Cost-effectiveness of intrauterine insemination with or without mild ovarian hyperstimulation

ESHRE Genk, Belgium, 15 December

B.W. Mol

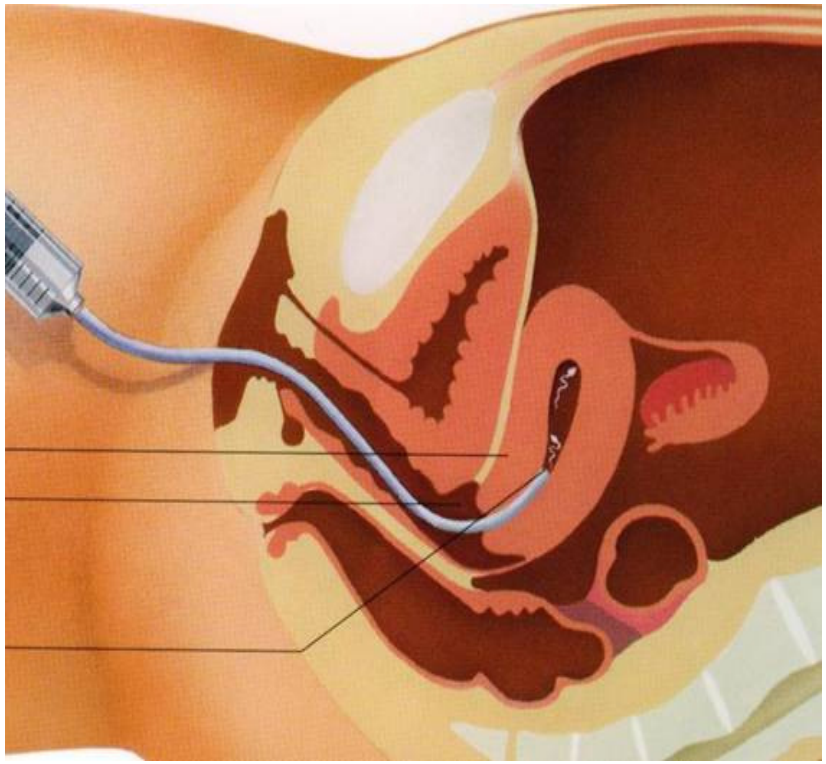
UNIVERSITEIT VAN AMSTERDAM

amc center for reproductive medicine

Introduction

- Definitions
- Principles of economic analysis
- Effectiveness of hyperstimulation in IUI
- Costs of hyperstimulation in IUI
- Costs and effects of hyperstimulation in IUI
- Conclusions

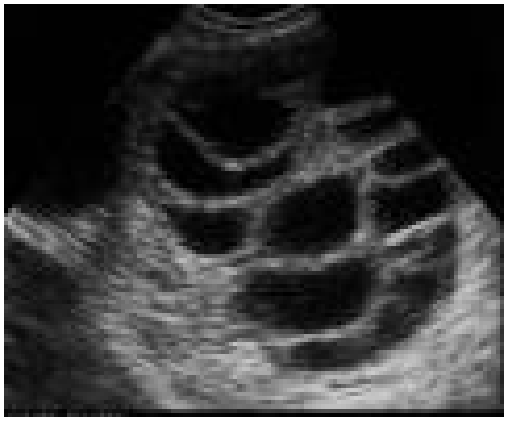
IUI



- Intrauterine insemination
  - Placing the catheter past the ostium internum cervix
  - Inject worked up semen

Hyperstimulation ≠ ovulation induction

- Ovulation induction
  - Aims to obtain a single follicle



- Hyperstimulation
  - Aims to obtain multiple follicles

Economic analysis

- Comparison of the effectiveness and the economic costs of two or more medical interventions
- Efficacy versus effectiveness
- Different perspectives of costs:
  - hospital, third payer, patient, society

Effectiveness in reproductive medicine

- Chemical pregnancy
- Clinical pregnancy
- Live birth
- Ongoing pregnancy
- Singleton pregnancy
- Multiple pregnancy
- Healthy baby

Is a twin that bad??

Human Reproduction Vol.21, No.11 pp. 2736–2738, 2006 doi:10.1093/humrep/del249
Advance Access publication June 22, 2006.

OPINION

Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies?

M.van Wely[1,3], M.Twisk[1], B.W.Mol[1,2] and F.van der Veen[1]

[1]Center for Reproductive Medicine, Academic Medical Center, Amsterdam and [2]Department of Obstetrics and Gynaecology, Máxima Medical Center, Veldhoven, The Netherlands

[3]To whom correspondence should be addressed at: Center for Reproductive Medicine, Academic Medical Center, Meibergdreef 9, H4-213, 1105 AZ Amsterdam, The Netherlands. E-mail: m.vanwely@amc.uva.nl

It has recently been suggested that the measure of success of assisted reproductive technologies (ART) should be the birth of a singleton baby, whereas a twin pregnancy should be considered as a complication. Although the maternal and neonatal complications in twin pregnancies are significantly higher than those in singleton pregnancies, the classification of a twin pregnancy as a complication of ART is in our opinion debatable. Most twin pregnancies result in the birth of two healthy babies, with little or no complication for the mother, and only few twin pregnancies results in serious morbidity of the mother and of one or both of the children. The crux of our arguments is that one should consider those cases as poor outcomes and not a twin pregnancy *per se*.

Key words: artificial reproductive technologies (ART)/complications/twin pregnancy

Is a twin that bad??

Human Reproduction Vol.21, No.11 pp. 2736–2738, 2006 doi:10.1093/humrep/del249
Advance Access publication June 22, 2006.

OPINION

Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies?

M.van Wely[1,3], M.Twisk[1], B.W.Mol[1,2] and F.van der Veen[1]

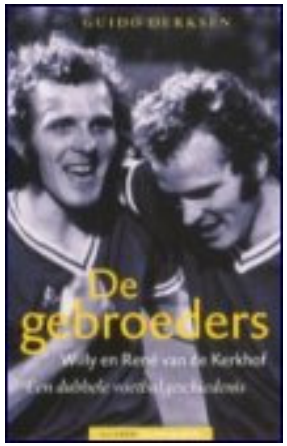
[1]Center for Reproductive Medicine, Academic Medical Center, Amsterdam and [2]Department of Obstetrics and Gynaecology, Máxima Medical Center, Veldhoven, The Netherlands

[3]To whom correspondence should be addressed at: Center for Reproductive Medicine, Academic Medical Center, Meibergdreef 9, H4-213, 1105 AZ Amsterdam, The Netherlands. E-mail: m.vanwely@amc.uva.nl

It has recently been suggested that the measure of success of assisted reproductive technologies (ART) should be the birth of a singleton baby, whereas a twin pregnancy should be considered as a complication. Although the maternal and neonatal complications in twin pregnancies are significantly higher than those in singleton pregnancies, the classification of a twin pregnancy as a complication of ART is in our opinion debatable. Most twin pregnancies result in the birth of two healthy babies, with little or no complication for the mother, and only few twin pregnancies results in serious morbidity of the mother and of one or both of the children. The crux of our arguments is that one should consider those cases as poor outcomes and not a twin pregnancy *per se*.

Key words: artificial reproductive technologies (ART)/complications/twin pregnancy

Is a twin that bad??



Is a live birth always good?

GA (wk)	Survival	Number of survivors	BPD	IVH3, PVHI	PVL	ROP	NEC
22	10-14	8	33-40	0-20	0	33-80	0
23	20-52	149	26-85	7-19	0-9	18-62	0-14
24	34-67	435	31-77	5-14	6-11	17-48	0-13
25	52-81	530	33-70	4-16	5-8	9-32	0-9
26							

Are conclusions based on live birth different?

		OR	95% CI	Total number of patients
ALL	PR	1.19	1.13 to 1.26	24272
	LBR	1.23	1.16 to 1.31	24272

Are conclusions based on live birth different?

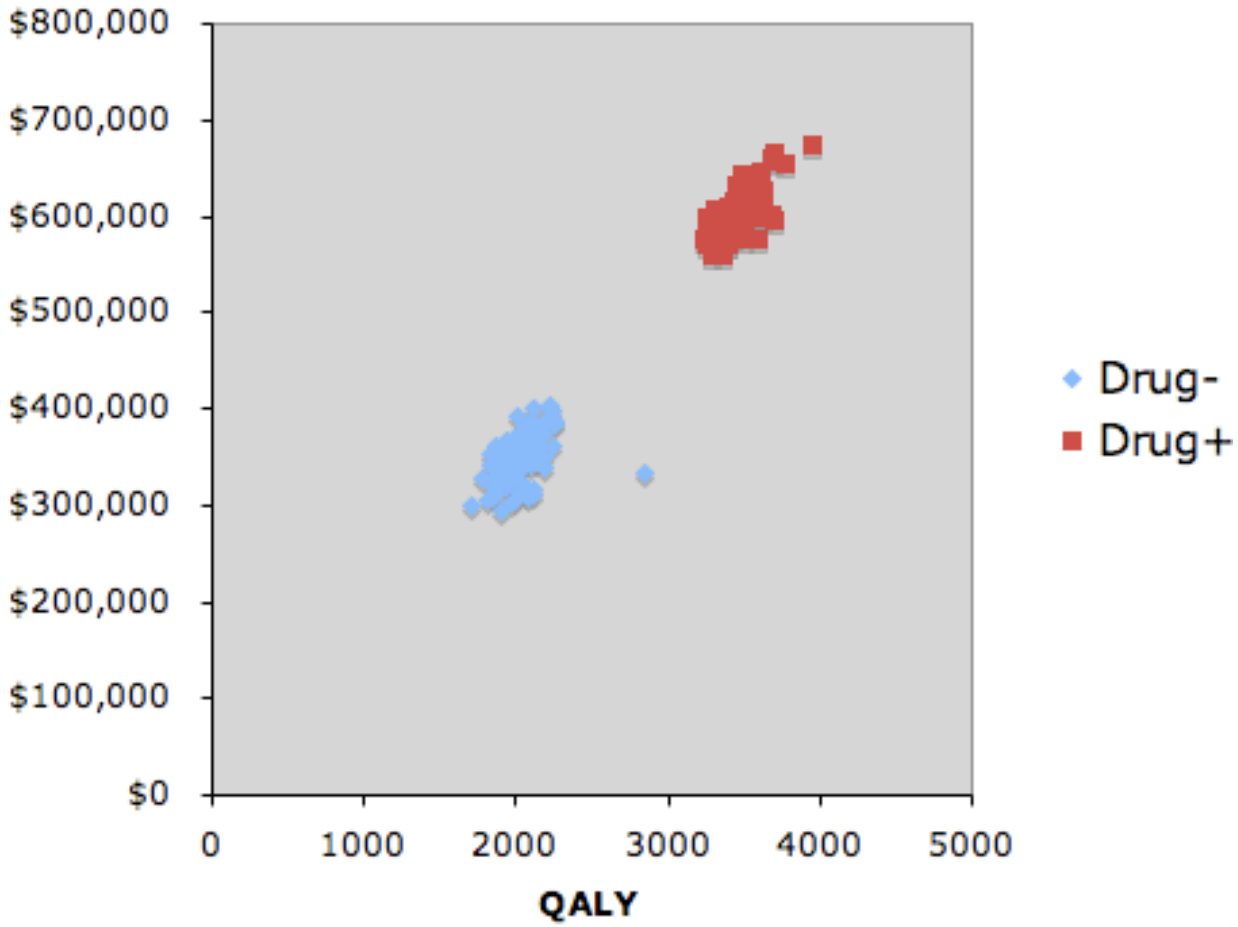
	ART or non-ART	Number of studies	Treatment group	Control group	Ratio of the odds ratios (95% CI)
			Difference between clinical pregnancy and live birth (%)		
Difference in proportions for CPR and LBR					
	All	143	5.4%	5.5%	1.01 (0.9, 1.12)

Are conclusions based on live birth different?

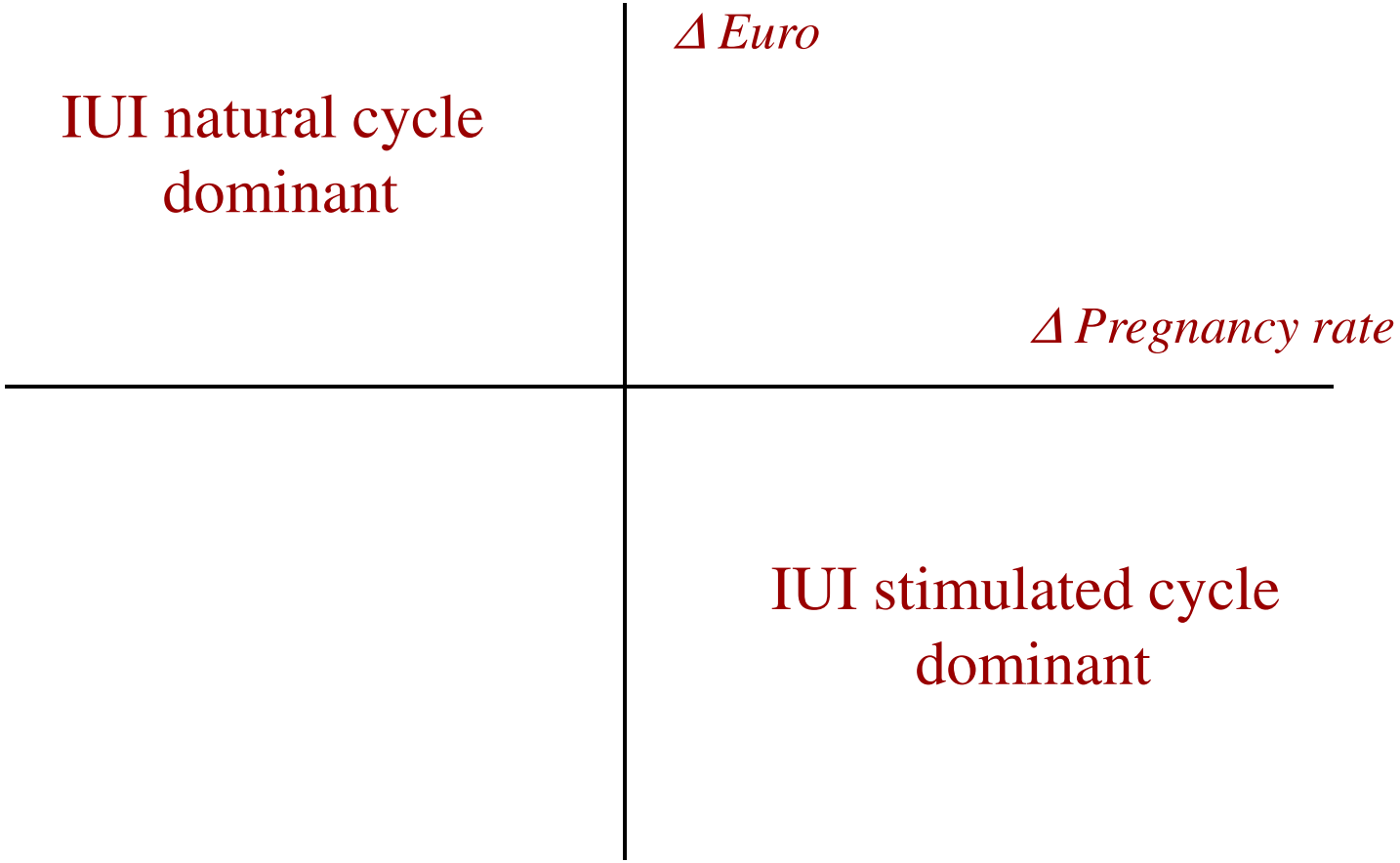
	ART or non-ART	Number of studies	Treatment group	Control group	Ratio of the odds ratios (95% CI)
			Difference between clinical pregnancy and live birth (%)		
Difference in proportions for CPR and LBR	ART	111	4.8%	4.9%	0.99 (0.87, 1.13)
	non-ART	32	7.2%	6.9%	1.03 (0.86, 1,23)
	All	143	5.4%	5.5%	1.01 (0.9, 1.12)

Ongoing pregnancy is an equally sound base for conclusions on effectiveness as live birth

Incremental cost-effectiveness (ICER)



Incremental cost-effectiveness (ICER)



Efficacy

Human Reproduction Update, Vol.14, No.6 pp. 563–570, 2008 doi:10.1093/humupd/dmn034
Advance Access publication August 6, 2008

The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis

M.M.E. van Rumste[1,4], I.M. Custers[2], F. van der Veen[2], M. van Wely[2], J.L.H. Evers[3] and B.W.J. Mol[1,2]

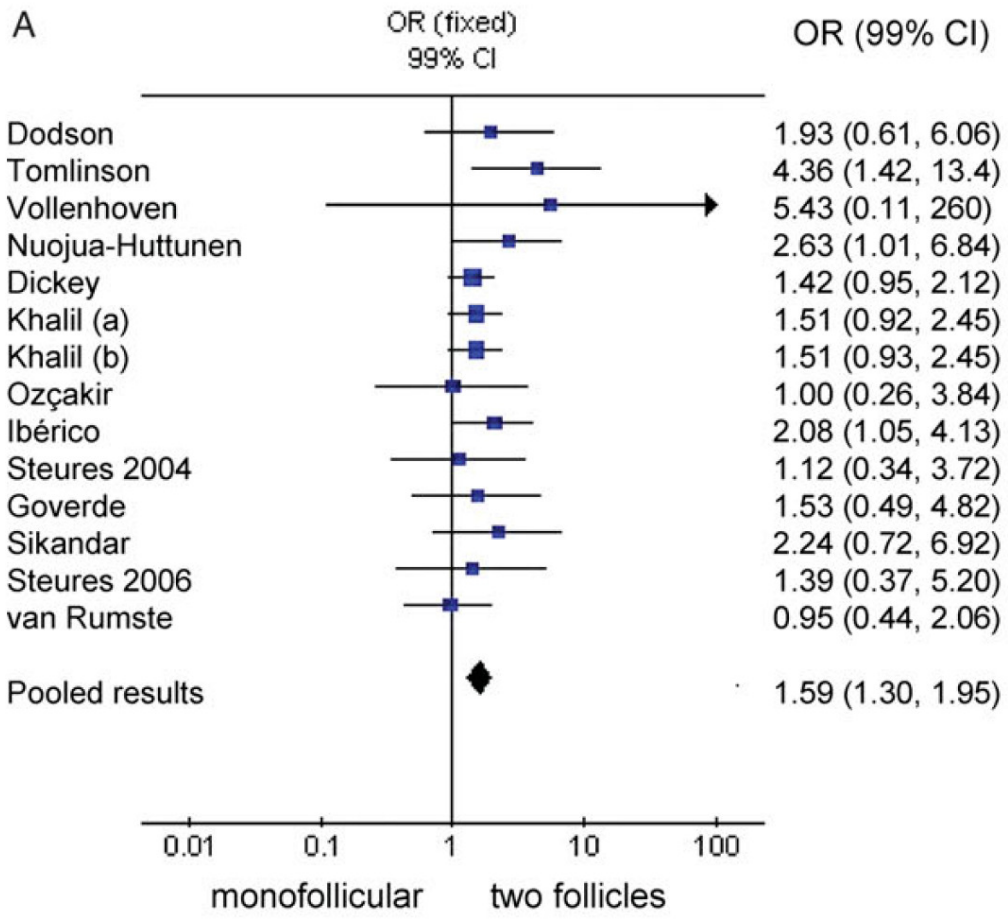
[1]Department of Obstetrics and Gynaecology, Máxima Medical Centre, De Run 4600, PO Box 7777, 5500 MB Veldhoven, NL, The Netherlands; [2]Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam, The Netherlands; [3]Department of Obstetrics and Gynaecology, Academic Hospital Maastricht, Maastricht, The Netherlands

[4]Correspondence address. Tel: +31-40-8888385; Fax: +31-40-8888387. E-mail: m.vanrumste@mmc.nl

BACKGROUND: The influence of multifollicular growth on pregnancy rates in subfertile couples undergoing intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) remained unclear. METHODS: Relevant papers were identified by searching MEDLINE, EMBASE and the Cochrane Library. A meta-analysis was performed and Mantel–Haenszel pooled odd ratios (ORs) and risk differences with 99% confidence intervals (CIs) were calcu-

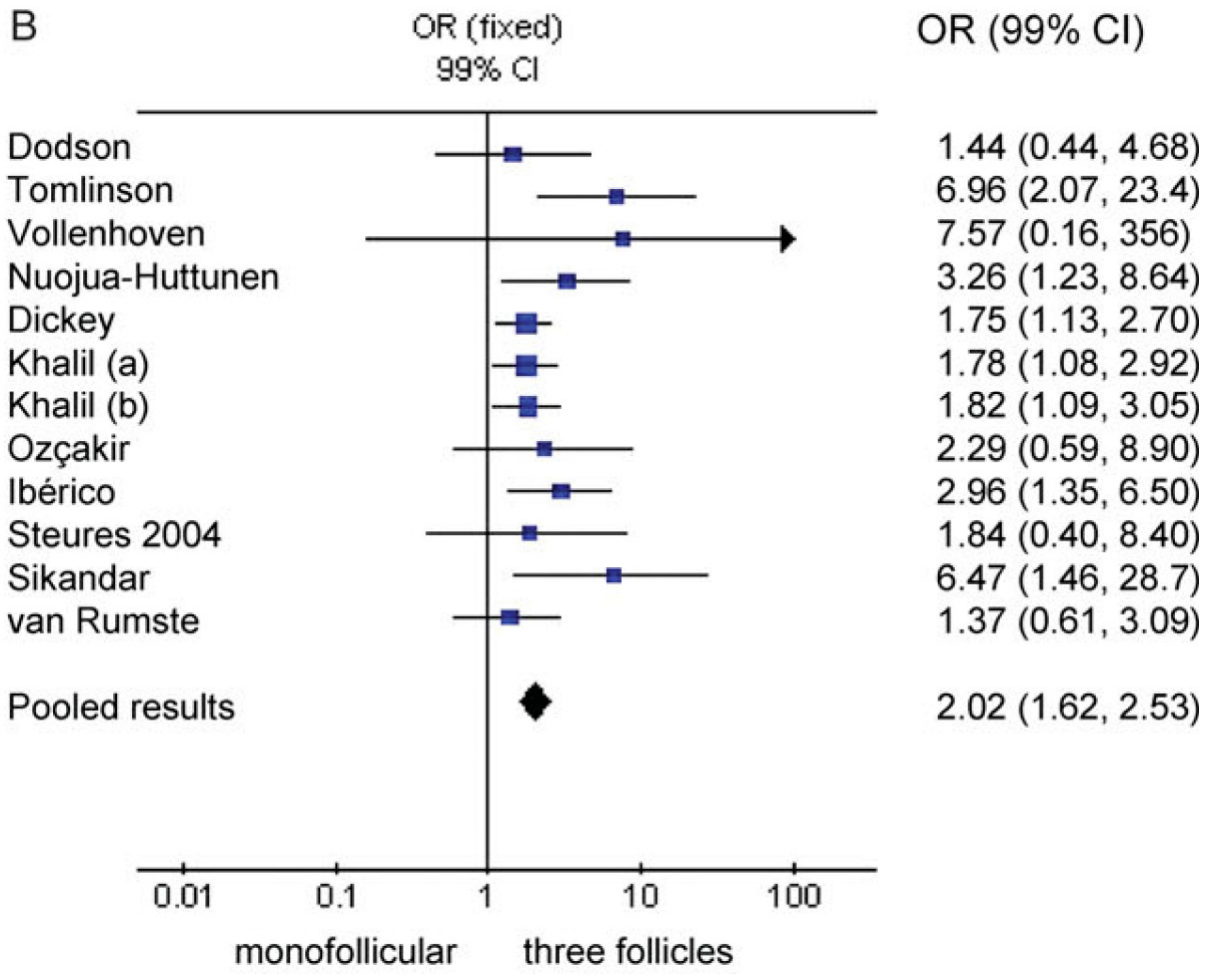
Van Rumste et al., 2009

Efficacy



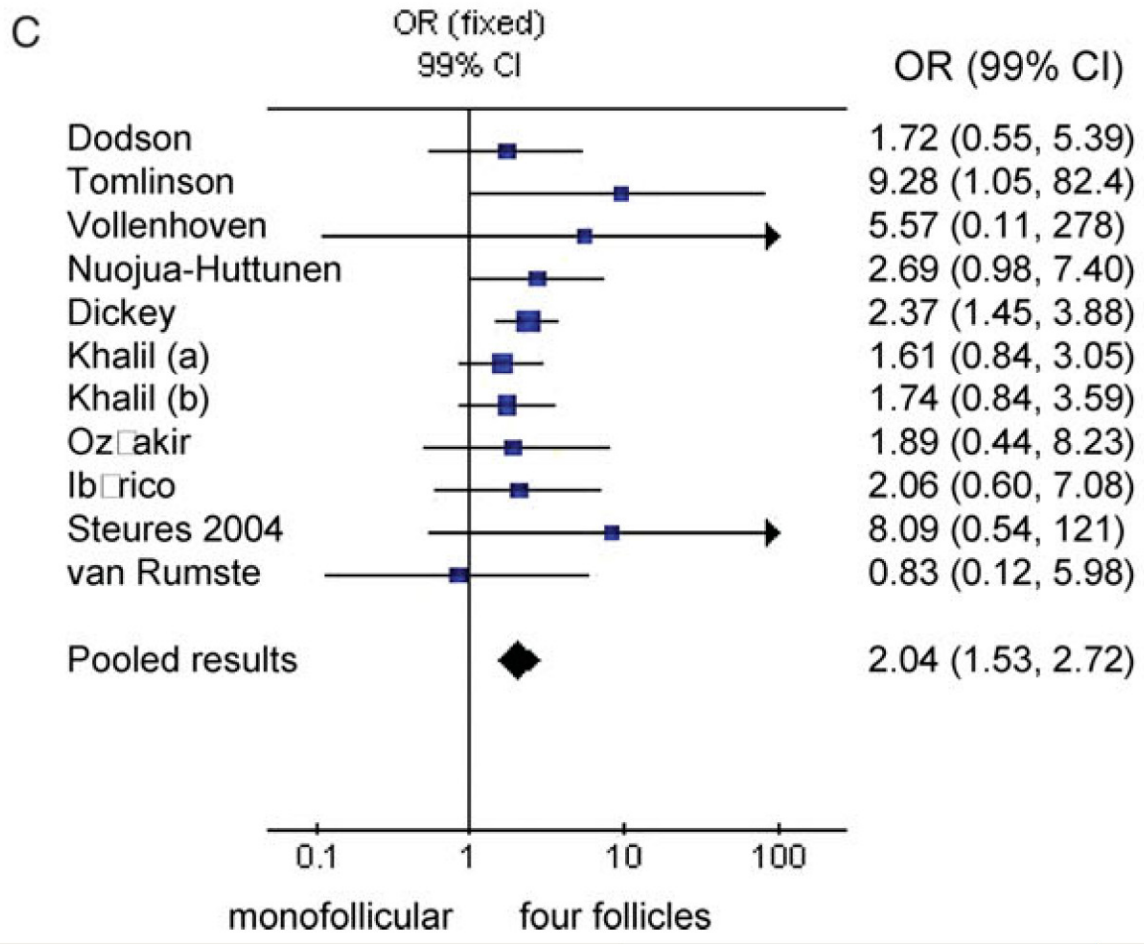
Van Rumste et al., 2009

Efficacy



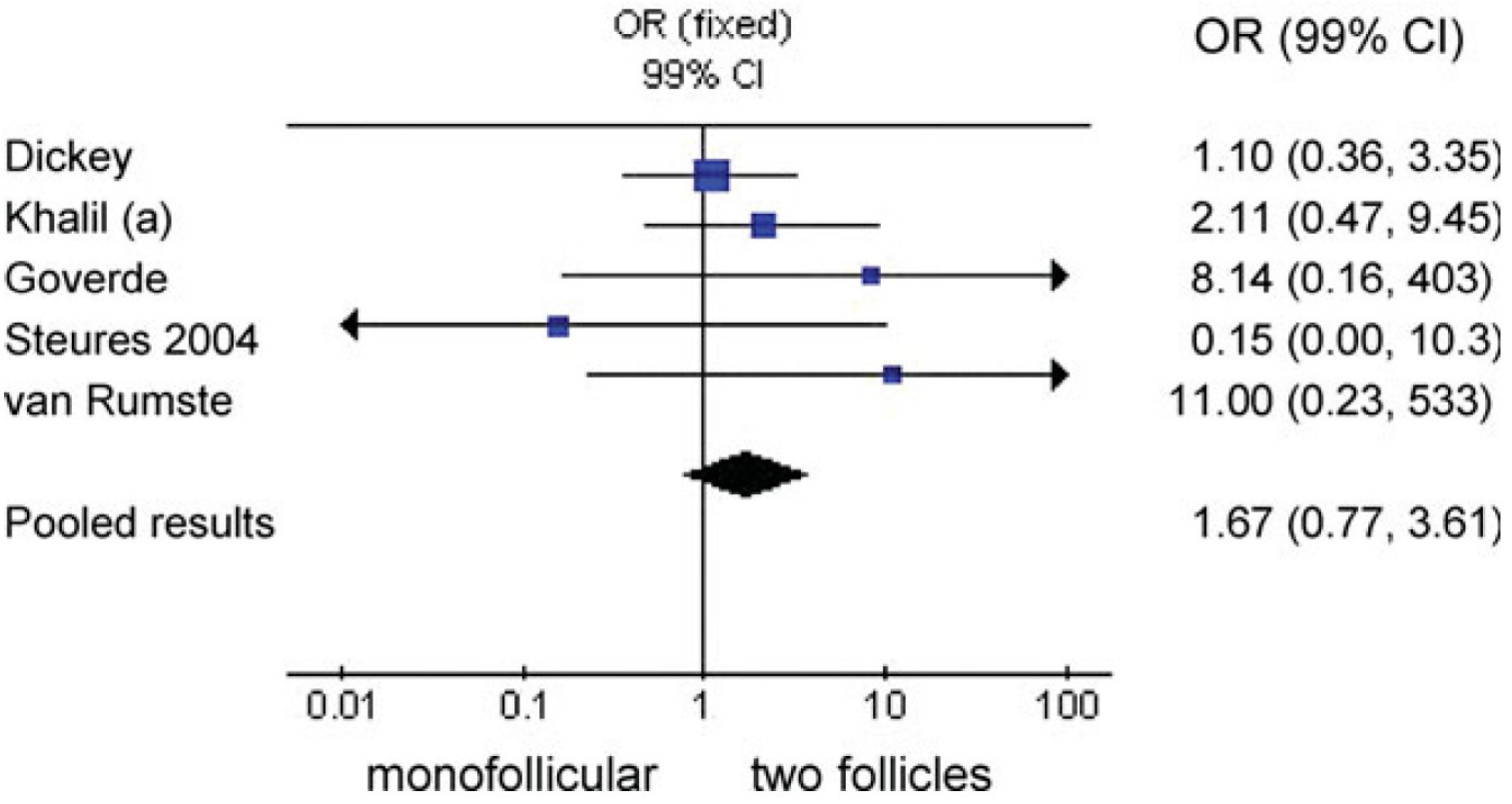
Van Rumste et al., 2009

Efficacy



Van Rumste et al., 2009

Efficacy (multiple pregnancy)



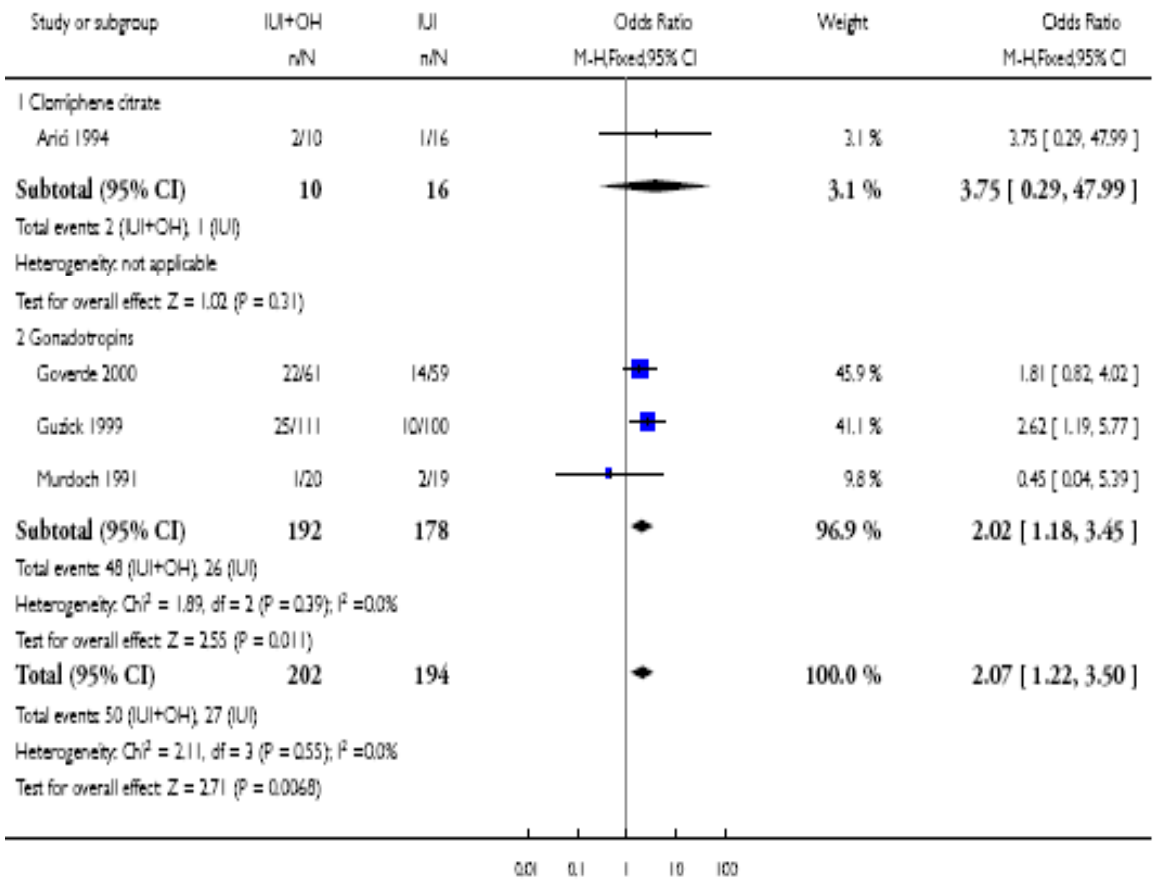
Van Rumste et al., 2009

Multifollicular growth efficacy (summary)

	Pregnancy OR 95% CI	Mutiples OR 95% CI
Two versus mono	1.6 (1.3 to 2.0)	1.7 (.77 to 3.6)
Three versus mono	2.0 (1.6 to 2.5)	2.8 (1.2 to 6.4)
Four versus mono	2.0 (1.5 to 2.7)	2.3 (0.9 to 5.9)

Hyperstimulation vs natural cycle IUI

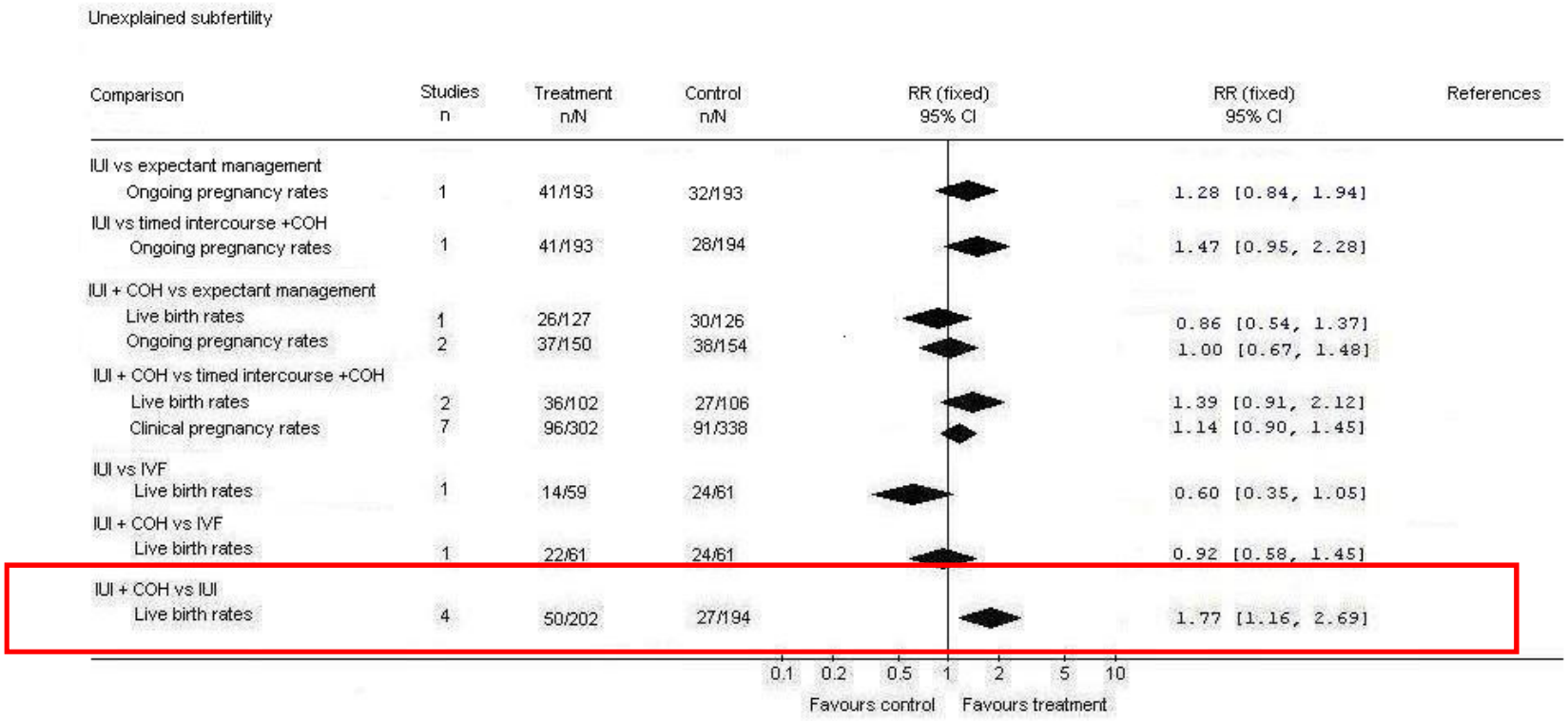
Analysis 2.2. Comparison 2 IUI in natural cycle versus IUI in a stimulated cycle, Outcome 2 Live birth rate per couple (all cycles).



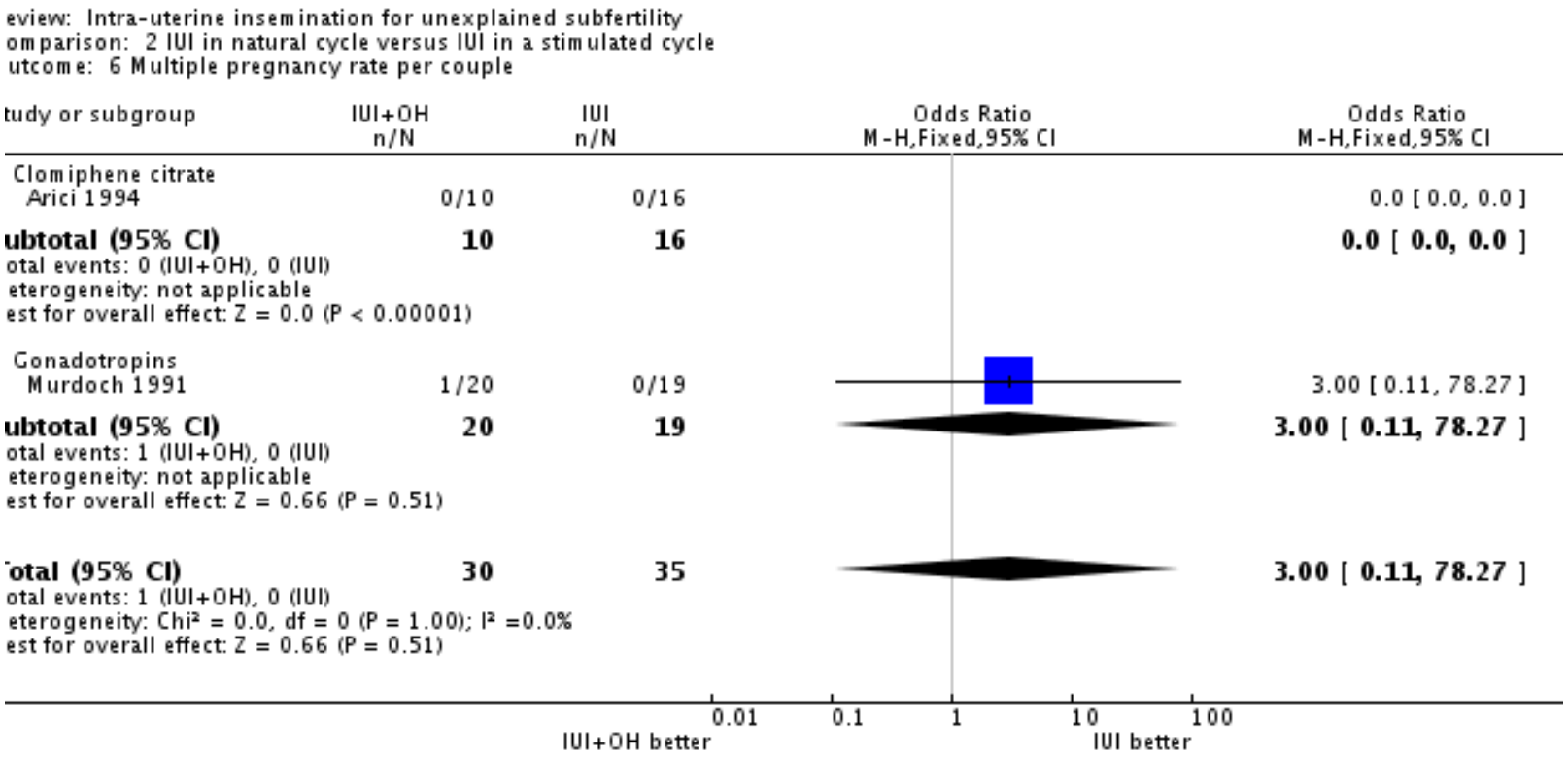
Favours IUI Favours IUI +OH

Verhulst, Cochrane 2006

Hyperstimulation vs natural cycle IUI

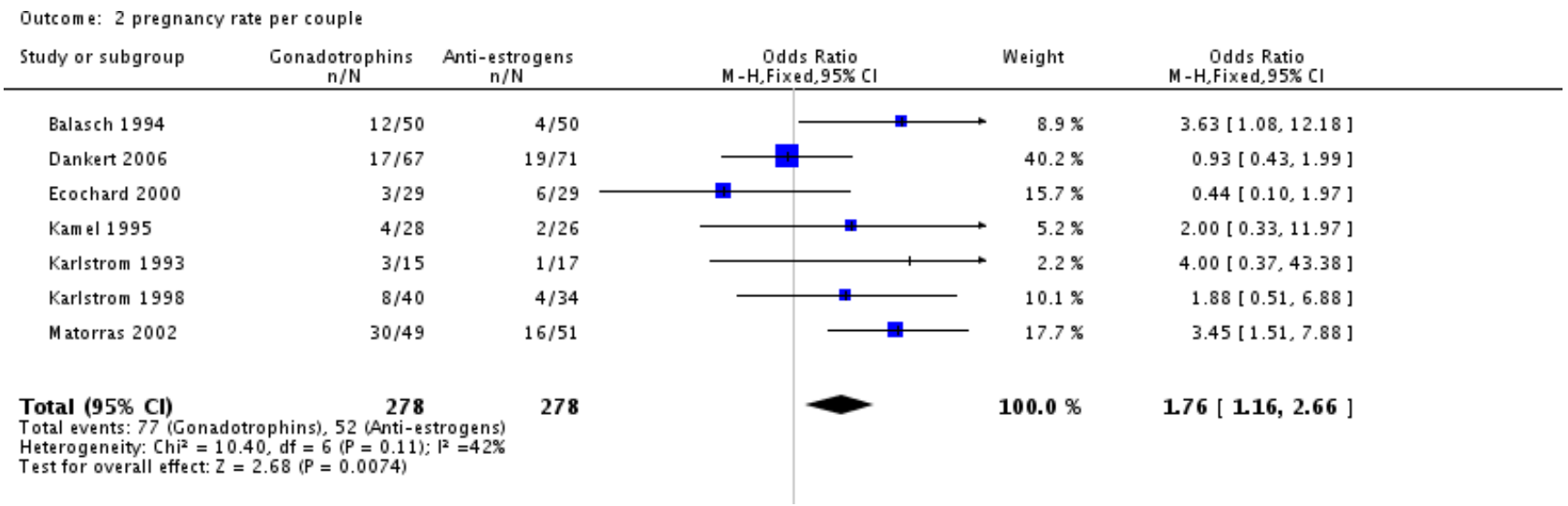


Hyperstimulation vs natural cycle IUI

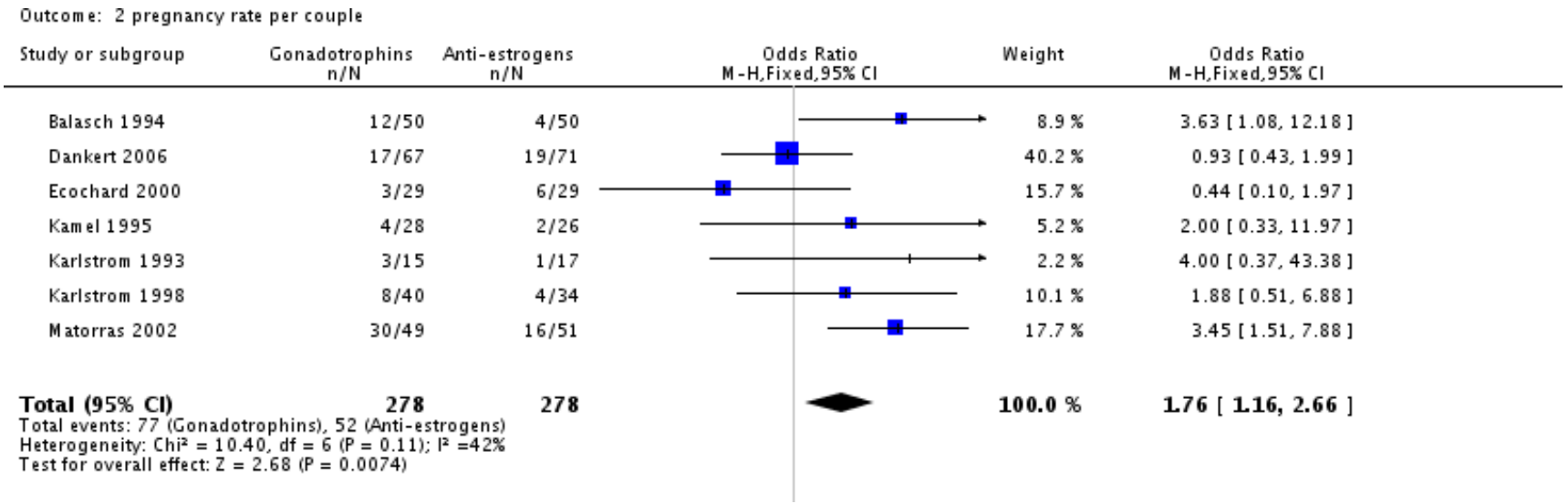


Verhulst, Cochrane 2006

Clomid versus gonadotrophins??



Clomid versus gonadotrophins??



There is a need for a large,
non commercially sponsored RCT on this issue

Consequences (effectiveness)

- 6 cycles IUI natural cycle generates
  - 40% ongoing pregnancies for a multiple rate of 1%
- Use of ovarian hyperstimulation (two follicles)
  - 60% ongoing pregnancies for a multiple rate of 8%
- Use of ovarian hyperstimulation (three follicles)
  - 70% ongoing pregnancies for a multiple rate of 12%

Consequences (costs)

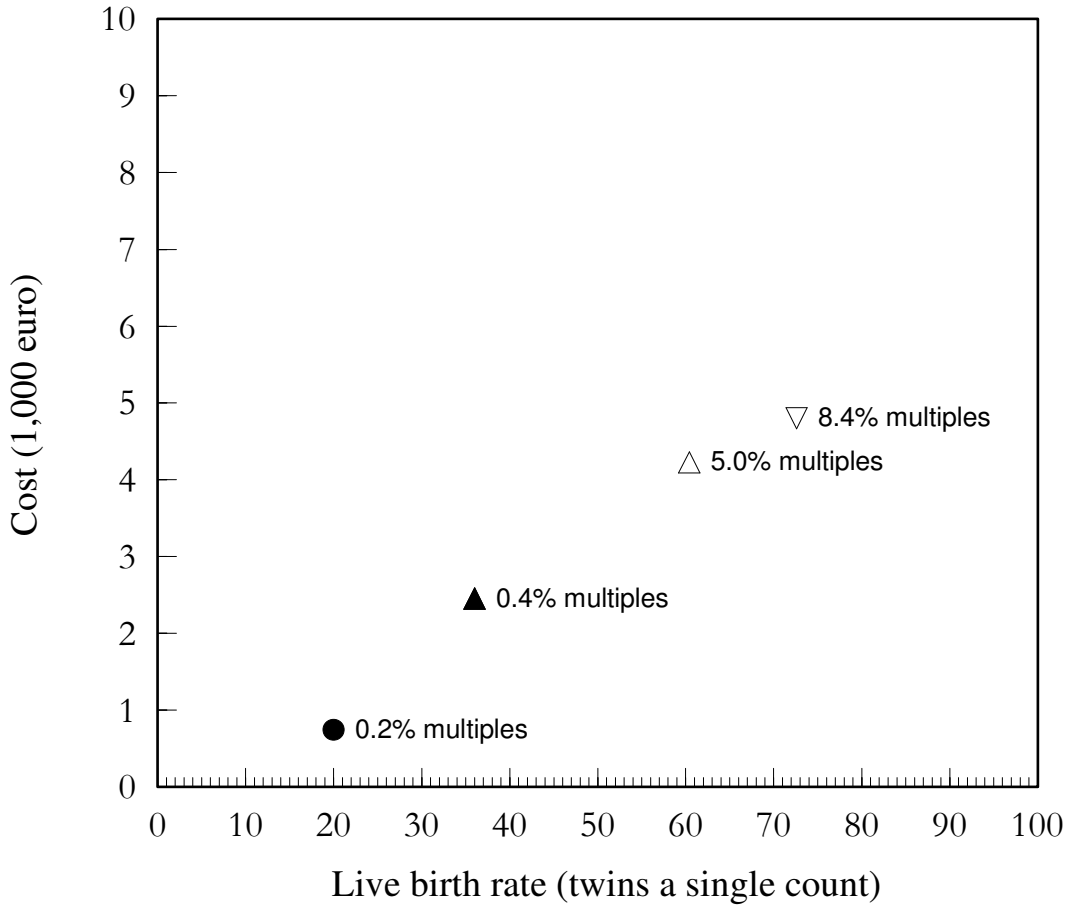
- Cycle IUI natural cycle 300 euro
- Cycle IUI stimulated cycle 450 euro

- Singleton pregnancy 1500 euro
- Twin pregnancy 14000 euro

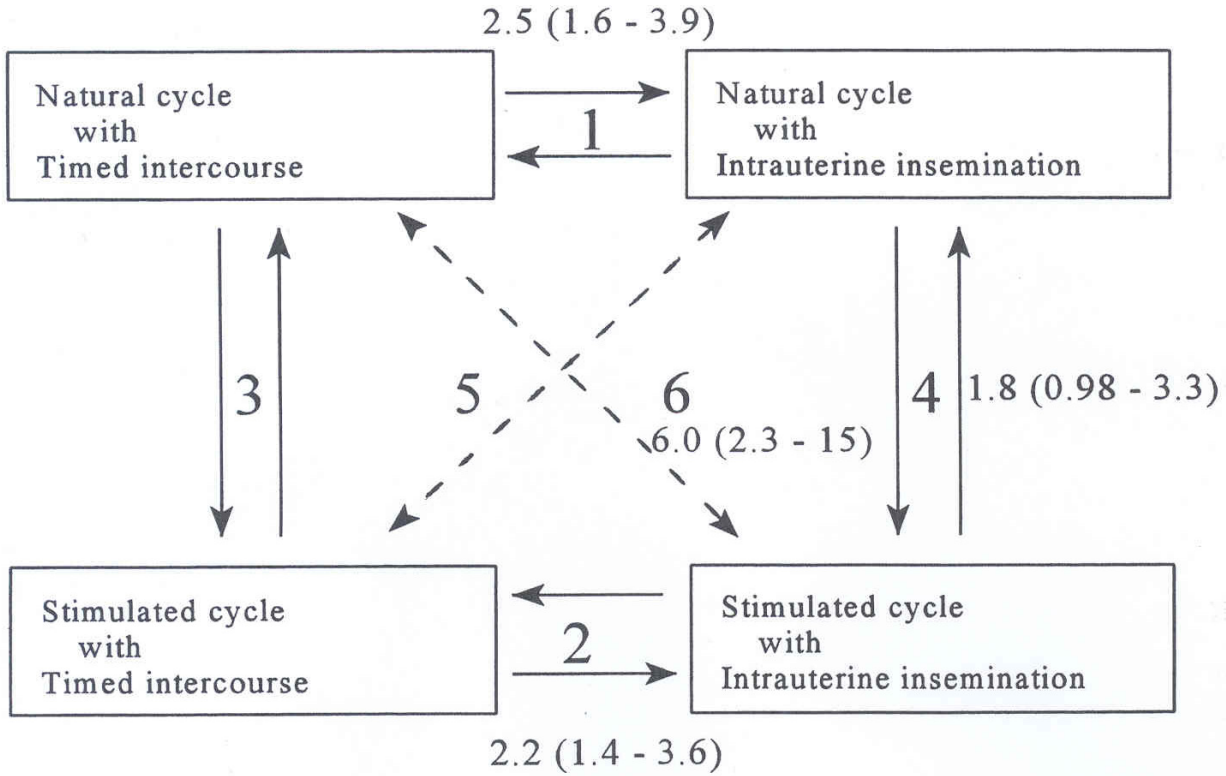
Consequences (effectiveness and cost)

- 6 cycles IUI natural cycle generates
  - 40% ongoing pregnancies for a multiple rate of 1%
  - Live birth rate: 36% 2450 euro
- Use of ovarian hyperstimulation (two follicles)
  - 60% ongoing pregnancies for a multiple rate of 8%
  - Live birth rate: 54% 4225 euro
- Use of ovarian hyperstimulation (three follicles)
  - 70% ongoing pregnancies for a multiple rate of 12%
  - Live birth rate: 63% 4800 euro

ICER plot


Cost (1,000 euro)
10
9
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
70
80
90
100
Live birth rate (twins a single count)
▽ 8.4% multiples
△ 5.0% multiples
▲ 0.4% multiples
● 0.2% multiples

Male subfertility



Cohlen 1997

Conclusions

- A twin is not bad
- Studies in reproductive medicine can focus on ongoing pregnancy as primary endpoint
- When hyperstimulation is applied in IUI, one should focus on two follicles, with three as escape
- There is no indisputable evidence that hyperstimulation should be performed with gonadotrophins in stead of clomid

Conclusions

- In male (and cervical) factor subfertility, IUI natural cycle is the treatment of first choice
- There is a need for RCTs comparing IUI in the natural cycle and IUI in the stimulated cycle as strategies