Treatment of Infertility in Women with PCOS

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PCOS

Prevalence

- 5-10% general female population
- Up to 30% of infertility population

ESHRE / ASRM Consensus, Thessaloniki 2007

The Thessaloniki ESHRE/ASRM Consensus Paper, 2008

SPECIAL CONTRIBUTIONS

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

0015-0282/08/$34.00
doi:10.1016/j.fertnstert.2007.09.041
Fertility and Sterility® Vol. 89, No. 3, March 2008

Human Reproduction Vol.23, No.3 pp. 462–477, 2008
doi:10.1093/humrep/dem426

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

PCOS: *Management*

- Life-style changes
- Ovulation induction
- Metformin and other insulin-sensitising drugs
- Laparoscopic ovarian surgery
- In Vitro Fertilization

PCOS: *Management*

- Life-style changes
  - Diet
  - Exercise

Weight Loss in PCOS: Results of RCT

	Control (n=84)	*Intervention (n=87)*
Weight loss (kg)	1.3 (0.2)	4.7 (0.3)*
Pregnancies at 18months	18 (21.4%)	53 (61%)*
Miscarriage	3 (16.6%)	6 (11.3%)
ART pregnancies	9%	37%*
Spontaneous pregnancies	11%	24%*

* $p<0.001$

Moran et al, 2003

PCOS: *Management*

- Life-style changes
- Ovulation induction
- Metformin and other insulin-sensitising drugs
- Laparoscopic ovarian surgery
- In Vitro Fertilization

PCOS: *Management*

- *Ovulation induction*
  - Clomiphene citrate
  - Aromatase inhibitors
  - Gonadotropins +/- GnRH analogues

CC ADMINISTRATION

- For 5 days
- Onset on days 2-5
- No difference between different days of onset
- Starting dose 50 mg/day per os

RESULTS OF TREATMENT WITH CC

5 STUDIES
(1968-1983): A total of 5878 cases

- **Ovulation rate: 70-86%**
- **Pregnancy rate: 34-43%**
- **Miscarriage rate: 13-25%**

Messinis I, 2002

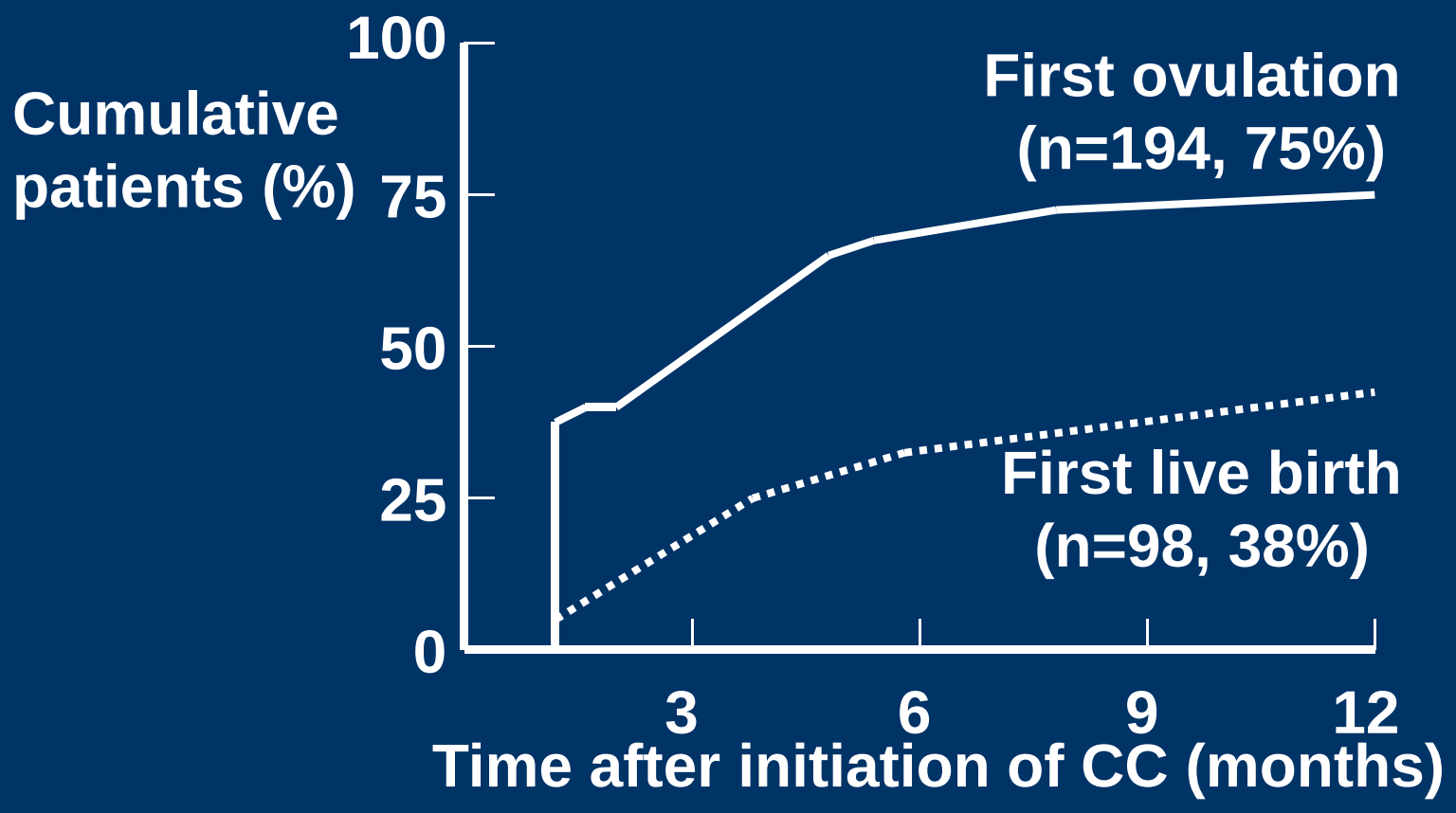
Clomiphene and Anti-estrogens for Ovulation Induction in PCOS

Clomiphene was effective in increasing pregnancy rate compared to placebo (OR 5.8, 95% CI 1.6 to 21.5) as was clomiphene plus dexamethasone treatment (OR 9.46, 95% CI 5.1 to 17.7) compared to clomiphene

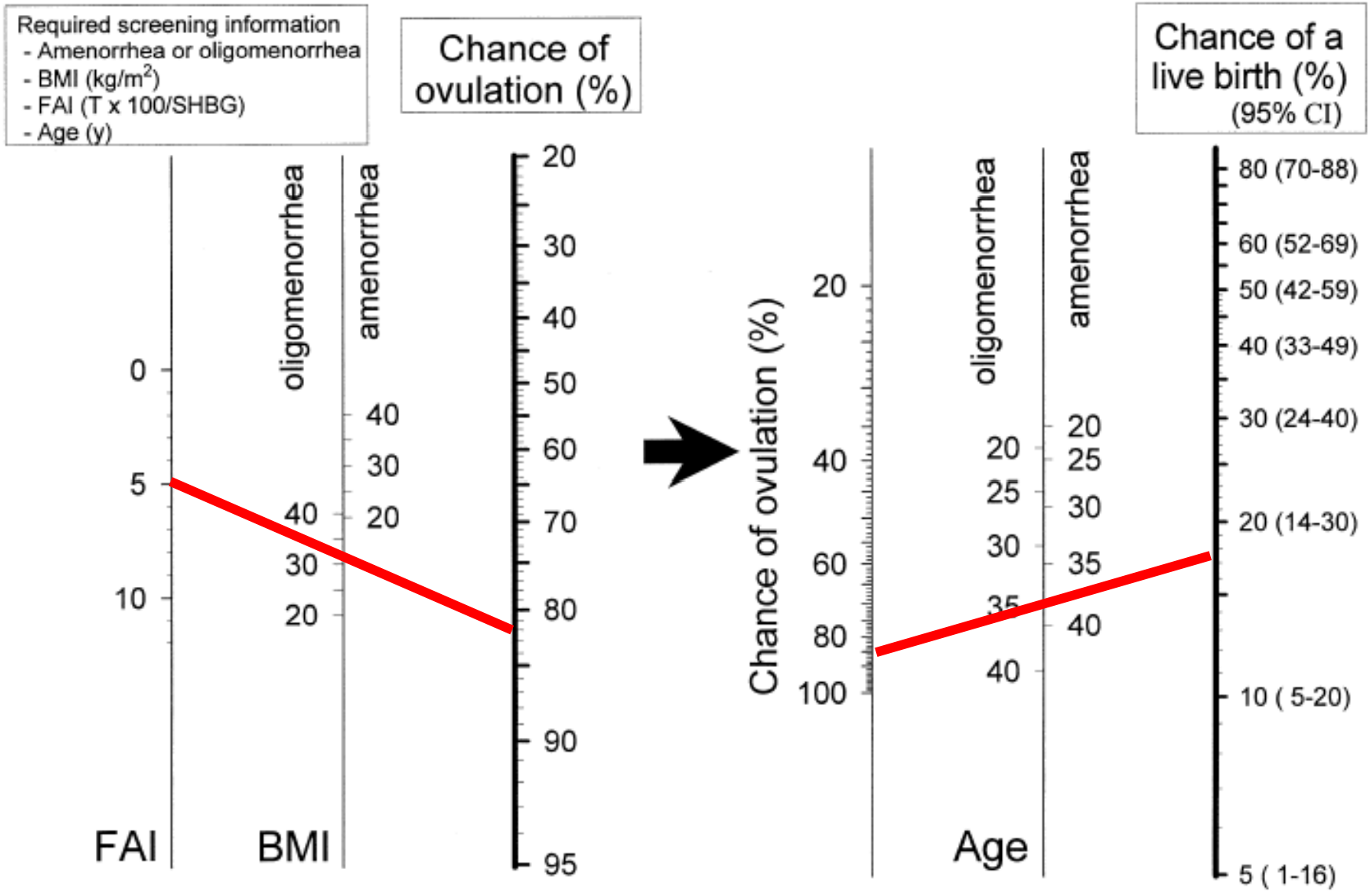
No evidence of a difference in effect was found between clomiphene versus tamoxifen or clomiphene in conjunction with human chorionic gonadotrophin (hCG) versus clomiphene alone.

Brown et al, Cochrane Database Syst Rev. 2009

OVULATION INDUCTION WITH CC (Chances to ovulate and conceive)



Van Santbrink et al, Trends Endocr. Metab. 16, 382-9, 2005



Imani B et al. Fertil Steril 77:91, 2002

Gonadotropin Therapy in PCOS

Clomiphene Resistance: Failure to ovulate after 2-3 successive cycles of CC at the maximal dose (20-30%)

Clomiphene Failure: Women who respond normally to CC but fail to conceive after 6 to 12 cycles of treatment (~60%)

PCOS: *Management*

- *Ovulation induction*

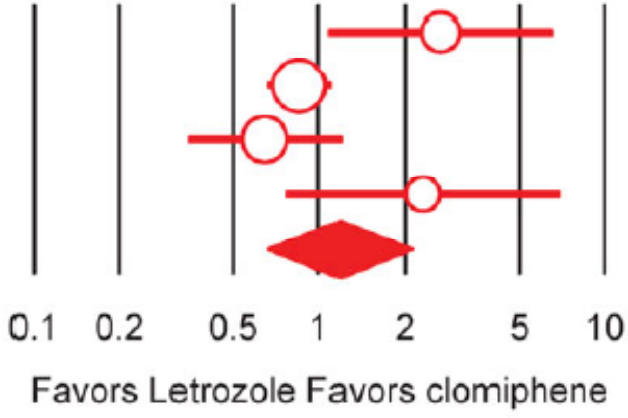
  Clomiphene citrate

  Aromatase inhibitors

  Gonadotropins +/- GnRH analogues

Letrozole in PCOS: Ovulation Rate per Cycle

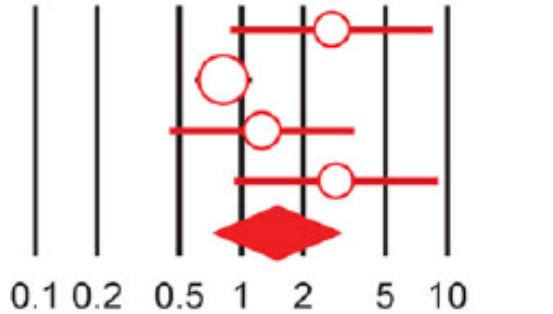
Study name	Odds ratio	Lower limit	Upper limit	Events / Total: Letrazole	Events / Total: Clomiphene
Atay, 2006	2.67	1.08	6.60	42 / 51	35 / 55
Badawy, 2007	0.85	0.66	1.11	365 / 540	371 / 523
Bayar, 2006	0.65	0.35	1.20	65 / 99	71 / 95
Sohrabvand, 2006	2.31	0.77	6.96	48 / 53	54 / 67
	1.17	0.66	2.09	520 / 743	531 / 740



Requena et al, Hum Reprod Upd, 2008

Letrozole in PCOS: Pregnancy Rate per Cycle

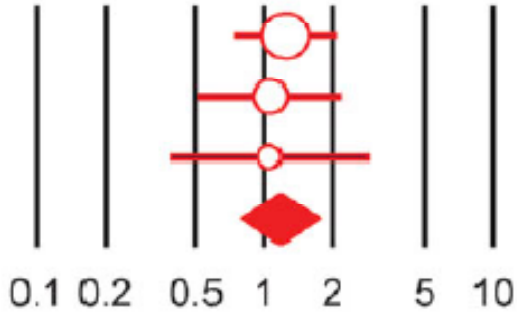
Study name	Odds ratio	Lower limit	Upper limit	Events / Total: Letrazole	Events / Total: Clomiphene
Atay, 2006	2.75	0.88	8.56	11 / 51	5 / 55
Badawy, 2007	0.82	0.59	1.13	82 / 540	94 / 523
Bayar, 2006	1.26	0.45	3.52	9 / 99	7 / 95
Sohrabvand, 2006	2.88	0.92	9.03	10 / 53	5 / 67
	1.47	0.73	2.96	112 / 743	111 / 740



Requena et al, Hum Reprod Upd, 2008

Letrozole in PCOS: Pregnancy Rate in IUI per Cycle

Study name	Odds ratio	Lower limit	Upper limit	Events / Total: FSH & Letrazole	Events / Total: FSH Alone
Bedaiwy 2007	1.24	0.73	2.10	92 / 483	20 / 125
Healey 2006	1.06	0.51	2.21	13 / 60	30 / 145
Mitwally 2003	1.05	0.38	2.88	8 / 36	12 / 56
	1.15	0.78	1.71	113 / 579	62 / 326



Requena et al, Hum Reprod Upd, 2008

Letrozole: Safety Results

- **Incidence of all malformations was not different between letrozole babies and normal deliveries**

(p=0.25; 95%CI 0.78-4.71)

The incidence of locomotor malformations
p=0.0005; 95% CI 2.64–27.0

The incidence of cardiac anomalies
p=0.0006; 95% CI 3.30–58.1

Biljan et al. ASRM, Abstract O-231, 2005

PCOS: *Management*

- *Ovulation induction*

  Clomiphene citrate

  Aromatase inhibitors

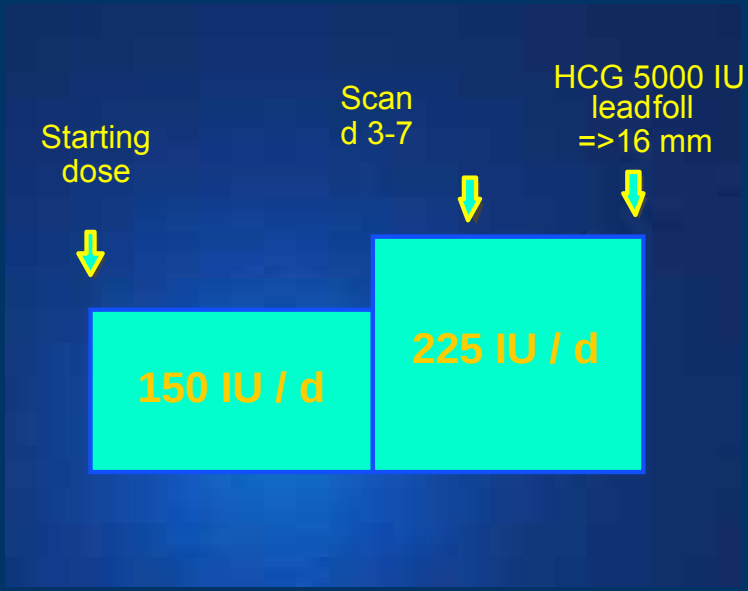
  Gonadotropins +/- GnRH analogues

Step up Protocols

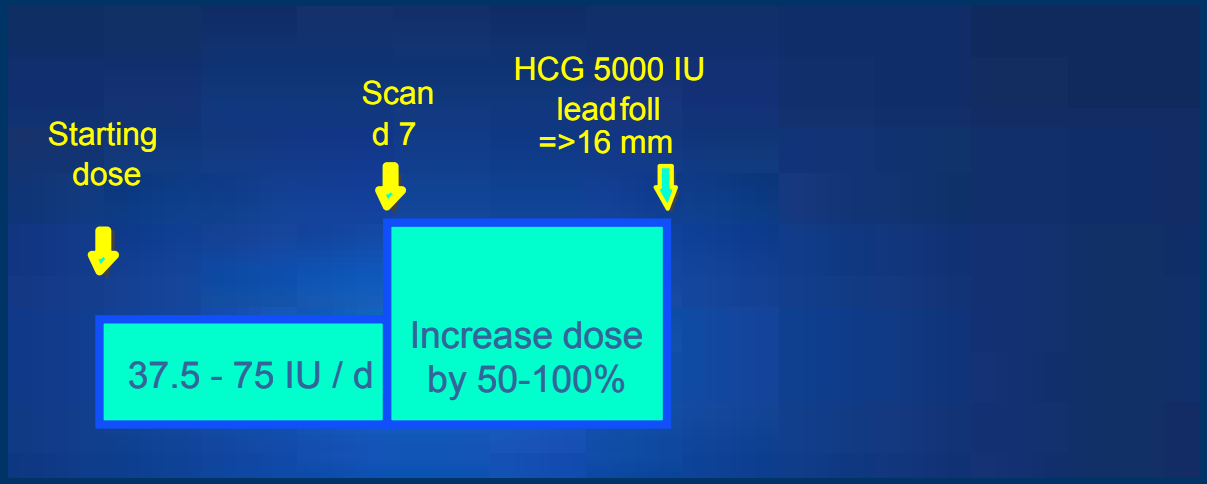
“ Conventional dose protocol “

High (150 IU/d) FSH dose

increased by 75 IU every 3-7 days

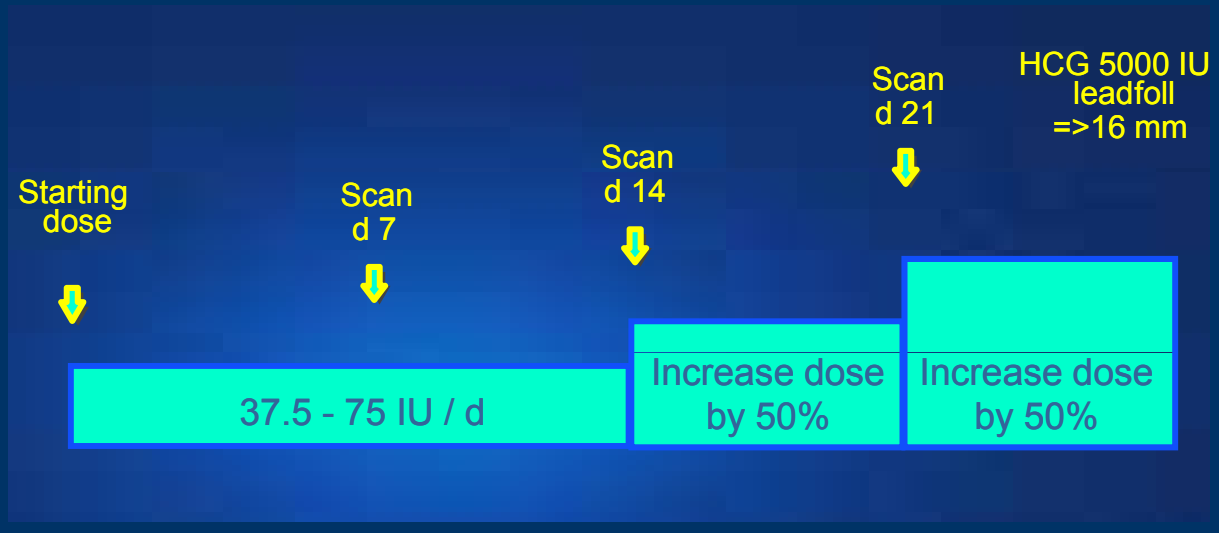


Step up protocols



“ Low dose protocol “

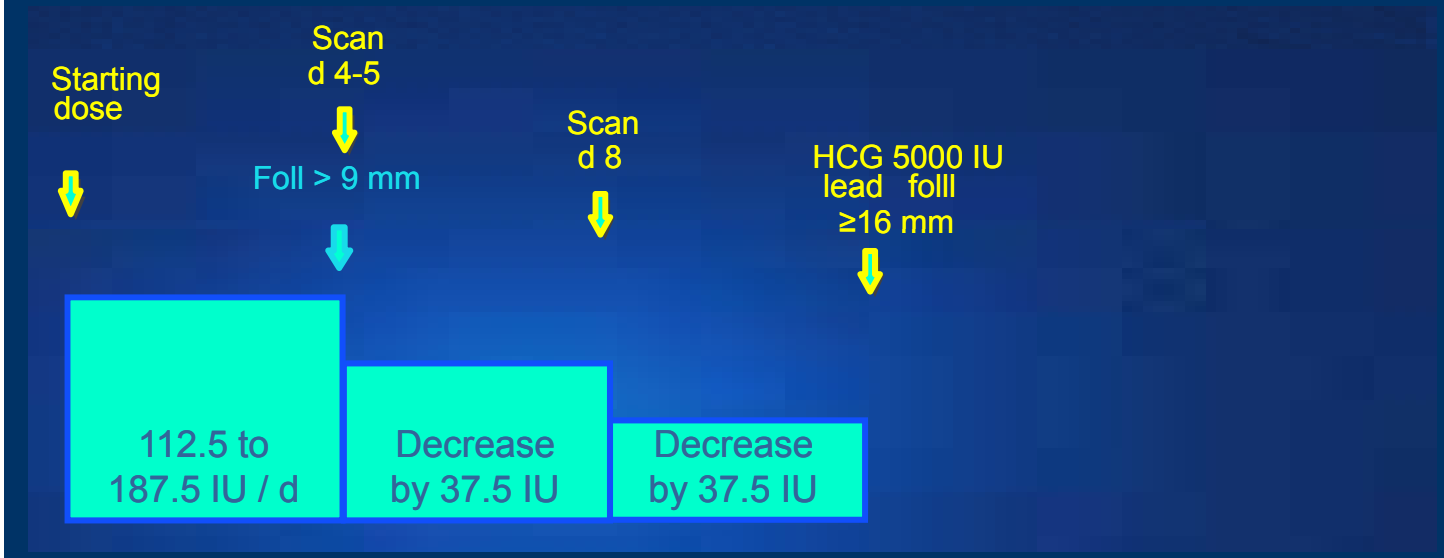
Low (37.5 - 75 IU/d) FSH dose increased by 50-100 % every 7 days



“ Chronic Low dose protocol “

Low (37.5 - 75 IU/d) FSH dose increased by 50% after 14 days

Step down protocols



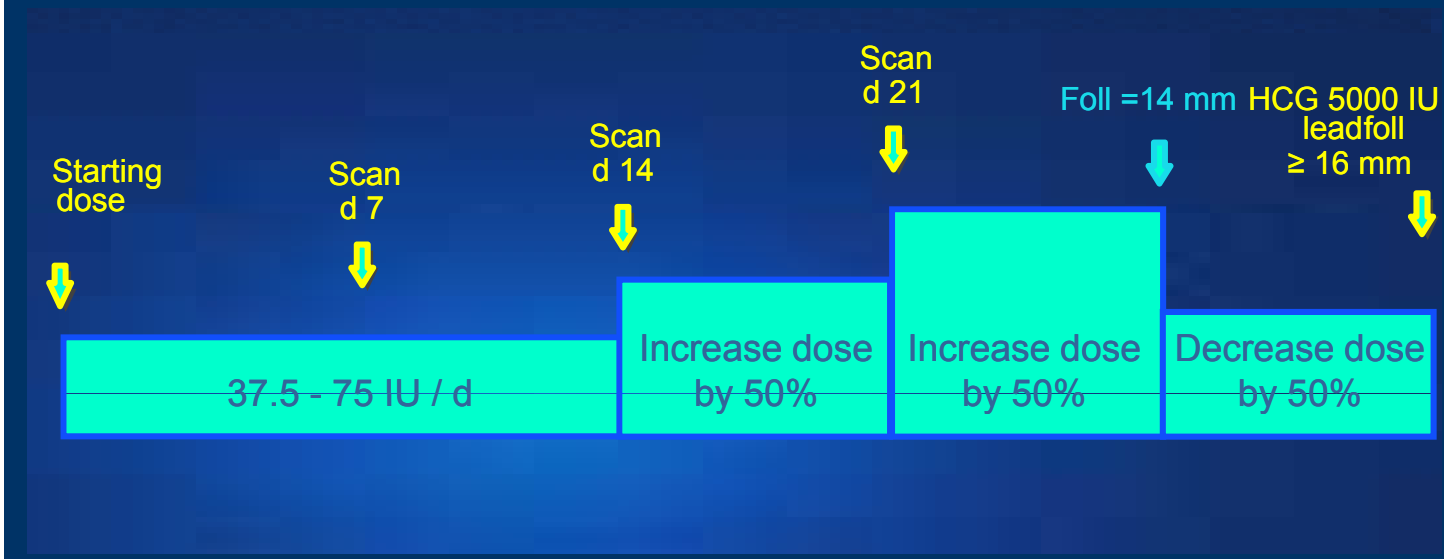
“ Step - down protocol “

Loading FSH dose

(112.5 to 187.5 0 IU/d)

decreased by 37.5 IU

every 3-5 days



“ Sequential protocol “

FSH threshold dose

decreased by 50%

when leading follicle

reaches 14 mm diameter

Human Reproduction Vol.18, No.8 pp.1626–1631, 2003 DOI: 10.1093/humrep/de

A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome

S.Christin-Maitre[1,3] and J.N.Hugues[2] on behalf of the Recombinant FSH Study Group*

	Step-Up (n=85)	Step-Down (n=72)	P
Duration stimulation	15.2	9.7	<0.001
Total amount rFSH	951	967	NS
Monofoll. Cycles (%)	68	32	<0.0001
E2 day hCG	454	849	<0.05
Rate hCG	85	62	0.001
Rate hyperstimulation	2.3	11	0.001
Pregnancy rate	19	16	NS

Step protocols: *Overall results*

Homburg & Howles (1999)

	n (%)	Range (%)
Patients	717	
Cycles completed	1391	
Clinical Pregnancies	280 (40%)	21 - 45
Fecundity / cycle	20 %	12 - 24
Uni-ovulatory cycles	69 %	54 - 88
OHSS	0.14 %	0 - 2.4
Multiples	5.7 %	0 -14.1

Data taken from Siebel et al., 1984 ; Shoham et al. 1991 ; Dale et al. 1993 ; Scheele et al 1993 ; Ares-serono 1995 ; Homburg et al., 1995 ; Aboulghar et al., 1996 ; White et al., 1996 ; Van Santbrink and Fauser, 1997 ; Coelingh-Bennink et al., 1998 ; Hedon et al., 1998.

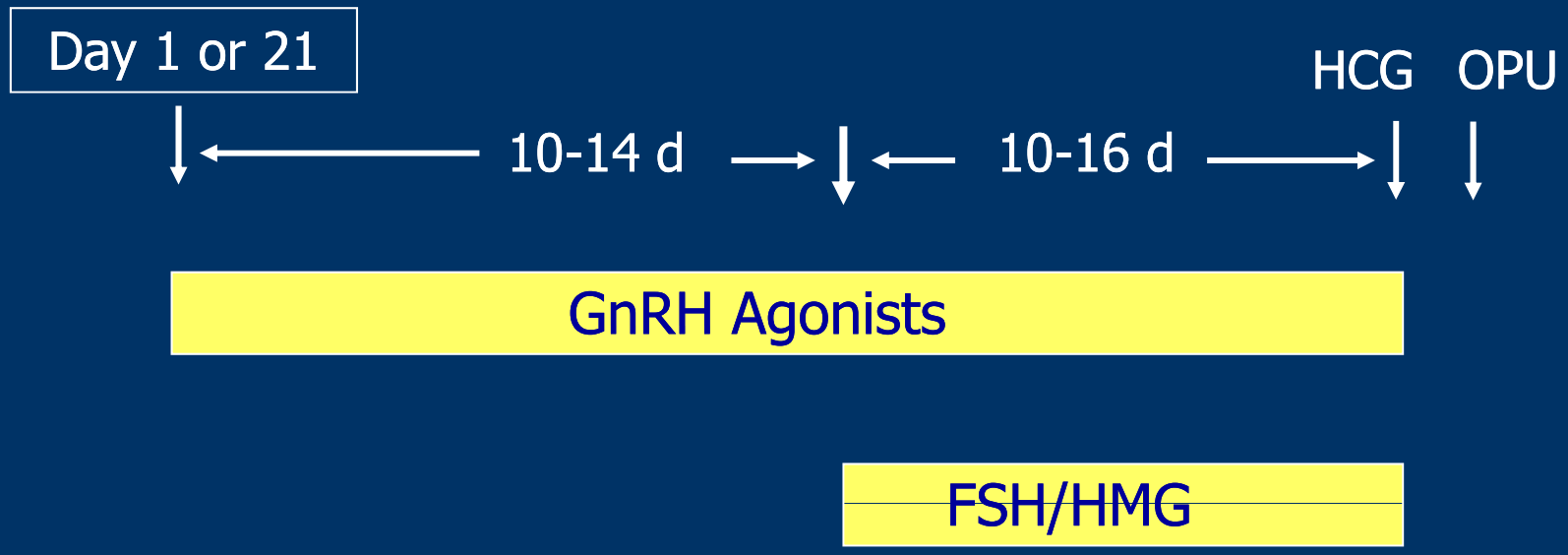
FSH OI in CRA / CC failures
- cumulative outcome rates -

Ovulation	82 %
Ongoing pregnancy	58 %
Singleton live birth	43 %
Multiple live birth	5 %

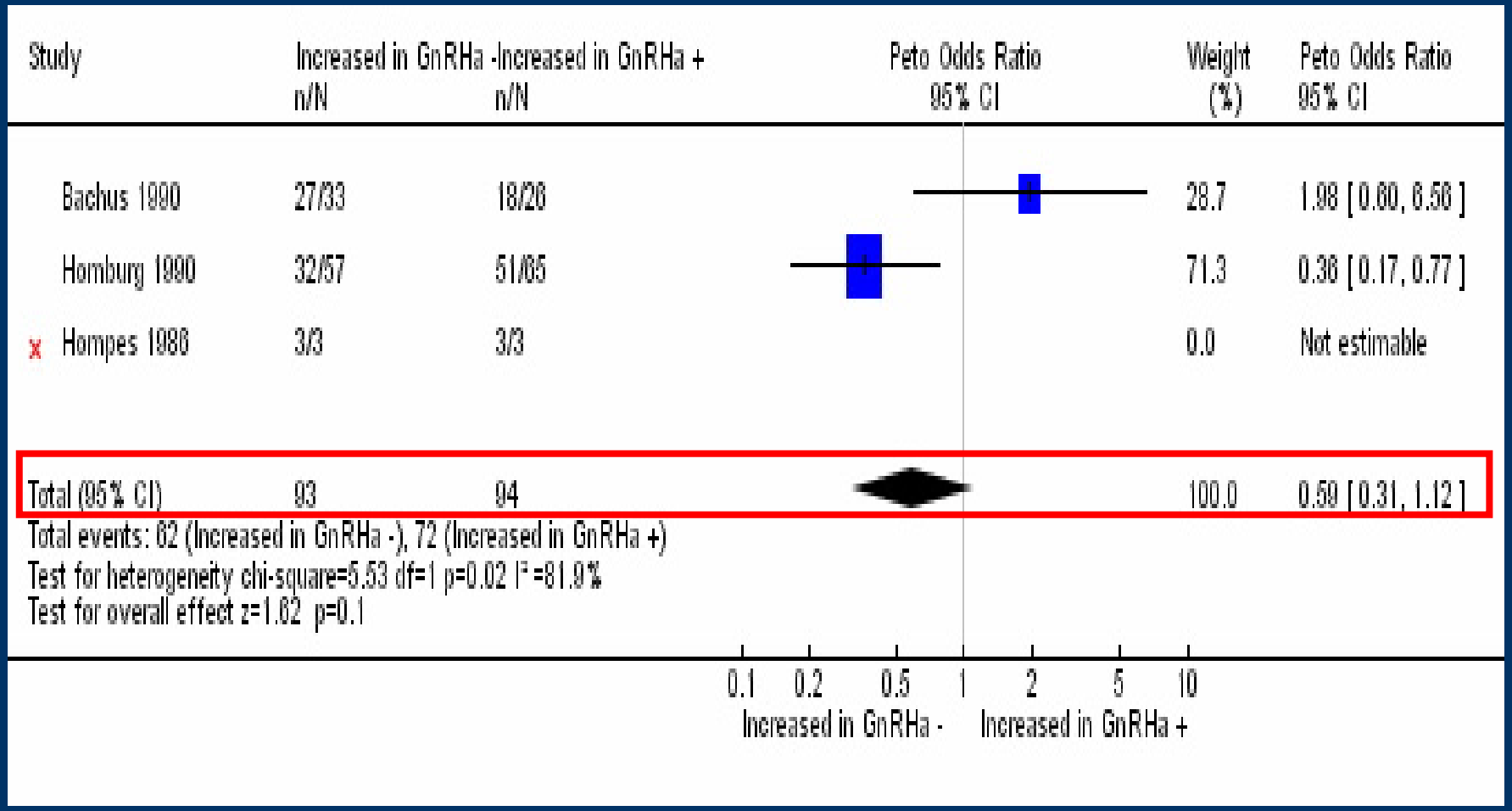
(5 twins, 1 triplet, 1 quadruplet)

Mulders, RBM 2003a
154 patients, 544 cycles

GnRH Agonist Long Protocol

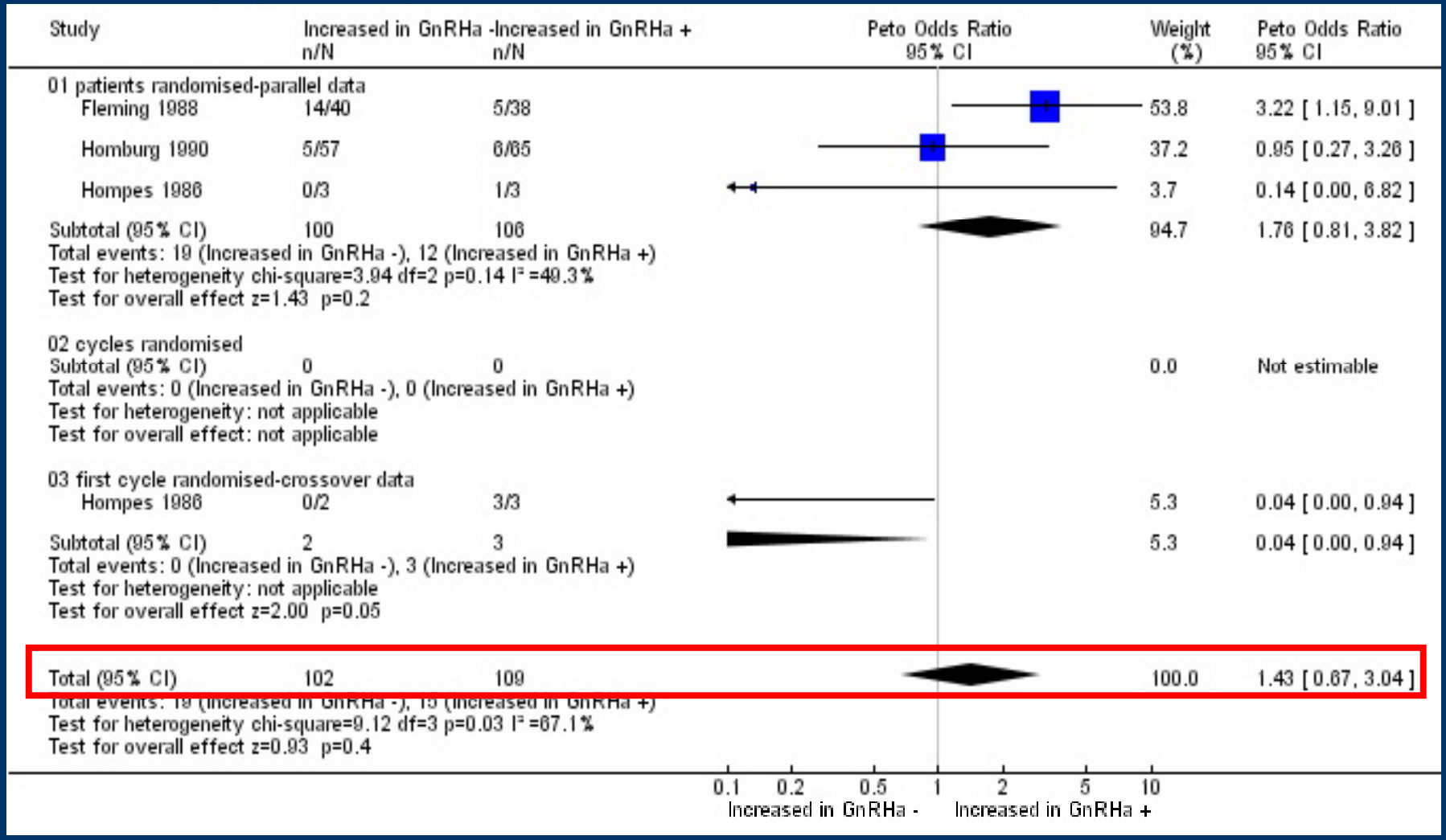


GnRH-A + GONADOTROPINS vs. GONADOTROPINS: *OVULATION RATE (PER CYCLE)*



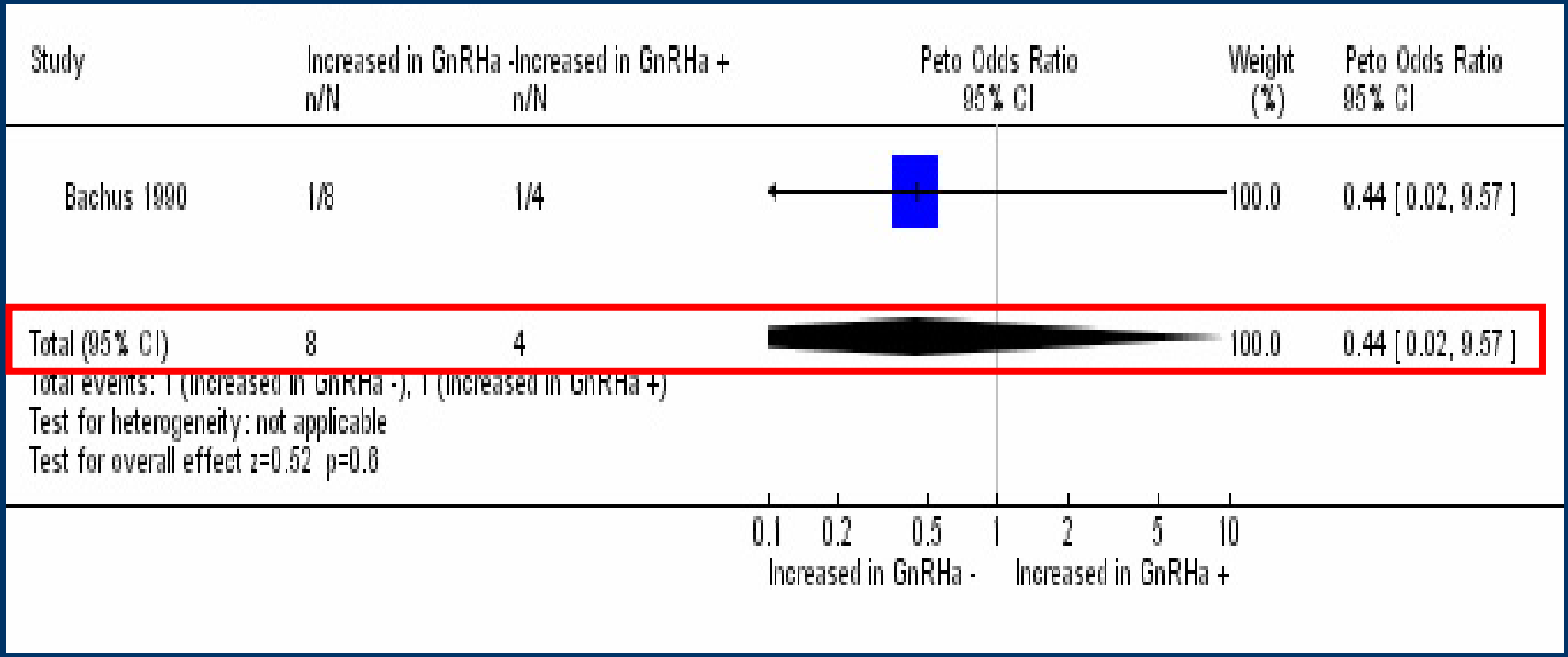
Nugent et al 2006 Cochran Database

GnRH-A + GONADOTROPINS vs. GONADOTROPINS: *PREGNANCY RATE (PER CYCLE)*



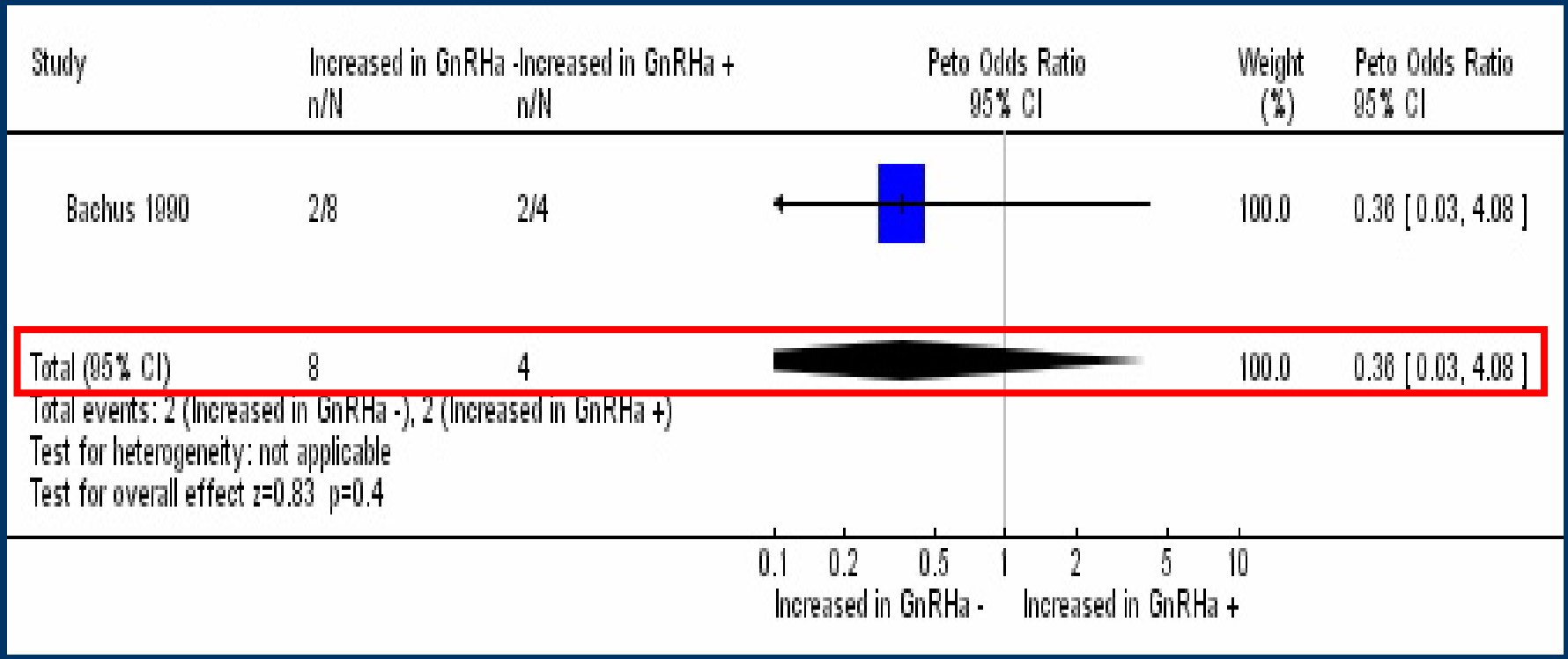
Nugent et al 2006 Cochran Database

GnRH-A + GONADOTROPINS vs. GONADOTROPINS:
MISCARRIAGE RATE (PER PREGNANCY)



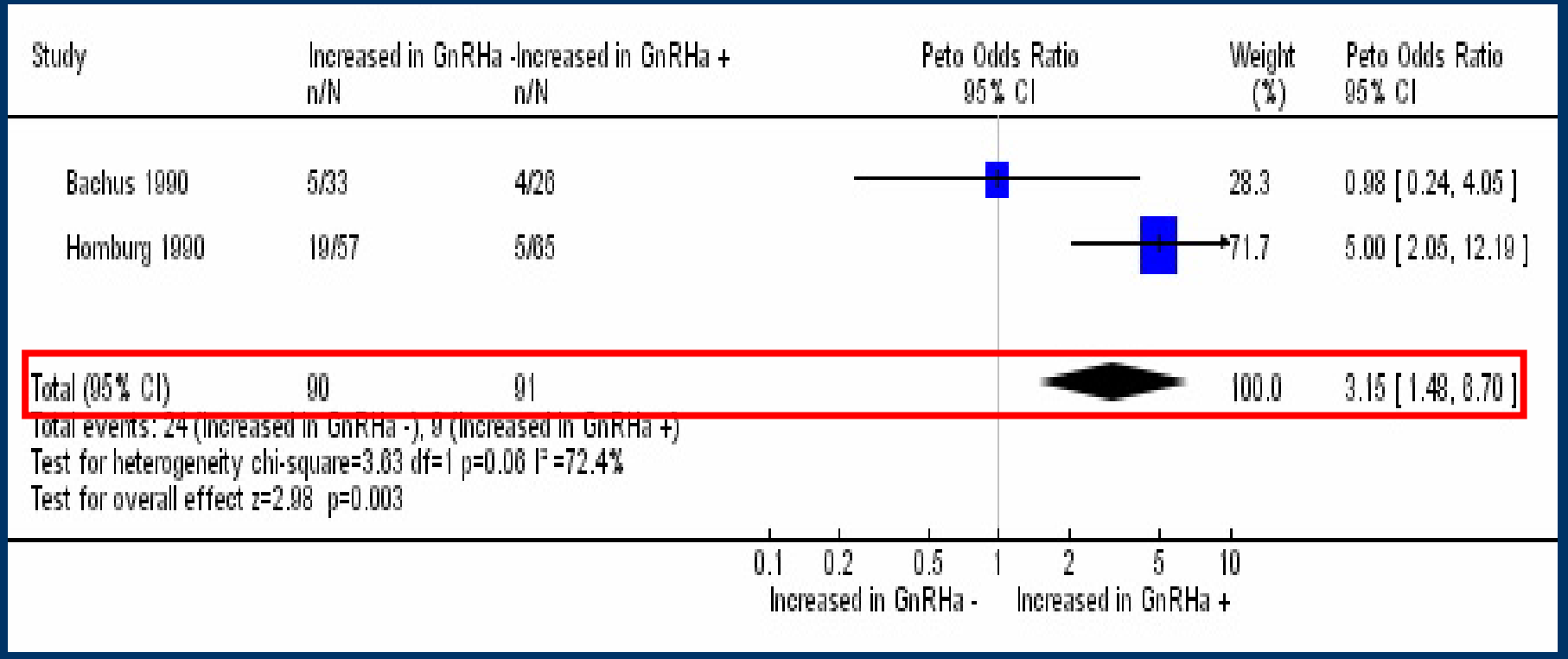
Nugent et al 2006 Cochran Database

GnRH-A + GONADOTROPINS vs. GONADOTROPINS:
MULTIPLE PREGNANCY RATE (PER PREGNANCY)



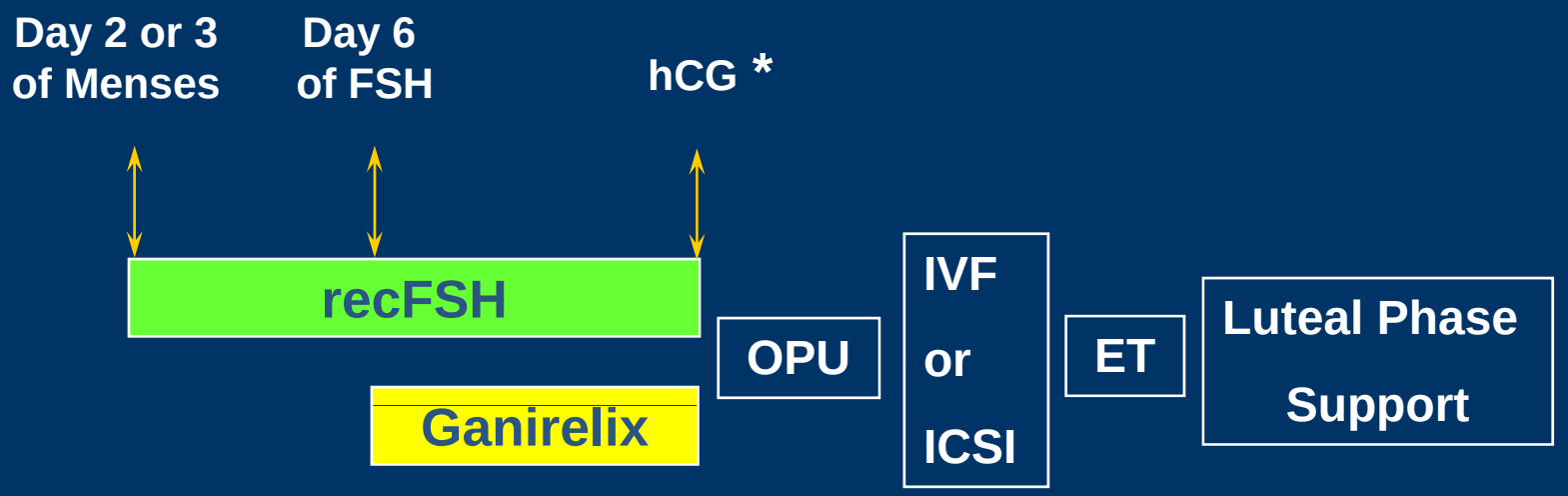
Nugent et al 2006 Cochran Database

GnRH-A + GONADOTROPINS vs. GONADOTROPINS: *OVERSTIMULATION RATE*



Nugent et al 2006 Cochran Database

Daily Regimen of GnRH Antagonists

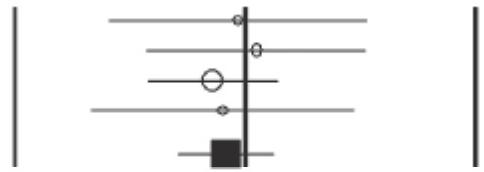


* ≥ 3 follicles ≥ 17 mm

GnRH Agonists vs Antagonists in PCOS

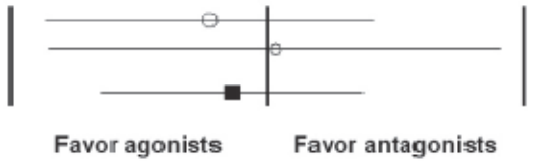
- **Clinical pregnancy rate**

Agonistprotocol	Protocol	Citation	Year	Antagonists	Agonists	Effect	Lower	Upper	PValue
long	flexible	Kim	2004	7 / 21	7 / 20	,93	,26	3,38	,91
long	fixed	Hwang	2004	10 / 27	10 / 29	1,12	,37	3,34	,84
long	flexible	Bahceci	2005	34 / 73	41 / 75	,72	,38	1,38	,32
long	flexible	Ashrafi	2005	5 / 30	6 / 30	,80	,22	2,97	,74
Combined (4)				**56 / 151**	**64 / 154**	**,82**	**,51**	**1,32**	**,42**



- **OHSS incidence**

Agonistprotoco	Protocol	Citation	Year	Antagonists	Agonists	Effect	Lower	Upper	PValue
long	flexible	Bahceci	2005	3 / 73	5 / 75	,60	,14	2,61	,49
long	fixed	Hwang	2004	2 / 27	2 / 29	1,08	,14	8,26	,94
Combined (2)				**5 / 100**	**7 / 104**	**,73**	**,22**	**2,38**	**,60**



Griesinger et al., RBMonline 2006

PCOS: *Management*

- Life-style changes
- Ovulation induction
- Metformin and other insulin-sensitising drugs
- Laparoscopic ovarian surgery
- In Vitro Fertilization - ART

CC+Placebo vs. CC+MET in PCOS

Table 2 Rates of ovulation, pregnancy, and spontaneous abortion. Figures are numbers (percentages) of women in each group

	Clomifene citrate + metformin (n=111)	Clomifene citrate + placebo (n=114)	Risk difference % (95% CI)	Relative risk (95% CI)
Ovulation	71 (64)	82 (72)	–8 (–20 to 4)	0.89 (0.7 to 1.1)
Ongoing pregnancy	44 (40)	52 (46)	–6 (–20 to 7)	0.87 (0.6 to 1.2)
Spontaneous abortion	13 (12)	12 (11)	1 (–7 to 10)	1.11 (0.5 to 2.3)

Moll et al, BMJ, 2006

NIH – Reproductive Medicine Network

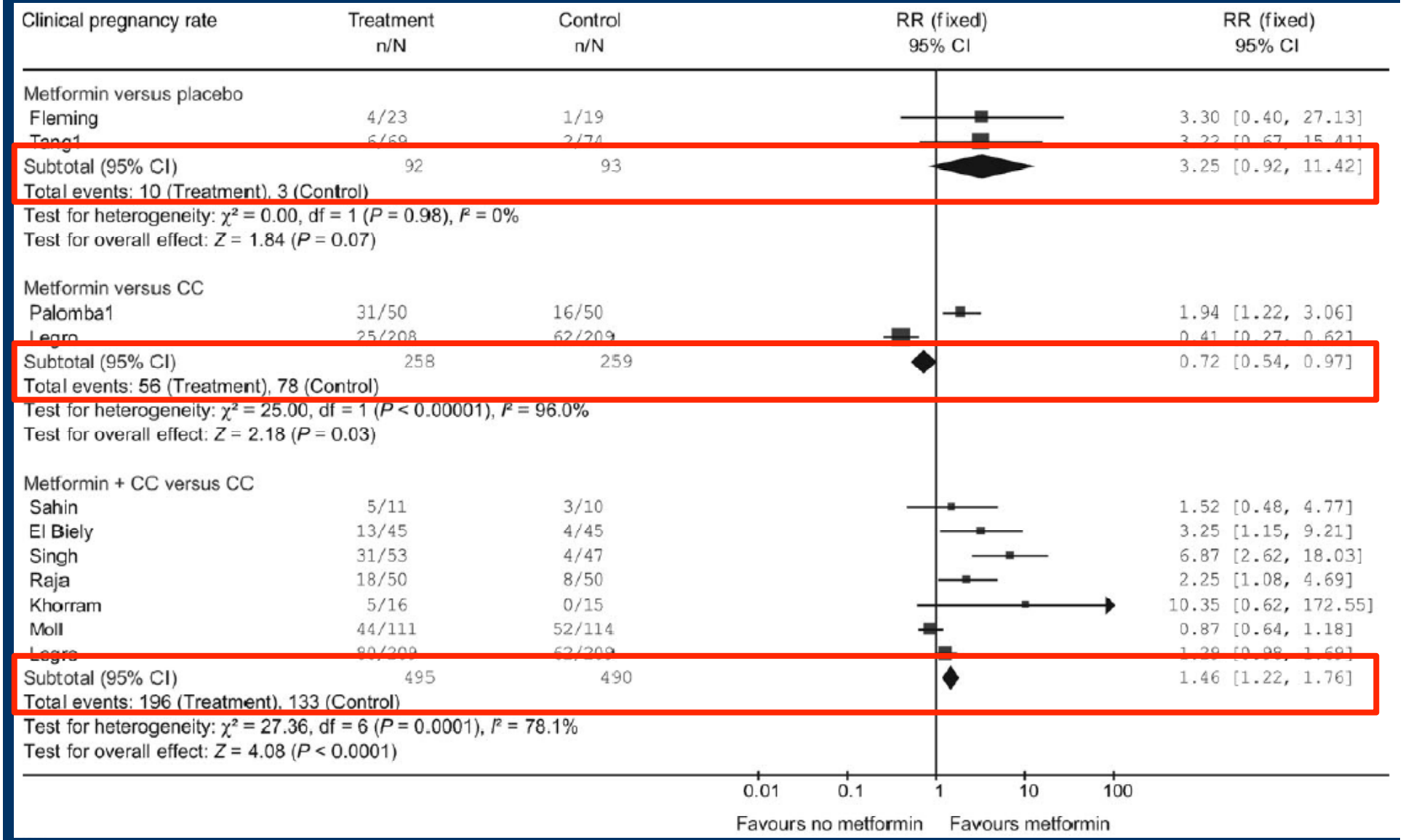
Legro, et al., NEJM, 2007

	Clomiphene 209	Metformin 208	Combination 209
%			
Ovulation	49*	29	60**
Conception	20*	12	38*
Pregnancy	24*	9	31*
Live birth	23*	7	27*
Multiple	6	0	3

*P <0.001

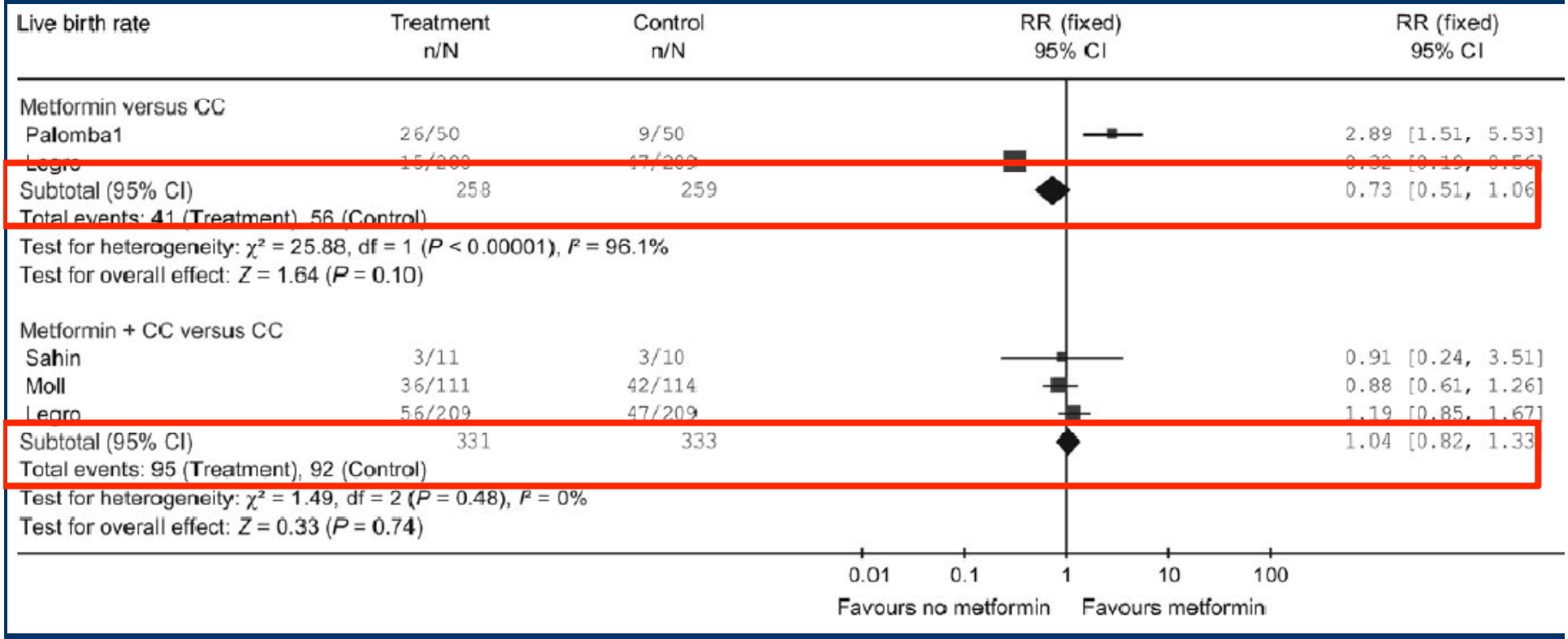
**P < 0.001 combination vs. clomiphene

Metformin in Clomiphene Naïve PCOS Women



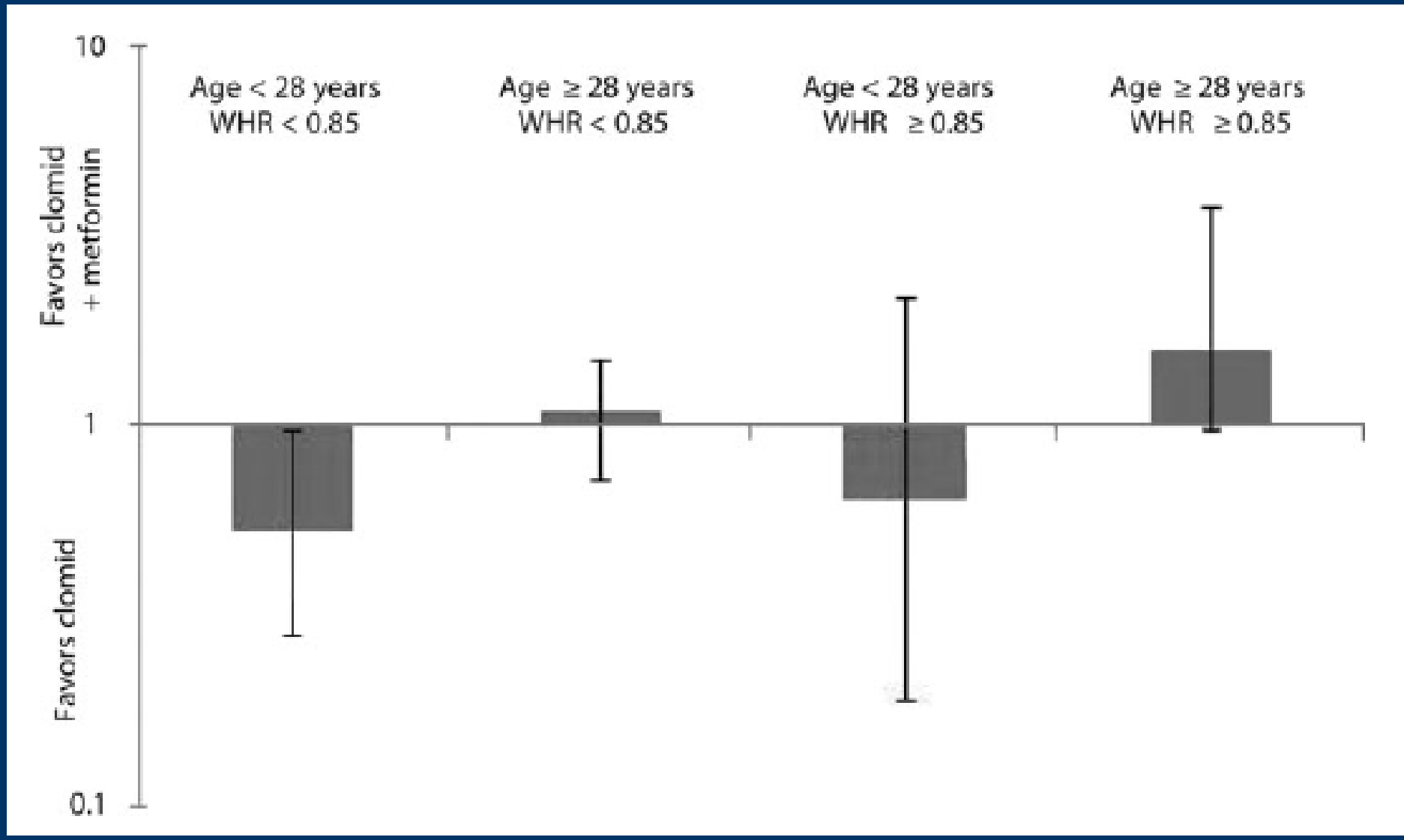
Moll et al, Hum Repr Upd, 2007

Metformin in Clomiphene Naïve PCOS Women



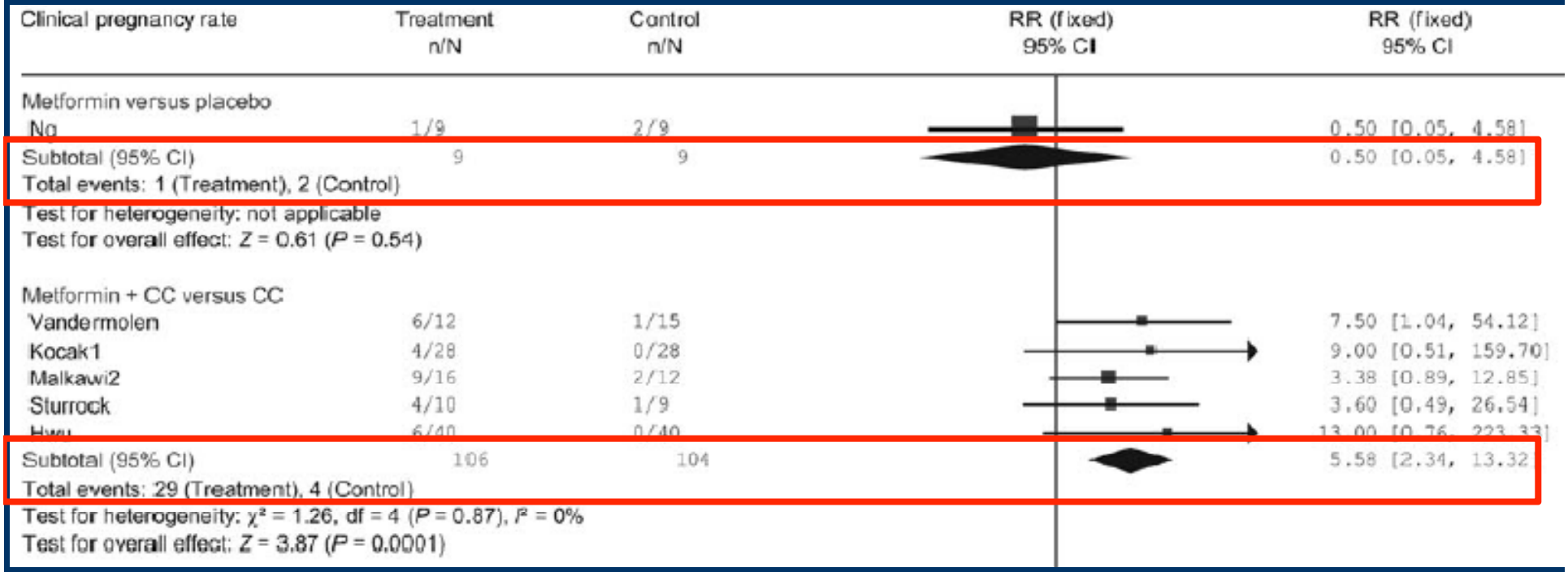
Moll et al, Hum Repr Upd, 2007

Metformin in Subgroups of Clomiphene Naïve PCOS Women



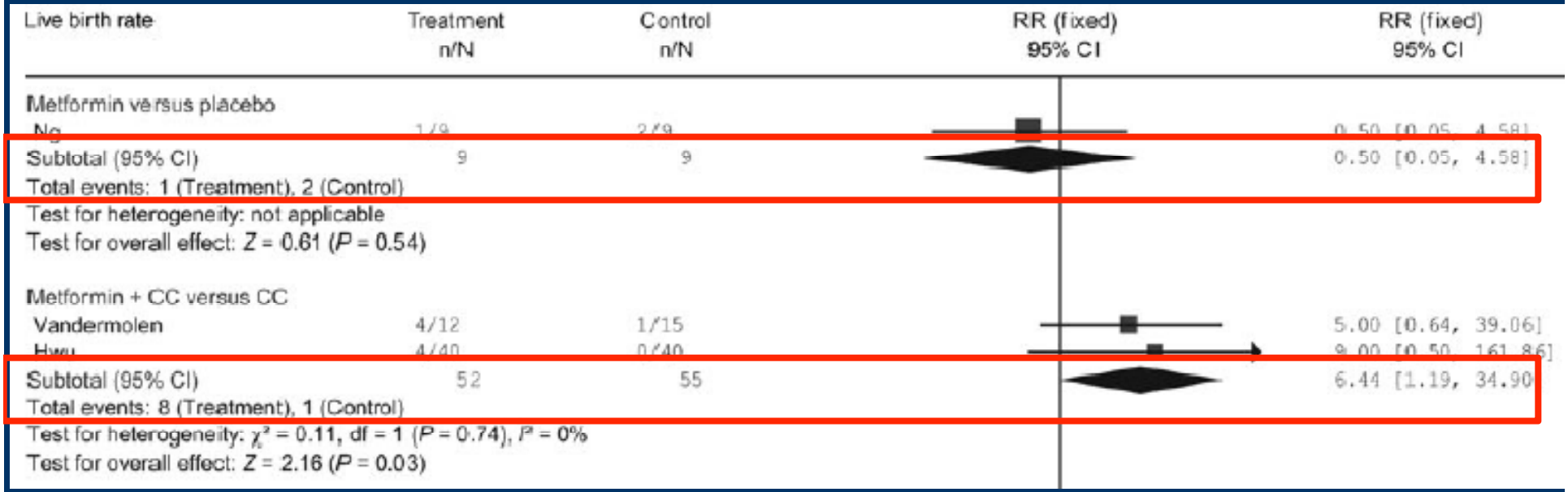
Moll et al, Hum Repr , 2008

Metformin in Clomiphene Resistant PCOS Women



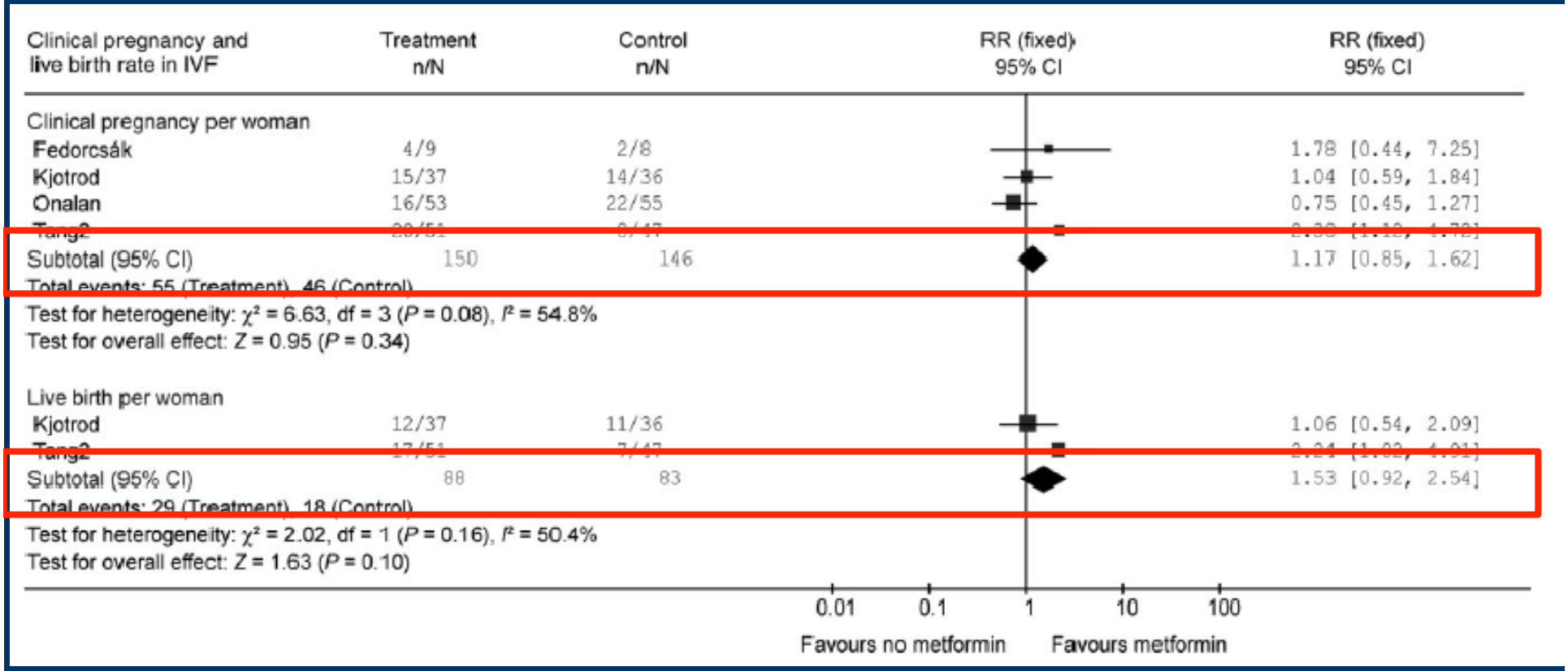
Moll et al, Hum Repr Upd, 2007

Metformin in Clomiphene Resistant PCOS Women



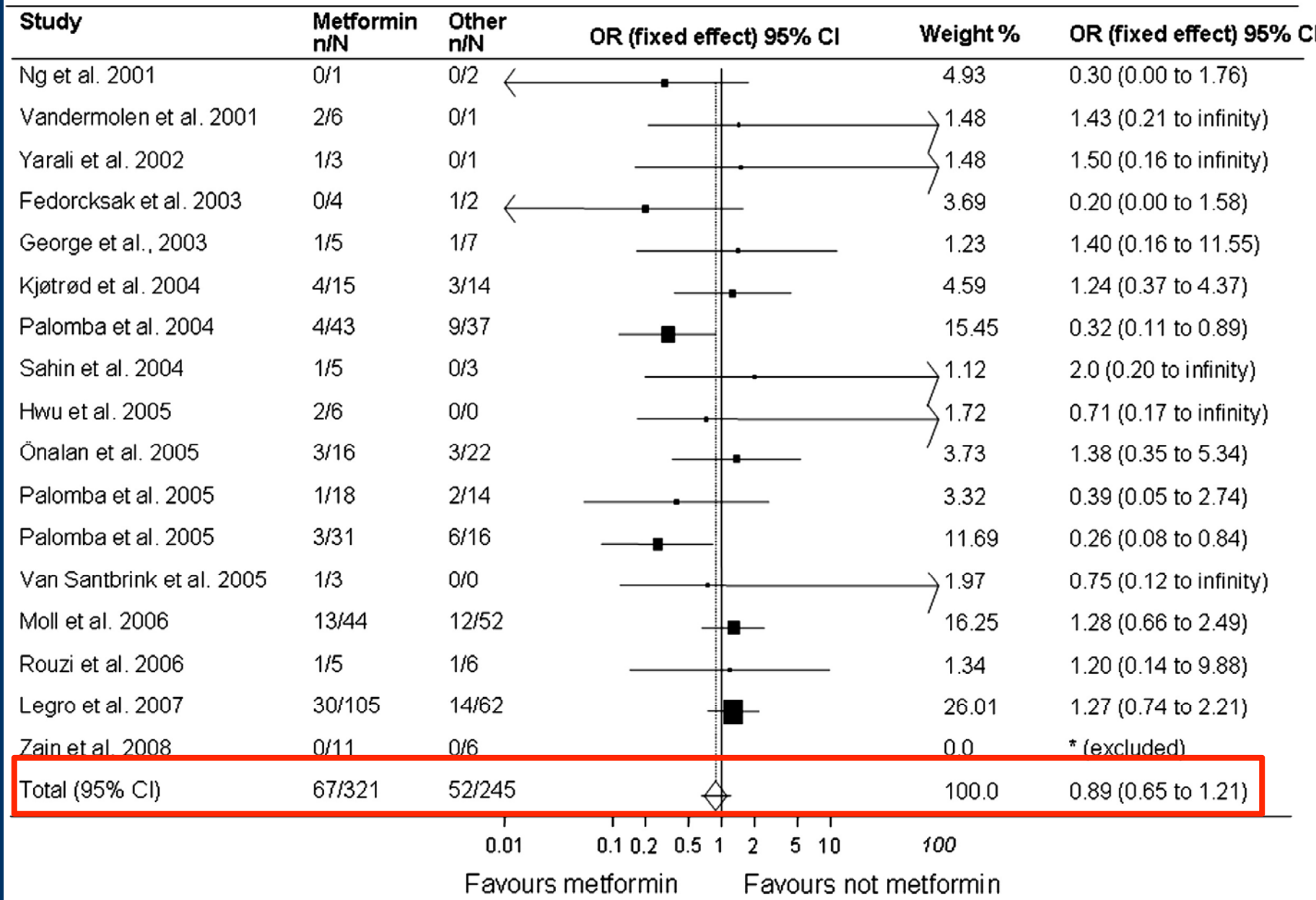
Moll et al, Hum Repr Upd, 2007

Metformin in IVF for PCOS Women



Moll et al, Hum Repr Upd, 2007

Review: Preconceptional metformin administration and abortion risk in PCOS
Outcome: Abortion rate
Comparison: Metformin versus not metfomin

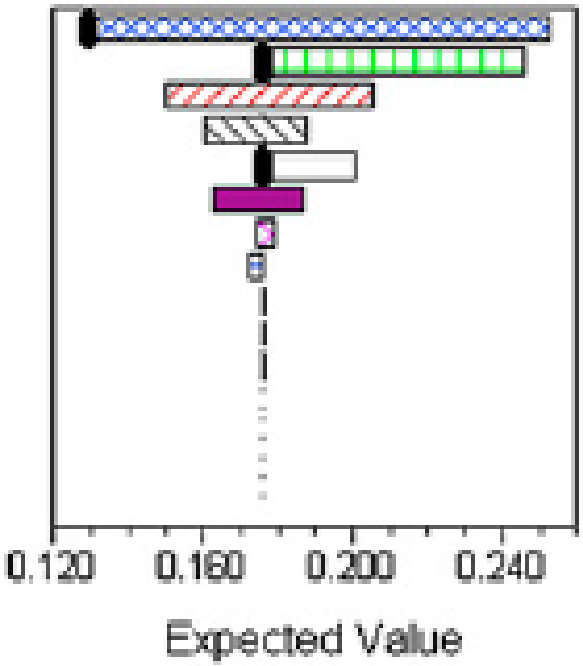


Test for heterogeneity: Cochran Q=13.584, P=0.557
Test for overall effect: Chi²=0.566, P=0.452

Palomba S et al, Fertil Steril. 2009

FIGURE 2

Tornado diagram summary of the 1-way sensitivity analysis for ovulation induction in women with polycystic ovary syndrome.



- probability of pregnancy on metformin + clomiphene citrate: 0.21 to 0.585
- probability of pregnancy on metformin: 0.08 to 0.62
- Utility of a miscarriage: 0.21 to 0.4
- probability of stopping metformin + clomiphene citrate: 0.0 to 0.162
- probability of pregnancy on clomiphene citrate: 0.076 to 0.46
- probability of live birth on metformin + clomid: 0.18 to 0.27
- probability of pregnancy without treatment: 0.0 to 0.09
- utility of a live birth: 0.96 to 1
- Utility of a live birth after d/c meds: 0.71 to 0.87
- Utility of a miscarriage after d/c meds: 0.13 to 0.29
- probability of miscarriage without treatment: 0.228 to 0.25
- probability of live birth with metformin: 0.07 to .52
- probability of stopping metformin: 0.0 to 0.029

Jungheim. Oral ovulation induction agents in PCOS. Fertil Steril 2010.

Insulin Sensitisers (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) in PCOS Women with Oligo-amenorrhoea and Subfertility

There is no evidence that metformin improves live birth rates whether it is used alone (Pooled OR = 1.00, 95% CI 0.16 to 6.39) or in combination with clomiphene (Pooled OR = 1.05, 95% C.I. 0.75 to 1.47).

However, clinical pregnancy rates are improved for metformin versus placebo (Pooled OR =OR 3.86, 95%C.I. 2.18 to 6.84) and for metformin and clomiphene versus clomiphene alone (Pooled OR =1.48, 95% C.I. 1.12 to 1.95) .

Tang et al, Cochrane Database Syst Rev. 2010

Metformin treatment before and during IVF or ICSI in women with PCOS

- No evidence that metformin treatment before or during ART cycles improved live birth or clinical pregnancy rates.

- The pooled odds ratio (OR) for live birth rate was 0.77 (95% CI 0.27 to 2.18) and for clinical pregnancy rate was 0.71 (95% CI 0.39 to 1.28).

- The risk of OHSS in women with PCOS undergoing IVF or ICSI cycles was reduced with metformin (pooled OR 0.27, 95% CI 0.16 to 0.47).

Tso et al., Cochrane Database Syst Rev. 2009

Pioglitazone (30 mg daily) and IVF Outcome

In vitro fertilization outcomes.

	Treatment group	Control group	*P* value
No. of cycles	30	30	
No. of oocytes retrieved	10.0 ± 4.1	13.6 ± 5.8	<.01
No. of MII oocytes	8.9 ± 3.1	11.2 ± 4.2	.02
No. of oocytes fertilized	8.7 ± 2.4	9.8 ± 2.9	NS[a]
No. of grade I, II embryos	6.2 ± 2.2	6.7 ± 2.8	NS[a]
No. of embryos transferred	2.9 ± 0.2	2.8 ± 0.2	NS[a]
No. of embryos frozen	3.7 ± 1.5	4.0 ± 2.0	NS[a]
Clinical pregnancy rate/cycle	36.7% (11/30)	30.0% (9/30)	NS[b]
Miscarriage rate	9.1% (1/11)	22.2% (2/9)	NS[b]
Multiple pregnancy rate	18.2% (2/11)	11.1% (1/9)	NS[b]
Delivered pregnancy rate/cycle	33.3% (10/30)	23.3% (7/30)	NS[b]
Severe OHSS incidence	3.3% (1/30)	10.0% (3/30)	NS[b]

Notes: MII, metaphase II; NS, not statistically significant; OHSS, ovarian hyperstimulation syndrome.

[a] Student's *t*-test.

[b] Chi-square test or Fisher's exact test.

Kim. Pioglitazone and IVF in PCOS women. Fertil Steril 2010.

PCOS: *Management*

- Life-style changes
- Ovulation induction
- Metformin and other insulin-sensitising drugs
- Laparoscopic ovarian surgery
- In Vitro Fertilization

Surgical management of polycystic ovary syndrome

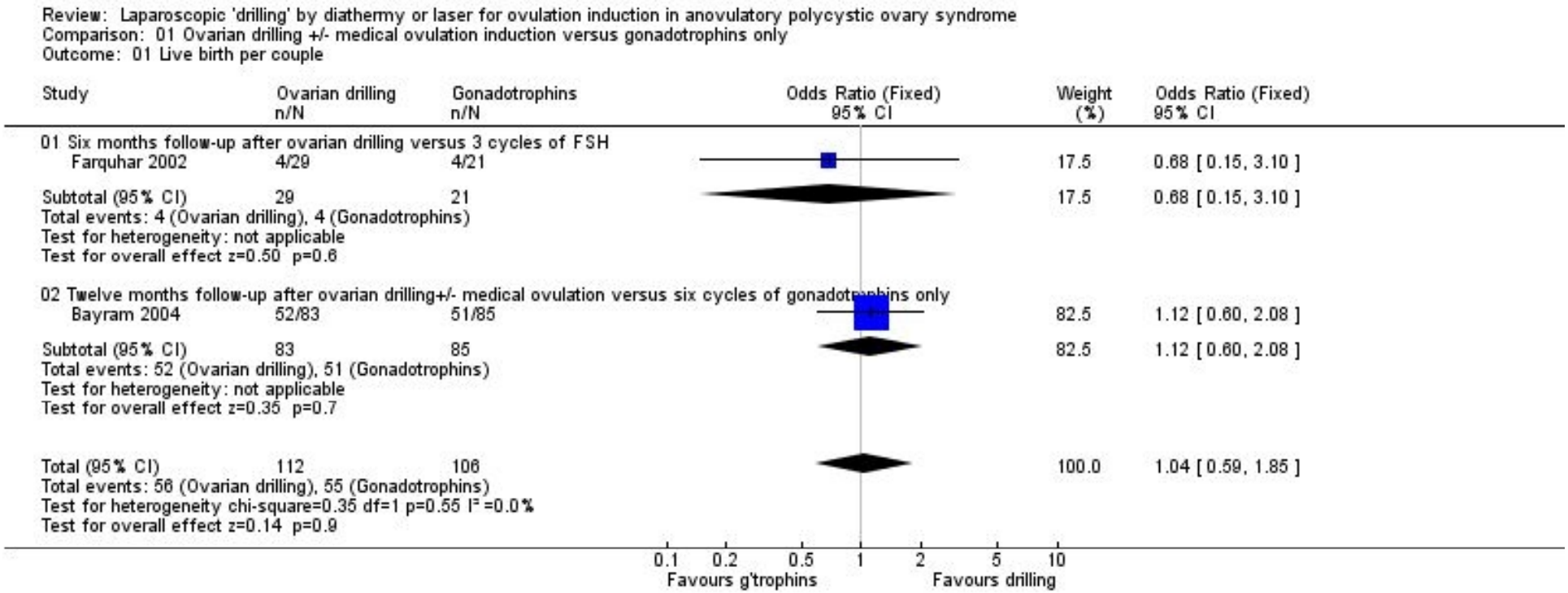
Surgical laparoscopic removal of ovarian tissue was introduced by *Palmer and De Brux in 1967*

Multiple ovarian puncture performed either by diathermy or by laser is well known as "***Ovarian drilling***"

Gjonnaess 1984

Ovarian drilling is a modification of ovarian wedge resection but less invasive

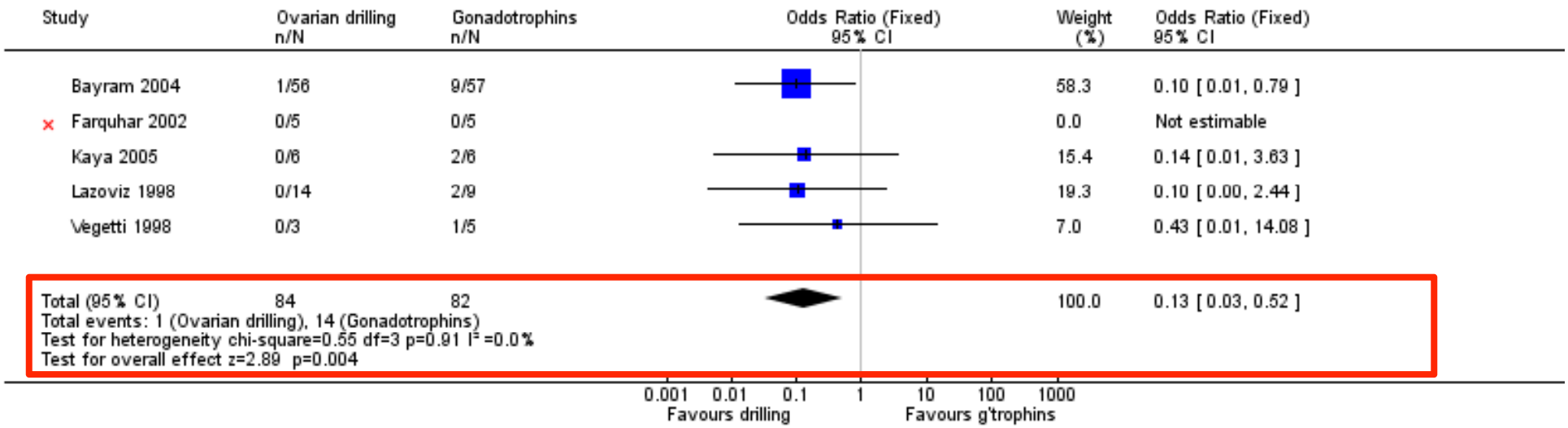
Laparoscopic Ovarian Surgery for Ovulation Induction in Anovulatory PCOS Women: *Live Births*



Farquahar et al 2007

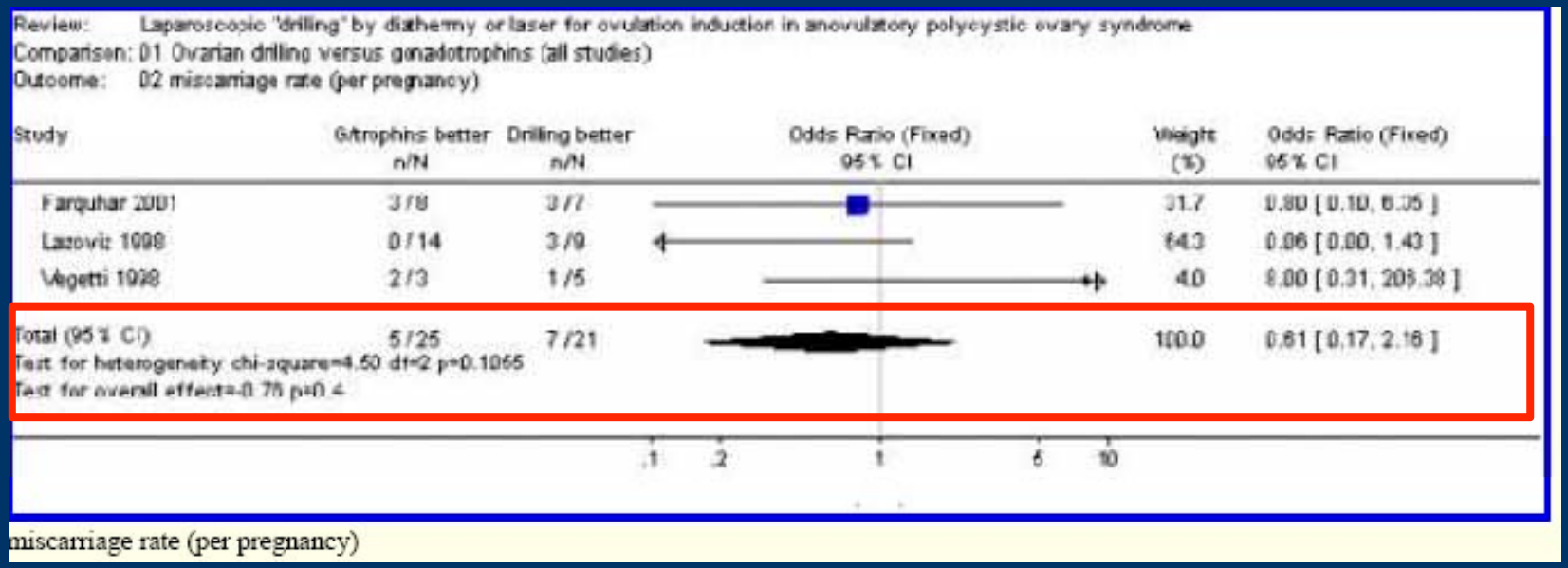
Laparoscopic Ovarian Surgery for Ovulation Induction in Anovulatory PCOS Women: *Multiples*

Review: Laparoscopic 'drilling' by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome
Comparison: 01 Ovarian drilling +/- medical ovulation induction versus gonadotrophins only
Outcome: 04 Multiple pregnancy rate (per ongoing pregnancy)



Farquahar et al 2007

Laparoscopic Ovarian Surgery for Ovulation Induction in Anovulatory PCOS Women: *Miscarriages*

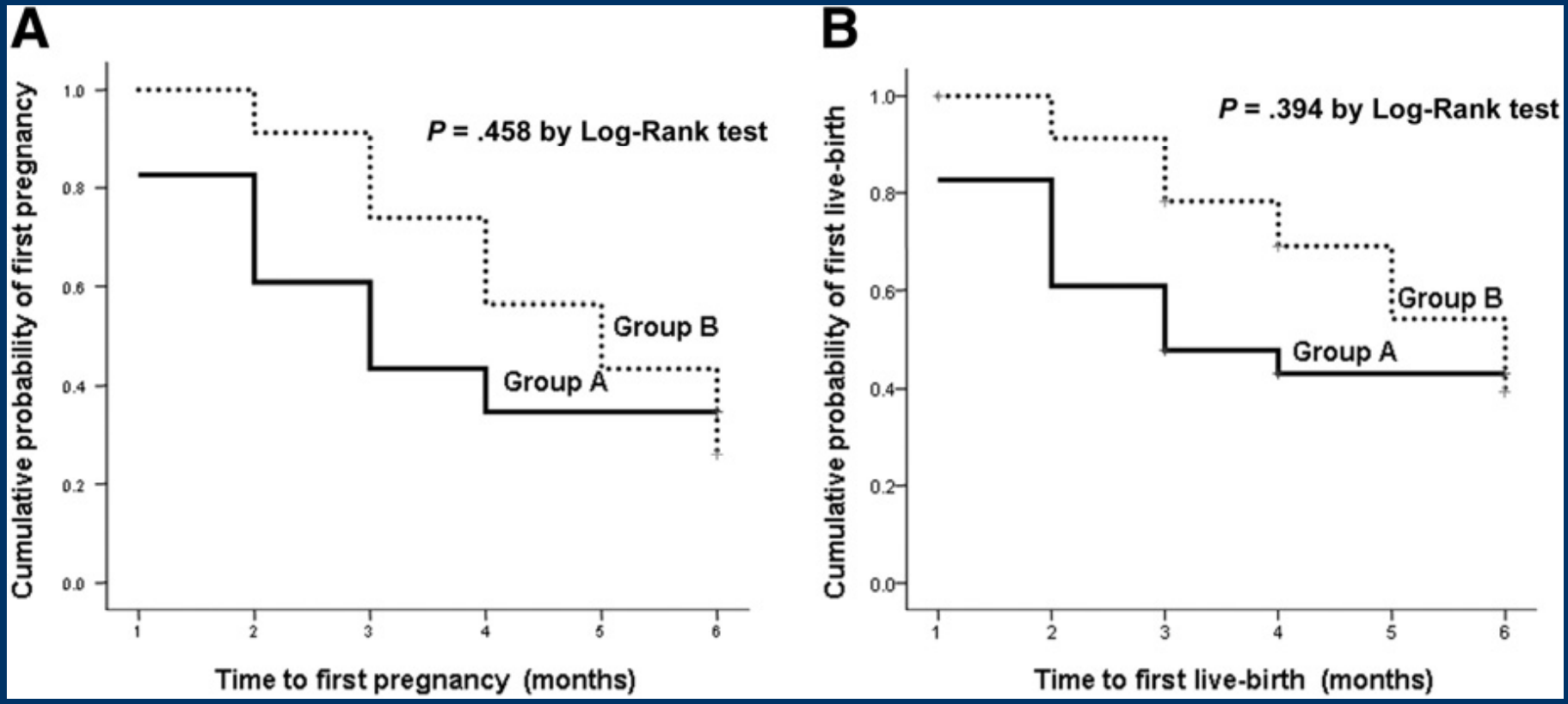


There was no difference in miscarriage rates in the drilling group when compared with gonadotrophin in these trials

OR 0.61, 95% 0.17-2.16

Farquahar et al 2007

Cumulative probability of first pregnancy and first live-birth by the Kaplan-Meier survival analysis in groups A (LOD) and B (CC+MET)



Palomba et al, Am J Obstet Gynecol 2010

PCOS: *Management*

- Life-style changes
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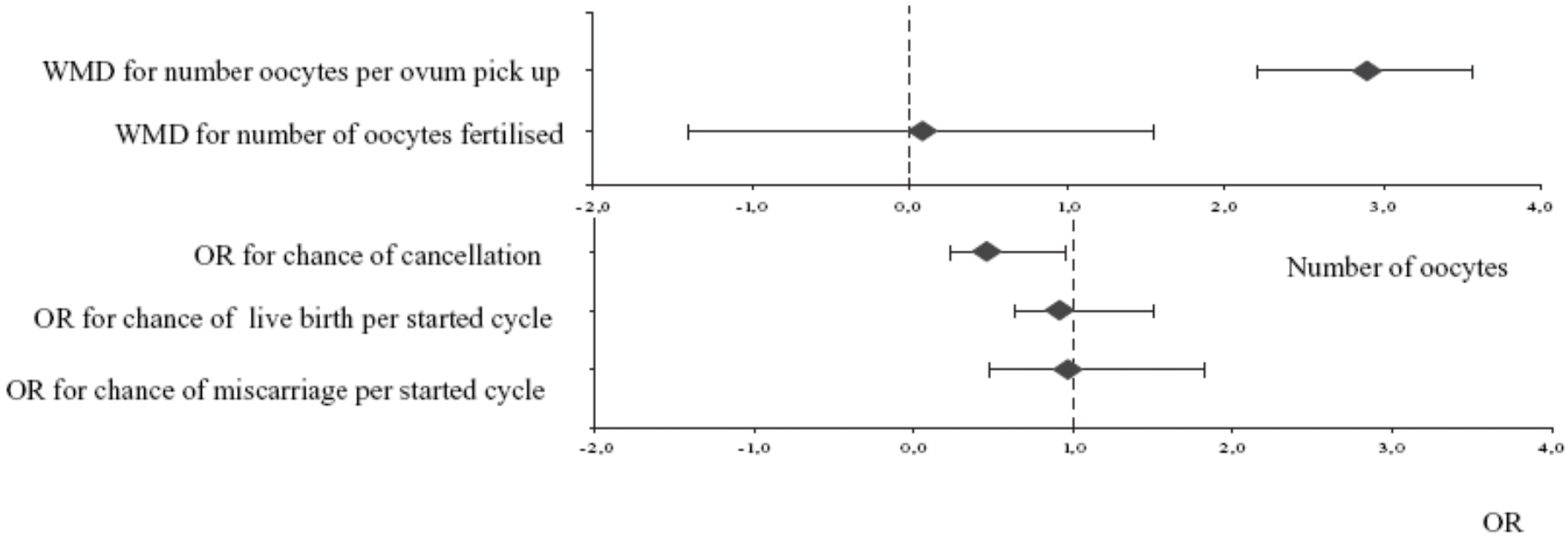
- Laparoscopic ovarian surgery
- In Vitro Fertilization

Clinical Outcomes of IVF in PCOS Women Compared with Matched Controls



Heijnen et al, HRU, 2005

PCOS: *Management*

- Life-style changes
- Ovulation induction
- Metformin and other insulin-sensitising drugs
- Laparoscopic ovarian surgery
- In Vitro Fertilization

PCOS: *Management*

Conclusions

Ovulation Induction in PCOS: *Conclusions*

Life-style modifications should be advised before ovulation induction in obese PCOS women

Clomiphene still remains the treatment of first choise

Aromatase inhibitors seem to be as effective as CC but more data are needed on efficacy and safety

Ovulation Induction in PCOS: *Conclusions*

Metformin alone is less effective than CC in inducing ovulation in women with PCOS

The addition of metformin to CC may be indicated in specific subgroups of women with PCOS

Gonadotropins, in low dose protocols aiming at monofollicular development, represent an effective treatment option

Ovulation Induction in PCOS: *Conclusions*

Laparoscopic ovarian drilling is as effective as gonadotropins for ovulation induction and achievement of pregnancy but with significantly less multiples

IVF is a reasonable option, because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos.

PCOS patients seem to have similar chances to achieve a pregnancy with IVF compared to non-PCOS women

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