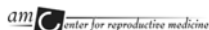# Risk factors for high order multiple births following artificial insemination

ESHRE Genk, Belgium, 15 December

A.J.Bensdorp

UNIVERSITEIT VAN AMSTERDAM

am Center for reproductive medicine

High order multiples; prevalence

- Hellin's Law
  - The principle that twins occur once in 89 births, triplets once in 89^2 births, and quadruplets once in 89^3 births.

- Spontaneous
  - Triplets 1/7925 [1]
  - Quadruplets 1/ 600.000 [1]

Petrikovsky 1989, Colins & Blye I, 3 Seoud, Practice Committee of ASRM, 2006, Verberg 2007

Trends in multiples

- Last decades increase
  - Number of Twins 52% (68.399 to 104.137)

  - Number of HOMPs 404% (1377 to 6727)

  - Infertility treatments account for 75% HOMP

  - Exact numbers from IUI unknown
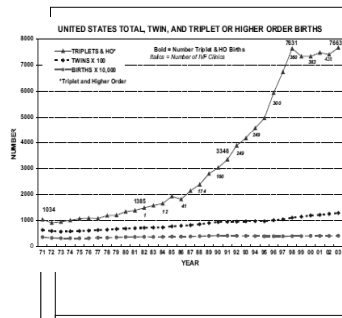
Dickey Fertility Sterility,2007

Maternal & Neonatal Morbidity

Outcome	Triplet versus Twin Adjusted* Odds Ratio (95% CI)	Quadruplet versus Twin Adjusted* Odds Ratio (95% CI)
Gestation Hypertension	1.19 (1.09-1.31)	1.35 (1.00-1.83)
Eclampsia	1.69(1.46-1.94)	1.67(0.99-2.83)
Diabetes Mellitus	1.64(1.51-1.78)	1.97(1.47-2.64)
PROM **	1.53 (1.43-1.64)	1.74(1.36-2.23)
Cesarean Delivery	6.55 (6.15-6.97)	7.38 (5.74-9.47)
Birth < 29 weeks	3.76 (3.55-3.97)	7.96 (6.71-9.44)
Infant death of ≥ babies	3.02 (2.77-3.29)	4.07 (3.06-5.41)

*Adjusted for confounding factors; maternal race, age, smoking, parity, marital status, education, prenatal care visit
* *PROM; premature rupture of membrane   *Luke AJOG, 2008, Wen AJOG, 2004*

Financial Consequences

- Medical costs during pregnancy
- Obstetric care costs compared to singletons
  - 4.5 fold higher for triplets, 7 fold higher for quadruplets

- Higher perinatal costs
  - Dysmaturity and prematurity
    - Costs ELBW (<1000g);US £39483, outside US £29.757
    - Costs VLBW (1000-1499g); US £22541,outside US £ 14.968
  - Hospitalization
    - Neonatal 4.6 days (singleton) → 10.0 days (HOMP)

Ombelet Human Reproduction Update2005, Mugford& Henderson RCOG 1995
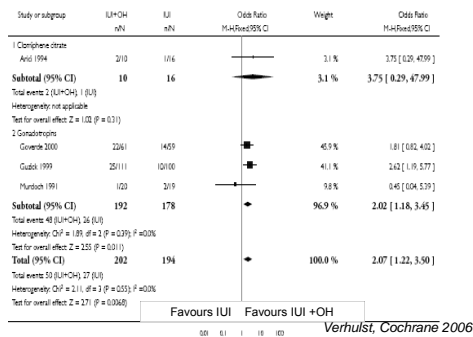

IUI
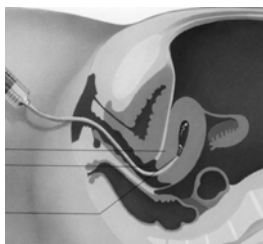
- Intrauterine insemination
  - Placing the catheter past the ostium internum cervix
  - Inject worked up semen

- Pregnancy rates
  - 20-30% after 6 cycles
  - 20% multiples

IUI OH

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

Study or subgroup	IUI+OH n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Clomiphene 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 (IUI+OH), 1 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
2 Gonadotropins					
Goverde 2000	22/61	14/59		45.9 %	1.81 [0.82, 4.02]
Gudick 1999	25/111	10/100		41.1 %	2.62 [1.19, 5.77]
Murdoch 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: Chi² = 1.89, df = 2 (P = 0.39); I² =0.0%					
Test for overall effect: Z = 2.55 (P = 0.011)					
Total (95% CI)	202	194		100.0 %	2.07 [1.22, 3.50]
Total events: 50 (IUI+OH), 27 (IUI)					
Heterogeneity: Chi² = 2.11, df = 3 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 2.71 (P = 0.0068)					

Favours IUI   Favours IUI +OH

0.01 0.1 1 10 100

Verhulst, Cochrane 2006

Artificial insemination

Prevalence	2001	2004
Countries	15	19
Cycles	52939	98388
Pregnancies (%)	6696 (12.6)	12216 (12.4)
Singleton (%)	5826 (88.8)	10499 (86.9)
Multiples (%)	732 (11.2)	1582 (13.1)

•No data available specifically for Higher Order Multiple Pregnancies

ESHRE Capri Workshop Group, Human Reproduction Update 2009

Risk factors for HOMP

- Initial dose of gonadotropin
- Number of follicles
- Early cycles number
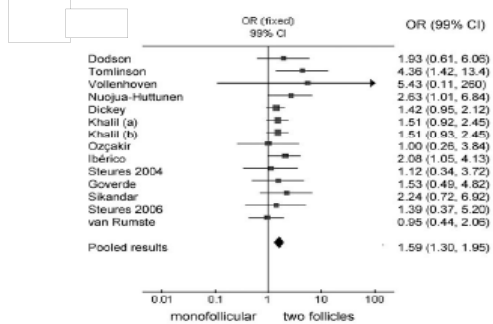- Cumulative effect of age, follicle number, E2 concentration

Dickey Fertility Sterility 2009

Initial dose of gonadoptrophins

- Thompson 1970;
  - No multiple pregnancies or HOMB if startdose 75 IU hMG compares with 13% twins and 4.8% HOMB with 150 IU hMG
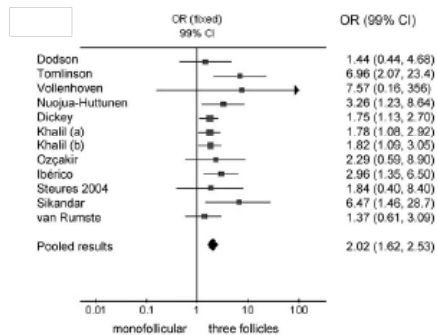
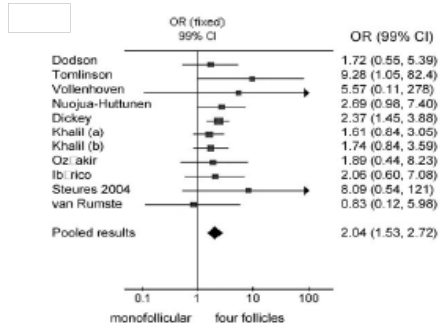*Gleicher NEJM, 2000*

Follicles (pregnancy rates)

	OR (fixed) 99% CI	OR (99% CI)
Dodson		1.93 (0.61, 6.06)
Tomlinson		4.36 (1.42, 13.4)
Vollenhoven		5.43 (0.11, 260)
Nuojua-Huttunen		2.63 (1.01, 6.84)
Dickey		1.42 (0.95, 2.12)
Khalil (a)		1.51 (0.92, 2.45)
Khalil (b)		1.51 (0.93, 2.45)
Ozçakir		1.00 (0.26, 3.84)
Ibérico		2.08 (1.05, 4.13)
Steures 2004		1.12 (0.34, 3.72)
Goverde		1.53 (0.49, 4.82)
Sikandar		2.24 (0.72, 6.92)
Steures 2006		1.39 (0.37, 5.20)
van Rumste		0.95 (0.44, 2.06)
Pooled results		1.59 (1.30, 1.95)

monofollicular — two follicles

Van Rumste Human Reproduction Update 2008

Pregnancy Rates; three follicles

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

monofollicular — three follicles

Van Rumste Human Reproduction Update 2008

Pregnancy Rates; Four follicles

	OR (fixed) 99% CI	OR (99% CI)
Dodson		1.72 (0.55, 5.39)
Tomlinson		9.28 (1.05, 82.4)
Vollenhoven		5.57 (0.11, 278)
Nuojua-Huttunen		2.69 (0.98, 7.40)
Dickey		2.37 (1.45, 3.88)
Khalil (a)		1.61 (0.84, 3.05)
Khalil (b)		1.74 (0.84, 3.59)
Ozcakir		1.89 (0.44, 8.23)
Iberico		2.06 (0.60, 7.08)
Steures 2004		8.09 (0.54, 121)
van Rumste		0.83 (0.12, 5.98)
Pooled results		2.04 (1.53, 2.72)

monofollicular   four follicles

Van Rumste Human Reproduction Update 2008

Follicles (HOMP)

- Multiple Pregnancy rate increased
  - Odds Ratio 2 follicles 1.7 (99% CI 0.8-3.6)
  - Odds Ratio 3 follicles 2.8 (99%CI 1.2-6.4)
  - Odds Ratio 4 follicles 2.3 (99% CI 0,9-5.9)

Van Rumste Human Reproduction Update 2008

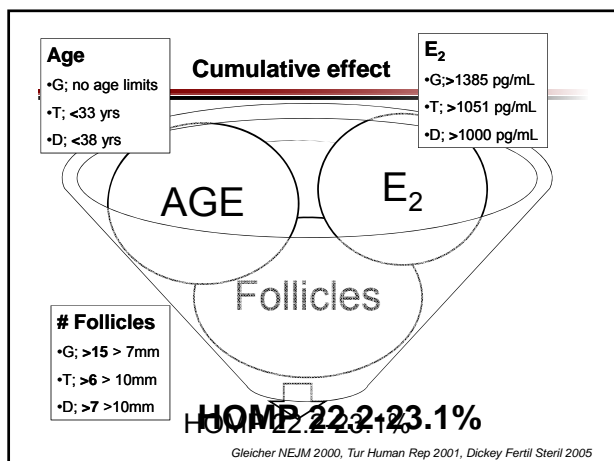
Early cycles of IUI

Dickey Fertility Sterility 2009

Slide 1

Age
- G; no age limits
- T; >33 yrs
- D; >38 yrs

Cumulative effect

E_2
- G; <1385 pg/mL
- T; <1051 pg/mL
- D; <1000 pg/mL

AGE E_2

Follicles

 # Follicles
- G; <10 < 7mm
- T; <6 < 10mm
- D; no data

HOMP 0%

Gleicher NEJM 2000, Tur Human Rep 2001, Dickey Fertil Steril 2005

Slide 2

Age
- G; no age limits
- T; <33 yrs
- D; <38 yrs

Cumulative effect

E_2
- G;>1385 pg/mL
- T; >1051 pg/mL
- D; >1000 pg/mL

AGE E_2

Follicles

 # Follicles
- G; >15 > 7mm
- T; >6 > 10mm
- D; >7 >10mm

HOMP 22.2-23.1%

Gleicher NEJM 2000, Tur Human Rep 2001, Dickey Fertil Steril 2005

Slide 3

Primary prevention HOMP

- Avoiding unnecesary treatments is the best way to prevent HOMP
- Low dose of gonadotrophins
- Use of CC

Prediction Model
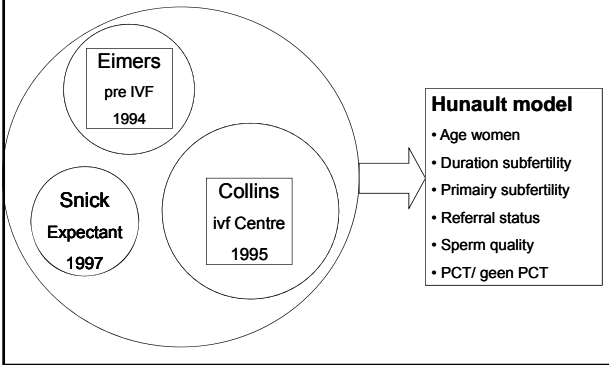
Eimers
pre IVF
1994

Snick
Expectant
1997

Collins
ivf Centre
1995

Hunault model
- Age women
- Duration subfertility
- Primairy subfertility
- Referral status
- Sperm quality
- PCT/ geen PCT

Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples*

J.W.van der Steeg[1,2,3,8], P.Steures[1,2,3], M.J.C.Eijkemans[1], J.D.F.Habbema[1], P.G.A.Hompes[3], F.J.Broekmans[4], H.J.H.M.van Dessel[5], P.M.M.Bossuyt[6], F.van der Veen[2] and B.W.J.Mol[2,7] on behalf of CECERM study group[†]
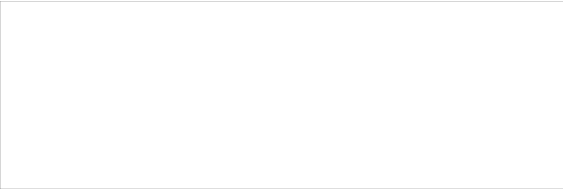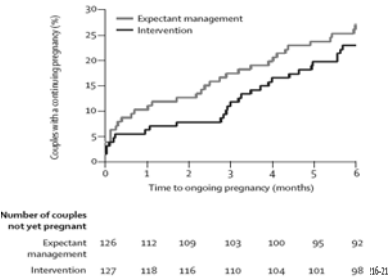

Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial

Pieternel Steures, Jan Willem van der Steeg, Peter G A Hompes, J Dik F Habbema, Marinus J C Eijkemans, Frank J Broekmans, Harold R Verhoeve, Patrick M M Bossuyt, Fulco van der Veen, Ben W J Mol, for the Collaborative Effort on the Clinical Evaluation in Reproductive Medicine*

Number of couples not yet pregnant
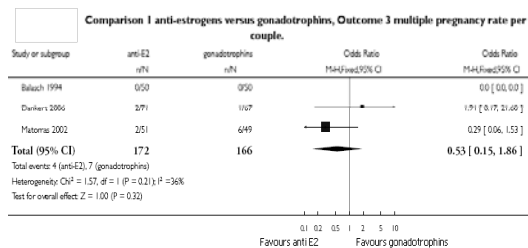
Expectant management	126	112	109	103	100	95	92
Intervention	127	118	116	110	104	101	98

116-21

Low dose of gonadoptrophins

Study	Clinical PR/ Cycle(%)	Frequency HOMP (%)	Cancel criteria
Balasch et al, 1994	12.8	0.0	No
Cohlen et al, 1998	13.2	0.0	Yes
Sengoku et al, 1999	14.3	0.0	No
Goverde et al, 2000	8.7	0.0	Yes
Ragni et al, 2004	20.0	0.0	Yes
Gerli et al, 2004	12.3	0.0	Yes
Papageorgiou 2004	10.4	0.4	Yes
Tur et al 2005	10.1	0.7	No
Tur et al 2005	14.0	2.4	Yes
Ragni et al 2006	9.2	0.0	Yes
Total all studies	**11.1**	**1.0**	**Yes/No**
Total all studies	**10.2**	**0.3**	**Yes**

Ragni, Ferility and Sterility, 2006

Clomiphene citrate

Comparison 1 anti-estrogens versus gonadotrophins, Outcome 3 multiple pregnancy rate per couple.

Cantineau Cochrane,2007

Secondary Prevention HOMP

- Cancellation
  - Grafiek over cancellation
- Aspiration of supernumary follicles
- Coasting
  - Ineffective for IUI
- Conversion to IVF
  - Unanticipated costs
- Multifetal pregnancy reduction (MFPR)

Dickey 2009, Evans 2004, Callahan 1994, Ukman 1992, Hazout 1984,

Summary

- Higher order multiples are a major problem in artificial insemination

- Consider expectant management for couples with a good prognosis

- With mild stimulation protocols and extensive monitoring higher order multiples can easily be prevented

Not too many please….