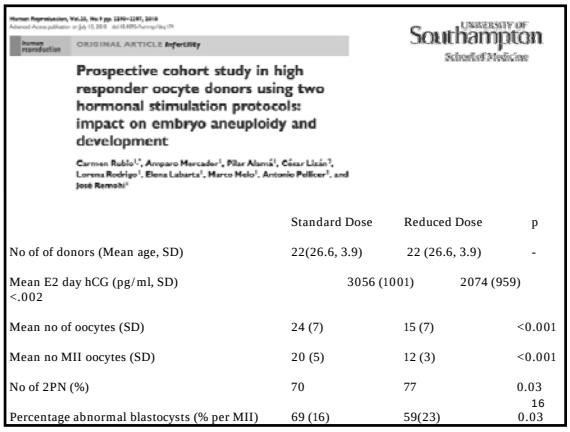
Women		33
Embryos		159
PGS	1 cell	38%
	2 cells	62%

Mild:

Women		40
Embryos		143
PGS	1 cell	33%
	2 cells	67%

36% aneuploid **No Stimulation**

Verpoest et al, HR 2008



ORIGINAL ARTICLE *Infertility*

Prospective cohort study in high responder oocyte donors using two hormonal stimulation protocols: impact on embryo aneuploidy and development

Carmen Rubio[1,*], Amparo Mercader[1], Pilar Alamá[1], César Lizán[1], Lorena Rodrigo[1], Elena Labarta[1], Marco Melo[1], Antonio Pellicer[1], and José Remohí[1]

	Standard Dose	Reduced Dose	p
No of of donors (Mean age, SD)	22(26.6, 3.9)	22 (26.6, 3.9)	-
Mean E2 day hCG (pg/ml, SD)	3056 (1001)	2074 (959)	<.002
Mean no of oocytes (SD)	24 (7)	15 (7)	<0.001
Mean no MII oocytes (SD)	20 (5)	12 (3)	<0.001
No of 2PN (%)	70	77	0.03
Percentage abnormal blastocysts (% per MII)	69 (16)	59(23)	16 0.03

The impact of IVF on Birthweight

IVF after ovarian hyperstimulation vs subfertile controls without treatment

	OR_{adj}	95% CI
LBW 1500-2500 g	**1.7**	**1.4-2.0**
VLBW <1500 g	**2.7**	**1.8-4.1**
Preterm 32-37 wk	**1.6**	**1.3-1.9**
VPT <32 wk	**2.2**	**1.4-3.3**

Kapiteijn et al, Hum Reprod 2006

Why are IVF babies are smaller?

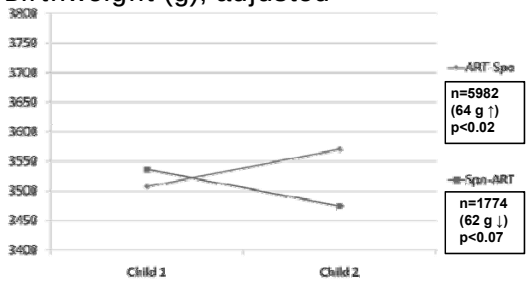
Perinatal outcome of singleton siblings born after Assisted Reproductive Technology and spontaneous conception

Danish National Sibling-Cohort study

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

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

Birthweight (g), adjusted*

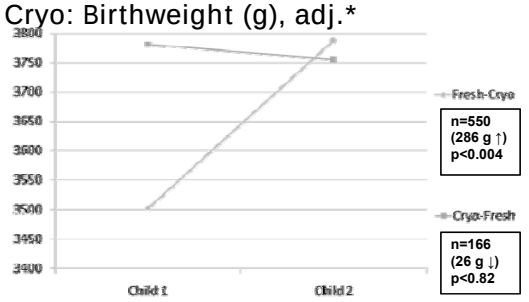


*maternal age, parity, year of birth, sex

19

IVF procedure or Ovarian Stimulation?

Cryo: Birthweight (g), adj.*



*maternal age, parity, year of birth, sex

20

IVF children also have higher blood pressure

Cardiometabolic Differences in Children Born After *in Vitro* Fertilization: Follow-Up Study

J Clin Endocrinol Metab 93: 1682–1688, 2008)
J Clin Endocrinol Metab 93: 1682–1688, 2008)

Manon Ceelen, Mirjam M. van Weissenbruch, Jan P. W. Vermeiden, Flora E. van Leeuwen, and

TABLE 2. Differences in blood pressure (mm Hg) and fasting glucose (mmol/liter) between IVF children and control children after adjustment for confounders: multivariate analysis

TABLE 3. Differences in blood pressure (mm Hg) and fasting glucose (mmol/liter) between IVF children and control children after adjustment for confounders: multivariate analysis

Multivariate models	Unstandardized regression coefficient	95% CI	*P* value
SBP difference (mm Hg) after adjustment for birth weight, gestational age, and sum of skinfolds	3.0	1.1–5.0	0.003
DBP difference (mm Hg) after adjustment for birth weight, gestational age, parity, and sum of skinfolds	1.4	0.03–2.8	0.046
Glucose difference (mmol/liter) after adjustment for subfertility cause	0.11	0.02–0.21	0.02

DBP, Diastolic blood pressure; SBP, systolic blood pressure.

Compensatory growth

Growth at above normal rates after a period of retarded growth. *Rapid growth has long-term physiological and* metabolic costs

Does cardiovascular risk relate to infancy growth rates?

- 233 IVF children aged 8–18 years
- 233 spontaneously conceived controls born to subfertile parents.
- Growth data from birth to 4 years of age
- Early post-natal growth velocity (weight gain) was related to blood pressure and skinfold measurements at follow-up.

Ceelen et al Hum Reprod 2009 24:2788

Results

	IVF	Controls	
Birthweight	3.2±0.6	3.4±0.6	p=0.001
Gestational age	38.9+2.5	39.5+1.8	p=0.004
<37 weeks	13%	6%	p=0.015
<2500g	11%	3.5%	p=0.004

Gain in weight, height and BMI during late infancy was significantly higher in IVF children as compared with controls

Rapid weight gain during early childhood in IVF children appeared to be related to higher blood pressure levels at follow-up, independently of birthweight, gestational age and height at follow-up, but not in controls.

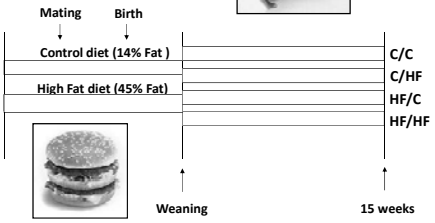
Ceelen et al Hum Reprod 2009 24:2788

The embryo, its dinner and its fertility



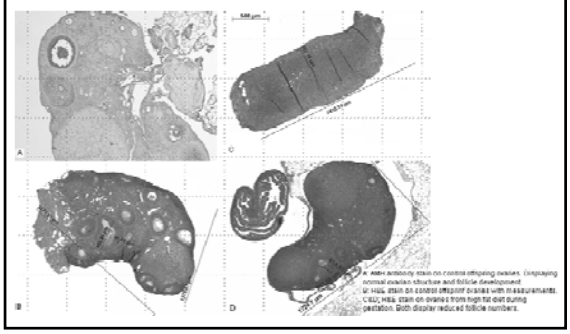
Nutrition during development alters the functional capacity of tissues and influences the risk of disease in adult life.

High Fat Mouse Model – Study protocol

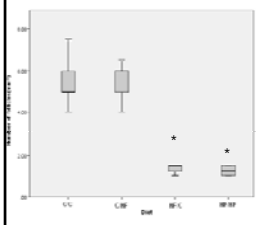


Bruce et al Hepatology 2009

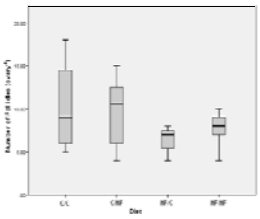
Results:
Ovarian Structure AMH & HE Stain



Maternal nutrition and ovarian follicle numbers in offspring



Effect of maternal overnutrition on primordial follicle numbers



Effect of maternal overnutrition on Antral follicle numbers

Sadek et al 2011

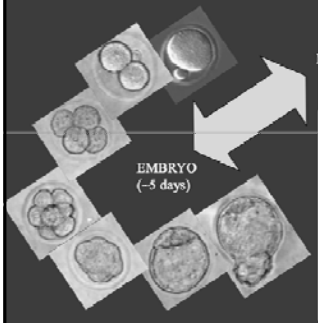
Maternal Smoking and Offpring Fertility

- 24 human first-trimester testes, aged 37-68 days post-conception, obtained from women undergoing legal termination of pregnancy . Historical controls.
- Testes exposed to maternal smoking:
- reduction in the number of germ cells: 55% [74-21%] P = 0.004
- Reduction in number of somatic cells by 37% [59-3%] P = 0.023
- The effect of maternal smoking was dose-dependent
- The number of germ cells in embryonic gonads, irrespective of gender, was also significantly reduced by 41% (95% CI 58-19%, P = 0.001) in exposed versus non-exposed embryonic gonads.

Mamsen et al Hum Rep 2010 25:2755

The Responsibility of Motherhood

MOTHER



EMBRYO
(~5 days)

Maternal-embryonic communication regulates:

- Features of blastocyst morphogenesis
- Coordination of implantation
- Maternal immunotolerance

- Developmental plasticity – 'selecting' the right phenotype to fit the anticipated future environment

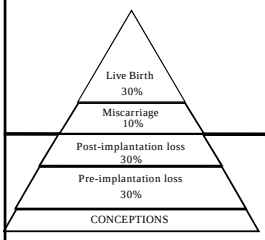
Implications: DOHaD; ART, maternal health at conception

Should we be encouraging poor embryos to implant?

The iceberg of pregnancy loss: Embryo selection?

Spontaneous

Chromosomal abnormalities



0.6%

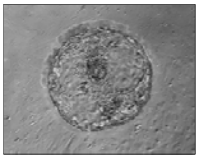
91%

(Macklon et al, Hum Reprod Update, 2002)

Embryo-endometrial cross talk: in vitro model

Day 4 — Thawing cryo-preserved embryos

Day 5 — in vitro extended culture



Day 8 Human Embryo

Day 8 — Assessment of Embryo quality ⟷ Cytokine profile

G. Teklenberg et al, 2009

University of Southampton School of Medicine

Decidual cell response to arresting vs developing embryos

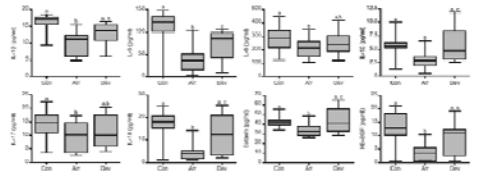


Figure 3. Developmentally impaired human embryos inhibit the secretion of selective implantation modulators by decidualizing PSCs. Primary (PSC) were first decidualized for 5 days and then co-cultured with human embryos or not (control cultures, Con). Over the 72-hour co-culture period, 30 embryos arrested (Arr) whereas 11 continued to develop normally (Dev). Analysis of the culture supernatants revealed that the presence of an arresting embryo inhibited the secretion of the indicated factors. The letters above the box plots indicate significant differences between groups. $P < 0.01$ for all comparisons except for IL-6 and IL-17 ($P < 0.05$).

doi:10.1371/journal.pone.0010258.g003

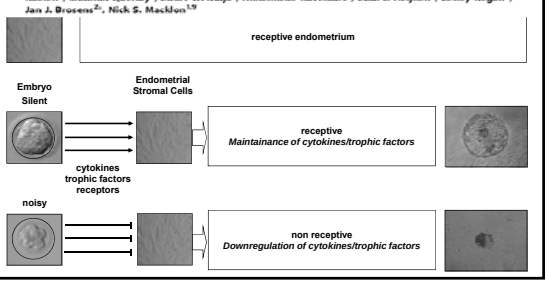
April 2010 | Volume 5 | Issue 4 | e10258

OPEN ACCESS Freely available online

PLoS one

Natural Selection of Human Embryos: Decidualizing Endometrial Stromal Cells Serve as Sensors of Embryo Quality upon Implantation

Gijs Teklenburg[1,2], Madhuri Salker[2], Mariam Molokhia[3], Stuart Lavery[2], Geoffrey Trew[2], Tepchongchit Aojanepong[2], Helen J. Mardon[4], Amali U. Lokugamage[2], Raj Pal[2], Christian Landles[3], Bernard A. J. Roelen[5], Siobhan Quenby[2], Ewart W. Kuijk[1], Annemieke Kavelaars[6], Cobi J. Heijnen[6], Lesley Regan[2], Jan J. Brosens[2]*, Nick S. Macklon[1,2]

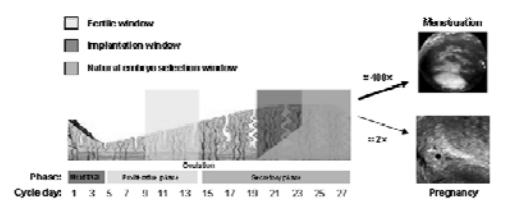


Molecular Human Reproduction, Vol.16, No.12 pp. 886–895, 2010

MHR NEW RESEARCH HORIZON *Review*

The molecular basis of recurrent pregnancy loss: impaired natural embryo selection

G. Teklenburg[1], Madhuri Salker[1], Cobi Heijnen[2], Nick S. Macklon[1,3], and Jan J. Brosens[1,*]



April 2010 | Volume 5 | Issue 4 | e10258 PLoS one

Natural Selection of Human Embryos: Impaired Decidualization of Endometrium Disables Embryo-Maternal Interactions and Causes Recurrent Pregnancy Loss

Madhuri Salker[1], Gijs Teklenburg[2,3], Mariam Molokhia[3], Stuart Lavery[1], Geoffrey Trew[1], Tepchongchit Aojanepong[3], Helen J. Mardon[4], Amali U. Lokugamage[5], Raj Rai[5], Christian Landles[1], Bernard A. J. Roelen[6], Siobhan Quenby[7], Ewart W. Kuijk[2], Annemieke Kavelaars[8], Cobi J. Heijnen[8], Lesley Regan[3], Nick S. Macklon[2,9], Jan J. Brosens[1]*

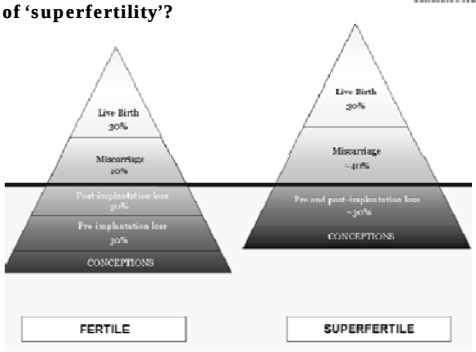
Table 1. Proportion of women achieving ≥3 consecutive pregnancies within 1, 3, or 6 months.

	1 month	3 months	6 months
Predicted:	0.8%	8%	41%
RPL patients:	13%	41%	68%

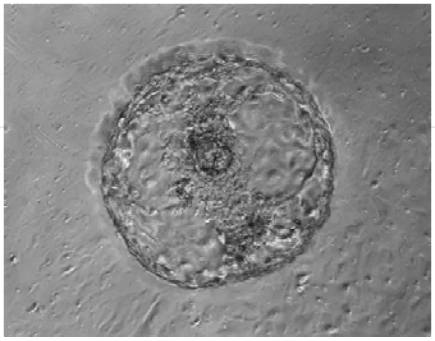
Predicted likelihoods are based on a MFR of 20%; $P<0.0001$.
doi:10.1371/journal.pone.0010287.t001

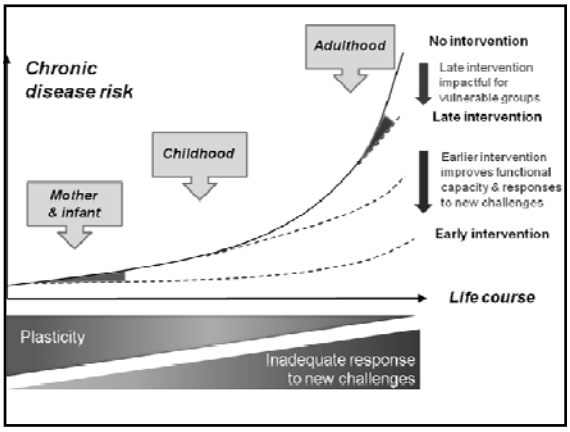
Recurrent miscarriage: the downside of 'superfertility'?

University of Southampton School of Medicine

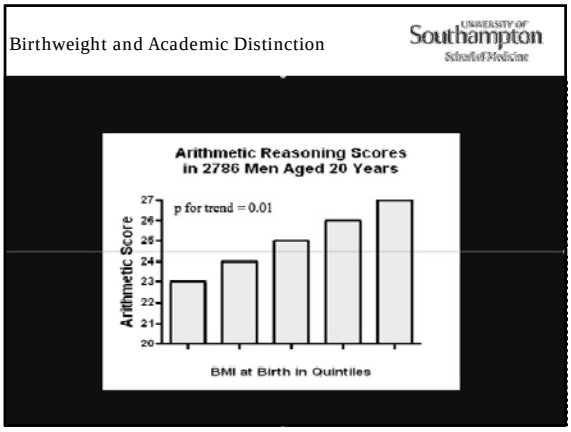


Our Patient

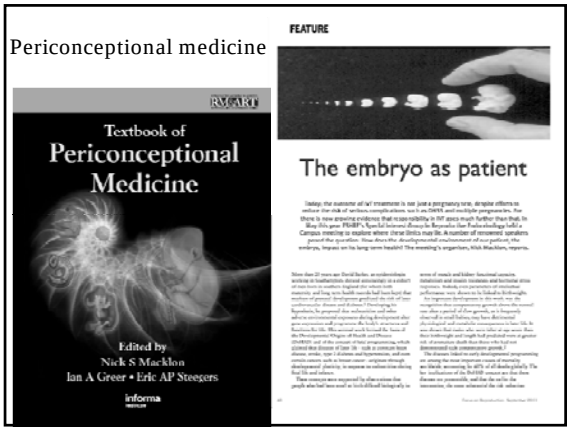




Birthweight and Academic Distinction



Periconceptional medicine



Acknowledgements

UTRECHT

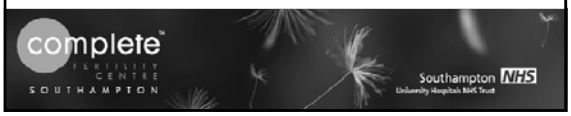
Esther Baart
Carolien Boomsma
Gijs Tecklenburg
Lotte Weimar
Cobi Heijnen
Bart Fauser

SOUTHAMPTON

Alex Kermack
Sarah Fin-Sell
Khaled Sadek
Julia Paget
Francesca Haughton
Judith Eckert
Tom Fleming
Ying Cheong
David Barker
Mark Hanson

WARWICK

Madhuri Salker
Jan Brosens



Mark your calendar for the upcoming ESHRE Campus events

- Basic Semen Analysis Course in Greek Language
  4-7 September 2012 - Athens, Greece
- Basic Genetics for ART practitioners
  7 September 2012 - Rome, Italy
- Regulation of quality and safety in ART – the EU Tissues and Cells Directive perspective
  14-15 September 2012 - Dublin, Ireland
- Basic Semen Analysis Course in Spanish language
  18-21 September 2012 - Galdakano,Vizcaya
- GnRH-antagonists in ovarian stimulation
  28 September 2012 - Hamburg, Germany
- The best sperm for the best oocyte
  6-7 October 2012 - Athens, Greece
- Basic Semen Analysis Course in Italian language
  8-11 October 2012 - Rome, Italy
- Accreditation of a preimplantation genetic diagnosis laboratory
  11-12 October 2012 - Istanbul, Turkey
- Endoscopy in reproductive medicine
  21-23 November 2012 - Leuven, Belgium
- Evidence based early pregnancy care
  29-30 November 2012 - Amsterdam, The Netherlands

www.eshre.eu
(see “Calendar”)

Contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES