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

### ESHRE Genk, Belgium, 15 December

B.W. Mol







Universiteit van Amsterdam

# 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





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 Advance Access publication June 22, 2006. doi:10.1093/humrep/del249

### **OPINION**

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

#### M.van Wely<sup>1,3</sup>, M.Twisk<sup>1</sup>, B.W.Mol<sup>1,2</sup> and F.van der Veen<sup>1</sup>

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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

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# 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	<b>5-8</b>	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	ART	111	4.8%	4.9%	0.99 (0.87, 1.13)
proportions for CPR and LBR	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)

	$\Delta Euro$
IUI natural cycle dominant	
	△ Pregnancy rate
	IUI stimulated cycle dominant

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

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

### M.M.E. van Rumste<sup>1,4</sup>, I.M. Custers<sup>2</sup>, F. van der Veen<sup>2</sup>, M. van Wely<sup>2</sup>, J.L.H. Evers<sup>3</sup> and B.W.J. Mol<sup>1,2</sup>

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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

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Dodson Tomlinson Vollenhoven Nuojua-Huttunen Dickey Khalil (a) Khalil (b) Ozçakir Ibérico Steures 2004 Goverde Sikandar Steures 2006 van Rumste		1.93 (0.61, 6.06) 4.36 (1.42, 13.4) 5.43 (0.11, 260) 2.63 (1.01, 6.84) 1.42 (0.95, 2.12) 1.51 (0.92, 2.45) 1.51 (0.93, 2.45) 1.00 (0.26, 3.84) 2.08 (1.05, 4.13) 1.12 (0.34, 3.72) 1.53 (0.49, 4.82) 2.24 (0.72, 6.92) 1.39 (0.37, 5.20) 0.95 (0.44, 2.06)
	<b>*</b>	1.59 (1.30, 1.95)
mon	ofollicular two follicles	100

Van Rumste et al., 2009

В	OR (fixed) 99% Cl	OR (99% CI)
Dodson Tomlinson Vollenhoven Nuojua-Huttunen Dickey Khalil (a) Khalil (b) Ozçakir Ibérico Steures 2004 Sikandar van Rumste		1.44 (0.44, 4.68) 6.96 (2.07, 23.4) 7.57 (0.16, 356) 3.26 (1.23, 8.64) 1.75 (1.13, 2.70) 1.78 (1.08, 2.92) 1.82 (1.09, 3.05) 2.29 (0.59, 8.90) 2.96 (1.35, 6.50) 1.84 (0.40, 8.40) 6.47 (1.46, 28.7) 1.37 (0.61, 3.09)
Pooled results	•	2.02 (1.62, 2.53)
0.01 mor	0.1 1 10 nofollicular three follicle	100 s

Van Rumste et al., 2009



Van Rumste et al., 2009

# Efficacy (multiple pregnancy)



Van Rumste et al., 2009

## Multifollicular growth efficacy (summary)

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

### Hyperstimulation vs natural cycle IUI

Study or subgroup	IUI+OH	IUI	Odds Ratio	Weight	Odds Ratio	
	ΝN	n/N	M-H, Fored, 95% CI		M-H,Fooed,95% CI	
I Clorriphene citrate						
Arici 1994	2/10	1/16		3.1 %	3.75 [ 0.29, 47.99 ]	
Subtotal (95% CI)	10	16	-	3.1 %	3.75 [ 0.29, 47.99 ]	
Total events 2 (UI+OH), 1 (IU	JI)					
Heterogeneity: not applicable						
Test for overall effect $Z = 1.02$	2 (P = 0,31)					
2 Gonadotropins						
Goverde 2000	22/61	14/59		45,9 %	1.81 [ 0.82, 4.02 ]	
Guzick 1999	25/111	10/100	-	41.1 %	2.62 [ 1, 19, 5.77 ]	
Mundoch 1991	1/20	2/19		9.8%	0.45 [ 0.04, 5.39 ]	
Subtotal (95% CI)	192	178	•	96.9 %	2.02 [1.18, 3.45]	
Total events 48 (IUI+OH), 26	(IUI)					
Heterogeneity: Chi <sup>2</sup> = 1.89, di	f = 2 (P = 0.39); I <sup>2</sup> =	:0,0%				
Test for overall effect $Z = 255$	5 (P = 0,011)					
Total (95% CI)	202	194	•	100.0 %	2.07 [ 1.22, 3.50 ]	
Total events 50 (IUI+OH), 27	(U))					
Heterogeneity: Chi <sup>2</sup> = 2.11, df = 3 (P = 0.55); l <sup>2</sup> = 0.0%						
Test for overall effect $Z = 2.71$	(P = 0.0068)					
			0.01 0.1 1 10 100			

#### 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

#### Unexplained subfertility

Comparison	Studies n	Treatment n/N	Control n/N	RR (fixed) 95% Cl	RR (fixed) 95% Cl	References
IUI vs expectant management			100 C		11 M. 1996. 1997	
Ongoing pregnancy rates	1	41/193	32/193		1.28 [0.84, 1.94]	
IUI vs timed intercourse +COH				125		
Ongoing pregnancy rates	1	41/193	28/194	-	1.47 [0.95, 2.28]	
IUI + COH vs expectant management						
Live birth rates	1	26/127	30/126		0.86 [0.54, 1.37]	
Ongoing pregnancy rates	2	37/150	38/154	· · · · · · · · · · · · · · · · · · ·	1.00 [0.67, 1.48]	
IUI + COH vs timed intercourse +COH					an opposite the second s	
Live birth rates	2	36/102	27/106		1.39 [0.91, 2.12]	
Clinical pregnancy rates	7	96/302	91/338	•	1.14 [0.90, 1.45]	
IUI vs IVF						
Live birth rates	1	14/59	24/61		0.60 [0.35, 1.05]	
IUI + COH vs IVF				Market Advis		
Live birth rates	1	22/61	24/61		0.92 [0.58, 1.45]	
IUI + COH vs IUI	2011			1037		
Live birth rates	4	50/202	27/194		1.77 [1.16, 2.69]	
LIVE MITTALES	4	50/202	20194	12 05 1 2 5	1.77 [1.16, 2.69]	

Favours control Favours treatment

### Hyperstimulation vs natural cycle IUI

eview: Intra-uterine insemination for unexplained subfertility omparison: 2 IUI in natural cycle versus IUI in a stimulated cycle utcome: 6 Multiple pregnancy rate per couple

tudy or subgroup	IUI+OH n/N	IUI n/N		Odds Ratio M-H,Fixed,95% Cl		Odds Ratio M-H,Fixed,95% Cl
Clomiphene citrate Arici 1994	0/10	0/16				0.0 [ 0.0, 0.0 ]
ubtotal (95% Cl) otal events: 0 (IUI+OH), 0 (IUI) eterogeneity: not applicable est for overall effect: Z = 0.0 (F	<b>10</b> ? < 0.00001)	16				0.0 [ 0.0, 0.0 ]
Gonadotropins Murdoch 1991	1/20	0/19	_			3.00 [ 0.11, 78.27 ]
ubtotal (95% Cl) otal events: 1 (IUI+OH), 0 (IUI) eterogeneity: not applicable est for overall effect: Z = 0.66	20 (P = 0.51)	19				3.00 [ 0.11, 78.27 ]
<b>'otal (95% Cl)</b> otal events: 1 (IUI+OH), 0 (IUI) eterogeneity: Chi <sup>2</sup> = 0.0, df = est for overall effect: Z = 0.66	<b>30</b> 0 (P = 1.00); I <sup>2</sup> = 0 (P = 0.51)	<b>35</b> 0%	-			3.00 [ 0.11, 78.27 ]
		IUI+0H bette	0.01 0.1	1	10 100 IUIbetter	

Verhulst, Cochrane 2006

## Clomid versus gonadotrophins??

Study or subgroup	Gonadotrophins n/N	Anti-estrogens n/N	Odds Ratio M - H, Fixed, 95% Cl	Weight	Odds Ratio M - H, Fixed, 95% Cl	
Balasch 1994	12/50	4/50		■ ► 8.9%	3.63 [1.08, 12.18]	
Dankert 2006	17/67	19/71	<b>_</b>	40.2 %	0.93 [ 0.43, 1.99 ]	
Ecochard 2000	3/29	6/29		15.7 %	0.44 [ 0.10, 1.97 ]	
Kamel 1995	4/28	2/26		→ 5.2 %	2.00 [ 0.33, 11.97 ]	
Karlstrom 1993	3/15	1/17		2.2 %	4.00 [ 0.37, 43.38 ]	
Karlstrom 1998	8/40	4/34		10.1 %	1.88[0.51,6.88]	
Matorras 2002	30/49	16/51		17.7 %	3.45 [1.51, 7.88]	
<b>Total (95% Cl)</b> Total events: 77 (Gonado Heterogeneity: Chi <sup>2</sup> = 10. Test for overall effect: Z =	<b>278</b> trophins), 52 (Anti-es .40, df = 6 (P = 0.11); = 2.68 (P = 0.0074)	278 (trogens)  ² =42%	•	100.0 %	1.76 [ 1.16, 2.66 ]	

#### Outcome: 2 pregnancy rate per couple

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Ecochard 2000	3/29	6/29 —		15.7 %	0.44 [ 0.10, 1.97 ]	
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Outcome: 2 pregnancy rate per couple

### 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
- Cycle IUI stimulated cycle 450 euro
- Singleton pregnancy
- Twin pregnancy

1500 euro 14000 euro

300 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



# 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