

Ovulation Induction for Anovulatory Infertility (PCOS)

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ESHRE Campus, Kiev, May 2010

Ovulation Induction for PCOS

Learning Objectives

1. Options for OI
2. Weight reduction
3. Oral agents (Clomiphene Citrate, Aromatase Inhibitors)
4. Gonadotrophin therapy
5. Laparoscopic ovarian diathermy
6. Metformin

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

The Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group

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

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**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

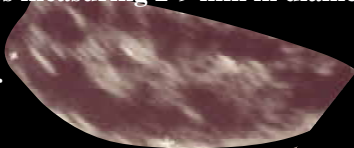
Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

**Ultrasound Assessment of the Polycystic Ovary:
International Consensus Definitions**

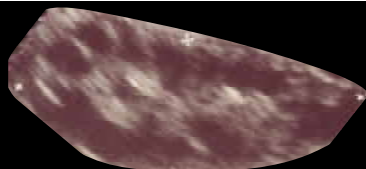
The polycystic ovary contains 12 or more
follicles measuring 2-9 mm in diameter

and/or

increased ovarian volume ($>10 \text{ cm}^3$)

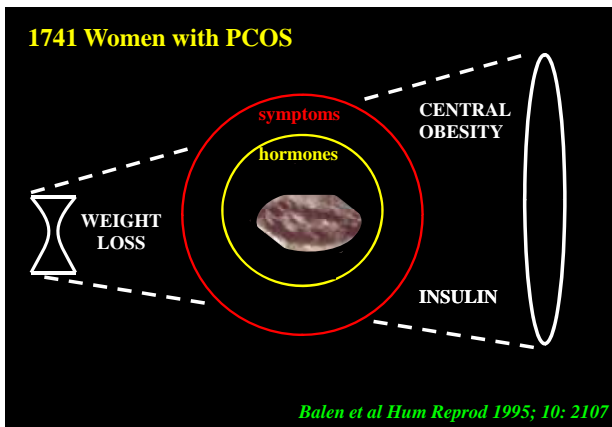


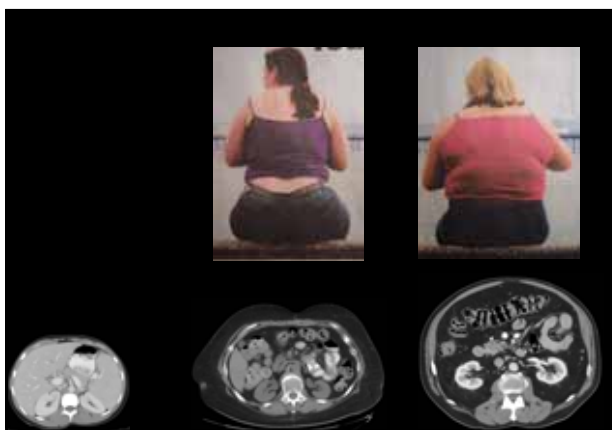
*Balen, Laven, Tan & Dewailly; Hum Reprod Update 2003; 9: 505
ESHRE/ASRM Consensus 2003*



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





- PCOS: Investigations**
1. Testosterone (SHBG)
 2. FSH, LH (E2)
 3. AMH?
 4. Prolactin / TFTs
 5. Ultrasound scan
 6. GTT, lipid profile
 7. Semen analysis
 8. Tubal patency assessment

First line therapy for anovulatory PCOS

- Weight loss
- Clomiphene citrate
- *Aromatase inhibitors*
- Gonadotrophins
- *In vitro maturation of oocytes*
- Ovarian surgery
- Insulin sensitisers???





Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM Sponsored PCOS Consensus Workshop Group¹ March 2-3, 2005, Thessaloniki, Greece

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM Sponsored PCOS Consensus Workshop Group¹ Thessaloniki 2005, Greece

1
Preconceptional care
- diet
- exercise
- other

2
Clomifene
(no Metformin
Aromatase inhibitors)

3
Gonadotropins
or
LOD

4
IVF
(single ET)

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 loss in PCOS

- 5-10% reduction in weight can achieve 30% reduction in visceral fat
- Metabolic & endocrine profile improve significantly
- Improvement reproductive function and outcomes

Kiddy et al Clin Endo 1992 36:105

Clark et al Hum Rep 1995 10:2705

Jakubowicz & Nestler JCEM 1997 82:556

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/m² although in those with more time (under 37y, normal ovarian reserve) a weight reduction to < 30 kg/m² is preferable”

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

Weight loss and exercise

BMI > 30, > 2y anovulatory infertility, CC resistance

13/18 completed 6 month study:
weight loss improved endocrinology
12 - lower insulin, testosterone
all ovulated
11 conceived (5 naturally)

Clark et al H. Rep 1995 10:2705

Clomifene Citrate

n = 5268 patients

Ovulation - 3858 (73%)

Pregnancies - 1909 (36%)

Miscarriage - 20%

Multiple pregnancy rate - 10%

Single live-birth rate – 25%

Homburg, Hum Reprod, 2005

To give hCG in CC cycles?

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

.....but helps in timing of intercourse
or IUI

Agrawal & Buyalos, 1995

Should we monitor clomiphene cycles with ultrasound?

3 cycles of CC

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

Konig, Homburg et al, ESHRE, 2009

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

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)

Stopping...

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

Non-Response to Clomiphene

Failure to ovulate

- FAI
- BMI
- LH
- Insulin

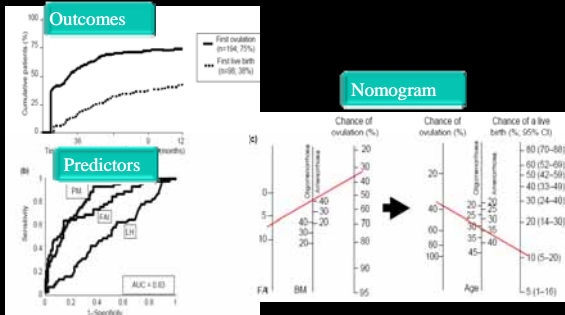


Reasons for Clomiphene Failure

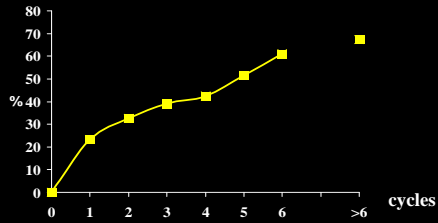
Ovulation but no conception

- Anti-estrogen effects
 - cervical mucus
 - endometrium
- High LH

CC ovulation induction in WHO 2 - outcomes, predictors, and nomogram



Modern use of clomiphene citrate in induction of ovulation



Kousta, White & Franks. Hum Reprod Update 1997; 3: 359

Aromatase Inhibitors - Theoretical Advantages

Letrozole (2.5 mg)

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

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

- Superiority or equivalence, CC (100mg vs letrozole 2.5mg)

Atay et al, 2006; Bayar et al, 2006

- CC, 100mg vs Letrozole, 5mg
- n=438 (1063 cycles)

- Pregnancy/cycle – CC 17.9%,
- letrozole 15.1% (NS)

Badawy et al, 2007

Aromatase inhibitors vs CC

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

Atay 2006; Bayar 2006; Sohrabvand 2008; Sipe 2006
Meta-analysis: Polyzos et al, Fertil Steril, 2008

Letrozole induction of ovulation in women with CC-resistant PCOS...

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

Elnashar et al, 2006

Anastrozole

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

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

Wu et al, 2007, n = 33

Anastrozole (1mg) vs Letrozole (2.5mg)

Letrozole superior in ovulation and pregnancy rates

Al-Omari et al, 2004, n = 40

Outcome – Letrozole vs CC

n=911 newborns in 5 centers

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

Tulandi et al, 2006

Outcome – Letrozole vs CC

	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%

Tulandi et al, 2006

Gonadotropin Regimens

■ Step up



■ Low dose step up



■ Step down



Low dose rec-FSH

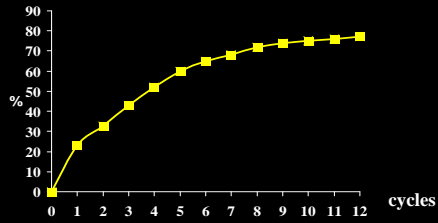


Reduction of multiple pregnancy rate



- Low dose regimens
- Careful monitoring
- Strict criteria for hCG:
 - 1 follicle > 17mm
 - ≤ 2 folls. in total > 14mm

Gonadotrophin therapy in 103 women with PCOS



Balen et al Human Reproduction 1994; 9:1563

**Low Dose Gonadotropins
Summary of Results
Patients - 1040, Cycles 2472**

Pregnancies	411 (40%)
Fecundity/ov.cycle	23%
Uniovulation	71%
OHSS	0.14%
Multiple pregs.	5.1%

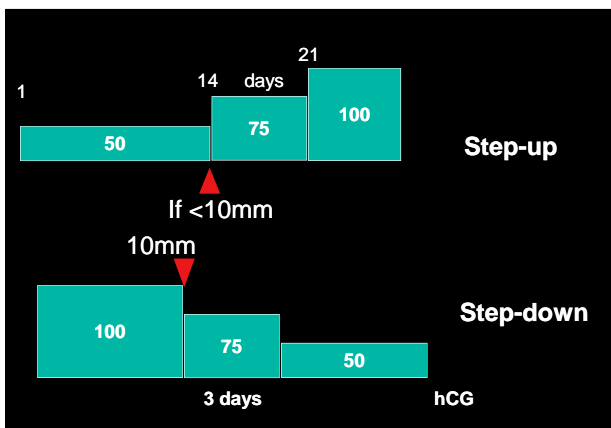
Updated from Homburg & Howles, 1999

**Results with low-dose gonadotrophins
-100 women**



Low-dose gonadotrophins -questions

- Step-up or step-down?
- Starting dose?
- Incremental dose rise?
- Use as first-line treatment?



Conclusions

- Step-up safer and more efficient than step-down
 - Lower rate of overstimulation
 - Higher rate of monofollicular cycles
 - Higher ovulation rate

Christin-Maitre & Hugues, 2003

**Comparison of 2 starting doses
(37.5 vs 50 IU) r-hFSH for 14 days**

N= 22: Mean Age 30.4 yrs: BMI 24.6 Increase after 14 days (37.5 & 50)

- Use of 37.5IU FSH as a starting dose resulted in similar outcome but with less IUs FSH vs 50 IU

Table 1. Ovarian Response and FSH Requirement in the Two Treatment Groups

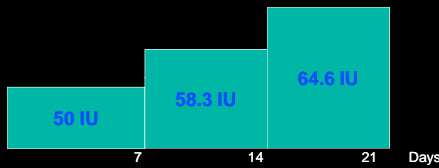
Parameter	37.5IU	50IU	P
FSH required			
Days of treatment	13.5 ± 0.9	12.47 ± 0.72	NS
IU	522.5 ± 45.9	623.3 ± 35.8	<0.05
Threshold dose (IU)	40.0 ± 2.5	50 ± 0	<0.005
No. of follicles on hCG day			
>10-13 mm	0.33 ± 0.16	0.2 ± 0.14	NS
>13-17 mm	0.27 ± 0.12	0.53 ± 0.17	NS
>17 mm	1.13 ± 0.09	1.13 ± 0.09	NS
Total	1.7 ± 0.24	1.7 ± 0.24	NS
E ₂ on hCG day (pg/ml)	286 ± 22.7	296 ± 24.7	NS
Inhibin A on hCG day (pg/ml)	52.2 ± 3.7	50.1 ± 4.5	NS

Values are mean ± SE; NS, not significant.

(Balasch et al 2000)

**Only minimal dose increment needed
(Orvieto & Homburg, 2008)**

- Incremental dose rise of 8.3 IU each week



- N=25, PCOS, CC failures, 69 cycles

**Only minimal dose increment needed
(Orvieto & Homburg, 2008)**

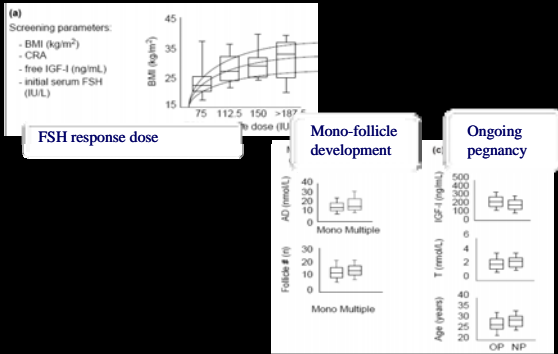
- Treatment days – 10.8 +/- 4.3 (range 5-25)
- Total dose of FSH (IU) – 622 +/- 286 (208-1641)
- Cycle cancellation – 1/69
- Ovulation rate – 98.5% of started cycles

Only minimal dose increment needed (Orvieto & Homburg, 2008)

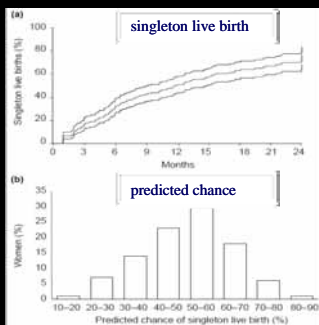
- 1 follicle only > 16mm 82.6%
- > 14mm 62.3%
- Clinical pregnancies 20 (29% cycles)
- Miscarriages 4
- Live births 16 / 25 patients
- Twins 1
- OHSS 0

Predictors FSH ovulation induction

- response dose, mono-follicle development, ongoing pregnancy



Conventional OI (CC + FSH)



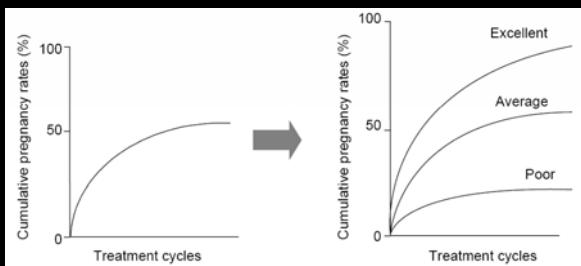
Pregnancy rates of 240 WHO anovulatory infertile women (CC, FSH, IVF)

	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%

Initial screening characteristics predicting treatment outcome in WHO 2 anovulatory infertility

	Goniphene citrate		FSH		CC followed by FSH	IVF	
	Ovulation	Pregnancy in ovulatory patients	FSH threshold	Pregnancy	Multifollicular growth	Clinical outcome ²	Clinical outcome ³
Age	Neg	Pos		Neg		Neg	Neg
Amenorrhea	Neg	Pos				Neg	Neg
BMI	Neg		Pos				
CC response			Pos		Pos		
Hyperandrogenism	Neg		Pos	Neg	Pos		
Insulin resistance	Neg					Neg	
References	[21,22]	[23,24]	[26]	[25]	[25]	[29,33]	[33]

The way forward towards patient tailored OI protocols



SPECIAL FEATURE
Editorial

Predicting Pregnancy in Women with Polycystic Ovary Syndrome
J Clin Endocrinol Metab, September 2009, 94(9):3183-3184

B. C. J. M. Fauser and M. J. C. Eijkemans

Predictors of ovarian response: progress towards individualized treatment in ovulation induction and ovarian stimulation
Human Reproduction Update, Vol.14, No.1 pp. 1-14, 2008

B.C.J.M. Fauser^{1,4}, K. Diedrich² and P. Devroey³ on behalf of the Eviar Annual Reproduction (EVAR) Workshop Group 2007

Treatment (study)	Outcome	Patients (n, achieving outcome)/total in study	Predictive factors	AUC/c-statistic
Clomiphene citrate (Itani <i>et al.</i> , 1998)	Ovulation	156/201	Amenorrhoea, BMI, FAI	0.82
Clomiphene citrate (Itani <i>et al.</i> , 1999)	Pregnancy	73/159	Age, oligomenorrhoea	AUC not calculated
FSH (Malders <i>et al.</i> , 2003a)	Ongoing pregnancy	57/154	IGF-I, testosterone, age	0.67
FSH (van Wely <i>et al.</i> , 2005)	Ongoing pregnancy	57/85	Oligomenorrhoea, FAI, duration of infertility	0.72
Clomiphene citrate/FSH (Eijkemans <i>et al.</i> , 2003)	Live birth	134/240	Age, insulin/glucose, duration of infertility	0.61

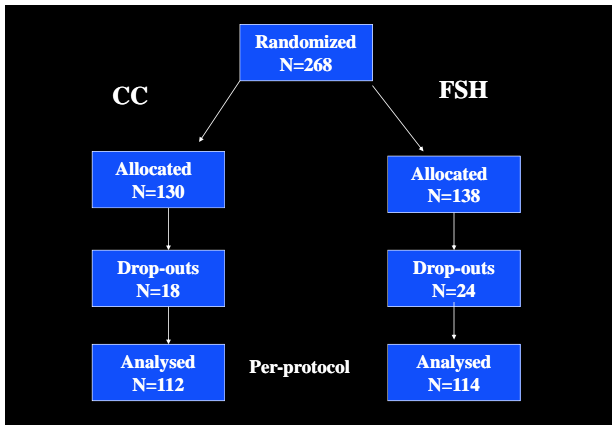
CC or rec-FSH for first-line treatment?

PCOS
Randomization

CC

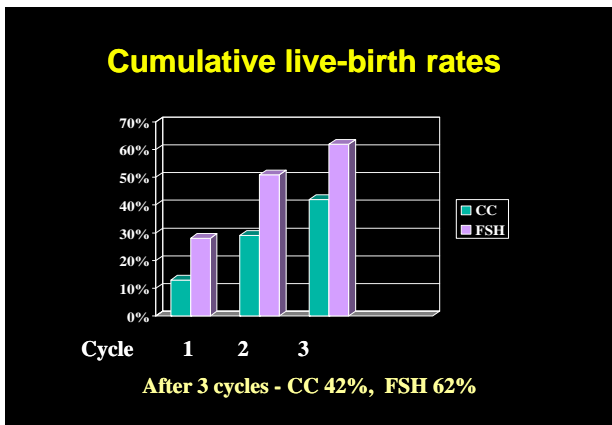
rec-FSH

3 cycles



Results

	<u>CC</u>	<u>FSH</u>	<u>P</u>
Patients per protocol	112	114	
Cycles	287	249	
Pregnancies	46 (41%)	64 (56%)	0.02
Miscarriage rates	15%	12.5%	
Multiple pregnancies	0	2 (3%)	
Pregnancies/cycle	16%	26%	0.006
Live births	40 (35.7%)	56 (49%)	0.03



Summary

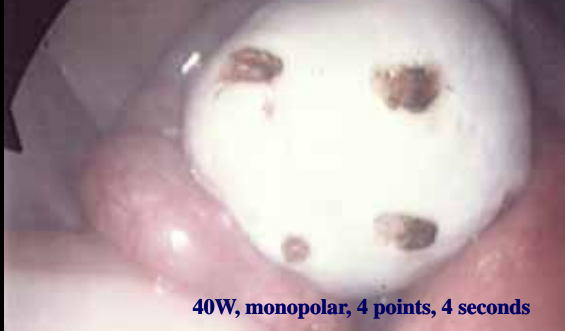
Clear superiority of low-dose FSH over CC for first line treatment of anovulatory PCOS

Absolute difference -

- of 24% in CCR over 3 cycles
- of 10% in pregnancy rates/cycle
- of 20% in cumulative live birth rates

- More than x2 chance of conception in 1st cycle
- Shorter treatment to pregnancy time

Laparoscopic ovarian surgery



LOD versus rFSH - RCT

	<u>LOD</u>	<u>rFSH</u>
n	83	85
ovulatory	63%	64%
pregnant	34%	67% CCR 6 cycles RR 0.54 (95%CI 0.39-0.76)
12m CCR	67%	67% RR 1.01 (95%CI 0.81-1.24)
miscarriage	9%	13%

After 8w 45 received addition of CC → 49% CCR
and 21 then received rFSH → 67% CCR at 12m

Bayram et al, BMJ 2004; 328:192

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Laparoscopic “drilling” by diathermy or laser in anovulatory PCOS

- studies small
- main outcomes ovulation & pregnancy
- 6 month pregnancy rate vs 6 cycles gonadotrophin therapy: OR 0.48, 95% CI 0.28 – 0.81
- 12 month pooled OR 1.27, 95% CI 0.77 – 2.09

Farquhar et al, Cochrane database 2002

Laparoscopic “drilling” by diathermy or laser in anovulatory PCOS

- miscarriage rates - similar
- multiple pregnancy rates - lower (OR 0.16, 95% CI 0.03 – 0.98)

Farquhar et al, Cochrane database 2002

Effects of metformin on PCOS

- Improve reproductive function
- Improve response to both clomifene and gonadotropin induced ovulation

Lord *et al*, 2003, Cochrane Review & BMJ

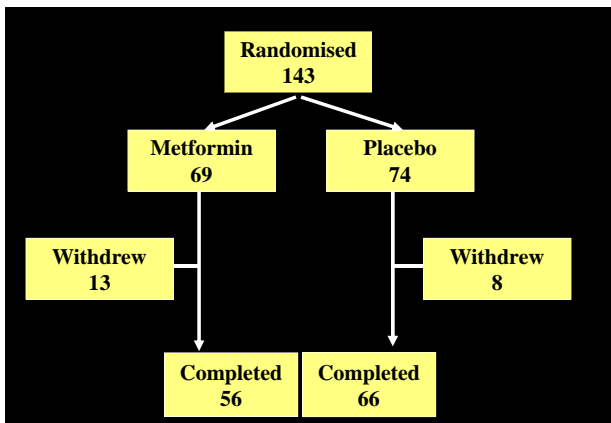
Costello *et al*, 2003, Human Reproduction

A multi-centre randomised, placebo-controlled, double-blind study, of combined life-style modification & metformin in obese patients with PCOS

- 8 centres U.K., co-ordinated by Leeds
- Placebo controlled, double blind RCT
- 6 months metformin 850mg b.d.
- 143 women randomised, with BMI > 30 kgm⁻²
mean BMI 38 kgm⁻²

power 0.90 for significance 0.05, requires 55 per arm of study)

Tang et al, Human Reproduction 2006; 21: 80-89.



Metformin vs Placebo

Significant increase in number of cycles,
and fall in BMI and waist circumference in both groups

No difference in ovulation rate between the groups

Improvements seen in those who lost weight in either group

Tang et al, Human Reproduction 2006; 21: 80-89.

**A randomised double blind clinical trial comparing
clomifene citrate plus metformin with clomifene citrate
plus placebo in newly diagnosed PCOS**

228 women with PCOS

Randomly allocated to receive either metformin 2000 mg/d
or placebo for 1 month

Then clomifene citrate 50 up to 150 mg for 6 ovulations or
until CC-resistance

BMI ~ 28 kg/m²

Moll et al, BMJ; 332: 1485

Ovulation per dosage clomifene citrate

	CC + metformin	CC + placebo	P
CC 50mg	49/80 (61%)	50/92 (54%)	0.36
CC 100mg	27/44 (61%)	35/53 (66%)	0.63
CC 150mg	8/17 (47%)	13/23 (57%)	0.55

Moll et al BMJ 2006; 332: 1485

Ovulation, pregnancy and spontaneous abortion rates

	CC + metformin	CC + placebo	Relative Risk (95% CI)
	n=111	n=114	
Ovulation	71 (64%)	82 (72%)	0.89 (0.7 - 1.1)
Ongoing Pregnancy	44 (40%)	52 (46%)	0.87 (0.6 - 1.2)
Spontaneous Abortion	13 (12%)	12 (11%)	1.11 (0.5 - 2.3)

Moll et al BMJ 2006; 332: 1485

Discontinuation due to side effects:

16% versus 5% (95% CI 5 - 16%)

Moll et al BMJ 2006; 332: 1485

CC and/or metformin alone or in combination

626 anovulatory PCOS

Metformin vs Placebo 2000 mg / day

Clomiphene or Placebo 50 – 150 mg for 5d

6 cycles or 30 weeks

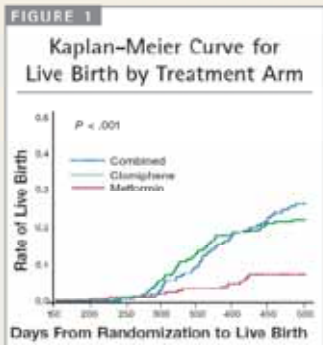
Mean BMI ~ 35 kg/m²

Legro et al, NEJM 2007, 356:551

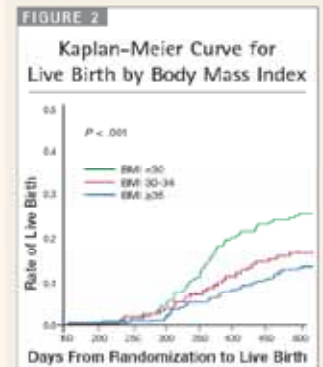
CC and/or metformin alone or in combination

	CC	M	CC + M
Conception /ovulation	39.5%	8.4%	46.0%
Miscarriage	8.3%	20.8%	9.2%
Live birth	22.5% (47/209)	7.2% (15/208)	26.8% (56/209)

CC superior to metformin and combination confers no advantage in achieving live birth
Legro et al, NEJM 2007, 356:551



Legro RS, et al. *N Engl J Med*. 2007;356:551-560. Copyright © 2007 Massachusetts Medical Society.



Legro RS, et al. *N Engl J Med*. 2007;356:551-560. Copyright © 2007 Massachusetts Medical Society.

Clomiphene with Metformin or Placebo

Two very large RCTs have failed to show any benefit from metformin

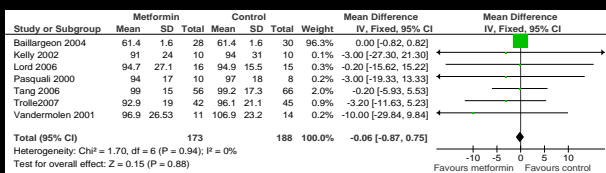
Clomiphene alone results in highest livebirth rate

Moll et al, BMJ 2006; 332:1485
Legro et al, NEJM 2007; 356:551

Revised Cochrane Meta-analysis

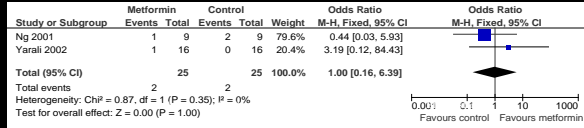
Tommy Tang, Rob Norman, Adam Balen
2009

Metformin vs placebo or no treatment: Body weight



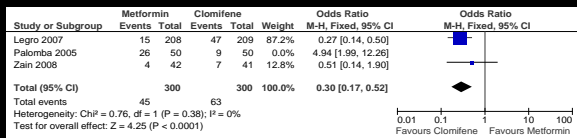
OR -0.06 95% CI -0.87, 0.75

Metformin versus placebo or no treatment: Live birth rate



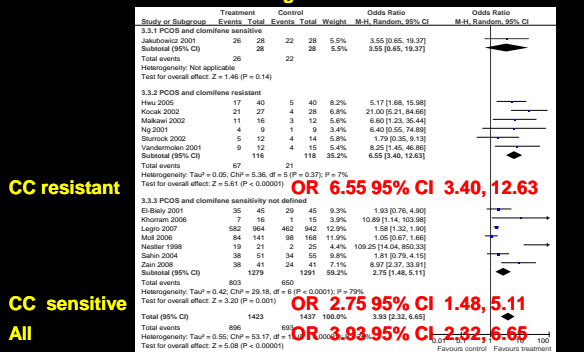
Live birth rate: OR 1.00 95% CI 0.16, 6.39

Metformin versus Clomifene Citrate: Live birth Rate



OR 0.30 95% CI 0.17, 0.52

Metformin plus ovulation induction agent vs ovulation induction agent alone: Ovulation Rate

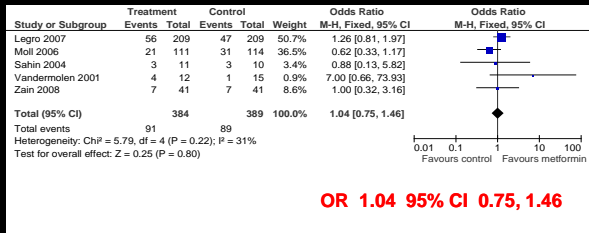


OR 6.55 95% CI 3.40, 12.63

OR 2.75 95% CI 1.48, 5.11

OR 3.93 95% CI 2.32, 6.65

**Metformin plus ovulation induction agent
vs ovulation induction agent alone: Live Birth Rate**



**Insulin sensitising agents in PCOS:
ESHRE/ASRM Consensus, 2007**

- No clear role of metformin in management anovulatory infertility either alone or in combination
- No evidence of improvement in pregnancy outcome

Human Reproduction 2008; 23:462

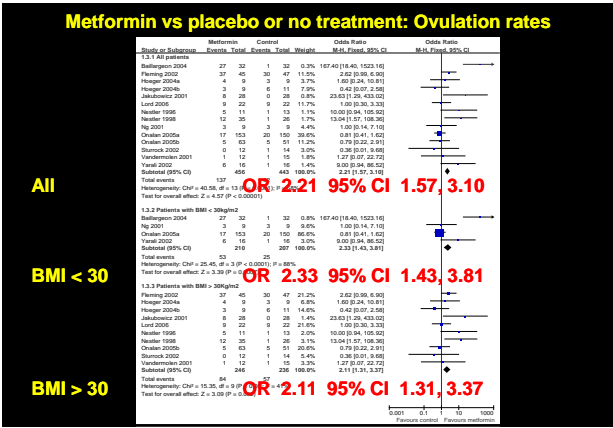
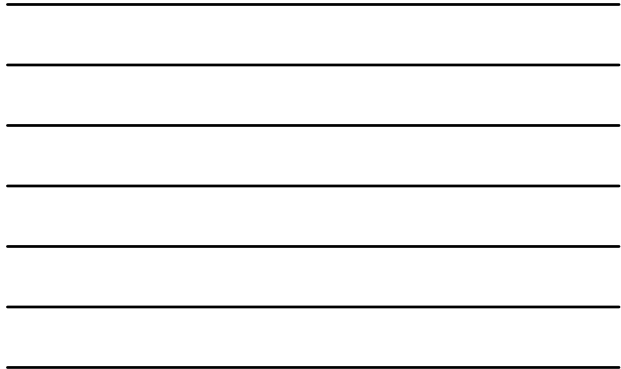
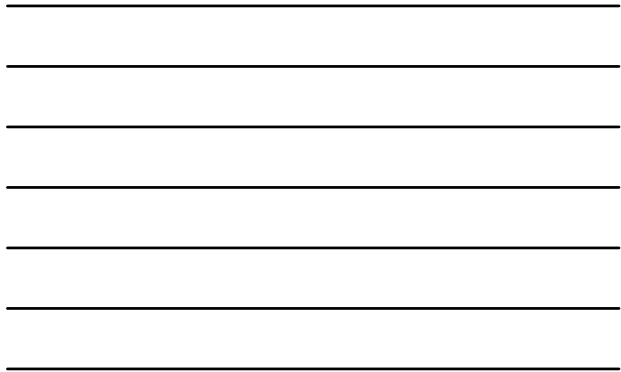
Fertility & Sterility 2008; 89: 505

RCOG Scientific Advisory Committee Guideline, 2008

Ovulation Induction for PCOS

Learning Objectives

1. Options for OI
2. Weight reduction
3. Oral agents (Clomiphene Citrate, Aromatase Inhibitors)
4. Gonadotrophin therapy
5. Laparoscopic ovarian diathermy
6. Metformin

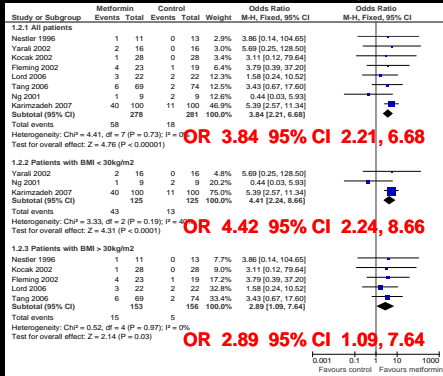


Metformin vs placebo or no treatment: Clinical pregnancy rates

All

BMI < 30

BMI > 30



Metformin plus ovulation induction agent vs ovulation induction agent alone: Clinical Pregnancy Rate

All

BMI < 30

BMI > 30

