PRECONGRESS COURSE 15

Controversies in assisted reproduction technology

Middle East Fertility Society Exchange course

Barcelona – Spain, 1 July 2018

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SCIENCE MOVING
PEOPLE
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CONTENTS

IS THE OOCYTE THE MAIN DETERMINANT OF EMBRYO QUALITY? STRATEGIES FOR THE SELECTION OF THE MOST COMPETENT OOCYTE

Sunday, 1 July 2018
Organised by The Middle East Fertility Society

Course coordination

Yacoub Khalaf *(United Kingdom)*

Course type

Advanced

Course description

This is an advanced course addressing some of the most controversial topics in reproductive medicine and surgery that directly affect patient care. The aim of this course is the to bring the audience up to date with the evidence based assessment of some of the commons intervention used in assisted reproduction treatment with an additional emphasis on risk benefit analysis as well as cost-effectiveness of the addressed interventions. The course educational material is delivered by world -class experts who are renowned for their expertise in the filed of human reproduction in general and in their respective topic in particular. Speakers are authorities who have contributed to the science and practice and ethics of assisted reproduction through their distinguished track record of plenary talks, outstanding publications in major journals including Nature, NEJM, Lancet, BMJ, Nature Cell Biology, Human Reproduction Update, American Journal of Obstetrics & Gynaecology, Human Reproduction, Fertility & Sterility, British Journal Of Obstetrics & Gynaecology, Reproductive biomedicine online and other medical journals The course particular emphasis is on providing authoritative assessment of the evidence base of some common important interventions that are used with a view to improving the outcome of assisted conception treatment and highlighting the fundamentals of applying evidence based medicine in practice.

Target audience

Assisted conception practitioners (physicians, nurses and embryologists) as well as researchers and those interested in advances in assisted reproduction practice, ethics and research.

Target audience

The topics chosen are widely used in clinical practice despite variable level of evidence in their support and the emerging strong evidence against the use of some of these interventions. These interventions are not free of harm from medical, emotional and financial point of view. The needs assessment process included different national and international scientific meeting through which it has become clear that the majority of practitioners are unclear about the added value of these intervention and expressed their need for further education on these areas where they can be better equipped to counsel patients about the appropriate application of these technologies and their risk benefit analysis. By highlighting the mismatch between theory and practice in some of these interventions it is expected that the audience will refrain to substitute robust clinical evidence with mere biological plausibility. The course will enable the audience to discuss the ethics of applying experimental intervention in practice before a solid evidence base has been established.

SCIENTIFIC PROGRAMME

	Chair: Mohamed Aboulghar, *Egypt*
09:00 - 09:30	**Blastocysts Culture - Is it time to stop and rethink?** Mohamed Aboulghar, *Egypt*
09:30 - 09:45	**Discussion**
09:45 - 10:15	**Pre-implantation Genetic Screening - What are we doing?** Sjoerd Repping, *The Netherlands*
10:15 - 10:30	**Discussion**
10:30 - 11:00	**Coffee break**
11:00 - 11:30	**Endometrial Scratching - Do we have enough evidence?** Yacoub Khalaf, *United Kingdom*
11:30 - 11:45	**Discussion**
11:45 - 12:15	**Hysteroscopy in IVF** Tarek El-Toukhy, *United Kingdom*
12:15 - 12:30	**Discussion**
12:30 - 13:30	**Lunch Break**
	Chair: Yacoub Khalaf, *United Kingdom*
13:30 - 14:00	**In vitro embryo culture, what have we learned?** Magdalena Zernicka-Goetz, *United Kingdom*
14:00 - 14:15	**Discussion**
14:15 - 14:45	**Mitochondrial donation and reproduction** Peter Braude, *United Kingdom*
14:45 - 15:00	**Discussion**
15:00 - 15:30	**Coffee break**
15:30 - 16:00	**Natural Killer Cells and Reproductions: Are we chasing a shadow?** Srividya Seshadri, *United Kingdom*
16:00 - 16:15	**Discussion**
16:15 - 16:45	**Poor Responders - Have we made any progress?** Johnny Awwad, *Lebanon*
16:45 - 17:00	**Discussion**

Blastocysts Culture
Is it time to stop and rethink?

M. Aboulghar
Professor, Cairo University, Cairo, Egypt
Clinical Director, The Egyptian IVF Center

Disclosure

- Travel grants from Ferring and IBSA.
- No other commercial relationships to disclose.

Learning Objectives

1. To find out why many IVF centers do embryo transfer on day 5.
2. To evaluate possible drawbacks of day 3 transfer.
3. To discuss the risks of blastocyst transfer.
4. To speculate the most suitable day for embryo transfer.

The first IVF pregnancy was achieved after transfer of day 2 embryos
(Steptoe and Edwards 1978)

Since then, all scientists wanted to improve pregnancy rate of IVF, using different techniques, among them extended embryo culture.

Improved laboratory standards and improved culture media have made extended culture to blastocyst a reality (Maheshwari 2016)

Advances in in-vitro culture conditions have led to development of sequentional media which allowed extended culture to blastocyst (Gardner 1998). Later, single media was developed for culture to blastocyst (Sfontouris et al., 2016)

The idea of extended culture was created with the objective of obtaining the best available embryo. That is when regulatory bodies were pushing for single embryo transfer to prevent multiple pregnancy (Maheshwari 2016)

Why do we transfer embryos on day 5?

- It is believed that it results in:
  - higher pregnancy rate
  - lower multiple pregnancy rate
  - Possibility of doing PGT on the 24 chromosomes.

Why extended culture?

1. To mimic natural physiology of a blastocyst reaching the uterine cavity day 5-6
2. Embryo selection: to ensure embryonic genome activation at 8 cell stage, and successful extended culture to blastocyst. However, this is not always true as in vitro survival is different from in vivo survival.

Risks of extended culture

3. By committing to ET on blastocyst stage there is a risk of loosing some embryos which might not survive extended culture but might have survived in vivo had it been transferred to the uterus.

The main advantage of day 5 embryo transfer is to have a higher pregnancy rate

- Q: what do you mean by higher pregnancy rate?
  - Clinical pregnancy rate after fresh embryo transfer

  Or
  - Cumulative pregnancy rate per started cycle

IVF with a single blastocyst versus single cleavage stage: a randomized study

- 351 infertile women (below 36 years) were randomized to ET of a single cleaved embryo or a single blastocyst.
- There was significantly higher pregnancy and delivery rate in the blastocyst stage group.

(Papanikolaou 2006)

Cumulative live birth rates were similar after day 3 and 5 after cryo-embryos transfer (De vos et al., 2016)

- Live birth rates per started cycle were significantly lower after transferring the fresh single cleavage-stage embryo, compared to a blastocyst (31.3% and 37.8%, respectively, P=0.041).
- However, the cumulative live birth rates were 52.6% for cleavage-stage and 52.5% for blastocyst-stage transfers (P=0.989).

A problem of several studies, that patients with good number of zygotes (at least 4) are randomized to day 3 or day 5 transfer. So all bad cases are excluded from extended culture. The study should be carried out per started cycles.

On the other hand, several studies showed no difference in clinical pregnancy rate between Day 3 and Day 5 embryo transfer (Utsunomiya et al., 2004; Aziminekoo et al., 2015)

Cleavage stage versus blastocyst stage embryo transfer in IVF/ICSI. A Cochrane review (Glujovsky et al., 2016) (1)

- 27 RCTs (4031 women)
- The live birth rate following fresh ET was higher in blastocyst stage OR 1.48, 95% CI 1.20-1.82 (low quality evidence).

Cochrane Review: Cleavage v. Blast (2)

- No significant difference in the cumulative pregnancy rate between blastocyst and cleavage stage embryo transfer.
- Failure to transfer any embryos is higher with blastocyst ET.
- OR 2.50 (95% CI 1.76-3.55).
- More embryos cryopreserved after cleavage stage ET.

(Glujovsky et al 2016)

Blastocyst versus cleavage stage embryo transfer: a meta analysis (Martins et al., 2016)

- Most recent metanalysis:
- 12 studies = 1200 women
- No significant difference in live birth/ongoing pregnancy in both single transfer or cumulative live birth rate.
- (RR 1.11, 95% CI 0.92-1.35)
- Low quality evidence

The objective was to have a single birth at term. However, new data showed that transfers on blastocyst stage are associated with higher risk of preterm labor, large for gestational age babies, monozygotic twins and altered sex ratio (Maheshwari 2016)

Pre-term delivery

- Two separate meta-analysis of observational studies have confirmed that IVF pregnancies from blastocyst stansfer were associated with a higher risk of premature labor. 95% CI less than 37 weeks 1.27 (1.22-1.31) and very preterm labor less than 32 weeks 1.22 (1.10-1.35). (Maheshwari et al. 2013, Dar et al 2014)
- These findings were not confirmed in one Australian study. (Chambers et al., 2015)

Increased perinatal mortality

- Several studies reported significantly higher perinatal mortality after blastocyst transfer (Dar et al., 2014; Ginström Ernstad et al., 2016; Martins et al., 2016)

Risk of monozygotic twins

- It is suggested that there is increase risk of transfer of blastocyst stage (Luke et al., 2014) with a pooled odd ratio of 3.04 (95% CI 1.54-6.01). The exact reason is unknown. (Chang et al 2009).
- Other studies confirmed this finding (Franasiak et al., 2015)

Monozygotic twins

- Over a period of 9 years, all clinical pregnancies after single embryo transfer (N=6096) were retrospectively analyzed for the incidence of monozygotic twins which was 2.2% in all cases 136/6096. Blastocyst transfer was associated with an odd ration of 2.7, 95% CI 1.36-5.34 (Mateizel et al., 2016)

Large for gestational age babies

- This is a questionable issue. Zhu et al., 2014; and Martin et al., 2016 suggest that this happens in human and animals. It could be due to a different culture media. A study from De Vos et al., 2015 seems to refute this.

Congenital malformation

- Dar et al (2014) reported that the odds of congenital malformation were significantly higher for babies born after embryo transfer at blastocyst stage (1.29, 95% IC 1.03-1.62).
- It was also repeated by Kallen (2010)
- Two large population based studies found no increased rate of malformation (Chambers et al., 2015; Ginstrom Ernstad et al., 2016)

Altered male: female ratio

- Chang (2009) reported a male : female ratio of 1.29 (95% CI 1.10 – 1.51).
- Several reports suggested the same findings.

Reasons of adverse perinatal outcome

- A possible explanation could be that extended culture may trigger genetic and epigenetic changes in trophodermal cells that can lead to abnormal placentation and implantation.
  (Rizos et al., 2002)

Why do we still continue extended culture?

- Most clinicians ignore:
  - the percentage of patients who do not have transfer as no embryos reached blastocyst stage.
  - Complications associated with blastocyst transfer
  - No higher cumulative pregnancy rate after blastocyst ET per started cycle.

Conclusion

- There is small (low quality) evidence of improved pregnancy rate per cycle after day 5 transfer. However, there is an extensive literature which shows no difference in pregnancy rate between day 3 and day 5.
- There is no significant difference in the cumulative pregnancy rate between Day 3 and Day 5 embryo transfer.
- There are certain risk of blastocyst transfer.
- The WHO idea of extended culture is to transfer one blastocyst.

Personal opinion

- It is recommended to do extended culture if you have four or more morphologically good cleaved embryos on day 3.

The Egyptian IVF Center

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Pre-implantation Genetic Screening
What are we doing?

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Universiteit van Amsterdam
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Conflict of interest

- I believe in the God of Spinoza
  - Everybody else: bring your data
- I head a University based Center for Reproductive Medicine
- I have no commercial interests in assisted reproduction
  - My salary is fixed
  - MAR is covered by insurance for all Dutch citizens

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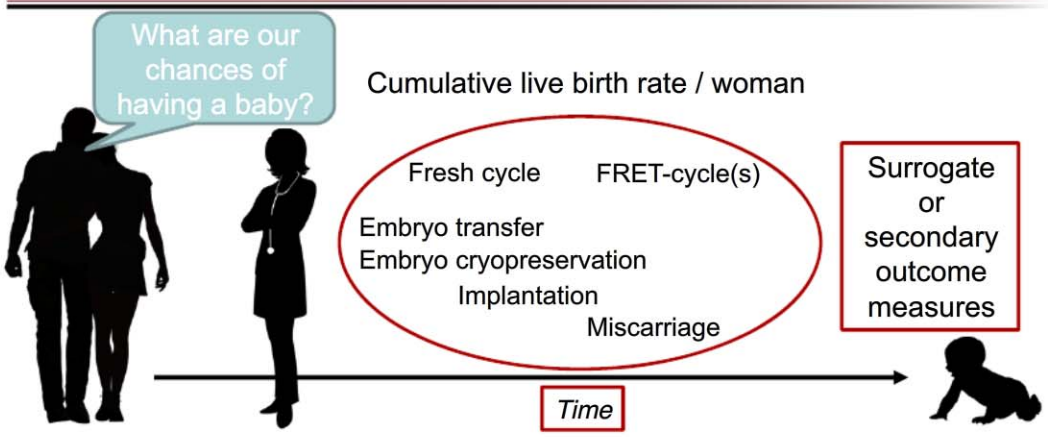
Spinoza (1677) Ethica ordine geometrico demonstrata, Sackett (1986) BMJ

Should be perform PGS on all patients?

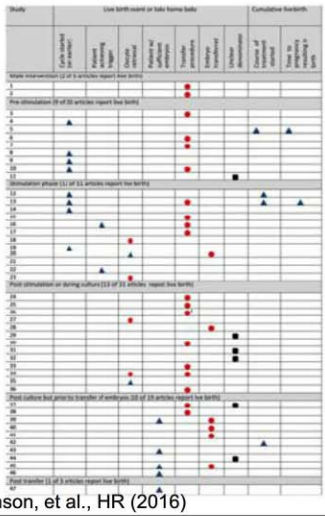
- Of course not on **all** patients!
  - Nearly all available data is in highly selected patient groups
  - What if there is only one embryo?
  - Not everyone can afford PGS
  - Unknown long term health effects of invasive procedure of PGS
  - Patients can and should decide for themselves
    - But should be properly and fully informed….

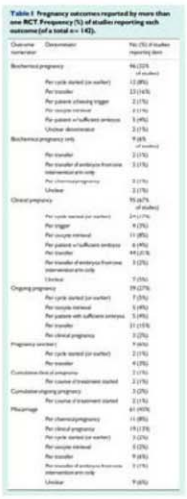
It is all about outcomes



Griesinger, HR (2016)

It is all about outcomes





No common denominator: a review of outcome measures in IVF RCTs

Table II Frequency (%) of definitions of 'live birth' in IVF RCTs reporting on this outcome in 2013–2014.

Definition of live birth	Frequency (%) of studes
Birth of ≥1 neonate 28 weeks or later	1 (2)
Individual baby born after 24 weeks of gestation	2 (4)
Individual viable foetus at 24 weeks of gestation	1 (2)
Live birth event/delivery	19 (36)
Live birth event and individual baby (both given in article)	1 (2)
Individual living baby	1 (2)
Pregnancy >28 weeks of gestation	1 (2)
Undefined	27 (51)

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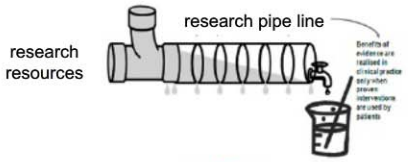
Wilkinson, et al., HR (2016)

It is all about outcomes

CROWN CORE OUTCOMES IN WOMEN'S HEALTH

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS



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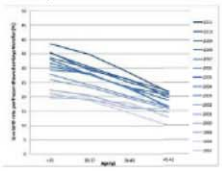
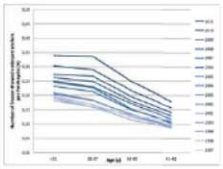
With permission of James Duffy

Cumulative live birth rate per woman

LBR per FET



No. of FET per started cycle



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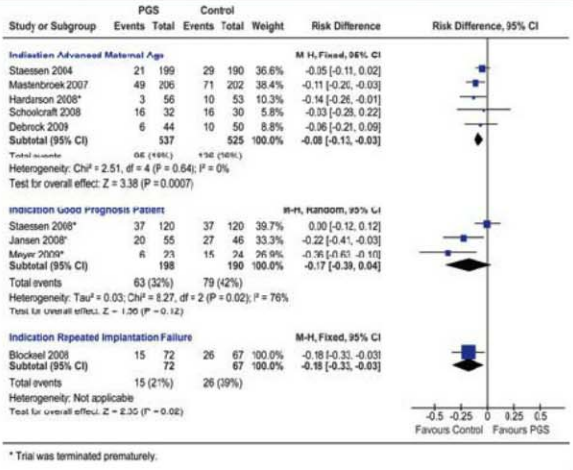
Wong et al. FS 2014; SART data

Meta-analysis PGS 2011



* Trial was terminated prematurely.

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Mastenbroek, et al., HRU (2011)

PGS 2.0

Mastenbroek & Repping, HR (2014)

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PGS 2.0

Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial

Richard T. Scott Jr., M.D.,[a,b] Kathleen M. Upham, B.S.,[a] Eric J. Forman, M.D.,[b] Kathleen H. Hong, M.D.,[b] Katherine L. Scott, M.S.,[a,c] Deanne Taylor, Ph.D.,[a,b] Xin Tao, M.S.,[a] and Nathan R. Treff, Ph.D.[a,b]

[a] Reproductive Medicine Associates of New Jersey, Morristown, New Jersey; [b] Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology, and Reproductive Science, Robert Wood Johnson Medical School, Rutgers University, New Brunswick New Jersey; and [c] Atlantic Reproductive Medicine Specialists, Raleigh, North Carolina

- All patients had a transfer
- No data on FRET cycles

In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial

Eric J. Forman, M.D.,[a,b] Kathleen H. Hong, M.D.,[a,b] Kathleen M. Ferry, B.Sc.,[a] Xin Tao, M.Sc.,[a] Deanne Taylor, Ph.D.,[a] Brynn Levy, Ph.D.,[a,c] Nathan R. Treff, Ph.D.,[a,b] and Richard T. Scott Jr., M.D.[a,b]

[a] Reproductive Medicine Associates of New Jersey, Department of Reproductive Endocrinology, Basking Ridge, New Jersey; [b] UMDNJ-Robert Wood Johnson Medical School, Department of Obstetrics, Gynecology & Reproductive Sciences, New Brunswick, New Jersey; and [c] Department of Pathology, Columbia University, College of Physicians and Surgeons, New York, New York

RESEARCH ARTICLE Open Access

Randomized comparison of next-generation sequencing and array comparative genomic hybridization for preimplantation genetic screening: a pilot study

Zhihong Yang[1,2,5*], James Lin[2], John Zhang[3], Wai leng Fong[4], Pei Li[5], Rong Zhao[5], Xiachong Liu[5], William Podevin[6], Yanping Kuang[7] and Jiaen Liu[5]

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Cumulative live birth rate per woman

- Exclusion of studies that
  - do not report on outcome of FRET-cyles
  - only report on patients who received a transfer
- What is the chance of a live birth per woman per cycle started?
  - Exclusion of studies that report on PGS with multiple OPUs for single ET

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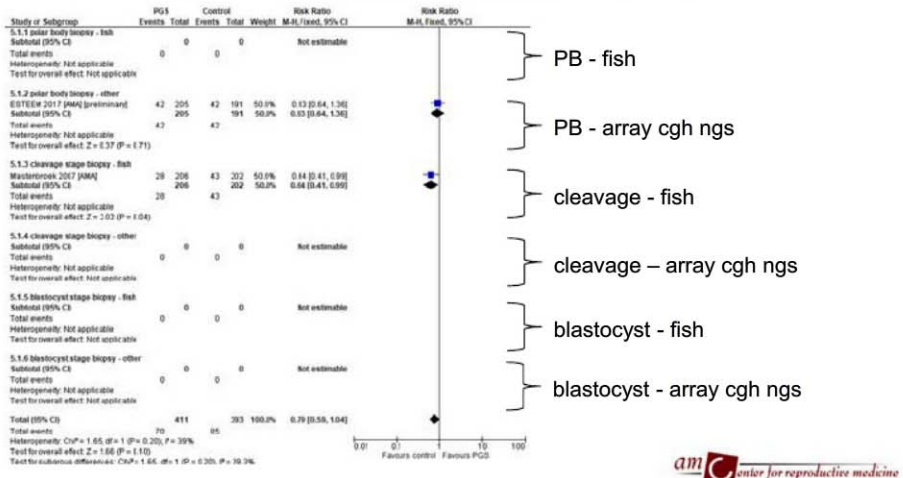
Cumulative live birth rate (one OPU per IVF)



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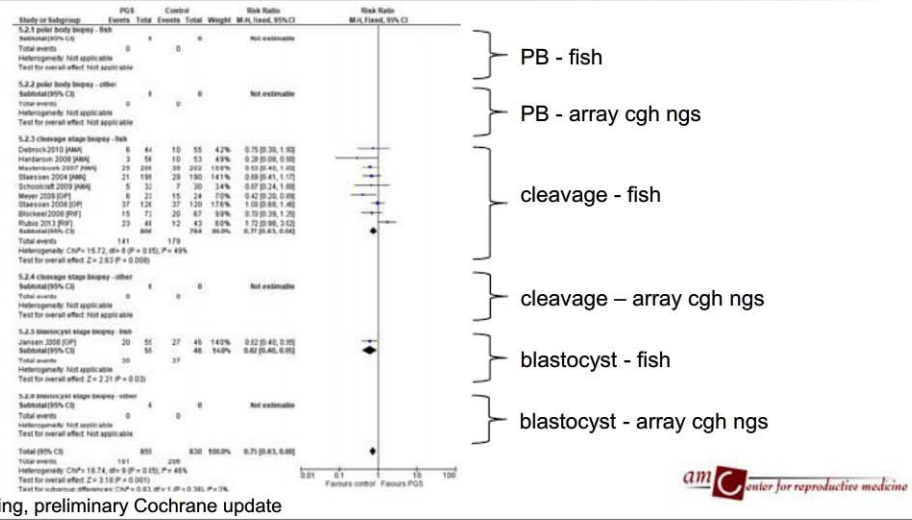
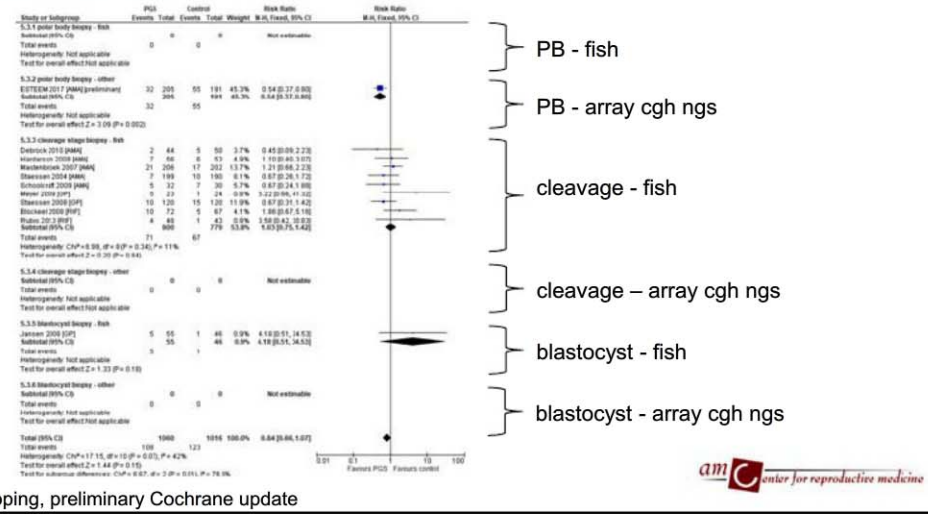
Mastenbroek & Repping, preliminary Cochrane update

Live birth rate per first transfer (one OPU per IVF)



Mastenbroek & Repping, preliminary Cochrane update

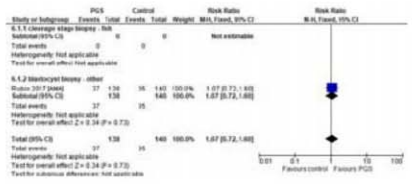
Miscarriage rate (one OPU per IVF)



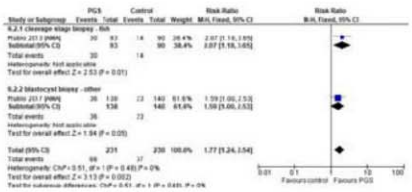
Mastenbroek & Repping, preliminary Cochrane update

Rubio 2013 + 2017 (AMA - multiple OPU per IVF)

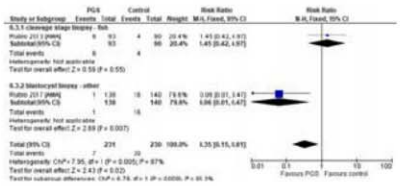
Cumulative live birth rate



Live birth rate per first transfer



Miscarriage rate



separate analysis as 'multiple OPU per IVF' favors PGS group by design

Mastenbroek & Repping, preliminary Cochrane update

STAR

- STAR: day 5 biopsy, vitrification, NGS
  - again implantation rate per transfer, not LBR/woman

Further study details as provided by Illumina, Inc.:

Primary Outcome Measures:

- Ongoing Pregnancy [Time Frame: Gestational Age of 20 Weeks]

  Rate of ongoing pregnancy at 20 weeks gestation between patients who received an embryo transfer in Groups A and and B.

Secondary Outcome Measures:

- Fetal Aneuploidy Status [Time Frame: Gestational Age of at least 10 Weeks]

  Fetal aneuploidy status by maternal cell-free DNA (cfDNA) testing using verifi® prenatal test compared to PGS result and/or fetal karyotype if available.

Estimated Enrollment:	600
Study Start Date:	September 2014
Estimated Study Completion Date:	June 2017
Estimated Primary Completion Date:	April 2017 (Final data collection date for primary outcome measure)

STAR

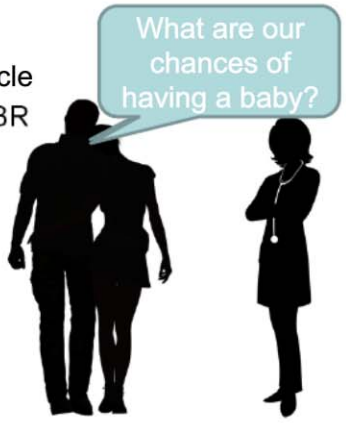
- Randomization PGS vs no-PGS 1:1
- 588 eligible woman with a transfer
  - 274 with PGS / 314 without PGS
  - Thus more no transfers with PGS
- Ongoing pregnancies
  - 136 with PGS / 144 without PGS
  - Per ET 49.6% (136/274) vs 45.9% (144/314)
  - Per OPU 39.0% (136/349) vs 41.3% (144/349)
- FRET cycles not even included…..

WARNING!
ESTIMATES!
(10% no ET in control)

Munné, et al (ASRM 2017, O-43)

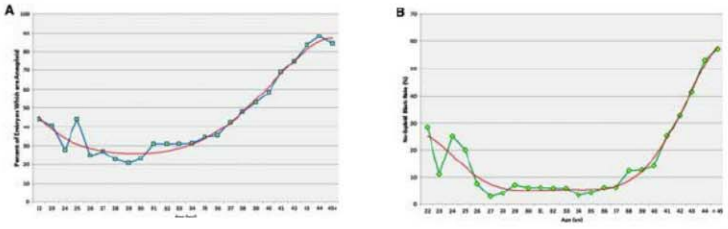
How should we inform patients?

- Chances of having a baby per woman
  - PGS 1.0 will decrease LBR per started cycle
  - PGS 2.0 almost no data, no increase in LBR perhaps fewer miscarriages
- Secondary outcomes?



Secondary outcomes: embryo transfer

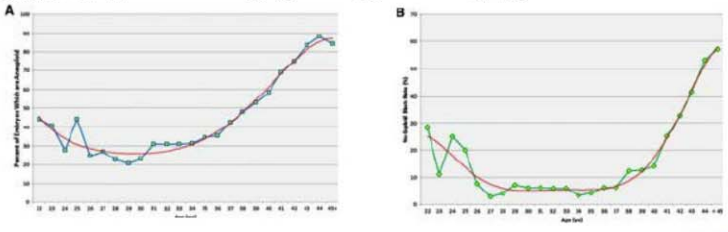
- No transfer is more common in PGS cycles
  - ESTEEM 27% vs 9%
  - Staessen 45% vs 14%
  - Rubio 2017 32% vs 9%



Franasiak, F&S (2014)

Secondary outcomes: cryopreservation

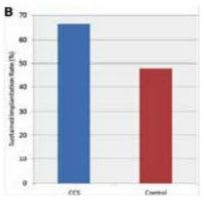
- Embryo cryopreservation is less common in PGS cycles
  - Mastenbroek 0.3 vs 0.8
  - Scott 2013 2.6 vs 3.4
  - ESTEEM 0.7 vs 2.2
  - Rubio 2017[a] 13% vs 52%

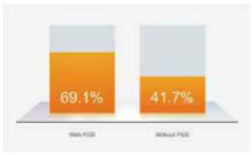


[a] percentage of cycles with cryopreservation

Secondary outcomes: implantation rate

- Implantation rate is higher in PGS cycles
  - Scott 80% vs 63%
  - Yang 69% vs 42%
  - Mastenbroek[a] 17% vs 15%
  - Staessen 17% vs 12%
  - Rubio 53% vs 28%
  - ESTEEM[b] 18% vs 11%





[a] excluding transfers of unknown embryos
[b] aggregate of fresh and frozen embryos

Secondary outcomes: (FR)ET-cycles

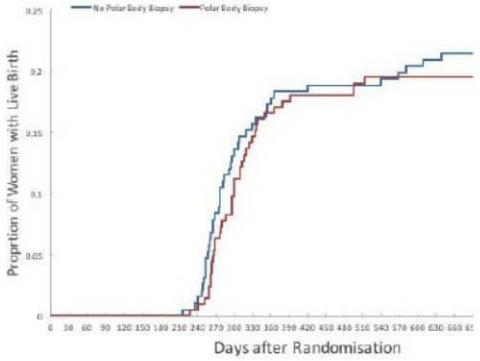
- There appear to be fewer (FR)ET cyles in PGS (limited data)
  - ESTEEM 0.87 vs 1.41
  - Rubio 2017 0.69 vs 1.24
- Due to
  - Less fresh transfers due to absence of normal embryos
  - Less frozen transfers due to lower number of cryopreserved embryos

Secondary outcomes: time to pregnancy

- No effect on time to pregnancy (limited data!)

Supplemental Table 4: Number of transfers and time to pregnancy for a healthy baby at home.

	PGD-A	Non PGD-A	*p-value*
Number of pregnancies at the first attempt	36	23	---
Number pregnancies after transfer of cryopreserved embryos	1	10	---
Mean time to ongoing pregnancy (SD, weeks)	4.5 (4.1)	5.8 (4.5)	*NS*
Mean number of transfer attempts (SD)	1.0 (0.2)	1.3 (0.4)	*<0.0001*

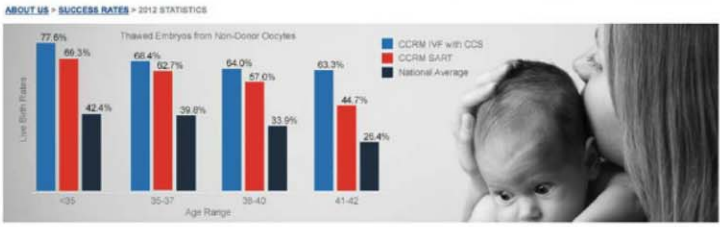


Rubio, F&S (2017), ESTEEM data (ESHRE 2017)

How should we inform patients?

- No increase in chances of having a baby
  - PGS 1.0 will decrease LBR per started cycle
  - PGS 2.0 almost no data, no increase perhaps fewer miscarriages
- Secondary outcomes
  - More no transfer, less transfers
  - Less embryos cryopreserved
  - Higher implantation rate per embryo
  - No effect on time to pregnancy
- High costs, invasive procedure……

How do we inform patients?



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http://www.colocrm.com, http://www.illumina.com

How do we inform patients?

- First: the baby!
- Then the famous trustworthy professor
- Then the (wrong) numbers
- Who can resist?

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http://www.illumina.com

How do we inform patients?

Improve your reproductive success with the specific selection of chromosomally normal embryos

Increase in implantation rate: Some embryos that are chromosomally abnormal will fail to implant into a woman's uterus. Therefore, by transferring chromosomally normal embryos, PGS using an array can increase the implantation rate.

Reduction in miscarriage rate: In the general population, 20% of all clinical pregnancies miscarry and about half are chromosomally abnormal. Since PGS evaluates numerical changes in chromosome numbers and large chromosome imbalances, embryo with chromosome abnormalities will not be transferred. Therefore, especially, in high-ri groups, PGS reduces the risk of miscarriage.

Increase in the chance of delivering a healthy baby: Some pregnancies with chromosome abnormalities will result in the birth of a child with multiple serious anomalies. Therefore, PGS can increase the chance of delivering a healthy baby by assisting physicians in identifying chromosomally healthy embryos for transfer. These conditions can also be detected by chorionic villus sampling (CVS) or amniocentesis late during the pregnancy.

Decrease in time to achieve a pregnancy: With this approach, the time to achieve healthy live-born decreases compared to a regular IVF cycle, avoiding multiple frozen embryo transfers before the transfer of the implanting embryo.

PGS 24 Chromosomes

Have a successful pregnancy and a healthy baby by selecting chromosomally normal embryos

Employing PGS for aneuploidy screening in IVF can double ongoing pregnancy rates.

Data summary of cycles performed at IVI Group 2011-2012 (with and without PGS). Cycles# AMA 880, IP 187, RM 204, IMF 116. Pregnancy of 12 weeks gestation or more.

2.5x higher	Advanced maternal age
2.3x higher	Implantation failure
1.7x higher	Recurrent miscarriage
1.6x higher	Male factor

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http://www.igenomics.com

How do we inform customers?

- We try everything to make them buy our products

  "No worries! You can trust us!"

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Moral obligation

Responsible innovation requires making potentially risky reproductive technologies the subject of research, ideally proceeding through the steps of preclinical investigations, clinical trials and (long-term) follow-up studies.

The liability in this is often left to the patient by means of 'informed consent'. But it is simply too easy to just hide behind the demand of the patient. The problem here is that a patient could agree with being treated with a technique of unknown effectiveness, but the clinician still remains responsible for what he or she does.

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Dondorp and de Wert, HR (2011)

Who benefits from PGS?

- The companies!

▪ **In Vitro Fertilization (IVF)**

IVF Package Fees	Price
CCRM IVF Package (Starts at Lupron consult and ends after first pregnancy test)	$ 7,975
Fertility Laboratories of Colorado (FLC)	$ 5,105
South Denver Anesthesia Services	$ 430
Medications (Paid directly to the pharmacy of your choice)	$ 3,500 to 6,500 (approximate)
Total Estimated Cost of IVF Cycle	$ 17,010 to 20,010

▪ **IVF with Comprehensive Chromosome Screening (CCS)**

IVF With CCS Package Fees	Price
CCRM IVF Package (Starts at Lupron consult and ends after first pregnancy test)	$ 7,975
Fertility Laboratories of Colorado (FLC)	$ 14,080
*CCS and ICSI Included	
South Denver Anesthesia Services	$ 430
Medications (Paid directly to the pharmacy of your choice)	$ 4,300 to 8,500 (approximate)
Total Estimated Cost of IVF Cycle with CCS	$ 27,285 to 31,485

$ 8975

- PGS/CCS at CCRM in 2013
  - 3309 cycles * 0.85 (cycles with CCS) * $ 8975 = **$ 25,246,675**

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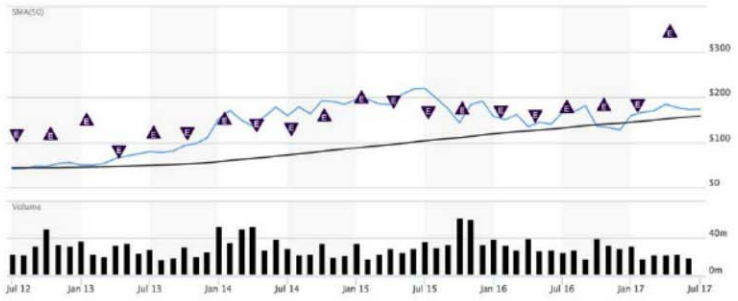
http://www.colocrm.com, http://www.sart.org, Repping, Best of ASRM/ESHRE, New York (2015)

Who benefits from PGS?

- The companies!
  - 1/1/2013: $50.63
  - 7/1/2017: $174.13
  - 344%



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www.marketwatch.com, Illumina Inc.

Endometrial Scratching - Do we have enough evidence?

Yacoub Khalaf, United Kingdom

Contribution not submitted by the speaker

Hysteroscopy and Salpingectomy before IVF - how significant is the evidence?

Tarek El-Toukhy

Consultant and Senior Lecturer in Reproductive Medicine

Guy's & St Thomas' Hospital and

King's College School of Medicine

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NHS Foundation Trust

Declaration

- No conflict of interest

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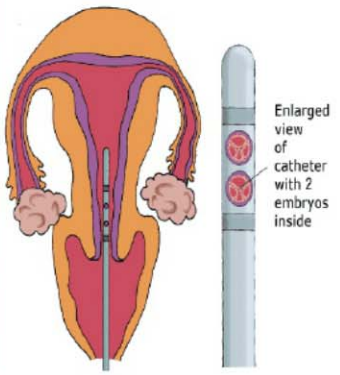
Aim of Uterine Optimisation



Undisturbed,pinpode-bearing functional endometrium

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Donoso et al, 2007

Overview

- **Technical feasibility of hysteroscopy**
- **Safety and diagnostic reliability**
- **Therapeutic effectiveness**

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Technical Feasibility

- **Feasibilityof standard hysteroscopy:**

  96% in pre- and post-menopausal population

  97% in pre-menopausal population (P=0.002)

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Human Reproduction Update 1999, Vol. 5, No. 1 pp. 73–81

Office mini-hysteroscopy

R.Campo[1], Y.Van Belle, L.Rombauts, I.Brosens and S.Gordts

Technical feasibility in 530 infertility patients

98%

Failures	No.	%
Pain	4	0.75
Internal cervical stenosis	3	0.57
Insufficient visualization	5	0.94
Complications	0	
Total	12/530	2.26

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Safety

- Standard Hysteroscopy:
  1% (16/1399) complication rate (SR of 17 studies)
  van Dongen et al, BJOG 2007

Vaso-vagal attack in 13
False track in 2
Fundal perforation in 1

BJOG

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Safety

- **Mini-hysteroscopy:**

0.16%

Table IV. Complications in 4204 conventional office hysteroscopies (1982–1989)

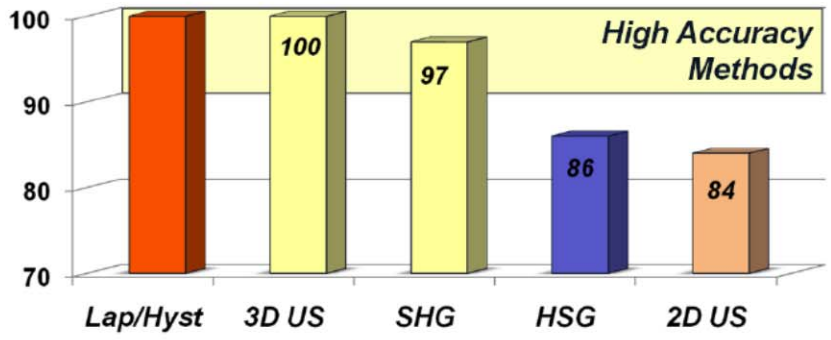
Complications	No.	%
Fundal perforation	2	
Prolonged vagal reaction	4	
Epileptic insult	1	
Infections	0	
Total	7	0.16

R.Campo[1], Y.Van Belle, L.Rombauts, I.Brosens and S.Gordts

Human Reproduction Update 1999, Vol. 5, No. 1 pp. 73–81

Uterine Abnormalities
Diagnostic accuracy of different methods

Diagnostic Accuracy=TP+TN/TP+FP+TN+FN



Saravelos et al, Hum Reprod Update, 14: 415-419, 2008

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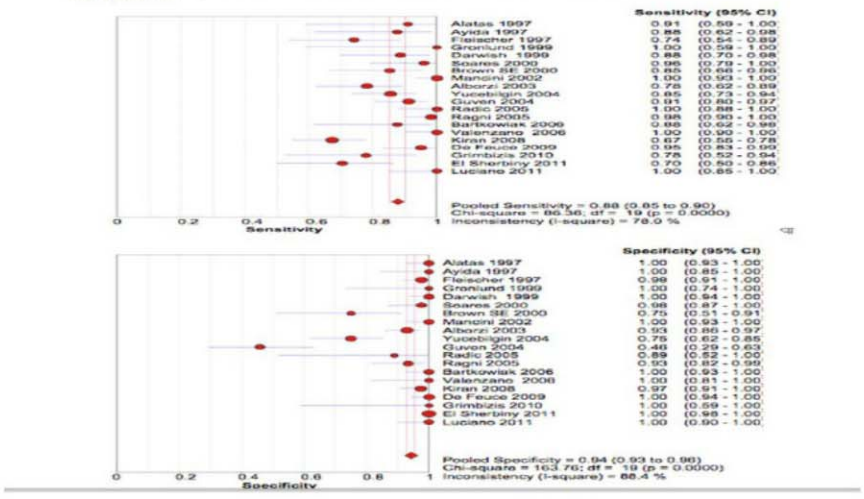
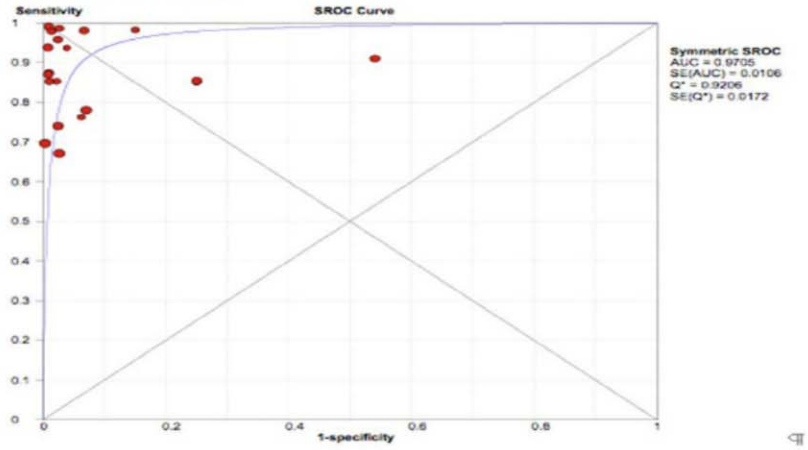
Saline hysterosonography

Figure 4: The sensitivity & sensitivity of SIS in the detection of all intrauterine abnormalities



Saline hysterosonography

Figure 5: The summary receiver operating curve (sROC) of SIS in the detection of all intrauterine abnormalities



Therapeutic Effectiveness

- **Studied in relation to a number of pathologies**
- **Analysis limited to subfertile population**
- **Effectiveness is measured by restoration of reproductive potential**

Observer agreement in the evaluation of the uterine cavity by hysteroscopy prior to *in vitro* fertilization

J.C. Kasius[1,*], F.J.M. Broekmans[1], S. Veersema[2], M.J.C. Eijkemans[3], E.J.P. van Santbrink[4], P. Devroey[5], B.C.J.M. Fauser[1], and H.M. Fatemi[5]

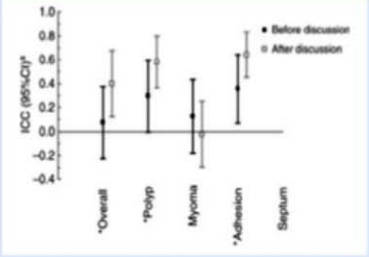


Figure 1 Level of interobserver agreement expressed as ICC[a] before and after discussion between observers. [a]ICC, intraclass correlation coefficient (equivalent of the overall weighted κ) (Fleiss and Cohen, 1973). *For diagnosing the uterine cavity to be normal or abnormal, diagnosing polyps and adhesions, the interobserver agreement significantly increased through discussion ($P < 0.01$). Impossible to compute ICC for diagnosing septa with ordinary statistics, as also used by SPSS version 15.1.

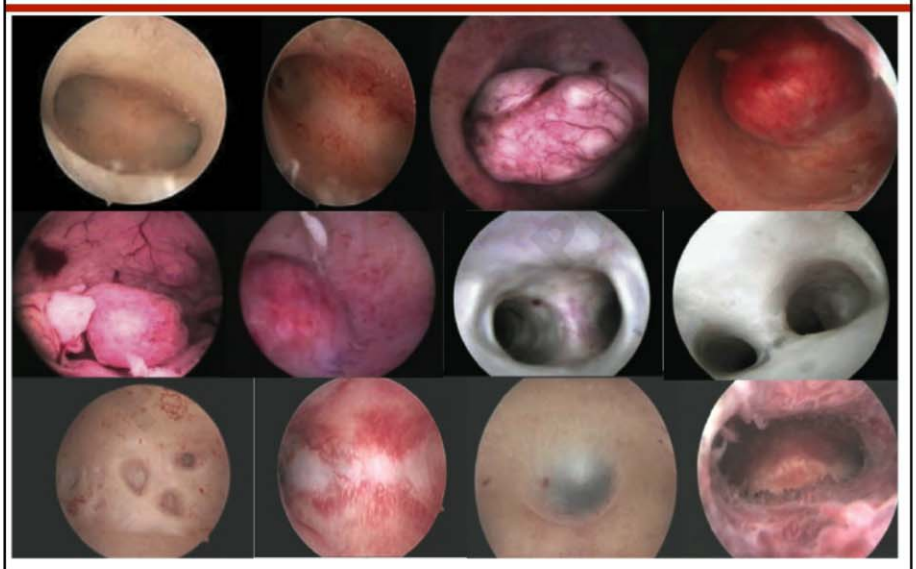
Table II Findings of the hysteroscopy performer at real-time hysteroscopy.

Findings	Prevalence	(%)
Normal cavity	94	87.9
Abnormal cavity	13[a]	12.1
Polyp	12	11.2
Myoma	1	0.9
Adhesion	0	0.0
Septa	2	1.9
Total	107[a]	100

[a]In two cases more than one abnormality was detected.

eshre

Overt and Subtle Endometrial Lesions



Uterine Pathology

1- Endometrial polyps

2- Uterine fibroids

3- Intra-uterine adhesions

4- Mullerian anomalies

5- Adenomyosis

11 - 45% in subfertile population

(Olivera et al., 2003; Levi Setti, 2004; Urman, 2005; Campo et al, 1999; Hinckley and Milki, 2004; Karayalcin et al, 2010; Al-Mazny et al., 2010; Fatemi et al., 2010)

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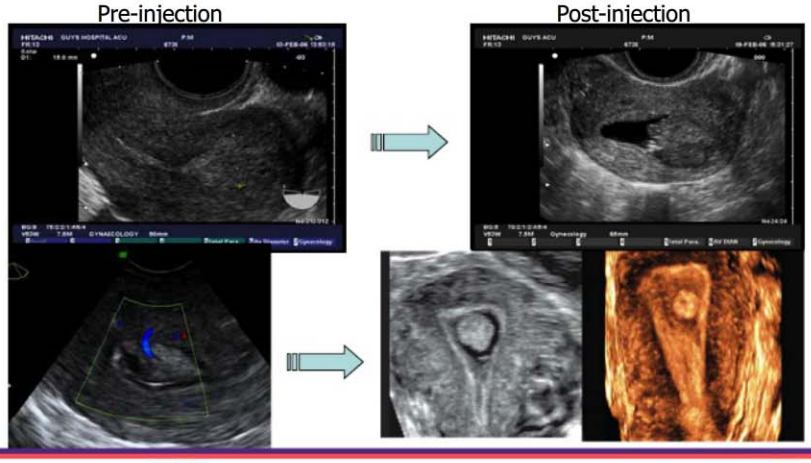
1- Endometrial Polyps

Pre-injection

Post-injection



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Prevalence of Endometrial Polyps

Table 2 Findings at hysteroscopy in 255 patients

Uterine cavity findings	Group 1		Group 2 ($n = 31$)
	Primary infertility ($n = 121$)	Secondary infertility ($n = 103$)	
Normal	87 (71.9%)	47 (45.6%)	30 (96.8%)
Polyps	18 (14.8%)	16 (15.5%)	1 (3.2%)
Adhesions	11 (9.1%)	34 (33%)	0
Fibroids	4 (3.3%)	3	0 (2.9%)
Adhesions and polyps	0	1	0 (0.97%)
Septa	1 (0.8%)	2 (1.9%)	1 (3.2%)

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Diagnosis of Endometrial Polyps

- **Before starting IVF treatment**
- **During IVF treatment**

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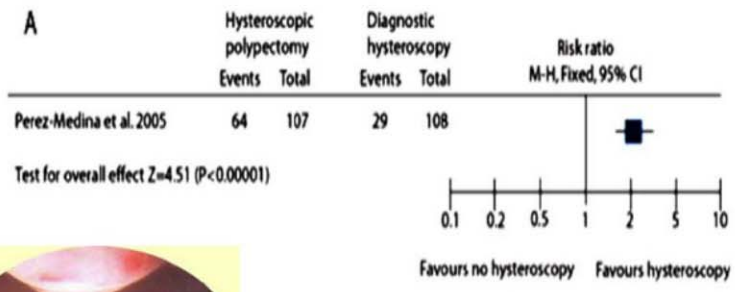
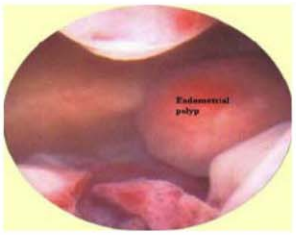
A-Endometrial Polyps before IVF



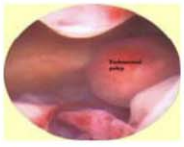


Human Reproduction Update, Vol.16, No.1 pp. 1–11, 2010
Advanced Access publication on September 10, 2009 doi:10.1093/humupd/dmp033
human reproduction update

A-Endometrial Polyps before IVF

- **Polypectomy prior to treatment:**

  - saves €728 - €6658 per clinical pregnancy after IUI



  - saves €6644 - €15,854 per ongoing pregnancy after IVF/ICSI

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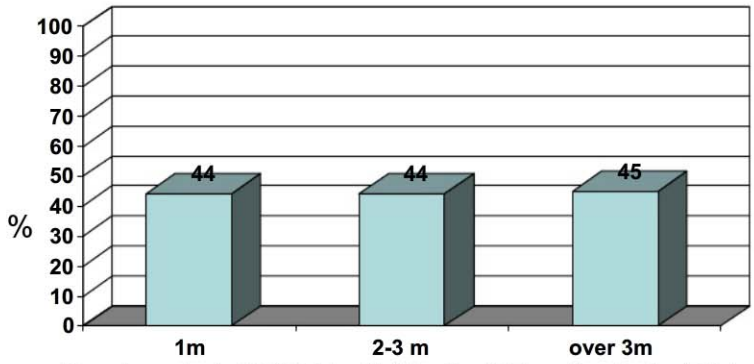
Mouhayar et al., 2017 RBMOnline

When to start IVF after polypectomy?



Pereira et al, 2016 Fertil Steril, 487 patients in USA

Erylimaz et al, 2012, 60 patients <6m and ≥6m, no difference

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Endometrial polyps during IVF

Management of endometrial polyps incidentally diagnosed during IVF: a case-control study **Vitrification**

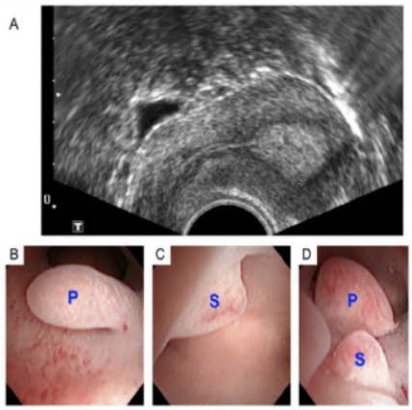

Table 2 – IVF outcomes for women with (group 1) and without (group 2) an endometrial polyp.

	Group 1 (n = 56)	Group 2 (n = 112)
Number of oocytes retrieved	7.5 (5–16.5)[a]	10 (5.3–14)
Number of oocytes fertilized	5.5 (3–9.8)	5 (3–9.8)
Day of embryo transfer		
Day 2, n (%)	3 (5)	25 (22)
Day 3, n (%)	36 (64)	63 (56)
Day 5, n (%)	17 (30)	24 (21)
Post-warming embryo survival, n (%)	162/171 (95)	–
Post-warming embryo partial degeneration, n (%)	155/162 (96)	–
Number of embryos transferred	2 (2–3)	2 (2–3)
Number of good embryos transferred	1 (0–2)	2 (0–2)
Clinical pregnancy rate[a], n (%)	35/56 (63)	46/112 (41)
Implantation rate, n (%)	38/144 (26)	55/276 (20)
Pregnancy outcome		
Live birth, n (%)	23 (41)	29 (26)
Miscarriage/ectopic pregnancy, n (%)	10 (18)	13 (12)
Lost to follow-up	2 (4)	4 (4)

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Yang et al REPRODUCTIVE BIOMEDICINE ONLINE 34 (2017) 285–25

B-Endometrial polyps during IVF

Do they reduce the success rate of IVF?

- Elias et al., J M I Gynecol 2015 (USA)
60 with untreated polyp(s) vs 2933 controls with no polyps = similar live birth rate (LBR)

- Tiras et al., RBM Online 2016 (Turkey)
128 with untreated polyp(s) vs 128 matched controls with no polyps = LBR 41% vs 40%

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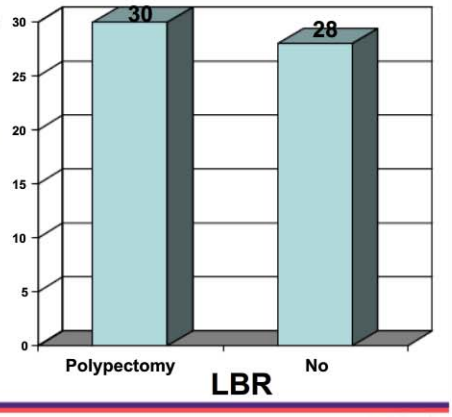
Endometrial polyps during IVF

- **Does the LBR improve after polypectomy?**

Ghaffari et al., 2016 EJOG
cohort study (Iran)
160 patients had polyp(s)

58 removal **102 no TTT**



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Hysteroscopic polypectomy for women undergoing IVF treatment: when is it necessary?

- **Treatment should be individualised**
  - **Number, size and location of polyp(s)**
  - **Number and quality of embryos available**
  - **Frozen embryo transfer success rate**

Curr Opin Obstet Gynecol 2016, 28:184–190

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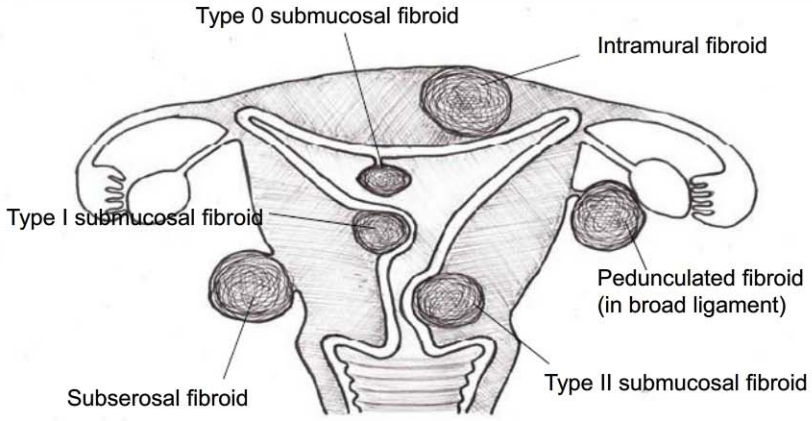
2- Uterine fibroids



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Can fibroids cause infertility?

Moon et al, 2015; Lu et al, 2015

Fibroids and IVF outcome

Human Reproduction Update, Vol.13, No.5 pp. 465–476, 2007
doi:10.1093/humupd/dmm013
Advance Access publication June 21, 2007

Fibroids and female reproduction: a critical analysis of the evidence

E. Somigliana[1,2], P. Vercellini[1,2,3,4], R. Daguati[1,2,3], R. Pasin[1,3], O. De Giorgi[1,2] and P.G. Crosignani[1,3]

[1]*Department of Obstetrics and Gynecology, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via Commenda 12, 20122 Milan, Italy;* [2]*Center for Research in Obstetrics and Gynecology (C.R.O.G.), Milan, Italy;* [3]*Università degli Studi di Milano, Milan, Italy*

[4]Correspondence address. Tel: +39-02-55032331; Fax: +39-02-55185028; E-mail: paolo.vercellini@unimi.it

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Fibroids and IVF outcome

Localization	Number of studies included[a]	Breslow–Day test (*P*-value)	Common OR (95% CI)
Clinical pregnancy rate			
Submucosal	2	0.92	0.3 (0.1–0.7)
Intramural	7	0.38	0.8 (0.6–0.9)
Subserosal	3	0.92	1.2 (0.8–1.7)
Intramural and/or subserosal	11	0.30	1.0 (0.8–1.2)
All types	16	0.24	0.8 (0.7–1.0)
Delivery rate			
Submucosal	2	0.79	0.3 (0.1–0.8)
Intramural	7	0.09	0.7 (0.5–0.8)
Subserosal	3	0.94	1.0 (0.7–1.5)
Intramural and/or	11	0.68	0.9 (0.7–1.1)

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Human Reproduction Update, Vol.13, No.5 pp. 465–476, 2007
Advance Access publication June 21, 2007

Cumulative probability of pregnancy after myomectomy

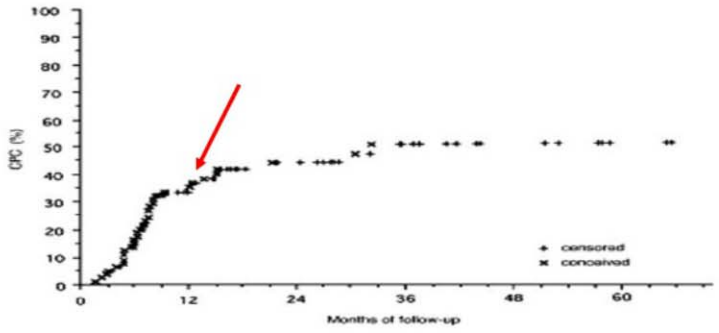

Figure 1. Cumulative probability of spontaneous intrauterine conception (CPC) after myomectomy using the Kaplan and Meier method (time 0 is the date of the myomectomy).

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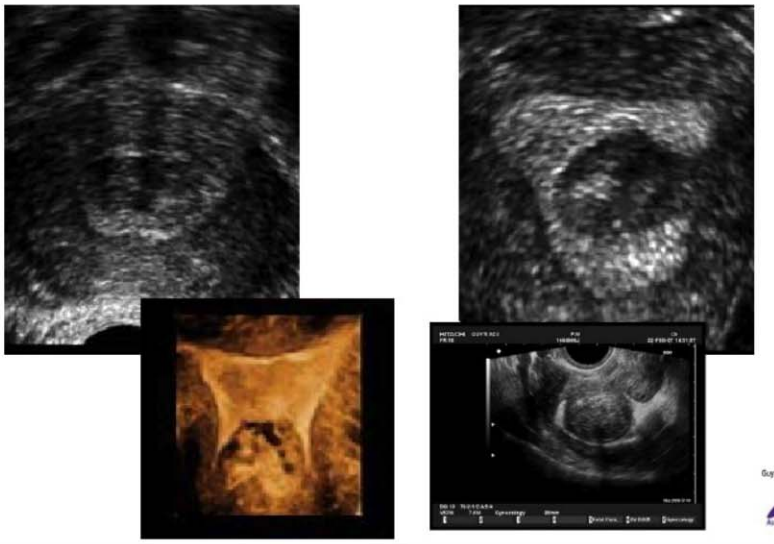
Fauconnier et al., Hum Reprod 15:1751-7, 2000

2a- Submucosal Fibroids



Submucous fibroids <4cm

B

	Surgery		Expectant management		Risk ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI
Casini et al. 2005	21	52	9	24	

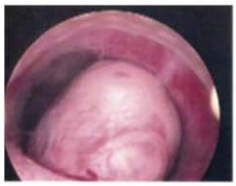
Test for overall effect Z=1.86 (P=0.06)

Human Reproduction Update, Vol.16, No.1 pp. 1–11, 2010
Advanced Access publication on September 10, 2009 doi:10.1093/humupd/dmp033
human reproduction update

Larger submucous fibroids

204 women with infertility and submucous fibroids randomised to either

101 hysteroscopic myomectomy



103 diagnostic hysteroscopy

CPR 63.4%

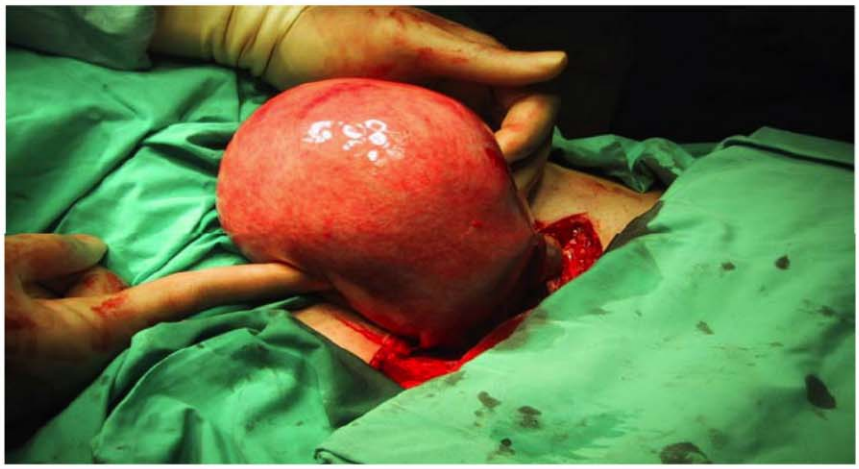
Follow up for 1 year

CPR 28.2%

RR-2.1, 95%CI 1.5-2.9

Shokeir et al, 2009 Fertil Steril

2b- Intramural fibroids



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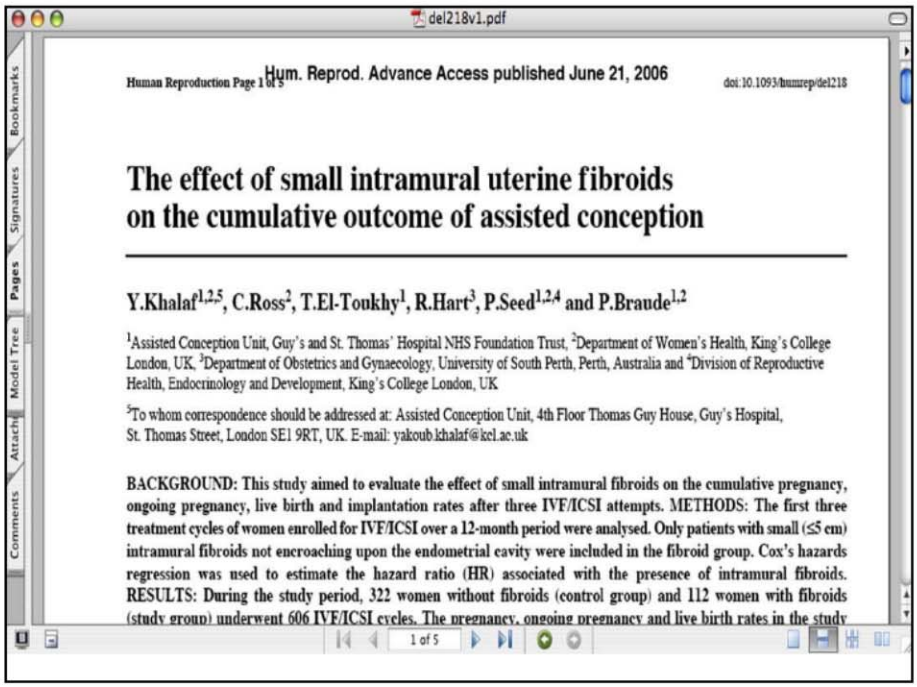


del218v1.pdf

Human Reproduction Page 1 of 5 Hum. Reprod. Advance Access published June 21, 2006 doi:10.1093/humrep/del218

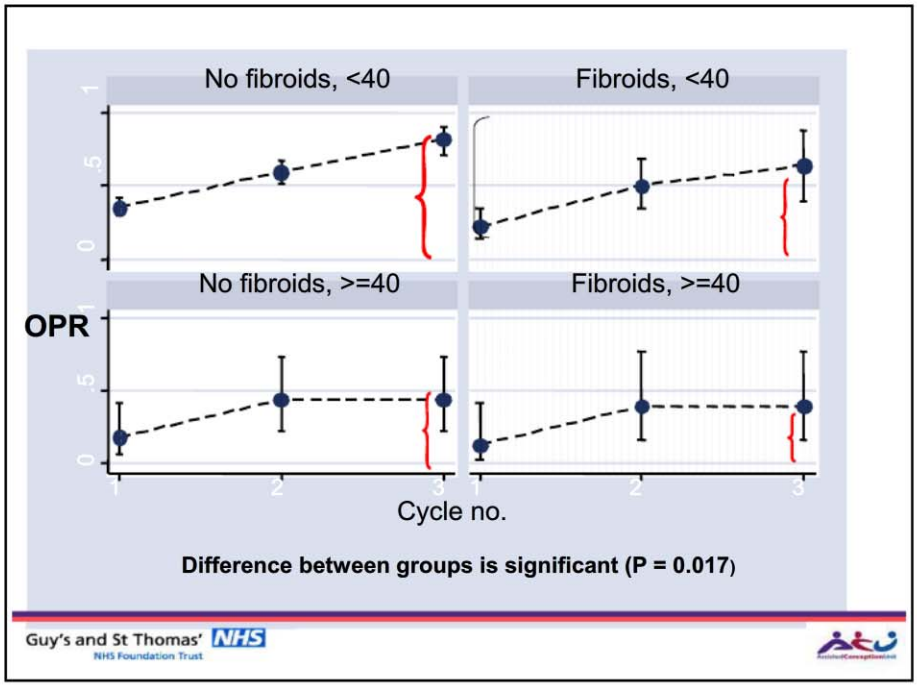
The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception

Y.Khalaf[1,2,5], C.Ross[2], T.El-Toukhy[1], R.Hart[3], P.Seed[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

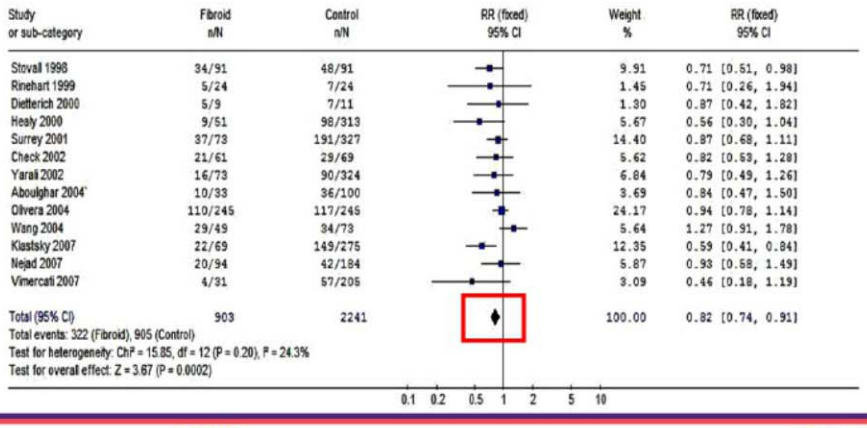
[5]To whom correspondence should be addressed at: Assisted Conception Unit, 4th Floor Thomas Guy House, Guy's Hospital, St. Thomas Street, London SE1 9RT, UK. E-mail: yakoub.khalaf@kcl.ac.uk

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 pregnancy, ongoing pregnancy and live birth rates in the study



Effect of small I/M fibroids on IVF outcome

Review: Fibroid Intra-mural
Comparison: 01 Fibroid intramural
Outcome: 02 Pregnancy Outcome



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Sunkara et al., Hum Reprod 2009

Fibroids that do not distort the uterine cavity and IVF success rates: an observational study using extensive matching criteria

Table 2. Clinical pregnancy and live birth rates of women with fibroids (cases) and their matched controls

Group	Outcome	Controls *n/N* (%)	Cases *n/N* (%)	Odds ratio (95% CI)	*P*
All	Clinical pregnancy	139/326 (42.6%)	53/163 (32.5%)	0.62 (0.41–0.94)	**0.03**
	Live birth	125/326 (37.4%)	44/163 (26.9%)	0.58 (0.48–0.78)	**0.01**
1 fibroid	Clinical pregnancy	58/138 (42%)	29/69 (42%)	1.00 (0.55–1.83)	1.00
	Live birth	52/138 (37.6%)	22/69 (31.8%)	0.77 (0.41–1.43)	0.41
2+ fibroids	Clinical pregnancy	81/188 (43.1%)	24/94 (25.5%)	0.42 (0.23–0.75)	**0.003**
	Live birth	73/188 (38.8%)	22/94 (23.4%)	0.47 (0.26–0.83)	**0.01**
Fibroids <30 mm	Clinical pregnancy	96/214 (44.8%)	42/107 (39.2%)	0.77 (0.47–1.27)	0.31
	Live birth	86/214 (40.1%)	34/107 (31.7%)	0.67 (0.40–1.12)	0.13
Fibroids ≥30 mm	Clinical pregnancy	43/112 (38.3%)	11/56 (19.6%)	0.39 (0.18–0.84)	**0.02**
	Live birth	39/112 (34.8%)	10/56 (17.8%)	0.41 (0.19–0.89)	**0.03**
Day-5 transfer	Clinical pregnancy	109/220 (49.5%)	40/110 (36.3%)	0.56 (0.35–0.92)	**0.02**
	Live birth	96/220 (43.6%)	34/110 (30.9%)	0.58 (0.35–0.94)	**0.03**

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BJOG 2017;124:615–621.

Effect of Myomectomy

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.

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Simple Guide

1. **Submucosal fibroids cause sub-fertility & miscarriage:**
   - warrant hysteroscopic removal
2. **Fibroids distorting the uterine cavity are likely to impair reproduction: - warrant removal**
3. **Intramural non-cavity distorting fibroids could impair fertility, but evidence of benefit after removal is inconclusive (if over 5cm, may warrant removal)**
4. **Subserosal fibroids: - probably don't warrant removal**

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3-Intra-uterine Adhesions

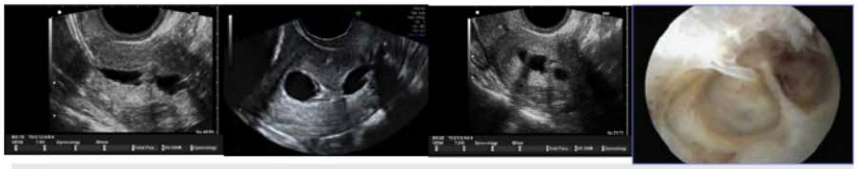

Table I Defined clinical categories to describe the extent and degree of intrauterine adhesions (IUAs) after miscarriage.

	Classification systems			
Clinical category	American Fertility Society (AFS), 1988	European Society of Hysteroscopy (ESH), 1989*	European Society of Gynecological Endoscopy (ESGE), 1995	March, 1978
Mild	Stage I	Stage I	Stage I	Mild
Moderate	Stage II	Stage II, IIa or III	Stage II, IIa or III	Moderate
Severe	Stage III	Stage IIIa, IIIb or IV	Stage IV, Va or Vb	Severe

*The European Society of Hysteroscopy (ESH) was adopted by the European Society of Gynecological Endoscopy (ESGE) in 1995.

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Treatment of Uterine Adhesions

- **No randomised trials**
- **No controlled trials**
- **Typically small case series (5-75)**
- **Very few studies >100 patients**

SUPPLEMENTAL TABLE 1

Study outcomes on restoration of healthy uterine anatomy and resumption of healthy menstrual pattern after surgery for Asherman syndrome.

First author and reference	Year	N	Successful restoration of healthy uterine anatomy (%)
Fedele (14)	1986	21	62.5
Capella-Allouc (17)	1999	31	51.6
Pace (15)	2003	75	93.3
Fernandez (16)	2006	71	43.6
			Healthy menstrual pattern restored (%)
Fedele (14)	1986	21	67.7
Valle (18)	1988	169	88.2
Pabuccu (29)	1997	34	81.0
Preutthipan (28)	2003	65	90.9
Zikopoulos (19)	2004	46	93.4
Yasmin (20)	2007	20	96.0
Thomson (21)	2007	30	81.5
Robinson (22)	2008	24	95.0

Hanstede. Reproductive outcomes of Asherman surgery. Fertil Steril 2015.

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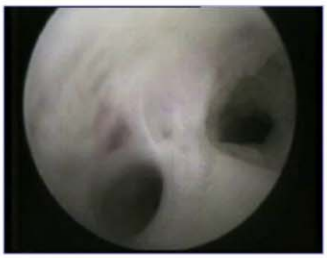
Prevention of adhesions recurrence

- Insertion of IU balloon or IUCD for 1 week
- Anti-adhesion Barrier Gel
- Estrogen for 4-8 weeks
- Second-look hysteroscopy in 4 weeks



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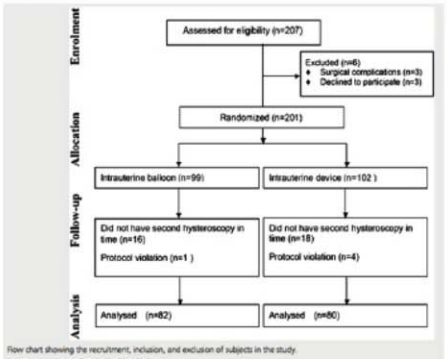
Randomized, controlled trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation after hysteroscopic adhesiolysis

Xiao-Na Lin, M.Sc.,[a] Feng Zhou, M.Med.,[a] Min-Ling Wei, M.Med.,[a] Yang Yang, M.Med.,[a] Ying Li, M.B., B.S.,[a] T. C. Li, M.D., Ph.D.,[b] and Song-Ying Zhang, M.D., Ph.D.[a]

FIGURE 2



Flow chart showing the recruitment, inclusion, and exclusion of subjects in the study.

Lin. Intrauterine adhesion reformation. Fertil Steril 2015.

TABLE 2

Comparison of the incidence of intrauterine adhesions reformation and the reduction of adhesion score at the second-look hysteroscopy between the intrauterine balloon and IUD groups.

Variable	Balloon	IUD	*P* value
Recurrence of adhesion[a]			
No	57 (70)	52 (65)	NS
Yes	25 (30)	28 (35)	
Median reduction of AFS score[b]	7 (2–12)	7 (0–12)	NS

[a] Number (percentage), χ^2 test.
[b] Median (95% confidence interval), Mann-Whitney *U* test.

Lin. Intrauterine adhesion reformation. Fertil Steril 2015.

Anti-adhesion Gel: the evidence

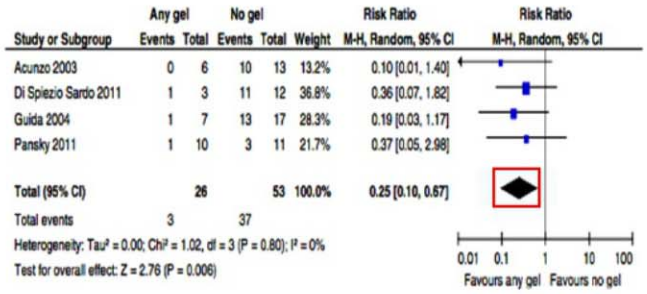
Gynecol Surg (2014) 11:113–127
DOI 10.1007/s10397-014-0832-x

REVIEW ARTICLE

Anti-adhesion barrier gels following operative hysteroscopy for treating female infertility: a systematic review and meta-analysis

Jan Bosteels · Steven Weyers · Ben W. J. Mol · Thomas D'Hooghe

Fig. 12 Any anti-adhesion gel versus no gel, outcome 5.3: AFS 1988 stage II (moderate) or stage III (severe) adhesions at second-look hysteroscopy



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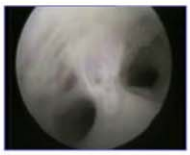
Overall Treatment Outcome

- Pregnancy rate 30-50%
- Live birth rate 10-35%
- Poor prognostic indicators:
  - **Adhesions obliterating both ostia**
  - **Age >35 years**
  - **Amenorrhea/oligomenorrhea**
  - **Abnormal ultrasound appearance**
  - **Reformation of adhesions at 2nd look**



Goldenberg et al., : Roge et al, ; Pabuccu et al, 2008; Yu et al, 2008; Thompson et al,2009; Capella-Allouc et al., ; Zikopoulos et al., ; Bhandari et al, 2016

4- Mullerian Duct Anomalies

TABLE 1

AFS classification of patients based on the anatomy of the female genital system, especially uterine anatomy.

Class I	Hypoplasia and agenesis	(a) Vaginal, (b) cervical, (c) fundal, (d) tubal
Class II	Unicornuate	(a) Communicating, (b) noncommunicating, (c) no cavity, (d) no horn
Class III	Didelphys	
Class IV	Bicornuate	(a) Partial, (b) complete
Class V	Septate	(a) Partial, (b) complete
Class VI	Arcuate	
Class VII	DES drug-related	

EDITOR'S CORNER

Congenital malformations of the female genital tract: the need for a new classification system

Grigoris F. Grimbizis, M.D., Ph.D.,[a] and Rudi Campo, M.D.[b]

TABLE 3

VCUAM classification of patients based on the anatomy of the female genital system, more specifically, the independent estimation of each organ's anatomy.

Vagina (V)	0	Normal
	1	(a) Partial hymenal atresia, (b) complete hymenal atresia
	2	(a) Incomplete septate vagina <50%, (b) complete septate vagina
	3	Stenosis of the introitus
	4	Hypoplasia
	5	(a) Unilateral atresia, (b) complete atresia
	S	[1] Sinus urogenitalis (deep confluence), [2] sinus urogenitalis (middle confluence), [3] sinus urogenitalis (high confluence)
	C	Cloacae
	+	Other
	#	Unknown
Cervix (C)	0	Normal
	1	Duplex cervix
	2	(a) Unilateral atresia/aplasia, (b) unilateral atresia/aplasia
	+	Other
	#	Unknown
Uterus (U)	0	Normal
	1	(a) Arcuate, (b) septate <50% uterine cavity, (c) septate >50% uterine cavity
	2	Bicornuate
	3	Hypoplastic
	4	(a) Unilaterally rudimentary or aplastic, (b) bilaterally rudimentary or aplastic
	+	Other
	#	Unknown

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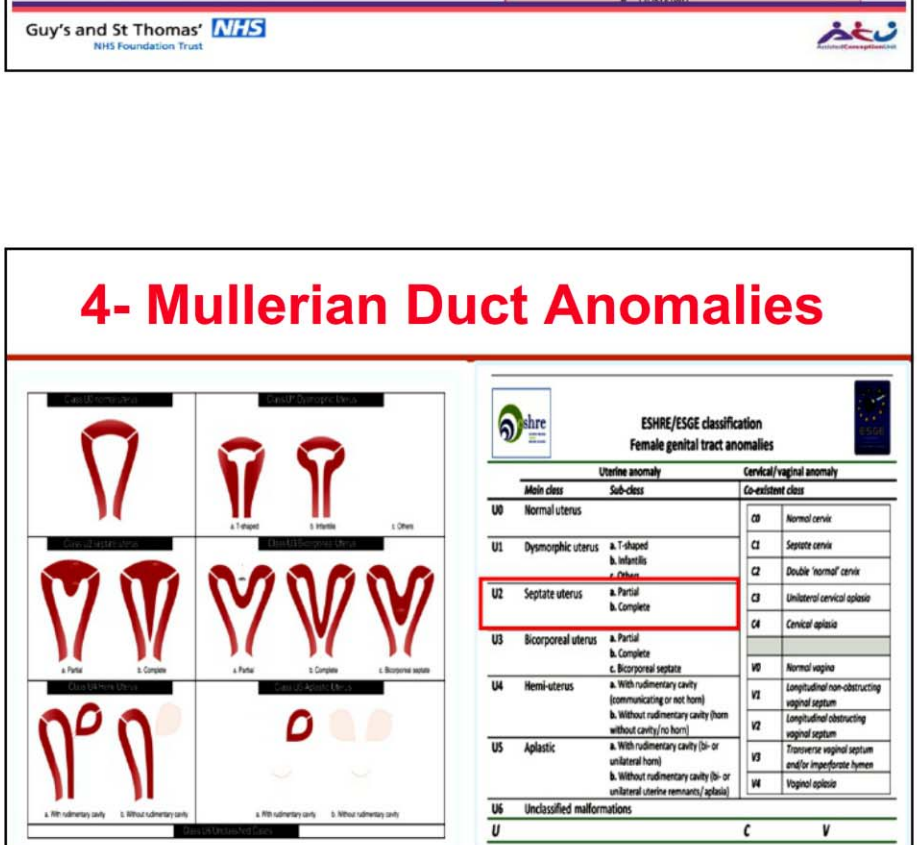

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Human Reproduction, Vol.28, No.8 pp. 2032–2044, 2013

Human Reproduction Update, Vol.14, No.5 pp. 415–429, 2008
Advance Access publication June 6, 2008
doi:10.1093/humupd/dmn018

Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal

Sotirios H. Saravelos[1,3], Karen A. Cocksedge[1] and Tin-Chiu Li[1,2]

Table XII. Congenital uterine anomalies: percentage of subtypes in different population groups[a].

Population	Hypoplastic, %	Unicornuate, %	Didelphys, %	Bicornuate, %	Septate, %	Arcuate, %
General/fertile (n = 250)	-	0.4	0.4	4.0	27.2	68.0
Infertile (n = 510)	9.4	6.1	2.9	10.8	46.1	24.7
RM (n = 132)	-	2.3	0.8	5.3	26.5	65.2

[a]Data based only on class Ia studies using an appropriate classification of the congenital uterine anomaly types.

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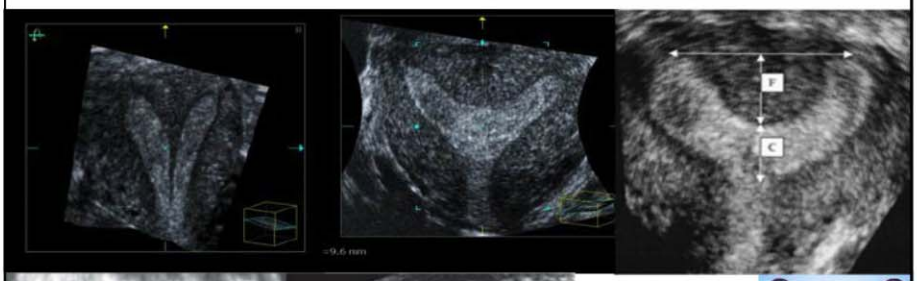
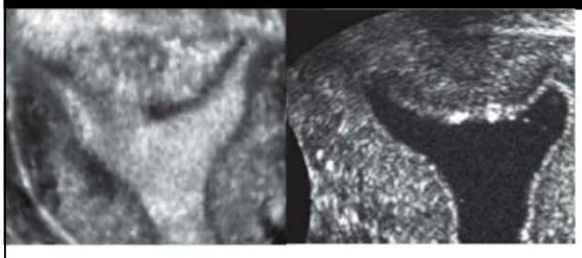
Septate/Subseptate uterus





F/F+C

>50%

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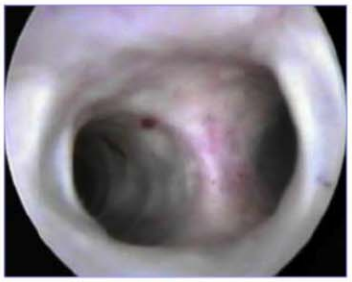
Uterine Septum Resection

- No randomised trials
- One controlled trial



- Case series typically with N<50

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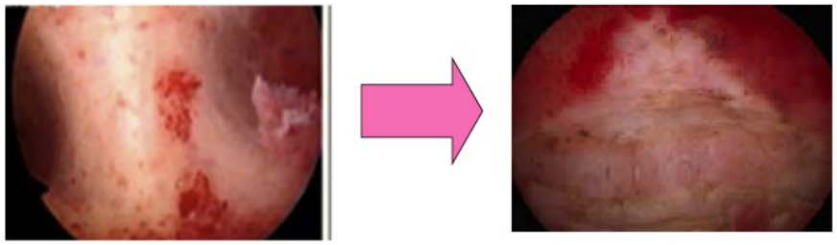
Uterine Septum Resection

Mollo et al, 2009 Fertil Steril

- Higher live birth rate after septal resection (n=44) compared to controls (n=132)

34% vs 19% (P<0.01)



Uterine Septum Resection

Table 2: Literature on pregnancy rates and live birth rates after hysteroscopic uterine septoplasty in women with septate uterus

Author	Year	Patient number	Uterine mal-formation	Patient characteristics	Pregnancy rate	Live birth rate
Venturoli et al. [13]	2002	141	IUS	Infertility; RM	74/141 (52%)	56/141 (39%); 14 ongoing
Doridot et al [14]	2003	70	CUS	21 PI; 33 RM; 16 LM or PT	8/21 (38%); 13/33 (38%); 10/16 (60%)	-
Jakiel et al. [15]	2004	31	CUS	PI; RM; LM and PT	18/31 (58%)	11 (38%)
Hollett-Caines et al. [20]	2006	26	CUS	Infertility; RM	21/26 (80%)	15/26 (57%)
Pace et al. [16]	2006	70	IUS; CUS	PI; RM; PT	30/40 (75%)	25/40 (62%)
Colacurci et al. [21]	2007	135	CUS	Infertility	99/135 (73%)	82/135 (60%)
Colacurci et al. [22]	1996	69	IUS; CUS	PI; RM	46/69 (66%)	36/69 (52%); 4 ongoing
Saygili-Yimaz et al. [23]	2003	361	CUS	PI; RM	180/361 (49%)	124/361 (34%)
Pabuçcu & Gomel [24]	2004	61	CUS	PI	25/61 (41%)	18/61 (29%)
Valle RF [26]	1996	124	CUS	RM	101/124 (81%)	91/124 (73%)
Ozgur et al. [11]	2007	119	IUS	IVF	57/119 (47%)	51/119 (42%)
Marabini et al. [27]	1994	40	CUS	Infertility; RM	19/26 (73%)	13/26 (50%); 4 ongoing
Kupesic & Kurjak [28]	1998	116	CUS	Infertility	59/116 (50%)	48/116 (41%)
Porcu et al. [29]	2000	63	CUS	RM	45/56 (80%)	28/56 (50%)
Guarino et al. [31]	1989	35	CUS	PI; RM	18/35 (51%)	16/35 (45%)
Wang et al. [30]	2008	25	CUS	PI and SI; RM	13/23 (56%)	6/23 (26%); 6 ongoing
Mollo et al. [17]	2009	44	CUS	-	17/44 (38%)	15/44(34%)
1587	IUS; CUS		-	892/1501 (60%)		686/1501 (45%)

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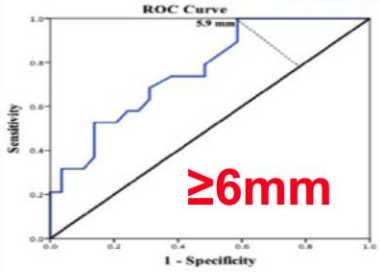
When to Resect a septum?

Relevance of Uterine Subseptations

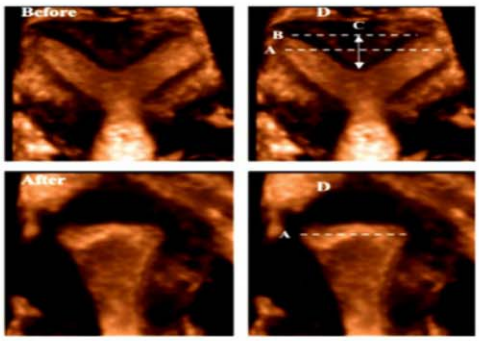
What Length Should Warrant Hysteroscopic Resection?

Laura Detti, MD, Holly Hickman, MD, Roberto Levi D'Ancona, MD, Alicia W. Wright, MD, Mary E. Christiansen, MD

J Ultrasound Med 2017; 36:757–765



Area under the curve (AUC)= 0.763; $P = 0.002$
—— = subseptation length in the 42 subjects who had surgical resection.
Reference variable = postoperative difference in cavity width: <7.0 mm; ≥7.0 mm.



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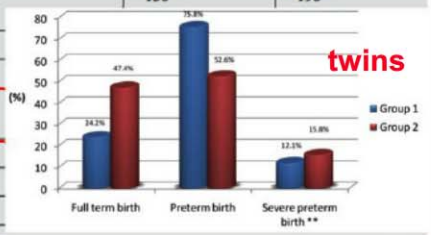
Subseptate and Arcuate Uterus

Reproductive outcome after IVF following hysteroscopic division of incomplete uterine septum/arcuate uterine anomaly in women with primary infertility

M. Abuzeid[1,2], G. Ghourab[2], O. Abuzeid[2], M. Mitwally[3], M. Ashraf[1,2], M. Diamond[4]

Table III. — Comparison of the best reproductive outcome among all the cycles (fresh and frozen) between group 1 and group 2.

	Group 1	Group 2
Number of patients	156	196
Number of cycles		
Cumulative clinical pregnancy rate per cycle*		
Cumulative delivery rate per cycle**		
Cumulative clinical pregnancy per patient		
Cumulative delivery Rate per patient		
Miscarriage rate		
Multiple pregnancy rate		
Ectopic pregnancy rate		



twins

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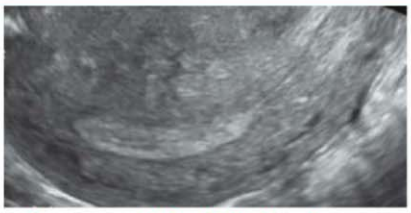
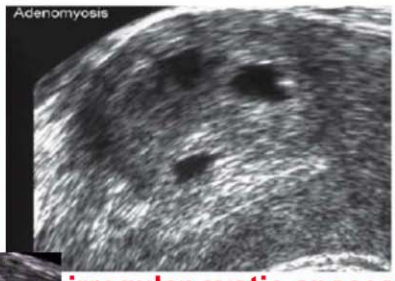
NHS Foundation Trust

Facts Views Vis Obgyn, 2014, 6 (4): 194-202

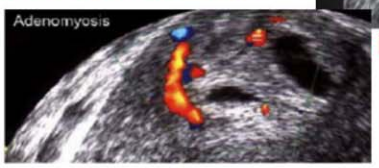
5- Adenomyosis



Asymmetric thickening



irregular cystic spaces



increased myometrial vascularity

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Adenomyosis and IVF Outcome

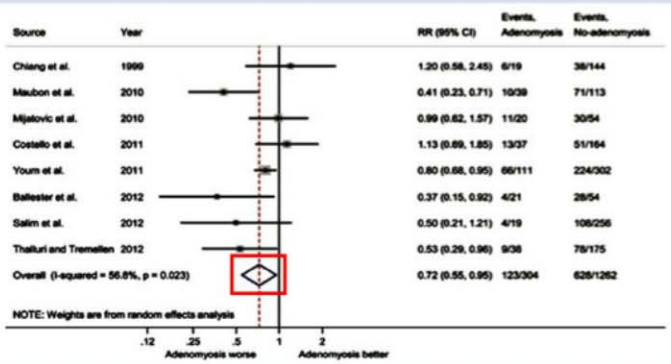

Figure 2 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of clinical pregnancy in infertile women with or without adenomyosis undergoing IVF/ICSI. Horizontal lines indicate 95% CIs; boxes show the study-specific

human reproduction META-ANALYSIS (Human Reproduction, Vol.29, No.5 pp. 964–977, 2014

Guy's and St Thomas' NHS Assisted Conception Unit

Optimisation Options

Long down-regulation protocol and FET Clin Exp Reprod Med 2016;43(3):169-173

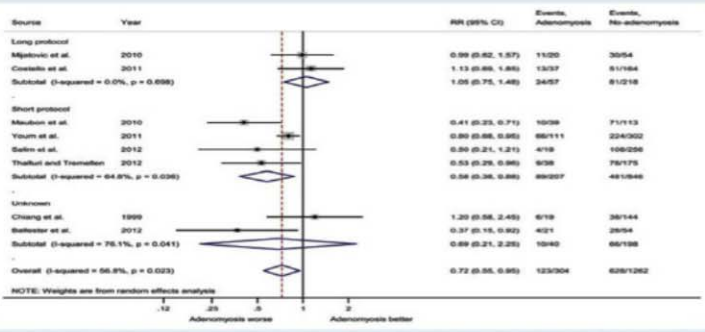

Table 2. Comparison of IVF outcomes according to adenomyotic region

Variable	Fresh ET following GnRH-a treatment (group B)		FET following GnRH-a treatment (Group C)		*p*-value
	Focal adenomyosis	Diffuse adenomyosis	Focal adenomyosis	Diffuse adenomyosis	
No. of patients	53	25	22	16	-
No. of cycles	70	35	23	20	-
No. of transferred embryos	3.4±0.5	2.9±0.9	3.2±0.8	2.9±1.1	NS
Clinical pregnancy rate	23/70 (32.9)	9/35 (25.7)	10/23 (43.5)	7/20 (35.0)	NS
Miscarriage rate	5/70 (7.1)	5/35 (14.3)	3/23 (13.0)	3/20 (15.0)	NS

Routine 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

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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)

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Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial

Tarek El-Toukhy, Rudi Campo, Yacoub Khalaf, Carla Tabanelli, Luca Gianaroli, Sylvie S Gordts, Stephan Gordts, Greet Mestdagh, Tonko Mardesic, Jan Voboril, Gian L Marchino, Chiara Benedetto, Talha Al-Shawaf, Luca Sabatini, Paul T Seed, Marco Gergolet, Grigoris Grimbizis, Hoda Harb, Arri Coomarasamy THELANCET-D-15-08731R2

Hypothesis: ***Does performing an OPH prior to starting an IVF cycle improve the LBR after 2-4 failed IVF cycles?***

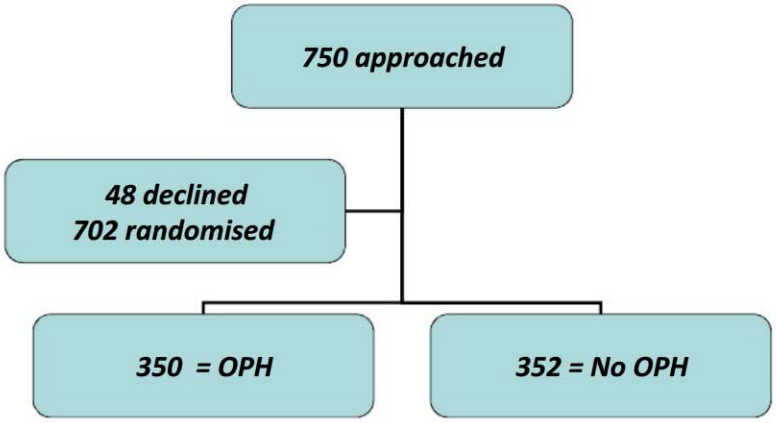
Population: ***Women under 38 years, Failed 2 - 4 IVF/ET cycles, Normal TVS of cavity***

Intervention: ***Saline OPH (2.9mm) cycle before IVF***

Control group: ***No hysteroscopy***

Primary outcome: ***LBR / cycle started***

Recruitment Results



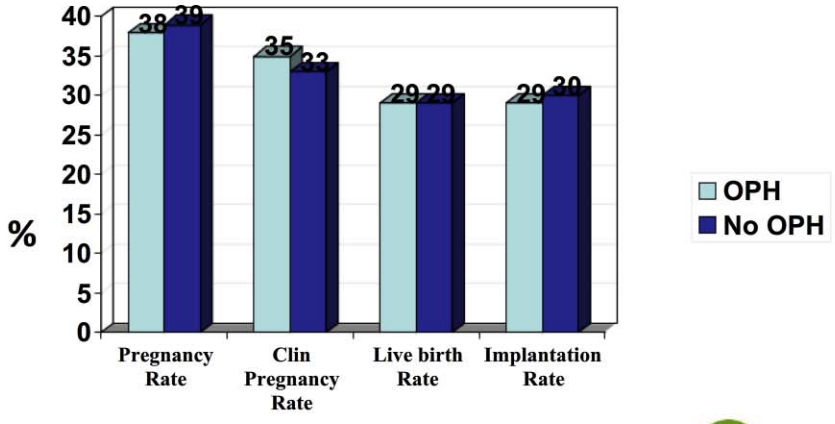
62

Hysteroscopy findings

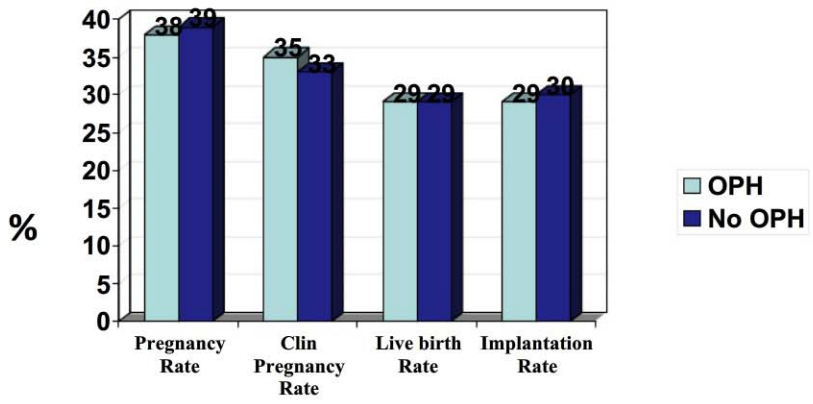
- Endometrial Cavity: 11% abnormality rate (34)
- Treatable abnormality: 16 Non-treatable: 18
  - Arcuate (dysmorphic) uterus: 15
  - Endometrial polyp(s): 8
  - Partial septum: 5
  - Hemi-uterus: 3
  - Submucous fibroid: 2
  - T-shaped cavity: 1

- 15 had surgical treatment:
7 conceived
- 19 had no treatment:
7 conceived

IVF Outcome: ITT Analysis



IVF Outcome: ITT Analysis



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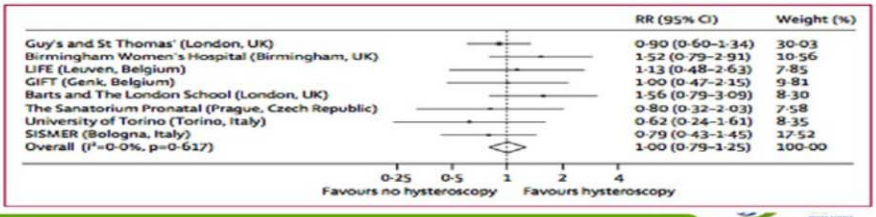
IVF Outcome: ITT Analysis

	Hysteroscopy group	Control group	Risk ratio (95% CI)
Rates per participant			
Pregnancy	38% (133/350)	39% (136/352)	0·97 (0·72–1·32); p=0·86
Clinical pregnancy	35% (121/350)	33% (116/352)	1·08 (0·79–1·47);p=0·65
Livebirth	29% (102/350)	29% (102/352)	1·0 (0·79–1·25); p=0·96
Rates per participant receiving embryo transfer			
Pregnancy	42% (125/301)	44% (128/290)	0·94 (0·78–1·13); p=0·52
Clinical pregnancy	38% (114/301)	38% (110/290)	0·99 (0·81–1·22); p=0·99
Livebirth	32% (95/301)	33% (96/290)	0·95 (0·76–1·20); p=0·69
Rates per participant receiving a top-quality embryo			
Pregnancy	45% (104/232)	46% (109/236)	0·97 (0·80–1·18); p=0·77
Clinical pregnancy	42% (97/232)	42% (98/236)	1·01 (0·84–1·21); p=0·99
Livebirth	35% (82/232)	36% (86/236)	0·98 (0·81–1·24); p=0·81

Outcome data are % (n/N).

Table 4: **Pregnancy and livebirth outcomes**



Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial

Janine G Smit, Jenneke C Kasius, Marinus J C Eijkemans, Carolien A M Koks, Ronald van Golde, Annemiek W Nap, Gabrielle J Scheffer, Petra A P Manger, Annemieke Hoek, Benedictus C Schoot, Arne M van Heusden, Walter K H Kuchenbecker, Denise A M Perquin, Kathrin Fleischer, Eugenie M Kaaijk, Alexander Sluijmer, Jaap Friederich, Ramon H M Dykgraaf, Marcel van Hooff, Leonie A Louwe, Janet Kwee, Corry H de Koning, Ineke C A H Janssen, Fernke Mol, Ben W J Mol, Frank J M Broekmans, Helen L Torrance

www.thelancet.com Vol 387 June 25, 2016

	Hysteroscopy group (n=369)	Immediate IVF group (n=373)	Relative risk (95% CI)	p value
Ongoing pregnancy resulting in livebirth at 18 months of follow-up	209 (57%)	200 (54%)	1·06 (0·93–1·20)	0·41
Ongoing pregnancy resulting in livebirth after:				
First cycle*	93 (27%); n=348	104 (30%); n=349	0·90 (0·71–1·14)	0·37
Second cycle	48 (22%); n=214	46 (22%); n=205	1·00 (0·70–1·43)	1·00
Third cycle	24 (23%); n=111	17 (17%); n=112	1·42 (0·81–2·50)	0·22
Fourth cycle	6 (2%); n=26	4 (19%); n=21	1·21 (0·39–3·74)	0·74
Fifth cycle	2 (28%); n=7	0 (0%); n=4	NA	–
Sixth cycle	1 (100%); n=1	1 (100%); n=1	NA	–
Ongoing pregnancy†	211 (57%)	203 (54%)	1·05 (0·92–1·19)	0·45
Multiple pregnancy	17/209 (8%)	8/200 (4%)	2·03 (0·88–4·62)	0·08
Conception method of livebirths				0·63
Natural	29/209 (14%)	25/200 (13%)	–	–
IVF and ICSI fresh	140/209 (67%)	133/200 (67%)	–	–
IVF and ICSI frozen	34/209 (16%)	39/200 (20%)	–	–
IUI cycle‡	6/209 (3%)	2/200 (1%)	–	–
Unknown	0	1/200 (1%)	–	–
Time to pregnancy leading to livebirth (days)§	161 (87–332)	141 (83–286)	–	0·52
Gestational age (weeks)	39 (2·2)	39 (2·3)	–	0·83
Birthweight (g)	3367 (599)	3331 (661)	–	0·47

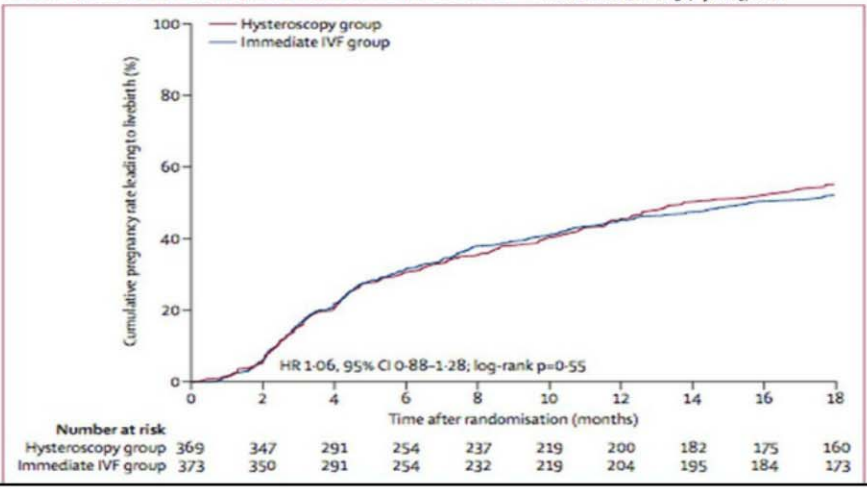
Data are n (%), n/N (%), or mean (SD). IVF=in-vitro fertilisation. ICSI=intracytoplasmic sperm injection. IUI=intrauterine insemination. *Livebirth rates include both fresh and frozen transfers. †Of the ongoing pregnancies, the outcome of the pregnancy is unknown for three women in the immediate IVF group due to loss to follow-up; in the hysteroscopy group one woman had a stillbirth after a premature delivery (gestational age 23 weeks) due to pre-eclampsia and one woman had a termination of pregnancy due to a chromosomal abnormality. ‡IUI cycles in the waiting period for IVF. §From moment of randomisation to positive pregnancy test.

Table 2: **Pregnancy data per woman**

Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial

Janine G Smit, Jenneke C Kasius, Marinus J C Eijkemans, Carolien A M Koks, Ronald van Golde, Annemiek W Nap, Gabrielle J Scheffer, Petra A P Manger, Annemieke Hoek, Benedictus C Schoot, Arne M van Heusden, Walter K H Kuchenbecker, Denise A M Perquin, Kathrin Fleischer, Eugenie M Kaaijk, Alexander Sluijmer, Jaap Friederich, Ramon H M Dykgraaf, Marcel van Hooff, Leonie A Louwe, Janet Kwee, Corry H de Koning, Ineke C A H Janssen, Fernke Mol, Ben W J Mol, Frank J M Broekmans, Helen L Torrance

www.thelancet.com Vol 387 June 25, 2016



Number at risk

Hysteroscopy group	369	347	291	254	237	219	200	182	175	160
Immediate IVF group	373	350	291	254	232	219	204	195	184	173

Evidence into Routine Practice

- Significant difference (p-value AND 95%CI)
- Biological plausability and clinical sense

H Evers, 2016

. Methodological robustness

. Reproducability

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Conclusions

- **Optimisation of the uterus before IVF improves outcome**
- **Resection of endometrial polyps and submucous fibroids before IVF improves outcome (Level I)**
- **Hysteroscopic adhesolysis and metroplasty may improve IVF outcome (Level II-III)**
- **There is yet no agreement on management of adenomyosis**
- **Routine hysteroscopy doesn't improve IVF outcome**

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THANK YOU
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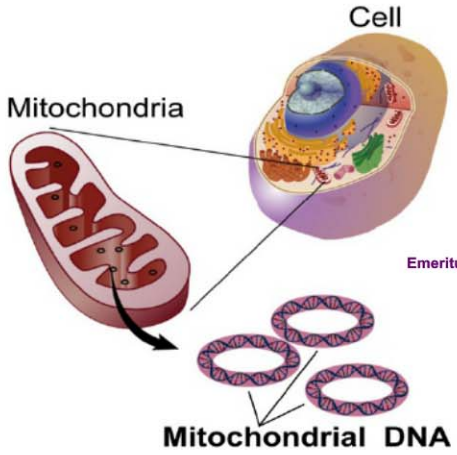
In vitro embryo culture, what have we learned?

Magdalena Zernicka-Goetz, United Kingdom

Contribution not submitted by the speaker

Mitochondrial Donation and Reproduction

Do we really know what we are doing?



Peter Braude PhD FRCOG FMedSci
Emeritus Professor of Obstetrics and Gynaecology
Division of Women's Health
King's College London

Conflicts statement

I have no commercial relationships with any companies or clinics involved with IVF or Mitochondrial Donation

I served on the Nuffield Council of Bioethics working group on the ethics of novel techniques for the prevention of mitochondrial DNA disorders

I served on the HFEA independent expert scientific advisory panels on methods to avoid mitochondrial disease

I am an external adviser to the Singapore National Bioethics Committee

Learning Objectives

1. Explore what we know about mitochondria and mitochondrial function, including understanding concepts of mitochondrial replication and the *mitochondrial bottleneck*.

2. Understand the genetic causes of mitochondrial diseases.

3. Explore and understand the concept of heteroplasmy and why this makes a difference to the expression of mtDNA disorders, and in prenatal and preimplantation genetic diagnosis

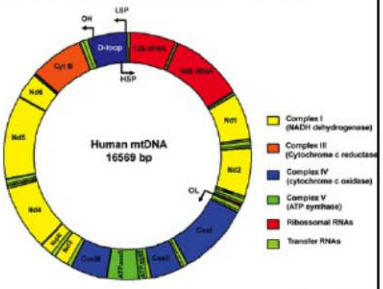
4. Review the options for avoidance of genetic mitochondrial disease including PGD, and the 3 types of mitochondrial replacement technologies - Pronuclear Transfer, Maternal Spindle Transfer and Polar Body Transfer, and review and understand the potential hazards of each.

5. Appreciate and understand the technique of cytoplasmic transfer and its application in assisted reproduction

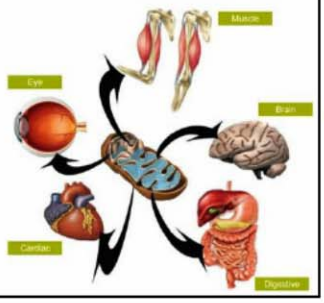
6. Take into account the ethics of each of these technologies and the international ramifications of introducing trans-generational genetic therapies.

What do we know about mtDNA?

- **mtDNA a circular molecule of 16,569 bp**
- **Arranged in DNA-protein assemblies (nucleoids) composed of single or multiple copies of mtDNA**
- **mtDNA more susceptible to mutation that nDNA** ***(probably due to oxidative damage and proximity to production and lack of repair mechanisms)***



- **Mutations in mtDNA affect function of tissues** ***(proportional to bioenergetic demand – high in heart and brain or specific tissue e.g.eye)***
- **Some mutations are age related, others can be heritable**
- **Many mutation sites known which are associated with specific clinical syndromes**



Mitochondrial DNA diseases

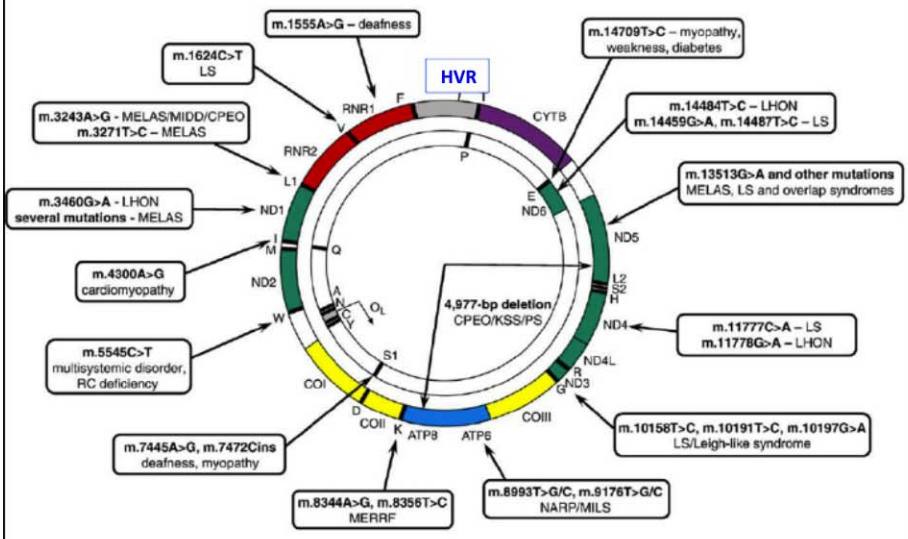
Strange acronyms for strange disorders

Genetic defects of the human mitochondrial genome were first described in 1988

- **MELAS** (**M**itochondrial **E**ncephalomyopathy; **L**actic **A**cidosis; **S**troke)
  - *TRNL1* (a tRNA gene) mutation
- **MERRF** (**M**yoclonic **E**pilepsy; **R**agged **R**ed **F**ibers)
  - 8344A>G *TRNK* (a tRNA gene) mutation
- **NARP** (**N**europathy; **A**taxia; **R**etinitis **P**igmentosa)
  - 8993T>G *MTATP6* (subunit 6 of mitochondrial ATP synthase)
- **LHON** (**L**eber's **H**ereditary **O**ptic **N**europathy)
  - 11778G>A 50% males; 10% females affected: Homoplasmic

Holt IJ, Harding AE, Morgan-Hughes JA. 1988. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature 331:717–19
Tuppen HA, Blakely EL, Turnbull DM, Taylor RW. 2009. Mitochondrial DNA mutations and human disease. Biochim. Biophys. Acta 1797:113–28

Mitochondrial disease mutations



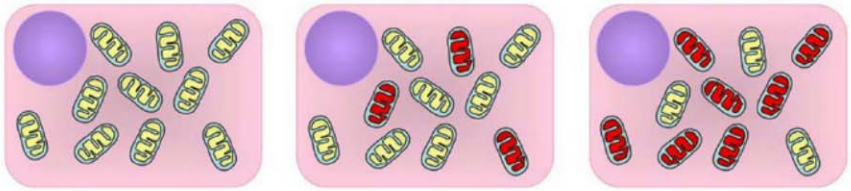
Tuppen HA, Blakely EL, Turnbull DM, Taylor RW. 2009. Mitochondrial DNA mutations and human disease. Biochim. Biophys. Acta 1797:113–28

What makes mitochondrial disease unusual?

Thousands of mitochondria in each cell and thousands of molecules of mtDNA in each mitochondrion

Homoplasmy:
a single mtDNA type

Heteroplasmy:
two or more mtDNA types



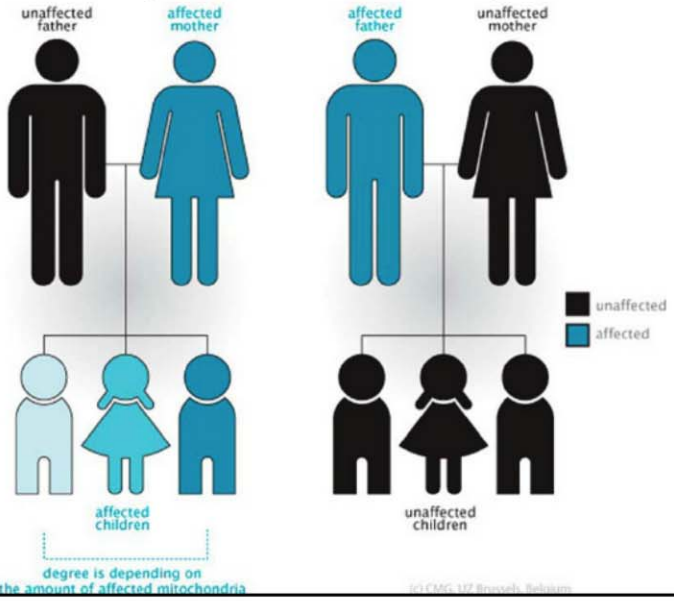
30% mutation load: no disease

70% mutation load: disease

Severity of the disease depends on the proportion of mutated mitochondria present in each cell or tissue

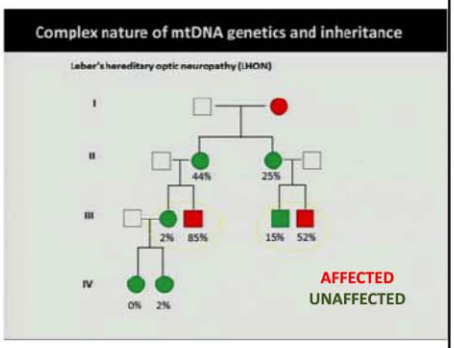
What makes mitochondrial disease unusual?

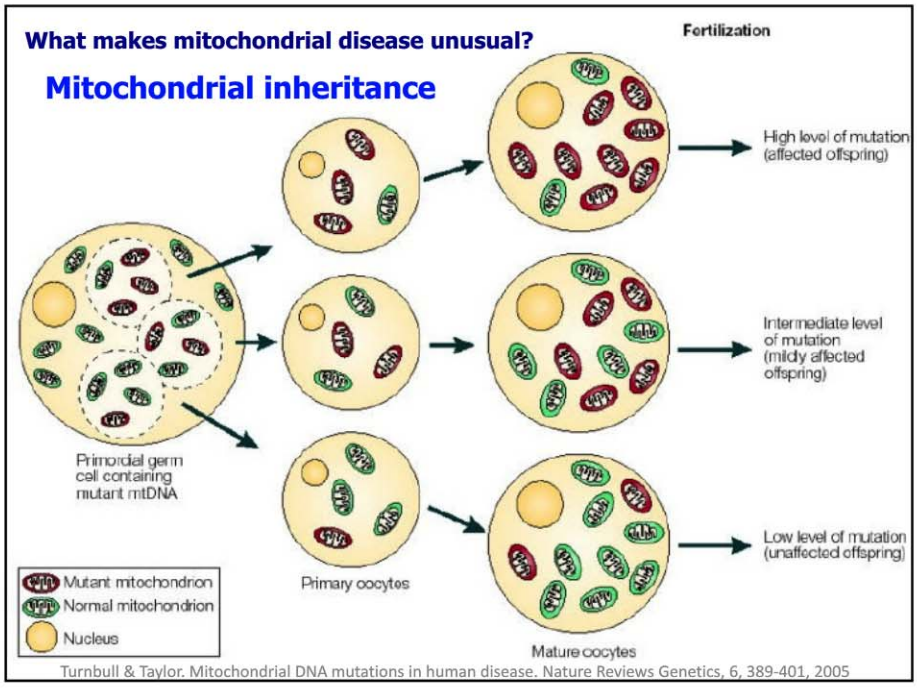
Maternally inherited with variable expression



What makes mitochondrial disease unusual?

- **Inheritance pattern is unique as mtDNA is wholly maternally inherited**
- **mtDNA inherited in the sperm ubiquinated and destroyed**
- **Clinical manifestations related to the proportion of normal to mutated mitochondria (heteroplasmy) and the particular gene**
- **Inheritance pattern in next generation is unpredictable as dependent on the inheritance proportion in the oocyte**

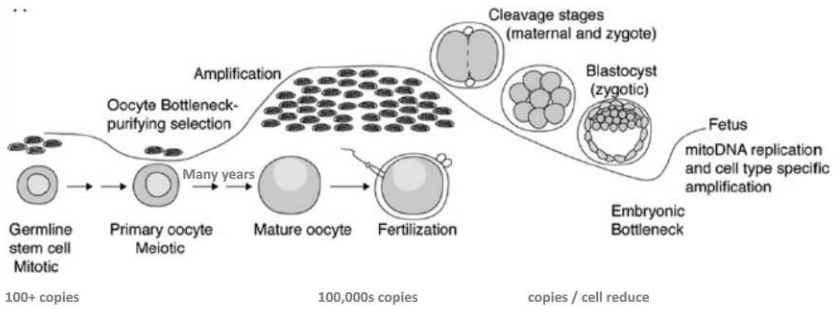




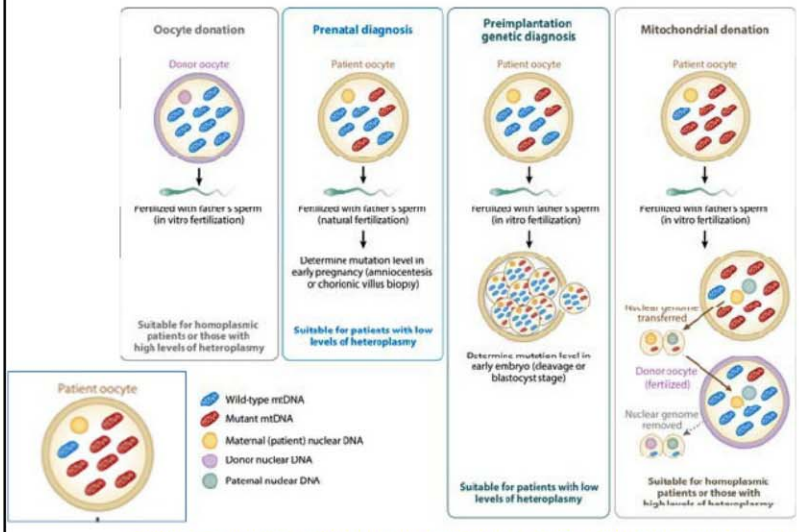
Turnbull & Taylor. Mitochondrial DNA mutations in human disease. Nature Reviews Genetics, 6, 389-401, 2005

The Mitochondrial Bottleneck

- **Believed that a mitochondrial bottleneck restricts the number /type entering the gametic pool probably at the primordial GC**
- **Either stochastic (random) or tissue specific selection**
- **Replication not linked to mitosis – can be rapid duplication between cell divisions**
- **Native mitochondria not preferentially selected for over acquired (foreign) mitochondria (Lee et al 2012; Yamada 2016)**



. Understanding and avoiding mitochondrial genetic disea

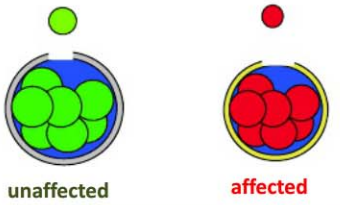


Recent Advances in Mitochondrial Disease Lyndsey Craven, Charlotte L. Alston, Robert W. Taylor, and Doug M. Turnbull
Annual Review of Genomics and Human Genetics 2017 18:1, 257-275

Testing Nuclear DNA is Different from testing Mitochondrial DNA

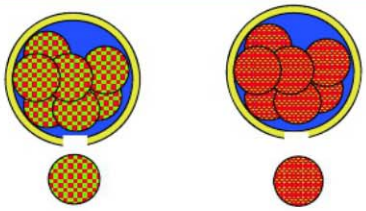
Nuclear DNA

Bad gene present
or not present

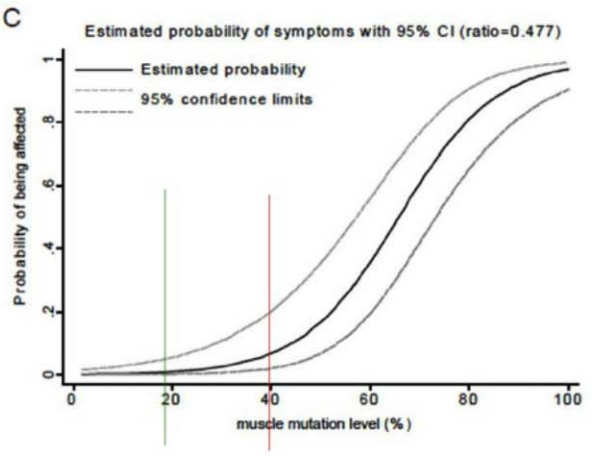


Mitochondrial DNA (mtDNA)

Mixture of mutated and normal mtDNA (heteroplasmy) in each cell



Disease may not be eliminated but probability reduced

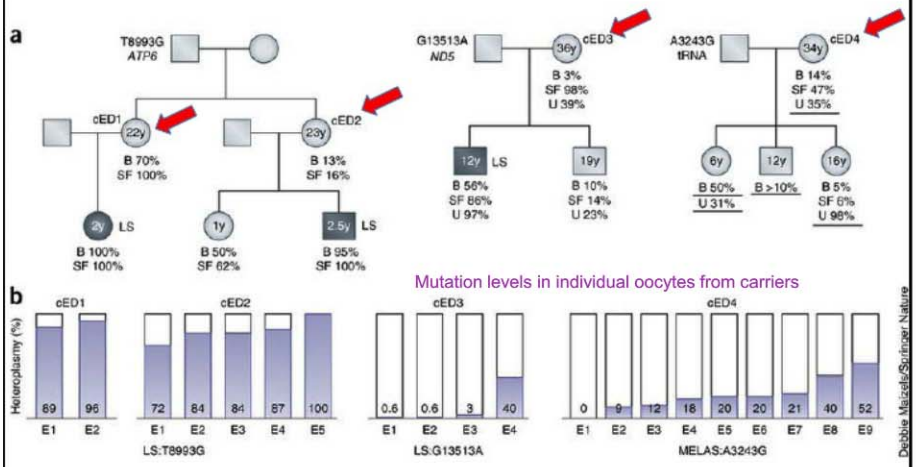


Adapted from : Smeets et al Preventing transmission of mtDNA disorders using prenatal or preimplantation genetic diagnosis. Ann. N.Y. Acad. Sci. 1350 (2015) 29–36

Not all families with Mitochondrial Mutations are suitable for PGD

Characteristics of three families and retrieved oocytes in women carrying pathogenic mtDNA mutations (carriers) or wild-type mtDNA (health

E Kang *et al. Nature* 1–6 (2016) doi:10.1038/nature20592



PGD data (2005-2016)

	Mutation	At biopsy	At birth	Comments	Reference
1	m.8993T>G	0% & 0%	0%	First report. Two embryos transferred	Steffann et al., 2006
2	m.8993T>G	2.5%	4%	3-5% cord blood & placenta; buccals 5% at age 4½y	Thorburn et al 2010*
3	m.3243A>G	5% & 13%	5%	Two embryos transferred; 15±5% placenta, 5±1% cord blood	Monnot et al., 2011
4	m.3243A>G	12%	15%	47% blood, 52% urine @ 1½m; 46/42%@18m	Treff et al., 2012/ Mitalipov et al., 2014
5	m.8993T>G	0%	0%	'Healthy son', no further details	Sallevelt et al., 2013
6	m.8344A>G	53% & 59%	63%	Two embryos transferred; no further details	Steffann et al., 2014
7	m.3243A>G	0%	0%	Male; measured in cord blood, urine, saliva	Heindryckx et al., 2014
8	m.36**G>A	2%	7%	Female, measured buccal and urine cells	Newcastle group 2016*
9	m.83**A>G	48%	Not available	Male; <60% generally asymptomatic	Newcastle group 2016*
10	m.130**T>C	1%	0%	Male; undetectable in cord and peripheral blood	Newcastle group 2016*
11	m.101**T>C	1%	1-2%	Male; cord blood	Newcastle group 2016*

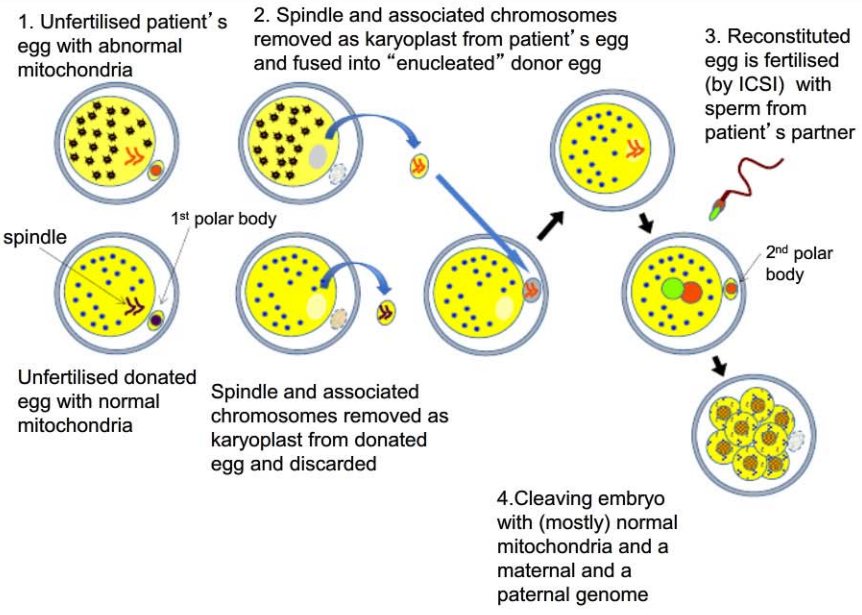
PGD for mtDNA mutations: Controversial questions

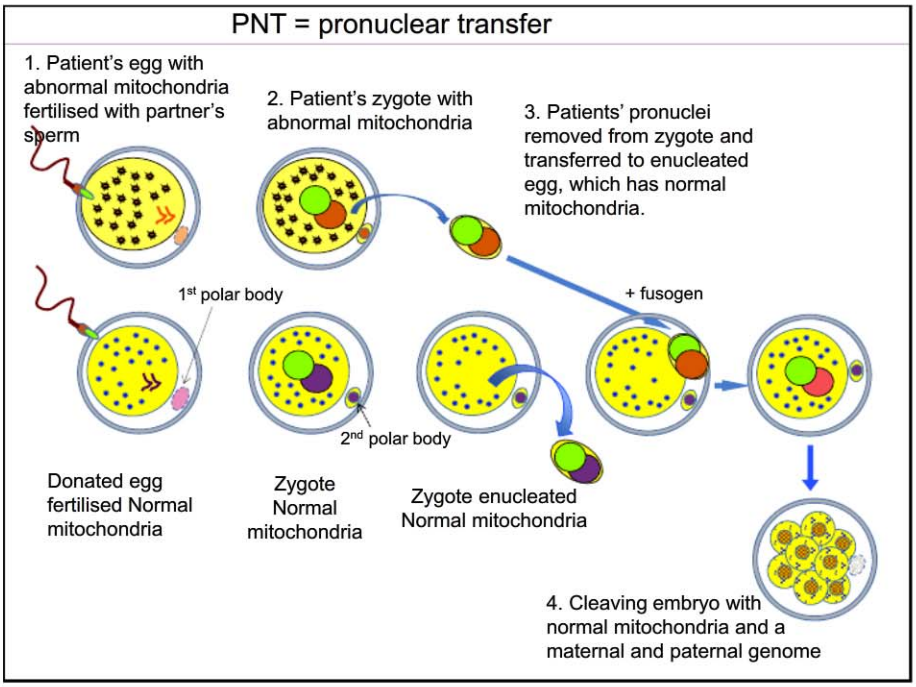
How will you decide what is an acceptable level of mutation?

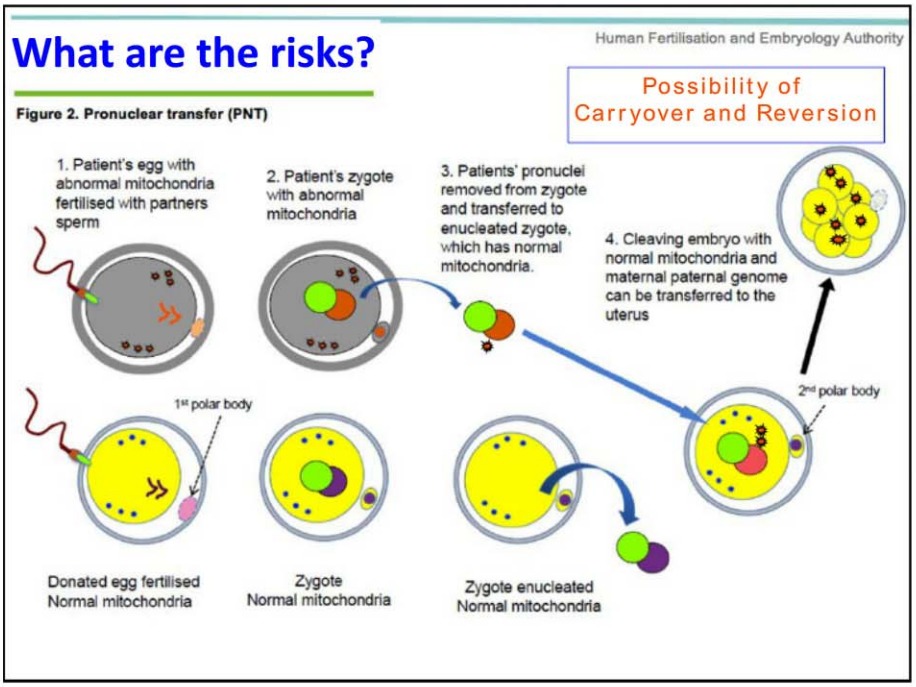
What do you do if all the embryos that you test exceed your safe point?

What do you do if the only embryo that you have to test exceeds your safe point?

MST = maternal spindle transfer



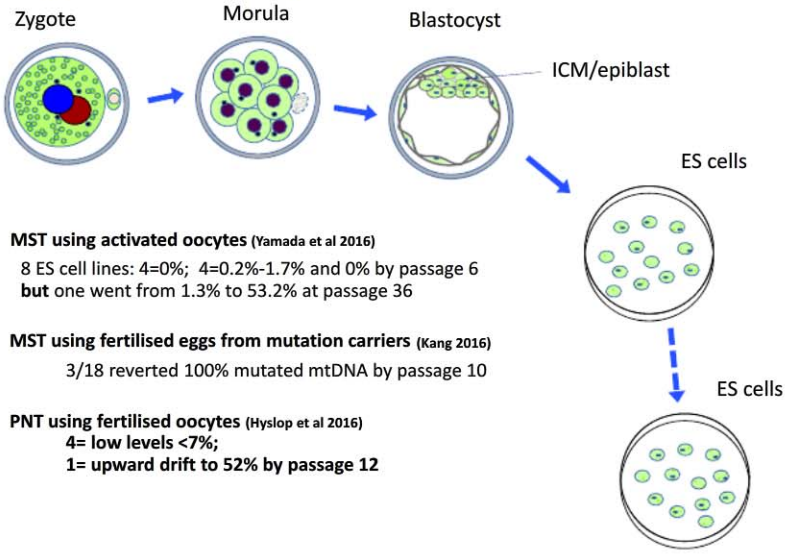

PNT = pronuclear transfer
1. Patient's egg with abnormal mitochondria fertilised with partner's sperm
2. Patient's zygote with abnormal mitochondria
3. Patients' pronuclei removed from zygote and transferred to enucleated egg, which has normal mitochondria.
1st polar body
+ fusogen
2nd polar body
Donated egg fertilised Normal mitochondria
Zygote Normal mitochondria
Zygote enucleated Normal mitochondria
4. Cleaving embryo with normal mitochondria and a maternal and paternal genome


What are the risks?
Human Fertilisation and Embryology Authority
Possibility of Carryover and Reversion
Figure 2. Pronuclear transfer (PNT)
1. Patient's egg with abnormal mitochondria fertilised with partners sperm
2. Patient's zygote with abnormal mitochondria
3. Patients' pronuclei removed from zygote and transferred to enucleated zygote, which has normal mitochondria.
4. Cleaving embryo with normal mitochondria and maternal paternal genome can be transferred to the uterus
1st polar body
2nd polar body
Donated egg fertilised Normal mitochondria
Zygote Normal mitochondria
Zygote enucleated Normal mitochondria

Carryover in PNT and MST embryos

- PNT using normally fertilised oocytes
  carryover usually <2%; none>5% (Hyslop et al 2016)
- MST using activated oocytes
  carryover <2% (avg 0.2%)(Yamada et al 2016)
- MST using fertilised eggs from mutation carriers
  carryover 25/26 <1%; 1=<2% (Kang et al 2016)

Using hES cell lines to explore the fate of carried over mtDNA



- **MST using activated oocytes** (Yamada et al 2016)
  8 ES cell lines: 4=0%; 4=0.2%-1.7% and 0% by passage 6
  but one went from 1.3% to 53.2% at passage 36
- **MST using fertilised eggs from mutation carriers** (Kang 2016)
  3/18 reverted 100% mutated mtDNA by passage 10
- **PNT using fertilised oocytes** (Hyslop et al 2016)
  4= low levels <7%;
  1= upward drift to 52% by passage 12

Figure 2. Polar body 1 transfer (PB1T) and maternal spindle transfer (MST)

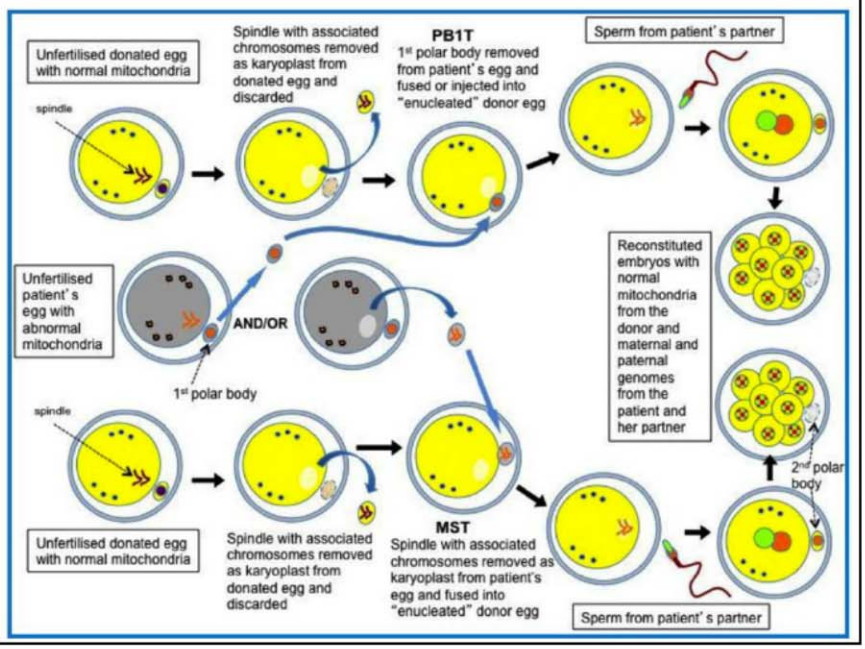
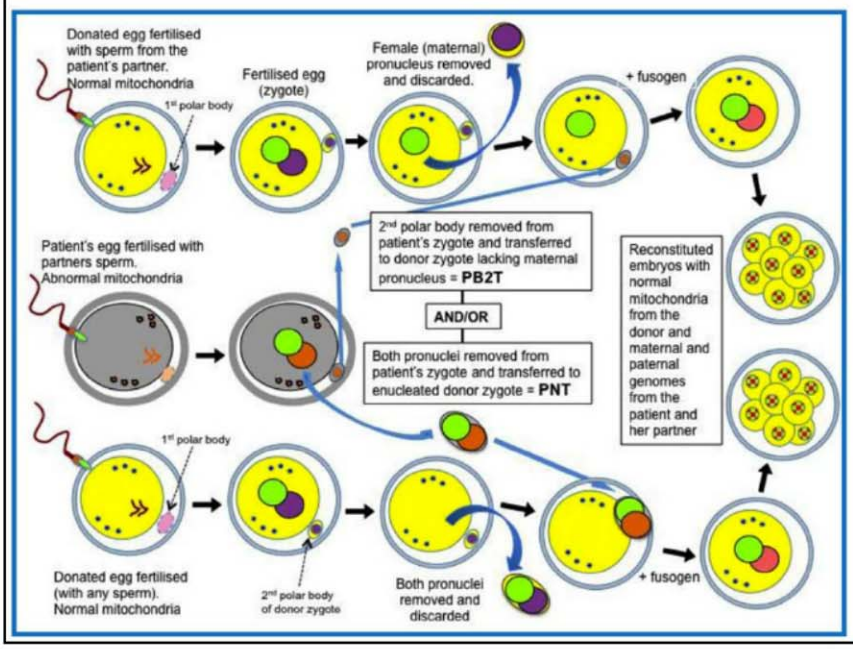


Figure 3. Polar body 2 transfer (PB2T) and pronuclear transfer (PNT)



Recommendations to HFEA of the independent scientific advisory Committee 2016

Since PGD is licensed for use in mtDNA disorders and often results in embryos being transferred with significant levels of mutant mtDNA (but is still useful as a risk reduction strategy), PNT and MST is safe enough to be used in a similar way as a risk reduction strategy where PGD is in appropriate or unlikely to work.

Cautious, specific implementation with long-term follow-up

Recommendations to HFEA of the independent scientific advisory Committee 2016

Cautious, specific implementation with long-term follow-up

- **Patients must be fully informed of the theoretical risk and PND offered**
- **Patients should be encouraged to take part in long-term follow-up**
- **Haplotype matching should be considered if feasible**

The panel could not recommend its use be extended to otherwise healthy individuals with fertility problems but not genetic disease

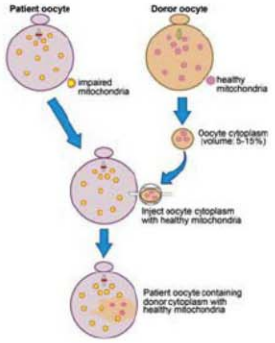
Mitochondrial donation: Ethical questions

- What is safe enough?
- Does it matter if there is a mismatch between mitochondrial haplotype origin and that of the donor?
- Who is taking the risk?
- Does it matter that when we use PBT, we are using '*egg offal*' to create the new person, and that is a person who would never have existed in nature?
- Should the technology be restricted to replacing males only – no intergenerational effects?

Clinical correlates: Or how do we use this information critically

1. Understanding and avoiding mitochondrial genetic disease

2. Understanding and improving fertility and IVF

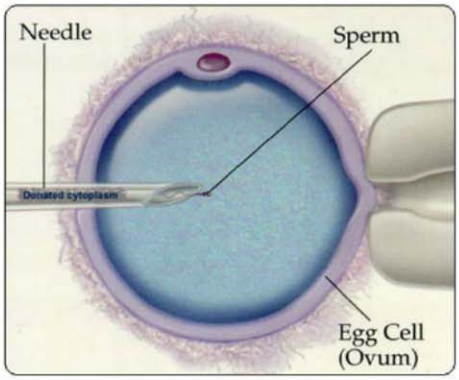


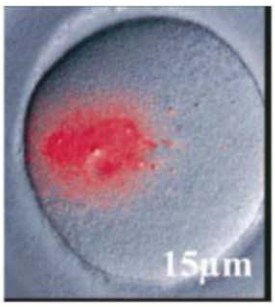
Molecular Human Reproduction vol.4 no.3 pp. 269–280, 1998

Ooplasmic transfer in mature human oocytes

Jacques Cohen[1,4], Richard Scott[1], Mina Alikani[1], Tim Schimmel[1], Santiago Munné[1], Jacob Levron[2], Lizi Wu[3], Carol Brenner[1], Carol Warner[3] and Steen Willadsen[1]

[1]The Institute for Reproductive Medicine and Science of Saint Barnabas, Livingston New Jersey, USA, [2]Department of Obstetrics and Gynecology, Tel Hashomer, Tel-Aviv, Israel, and [3]Department of Biology, Northeastern University, Boston, Massachusetts, USA

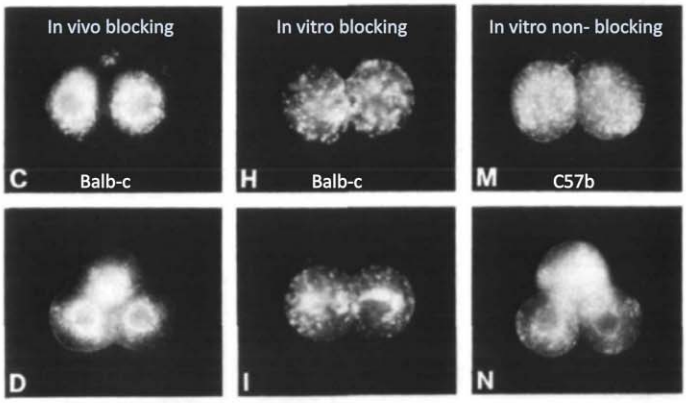




J. Embryol. exp. Morph. 73, 111–133, 1983
Printed in Great Britain © The Company of Biologists Limited 1983

Control of events during early cleavage of the mouse embryo: an analysis of the '2-cell block'

By MARTIN J. GODDARD AND HESTER P. M. PRATT [1]
From the Department of Anatomy, University of Cambridge

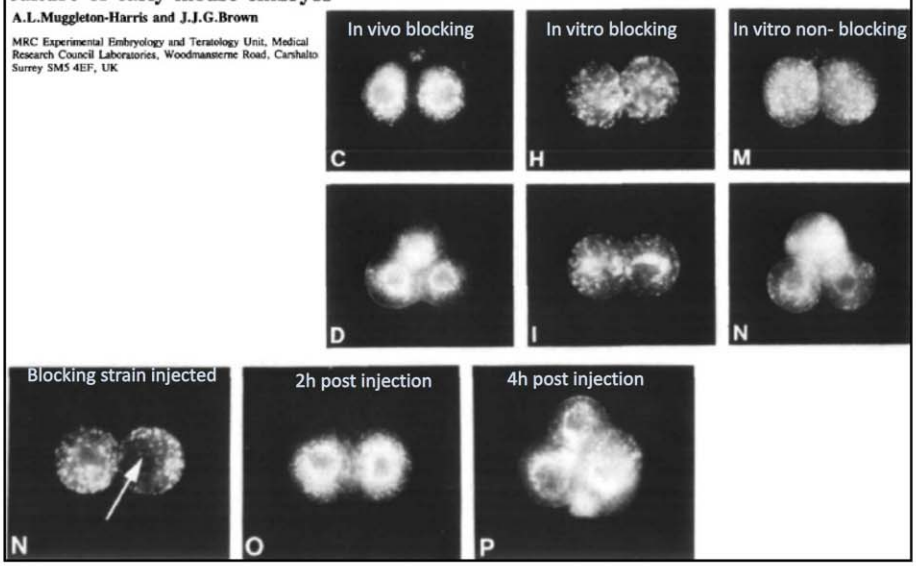


Human Reproduction vol.3 no.8 pp.1020–1028, 1988

Cytoplasmic factors influence mitochondrial reorganization and resumption of cleavage during culture of early mouse embryos

A.L.Muggleton-Harris and J.J.G.Brown

MRC Experimental Embryology and Teratology Unit, Medical Research Council Laboratories, Woodmansterne Road, Carshalto Surrey SM5 4EF, UK



Outcome of 37 attempts of OI at St Barnabas (1996-2001)

13 pregnancies

Maternal age at cytoplasmic transfer cycle (years)	*Number of previous cycles*	*Number of embryos transferred/fetal heartbeat after cytoplasmic transfer*	
39.5	4	3/1	
38.4	6	6/1	
37.6	9	5/1	
30.5	3	4/1	
37.2	3	2/1	
35.7	4	5/2	(1) XO TOP: (2) XX
31.6	3	4/1	
34.1	6	3/1	
36.5	6	5/2	(1) OI; (2) OD
33.8	4	6/4	
34.8	10	4/1	
36.6	3	4/1	
36.3	3	4/2	

+ 1 preclinical loss (XO)

Chen, S.H., Pascale, C., Jackson, M., Szvetecz, M.A., and Cohen, J. A limited survey-based uncontrolled follow-up study of children born after ooplasmic transplantation in a single centre. *Reprod. Biomed. Online*. 2016; 33: 737–744

Molecular Human Reproduction vol.4 no.3 pp. 269–280, 1998

Ooplasmic transfer in mature human oocytes

What factors might be added in OT

Cohen et al MHR 1988

1. Mitochondria from the donor supplement pool of mitochondria
2. Internal pool of inherited (maternal) mRNAs may be boosted
3. Other organelles (ribosomes, proteins, spindle organizing units)
4. Specific consequences by altering a single mechanism

   e.g. change in the polarization of mitochondria

"The transfer of small amounts of donor ooplasm (5–15%) probably includes mRNAs, proteins, mitochondria, as well as other factors and organelles".

Molecular Human Reproduction vol.4 no.3 pp. 269–280, 1998

Ooplasmic transfer in mature human oocytes

" The supposition that this procedure is a form of genetic manipulation or gene therapy confuses the issue, even if only justifiable from a puritan point of view, since it involves incorporation of foreign ribosomal DNA, mRNA and mtDNA."

" In our opinion, the presented technology is highly experimental and it would be wise to delay its widespread medical application until further studies in animal models and donated human material indicate the best approaches".

Outcome of 37 attempts of OI at St Barnabas (1996-2001)

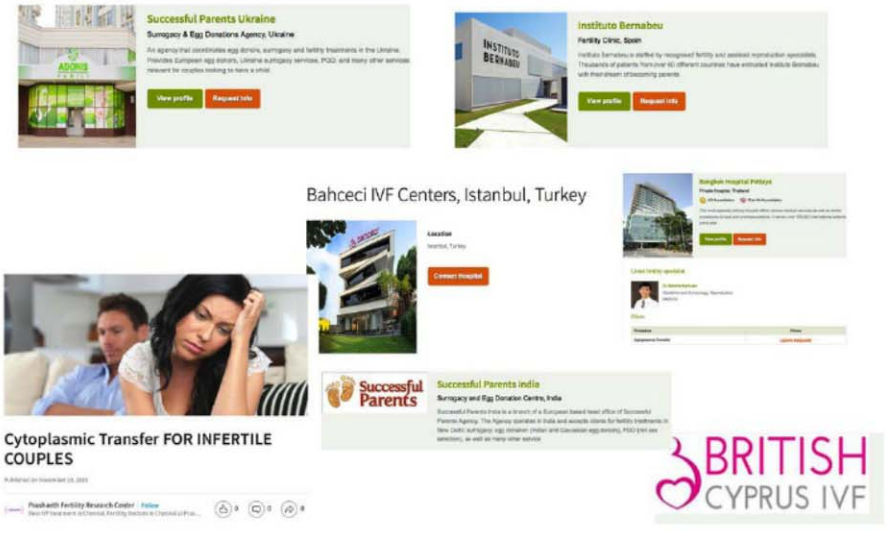
Maternal age at cytoplasmic transfer cycle (years)	Number of previous cycles	Number of embryos transferred/fetal heartbeat after cytoplasmic transfer	Heteroplasmy at birth (+) Heteroplasmy confirmed (–) No heteroplasmy detected
39.5	4	3/1	Not sampled
38.4	6	6/1	Not sampled
37.6	9	5/1	Not sampled
30.5	3	4/1	+
37.2	3	2/1	+
35.7	4	5/2 (1) XO TOP: (2) XX	–
31.6	3	4/1	–
34.1	6	3/1	–
36.5	6	5/2 (1) OI; (2) OD	–
33.8	4	6/4	–
34.8	10	4/1	–
36.6	3	4/1	Not sampled
36.3	3	4/2	Not sampled

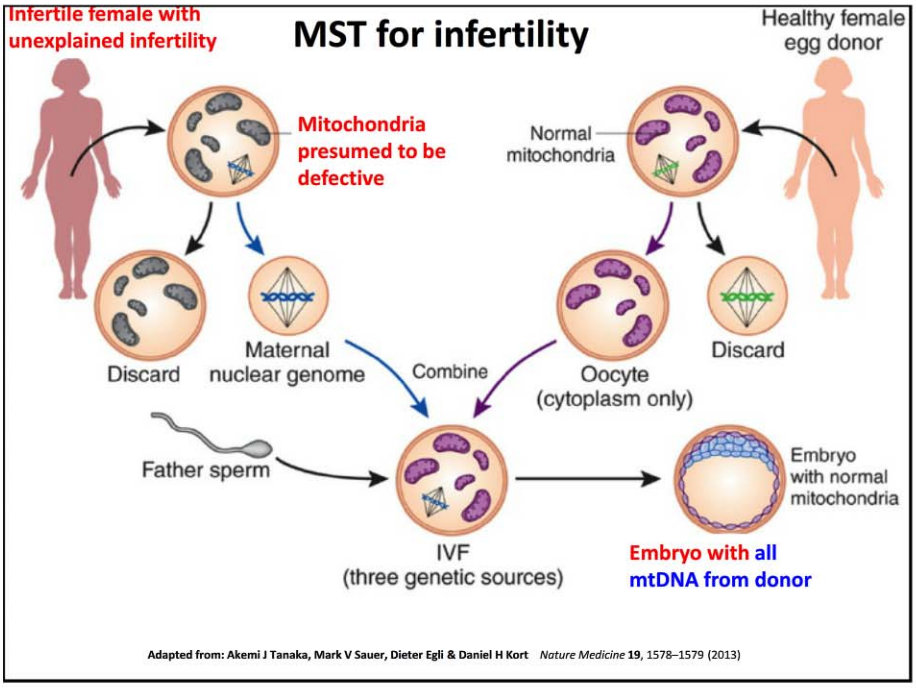
6/8 showed no evidence of donor mtDNA

Chen et al RBMOnline 33, 737 (2016)

Cytoplasmic Transfer Abroad - Medical Tourism Guide

Details of leading clinics and hospitals performing Cytoplasmic Transfer to foreign patients.

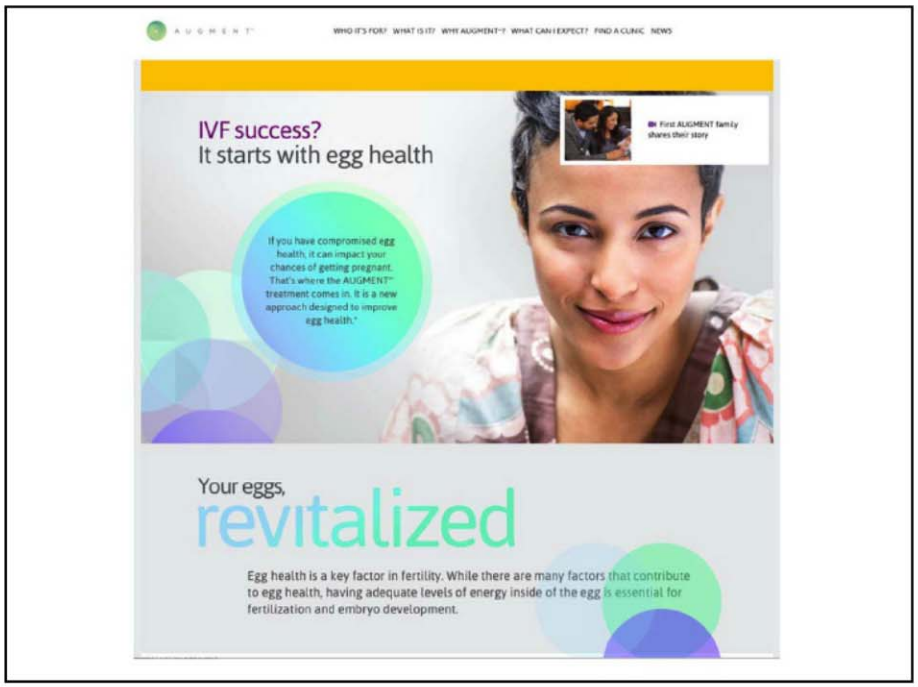




Adapted from: Akemi J Tanaka, Mark V Sauer, Dieter Egli & Daniel H Kort *Nature Medicine* **19**, 1578–1579 (2013)

First baby born using 3-parent technique to treat infertility

Clinic director Valery Zukin holding the baby girl
Nadiya Clinic



Mitochondrial replacement or augmentation
Some difficult questions?

- Do we really have evidence that defective mitochondria are the cause of embryonic delay or IVF failure?
  If most embryo failure is due to meiotic aneuploidy, how does mitochondrial replacement help this?
- Is the risk of some unexpected heteroplasmy after OI worth the risk?
- How do we justify replacement of the whole mtDNA genome with donor mtDNA to treat infertility?
- If we do so, should we limit effects by replacing males only?

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Mitochondrial diseases. Gorman, Chinnery, DiMauro, Hirano, Koga, McFarland, Suomalaine, Thorburn Zeviani and Turnbull. Nature Reviews Primers. 2, 16080 (2016)

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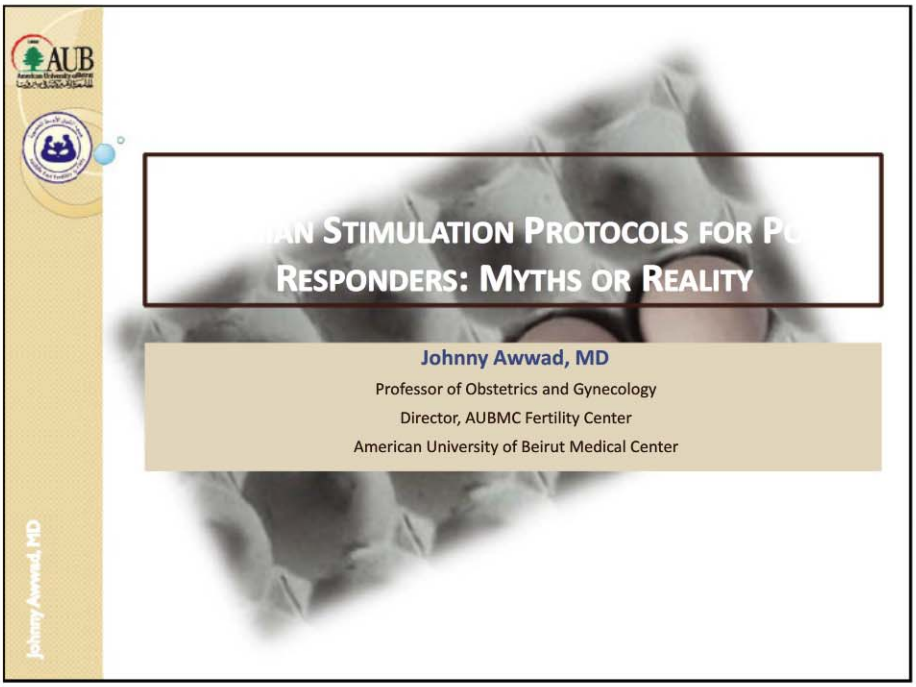
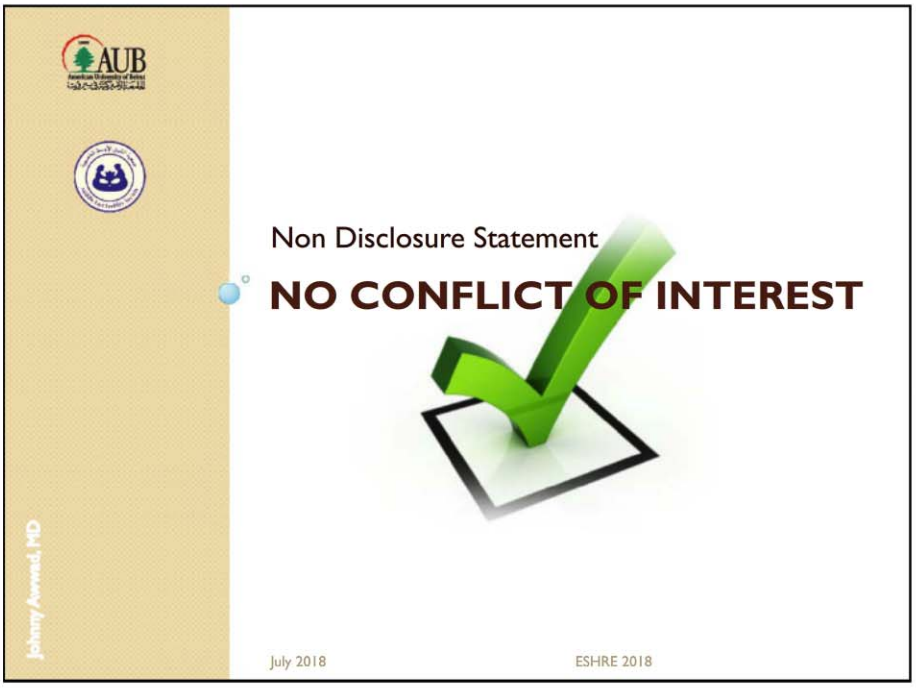
Natural Killer Cells and Reproductions: Are we chasing a shadow?

Srividya Seshadri, United Kingdom

Contribution not submitted by the speaker


AUB
AN STIMULATION PROTOCOLS FOR P
RESPONDERS: MYTHS OR REALITY
Johnny Awwad, MD
Professor of Obstetrics and Gynecology
Director, AUBMC Fertility Center
American University of Beirut Medical Center
Johnny Awwad, MD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Non Disclosure Statement
NO CONFLICT OF INTEREST
Johnny Awwad, MD
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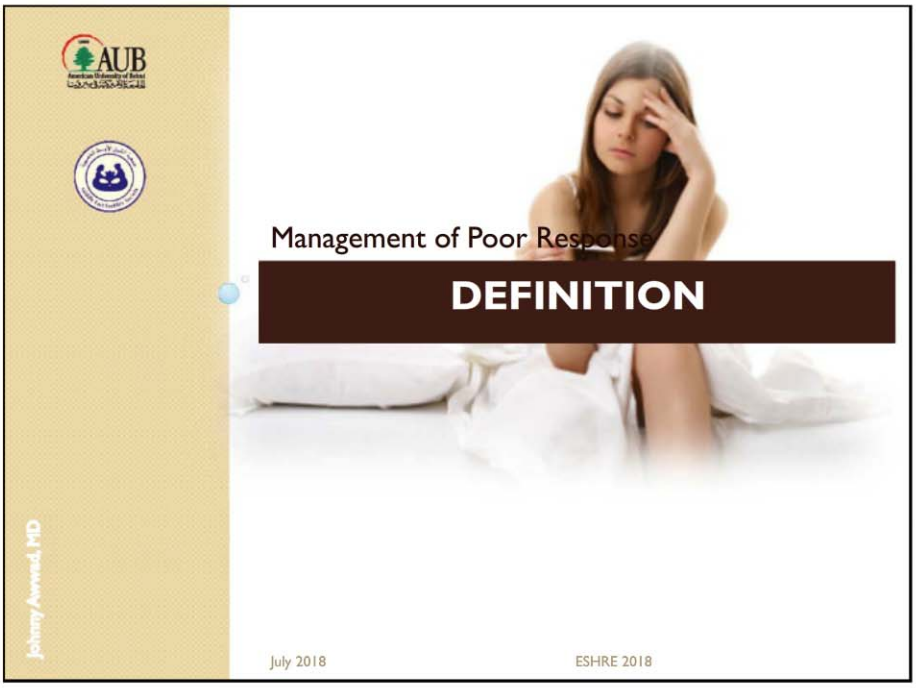
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Management of Poor Response
DEFINITION
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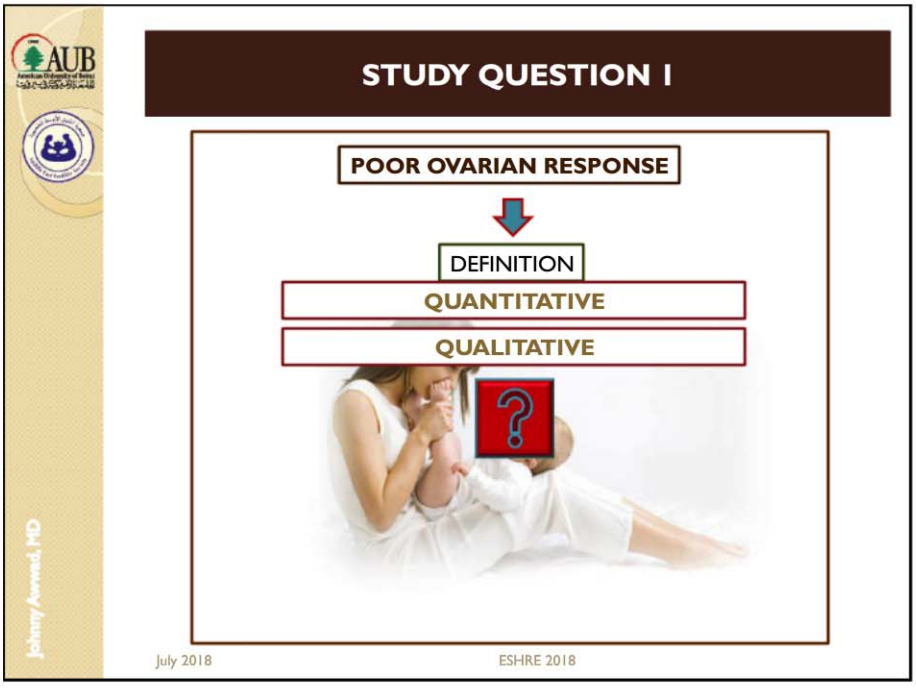
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STUDY QUESTION 1
POOR OVARIAN RESPONSE
DEFINITION
QUANTITATIVE
QUALITATIVE
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No more than 3 trials used the same definition. Even trials from the same research groups used different definitions across different trials.

for the tr… …onders: is there a… …nnel?

Nikolaos P. Polyzos

Centre for Reproducti… …ssel, Brussels, Belgium

Design: Systematic r…
Setting: None.
Patient(s): Poor ovari…
Intervention(s): Treat…
Main Outcome Measu… …response to stimulation
and threshold values …

No. of follicles on the final day of stimulation	21 (45%)
≤2	4
≤3	11
≤4	4
≤5	2
No. of oocytes retrieved	19 (40%)
≤2	2
≤3	8
≤4	7
≤5	2
No. of mature oocytes retrieved	5 (11%)
≤3	4
≤4	1
Levels of E_2 on the final day of stimulation	16 (34%)
450	1
500	9
Other higher threshold	6
Good quality embryos	2 (4%)
Gonadotropin doses per day	14 (30%)
225 IU	2
300 IU	7
Other/not stated	5

Johnny Awwad, MD

July 2018 ESHRE 2018

Human Reproduction, Vol.26, No.7 pp. 1616–1624, 2011
Advanced Access publication on April 19, 2011 doi:10.1093/humrep/der092

human reproduction ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria†

	1	2	3	4
Advanced age	≥40 years	≥40 years	Any age	Any age
Low number of oocytes in previous cycles	≤3 oocytes in 1 previous cycle	_____	≤3 oocytes in 2 previous cycles >300 IU FSH	≤3 oocytes in 1 previous cycle
Abnormal ovarian reserve tests	_____	AFC <7 follicles **or** AMH <1.1 ng/ml	_____	AFC <7 follicles **or** AMH <1.1 ng/ml
	1- Specificity FSH > 10–15 IU/L		1- Specificity AMH <0.5–1.1 ng/ml AFC <5–7	

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Bologna poor responders demonstrate very low live birth rates, irrespective of age and treatment protocol used.

Table 2 Ovarian response and reproductive outcomes.

	All patients	<40 years	≥40 years	OR (95% CI)
No. of patients	485	201	284	–
No. of treatment cycles	823	327	496	–
Ovarian response				
Oocytes retrieved	3 (0–5)	2 (0–4)	3 (0–5)	NA
Cycles cancelled	196 (23.8)	88 (26.9)	108 (21.8)	1.33 (0.96–1.83)
Cycles with oocyte retrieval	609 (74.0)	230 (70.3)	379 (76.4)	0.73 (0.54–1.00)
Reproductive outcomes				
Clinical pregnancy				
Per patient	68 (14.8)	29 (14.4)	39 (13.7)	1.06 (0.63–1.78)
Per cycle	71 (8.6)	29 (8.9)	42 (8.5)	1.06 (0.64–1.73)
Ongoing pregnancy				
Per patient	61 (12.6)	27 (13.4)	34 (12.0)	1.14 (0.66–1.96)
Per cycle	63 (7.7)	27 (8.3)	36 (7.3)	1.15 (0.68–1.94)
Live birth				
Per patient	48/483 (9.9)	23/199 (11.6)[a]	25 (8.8)	1.36 (0.75–2.46)
Per cycle	49/821 (6.0)[a]	23/325 (7.1)[a]	26 (5.2)	1.38 (0.77–2.46)

Values are median (interquartile range), *n* (%) or *n*/total (%).
NA = not applicable.
[a]Data regarding live births could not be retrieved for two patients/cycles with an ongoing pregnancy.

Poor ovarian responders, as described by the Bologna criteria, have a very poor prognosis, which do not appear to improve substantially with natural cycle IVF regardless of patients' age.

Table III Outcomes according to cycle rank in poor responders according to the Bologna criteria.

Parameters	Number of consecutive cycles				
	1	2	3	4	≥5
No. of cycles	136	97	62	29	66
Oocytes retrieved	101 (74.3)	73 (75.3)	46 (74.2)	22 (75.9)	49 (74.2)
MII oocytes	86 (63.2)	57 (58.8)	40 (64.5)	21 (72.4)	43 (65.2)
Embryo transfer	52 (38.2)	38 (39.2)	30 (48.4)	16 (55.2)	28 (42.4)
Positive hCG	4 (2.9)	4 (4.1)	5 (8.1)	3 (10.3)	2 (3)
Ongoing pregnancy	0%	2 (2)	3 (4.8)	3 (10.3)	2 (3)
Live birth rate	0%	2 (2)	3 (4.8)	3 (10.3)	2 (3)

Results are expressed as the number of cycles (and percentage).

Poor responders of a younger age did better in terms of reproductive performance.

microdose gonadotropin-releasing
hormone analog flare cycles in poor

TABLE 2

Data of poor responders treated with natural-cycle IVF (NC) or COH, stratified by women's age.

	≤35 y		≥36–39 y		≥40 y	
Parameters	N C	COH	N C	COH	N C	COH
No. of patients	11	16	13	22	36	32
No. of cycles	28	20	24	31	62	50
Cycles with oocytes (%)	67.8	80.0	87.5	96.7	72.6	80.0
FSH amount (IU), mean ± SD	—	5,432 ± 2,906	—	5,432 ± 2,906	—	5,432 ± 2,906
E_2/hCG day (pg/mL), mean ± SD		1,278 ± 442		1,585 ± 592		1,378 ± 804
Cycles with transfer (%)	42.8	65.0	41.7	80.6	40.3	62.0
No. of embryos obtained	12	24	10	39	25	60
No. of embryos/transfer, mean ± SD	1.0	1.8 ± 0.3	1.0	1.8 ± 0.3	1.0	1.8 ± 0.3
Pregnancy/cycle (%)	14.3	15.0	3.9	3.3	3.2	6.0
Pregnancy/transfer (%)	33.3	23.1	10.0	4.0	8.0	9.7
Implantation rate (%)	33.3	12.5	10.0	2.6	8.0	5.0
Abortion rate (%)	25.0	0	0	0	50.0	33.3

Morgia. IVF with natural cycle in poor responders. Fertil Steril 2004.

implantation rate.

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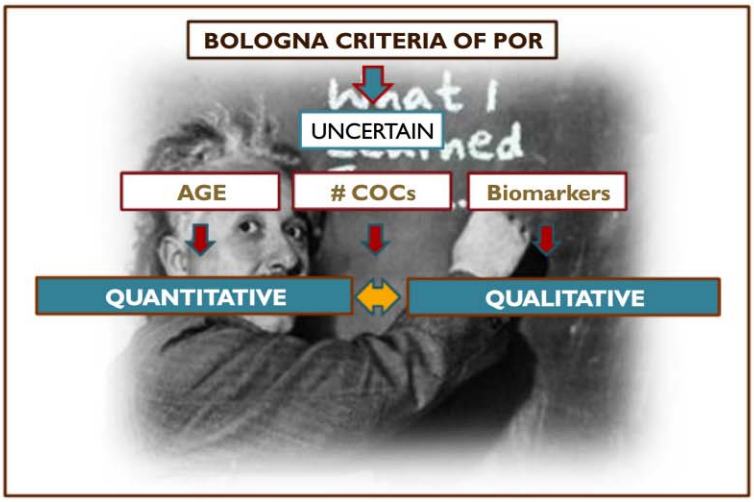
TAKE HOME MESSAGES



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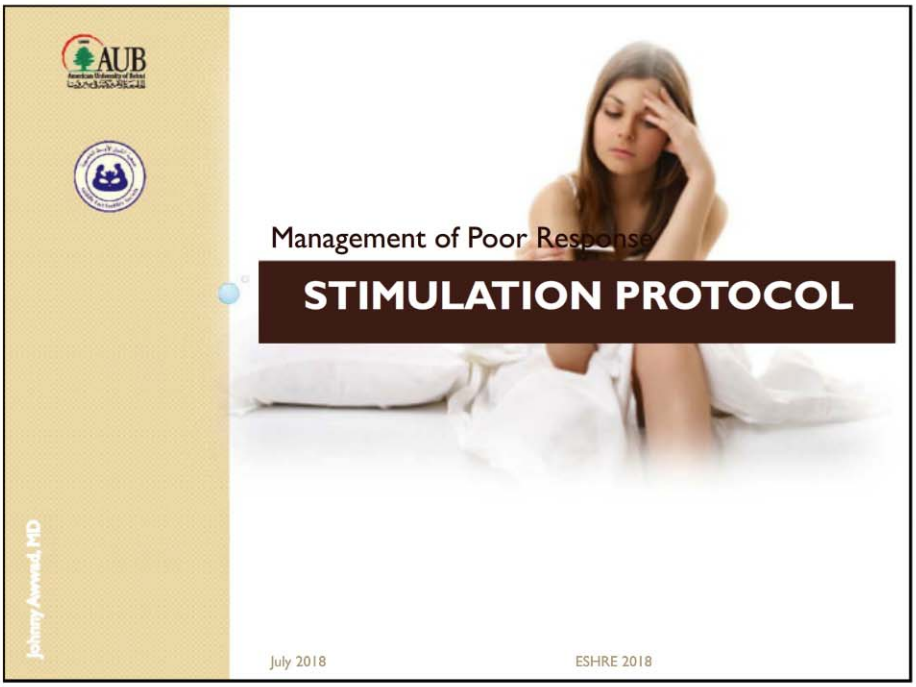
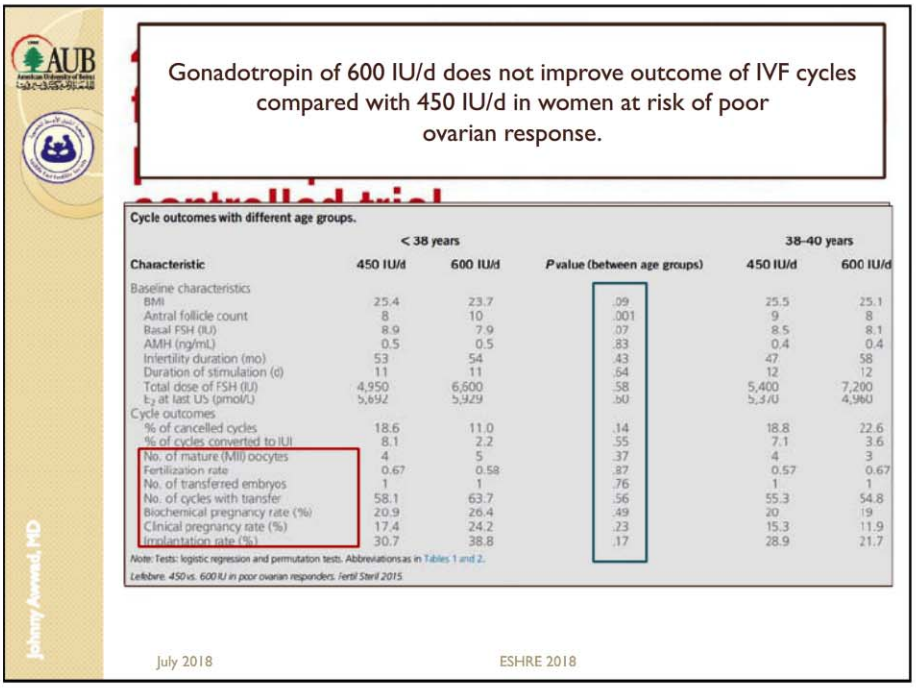

AUB
Management of Poor Response
STIMULATION PROTOCOL
Johany Awwad, MD
July 2018
ESHRE 2018


AUB
Gonadotropin of 600 IU/d does not improve outcome of IVF cycles compared with 450 IU/d in women at risk of poor ovarian response.
Cycle outcomes with different age groups.
< 38 years
38–40 years
Characteristic
450 IU/d
600 IU/d
P value (between age groups)
450 IU/d
600 IU/d
Baseline characteristics
BMI 25.4 23.7 .09 25.5 25.1
Antral follicle count 8 10 .001 9 8
Basal FSH (IU) 8.9 7.9 .07 8.5 8.1
AMH (ng/mL) 0.5 0.5 .83 0.4 0.4
Infertility duration (mo) 53 54 .43 47 58
Duration of stimulation (d) 11 11 .64 12 12
Total dose of FSH (IU) 4,950 6,600 .58 5,400 7,200
E2 at last US (pmol/L) 5,692 5,929 .60 5,340 4,980
Cycle outcomes
% of cancelled cycles 18.6 11.0 .14 18.8 22.6
% of cycles converted to IUI 8.1 2.2 .55 7.1 3.6
No. of mature (MII) oocytes 4 5 .37 4 3
Fertilization rate 0.67 0.58 .87 0.57 0.67
No. of transfered embryos 1 1 .76 1 1
No. of cycles with transfer 58.1 63.7 .56 55.3 54.8
Biochemical pregnancy rate (%) 20.9 26.4 .49 20 19
Clinical pregnancy rate (%) 17.4 24.2 .23 15.3 11.9
Implantation rate (%) 30.7 38.8 .17 28.9 21.7
Note: Tests: logistic regression and permutation tests. Abbreviations as in Tables 1 and 2.
Lefebvre. 450 vs. 600 IU in poor ovarian responders. Fertil Steril 2015.
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July 2018
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STUDY QUESTION 2

LH is fundamental in promoting steroidogenesis and folliculogenesis

GnRH analogues are associated with low LH

INTERVENTIONS

Does LH supplementation benefit POR

?

Follicle number ↑

Gonadotropin dose ↓

Pregnancy rate ↑

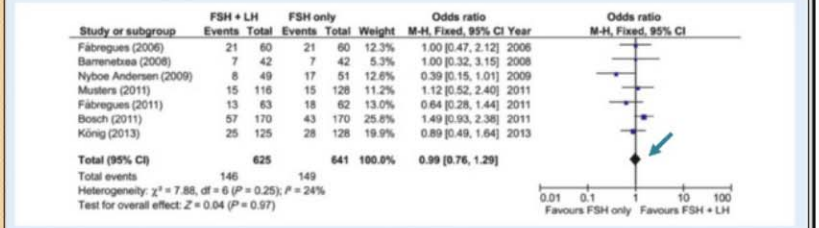
Johnny Awwad, MD

July 2018 ESHRE 2018

Human Reproduction, Vol.28, No.10 pp. 2804–2812, 2013
Advanced Access publication on July 9, 2013 doi:10.1093/humrep/det266

Mid-follicular LH supplementation had no effect on pregnancy outcome or ovarian response in women of 35 years and older undergoing GnRH antagonist IVF/ICSI cycles.

Table III Serum hormone concentrations.



Study or subgroup	FSH + LH Events	Total	FSH only Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI	Year
Fábregues (2006)	21	60	21	60	12.3%	1.00 [0.47, 2.12]	2006
Barrenetxea (2008)	7	42	7	42	5.3%	1.00 [0.32, 3.15]	2008
Nyboe Andersen (2009)	8	49	17	51	12.6%	0.39 [0.15, 1.01]	2009
Musters (2011)	15	116	15	128	11.2%	1.12 [0.52, 2.40]	2011
Fábregues (2011)	13	63	18	62	13.0%	0.64 [0.28, 1.44]	2011
Bosch (2011)	57	170	43	170	25.8%	1.49 [0.93, 2.38]	2011
König (2013)	25	125	28	128	19.9%	0.89 [0.49, 1.64]	2013
Total (95% CI)		**625**		**641**	**100.0%**	**0.99 [0.76, 1.29]**	
Total events	146		149				

Heterogeneity: $\chi^2 = 7.88$, df = 6 ($P = 0.25$); $I^2 = 24\%$
Test for overall effect: $Z = 0.04$ ($P = 0.97$)

Odds ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favours FSH only Favours FSH + LH

Figure 3 Forest plot of ongoing pregnancy based on studies performed to date. OR of ongoing pregnancy using a fixed effect model. 'Year' refers to the year the study was performed. CI, confidence interval.

1 2 3 4 5 6

Figure 1 Stimulation protocol for 'r-FSH and r-LH' and 'r-FSH-only' group. r-FSH, recombinant FSH; r-LH, recombinant LH.

Johnny Awwad, MD

July 2018 ESHRE 2018

The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis

Micah J. Hill, D.O.,[a] Eric D. Levens, M.D.,[a,b] Gary Levy, M.D.,[a] Mary E. Ryan, M.L.S.,[c] John M. Csokmay, M.D.,[a] Alan H. DeCherney, M.D.,[a] and Brian W. Whitcomb, Ph.D.[d]

[a] Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; [b] Shady Grove Fertility Reproductive Science Center, Rockville, Maryland; [c] National Institutes of Health Library, Bethesda, Maryland; and [d] Division of Biostatistics and Epidemiology, University of Massachusetts School of Public Health and Health Sciences, Amherst, Massachusetts

Fertility and Sterility® Vol. 97, No. 5, May 2012 0015-0282/$36.00

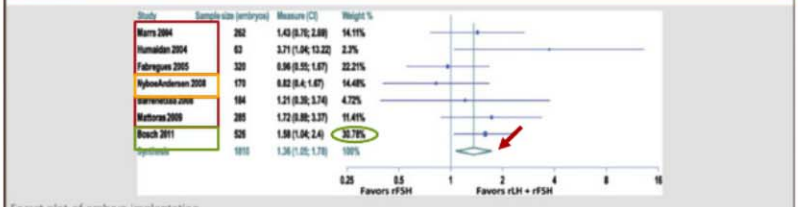
doi:10.1016/j.fertnstert.2012.01.130

Objective: To evaluate the effect of recombinant LH in assisted reproduction technology (ART) cycles in patients of advanced reproductive age.
Design: A systematic review and meta-analysis.
Setting: Published randomized controlled clinical trials comparing recombinant LH plus recombinant FSH versus recombinant FSH only in patients of advanced reproductive age.
Patient(s): Patients 35 years and older undergoing assisted reproduction.
Intervention(s): Recombinant LH plus recombinant FSH controlled ovarian hyperstimulation (COH) versus recombinant FSH stimulation only in assisted reproduction cycles.
Main Outcome Measure(s): Implantation and clinical pregnancy.

Does the addition of recombinant LH to ART cycles improve implantation and clinical pregnancy in patients of advanced reproductive age?

Pituitary down-regulation	Recombinant LH stimulation protocol
Long luteal agonist	Mid follicular onward
Short flare agonist	Mid follicular onward
OCP pre-treatment/antagonist	Early follicular onward

FIGURE 1



Forest plot of embryo implantation.

Hill. Recombinant LH in patients of advanced reproductive age. Fertil Steril 2012.

Human Reproduction Update, Vol.18, No.2 pp. 127–145, 2012
Advanced Access publication on February 3, 2012 doi:10.1093/humupd/dmr051

human reproduction update

The use of androgens or androgen-modulating agents in poor responders undergoing *in vitro* fertilization: a systematic review and meta-analysis

J.K. Bosdou [1], C.A. Venetis [1,*], E.M. Kolibianakis [1], K.A. Toulis [2], D.G. Goulis [2], L. Zepiridis [1], and B.C. Tarlatzis [1,2]

[1]Unit for Human Reproduction, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece [2]Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

METHODS: Medline, EMBASE, CENTRAL, Scopus and Web of Science databases were searched for the identification of randomized controlled trials evaluating the administration of testosterone, dehydroepiandrosterone (DHEA), aromatase inhibitors, recombinant luteinizing hormone (rLH) and recombinant human chorionic gonadotrophin (rhCG) before or during ovarian stimulation of poor responders.

There is insufficient data to support a beneficial role of rLH administration in the probability of pregnancy in poor responders undergoing ovarian stimulation for IVF.

Pituitary down-regulation	Recombinant LH stimulation protocol
OCP pre-treatment/Short flare agonist	Mid follicular onward
Long luteal agonist	Not reported
Short flare agonist	Mid follicular onward
Short flare agonist	Mid follicular onward

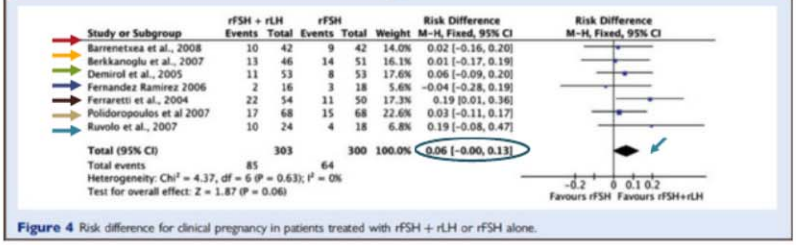
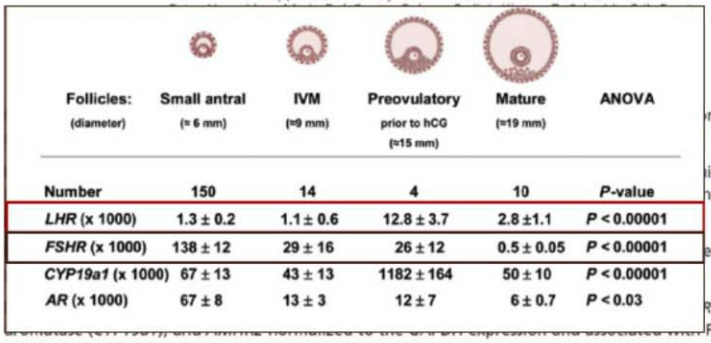


Figure 4 Risk difference for clinical pregnancy in patients treated with rFSH + rLH or rFSH alone.

LHR is expressed in GC from small antral follicles. LH may affect follicular development at earlier stages than previously considered.

Janni Vikkelsø Jeppesen, Stine Gry Kristensen, Maria Eilsø Nielsen,



Follicles: (diameter)	Small antral (≈ 6 mm)	IVM (≈9 mm)	Preovulatory prior to hCG (≈15 mm)	Mature (≈19 mm)	ANOVA
Number	150	14	4	10	*P*-value
LHR (x 1000)	1.3 ± 0.2	1.1 ± 0.6	12.8 ± 3.7	2.8 ±1.1	*P* < 0.00001
FSHR (x 1000)	138 ± 12	29 ± 16	26 ± 12	0.5 ± 0.05	*P* < 0.00001
CYP19a1 (x 1000)	67 ± 13	43 ± 13	1182 ± 164	50 ± 10	*P* < 0.00001
AR (x 1000)	67 ± 8	13 ± 3	12 ± 7	6 ± 0.7	*P* < 0.03

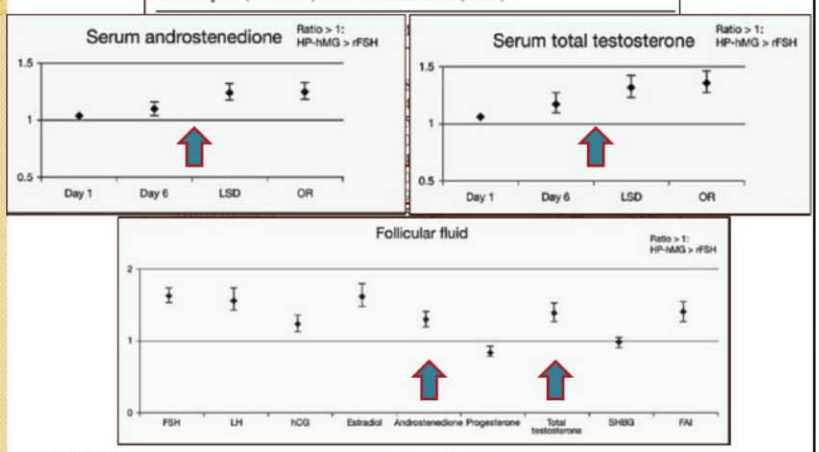
levels of anti-Mullerian hormone, inhibin-B, and steroids.

Human Reproduction Vol.22, No.3 pp. 676–687, 2007
Advance Access publication November 16, 2006
doi:10.1093/humrep/del445

Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients

Type of gonadotropin	Commercial name	LH content/ vial	hCG content/ vial
Human derived			
hMG	Menogon	6-14IU	3-7IU
HP HMG	Menopur	0.4	9.9
Recombinant			
rLH	Luveris	75IU	-

Major differences in serum and follicular fluid endocrine profile exist after stimulation with HP-hMG or rFSH.



Johany Awwad, MD

July 2018 ESHRE 2018

The addition of hp-HMG after corifollitropin alfa in the antagonist setting may be worth exploring in women ≤ 40 years old with a POR according to the Bologna criteria.

Number of patients	47	29	18	
Ovarian response				
Cycle cancellation, *n* (%)	13 (28)	8 (28)	5 (28)	*1.00*
Cycles with oocyte retrieval, *n* (%)	31 (66)	19 (66)	12 (67)	*1.00*
Number of oocytes, median (IQR)[a]	3 (0–5)	3 (0–6)	2 (0–4)	*0.52*
Embryo transfer and embryo quality				
Cycles with embryo transfer, *n* (%)	29 (62)	18 (62)	11 (61)	*1.00*
Number of embryos transferred, mean (SD)	1.9 (0.6)	2.0 (0.6)	1.8 (0.6)	0.52
Cycles with top-quality embryos, *n* (%)	18 (38)	13 (45)	5 (28)	0.24
Cycles with supernumerary frozen embryos, *n* (%)	7 (15)	6 (21)	1 (5)	0.16
Reproductive outcome, *n* (%)				
Per patient				
Positive hCG[b]	12 (26)	11 (37)	1 (6)	***0.017***
Ongoing pregnancy	8 (17)	8 (28)	0	***0.017***
Per oocyte retrieval		*n* = 19	*n* = 12	
Positive hCG[b], *n* = 31	12 (39)	11 (58)	1 (8)	***0.008***
Ongoing pregnancy, *n* = 31	8 (26)	8 (42)	0	***0.012***
Per embryo transfer		*n* = 18	*n* = 11	
Positive hCG[b], *n* = 29	12 (41)	11 (61)	1 (9)	***0.008***
Ongoing pregnancy, *n* = 29	8 (28)	8 (44)	0	***0.012***

One patient with a positive hCG in the group aged ≥40 years had a clinical pregnancy which ended in a spontaneous abortion at 8 weeks of gestation.
[a]Skewed data are presented as medians (IQR).
[b]Three patients with a positive hCG test among women aged <40 years did not progress (one patient had a biochemical pregnancy, one had a clinical pregnancy with a gestational sac without an embryonic pole and one a clinical pregnancy with an embryonic pole with a positive heartbeat which ended in a miscarriage at 10 weeks of gestation.

Johany Awwad, MD

July 2018 ESHRE 2018

Human Reproduction Update, Vol.15, No.3 pp. 309–321, 2009
Advanced Access publication on January 30, 2009 doi:10.1093/humupd/dmn065

human reproduction update

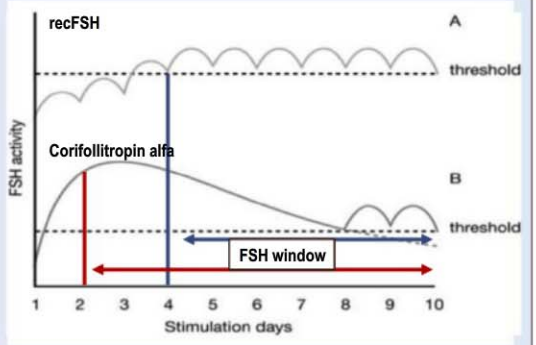
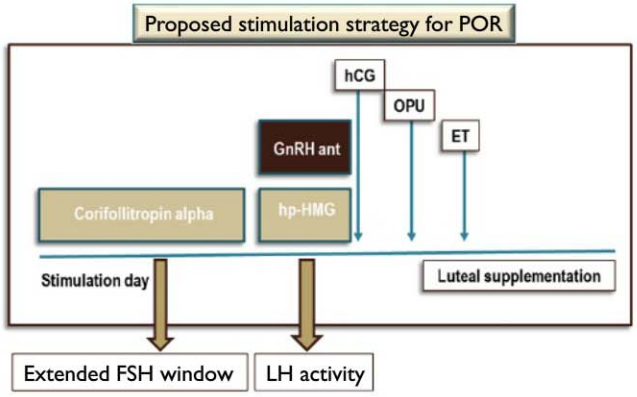
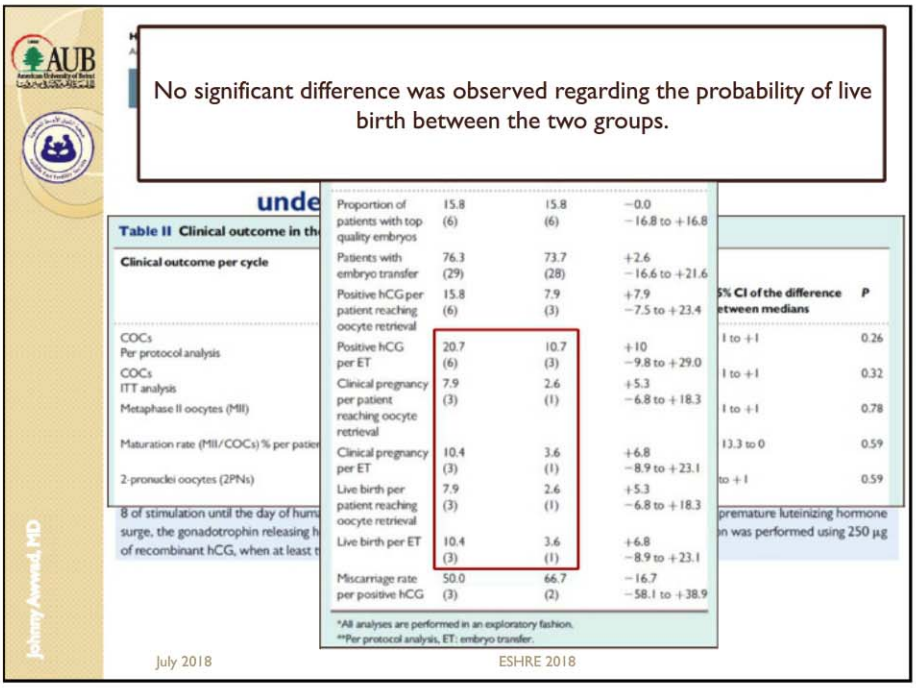
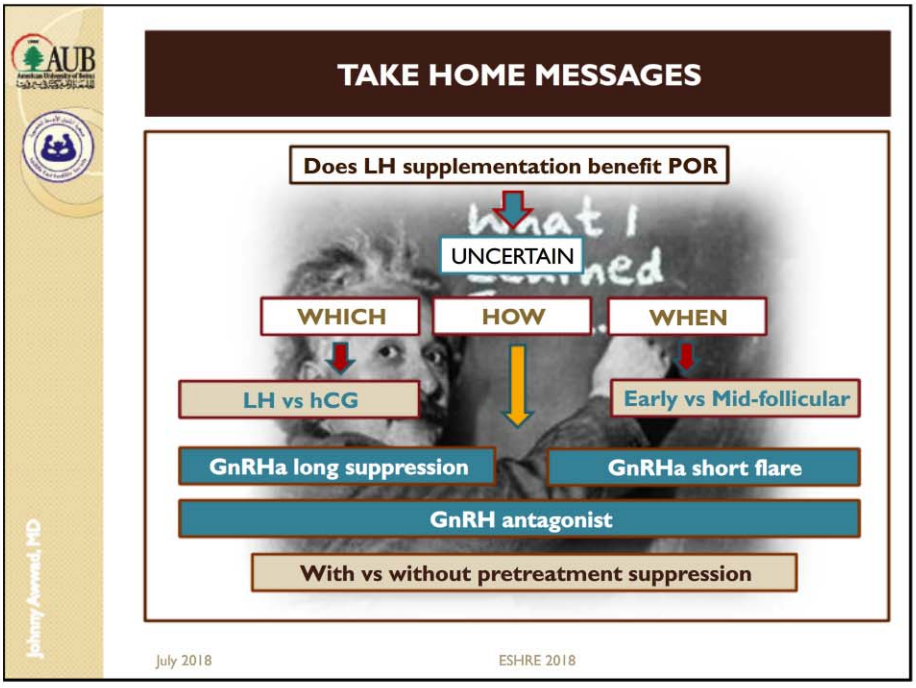


Figure 2 The FSH threshold/window concept using (**A**) daily FSH treatment or (**B**) a single injection of corifollitropin alfa to induce and sustain multi-follicular development during the first week of stimulation. The FSH threshold represents the FSH concentration above which follicle development is stimulated. The FSH window represents the number of days where FSH levels are above the threshold (See also Fauser *et al.*, 2005).




No significant difference was observed regarding the probability of live birth between the two groups.
Table II Clinical outcome in th
Clinical outcome per cycle
Proportion of patients with top quality embryos 15.8 (6) 15.8 (6) −0.0 −16.8 to +16.8
Patients with embryo transfer 76.3 (29) 73.7 (28) +2.6 −16.6 to +21.6
Positive hCG per patient reaching oocyte retrieval 15.8 (6) 7.9 (3) +7.9 −7.5 to +23.4
Positive hCG per ET 20.7 (6) 10.7 (3) +10 −9.8 to +29.0
Clinical pregnancy per patient reaching oocyte retrieval 7.9 (3) 2.6 (1) +5.3 −6.8 to +18.3
Clinical pregnancy per ET 10.4 (3) 3.6 (1) +6.8 −8.9 to +23.1
Live birth per patient reaching oocyte retrieval 7.9 (3) 2.6 (1) +5.3 −6.8 to +18.3
Live birth per ET 10.4 (3) 3.6 (1) +6.8 −8.9 to +23.1
Miscarriage rate per positive hCG 50.0 (3) 66.7 (2) −16.7 −58.1 to +38.9
*All analyses are performed in an exploratory fashion.
**Per protocol analysis, ET: embryo transfer.
COCs Per protocol analysis
COCs ITT analysis
Metaphase II oocytes (MII)
Maturation rate (MII/COCs) % per patie
2-pronuclei oocytes (2PNs)
5% CI of the difference etween medians
P
1 to +1 0.26
1 to +1 0.32
1 to +1 0.78
13.3 to 0 0.59
to +1 0.59
premature luteinizing hormone
n was performed using 250 µg
July 2018
ESHRE 2018


TAKE HOME MESSAGES
Does LH supplementation benefit POR
UNCERTAIN
WHICH
HOW
WHEN
LH vs hCG
Early vs Mid-follicular
GnRHa long suppression
GnRHa short flare
GnRH antagonist
With vs without pretreatment suppression
July 2018
ESHRE 2018

STUDY QUESTION 3

Luteal estradiol pretreatment suppresses luteal follicular wave and enhances synchronization

INTERVENTIONS

Is E2 pre-treatment beneficial in POR

- **Follicle number** ↑
- **Gonadotropin dose** ↓
- **Pregnancy rate** ↑

Johany Awwad, MD

July 2018 ESHRE 2018

Gynecological Endocrinology, 2013; 29(3): 196–200
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ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.3109/09513590.2012.736558

informa healthcare

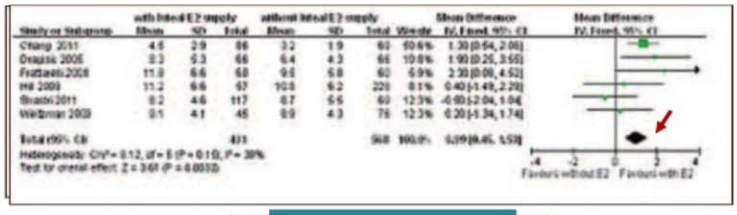
ESTRADIOL TREATMENT IN IVF

Effects of luteal estradiol pre-treatment on the outcome of IVF in poor ovarian responders

Xiaoxia Chang[1,2] & Jie Wu[1,2]

[1]*Department of Obstetrics and Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China and* [2]*State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing, China*

RCTs with usable information included in meta-analysis: n=7



no. of oocytes retrieved

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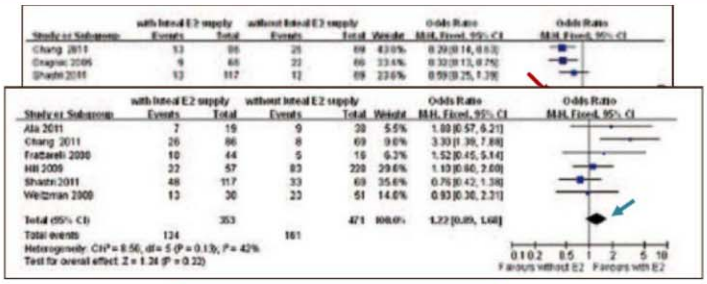
July 2018 ESHRE 2018

The addition of estradiol in the luteal phase preceding IVF in poor responders increased the number of oocytes retrieved, decreased cycle cancellation; but, failed to improve clinical pregnancy rate.



Clinical pregnancy rate

Human Reproduction, Vol.28, No.11 pp. 2981–2989, 2013
Advanced Access publication on July 25, 2013 doi:10.1093/humrep/det306

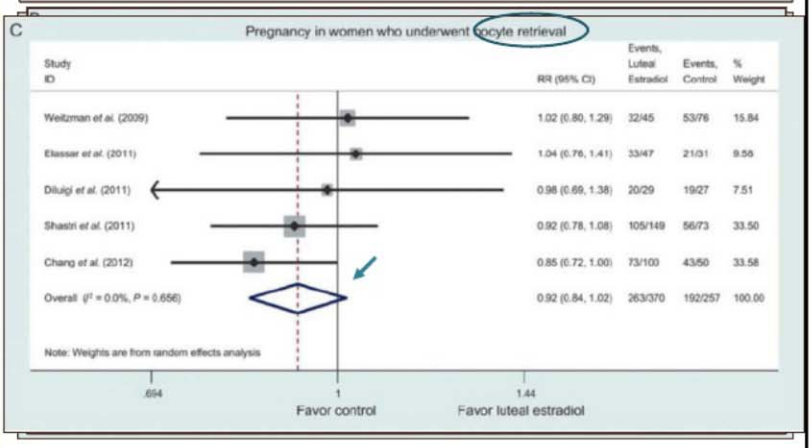
human reproduction META-ANALYSIS *Infertility*

Cycle cancellation and pregnancy after luteal estradiol priming in women defined as poor responders: a systematic review and meta-analysis

Table I Definition of 'poor responders' in IVF for publications included in meta-analysis.

Chang et al. (2012)	<5 oocytes retrieved or maximum E2 < 500 pg/ml in previous cycle or previous cycle cancellation due to poor follicular recruitment
DiLuigi et al. (2011)	Prior poor response (at least one of the following: ≤4 mature follicles, ≤4 oocytes retrieved, peak E2 ≤ 1000 pg/ml or prior IVF cycle cancelled for poor response), or predicted poor response [at least one of the following: age >40 years, FSH ≥ 10 mIU/ml or poor response in prior gonadotrophin cycle (E2 < 500 pg/ml)]
Dragisic et al. (2005)	One or more of the following: ≤4 oocytes retrieved in previous stimulation, basal FSH > 12 mIU/ml or E2 < 500 pg/ml in previous stimulation
Elassar et al. (2011a,b)	One or more of the following: two or more prior ovarian stimulation cycles at a starting dose of gonadotrophins >300 IU with a yield of <5 oocytes, or prior cycle cancellation due to low follicular recruitment (≤3 follicles, ≤15 mm, after 10 days of stimulation)
Weitzman et al. (2009)	At least one of the following: age ≥ 40 years, previous poor response to stimulation (≤4 follicles or oocytes), Day 3 FSH ≥ 10 mIU/ml or previously cancelled cycle for inadequate ovarian response
Shastri et al. (2011)	At least one of the following: history of previously cancelled cycles, poor response to stimulation or (<3 dominant follicles or E2 < 500 pg/ml or basal FSH > 12 mIU/ml)
Hill et al. (2009)	At least one of the following: ≤5 oocytes retrieved, poor-quality oocytes or embryos, cycle cancellation due to poor response, or anticipated poor responder (basal FSH > 12 mIU/ml or basal antral follicle count ≤5)
Ata et al. (2011)	Definition not included

The increased clinical pregnancy rate demonstrated when using the LE protocol may be principally related to the decreased cycle cancellation rate.



Human Reproduction, Vol.29, No.3 pp. 634–638, 2014

human reproduction LETTERS TO THE EDITOR

Table I Number of oocytes retrieved and pregnancy rates in the control group (no LE priming) in the trials included in the meta-analysis by Reynolds *et al.*

Author (year)	Mean number of oocytes retrieved (mean ± SD)[a]	Pregnancy rates (%)[b]
Hill *et al.* (2009)	10.8 ± 6.2	36.4
Weitzman *et al.* (2009)	8.9 ± 4.3	30.3
Elassar *et al.* (2011)	6.1 ± 3.0	21.3
DiLuigi *et al.* (2011)	5.4 ± 4.7	28.6
Shastri *et al.* (2011)	8.7 ± 5.5	24.6
Chang *et al.* (2012)	3.2 ± 1.9	10.1
Ata *et al.* (2011)	7 (4–9)[c]	23.6

[a]As extracted from original trials.
[b]As presented by Reynolds *et al.*
[c]Number refers to median (interquartile range).

A randomized trial of microdose leuprolide acetate protocol versus luteal phase ganirelix protocol in predicted poor responders

And

Results of our study demonstrate that the LPG protocol appears to be as efficacious as the ML protocol in poor responders undergoing IVF. This protocol may offer hope to poor responder patients who have previously undergone cycle cancellation or have failed to conceive after a ML protocol for IVF.

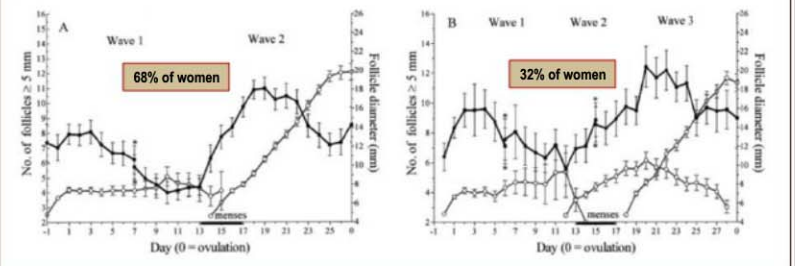
TABL

Cycle			P value
No. of			.60[a]
Total			.75[a]
Peak			.76[a]
No. of			.87[a]
ICSI			.59[b]
No. of			.57[a]
No. of embryos transferred	3.4 ± 2.8	3.8 ± 3.8	.66[a]
Cancelled cycles (%)	6/26 (23.1)	9/28 (32.1)	.57[b]
Underwent retrieval (%)	19/26 (73.1)	21/28 (75)	.87[b]
Underwent ET (%)	15/26 (57.7)	19/28 (67.9)	.44[b]
Implantation rate (%)	28.7	28.2	.46[b]
Clinical PR (%)	9/26 (34.6)	8/28 (28.6)	.63[b]
Ongoing PR (%)	6/26 (23.1)	7/28 (25)	.87[b]
Delivered (%)	6/26 (23.1)	7/28 (25)	.87[b]

The follicular wave phenomenon in women provides a new model for ovarian function and stimulation in women.

FIGURE 3

Day-to-day profiles (mean ± SEM) of the number of follicles ≥5 mm detected (■) and the diameter of the largest follicle of each wave (Non-Identity Method, ○) for women exhibiting (**A**) two waves (n = 34) and (**B**) three waves (n = 16) during one interovulatory interval. *Asterisks* indicate follicle number data overlap.

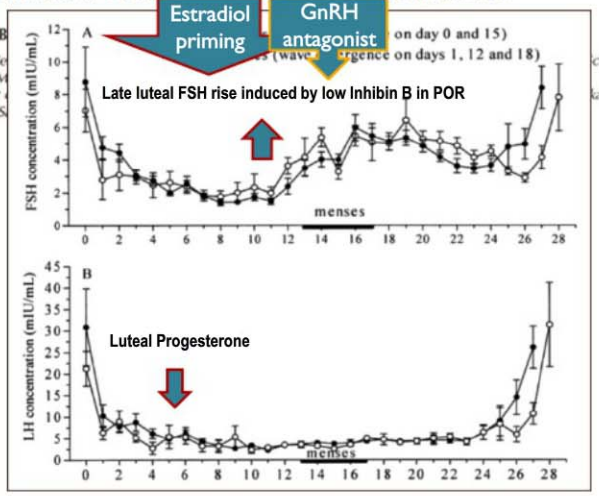


Baerwald. Human ovarian follicular development. Fertil Steril 2003.

BIOLOGY OF REPRODUCTION 69, 1023–1031 (2003)
Published online before print 14 May 2003.
DOI 10.1095/biolreprod.103.017772

Characterization of Ovarian Follicular Wave Dynamics in Women[1]

Angela R. B
Women's He
College of M
Department
Saskatoon, S
iences,
katchewan,



TAKE HOME MESSAGES

Does E2 luteal pretreatment benefit POR

UNCERTAIN

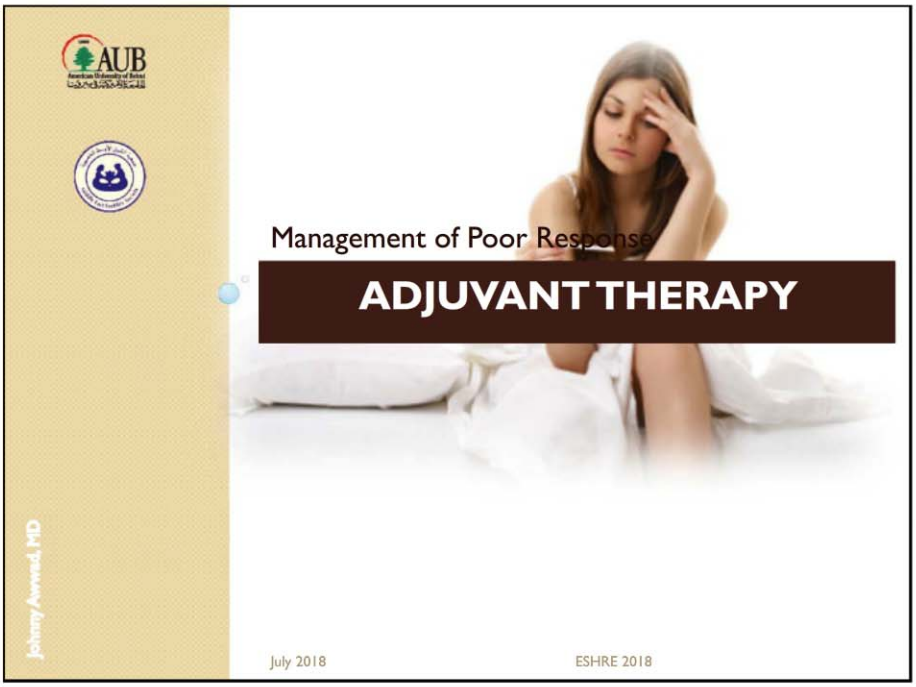
WHO | HOW | WHEN

POR definition

Early vs Mid-luteal

Estradiol / GnRH antagonist

Estradiol / Progestin


AUB
Management of Poor Response
ADJUVANT THERAPY
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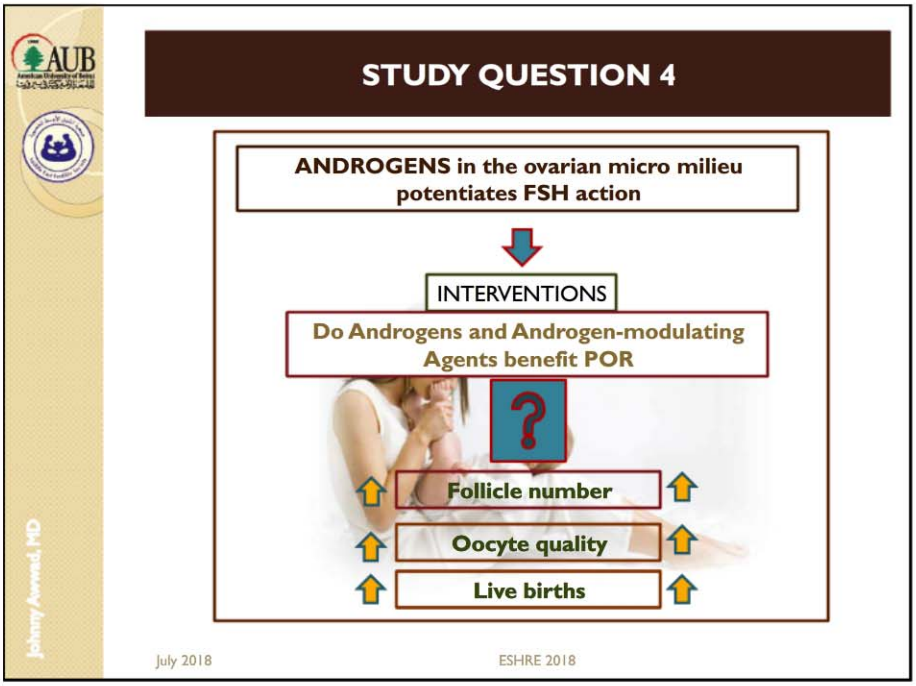
AUB
STUDY QUESTION 4
ANDROGENS in the ovarian micro milieu potentiates FSH action
INTERVENTIONS
Do Androgens and Androgen-modulating Agents benefit POR
?
Follicle number
Oocyte quality
Live births
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July 2018
ESHRE 2018

Reproductive BioMedicine Online (2012) 25, 450–459

www.sciencedirect.com
www.rbmonline.com

ELSEVIER

REVIEW

Effects of transdermal testosterone in poor responders undergoing IVF: systematic review and meta-analysis

Mireia González-Comadran [a,b], Montserrat Durán [b], Ivan Solà [c,d], Francisco Fábregues [e], Ramón Carreras [a,f], Miguel A Checa [a,f,g,*]

When the clinical pregnancy rate was adjusted per embryo transferred, differences among the two groups were not statistically significant.

(a) Live birth

Study or Subgroup	Testosterone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fábregues et al., 2009	6	31	4	31	33.3%	1.50 [0.47, 4.80]
Kim et al., 2011	15	55	7	55	58.2%	2.14 [0.95, 4.84]

Risk Ratio M-H, Fixed, 95% CI

(c) Clinical pregnancy per embryo transferred

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Fábregues et al., 2009	-0.0317	0.603	29.1%	0.97 [0.30, 3.16]
Kim et al., 2011	0.6811	0.413	62.0%	1.98 [0.88, 4.44]
Massin et al., 2006	1.4787	1.0901	8.9%	4.39 [0.52, 37.16]
Total (95% CI)			**100.0%**	**1.72 [0.91, 3.26]**

Heterogeneity: $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0\%$
Test for overall effect: Z = 1.67 (P = 0.09)

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100
Favours Control Favours Testosterone

Total events 27 13
Heterogeneity: $Chi^2 = 0.63$, df = 2 (P = 0.73); $I^2 = 0\%$
Test for overall effect: Z = 2.36 (P = 0.02)

0.1 0.2 0.5 1 2 5 10
Favours Control Favours Testosterone

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Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD009749.
DOI: 10.1002/14651858.CD009749.pub2.

Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction (Review)

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B

DHEA or testosterone versus placebo/no treatment for women undergoing assisted reproduction

Population: Women undergoing assisted reproduction
Settings: Outpatient clinic
Intervention: DHEA or testosterone versus placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	DHEA or testosterone				
Live birth/ongoing pregnancy rate - DHEA	116 per 1000	192 per 1000 (141 to 256)	OR 1.81 (1.25 to 2.62)	878 (8 studies)	⊕⊕⊕◯ moderate[1]	
Live birth/ongoing pregnancy rate - Testosterone	82 per 1000	188 per 1000 (104 to 317)	OR 2.6 (1.3 to 5.2)	345 (4 studies)	⊕⊕⊕◯ moderate[1]	

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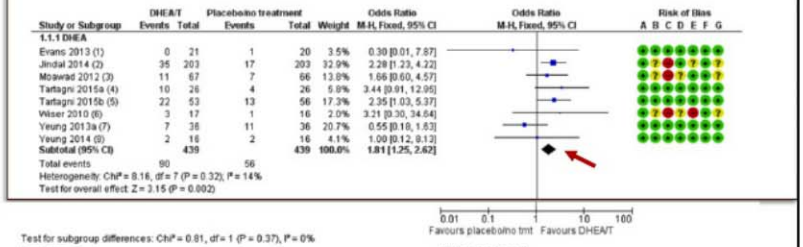
When compared with placebo or no treatment, pre-treatment with DHEA was associated with higher live birth rates.

Figure 4. Forest plot of comparison: 1 DHEA or testosterone versus placebo/no treatment, outcome: 1.1 Live birth/ongoing pregnancy rate.



Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%

Footnotes
(1) Comparison was placebo
(2) Comparison was no treatment. This study transferred more embryos in the intervention arm
(3) Comparison was no treatment; reported as ongoing pregnancy rates
(4) Comparison was placebo; participants were infertile but not poor responders
(5) Comparison was placebo
(6) Comparison was no treatment
(7) Comparison was placebo; reported as ongoing pregnancy rates; participants were normal
(8) Comparison was placebo

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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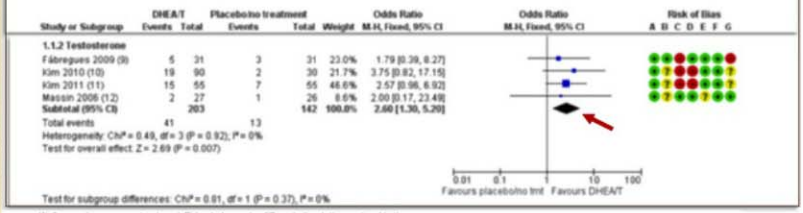
When compared with placebo or no treatment, pre-treatment with testosterone was associated with higher rates of live birth.

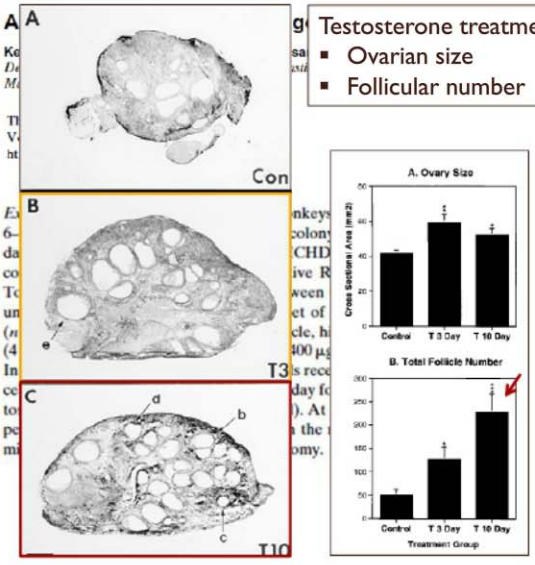
Figure 4. Forest plot of comparison: 1 DHEA or testosterone versus placebo/no treatment, outcome: 1.1 Live birth/ongoing pregnancy rate.



(9) Comparison was no treatment. This study used a different stimulation protocol in the...
(10) Comparison was no treatment. 3 treatment groups: 2 weeks, 3 weeks or 4 weeks of T
(11) Comparison was no treatment
(12) Comparison was placebo

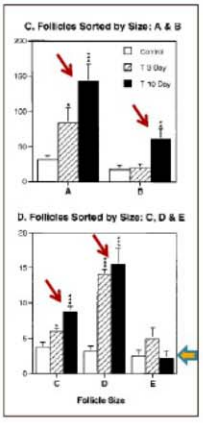
4 Live birth rate by length of T administration	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 7 days	1	62	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.39, 8.27]
4.2 14 to 20 days	2	113	Odds Ratio (M-H, Fixed, 95% CI)	2.10 [0.50, 8.88]
4.3 21 to 28 days	2	200	Odds Ratio (M-H, Fixed, 95% CI)	3.16 [1.38, 7.23]

Testosterone treatment increased
- Ovarian size
- Follicular number



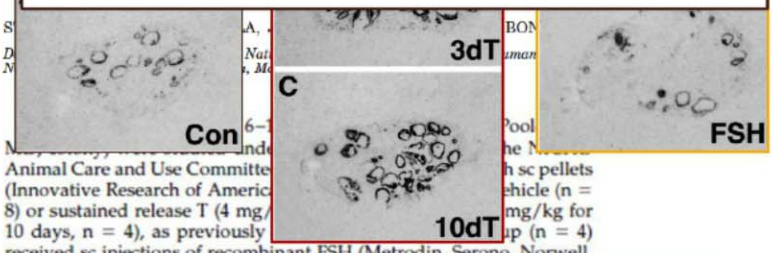
Androgen treatment stimulated early stages of primate ovarian follicular growth, independently of cycle stage or gonadotropin effect.

E	Large antral	> 1000	Mature graffian follicles with well developed granulosa, thecal, and antral elements.



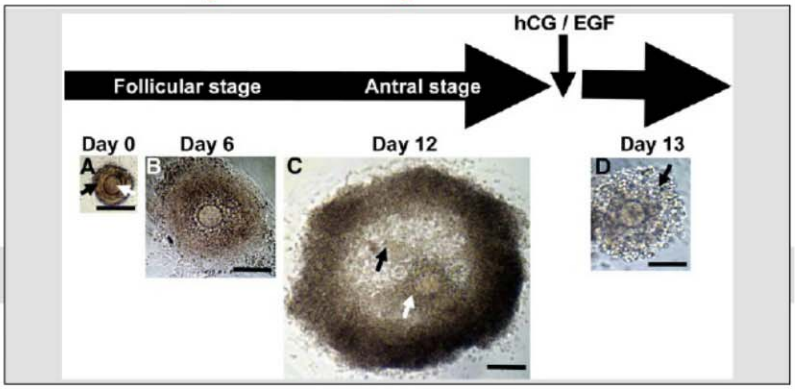
Testosterone treatment
- Significantly increased the numbers of small follicles (primary to small antral)
- Did not increase the abundance of large antral follicles (pre-ovulatory)

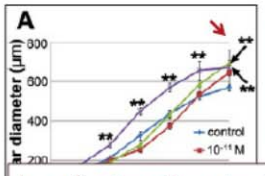
Androgens promoted follicular growth indirectly by amplifying FSH effect.



FSHR mRNA expression was
- Significantly increased following testosterone treatment
- Only modestly increased following FSH treatment

Androstenedione induces abnormalities in morphology and function of developing oocytes, which impairs oocyte meiotic



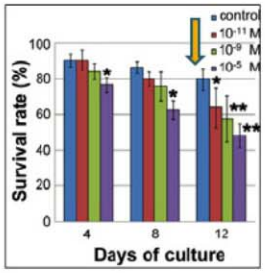


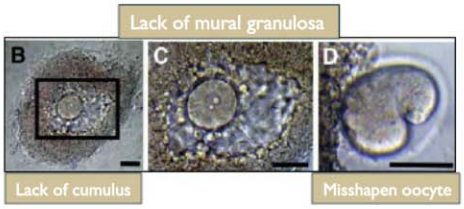
Equivalent to ovarian follicular fluid concentrations:

- PCOS - 10^{-5} M
- Healthy women - 10^{-9} M

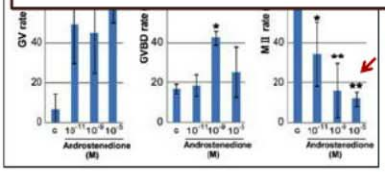
In androstenedione-treated follicles,

- Survival rate of follicles decreased in a dose-dependent manner
- Rate of follicles with abnormal morphology higher

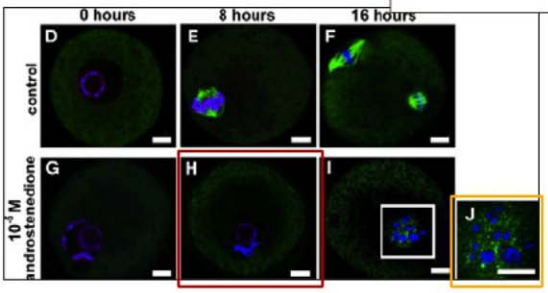




Excess androgen induced abnormalities in the morphology and function of developing oocytes, which impairs oocyte meiotic competence.



lower
- Failure of spindle assembly higher
- Misaligned chromosomes more frequent



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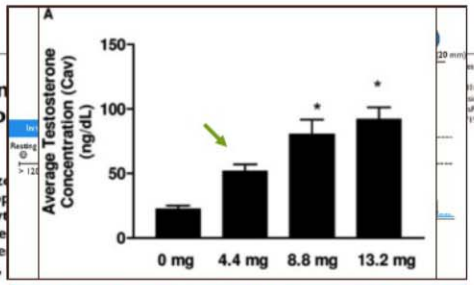
Position Paper

Testosteron
Lessons Fro

Nikolaos P. Polyz
Panagiotis Drakop
Christian De Geyt
Francisca Martine
Arne van de Vijve
Pedro Barri, MD,



Does clinical research follow principles of ovarian physiology

The transition from preantral to antral follicular stage ≈ 70 days

of Transdermal Testosterone Preceding Gonadotropin Treatment in

Testosterone in excess to 5.5 mg/d may be detrimental to follicle development

Study	Sample Size	Duration, days	Dose (per day)
Bosdou et al[7]	50	21	10 mg
Kim et al[4]	110	21	12.5 mg
Fábregues et al[5]	62	5	0.02 mg/kg
Massin et al[6]	49	15	10 mg

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No significant difference in the oocytes obtained, clinical pregnancy, ongoing pregnancy, live birth or miscarriage was observed.

Follicular fluid - DHEA-S | Follicular fluid - testosterone | Follicular fluid - Estradiol

IVF cycle characteristics of the DHEA and placebo groups.

Cycle characteristic	DHEA group (n = 16)	Placebo group (n = 16)	*P* value
Insemination			
IVF	10	11	.648
ICSI	4	2	
Gonadotropin			
Duration (d)	10 (9–12)	12 (9–15)	.114
Dose (IU)	2,475 (2,194–3,206)	3,150 (2,475–4,388)	.069
E_2 on day of hCG	3,947 (2,781–4,408)	5,101 (1,479–6,222)	.347
Follicle size			
14–15 mm	0.5 (0–1)	0 (0–0.5)	.169
16–17 mm	0 (0–2)	0 (0–1)	.550
≥ 18	1 (1–2)	2 (1–2)	.430
Endometrial thickness (mm)	11.2 (9.4–13.8)	10.7 (9.3–12.5)	.705
Number of			
Oocytes obtained	3 (1.25–6.75)	2.5 (1–3)	.186
Fertilized embryos	3 (0.5–4)	1 (0–2)	.155
Cleaved embryos	3 (0.5–3.75)	1 (0–2)	.169
Transferred embryos	2 (0.25–2)	1 (0–2)	.430
Frozen embryos	0 (0–1.75)	0 (0)	.202
TQE	1 (0–2)	0 (0–0.75)	.141

Note: Data are expressed as median (25th to 75th centile) or number (percentage) as appropriate. $P < .05$ was considered statistically significant. TQE = top-quality embryos.

Yeung. *Effect of DHEA in poor responders. Fertil Steril 2014.*

Human Reproduction, Vol.31, No.5 pp. 977–985, 2016
Advanced Access publication on March 7, 2016 doi:10.1093/humrep/dew028

human reproduction ORIGINAL ARTICLE *Endocrinology*

Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial

J.K. Bosdou[1], C.A. Venetis[2], K. Dafopoulos[3], L. Zepiridis[1], K. Chatzimeletiou[1], G. Anifandis[3], A. Mitsoli[1], A. Makedos[1], I.E. Messinis[3], B.C. Tarlatzis[1], and E.M. Kolibianakis[1,*]

[1]Unit for Human Reproduction, 1st Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece [2]School of Women's and Children's Health, UNSW Medicine, University of New South Wales, Sydney, Australia [3]Unit for Human Reproduction, Department of Obstetrics and Gynecology, Medical School, University of Thessaly, Larissa, Greece

STUDY DESIGN, SIZE, DURATION: The present RCT was designed to detect a difference of 1.5 COCs (sample size required = 48 patients). From 02/2014 until 04/2015, 50 poor responders fulfilling the Bologna criteria have been randomized (using a randomization list) to either testosterone pretreatment for 21 days ($n = 26$) or no pretreatment ($n = 24$).

All patients underwent a long follicular protocol with GnRH agonist triptorelin (Arvekap, Ipsen Ltd, France) 3.75 mg depot, starting on the first day of the menstrual cycle, followed by daily injections of triptorelin (Arvekap, Ipsen Ltd, France) 0.1 mg, if necessary. In the testosterone group, a daily dose of 10 mg of testosterone gel (Tostran 2% Gel, ProStrakan) was applied transdermally onto the inner thigh daily, for 21 days as suggested by Kim *et al.* (2011), starting from the GnRH agonist initiation. Testosterone was supplied in a canister with a dosing pumping mechanism, which delivered one half gram of gel containing 10 mg of testosterone each time the piston was depressed.

The non-significant increase in the number of COCs, following transdermal testosterone pretreatment was not associated with the probability of embryo transfer.

	(4)	(5)	−28.2 to +21.5 0.72
Patients with embryo transfer	83.3 (20)	91.3 (21)	−8.0 −28.2 to +12.7 0.47
Cancelation rate	7.7 (2)	4.2 (1)	+3.5 −13.5 to +20.3 1.00
Positive hCG (intention to treat [ITT] analysis)	7.7 (2)	8.3 (2)	−0.6 −19.0 to +16.9 1.00
Positive hCG per embryo transfer	10.0 (2)	9.5 (2)	−0.5 −20.2 to +21.7 1.00
Clinical pregnancy (ITT analysis)	7.7 (2)	8.3 (2)	−0.6 −19.0 to +16.9 1.00
Clinical pregnancy per embryo transfer	10.0 (2)	9.5 (2)	−0.5 −20.2 to +21.7 1.00
Live birth rate (ITT analysis)	7.7 (2)	8.3 (2)	−0.6 −19.0 to +16.9 1.00
Live birth per embryo transfer	10.0 (2)	9.5 (2)	−0.5 −20.2 to +21.7 1.00

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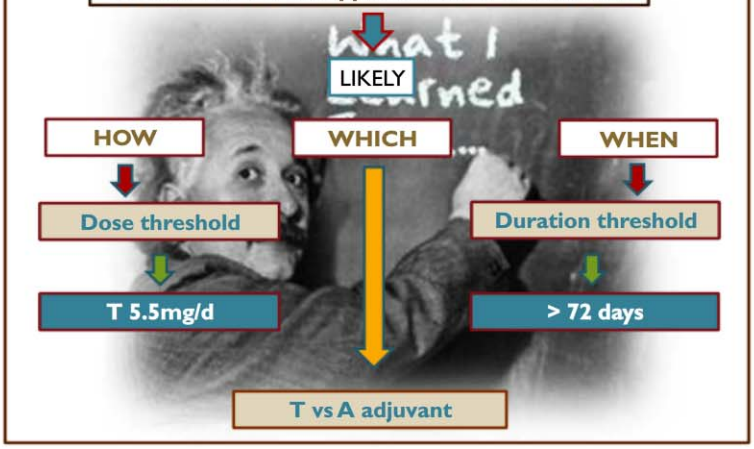
TAKE HOME MESSAGES

Does ANDROGEN supplementation benefit POR



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STUDY QUESTION 5

GROWTH HORMONE increases granulosa response to gonadotropins and IGF-1 enhanced steroidogenesis

INTERVENTION

Is GH beneficial in POR

- **Follicle number**
- **Oocyte quality**
- **Live birth**

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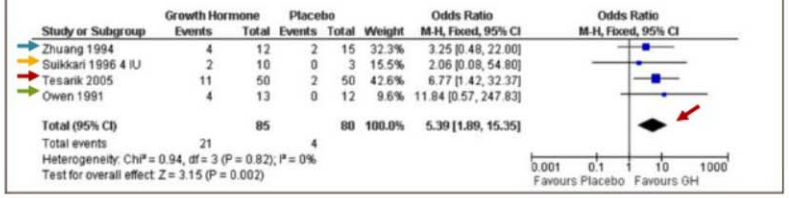
There was a statistically significant difference in live birth rates and pregnancy rates favoring the use of adjuvant growth hormone in

GH protocol	POR definition
12 IU IM on alternate days	Previous sub-optimal response
4 - 12 IU SC daily from CD 3	Previous ≤2 oocytes or ≥48 AMP hMG
8 IU SC daily	Women >40 years
24 IU IM on alternate days from CD 1	Previous < 6 oocytes

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.



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There was no significant difference in the clinical pregnancy or live birth rate per cycle.

antagonist protocol improve outcomes in poor responders? A randomized, controlled trial

Reproductive outcomes.

Variable	Group A, GH/hMG/GnRHant (n = 68)	Group B, hMG/GnRHant (n = 73)	*P* value
Cycles reaching ET, n/n (%)	57/68 (83.8)	59/73 (80.8)	.641
Fertilization rate (%)	53.95	49.36	.050
Implantation rate (%)	11.98	9.88	.608
Chemical pregnancy rate/cycle start, n/n (%)	28/68 (41.2)	22/73 (30.1)	.171
Chemical pregnancy rate/ET, n/n (%)	28/57 (49.1)	22/59 (37.3)	.198
Clinical pregnancy rate/cycle start, n/n (%)	15/68 (22.1)	11/73 (15.1)	.285
Clinical pregnancy rate/ET, n/n (%)	15/57 (26.3)	11/59 (18.6)	.322
Single intrauterine sac, n/n (%)	11/15 (73.3)	8/11 (72.7)	.972
Double intrauterine sacs, n/n (%)	4/15 (26.7)	3/11 (27.3)	.972
Early miscarriage rate/cycle start, n/n (%)	5/68 (7.4)	3/73 (4.1)	.405
Early miscarriage rate/ET, n/n (%)	5/57 (8.8)	3/59 (5.1)	.433
Ongoing pregnancy rate/cycle start, n/n (%)	10/68 (14.7)	8/73 (10.9)	.505
Ongoing pregnancy rate/ET, n/n (%)	10/57 (17.5)	8/59 (13.6)	.553
Live birth rate/cycle start, n/n (%)	10/68 (14.7)	8/73 (10.9)	.505
Live birth rate/ET, n/n (%)	10/57 (17.5)	8/59 (13.6)	.553

Note: *P* value < .05 is considered statistically significant.

Bassiouny. Growth hormone in poor responders. Fertil Steril 2016.

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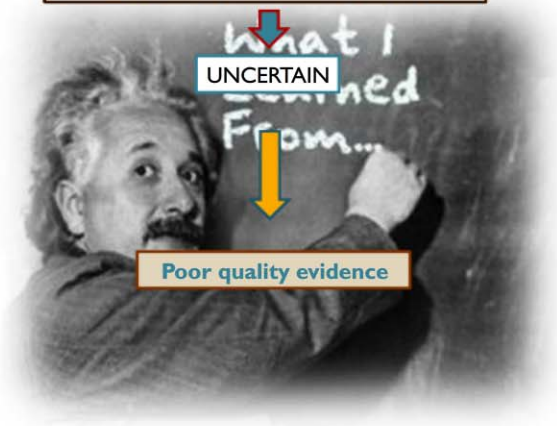
TAKE HOME MESSAGES

Does GH supplementation benefit POR



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