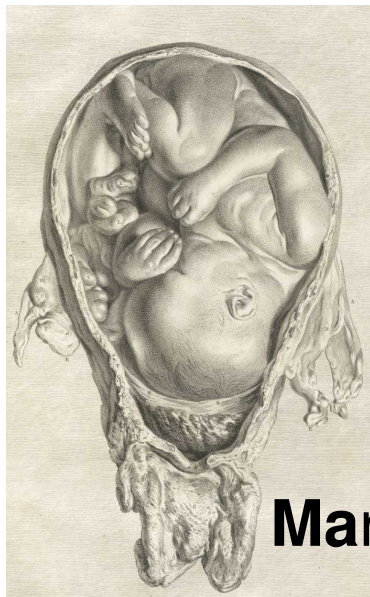
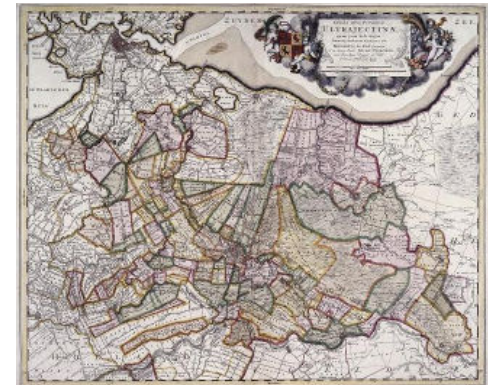


Ovarian response and Pregnancy



ESHRE Campus
March 2010 Bologna

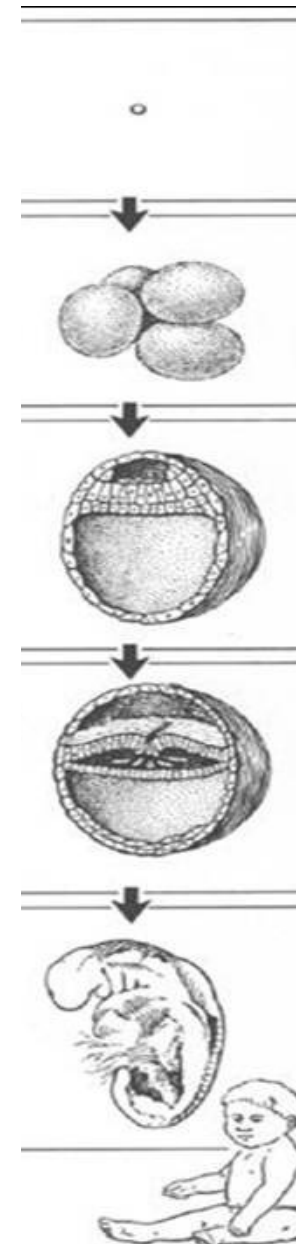


(No conflict of interests)

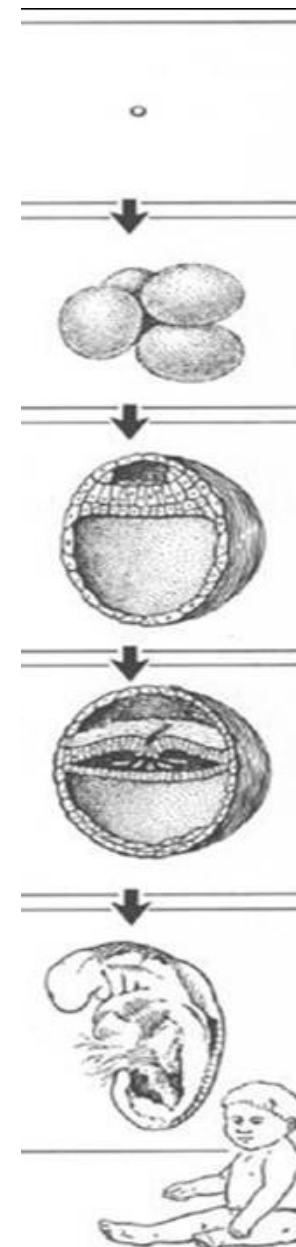
Carolien Boomsma
Utrecht University
The Netherlands

Overview

- Effects of ovarian stimulation on the intra-uterine milieu
- Adjuvant glucocorticoids/ aromatase inhibitors to improve ovarian response and implantation
- Early pregnancy after IVF
- Hypertensive pregnancy complications in poor and normal responders following IVF
- PCOS and pregnancy outcome



Effects of ovarian stimulation on the intra-uterine milieu

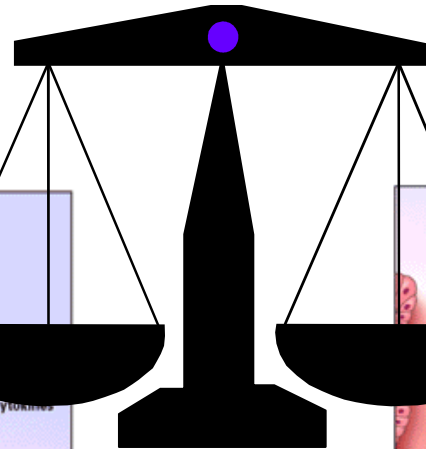
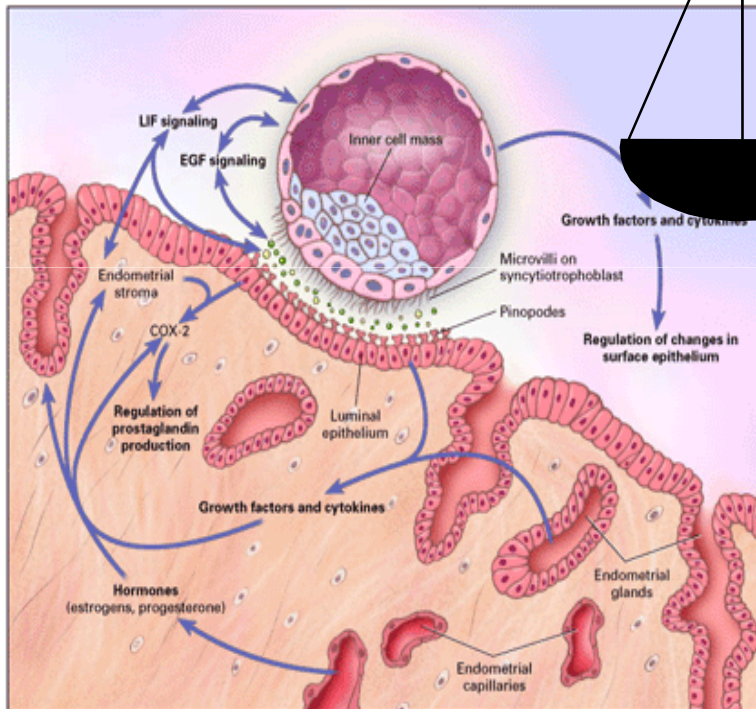


Effect ovarian stimulation on the endometrium

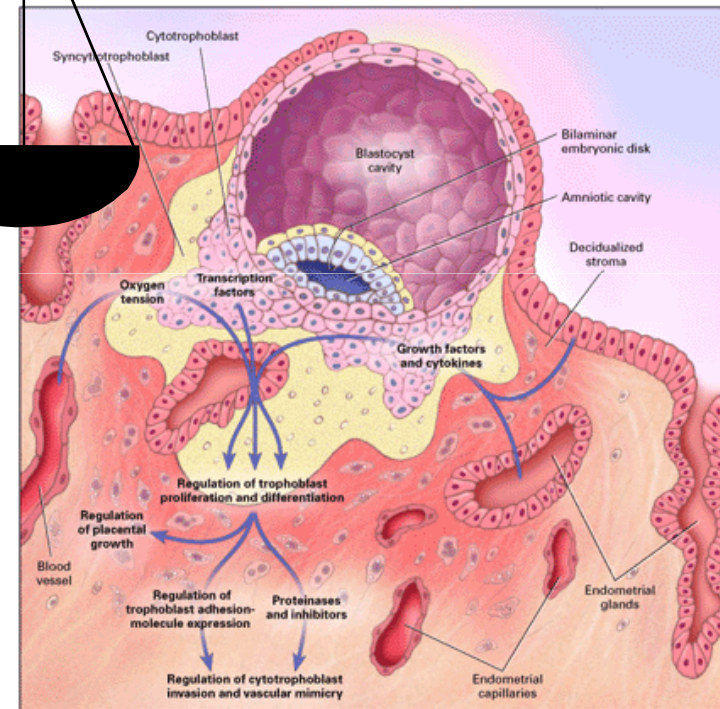
- Ovarian stimulation results in supraphysiological levels of estradiol and progesteron.
- Effects on endometrial receptivity
 - Detrimental to implantation rates
 - advance down-regulation of steroid receptors
 - accelerated transformation to secretory endometrium at the time of embryo transfer
 - Differentially expression of key regulators implantation process

Cytokines, chemokines and growth factors

Anti-inflammatory
(eg. IL-5, IL-10)



Pro-inflammatory
(eg. TNF- α , IL-1 β)



(Wegmann 1993.)

Study on the endometrial factor in human embryo implantation

- Study of human implantation restricted
 - risk of disrupting the process by current approaches
- Endometrial secretion analysis. Advantages:
 - Represent *in-vivo* milieu encountered by embryo
 - Applicable during window of implantation: non-disruptive to implantation

RBM Online - Vol 7, No 1, 105-109 Reproductive BioMedicine Online; www.rbmonline.com/Article/885 on web 20 May 2003

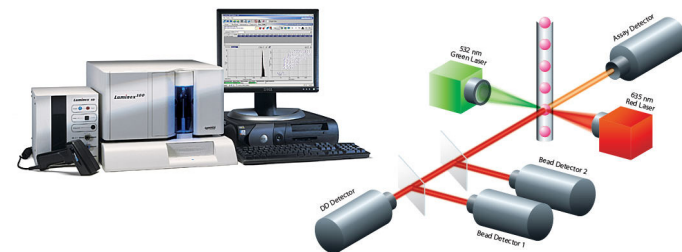
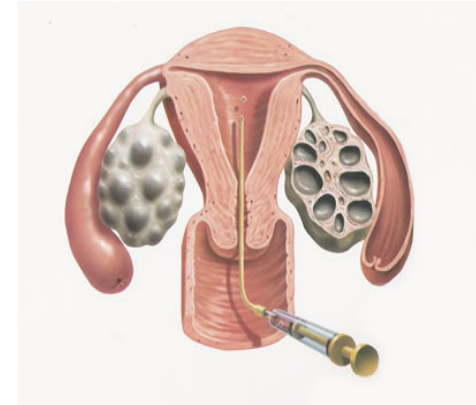
Article

Endometrial secretion aspiration prior to embryo transfer does not reduce implantation rates

MH van der Gaast¹, K Beier-Hellwig², BCJM Fauser¹, HM Beier², NS Macklon^{1,3}

Material and Methods

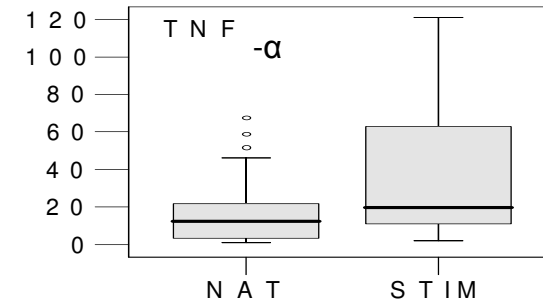
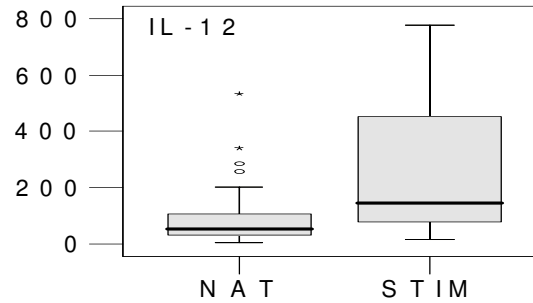
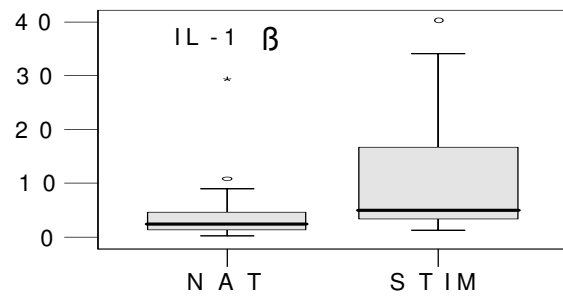
- 41 women undergoing IVF
 - endometrial secretion aspiration prior to ET
 - endometrial secretion aspiration LH+6 natural cycle
- Multiplex immunoassay:
 - IL1 β , IL5, IL6, IL10, IL12, IL15, IL17, IL18
TNF α , IFN γ , MIF
 - VEGF, HbEGF
 - Eotaxin, MCP-1, IP-10,
 - Dkk-1



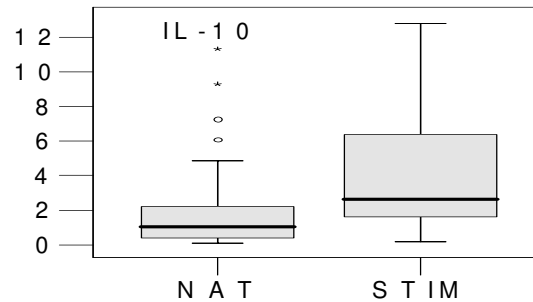
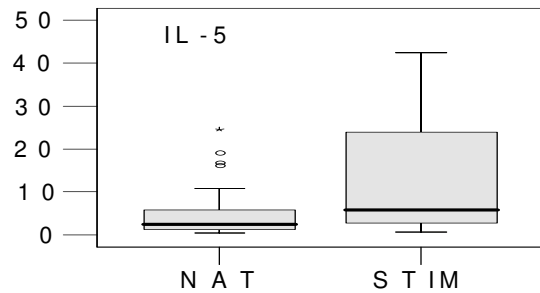
(de Jager 2003)

Results: Effect of ovarian stimulation on intra-uterine cytokine profile

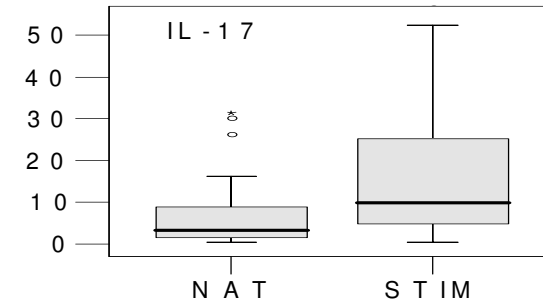
Pro-inflammatory cytokines



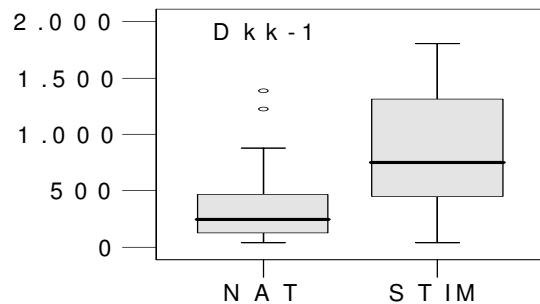
Anti-inflammatory cytokines



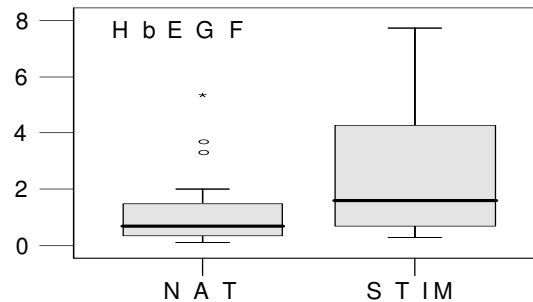
Pro- and anti-inflammatory properties



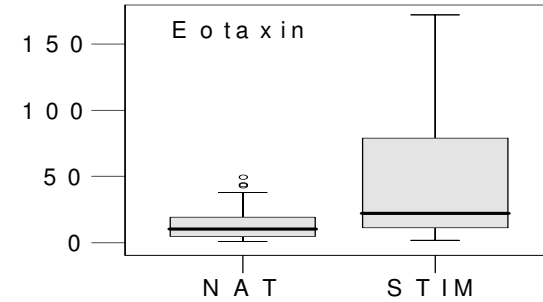
Wnt signalling inhibitor



Growth Factor



Chemokine

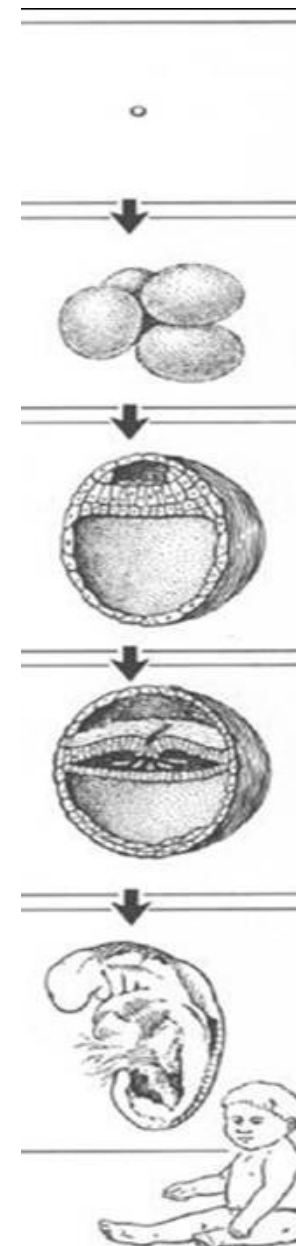


(Boomsma et al, 2010)

Conclusion

- Cytokine profiling in endometrial secretion analysis offers a novel, non-disruptive approach to study the endometrial factor in human embryo implantation.
- The intra-uterine milieu is significantly altered by ovarian stimulation.

Glucocorticoids
and aromatase inhibitors
to improve
ovarian response



Adjuvant Aromatase inhibitors to improve ovarian response

- Aromatase inhibitors block conversion of androgens to estrogens
 - amount of estrogens synthesised ↓
 - gonadotropin secretion ↑.
- 1 RCT : women with poor ovarian response
 - significantly lower total dose of FSH
 - Pregnancy rates comparable.
- 3 non randomised trials: women with normal ovarian response
 - Only a subgroup of women with PCOS showed significantly higher pregnancy rates.

(Mitwally 2001 and 2003, Goswami 2004, Healy 2003)

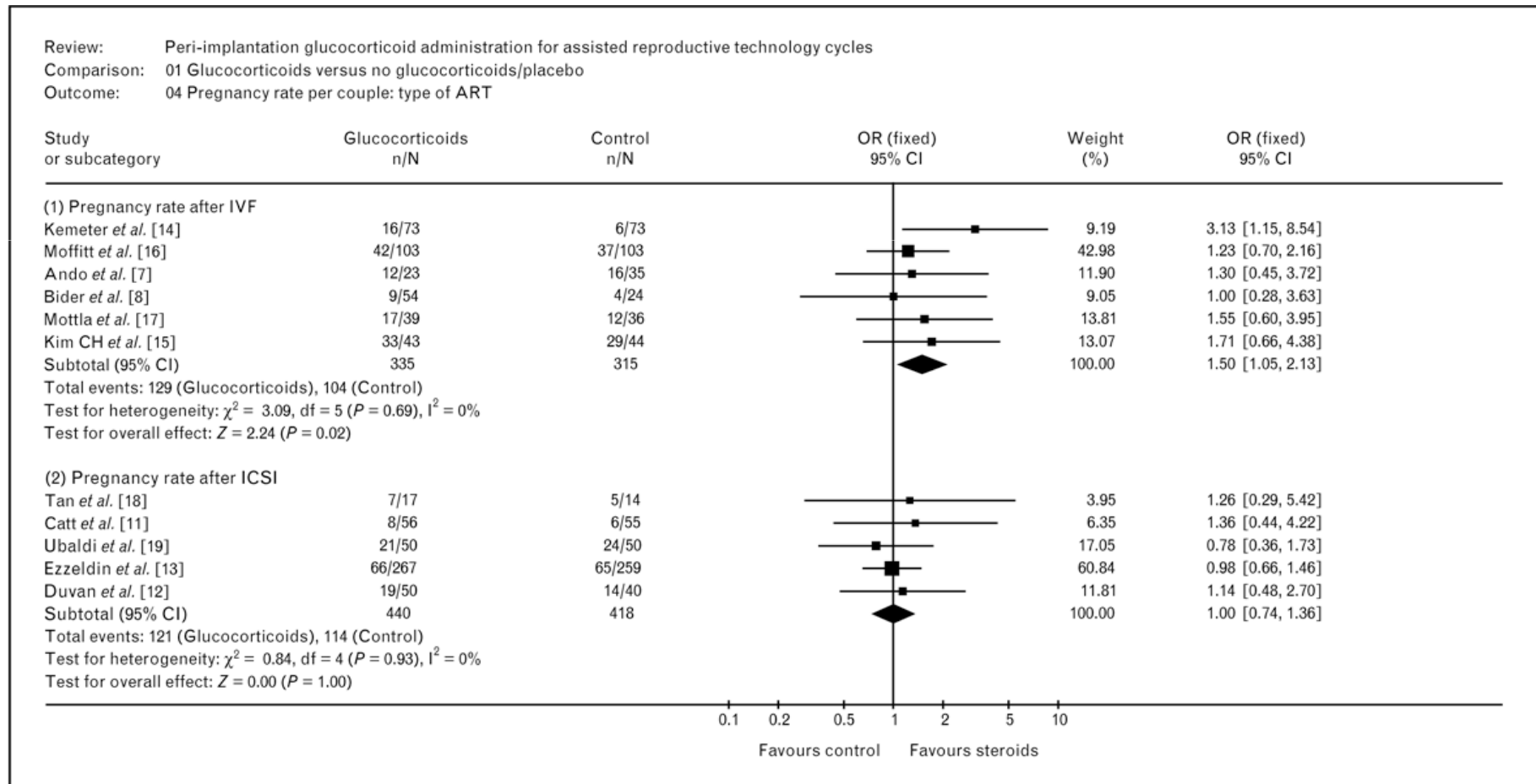
Adjuvant glucocorticoids to improve ovarian response

- Rationale:
 - Physiological follicular rise cortisol prior to ovulation
 - Higher follicular cortisol: cortisone ratios in successful treatment cycles
- No beneficial effect of adjuvant glucocorticoids:
 - RCT: 42 poor responders undergoing ovulation induction + rFSH.
 - RCT 20 women with PCOS undergoing IVF.
 - RCT 25 women with higher levels of DHEA undergoing IVF.
- Beneficial effect of adjuvant glucocorticoids:
 - Non randomised controlled study: 169 women undergoing IUI + stimulation.

(Bider 1997, Fridstrom 1999, Rein 1996, Kim 1996)

Glucocorticoids to improve implantation

- Meta-analysis 13 RCTs on efficacy of peri implantation adjuvant glucocorticoids vs placebo/ no glucocorticoids in women undergoing IVF/ ICSI

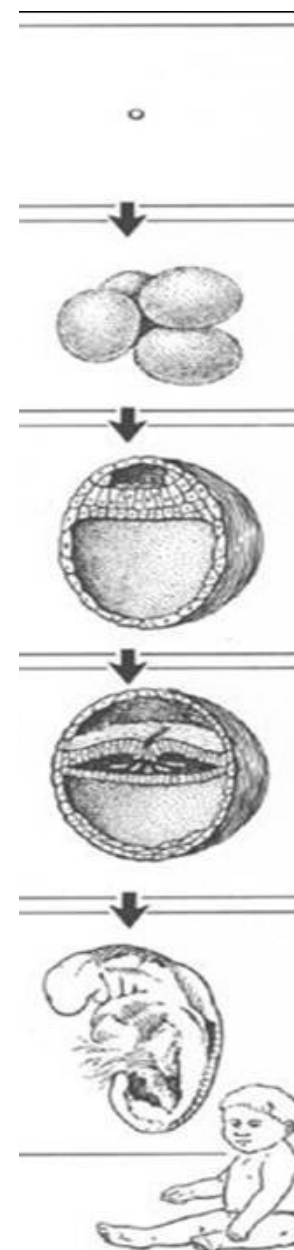


(Boomsma et al, 2008)

Conclusions

- No evidence from RCTs for a beneficial effect of glucocorticoids on ovarian response.
- Meta-analysis shows there is no clear evidence for the empirical use of adjuvant glucocorticoids in IVF/ ICSI.
- Aromatase inhibitors may be of considerable potential value, further studies are required to confirm value and safety.

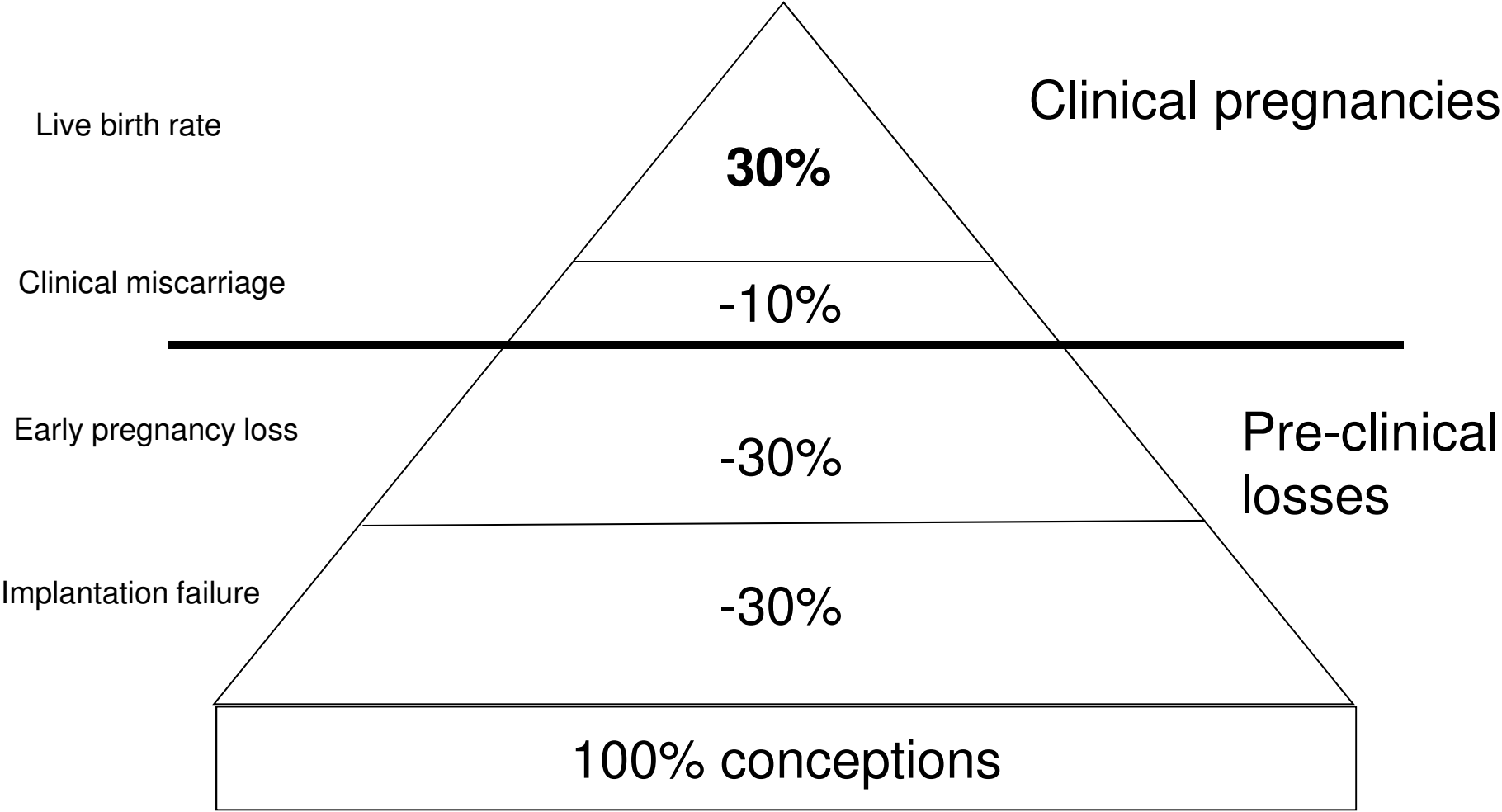
Early pregnancy after IVF



Early pregnancy

“Black Box”

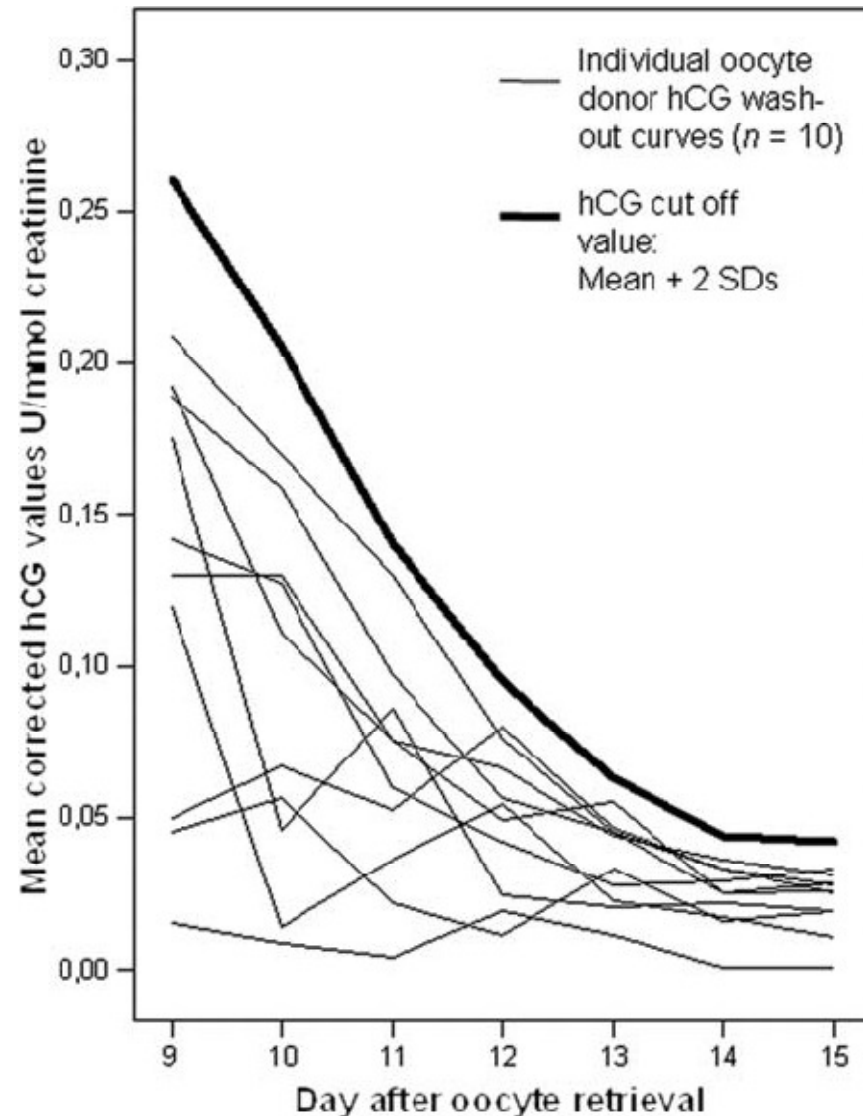
Early pregnancy



(Macklon et al, 2002)

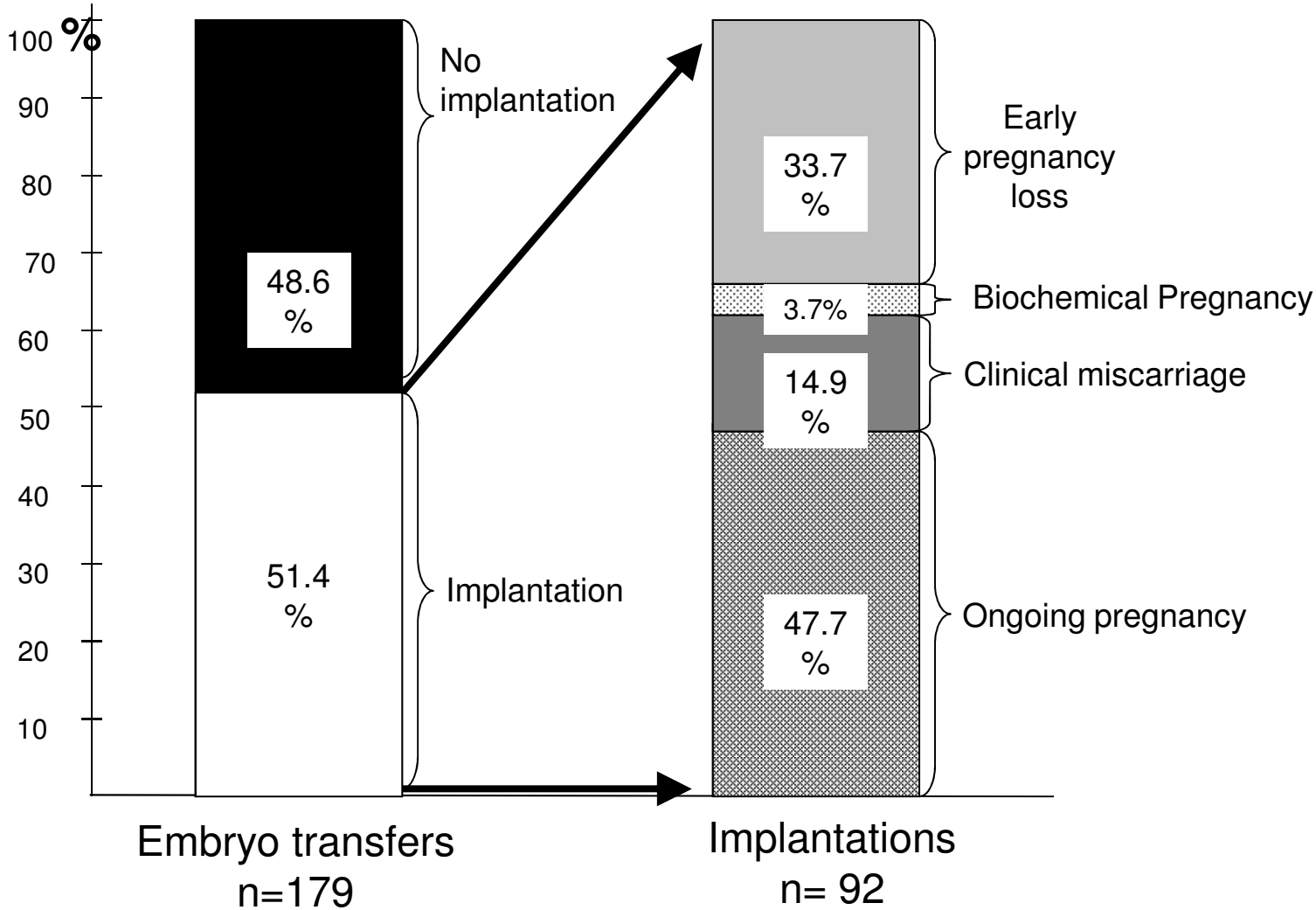
Material and Methods

- 179 women collected daily urine samples (ovum pick-up + 9 to 19)
- **Figure:**
 - Wash-out curve of exogenous hCG in oocyte donors
 - following 10 000 IU hCG prior to oocyte retrieval.



(Boomsma et al, 2009)

Results: early pregnancy after IVF

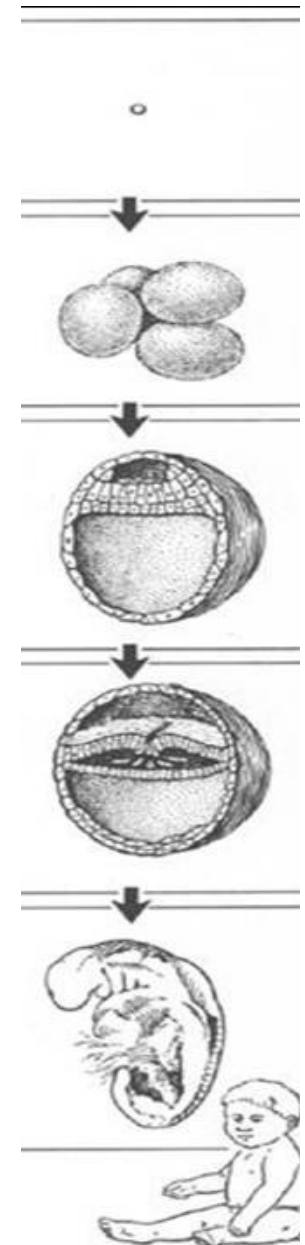


(Boomsma et al, 2009)

Conclusion

- > than 50% of women undergoing ET demonstrated hCG rises, indicating an implanting embryo.
- Approximately one third of these implantations resulted in pre-clinical pregnancy loss.

Hypertensive pregnancy complications in poor and normal responders following IVF



Methods

- Case-control study:
 - 150 pregnant poor responders
 - 150 pregnant normal responders

- Matching for:
 - age at follicle aspiration
 - primary or secondary infertility
 - dose of recombinant FSH
 - singleton or twin pregnancy
 - IVF or ICSI treatment.

Results

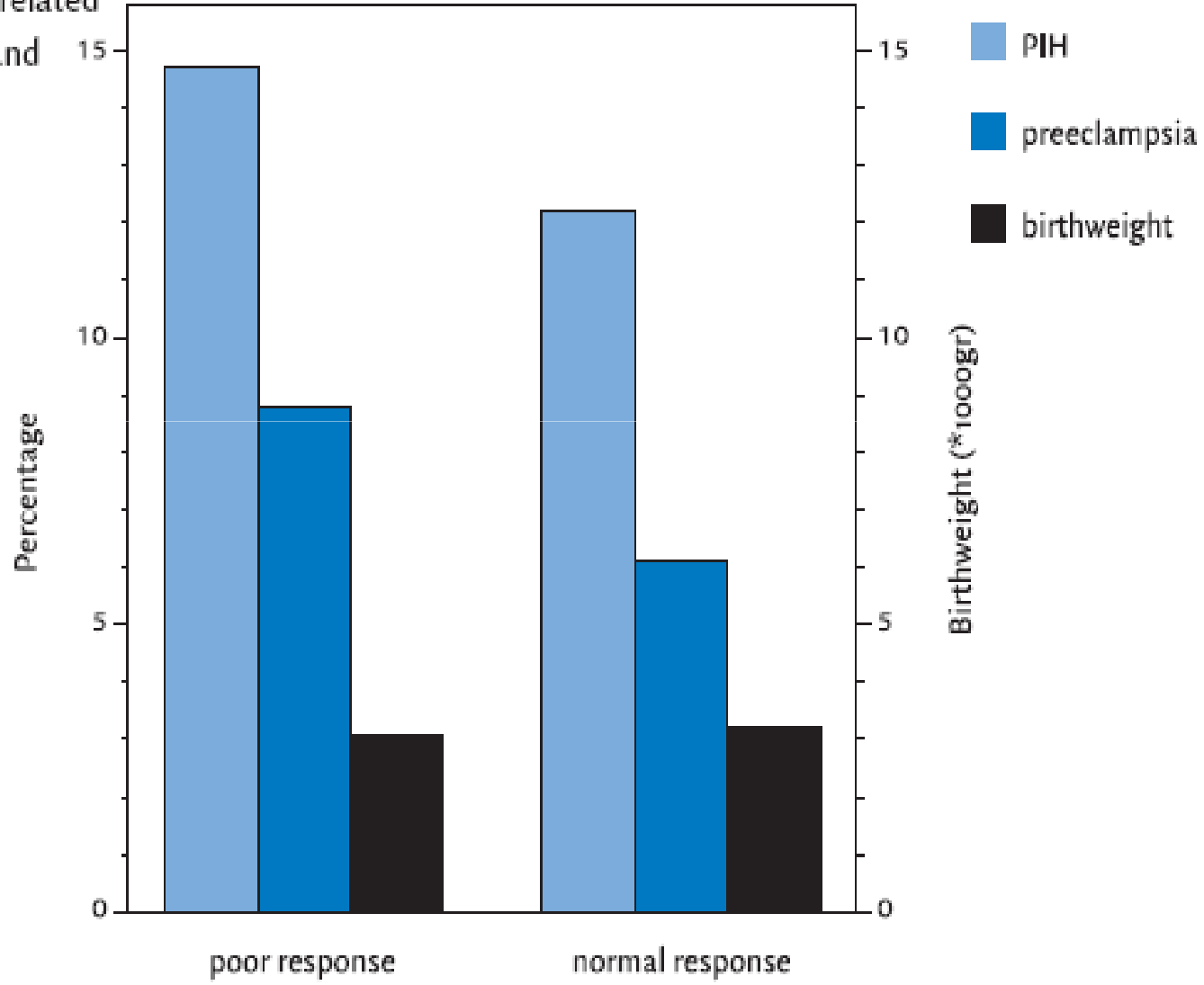
Outcomes for poor and normal responders to ovarian stimulation for IVF who achieved an ongoing pregnancy.					
	Pregnant after poor response (N=136)		Pregnant after normal response (N=131)		p-value
Pregnancy induced hypertension	14,7%		12,2%		0,29 ^a
Pre-eclampsia	8,8%		6,1%		0,27 ^a
Birth weight (gram)	3068	± 937	3190	± 785	0,40 ^b
Duration of pregnancy (weeks)	37,9	± 4,6	38,3	± 4,4	0,18 ^b
Spontaneous delivery	63,4%		65,1%		0,62 ^a
Live birth	96,4%		95,5%		1,0 ^a

(van Disseldorp et al, 2010)

Results

Figure 1

Incidence of pregnancy-related hypertensive disorders and birth weight.

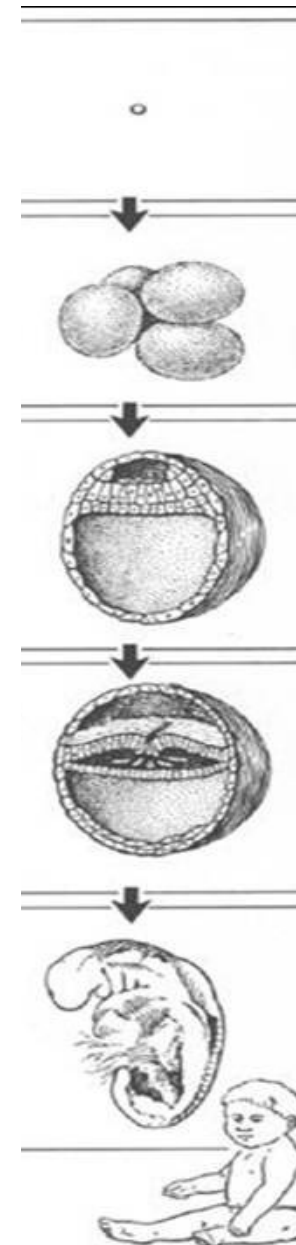


(van Disseldorp et al, 2010)

Conclusions

- Unable to confirm our hypothesis.
- Women pregnant after a poor response in IVF do not have a higher risk of PIH/ PE vs pregnancies after a normal response in IVF.
- These results do not support a vascular etiology of poor response.

Pregnancy complications in women with PCOS



PCOS and pregnancy

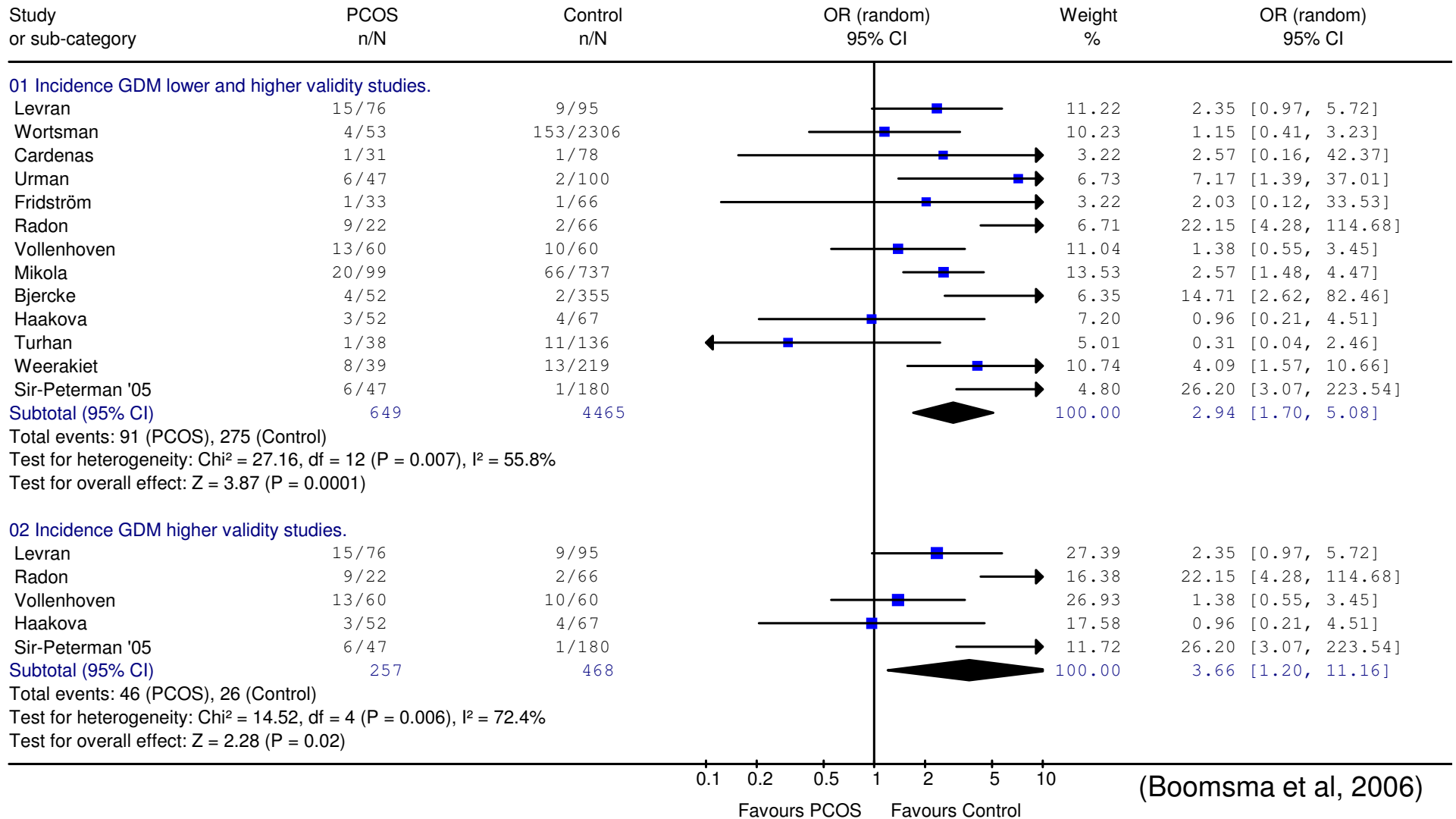
- PCOS coincides with metabolic syndrome.
- Normal pregnancy induces insulin resistance.
- Meta-analysis of PCOS and pregnancy outcome

PCOS and pregnancy outcome

- Meta-analysis of women with PCOS versus non-PCOS controls.
- Result:
529 publications → 15 studies included.
720 women with PCOS vs 4505 controls
- Outcomes
gestational diabetes,
hypertensive disorders,
Admission neonatal intensive care unit,
neonatal mortality,

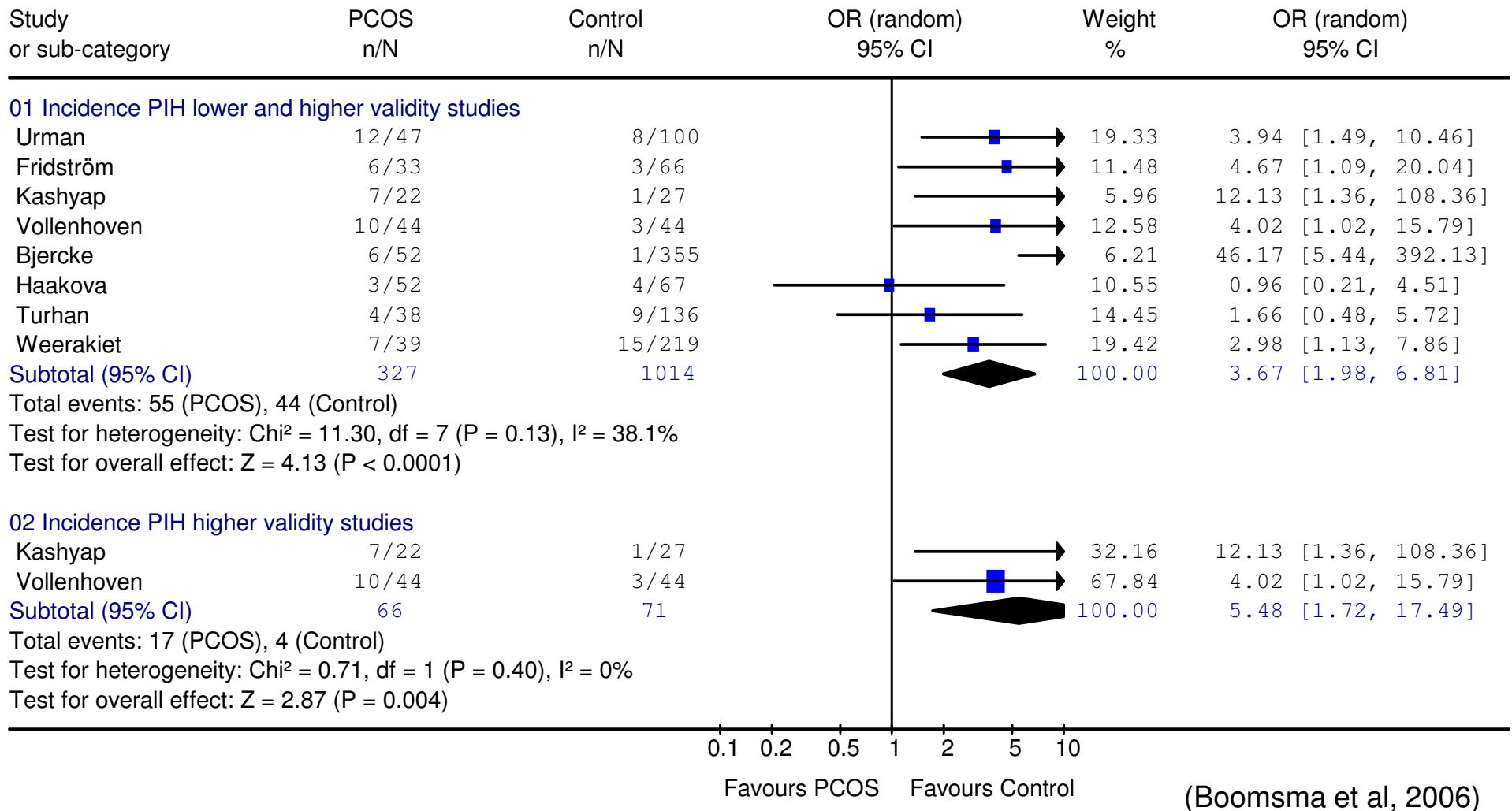
Gestational diabetes

Review: PCOS and pregnancy outcome analysis (1)
 Comparison: 01 Incidence of gestational diabetes
 Outcome: 01 OR incidence of GDM



Pregnancy induced hypertension

Review: PCOS and pregnancy outcome analysis (1)
 Comparison: 04 Incidence of pregnancy induced hypertension
 Outcome: 01 OR for incidence PIH

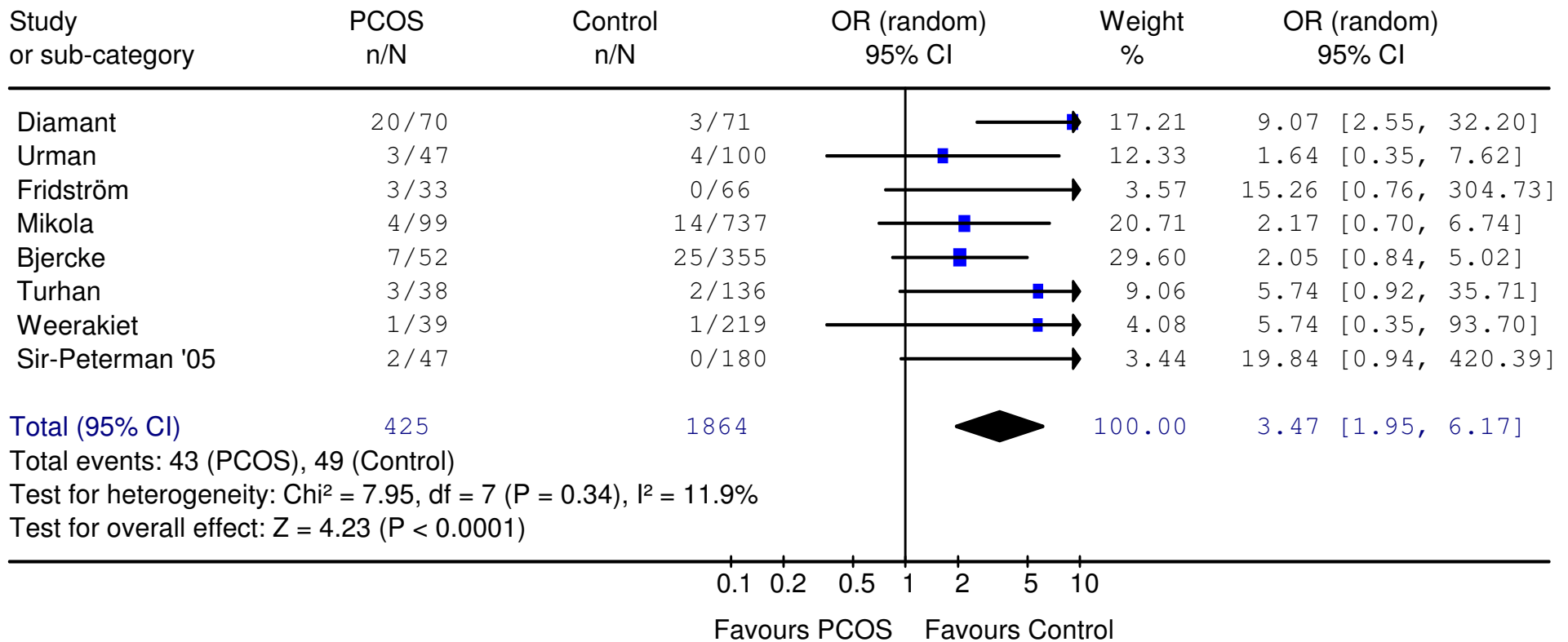


Pre eclampsia

Review: PCOS and pregnancy outcome analysis

Comparison05 Incidence of preeclampsia

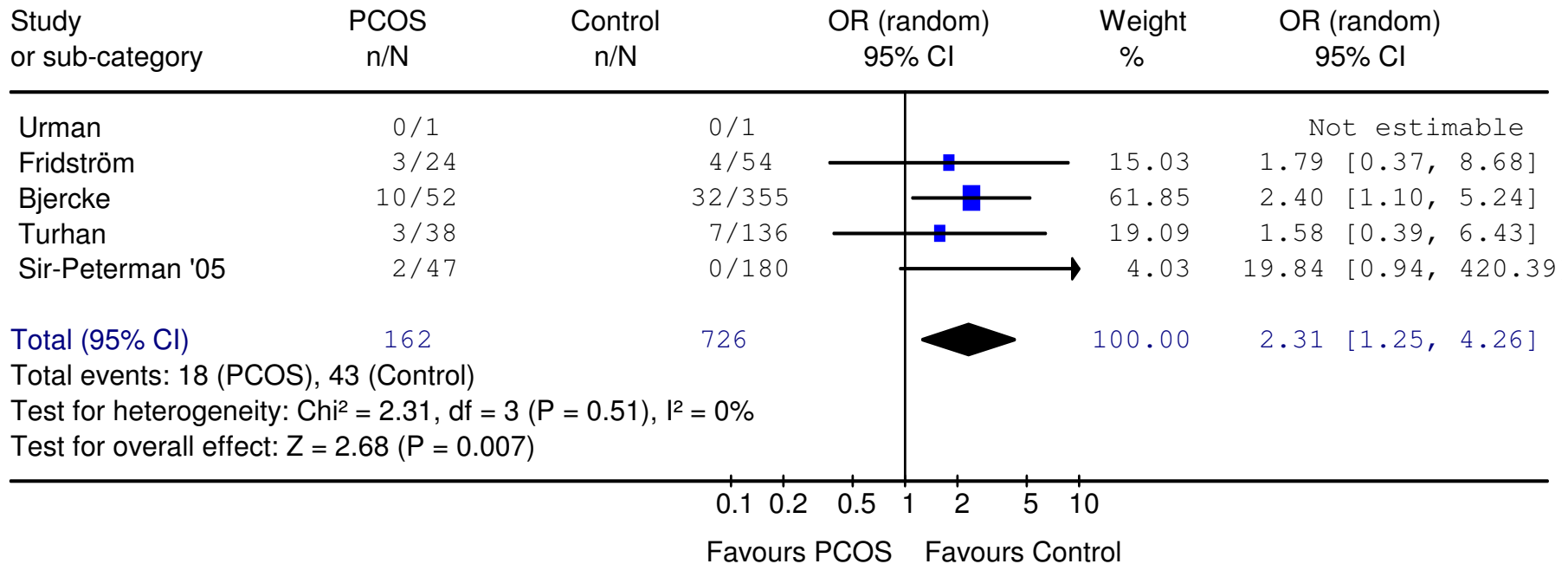
Outcome: 01 OR for incidence PE.



(Boomsma et al, 2006)

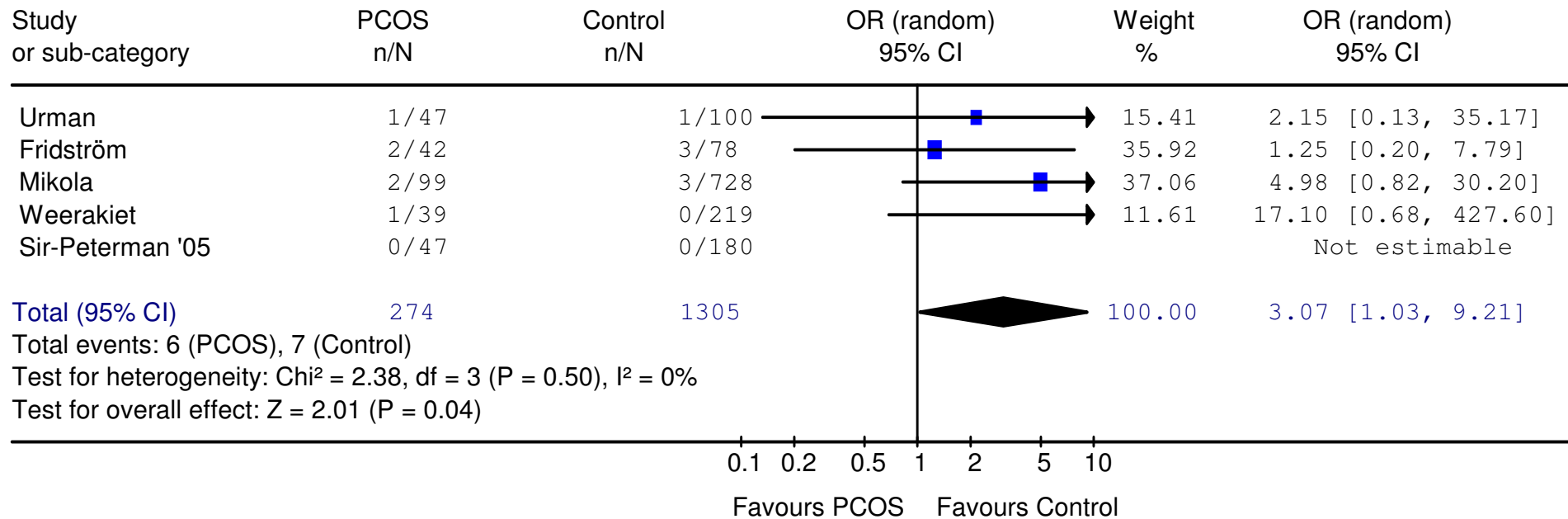
NICU admission

Review: PCOS and pregnancy outcome analysis (1)
 Comparison: Incidence of admission at NICU
 Outcome: OR NICU admission



Perinatal mortality

Review: PCOS and pregnancy outcome analysis (1)
 Comparison: 16 Incidence perinatal death
 Outcome: 01 OR perinatal death



Conclusion

- PCOS is associated with significant higher rates of pregnancy and neonatal complications.
- The long term health issues and pregnancy risks associated with PCOS go beyond infertility
- Pre conceptional screening

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