eshre

SCIENCE MOVING
PEOPLE
MOVING SCIENCE

The lost art of ovulation induction

Special Interest Group Reproductive Endocrinology

5

27 June 2010
Rome, Italy

PRE-CONGRESS COURSE 5 – Table of contents

The lost art of ovulation induction

Organised by the Special Interest Group Reproductive Endocrinology

ESHRE – European Society of Human Reproduction and Embryology

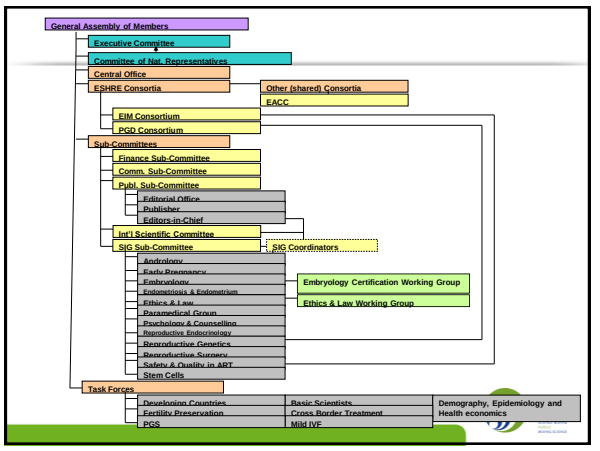
What is ESHRE?

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

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

Executive Committee 2009/2011

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



ESHRE Activities – Annual Meeting

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

Track record:

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

Future meetings:

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

ESHRE Activities – Scientific Journals

Human Reproduction with impact factor 3.773

Human Reproduction Update with impact factor 7.590

Molecular Human Reproduction with impact factor 2.537

ESHRE Activities – Campus and Data Collection

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

ESHRE Activities - Other

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

ESHRE Membership (1/3)

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

ESHRE Membership (2/3)

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

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

ESHRE Membership – Benefits (3/3)

1) Reduced registration fees for all ESHRE activities:

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

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

3) ESHRE monthly e-newsletter

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

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

Special Interest Groups (SIGs)

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

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

Task Forces

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

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

Annual Meeting

Rome, Italy 27 June to 30 June 2010

Pre-congress courses (27 June):

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

Annual Meeting – Scientific Programme (1/2)

Rome, Italy 27 June to 30 June 2010

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

Annual Meeting – Scientific Programme (2/2)

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

Certificate of attendance

1/ Please fill out the evaluation form during the campus

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

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

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

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

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

Contact

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E-mail: info@eshre.eu

www.eshre.eu

PRE-CONGRESS COURSE 5 - Programme

The lost art of ovulation induction

Organised by the Special Interest Group Reproductive Endocrinology

Course co-ordinator: Adam Balen (United Kingdom)

Teaching aims & course description: To reinforce the need to have a full understanding of ovulation induction for anovulatory infertility in the context of a Reproductive Medicine Service.

Course description including main topics: To cover the causes of anovulation, modern management, safety and complications.

Target audience: Reproductive physicians and nurses

Scientific programme:

Chairperson: Georg Griesinger (Germany)

09:00 – 09:10 Introduction - **Adam Balen (United Kingdom)**
09:10 – 09:40 Current understanding of ovulation - **Richard Anderson (United Kingdom)**
09:40 – 09:50 Discussion
09:50 – 10:20 Causes of anovulatory infertility - **Adam Balen (United Kingdom)**
10:20 – 10:30 Discussion
10:30 – 11:00 Coffee break

Chairperson: Richard Anderson (United Kingdom)

11:00 – 11:30 Obesity and reproduction (to include diet, bariatric surgery) - **Lisa Webber (United Kingdom)**
11:30 – 11:40 Discussion
11:40 – 12:15 First line therapy: Clomiphene citrate, anti-oestrogen therapy and aromatase inhibitors - **Roy Homburg (Israel)**
12:15 – 12:30 Discussion
12:30 – 13:30 Lunch

Chairperson: Nick Macklon (United Kingdom)

13:30 – 13:50 Algorithms for predicting response to ovulation induction - **Joop Laven (The Netherlands)**
13:50 – 14:00 Discussion
14:00 – 14:20 Gonadotrophin protocols - **Jean Noel Hugues (France)**
14:20 – 14:30 Discussion
14:30 – 14:50 Ovarian surgery - the evidence - **Fulco van der Veen (The Netherlands)**
14:50 – 15:00 Discussion
15:00 – 15:30 Coffee break

Chairperson: Adam Balen (United Kingdom)

15:30 – 16:00 Insulin sensitising agents - Where do they fit in? - **Etelka Moll (The Netherlands)**
16:00 – 16:15 Discussion
16:15 – 16:35 How should ovulation induction be managed? - **Nick Macklon (United Kingdom)**
16:35 – 17:00 Panel discussion (all speakers)

Current understanding of ovulation

or
the life and times of a follicle

Richard A Anderson
Reproductive and Developmental Science
University of Edinburgh

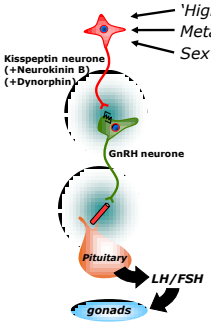
ESHRE, Rome June 2010

Overview

Intraovarian factors

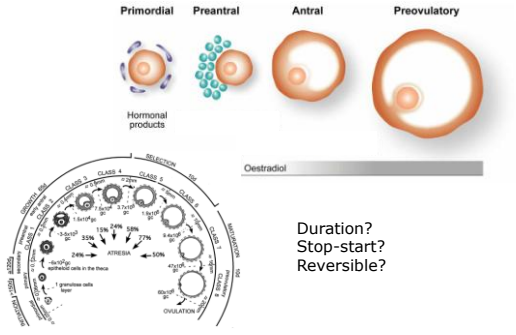
- Initiation of growth
- Angiogenesis
- FSH action
- Mediation of LH surge
- Cumulus: role and biomarker
- Novel directions

Neuroendocrine regulation



Animal data:
Pubertal timing
Ovulation
Mediation of metabolic inputs

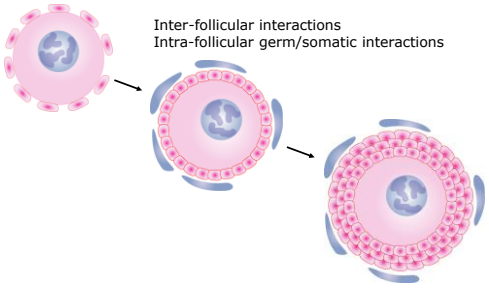
Human data:
Mutations: Puberty
Stimulation of LH secretion



Duration?
Stop-start?
Reversible?

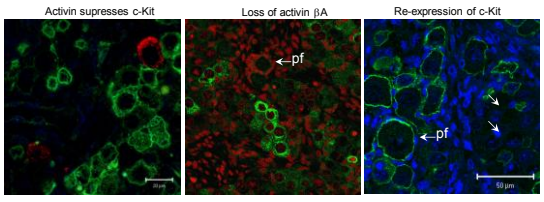
Gougeon A. Hum Reprod 1986;1:81

Initiation and early follicle growth



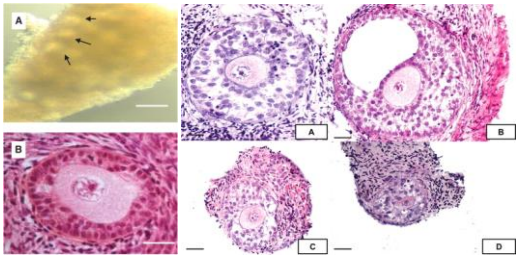
Inter-follicular interactions
Intra-follicular germ/somatic interactions

Interaction between activin βA and kit ligand/c-Kit at primordial follicle formation



Coutts et al 2008 Dev Biol 314, 189
Childs and Anderson 2009 Fertil Steril

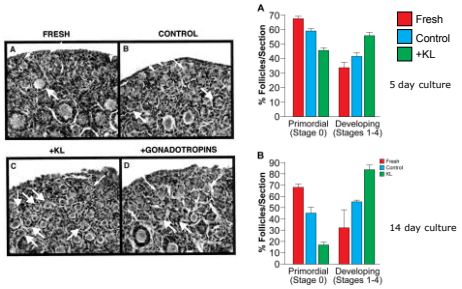
FSH-independent human follicle growth in vitro



In vitro grown human follicles cultured first in cortical strips for 6 days (Step 1) then isolated at the pre-antral stage and cultured for a further 4 days (step 2) in the presence (A and B) or absence (C and D) of 100 ng/ml of activin A.

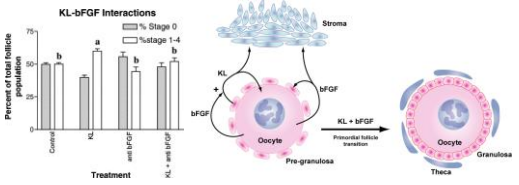
Telfer EE et al. Hum. Reprod. 2008 23:1151-1158

Kit ligand activates primordial follicle growth in vitro



Parrott et al. Endocrinology 1999;140:4262-4271

Cooperative germ cell/somatic interactions

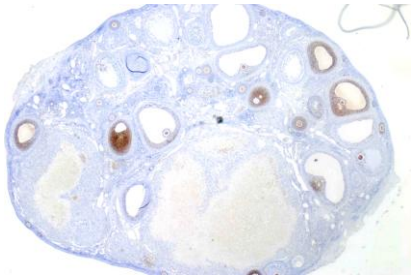


bFGF needs to be present for
KL to promote primordial follicle transition

FGF not essential as KO are fertile

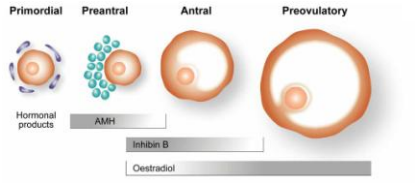
Nilsen and Skinner 2004 Mol Cell Endo 214, 19

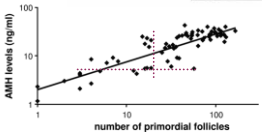
AMH is expressed in small but not larger follicles



Macaque ovary: Prof Hamish Fraser

Markers of follicle number



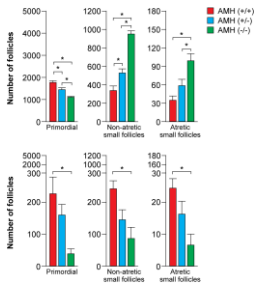


Kevenaar et al. Endocrinology 2006;147:3228-3234

Follicle activation and depletion in AMH ko

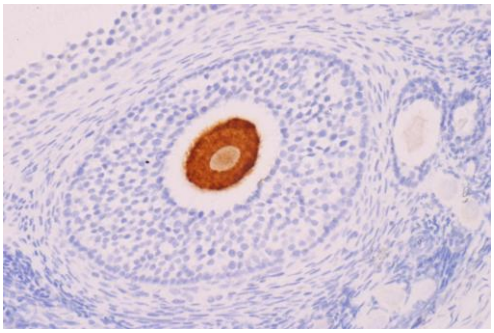
4 months

13 months

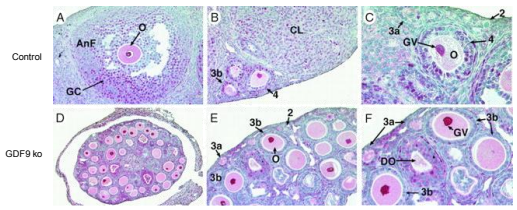


Durlinger, A. L. L. et al. Endocrinology 1999;140:5789-5796

GDF9: a critical oocyte factor



Oocyte-derived GDF9 is required for progression beyond the primary stage



Elvin, J. A. et al. Mol Endocrinol 1999;13:1018-1034

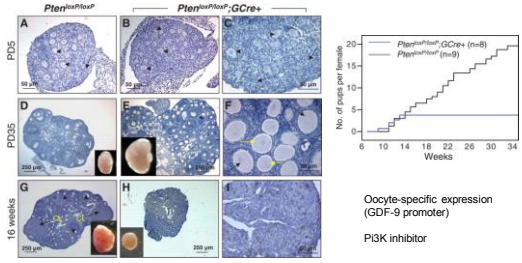
Crucial role of oocyte factors

Oocyte-specific GDF9 and BMP15 determine ovulation rate in sheep

Human:
GDF9 mutation and DZ twinning: Montgomery et al 2004

Photos: AS McNeilly

Oocyte-dependent follicle activation



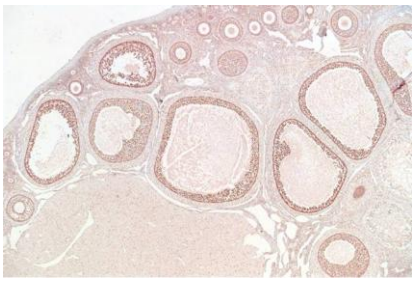
Oocyte-specific expression (GDF-9 promoter)

PI3K inhibitor

Normal at PD5
Widespread activation from PD5, few primordials by PD23
Excess follicles at transient stage ( )

Reddy P et al 2008 Science 319, 611

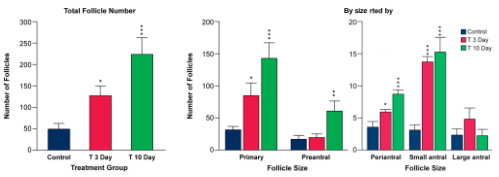
Androgen receptor expression



Marmoset ovary: AR present in all sizes of follicle (human data similar)

Saunders PTK et al. Biol Reprod 2000;63:1098-1105

Androgens stimulate early follicular growth in the primate

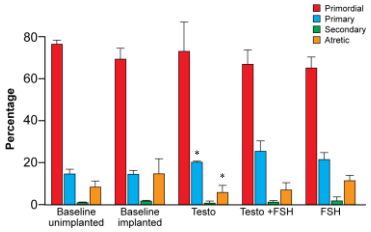


Rhesus monkey
Treated with T or DHT

Mediated by increased IGF1 / IGF1 receptor?

Vendola KA et al 1998 J Clin Invest 12, 2622

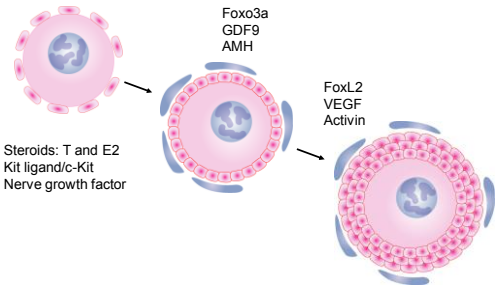
Testosterone increases primary follicle number and reduces atresia



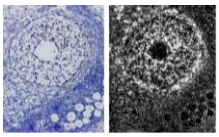
Lamb ovarian cortex grafted onto CAM 'in ovo'

Qureshi et al 2008 Reproduction 136, 187

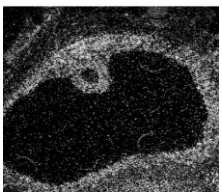
Interplay: Oocyte factors/Somatic factors
Inhibition/Stimulation



VEGF mRNA first expressed in late secondary follicles

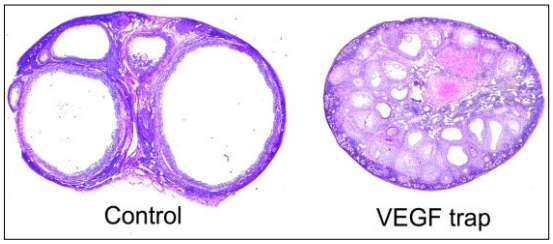


Highest in granulosa cell layer



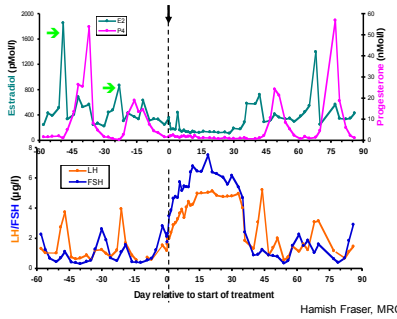
Hamish Fraser, MRC HRSU, Edinburgh

Inhibition of angiogenesis suppresses follicular development



Hamish Fraser, MRC HRSU, Edinburgh

VEGF Trap blocks follicular phase in macaques

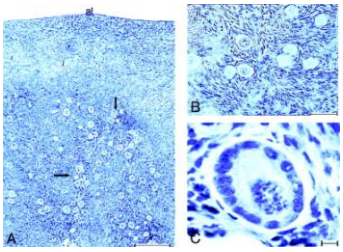


Hamish Fraser, MRC HRSU, Edinburgh

Need for LH vs FSH Kallmanns paper Bill?

- KO data in humans Themmen Ilpo paper
- LH EGF cascade at ovulation
- Ovulation as inflammation/resolution
- Cumulus array data all we don't know

Inactivating FSH receptor mutation



Primary Amen

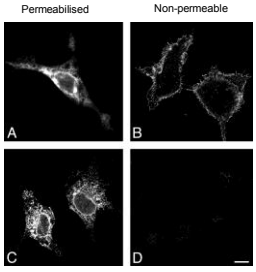
High FSH/low E2

Large numbers of primordial follicles

None at primary or later stages

Meduri, G. et al. J Clin Endocrinol Metab 2003;88:3491-3498

Mutant FSH-R is not exported to the membrane

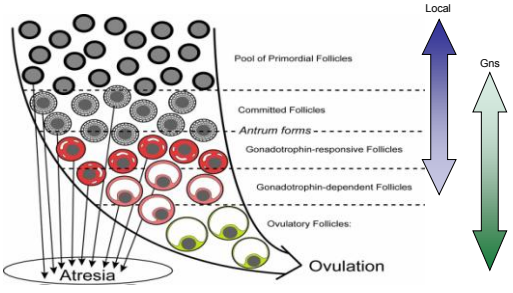


Normal FSH-R

Mutant

Meduri, G. et al. J Clin Endocrinol Metab 2003;88:3491-3498

New early roles of FSH?

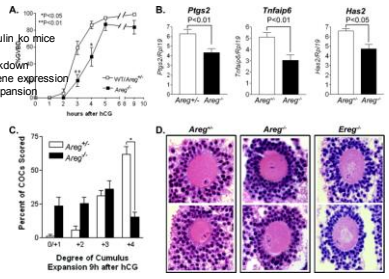


Scaramuzzi R et al 1993 Reprod Fertil Develop 5: 459-478

LH activation of the EGF network is essential for ovulation

Amphiregulin/Epiregulin ko mice

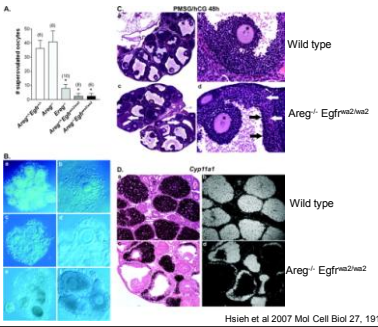
Delayed GVBD breakdown
Reduced cumulus gene expression
Impaired cumulus expansion



Hsieh et al 2007 Mol Cell Biol 27, 1914

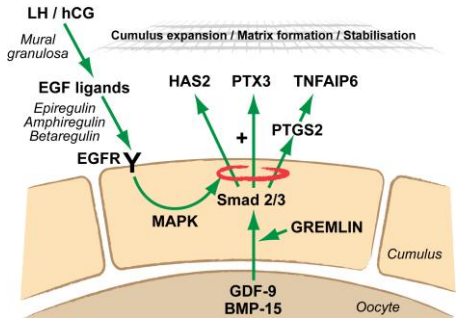
Impaired ovulation and luteinisation in EGF ligand/receptor deficient mice

Fewer oocytes ovulated
Reduced cumulus expansion
Trapped, unexpanded COCs
Reduced luteinisation

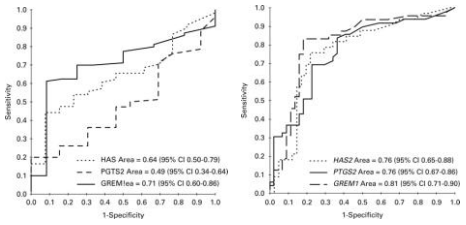


Hsieh et al 2007 Mol Cell Biol 27, 1914

Cumulus mediation: a biomarker?

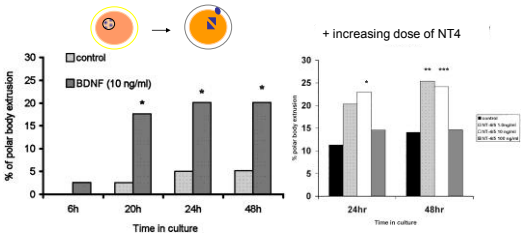


Cumulus prediction of oocyte maturity and embryo quality



McKenzie, L.J. et al. Hum. Reprod. 2004 19:2869-2874

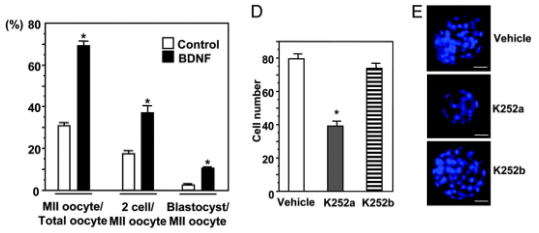
BDNF and NT4 promote meiotic maturation in mouse oocytes



NT3 had no effect (and TrkC not found)

Seifer DB et al. J Clin Endocrinol Metab 2002;87:4569-4571 and 88, 87:655-659

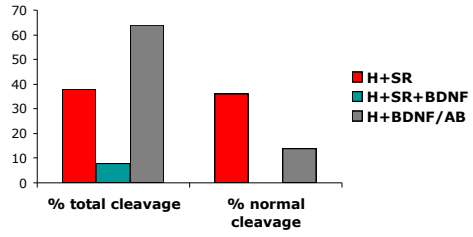
BDNF promotes nuclear maturation and developmental competence in mouse (and bovine) oocytes



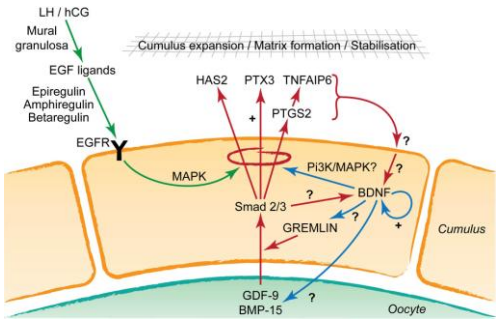
Comparable effects in bovine: Martins da Silva et al

Kawamura et al. (2005) Proc. Natl. Acad. Sci. USA 102, 9206-9211

Human IVM/parth activation BDNF and embryo cleavage

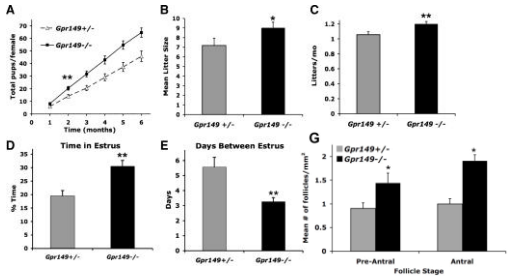


Anderson et al 2009 Fertil Steril



Copy to simplify without BDNF

New genes that enhance fertility



GPR149: an orphan GPCR expressed by maturing oocytes, until fertilisation
No detectable changes in LH/FSH, increased *gdf9* expression

Edson, M. A. et al. Endocrinology 2010;151:358-368

Summary

- Basic gonadotrophic requirement for later follicle growth remains
- How early is FSH required?
- AMH: useful maker of small follicle number
- New potential targets for regulating follicle growth and oocyte maturation

Causes of Anovulatory Infertility

ESHRE, Rome 2010

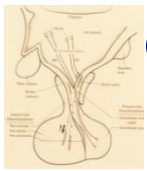
Adam Balen MD, FRCOG
Professor of Reproductive Medicine
Leeds Teaching Hospitals, UK

Disclosures: Medical advisor to Ferring, Organon SP

Causes of Anovulatory Infertility

Learning Objectives

1. To understand the causes of anovulation
2. Knowledge of the correct diagnostic tests
3. Effective assessment and diagnosis to plan appropriate ovulation induction therapy

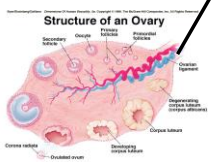


Hypothalamus

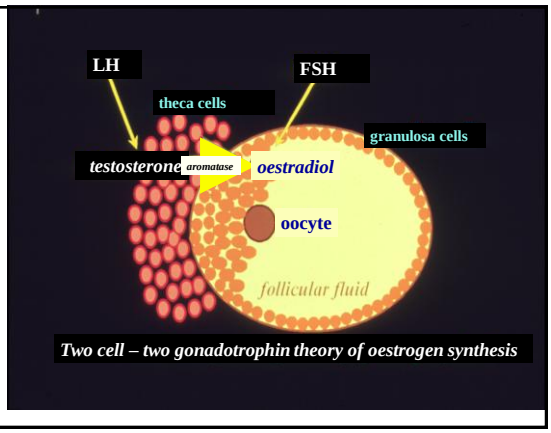
GnRH

Pituitary

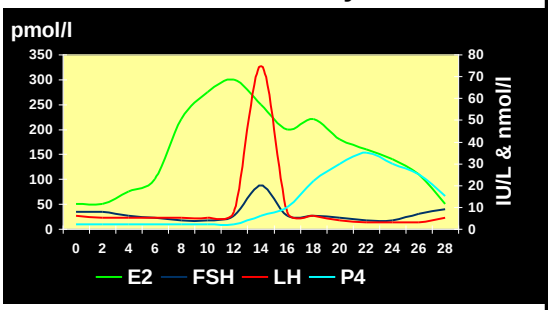
FSH LH



Oestradiol, inhibins
Progesterone…….



The Menstrual Cycle



Causes of Anovulatory Infertility

Group I: *Hypothalamic/ pituitary failure*	weight loss, systemic illness Kallmann's syndrome hypogonadotrophic hypogonadism	5%
	Hyperprolactinaemia Hypopituitarism	
Group II: *h/p dysfunction*	PCOS	90%
Group III: *Ovarian failure*	Premature ovarian failure (POF) Resistant ovary syndrome (ROS)	5%

Investigations

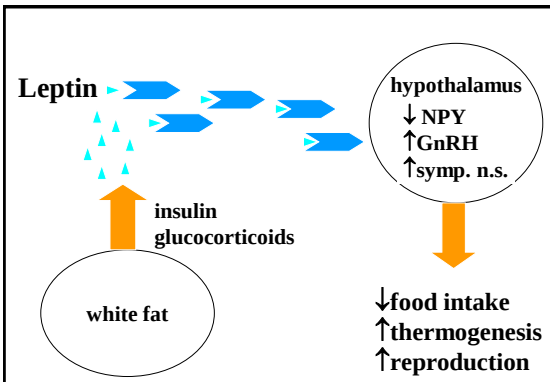
1. **FSH, LH, (oestradiol)**
2. **Prolactin / TFTs**
3. **Testosterone (SHBG)**
4. **AMH.....**
5. **GTT, lipid profile**
6. **Ultrasound scan**
7. **Semen analysis**
8. **Tubal patency assessment**

Causes of Anovulatory Infertility

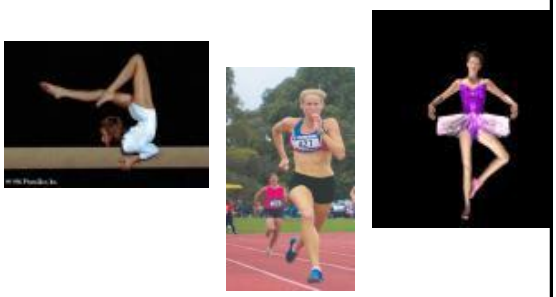
Group I: ***Hypothalamic/ pituitary failure***	**weight loss, systemic illness** **Kallmann's syndrome** **hypogonadotrophic hypogonadism**
	Hyperprolactinaemia **Hypopituitarism**
Group II: ***h/p dysfunction***	**PCOS**
Group III: ***Ovarian failure***	**Premature ovarian failure (POF)** **Resistant ovary syndrome (ROS)**

Hypothalamic causes ***(hypogonadotropic hypogonadism)***	**Weight loss** **Exercise** **Chronic illness** **Psychological distress** **Idiopathic**
Causes of hypothalamic/ pituitary damage	**Tumours (e.g. craniopharyngiomas)** **Cranial irradiation** **Head injuries** **Sarcoidosis** **Tuberculosis**
Systemic causes	**Chronic debilitating illness** **Weight loss**
Endocrine disorders	**Thyroid, Cushing's syndrome …**


Hypothalamic:
⇧ exercise
⇩ weight

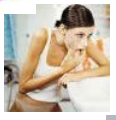

Leptin
hypothalamus
↓ NPY
↑GnRH
↑symp. n.s.
insulin
glucocorticoids
white fat
↓food intake
↑thermogenesis
↑reproduction

Exercise



Eating disorders

The high-intensity exercise may be part of the expression of a severe eating disorder



"Undereating and over-exercising are mutually reinforcing and self-perpetuating behaviours"

Garner et al 1998

Causes of Anovulatory Infertility

Group I: *Hypothalamic/ pituitary failure*	**weight loss, systemic illness Kallmann's syndrome hypogonadotrophic hypogonadism Pulsatile GnRH or FSH/LH (hMG)**
	

Causes of Anovulatory Infertility

Hypothalamic:	**↓FSH, ↓LH, ↓Oestradiol (E2)**
underweight	**n FSH, ↓LH, ↓E2**
Hyperprolactinaemia	**↓FSH, ↓LH, ↓E2**
Ovarian failure / menopause:	**↑↑FSH, ↑LH, ↓E2**
Mid-cycle	**↑FSH, ↑↑LH, ↑E2**
PCOS:	**↓/n FSH, ↑/n LH, ↑/n E2**

Treatment of hyperprolactinaemia

Dopamine agonists:

Restore ovarian function in 85%
85% conceive

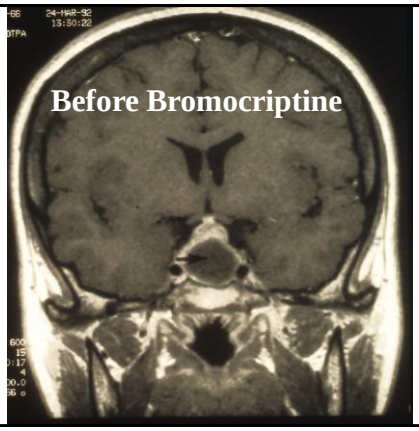
Macroadenomas: 70% shrink
65% ovulate
50% conceive

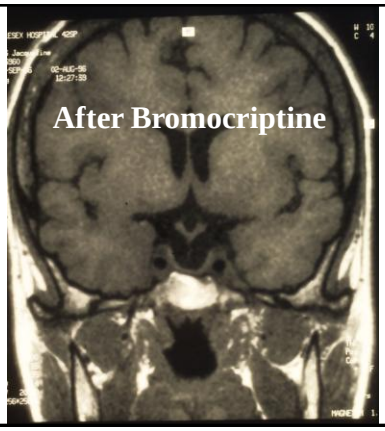
Dopamine agonists

Bromocriptine 2.5 - 20mg daily

Cabergoline 0.25 - 1 mg twice weekly

Quinagolide 25 - 150 mcg daily





Causes of Anovulatory Infertility

Group I: *Hypothalamic/ pituitary failure*	**weight loss, systemic illness** **Kallmann's syndrome** **hypogonadotrophic hypogonadism**
	Hyperprolactinaemia ***Hypopituitarism FSH/LH (hMG)***
Group II: *h/p dysfunction*	**PCOS**
Group III: *Ovarian failure*	**Premature ovarian failure (POF)** **Resistant ovary syndrome (ROS)**

The Rotterdam ESHRE/ASRM Consensus Group Revised 2003 Diagnostic Criteria for PCOS

2 out of 3 criteria required

- **Oligo- and/or anovulation**
- **Hyperandrogenism (clinical and/or biochemical)**
- **Polycystic ovaries**

Exclusion of other causes of menstrual disturbance and hyperandrogenism

Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

PCOS

FSH normal

LH ↑ or normal

Oestradiol (E2): normal or slightly elevated

Testosterone – normal or slightly elevated (0.5 – 3.5 nmol/l – usually < 5.0 nmol/l)

Sex hormone binding globulin (SHBG) (16-119 nmol/l)
Free androgen index: (T x 100) / SHBG

Elevated Luteinising Hormone:

- **not mandatory for diagnosis**
- **most likely to be elevated in slim women**
- **may help predict outcome of fertility therapy:**
  - **Worse outcome after CC if elevated day 8**
  - **Better prognosis for response to ovarian drilling**

Insulin Resistance and PCOS

- **Failure of insulin action at receptor**
- **Selective insulin resistance:**

  Glucose uptake by cells impaired

  Trophic actions of insulin continue

  Insulin augments LH → ↑ testosterone

75 g Glucose Tolerance Test

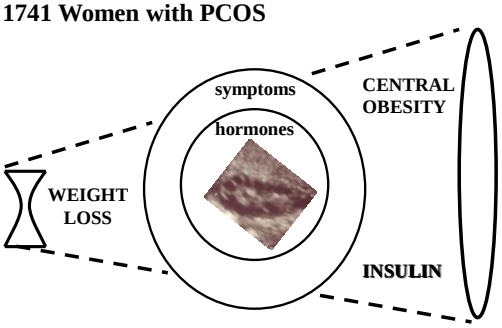
	Diabetes Mellitus	Impaired Glucose Tolerance (IGT)
Fasting glucose (mmol/l)	≥ 7.0	< 7.0
2 hour glucose (mmol/l)	≥ 11.1	≥ 7.8 < 11.1

Insulin Resistance and PCOS

	Ovulatory normal	Ovulatory PCO(S)	Anovulatory PCOS
Testosterone	N	↑	↑
LH	N	↑	↑
Insulin	N	N	↑

Steve Franks

1741 Women with PCOS

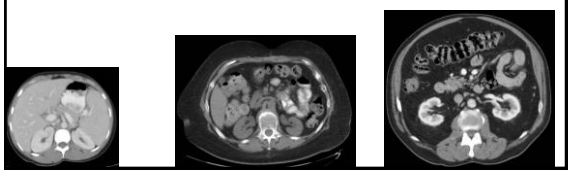


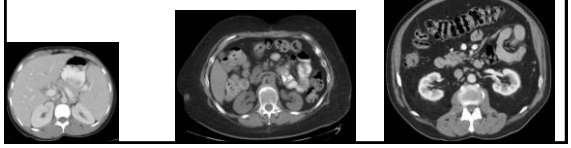
Balen et al Hum Reprod 1995; 10: 2107

Obesity:

BMI – WHO criteria (overweight 25-30, obese > 30 kg/m^2)

Waist Circumference > 80 cm



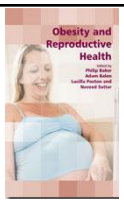


Should there be a cut off weight / BMI before any treatment?

- **Reduced chance conception**
- **Increased risk miscarriage**
- **Increased rate of congenital anomalies**
- **Obstetrical problems (Gest DM, PET, delivery ….)**

Balen, Dresner, Scott & Drife
BMJ 2006;332;434-435

Weight Reduction: RCOG Guidelines, 2007



No evidence for one type of diet

Strategies may include pharmacotherapy (Orlistat, not sibutramine or rimonabant)

Bariatric surgery

Avoid pregnancy during rapid weight loss

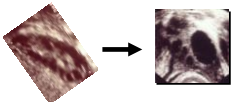
BFS Guidelines, 2007

"Treatment should be deferred until BMI < 35 kg/m^2 although in those with more time (under 37y, normal ovarian reserve) a weight reduction to < 30 kg/m^2 is preferable"

Balen & Anderson, Human Fertility 2007; 10: 195-206

First line therapy for anovulatory PCOS

- **Weight loss**
- **Clomiphene citrate**
- **Gonadotrophins**
- **Ovarian surgery**



?

- ***Insulin sensitisers???***
- ***Aromatase inhibitors***
- ***In vitro maturation of oocytes***

References

Infertility in Practice, *Third Edition* , Balen AH
Informa Healthcare, London, 2008

Clinical Management of Polycystic Ovary Syndrome
Balen AH , G. Conway, R. Homburg, R. Legro
Taylor & Francis, London & New York, 2005, 234 pages. 1st reprint: 2005.

Obesity and Reproductive Health. Edited by P Baker, A Balen, L Poston and Naveed Sattar. Proceedings of 53rd RCOG Study Group, RCOG Press, London 2007.

Polycystic Ovary Syndrome. Edited by A Balen, S Franks and R Homburg. Proceedings of 56th RCOG Study Group, RCOG Press, London 2010.

European Society of Human Reproduction and Embryology

Obesity & Reproduction

Pre-congress course: The Lost Art of Ovulation Induction ROME 2010

Lisa Webber PhD MRCOG

Consultant Gynaecologist, Specialist in Reproductive Medicine

Imperial College Healthcare NHS Trust

esco

Learning Objectives

- Impact of obesity on reproduction
  - fertility, pregnancy, offspring
- Methods of weight reduction
  - lifestyle, pharmacotherapy, bariatric surgery
- Impact of weight loss on reproduction
  - fertility, pregnancy, offspring

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Definition of Obesity

- BMI > 30 kg/m^2 = obese

30.0 - 34.9 kg/m^2	moderate or class I
35.0 - 39.9 kg/m^2	severe or class II
> 40.0 kg/m^2	very severe ("morbid") or class III

- *NB based on Caucasian populations: functional limits lower for Asians*

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Impact of obesity on reproduction
Fertility

- Spontaneous conception rate probably reduced in ovulatory women

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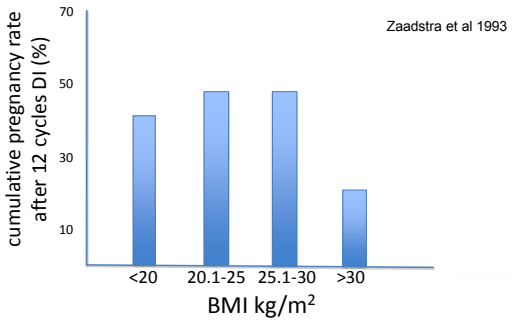
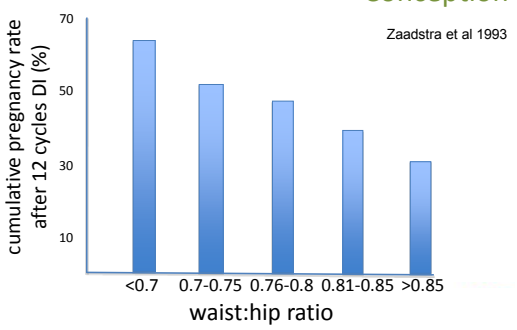
Impact of obesity on reproduction
Conception



Impact of obesity on reproduction
Conception



Impact of obesity on reproduction
Fertility

- Spontaneous conception rate probably reduced in ovulatory women
- Ovulation rate reduced in women with PCOS

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Impact of obesity on reproduction
Ovulation

Women with PCOS vs weight-matched controls:

- insulin resistant (Robinson et al 1993)
  - downstream to insulin receptor (Dunaif et al 1995)
- hyperinsulinaemic
  - increased secretion from β cells (Holte et al 1994)

➔*contributes to obesity*

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Impact of obesity on reproduction
Ovulation

Obesity causes:

- peripheral insulin resistance
- resulting in hyperinsulinaemia

PCOS and obesity have synergistic detrimental effects on insulin metabolism

Insulin is a gonadotroph

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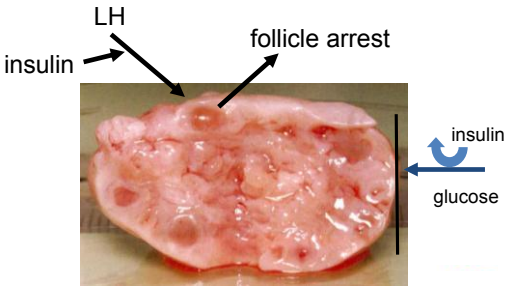
Impact of obesity on reproduction
Ovulation



Willis et al 1996

Impact of obesity on reproduction
Fertility

- Spontaneous conception rate probably reduced in ovulatory women
- Ovulation rate reduced in women with PCOS
- Ovulation induction is less successful

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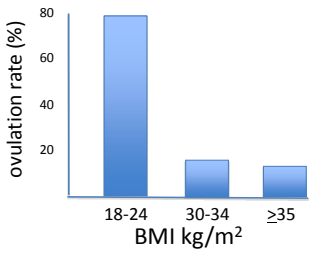
Impact of obesity on reproduction
Ovulation induction: clomifene/FSH

Al-Azemi et al 2004



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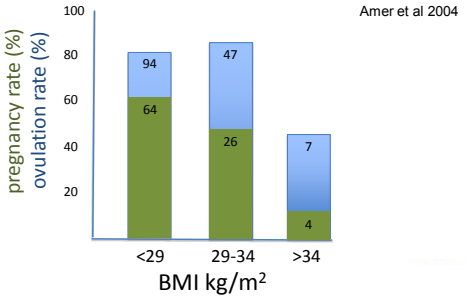
Impact of obesity on reproduction
Ovulation induction: LOD



Impact of obesity on reproduction
Ovulation induction

- Clomifene
  - higher dose
- Gonadotrophins
  - more treatment days
  - higher threshold dose
  - higher total dose
  - higher cost

Balen et al 2006

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Impact of obesity on reproduction
Ovulation induction

- Higher risk of hyperstimulation
- Ultrasonographic monitoring more difficult

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Impact of obesity on reproduction
Fertility

- Spontaneous conception rate probably reduced in ovulatory women
- Ovulation rate reduced in women with PCOS
- Ovulation induction is less successful
- ART outcomes compromised

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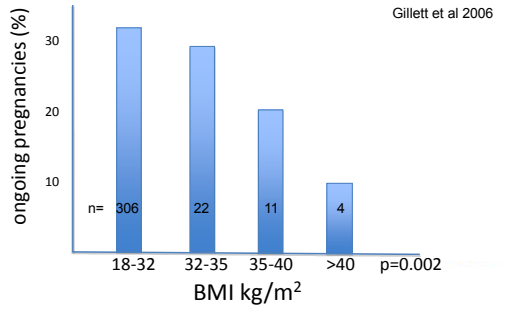
Impact of obesity on reproduction
All fertility treatments



Impact of obesity on reproduction
ART

- Higher doses of gonadotrophin for SO & COH
- Live birth rates after IVF probably reduced
  - oocyte quality?
  - embryo quality?
  - endometrium?

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Impact of obesity on reproduction
ART

Bellver et al 2010

6500 ICSI cycles / 6.4% (419) BMI $\geq$ 30 kg/m^2

= fertilization rate

= embryo quality (day of ET, nº of embryos, blastocyst transfers, embryo Q on D2/3)

🡻 implantation

🡻 pregnancy

🡻 live birth

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Impact of obesity on reproduction
Fertility

- Spontaneous conception rate probably reduced in ovulatory women
- Ovulation rate reduced in women with PCOS
- Ovulation induction is less successful
- ART outcomes compromised

Probability of pregnancy, spontaneous & assisted, is reduced

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Impact of obesity on reproduction
Pregnancy

- gestational diabetes
- gestational hypertension / pre-eclampsia
- miscarriage
- caesarean section
- preterm delivery
- urinary tract & wound infections
- thromoboembolism

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Impact of obesity on reproduction
Pregnancy

Villamor & Cnattingius Lancet 2006

Inter-pregnancy weight gain: >3 kg/m^2

outcome	OR	95%CI
PET	1.78	1.52-2.01
Gestational HPT	1.76	1.39-2.73
GDM	2.09	1.68-2.61
CS	1.32	1.22-1.44
Stillbirth	1.63	1.2-2.21
LGA	1.87	1.72-2.04

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Impact of obesity on reproduction
Pregnancy

Average female height

- UK 1.63m Δ 3kg/m2 – 8kg
- China 1.55m 7.2kg
- India 1.52m 6.9kg

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Impact of obesity on reproduction
Gestational diabetes

16,102 New York women
gestational diabetes rate

- 2.3% control
- 6.3% obese (OR 2.6)
- 9.5% morbidly obese (OR 4.0)

Weiss & Malone 2004

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Impact of obesity on reproduction
Gestational diabetes

Torloni et al 2009

class	risk of GDM: OR	95% CI
underweight	0.75	0.69-0.82
overweight	1.97	1.77-2.19
obese	3.01	2.34-3.87
morbidly obese	5.55	4.27-7.21

Meta-analysis 671 945 women

For every 1kg/m^2 ↑in BMI →prevalence ↑by 0.92%

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Impact of obesity on reproduction
Gestational diabetes

BMI was strongest predictor for GDM treated with insulin

Ogonowski et al 2009

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Impact of obesity on reproduction
Pre-eclampsia

Meta-analysis 1.4 million pregnancies, 13 cohort studies

- risk of PET doubles for each 5-7kg/m^2

O'Brien et al 2003

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Impact of obesity on reproduction
Pre-eclampsia

weight	risk of pre-eclampsia	95% CI
underweight BMI<20	0.6	0.5-0.7
morbidly obese BMI>35	7.2	4.7-11.2

Bhattacharya et al 2007

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Impact of obesity on reproduction
Pre-eclampsia

HAPO Study 2010: associations with BMI

- ↑ pregnancy complications, especially PET
- independent of maternal glycaemia

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Impact of obesity on reproduction
Miscarriage

Metwally et al 2008

Meta-analysis of 16 eligible studies

- Risk of miscarriage increased when BMI >25kg/m^2 (OR 1.67, 95% CI 1.25-2.25)

Lashen et al 2004

- Risk of recurrent miscarriage increased when BMI >30kg/m^2 (OR 3.5, 95% CI 1.03-12.01)

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Impact of obesity on reproduction
Spontaneous labour

Higher 1st trimester BMI

Greater change in BMI during pregnancy:

- lower chance of spontaneous delivery at term
- ↑risk of post-dates pregnancy

Denison et al 2008

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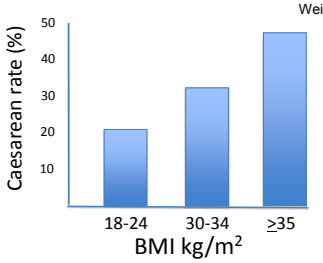
Impact of obesity on reproduction
Caesarean delivery

Weiss & Malone 2004



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Impact of obesity on reproduction
Caesarean delivery

- ↑ induction of labour & ↑ failed induction
- ↑ failure to progress:
  - LGA fetus
  - sub-optimal uterine contractions
  - ↑fat deposition in soft tissues of pelvis→ dystocia during labour

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Impact of obesity on reproduction
Preterm delivery

Aly et al 2009

BMI	% preterm delivery
<30	14.5
30-39	16.7
>40	20.3

Once smoking, ↑bp, diabetes & CS controlled

– no direct link between obesity & prematurity

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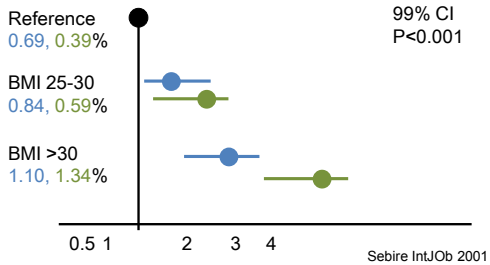
Urinary tract infection
Wound infection



Sebire IntJOb 2001

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Impact of obesity on reproduction
Venous thrombosis

Jacobsen et al 2008 – antenatal VT

BMI	aOR	95% CI
<25kg/m^2, immobilised	1.8	1.3-2.4
≥25kg/m^2, not immobilised	7.7	3.2-19.0
≥25kg/m^2, immobilised	62.3	11.5-337.6

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Impact of obesity on reproduction
Venous thrombosis

Jacobsen et al 2008 – postnatal VT

BMI	aOR	95% CI
<25kg/m^2, immobilised	2.4	1.7-3.3
≥25kg/m^2, not immobilised	10.8	4.0-28.8
≥25kg/m^2, immobilised	40.1	8.0-201.5

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Impact of obesity on reproduction
Maternal mortality

CEMACH 2003-5:

- 28% of mothers who died were obese
- 16-19% of maternity population obese

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Impact of obesity on reproduction
Offspring

- congenital anomaly
- stillbirth
- neonatal death
- vertical transmission

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Impact of obesity on reproduction
Congenital abnormality

Stothard et al 2009

Systematic review & meta-analysis: >30kg/m^2

- Neural tube defects
- Cardiovascular anomalies
- Cleft palate +/- cleft lip
- Anorectal atresia
- Hydrocephaly
- Limb reduction anomalies

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Impact of obesity on reproduction
Stillbirth

Chu et al 2007

Meta-analysis of 9 studies

	OR	95% CI
25-30kg/m2	1.47	1.08-1.94
>30kg/m2	2.07	1.59-2.74

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Impact of obesity on reproduction
Neonatal death

Kristensen et al 2005

- BMI >30kg/m^2 associated with neonatal death
- OR 2.6, 95% CI 1.2-5.8
- No single cause of death
- Risk remained after adjustment for socio-economic factors, HT disorders, DM
  - No association with BMI 25-30kg/m^2

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Impact of obesity on reproduction
Vertical transmission

Sebire et al 2001

287 213 pregnancies – risk of birth weight >90thC

	OR	95% CI
25-30kg/m2	1.57	1.5-1.64
>30kg/m2	2.36	2.23-2.5

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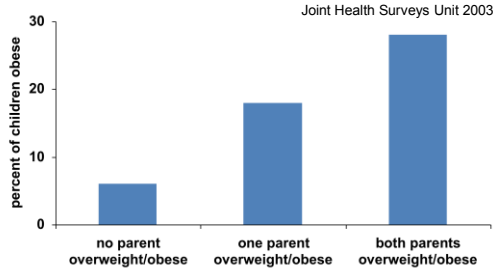
Impact of obesity on reproduction
Vertical transmission

Joint Health Surveys Unit 2003



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Impact of obesity on reproduction
Pregnancy

Increased risks for mother and child

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Lifestyle changes
NICE guidelines

- realistic healthy target weight
- long-term lifestyle changes
- address both diet and activity
- balanced, healthy-eating approach
- practical, safe advice about being more active
- include some behaviour-change techniques
- ongoing support

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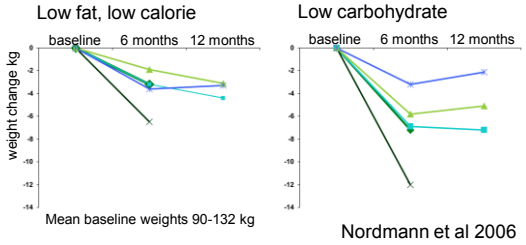
Diet
Low fat or low carb?



Nordmann et al 2006

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Diet
Low fat or low carb?

	Low fat	Low carbohydrate
bp	→	→
triglycerides		↓
HDL-C		↑
total cholesterol	↓	
LDL-C	↓	
drop out rate	43% at 6/12	30% at 6/12

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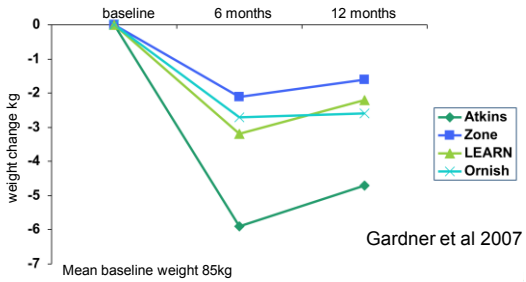
Diet

Low fat or low carb?



Gardner et al 2007

Mean baseline weight 85kg

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Diet

High protein/low carb vs low protein/high carb in PCOS

No difference high in:

- Weight loss
- Menstrual cyclicity & pregnancies
- Insulin resistance
- Total cholesterol, triglyceride & LDL-C
- HDL-C decreased on LP/HC but unchanged on HP/LC

Moran et al 2003

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Lifestyle changes

Exercise

NIH consensus

- ≥30mins moderate intensity activity in total most days
- Compliance better with short bursts of activity and home-based exercise
- Active lifestyle may be more sustainable and therefore more beneficial

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Lifestyle changes
Effectiveness

5% loss of initial weight

(Average height woman 1.63m tall)

starting BMI	5% weight loss	resulting BMI
35	4.7kg	33
40	5.3kg	38

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Lifestyle changes
Effectiveness

Increased ovulation & pregnancy rates in obese anovulatory women with modest weight loss

- >5% weight loss — Kiddy et al 1992
- average weight loss 6.3kg — Clark et al 1995
- improvement in insulin sensitivity & central fat — Huber-Buchholz et al 1999

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Lifestyle changes
Effectiveness

4102 women with 2 single pregnancies Seattle.

- Lost 10lb (4.5kg) between pregnancies decreased risk GDM RR=0.63 (0.38-1.02)

Glazer et al 2004

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Lifestyle changes
Effectiveness

starting BMI	target BMI	target weight loss (%)	target weight loss (kg)
35	30	14.7%	13.3 kg
40	35	12.5%	13.3 kg
40	30	25.4%	26.6 kg

(Average height woman 1.63m tall)

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Weight reduction
Successful strategies

Hill 2006

- low fat, high carbohydrate diet
- self-monitoring of weight, intake, activity
- breakfast
- high levels of activity (60 min/day moderate intensity)

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Causes of obesity
Toxic environment

- Over-abundance of food
- Change in dietary composition: more fat
- Sedentary jobs
- Sedentary recreation
- Transport – more cars

Mark 2008

Imperial College Healthcare NHS Trust

Causes of obesity
Sensitivity

Concept of obesity sensitive & resistant

- Genetic predisposition
  - twin studies
  - leptin – satiety factor, increases energy output
- Metabolic imprinting – maternal
- Compensatory adaptations to weight loss

Mark 2008

Imperial College Healthcare NHS Trust

Causes of obesity
Sensitivity

Women with PCOS have altered

- subjective measures of satiety
- measures of ghrelin homeostasis
- not altered by diet

Moran et al 2004

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Methods of weight reduction
Pharmacotherapy

- orlistat
- ~~rimonabant~~
- ~~sibutramine~~,
- insulin-sensitizing agents?

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Methods of weight reduction
Pharmacotherapy

Orlistat

- blocks GI lipases, reducing absorption of fat by 30%
- <1% of drug absorbed
- Adjunct to low calorie (low fat) diet
- 6-10% weight loss

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Methods of weight reduction
Pharmacotherapy

Metformin

Meta-analysis Nieuwenhuis-Ruifrok et al 2009

- metformin may contribute to weight loss
- ? high dose (>1500mg/day)
- ? treatment >8 weeks
- approx 3% loss of body weight

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Methods of weight reduction
Bariatric surgery

- Laparoscopic adjustable gastric band (LAGB)
- Sleeve gastrectomy
- Roux-en-Y gastric bypass
- Biliary pancreatic diversion with duodenal switch (BPD)

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Methods of weight reduction
Bariatric surgery

	LAGB	gastrectomy	bypass
suitable BMI	35-45	>55	40-55
start of weight loss	6 weeks	immediate	immediate
average weight loss	25%	25-30%	30%
remission of T2DM	60% with weight loss	81% immediate-months	80% immediate

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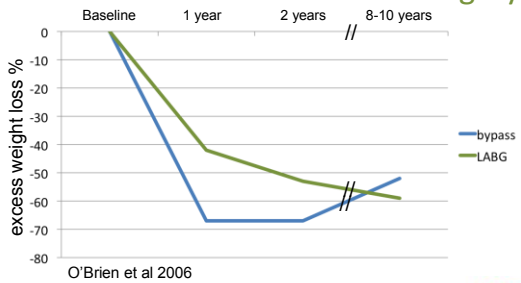
Methods of weight reduction
Bariatric surgery



O'Brien et al 2006

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Reproduction after bariatric surgery
Fertility

- Pregnancy rates higher
- Increased number of pregnancies post-surgery in adolescents compared to national average
- Oral contraceptives possibly less reliable
- PCOS – clinical & biochemical improvement

Maggard et al 2008

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Reproduction after bariatric surgery
Timing of conception

- 10kg gestational weight gain statistically associated with best fetal outcome - based on the whole population, lean and obese
- Delay until after rapid weight loss (i.e. 1 year)
- No conclusive evidence – number of cases small

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Reproduction after bariatric surgery
Pregnancy

Maternal outcomes appear improved

- Reduced gestational diabetes
- Reduced PET/PIH
- No consistent effect on CS rates

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Reproduction after bariatric surgery
Offspring

- Incidence of macrosomia probably reduced
- Inconclusive effects on
  preterm delivery
  low birth weight
  miscarriage
- ↑ neural tube defects – in non-compliant mothers Maggard et al 2008

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Reproduction after bariatric surgery
Offspring

BPD procedure	born before surgery	born after surgery
birth weight	3.3 +/- 0.1kg	2.9 +/- 0.1kg
macrosomia	14.8%	1.8%
severe obesity	35%	11%
HOMA	4.8 +/- 0.5	3.4 +/- 0.3
Cholesterol:HDL-C	3.4 +/- 0.18	2.96 +/- 0.11
CRP	2.0 +/- 0.34 mcg/ml	0.88 +/- 0.17 mcg/ml
leptin	19.7 +/- 2.5 ng/ml	11.5 +/- 1.5 ng/ml
ghrelin	1.03 +/- 0.06 ng/ml	1.28 +/- 0.06 ng/ml

Smith et al 2009

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Reproduction after bariatric surgery
Complications

Maggard et al 2008

20 reports of complications

- 14 bowel obstructions (11 internal hernias)
- 1 gastric ulcer
- 4 band events
- 1 staple-line stricture

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Reproduction after bariatric surgery
Complications

- Presentation: non-specific abdominal pain from 13-37/40
- Delays to therapeutic intervention
- 5 perinatal deaths
- 3 maternal deaths

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Obesity & Reproduction

- Obesity impacts negatively on all aspects of reproduction
- Risks to mother & fetus probably most significant when BMI > 35 kg/m^2
  strongest argument for withholding fertility treatment
- Limited evidence that weight loss improves reproductive outcomes

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The barriers to weight loss

- Women present with delayed conception not obesity – the fat friend
- Inaccurate self-categorisation of weight
- Lifetime of diets
- Target BMI/time frame may be unrealistic
- Compensatory adaptations to weight loss

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Methods of weight loss

- Bariatric surgery only effective method for substantial longterm weight reduction
- Limited safety data for mother & child
- Modest weight loss also of reproductive (metabolic) benefit

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First-line therapy

Roy Homburg FRCOG

Maccabi Medical Services and Barzili Medical Centre, Ashkelon, Israel
and Homerton University Hospital, London

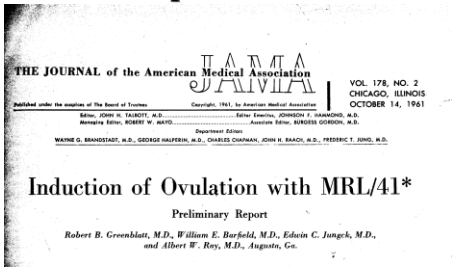
ESHRE, Rome, 2010

Learning objectives

At the conclusion of this presentation, the participants should be able to:

- **Recognise the pros and cons of clomiphene treatment.**
- **Contrast the modes of action of clomiphene and aromatase inhibitors.**
- **To compare the results of these two modes of treatment for WHO II anovulation.**

Clomiphene citrate



THE JOURNAL of the American Medical Association JAMA

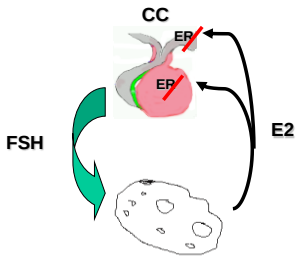
VOL. 178, NO. 2
CHICAGO, ILLINOIS
OCTOBER 14, 1961

Induction of Ovulation with MRL/41*

Preliminary Report

Robert B. Greenblatt, M.D., William E. Barfield, M.D., Edwin C. Jungck, M.D., and Albert W. Roy, M.D., Augusta, Ga.

Clomiphene Citrate Treatment



Day 5

Adapted from Casper & Mitwally with permission

Clomifene

Homburg, Hum Reprod, 2005

n = 5268 patients

Ovulation - 3858 (73%)

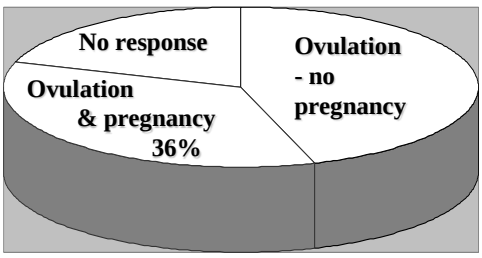
Pregnancies - 1909 (36%)

Miscarriage - 20%

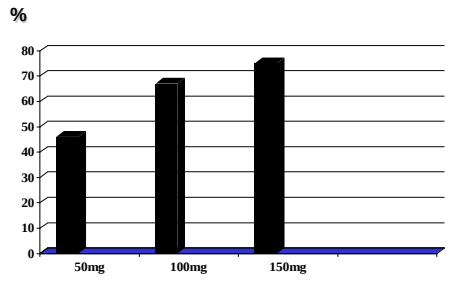
Multiple pregnancy rate - 8%

Single live-birth rate – 25%

Response to clomiphene



Response (ovulation) by dose -Metanalysis of 13 reports



Rostami-Hodjegan et al, 2004

Clomiphene Citrate

Starting…

- **on day 2,3,4 or 5 makes no difference (Wu, 1989).**
- **dose 50 mg/day, rising by 50mg if no ovulation.**
- **even without withdrawal bleeding (Farhi, 2009).**

Reasons for Clomiphene Failure

Failure to ovulate

- **FAI**
- **BMI**
- **LH**
- **Insulin**

Ovulation but no conception

Anti-estrogen effects

- **cervical mucus**
- **endometrium**

- **High LH**

Anti-estrogen effect on endometrium

- **Endometrial thinning in 15-50%**

  (Gonen &Casper, 1990)
- **Causes ER downregulation and depletion.**
- **Suppresses pinopode formation** ***(Creus et al, 2003)***
- **No pregnancies when endometrial thickness at midcycle < 7mm**
- **Not dose related and recurs in repeat cycles**

(Homburg et al, 1999)

Effect of CC on endometrial proliferation – comparative study

Multiple examinations (n=446) of E2 & endometrial thickness throughout the follicular phases

- **CC** **n=110, 130 cycles**
- **FSH** **n=19, 37 cycles**
- **Natural cycles** **n=43, 43 cycles**

Avnon, Homburg, 1994

Mean E2 & endometrial thickness throughout follicular phase

	E2(pmol/l)	ED (mm)
Normal cycles	616	7.64
FSH	574	7.99
CC	1480	6.98
		(p<0.0001)

No correlation in CC cycles.
Good correlation in natural and FSH cycles.

CC and endometrium

- **Doses of 50,75,100 or 150mg**
  - no significant difference in endometrial thickness. Not dose dependent.
- **Endometrial suppression recurred in repeat cycles in the same woman.**
- **No pregnancies when endometrial thickness < 8mm.**

CC and the endometrium

- **Endometrial biopsies 10 days after ovulation**
- **CC patients (n=149)**
- **Normally ovulating women (n=240)**

Homburg et al, 2006

CC and the endometrium

	CC (n=149)	Controls (n=240)
In phase	126	233
Out of phase	23 (16%)*	7 (3%)*

*p<0.0001

Clomiphene Citrate

Stopping…

- **when 6 ovulatory cycles fail to yield a pregnancy.**
- **when no ovulation with 150mg/day.**
- **if endometrial thickness <7mm at ovulation.**

Clomiphene questions

- **Spelling – clomiphene or clomifene?**
- **? Give hCG at mid-cycle?**
- **? Monitor CC cycles with ultrasound?**
- **? Is CC still the best first-line treatment?**

To give hCG in CC cycles?

Agrawal & Buyalos, 1995

" Routine addition of hCG at mid-cycle does not improve conception rates"

Kosmas et al, 2007

No significant difference

……but helps in timing of intercourse or IUI.

Should we monitor clomiphene cycles with ultrasound?

Konig, Homburg et al, ESHRE, 2009

3 cycles of CC

- **Group 1: N=105,**
  with U/S monitoring + hCG
- **Group 2: N=150,**
  no U/S monitoring, no hCG

Should we monitor clomiphene cycles with ultrasound?

Konig, Homburg et al, ESHRE, 2009

With U/S + hCG		**No U/S or hCG**
48%	**Cumulative conception rate**	**34.7%**
35.6%	**Deliveries**	**26.7%**
0	**Multiple pregnancies**	**1**

Improvement of results with CC

- **Monitor for anti-oestrogen effects**
- **Decrease insulin**
  - **weight loss**
  - **insulin lowering medications**
- **Adjuvants**
- **Decrease LH**
  - **progesterone pre-treatment**
  - **LOD**

Adjuvants to CC –for ovulation but no pregnancy

- Ethinyl estradiol
- hCG

Adjuvants to CC –for CC resistance

- Dexamethasone
- Metformin
- Micronised progesterone

Progesterone pre-treatment

- n=10, CC resistant, anovulatory PCOS
- Given micronised progesterone, 50mg/d for five days.
- Decreased frequency, increased amplitude of LH pulses.
- 7/10 reduced LH concentrations significantly and all 7 ovulated on CC.
- 3/7 conceived in a single cycle of CC.

Homburg et al, Hum Reprod, 1988

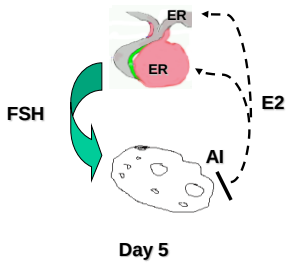
Alternative to CC

- **Aromatase inhibitors ?**

Aromatase Inhibitors (Letrozole, Anastrozole)

- **Non-steroidal. Block conversion of androstendione to estrogens.**
- **Used for treatment of breast Ca in postmenopausal women.**
- **Letrozole dose 2.5 – 5 mg/day, almost free of side effects.**

Aromatase Inhibitor Treatment - day 3-7 of cycle



Day 5

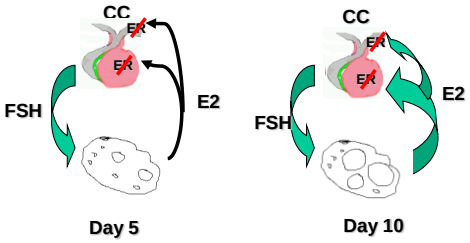
Casper & Mitwally

Aromatase Inhibitors - Theoretical Advantages

Do not block estrogen receptors –

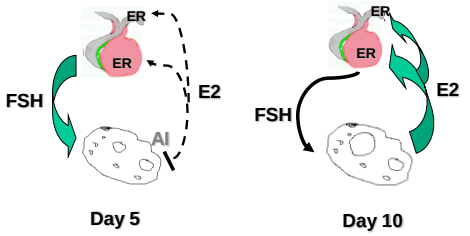
- **No detrimental effect on endometrium or cervical mucus.**
- **Negative feedback mechanism not turned off – less chance of multiple follicular development.**

Clomiphene Citrate Treatment



Casper & Mitwally

Aromatase Inhibitor Treatment



Casper & Mitwally

Aromatase inhibitors -questions

- Do they work?
- Better than CC for first-line treatment?
- Useful in CC resistance?
- Letrozole or anastrozole?
- Safety?

Aromatase inhibitors for PCOS – RCT's vs CC

CC 100mg vs letrozole 2.5mg

Atay et al, 2006 **Superiority of letrozole**

Bayar et al, 2006 **Equivalence**

CC 100mg vs Letrozole, 5mg

Badawy et al, 2007

Pregnancy/cycle – CC 17.9%,

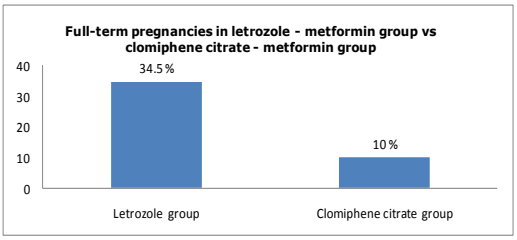
- letrozole 15.1% (NS)

Aromatase inhibitors vs CC

Polyzos et al, Fertil Steril, 2008

- Meta-analysis, 4 RCT's
- Clear superiority of aromatase inhibitors in pregnancy rates (OR 2.0) and deliveries (OR 2.4).

Metformin + Letrozole (2.5mg) or metformin + CC (100mg)



n-=59 **Sohrabvand et al, 2006**

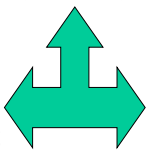
Letrozole induction of ovulation in women with CC–resistant PCOS… (Elnashar et al, 2006)

- **Ovulation- 24/44 cases (54.6%)**
- **Clinical pregnancy- 6/44 cases (25%of ovulators)**

Resistance to CC 100mg

Begum et al, 2009

N=64 PCOS resistant to 100mg CC



Letrozole 7.5mg **CC 150mg**

Resistance to CC 100mg

	Letrozole	CC 150mg
Ovulation	20 (62.5%)	12 (37.50%)
E2 dhCG (pg/mL)	448	817.75
Endometrial thickness on dhCG	10.37 mm	9.03 mm
Pregnancies	13 (40.6%)	6 (18.75%)

Begum et al, 2009

Anastrozole

Wu et al, 2007, n = 33

Anastozole (1mg/day) vs CC (100mg/day)

Anastrozole produced fewer follicles, thicker endometrium. May be used successfully for ovulation induction.

Al-Omari et al, 2004, n = 40

Anastrozole (1mg) vs Letrozole (2.5mg)

Letrozole superior in ovulation and pregnancy rates.

Outcome of babies following treatment with letrozole

Biljan et al, 2005

- N=110 singleton and 20 twin pregnancies from letrozole +/- gonadotrophins compared with 36,050 'low risk' babies

- All malformations – no difference
- Locomotor malformations
  Cardiac anomalies
  - higher in letrozole group

Health Canada Endorsed Important Safety Information on Femara* (letrozole)
~November17,2005
Dear Health Care Professional:
Subject: Contraindication of Femara* (letrozole) in premenopausal women Following discussions with Health Canada, Novartis is advising you of concerns about the use of the aromatase inhibitor Femara* (letrozole) for the purpose of ovulation induction in the treatment of infertility. Novartis is aware that Femara* has been or is being used to treat infertility even though statements in the Canadian Product Monographs warn physicians about potential embryo- and fetotoxicity with or without teratogenicity. There have been post-market reports of congenital anomalies in infants of mothers exposed to Femara* for the treatment of infertility. **Femara* (letrozole) is contraindicated in women with premenopausal endocrine status, in pregnancy, and/or lactation due to the potential for maternal and fetal toxicity and fetal malformations.**

Outcome – Letrozole vs CC

- **Tulandi et al, 2006 n=911 newborns in 5 centers**

	CC	Letrozole
Pregnancies	**397**	**514**
Congenital malformations + Chromosomal abnormalities	**19 (4.8%)**	**14 (2.4%)**

Outcome – Letrozole vs CC

- **Tulandi et al, 2006 n=911 newborns in 5 centers**

	CC	Letrozole
Pregnancies	**397**	**514**
Major malformations	**12 (3%)**	**6 (1.2%)**
VSD	**4 (1.0%)**	**1 (0.2%)**
Total cardiac anomalies	**1.8%**	**0.2%**

Aromatase inhibitors

Aghssa et al, 2007 (PCOS, eds Allahbadia,Agrawal)

- Letrozole 2.5-10mg/day, n=1102
- Pregnancies 368 (33.4%)
  - miscarriages 99 (27.3%)
  - twins 2 (0.5%)
  - fetal anomalies 1 (0.2%)

Summary

- Clomiphene citrate (CC) remains the first-line treatment for WHO II anovulation.
- With CC, the singleton live-birth rate is impeded by anti-estrogen effects and high miscarriage and multiple pregnancy rates.

Summary

- Aromatase inhibitors have no adverse effects on estrogen receptors. In comparison with CC for ovulation induction, they should produce a higher singleton live birth rate.
- Possible teratogenicity with aromatase inhibitors is unproven but their use for ovulation induction is still off-label in most countries.

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Erasmus MC
Universitair Medisch Centrum Rotterdam

ESHRE Pre-Congress Course 5
The Lost Art of Ovulation Induction

Algorithms for Predicting Response to Ovulation Induction

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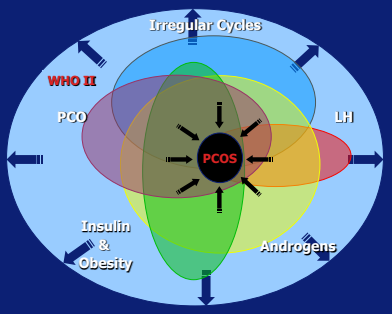
WHO II Anovulatory Infertility: Paradigm Shift

(Laven et al., Obstet Gynecol Survey, 2002)



Problems with PCOS

- Heterogeneity
- Phenotype assessment
- Male Phenotype
- Phenotype in time
- Phenotype alterations
- Phenotype and Fertility

Consensus !!!!

Patient Tailored Ovulation Induction

(van Santbrink et al., Trends in Endocrinol & Metabolism 2005)

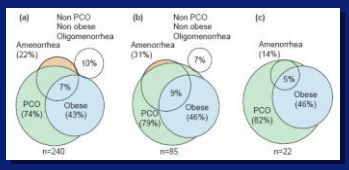


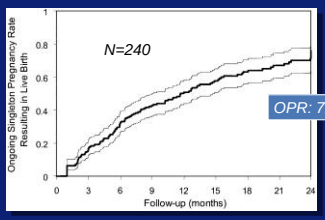
Table 1. Pregnancy rates of 240 normogonadotrophic anovulatory infertility patients (WHO 2) treated subsequently with CC, FSH and IVF

	Cumulative pregnancy rate	Cumulative singleton live birth rate
CC	47%	37%
FSH	58%[a]	43%
CC + FSH	78%	71%
IVF	68%	28%
CC + FSH + IVF	83%	77%

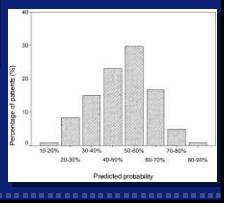
[a]Cumulative *ongoing* pregnancy rate.

Live Birth rate in WHO 2 and PCOS

(Eijkemans et al. Human Reprod, 2003)

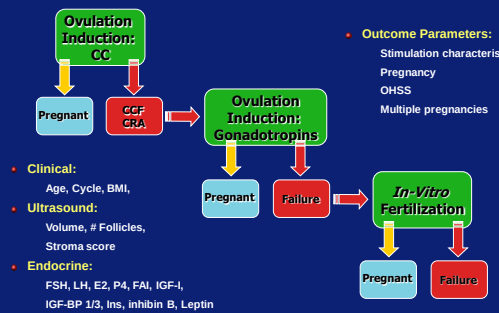


OPR: 71% after 2 yrs follow-up



WHO II Anovulatory Infertility: Ovulation Induction

(The Rotterdam Approach)



- Outcome Parameters:
  - Stimulation characteristics
  - Pregnancy
  - OHSS
  - Multiple pregnancies

- Clinical:
  - Age, Cycle, BMI,
- Ultrasound:
  - Volume, # Follicles, Stroma score
- Endocrine:
  - FSH, LH, E2, P4, FAI, IGF-I, IGF-BP 1/3, Ins, inhibin B, Leptin

Predictors of Response in WHO II

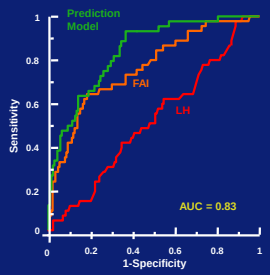
(Imani et al., JCEM 1998)

Predictors of Ovulation after CC (MVA)

- Cycle History
- Free Androgen Index (FAI)
- BMI
- Ovarian Volume

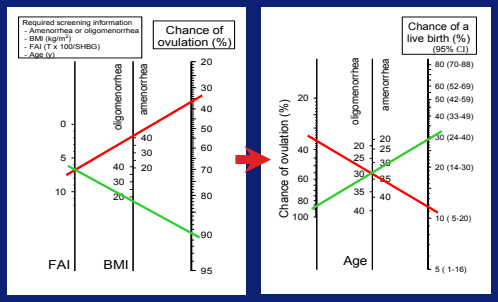
Predictors of Conception (MVA)

- Age
- Cycle history



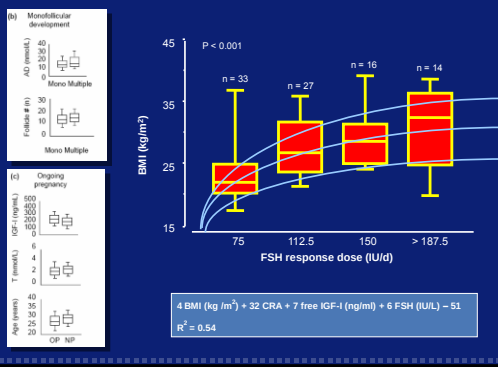
Prediction of Ovulation Induction Outcome

(Imani et al., Fertil Steril, 2002)



Prediction of Ovulation Induction Outcome

(Mulders et al., Reprod Biomed Online, 2003)



4 BMI (kg /m²) + 32 CRA + 7 free IGF-I (ng/ml) + 6 FSH (IU/L) – 51

R^2 = 0.54

Validation of FSH prediction Models

(van de Wely et al. Fertil Steril, 2006)

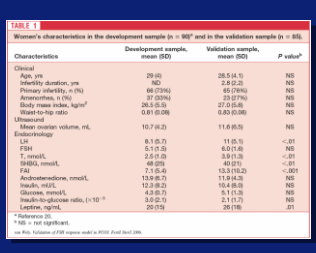


TABLE 1

Women's characteristics in the development sample (n = 90)* and in the validation sample (n = 85).

Characteristics	Development sample, mean (SD)	Validation sample, mean (SD)	P value†
Clinical			
Age, yrs	29 (4)	28.5 (4.1)	NS
Infertility duration, yrs	ND	2.8 (2.2)	NS
Primary infertility, n (%)	66 (73%)	65 (76%)	NS
Amenorrhea, n (%)	37 (33%)	23 (27%)	NS
Body mass index, kg/m²	26.5 (5.0)	27.0 (5.8)	NS
Waist-to-hip ratio	0.81 (0.09)	0.83 (0.08)	NS
Ultrasound			
Mean ovarian volume, mL	10.7 (4.2)	11.6 (6.5)	NS
Endocrinology			
LH	8.1 (5.7)	11 (5.1)	<.01
FSH	5.1 (1.5)	6.0 (1.6)	NS
T, nmol/L	2.6 (1.0)	3.9 (1.3)	<.01
SHBG, nmol/L	48 (25)	40 (21)	<.01
FAI	7.1 (5.4)	13.3 (10.2)	<.001
Androstenedione, nmol/L	13.9 (6.7)	11.9 (4.3)	NS
Insulin, mU/L	12.3 (8.2)	10.4 (6.0)	NS
Glucose, mmol/L	4.3 (0.7)	5.1 (1.3)	NS
Insulin-to-glucose ratio, (×10⁻³	3.0 (2.1)	2.1 (1.7)	NS
Leptine, ng/mL	20 (15)	26 (18)	.01

* Reference 20.
† NS = not significant.

van Wely. Validation of FSH response model in PCOS. Fertil Steril 2006.

TABLE 2

FSH response dose in the development sample and the validation sample.

Response dose	Development sample, n (%)	Validation sample, n (%)
75 IU/d	33 (37)	26 (31)
112.5 IU/d	27 (30)	26 (31)
150 IU/d	16 (18)	27 (32)
187.5 IU/d	10 (11)	6 (7)
>187.5 IU/d	4 (4)	—

van Wely. Validation of FSH response model in PCOS. Fertil Steril 2006.

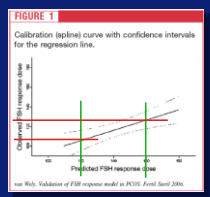


FIGURE 1

Calibration (spline) curve with confidence intervals for the regression line.

van Wely. Validation of FSH response model in PCOS. Fertil Steril 2006.

AMH and Ovulation Induction Outcome

(El-Halawaty et al. RBM Online, 2007)

Table 2. Comparison between women with PCOS who responded to clomiphene citrate and those who did not respond.

Parameter	Responsive cases (n = 17)	Non-responsive cases (n = 51)	P-value
Age (years)	28.82 ± 3.80	29.55 ± 4.40	NS
Duration of infertility (years)	4.71 ± 2.66	5.39 ± 3.12	NS
Body weight (kg)	101.94 ± 9.85	95.95 ± 14.61	NS
Height (m)	1.64 ± 0.06	1.64 ± 0.05	NS
BMI (kg/m²)	38.25 ± 4.77	35.58 ± 5.75	NS
LH (mIU/ml)	10.38 ± 2.08	10.03 ± 2.41	NS
FSH (mIU/ml)	5.94 ± 4.22	4.53 ± 1.58	NS
Fasting glucose (mg/dl)	85.29 ± 17.01	88.18 ± 24.39	NS
Fasting insulin (µIU/ml)	10.95 ± 10.52	8.63 ± 3.14	NS
HOMA IR	2.36 ± 1.67	1.89 ± 1.33	NS
AMH (ng/ml)	4.38 ± 3.30	1.89 ± 1.33	0.0001
Estradiol (pg/ml)	181.06 ± 60.22	Not measured*	–
Follicles >18 mm on day of HCG (n)	1.65 ± 0.49	0	–
Endometrial thickness (mm)	8.35 ± 0.70	5.54 ± 0.74	0.0001
Progesterone (ng/ml)	11.76 ± 2.02	1.55 ± 1.62	<0.0001

All values are mean ± standard deviation; AMH = anti-Müllerian hormone; BMI = body mass index; HCG = human chorionic gonadotrophin; HOMA IR = Homeostasis Assessment Model insulin resistance; NS = not statistically significant.
*Estradiol was not measured as no ovarian response was detected by ultrasound.

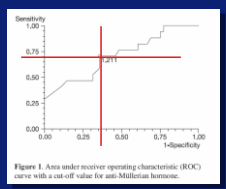
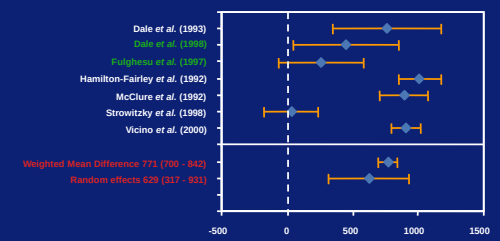


Figure 1. Area under receiver operating characteristic (ROC) curve with a cut-off value for anti-Müllerian hormone.

Monitoring: Patient Related Factors (BMI)

(Mulders et al., Human Reprod Update, 2003)

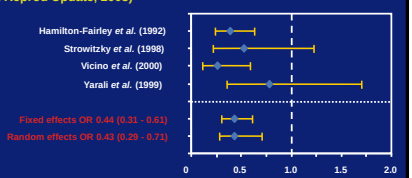
Total IU of FSH Obese vs Non-Obese



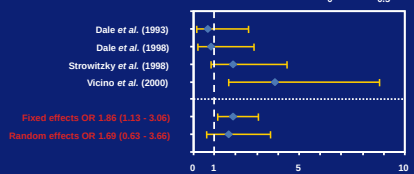
Monitoring: Patient Related Factors (BMI)

(Mulders et al., Human Reprod Update, 2003)

Ovulation

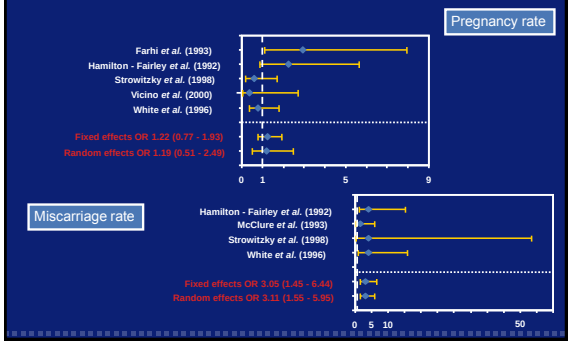


Cancellation



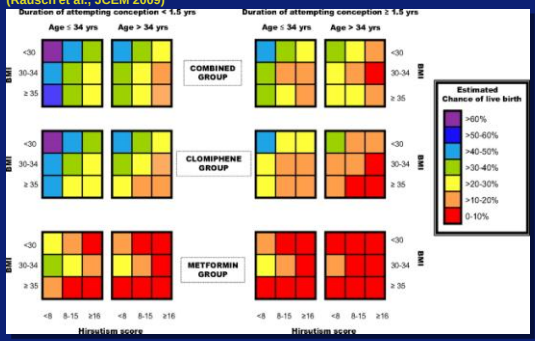
Monitoring: Patient Related Factors (BMI)

(Mulders et al., Human Reprod Update, 2003)



Predictors of Pregnancy in women with PCOS

(Rausch et al., JCEM 2009)



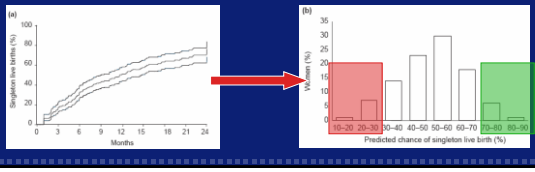
Predictors of Ovulation Induction in PCOS

(van Santbrink et al., Best Practive & Research in Endo Metab: 2006)

Table 2. Initial screening characteristics predicting treatment outcome in normogonadotropic anovulatory infertility[a]

	Clomiphene citrate		FSH			CC followed by FSH	IVF
	Ovulation	Pregnancy in ovulatory patients	FSH threshold	Pregnancy	Multifollicular growth	Clinical outcome[b]	Clinical outcome[c]
Age		Neg		Neg		Neg	Neg
Amenorrhea	Neg	Pos					
BMI	Neg		Pos			Neg	Neg
CC response			Pos		Pos		
Hyperandrogenism	Neg		Pos	Neg	Pos		
Insulin resistance	Neg					Neg	
References	[21,22]	[23,24]	[26]	[25]	[25]	[29,32]	[33]

[a]Pos/Neg, positive/negative correlation between patient characteristics and treatment outcome.
[b]Amount of FSH administered, cancellation, ovulation, pregnancy, miscarriage rate.
[c]Amount of FSH administered, cancellation.



Practice Points & THM

Erasmus MC Teaching

- Predicting Success in terms of Ovarian response, Pregnancy rates and Live Birth Rate is possible
- Predictors of response on CC OI are BMI, Cycle history, Hyperandrogenism and Ovarian Volume
- Predictors of response on FSH OI are BMI, previous response to CC, initial follicular early phase FSH levels and IGF-I levels
- Predictors of Pregnancy, miscarriage and Live Birth rates are different from OI response predictors and are generally Age, Cycle history and Free Androgen Levels.
- LH levels do neither predict outcome nor pregnancy and miscarriage rates
- OI protocols should aim at identifying those women with a favorable response as well as offering each women the best treatment option !!!!

Gonadotrophin protocols

Hugues JN M.D, Ph.D

Reproductive Medicine Unit; University Paris XIII, France

Consultant : Merck-Serono

ESHRE 2010

Pre-congress course « The lost Art of ovulation induction »

The Special Interest Group Reproductive Endocrinology

Learning objectives

At the conclusion of this presentation, participants should be able to :

1. Classify patients according to the ovulatory status
2. Manage ovulation induction protocols accordingly
3. Predict the ovarian sensitivity to FSH
4. Adjust the starting dose to patients 'characteristics
5. Comply to exclusion criteria to prevent from the risk of multiple pregnancy

Main issues

Ovulation regimens

- for women with chronic anovulation
- for normo-ovulatory women (prior to IUI)
- for women with short follicular phase

Objectives of ovarian stimulation

- **To get a singleton live birth**

Cumulative pregnancy rate : 71% (Eijkemans et al. 2003)

- **To reduce the risk of high order multiple pregnancies**

~ 2/3 of twins and ~ 1/2 of triplets from cycles without ART

Critical issue: the choice of stimulation regimen for women with chronic anovulation

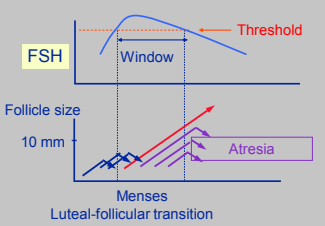
Concepts derived from Gonadotrophin Therapy

J.B. Brown,1978 & D Baird, 1989

« The FSH threshold and window » concepts

« FSH requirement operates in a very narrow range according to the follicle sensitivity to FSH »

A small therapeutic window

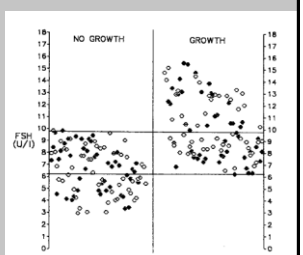


FSH values (U/L) associated with follicle growth in PCOS

Van Weissenbruch et al 1993

- IV pulsatile FSH administration
- A large overlap between individuals
- Demonstrated inter - patient variability in the stable FSH threshold

Key recommendations for ovulation induction



« 30% over the threshold : Risk of multifoll development »

« FSH requirement in late follicular phase is reduced »

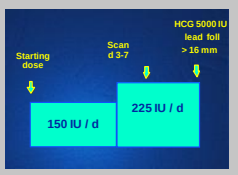
→ **Step protocols**

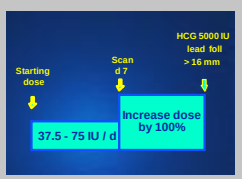
Step up Protocols

" Conventional dose protocol "

High (150 IU/d) FSH dose

increased by 75 IU every 3-7 days





" Low dose protocol "

Low (37.5 - 75 IU/d) FSH dose

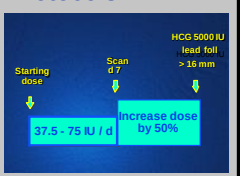
increased by 100 % every 7 days

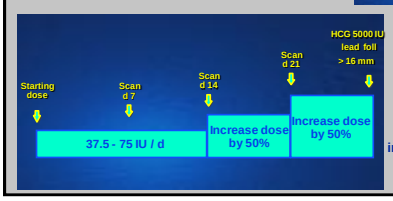
Low dose Step up Protocols

" Low dose protocol "

Low (37.5 - 75 IU/d) FSH dose

increased by 50 % every 7 days





" Chronic Low dose protocol "

Low (37.5 - 75 IU/d) FSH dose

increased by 50% after 14 days

Overall results with 75 IU for 14 days

Homburg, 2005

Table IV. Results of treatment of clomiphene-resistant patients with low dose, step-up FSH

No. of patients	841
No. of cycles	1556
Pregnancies (% patients)	320 (38%)
Fecundity/cycle	20%
Uni-ovulation	70%
OHSS	0.14%
Multiple pregnancies	5.7%

Updated from Homburg and Howles (1999).

A starting dose of 75 IU for 14 days has been demonstrated to be safe and effective in PCOS patients

Low Dose Step - up protocols

	Ovul Cycle (%)	Uni-Ov / Ovul (%) Uni-Ov / Cycle (%)
Polson 1987	23/33 (70)	18/33 (78) (55)
Buvat 1989	33/44 (75)	26/44 (79) (59)
Sagle 1991	27/35 (77)	19/35 (70) (54)
Shoham 1991	9/9 (100)	6/9 (66) (66)
Hamilton-Fairley 1991	289/401 (72)	219/401 (76) (55)
Balasch 1996	419/534 (78)	198/534 (48) (37)
White 1996	305/429 (71)	256/429 (84) (59)
Loumaye 1996	333/513 (65)	279/513 (84) (54)
Total	1438/1998 (72)	1021/1998 (71) (51)

Even with careful step protocols, only half of ovulatory cycles are mono-follicular

Comparative studies : starting dose

Conventional dose (150 IU/d) vs low dose (75 IU/d)

	Buvat et al. 1989		Brzyski et al. 1995	
	Conventional 150 IU	Low dose 75 IU	Conventional 150 IU	Low dose 75 IU
Patients	17	23	17	17
Cycles	21	44	16	16
Duration	10.6 ± 2.9	15.5 ± 5.8 *	7.5 ± 0.2	14.1 ± 1.2 *
FSH amp	22.1 ± 7.2	18.7 ± 9.1	17.5 ± 2.8	12.4 ± 0.8
Foll > 10 mm	3.7 ± 3.7	1.6 ± 0.9 *	5.4 ± 0.4	2.7 ± 0.6 *
Mono-foll Cycles (%)	9.5	59 *	NA	NA

With low FSH dose, longer duration but reduction by 50% in the nb of follicles

Comparative Studies : duration of the first step

(Homburg et al. 1995 & Hedon et al. 1998)

	Low dose (1st step : 7d)				C L D (1st step : 14 d)			
	Cycles	Preg.	Mult	OHSS	Cycles	Preg.	Mult.	OHSS
Homburg 1995	48	6	2	5	59	10	0	0
Hedon 1998	46	9	2	1	42	14	2	1
Total	94	15 (16%)	4 (27%)	6 (6.3%)	101	24 (24%)	2 (8.3%)	1 (0.9%)

First step of 14 days : lower incidence of multiple pregnancies and OHSS

Low dose (50 IU/d) Step-Up Regimen

Increments after 7 days

Leader et al. 2006

	25IU (n=80)	50IU (n=78)	p
Ovulation Rate	81.3 %	60.3 %	0.009
Monofollicular growth	41.3 %	21.8 %	0.010
Total FSH dose	887 IU	984 IU	0.013
Treatment duration	14.0 d	13.4 d	NS
Cancellations	5.0 %	20.5 %	0.004
Ongoing pregnancy	20 %	12.8 %	NS

With 50% dose increment, monofollicular development is higher

Recommendations for step-up regimens

- Duration of first step:14 days safer than 7 days
- Dose increment : 50% is safer than 100%

« CLD : the safest step-up regimen »

- Starting dose : 37.5 to 75 IU / day

according to patients' characteristics

objective : to achieve FSH threshold within 14 days

and with no need for FSH dose increment

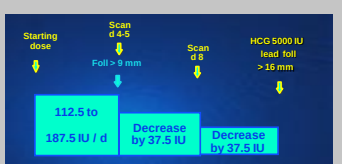
Step down Protocols

" Step - down protocol "

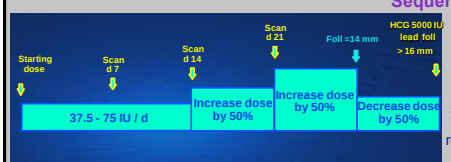
Loading FSH dose

(112.5-187.5 0 IU/d)

decreased by 37.5 IU every 3-5 d



" Sequential protocol "



FSH threshold dose decreased by 50% when leading follicle reaches 14 mm diam

Step up versus Step down: randomized studies

	Van Santbrink et al, 1997			Christin-M & Hugues, 2003		
	Step-up (19)	Step-down (18)	p	Step-up (85)	Step-down (72)	p
Median duration of treatment (day)	18	9	0.003	15	10	<.001
Monofollicular growth	56%	88%	0.04	68%	32%	<.0001
Ovulation rate	84%	89%	NS	70%	61%	< 0.02

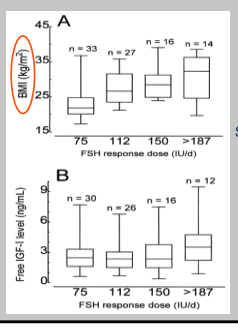
Reasons for discrepancies

- Patients characteristics: BMI - Cycle duration - PCOS features
- Dose regimens: FSH starting dose & FSH dose adjustment

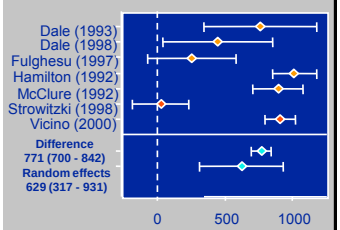
In clinical practice, step up protocol is a preferred option

Predictive factors : threshold of FSH response

Imani et al., 2002



Mulders et al., 2003



BMI : the most significant predictive factor

of the FSH threshold dose

Predictive factors : success of ovarian response to FSH

Mulders et al., 2003 154 women Step-up (1st cycle) - step down

Predictors of multi-follicular development

Androstenedione & AFC

Mulders et al., 2003 Meta-analysis of 13 studies

Predictors of cycle outcome :

Obesity & insulin resistance

Ovarian stimulation for chronic anovulation

Conclusions

Step protocols are effective but safety still questionable.

First line regimen : CLD step-up regimen
Second line regimen: Step down regimen with an adjusted starting dose

A decremental dose regimen for FSH administration must be applied in patients at risk of overstimulation.

Compliance to guidelines: Individual adjustment of the starting dose according to patient's characteristics (BMI - AFC - Hyperandrogenism)

Conclusions

First line therapy

CC is superior to metformin
the efficacy of the association CC - Metformin should be better assessed

Second line therapy

a « dose - finding » chronic low dose step - up protocol
the FSH threshold dose is determined

Step - down protocol	Low dose step-up protocol
Starting dose 37.5 IU above the effective dose.	Starting dose: the effective dose Dose increment after 7 days Sequential if > 3 foll > 10 mm

Ovarian stimulation in normo - ovulatory women prior to IUI

Independent benefit before IUI in unexplained infertility

- to overcome subtle ovarian defect
- to increase the number of oocytes available for fertilization

Major concern : multiple pregnancy

- what objective in terms of number of follicles ?
- the choice of ovarian stimulation regimen

Multiple pregnancy recommendations

NICE Clinical Guidelines (2004)

Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment C

Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of patient management during gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation C

Risk factors for multiple pregnancy

YES	NO
• Patient age	• BMI
• Anovulation	• Duration of infertility
• Total dose of Gns	• Primary/secondary infertility
• No. of follicles / day hCG	• No. of cycle attempts
• Serum estradiol /day hCG	• Hormone profile
• Endometrial thickness / day hCG	• Length of stimulation
• No. spermatozoa inseminated	
• Spermatozoa lateral movement	
• Insemination technique	

Risk factors for multiple pregnancy

"Follicular size at time of hCG administration predicts ovulation outcome in hMG-stimulated cycles"

Follicular size	Ovulation
≤ 14 mm	0.5%
15-16 mm	37.4%
17-18 mm	72.5%
18-20 mm	81.2%
>20 mm	95.5%

Silverberg et al, Fertil Steril 9 : 263, 1991

Cut-off values for prediction of HOMP

	Single	Multiple	Age of patient	Estradiol hCG day	No of follicles hCG day
Navot 1991	51	51			Foll 15-17 mm
Fahri, 1996	180	28			> 3 Foll ≥ 14 mm
Valbuena, 1996	366	126	< 30 yrs	> 1000 pg/ml	> 6 Foll ≥ 12 mm
Goldfard 1997	78	13			Foll > 10 mm
Stone 1999	198	25			> 6 Foll > 18 mm
Pasqualotto, 1999	100	22		> 583 pg/ml	NS
Gleicher, 2000	314	127		> 1385 pg/ml	> 7 Foll ≥ 10 mm
Dickey, 2001	335	73	< 35 yrs	> 1000 pg/ml	> 6 Foll ≥ 12 mm
Tur, 2001	1477	401	≤ 32 yrs	> 862 pg/ml	> 3 Foll ≥ 10 mm
Kaplan, 2002	85	14	Significant		Foll ≥ 15 mm
Dickey, 2005	441	146	≤ 37 yrs	> 1000 pg/ml	> 4 Foll ≥ 10 mm

no consensus: wide range for E 2 values, number and size of follicles

"Risk factors for high-order multiple implantation after ovarian stimulation

Period analysed
1988 - 1998 (single center)

- **1878** gonadotrophin pregnancy cycles :
  - IUI- H n = 1041
  - IUI- D n = 452
  - OI n = 385
- Statistical analysis :
  - Univariate
  - Multivariate
  - ROC

Tur et al, Hum Reprod 16 : 2129, 2001

1771 Singletons + Twins
107 ≥Triplets

Age (years)	≤ 32
Estradiol (pg/ml)	>862
No. of follicles >10mm Ø	>3

Strategy for ovulation + IUI

≥ 3 follicles > 10 mm.

≤ 32 yrs | > 32 yrs

E_2 > 862 pg / ml | E_2 < 862 pg / ml | E_2 > 862 pg / ml | E_2 < 862 pg / ml

Cancel | Cancel if more than 3 follicles ≥ 14 mm. | Cancel if more than 4 follicles ≥ 14 mm. | OK

Validation of prediction model validated (Tur et al., 2005)

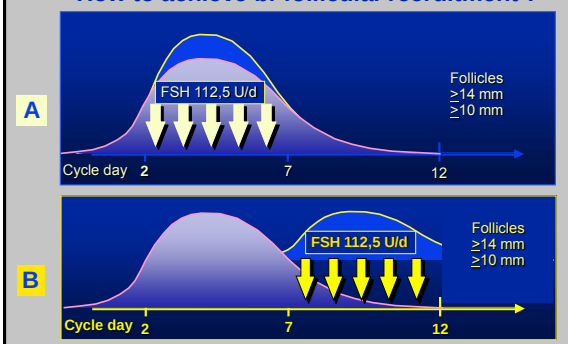
reduction in 285% of HOMP, 8% of pregnancy

Protocols for OI + IUI & criteria for cancellation

	Protocol	Criteria of cancellation	Pregnancy rate	Multiple pregnancy rate
Balasch, 1994	75 IU FSH / day from D7	None	13 %	0 %
Gregoriou, 1995	75 IU hMG / day from D3 Step-up	> 4 Foll ≥16 mm E2 > 450 pg/ml	25.7 %	9.1 % Twins only
Cohlen, 1998	75 IU FSH / day from D3 Step-up	> 3 Foll ≥ 18 mm E2 > 1.800 pg/ml	13.7 %	9.5 % Twins only
Guzick, 1999	150 IU FSH / day fixed dose from D3	E2 > 3.000 pg/ml	9 %	25 % including HOMP
Goverde, 2000	75 IU FSH / day from D3 Step-up	> 3 Foll ≥ 18 mm > 6 Foll ≥ 14 mm	8.7 %	29 % Twins only
Papageorgiou, 2004	50-75 IU FSH from D4	> 2 Foll ≥ 15 mm	10%	8% Twins mainly
Ragni, 2004	50 IU FSH from D3 GnRH antag	> 2 Foll ≥ 15 mm	36.6 %	0 %

Compliance to strict cancellation criteria is crucial to achieve a singleton pregnancy

How to achieve bi-follicular recruitment ?



Cédrin-Durnerin et al., Hum Reprod, 2006

Protocol for bi - follicular recruitment

Assessment on day 12

	GROUP A n = 24	GROUP B n = 24	p
Follicles ≥ 14 mm			
1	9	11	
2	1	10 42 %	0,002
3	6	2	
> 3	5	0	
Follicles ≥ 10 mm			
< 3 - 3	13	13	
4 - 6	5	8	NS
7 - > 7	6	3	

Cédrin-Durnerin et al., Hum Reprod, 2006

Ovarian stimulation in normo-ovulatory women

Main recommendations

- Low starting dose
- No need for initiating ovarian stimulation in the early follicular phase
- Careful assessment by US and hormonal determinations
- Strict application of criteria to trigger ovulation or to cancel the cycle
- All follicles larger than 10 mm should be considered
- Further studies required to determine the best protocol

Short follicular phase

a clinical feature of premature ovarian failure

- Overall cycle duration < 25 days
- Follicular phase duration < 10 days
- Luteal phase duration = 14 days

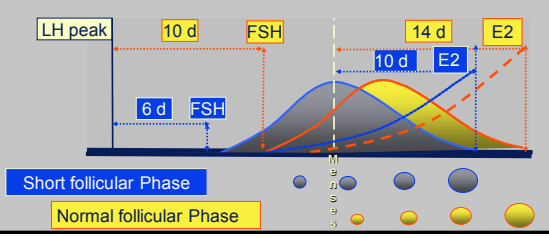
Hormonal status at day 3 of the cycle

FSH = Nl ; E2 > 60 - 80 pg / ml ; Inhibin B > 45 ng / ml

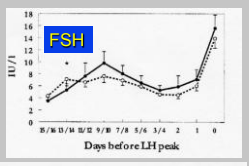
Short Follicular Phase

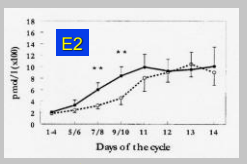
An age-related decline in the length of cycle (Treolar 1967)
mainly the follicular phase
(10 ± 2 d at 40 yrs vs 16 ± 4 d at 18-30 yrs)

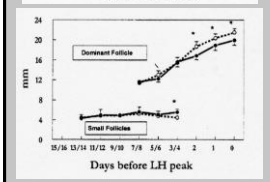
Sherman & Korenmam 1975 ; Lenton 1984



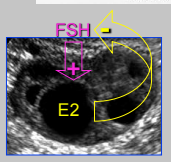
Advanced follicular maturation







Accelerated follicular growth



At day 3

- FSH = normal
- E2 = increased

Van Zonneveld et al. JCEM, 2003

Short Follicular Phase

Consequences : Reduced fertility rate

Critical factor : age-related ovocyte quality (aneuploidy)

But also

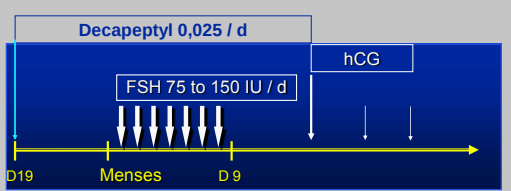
Inadequate cervical mucus

Altered endometrial receptivity

Related to the short duration of the follicular phase

Even worsened by any FSH stimulation

Protocol for Short Follicular Phase



Cédrin-Durnerin et al., RBM Online, 2003

Results and cycle outcome

	Spontaneous Cycle	Protocol Decapeptyl	p
On ovulation day	n = 69	n = 69	
Follicular phase (d)	9,6 ± 1,2	12,5 ± 0,3	0,001
Foll ≥ 17 mm (n)	1,1 ± 0,3	1,7 ± 1,1	0,001
Endomètre (mm)	7,7 ± 1,9	8,5 ± 2	0,005
	n = 49	n = 49	
E2 (pg / ml)	258 ± 180	345 ± 288	0,05
LH (UI/l)	12,8 ± 13	2,3 ± 1,5	0,001
Progestérone (ng/ml)	1 ± 1,1	0,5 ± 0,3	0,001

Cédrin-Durnerin et al., RBM Online, 2003

Results and cycle outcome

Cycles n = 176 (2.6 / patient)

Cancellation : 5 (3.4 %)

Starting FSH dose : 91 + 32 IU

Total FSH dose : 997 + 472 IU - IUI : 67 %

Cycle outcome

Pregnancy rate : n = 27 (15.1 %)

Miscarriage rate : n = 12 (44 %)

	Follicles ≥ 17mm			
	1	2	3 ou 4	p
Cycles	79	64	28	
FSH starting dose	89 ± 35	86 ± 24	104 ± 35	NS
J hCG	13,2 ± 3,7	12,4 ± 2,3	12,1 ± 2,9	NS
E2 (pg/ml)	216 ± 115	308 ± 146	643 ± 376	0,001
Pregnancy (% / cycle)	6 (7,6)	10 (15,6)	8 (28,6)	0,02
Twins	0	2 (20)	2 (25)	

Short Follicular Phase : Conclusions

Ovarian Stimulation

- Not recommended in spontaneous cycle
- Prior suppression of the inter- cycle FSH rise

- Low dose GnRH-a : effective
- Alternative : OCP or estrogens alone

- Starting FSH dose : 100 à 112.5 UI / d to get 2 or 3 follicles
- Luteal support (hCG) : required

Fair pregnancy rate but high risk of miscarriage

Conclusions

Stimulation regimens adjusted to ovulatory status

- Chronic anovulation

Chronic low dose protocol effective and safer than others
Strict compliance to cancellation criteria : patients highly sensitive to FSH

- Normo-ovulatory women prior to IUI

Objective : to get no more than 3 follicles > 10 mm
No need to start stimulation in the early follicular phase

- Short Follicular phase

Prevent the FSH inter-cycle rise
High miscarriage rate

Ovarian surgery- the evidence

Fulco van der Veen

Universiteit van Amsterdam

am center for reproductive medicine

Learning Objectives

- To have knowledge of the available evidence on ovarian surgery, especially laparoscopic electrocoagulation of the ovaries (LEO)
- To understand the indications for LEO in relation to Clomiphene citrate, gondadotrophins and metformin
- To know the cost effectiveness of LEO, relative to medical ovulationinduction

am center for reproductive medicine

Contents

- History
- Evidence on laparoscopic electrocautery in CC resistent women
- Metformin
- Evidence on laparoscopic electrocautery in CC naive women
- Longterm follow up

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History

Instead of resecting the ovaries, I simply puncture those cysts which are upon the surface with as little handling of the ovaries as possible

McGlinn Am J Obstet Dis Women Child 1916;73:435

History

Irving Freiler Stein (1887–).

Michael Leo Leventhal (1901–).

AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES*

IRVING F. STEIN, M.D., AND MICHAEL L. LEVENTHAL, M.D.,
CHICAGO, ILL.
(From Michael Reese Hospital and Northwestern University Medical School)

ACCORDING to leading authoritative works on gynecology, the bilateral polycystic ovary is most commonly found in association with *uterine bleeding* (Fig. 1). This association has been recognized by the medical profession and is not infrequent in occurrence.

Bilateral ovarian wedge resection

Case series 1935-1983 N=1915

- Ovulation rate: 60 -100%
- Pregnancy rate: 30 - 60%

Donesky & Adashi, Fertil Steril 1995, Lunde, Hum Rep 2001

Demise of BOWR

- Adhesion formation: 14-100%
- Medical ovulation induction
  - 1958 Gonadotropines
  - 1961 MRL-41
- 1984 laparoscopic electrocoagulation

Kaaijk, Lasers Surg Med 1995, Gemzell, JCEM 1958
Greenblatt, JAMA 1961, Gjönnæss, Fertil Steril 1984

Laparoscopic techniques

The pioneers

- ovarian biopsy 1967 Palmer
- electrocoagulation 1984 Gjönnæss
- laser treatment 1988 Huber

Palmer, Soc nat de gyn et d'ob de Fr 1967,
Gjönnæss, Fertil Steril 1984, Huber, Lancet 1988

Laparoscopic electrocautery ovaries

Studies(n)	12
Study period	1984-2001
Voltage (watt)	30-300
Electrode	Uni-bipolar
Punctures(n)	3-15
Depth (mm)	2-5
Follow up (months)	2-4
Patients (n)	555
Ovulation/patient (n)%	(384/528) 73
Pregnancy/patient (n)%	(262/529) 50

Laparoscopic electrocautery vs Gonadotrophins?

Randomised Controlled Trial

29 Centres

Feb 1998-oct 2001

In-exclusion criteria

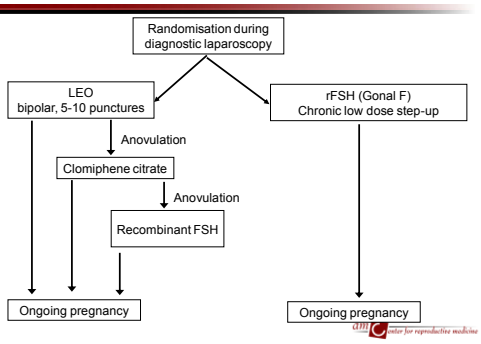
- Chronic anovulation
- Polycystic ovaries
- CC resistant

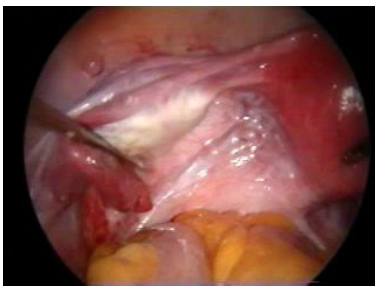
- Other causes infertility
- Severe male factor
- Age above 40 years

- Tubal obstruction
- Extensive adhesions
- Severe endometriosis

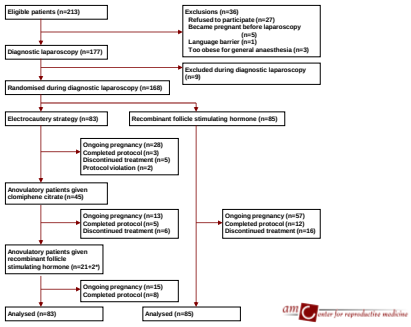
Bayram et al BMJ 2004;328:192

Study design





Flow diagram



Baseline characteristics

	LEO	FSH
age	28.5 (3.7)	28.7 (4.1)
primary infertility	63 (76%)	64 (75%)
secondary infertility	20 (24%)	21 (25%)
duration of infertility	2.8 (2.2)	2.8 (2.1)
body mass index	27.9 (6.3)	27.3 (8.8)
waist to hip ratio	0.8 (0.1)	0.8 (0.1)
LH/FSH ratio	1.99 (0.96)	1.93 (0.90)
testosterone	4.0 (1.7)	3.9 (1.3)
free androgen Index	14 (10.5)	13.3 (10.2)
volume of ovaries	10.6 (4.50)	11.6 (6.5)
total motile sperm count (x106)	108 (136)	96 (106)

Ovulation per cycle

	n/N	%
LEO strategy	228/375	61
LEO	127/182	70
LEO+CC	69/152	45
LEO+CC+rFSH	32/41	78
rFSH	188/272	69

Cancelled cycles rFSH

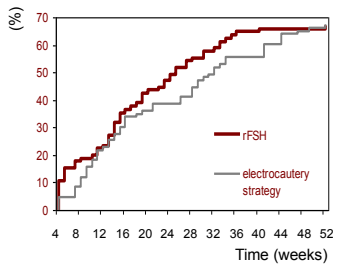
	n/N	%
Total	80/272	29
Poor response	34/80	43
Risk of OHSS	24/80	30
Risk of multiple pregnancy	13/80	16
Other	9/80	11

Cancel criteria: Cd 30: no follicle > 10 mm
>6 follicles ≥ 14 mm, >3 follicles ≥ 16 mm

Ongoing pregnancy per patient

	n/N	%
LEO strategy	56/83	67
LEO	28/83	34
LEO+CC	13/45	29
LEO+CC+rFSH	15/23	65
rFSH	57/85	67

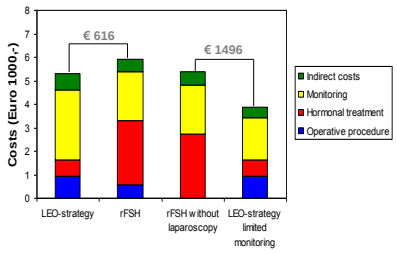
Cumulative ongoing pregnancy rate



Multiple pregnancy/ongoing pregnancy

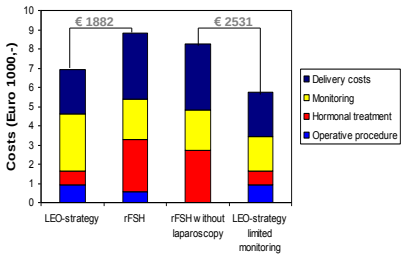
	n/N	%
LEO strategy	1/56	2
LEO	0/28	
LEO+CC	0/13	
LEO+CC+rFSH	1/15	6
rFSH	1/57	16

Scenario-analysis ongoing pregnancy



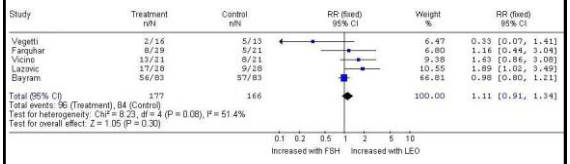
Van Wely et al Human Reprod 2004;19:1741

Scenario-analysis delivery



Van Wely et al Human Reprod 2004;19:1741

Laparoscopic electrocautery vs FSH



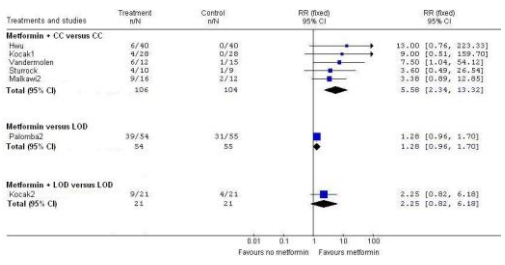
ongoing pregnancy 12 months

Why does LEO work?

- Reduction of all ovarian hormones
- Restoration feedback to hypthalamus
- Increased pituitary sensitivity
- Increase LH/FSH
- Increased ovarian sensitivity to FSH

Hendriks et al HRU 2007;13:249

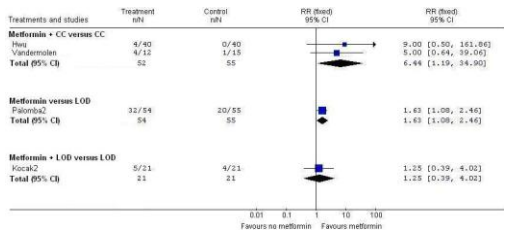
Metformin and CC resistent PCOS



Clinical Pregnancy rate

Moll et al, HRU 2007;13:527

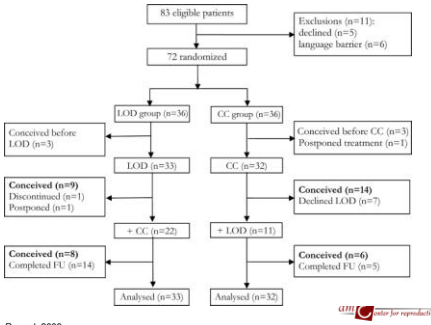
Metformin and CC resistent PCOS



Moll et al, HRU 2007;13:527

Live birth rate

LEO in therapy naïve women



Amer et al. Hum. Reprod. 2009

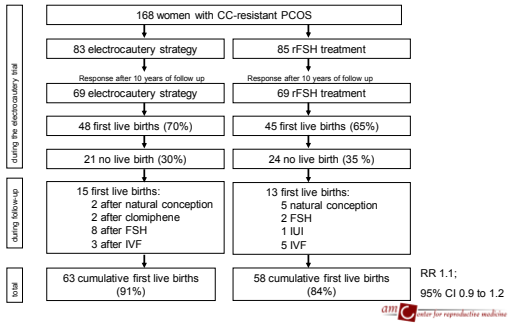
Longterm outcomes of LEO

- Duration of follow-up: 10 years after starting the LEO trial
- Data on menstrual cycle, anticonception use, pregnancies and pregnancy outcomes
- Primary outcome: time to a first live birth
- Secondary outcomes: second and third live births, conceptions, multiple pregnancies, ectopic pregnancy, miscarriage, immature delivery, intrauterine fetal death/stillbirth, as well as minimal en maximal menstrual cycle length

Baseline characteristics

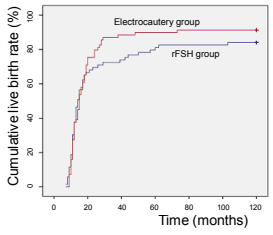
	LEO (n=69) Mean (SD)	FSH (n=69) Mean (SD)
Completeness (%)	138/168 (83)	
Duration of follow up (yrs)	7.3 - 11.8 (10)	
Mean age	39.7 (3.4)	39.6 (4.5)
BMI	28.2 (6.3)	27.0 (6.5)

A first live born child

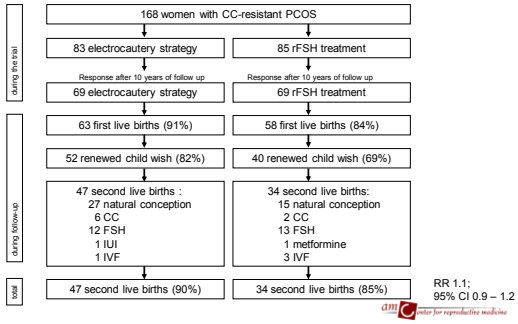


RR 1.1;
95% CI 0.9 to 1.2

A first live born child

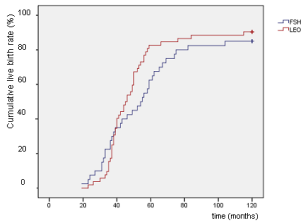


A second live born child



RR 1.1;
95% CI 0.9 – 1.2

A second live born child



Live birth rate after 10 years of followup

Live births	LEO strategy N=69	rFSH N=69	RR (95% CI)
1st live birth	63 (91%)	58 (84%)	1.07 (0.93-1.2)
2nd live birth	47/ 52 (90%)	34/ 40 (85%)	1.06 (0.91-1.2)
3rd live birth	10/?	9/?	-
4th live birth	0/?	2/?	-

Menstrual cycle

	LEO N=69 (%)	rFSH N=69 (%)	
OAC / IUD	32 (46)	31 (45)	RR 1.0, 95%CI 0.7 – 1.5
Regular cycle	19 (27)	12 (17)	RR 1.6, 95% CI 0.8 – 3.0
Irregular cycle	16 (23)	21 (30)	RR 0.8, 95% CI 0.4 – 1.3
Hysterectomy	2 (3)	1 (1)	
Pregnant	0	2 (3)	
FSH treatment	0	1 (1)	
Unknown	0	1 (1)	

Summary

- The LEO strategy is equally effective as ovulation induction with rFSH alone in CC resistant women
- LEO plus CC prevents ovulation induction with rFSH in 50% of women
- LEO plus CC prevents multiple pregnancies
- The costs of the LEO-strategy and ovulation induction with rFSH are comparable
- The costs of the LEO-strategy are lower in a scenario with minimal monitoring
- Addition of Metformin to CC is indicated before LEO
- Long term follow up LEO favorable

Bibliography

- Amer et al. (2009) Hum Reprod;24:219
- Bayram et al (2004) BMJ;328:192
- Donesky & Adashi (1995) Fertil Steril;63:439
- Farquhar et al 2002 Fertil Steril;78:404
- Gemzell (1958) JCEM;18:1333
- Gjönnæss (1984) Fertil Steril;41:20
- Greenblatt (1961) JAMA;178:127
- Hendriks et al (2007) HRU;13:249
- Huber et al (1988) Lancet 2,215
- Kaaijk et al (1995) Lasers Surg Med;16:292
- Lazovic et al (1998) Fertil Steril;70:s472
- Lunde et al (2001) Hum Reprod;16:174
- Moll et al (2007) HRU;13:527
- McGlinn (1916) Am J Obstet Dis Women Child;73:435
- Palmer & de Brux (1967) Soc nat de gyn et d'ob de Fr;19:405
- Stein & Leventhal (1935) AJOG;29:181
- Vicino et al (2000) Gyn End;14:42
- Vegetti et al (1998) Hum Reprod;13:s120
- Van Wely et al (2004) Hum Reprod;19:1741

Insulin sensitizing agents: where do they fit in?

ESHRE, 26th annual meeting, Rome
27-30 June 2010

Etelka Moll

Universiteit van Amsterdam

amc center for reproductive medicine

Contents

- ESHRE Guidelines
  - Definition PCOS
  - Treatment PCOS
- Available evidence
  - Systematic review and meta-analysis
- Conclusions and advise

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Diagnosis of PCOS

FERTILITY AND STERILITY®
VOL. 81, NO. 1, JANUARY 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

CONSENSUS STATEMENT

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group

Rotterdam, The Netherlands

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Diagnosis of PCOS

Revised diagnostic criteria of PCOS (2 out of 3)

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries
4. Exclusion of other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome)

Fauser, Fertil Steril 2004 EN Hum Reprod 2004;19(1):41

Hyperandrogenism

Jusepe de Ribera 1631
Tavera Hospital Toledo

Definition ultrasound PCO

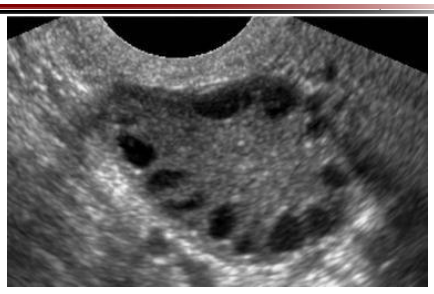
- 12 follicles
- 2-9mm

or

- Ovarian volume >10cm^3

Balen, Hum Reprod Update; 2003;9:505–14

Ultrasound

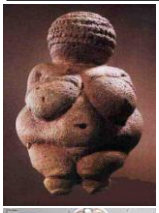


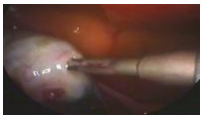
Treatment of PCOS

- Life style advisement
- Clomifene citrate (CC)
- Laparoscopic Ovarian Drilling (LOD)
- FSH
- IVF
- Wedge resection
- Unilateral oophorectomy

- Insulin sensitizers?

Treatment of PCOS







Insulin-resistance

- 1921: diabète des femmes à barbe
- 1935: amenorrhea with polycystic ovaries
- 1980: hyperandrogenism and hyperinsulinemia
- 1983: hyperinsulinemia independant of weight
- 1986: GnRH-agonist > no effect hyperinsulinemia
- 1989: diazoxide > hyperandrogenism ↓
- 1992: wedge resection > no effect hyperinsulinemia
- 1996: metformin > regular menstruation

Achard, Bull Acad Natl Med 1921; Stein, AM J Obstet Gynecol 1935; Burghen, J Clin Endocrinol Metab 1980; Chang, J Clin Endocrinol Metab 1983; Geffner, Fertil Steril 1986; Nestler, J Clin Endocrinol Metab 1989; Dahlgren, Fertil Steril 1992 ; Nestler, NEJM 1996

Insulin sensitizers

- Metformin (biguanide)
  - antihyperglycemic
- Troglitazon (thiazolidinedione) > liver damage, off market 2000
- Rosiglitazon (thiazolidinedione) > risk of myocardial infarction, fetal growth restriction
- Pioglitazon (thiazolidinedione) > weight gain, fetal growth restriction
  - Lower elevated sugar levels, lower insulin levels, insulin sensitivity increases
- D-chiro inositol
  - Mediates insulin action

Insulin sensitizers

- Tazones: not applicable in women with PCOS due to side effects
- D-chiro-inositol: not available in pharmacies. Too little data.
- Metformin: many data, safe drug

Metformin

Biguanide, oral antihyperglycaemic agent

1. Decreases glucoseproduction in liver by decreasing gluconeogenesis and glycogenolysis in muscle
2. Increases insulin-sensitivity and glucolysis in cells and decreases glucose uptake
3. Stimulates synthesis of glycogene and activity of membrane glucose transporters (GLUT).

Metformin cascade

- Decreases insulin resistance
- Increase SHBG
- Decreases androgens
- Normalisation LH en FSH
- (Partly) Regular ovulation

Metformin and PCOS

What is the evidence?

Metformin and PCOS

Human Reproduction Update, pp. 1–11, 2007 doi:10.1093/humupd/dmm026

The role of metformin in polycystic ovary syndrome: a systematic review

Etelka Moll[1], Fulco van der Veen and Madelon van Wely

Centre for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Centre, PO Box 22700, 1100 DE, Amsterdam, The Netherlands

And updated in October 2009

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Metformin and PCOS

Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review)

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

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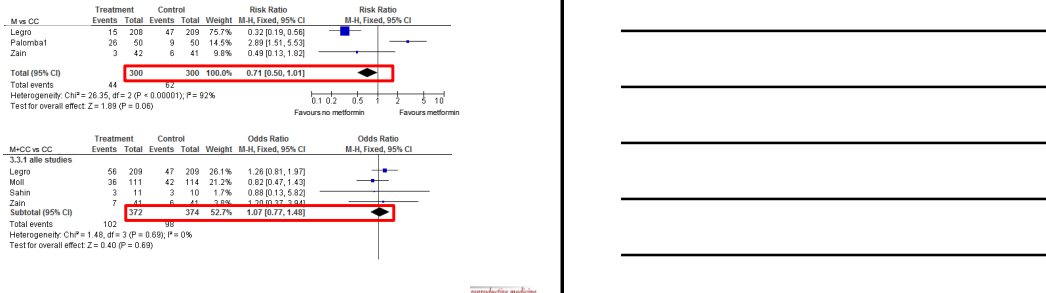
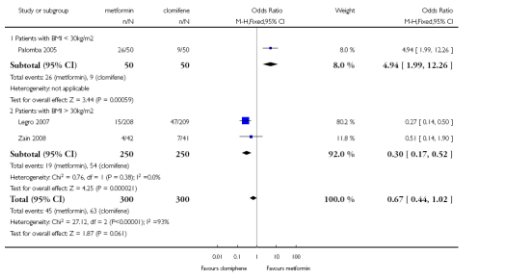
CC naïve – LBR, update 2009



reproductive medicine

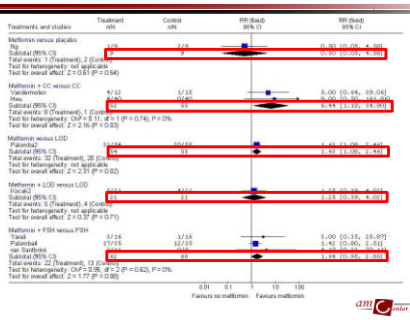
Cochrane, m vs CC



Summary CC naive

- Trend towards advantage CC versus metformin (ns)
- No advantage metformin + CC versus CC
- Multiple pregnancy rate: RR 0.38; 95% CI 0.09–1.5; (n=193)

CC resistant – live birth rate



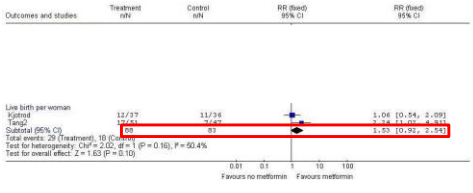
Summary CC resistant - 1

- Metformin + CC versus CC
  - favours m+CC
  - multiple pregnancy rate: only reported in 1 study, ns
- Metformin versus LOD
  - favours metformin
  - multiple pregnancies not observed
- Metformin + LOD versus LOD
  - ns
  - multiple pregnancies not observed

Summary CC resistant - 2

- Metformin + CC versus FSH
  - 1 study, only CPR: ns
- Metformin + FSH versus FSH
  - trend towards metformin + FSH (ns)
  - multiple pregnancy rate, less in metformin group: RR 0.26; 95% CI 0.07–0.96; (n=35)

IVF – life birth rate



Summary IVF

- NS
- Multiple pregnancy rate: ns
- OHSS less in metformin group: RR 0.33; 95% CI 0.13–0.80; (n=296)

Fedorcsak, Gynecol Endocrinol 2003; Onalan, Fertil Steril 2005

Metabolic syndrome

3 out of 5

1. Abdominal obesity (waist circumference) > 88 cm (>35 inch)
2. Triglycerides > 1.7 mmol/l (150 mg/dl)
3. HDL-C < 1.29 mmol/l (50 mg/dl)
4. Blood pressure > 130/>85 mmHg
5. Fasting and 2 h glucose from OGTT:

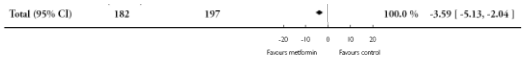
6.1-7 mmol/l (110-126 mg/dl) and/or 7.8-11 mmol/l (140-199 mg/dl)

Cochrane, m vs plac

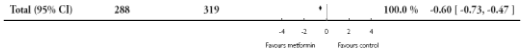
- No difference after treatment in BMI, WHR, diastolic RR, SHBG, insulin, total cholesterol, HDL, triglycerides

Cochrane, m vs plac

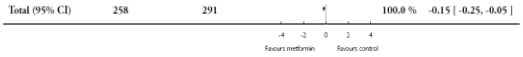
- Significant difference in systolic bloodpressure 0.3-15.7 mm Hg



- Significant difference in testosteron 0.0-2.87 nmol/l



- Significant difference in glucose 0.0-0.7 mmol/l



Conclusions - 1

Therapy naïve women:

- No difference between metformin and CC
- No difference between metformin + CC versus CC alone

Conclusions - 2

CC-resistant women

- benefit metformin + CC over CC alone
  - n=107
- benefit metformin over LOD
  - n=109
- no benefit in metformin + LOD versus LOD
  - n=42
- no benefit metformin + FSH versus FSH
  - n=122

Conclusions - 3

IVF

- no benefit metformin
- benefit of metformin in OHSS

Advise

Treatment strategy

1. CC
2. Metformin + CC
3. LOD strategy
4. FSH
5. Metformin + IVF

More research metabolic syndrome, late effects, metformin

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School of Medicine

How should ovulation induction be managed?

N.S.Macklon
Professor of Obstetrics and Gynaecology
University of Southampton

University of Southampton
School of Medicine

Disclosures

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

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Objective

- To discuss a number of common but potentially challenging clinical scenarios relating to the management of Ovulation Induction.

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Principles of Ovulation Induction

- Aim: to restore normal fertility to anovulatory women
- Means: Generating normo-ovulatory cycles
- Mimic physiology and induce a single dominant follicle
- Avoid multiple pregnancy and OHSS

TIGHT THERAPEUTIC MARGIN

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The ESHRE Ovulation Induction Clinic, Rome

Your first Patient..

Mrs B. Alen

- 28
- Secondary, WHO type 2 anovulation
- PCOS, no glucose intolerance
- BMI 25
- No male factor subfertility
- Non-smoker

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What is your first line treatment?

- Clomiphene Citrate?
- Aromatase Inhibitor?
- FSH?
- Metformin?
- LOD?
- Other?

Clomiphene: to monitor or not?

- Monitoring by ultrasound is not mandatory to ensure good outcome (Legro et al., 2007).
- Many monitor first cycle to adjust dose in next cycles based on the observed response.
- Pretreatment ultrasound to evaluate ovarian and endometrial morphology.
- Luteal phase progesterone measurements to confirm
- ovulation.

Clomiphene: hCG midcycle or not?

- There is no evidence that administration of human chorionic gonadotrophin (hCG) in mid-cycle improves the chances of conception (Kosmas et al., 2007).

You monitor:

On cycle day 13 she has one follicle of 18mm

The endometrium is 4mm thick

What do you advise?

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She remains anovulatory on 150mg CC

Do you offer combination therapy with Metformin offer dexamethasone?

- Moll et al 2006
- Legro et al 2007a
- Daly et al 2004
- Tang et al 2010

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You treat her with a low dose step up gonadotropin protocol

- Do you co-treat with GnRH analogues?
- What are the risks of co-treatment?

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You treat her with a low dose step up gonadotropin protocol

- On day 31 of stimulation you note on ultrasound the following:
- Endometrium 12mm
- Left ovary: two follicles of 14mm
- Right ovary: one follicle of 17 mm and one of 15mm

What is your management?

Avoiding multiple pregnancy

- Variable criteria for cancellation are published
- Thessaloniki Consensus:

'..prudent to withhold hCG in presence of more than 2 follicles ≥ 16mm and two additional follicles ≥ 14mm'

Case 2: Mrs A.N. Derson

- 35 years old
- Gravida 0

- PCOS, anovulatory
- Body mass index: 37
- Smokes
- No male factor

What first line therapy is indicated?

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Prognosis with Clomiphene?

Anovulation

No conception

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When do you move to IVF?

- First line?
- Second line?
- When all OI options fail?
- No IVF?

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How to manage pregnancy after OI?

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

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

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

Meta-analysis: 720 women with PCOS vs 4505 controls

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

Art of Ovulation Induction

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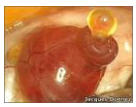

1. Exclude other health issues
2. Optimise preconceptional health
3. Clomiphene remains first line
4. Second line: Gonadotropins or LOS
5. Ovulation induction works: cumulative singleton live birth rate =72%
6. Third line: IVF
7. Metformin when glucose intolerance.
8. More evidence required for aromotase inhibitors

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Further Reading

- Van Santbrink et al (2005) TEM, 16:381
- Macklon et al, (2006) Endocrine Reviews 27, 170
- Macklon and Fauser (2009) Chapter 29 in Yen and Jaffes Repruductive Endocrinology (6th edition)
- Tang et al (2010) Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003053
- Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008). Hum Reprod. 23:462-77
- Legro et al (2007) N Engl J Med 356, 551
- Boomsma et al (2006) Hum Rep Update 12:673

Mark your calendar for the upcoming ESHRE campus workshops!

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

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

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

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

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

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

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

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

www.eshre.eu
(see "Calendar")

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Keep an eye on our calendar section for more information on

Upcoming events

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

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