From intrauterine to extrauterine - Pregnancies following artificial insemination

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ESHRE Genk 2009

The absolute figures

IUI cycles performed in Europe using partner's or donor's semen (Andersen *et al*., 2005, 2006, 2007, 2008)

	2001	2002	2003	2004
IUI partner				
Countries	15	16	18	19
Cycles	52 939	78 505	82 834	98 388
Pregnancies (%)	6696 (12.6)	8961 (11.4)	9995 (12.1)	12 216 (12.4)
Singleton births (%)	5826 (88.8)	6553 (88.7)	3880 (86.9)	10 499 (86.9)
Multiple births (%)	732 (11.2)	831 (11.3)	585 (13.1)	1582 (13.1)
IUI donor				
Countries	15	17	16	15
Cycles	14 185	14 779	16 743	17 592
Pregnancies (%)	2307 (16.3)	2327 (15.7)	2620 (15.6)	3108 (17.7)
Singleton births (%)	1980 (89.6)	1928 (90.0)	2283 (88.6)	2686 (88.2)
Multiple births (%)	230 (10.4)	215 (10.0)	294 (11.4)	360 (11.8)

(Singleton) Pregnancy outcome

Obstetrical and neonatal data

Human Reproduction Vol.20, No.6 pp. 1642–1646, 2005
Advance Access publication March 24, 2005
doi:10.1093/humrep/deh807

Comparison of outcome of pregnancy after intra-uterine insemination (IUI) and IVF

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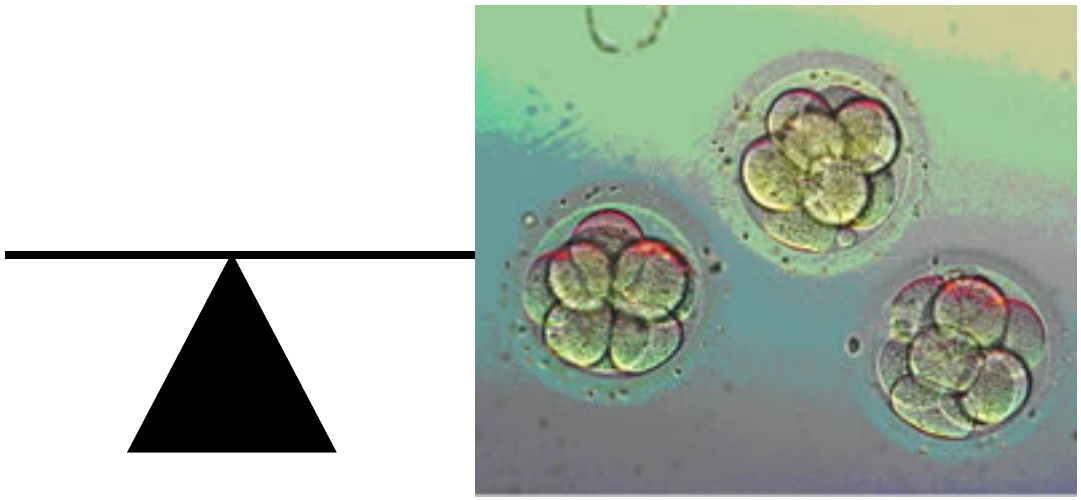
For Dulcie it was the perfect Valentine's Day gift.. everything a cow could want without all the rest of the bull.



Pregnancies after IUI vs IVF

- Pregnancy outcome after IVF has been shown to be worse than after spontaneous conception (IVF technique or patient characteristics?)
- -> comparison of pregnancy outcome after IVF and IUI in a matched patient group (2 x 126 patients)
- Matching for maternal age, parity and plurality
- Outcome variables: pregnancy duration, birth weight, CS rates, preterm contraction rates, NICU admission, Apgar score, blood loss rates and maternal hypertension.

Table I. Comparison of primary and secondary outcome parameters between pregnancies and children born after IVF and IUI

	IVF	IUI	*P*-value
No. of pregnancies	126	126	
Caesarean section rate	21.0%	27.8%	0.256
Duration of pregnancy (days±SD)	272.8±25.0	271.9±15.5	0.402
Birth weight (g±SD)	3140±633	3157±670	0.552
No of preterm births (%)	21 (16.7%)	19 (15.1%)	0.432
Preterm contraction rate	15.8%	16.7%	0.866
NICU stay (% of children)	12.8%	19.4%	0.151
% of children with Apgar score after 1 min of <7	7.1%	6.7%	0.563
% of children with Apgar score after 5 min of <7	1.8%	1.0%	0.574
Blood loss first trimester (%)	16.3	21.4	0.337
Blood loss second trimester (%)	6.5	5.6	1.000
Blood loss third trimester (%)	8 (5.7%)	7 (5.0%)	1.000
No. of intrauterine deaths (%)	1 (0.7%)	2 (1.4%)	1.000
Pregnancy-induced hypertension (%)	15.1%	9.5%	0.263
No. of children in head presentation (%)	116 (95%)	109 (89%)	0.150

Pregnancies after IUI vs IVF

- None of the analysed parameters was statistically different between the groups.

- Conclusion: no different pregnancy outcomes after IVF and IUI

- This suggests that the “worse” pregnancy outcome after IVF as compared with spontaneous conceptions is due to the specific patient characteristics / infertility in se, rather than to the use of IVF itself or that IUI in itself also leads to a worse outcome.

IUI or stimulation?

- IUI without pretreatment with gonadotrophins: duration of pregnancy and neonatal birth weight were similar between IUI and IVF (De Sutter et al., 2005)
- Also if IUI was preceded by treatment with gonadotrophins in a majority of the patients, neonatal birth weight was significantly lower compared with women having delivery after natural conception (Nuojua-Huttunen et al., 1999)
- De Geyter et al., 2006: neonatal birth weight after ovulation induction with gonadotrophins and IUI was lower than in the comparison group

- Effect of IUI rather than ovarian hyperstimulation? -> Effect of infertility?

IUI or infertility?

Human Reproduction Vol.21, No.12 pp. 3228–3234, 2006 doi:10.1093/humrep/del311
Advance Access publication October 5, 2006.

Does subfertility explain the risk of poor perinatal outcome after IVF and ovarian hyperstimulation?

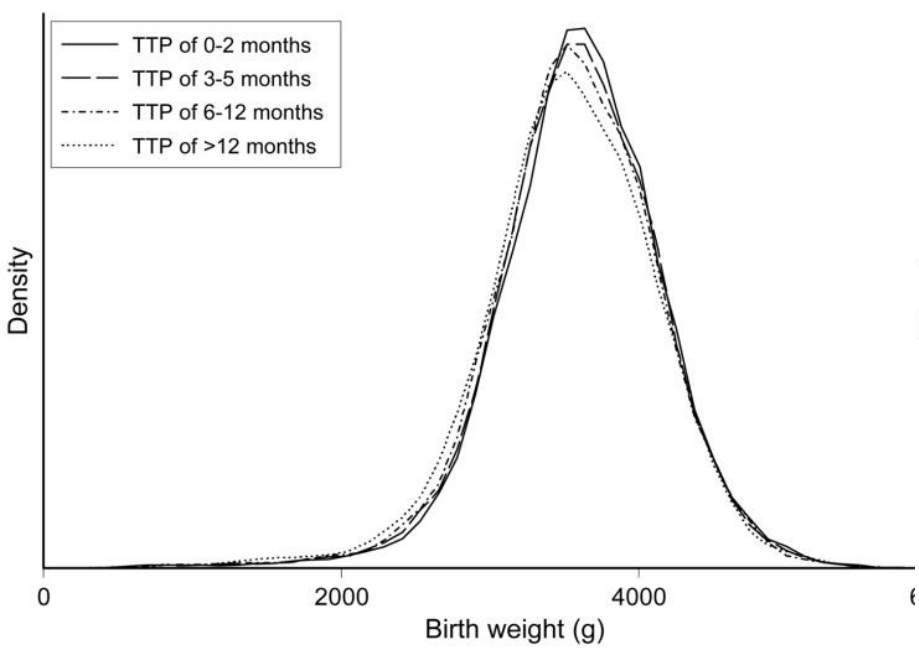
K.Kapiteijn[1], C.S.de Bruijn[1], E.de Boer[2], A.J.M.de Craen[3], C.W.Burger[4], F.E.van Leeuwen[2] and F.M.Helmerhorst[1,5,6]

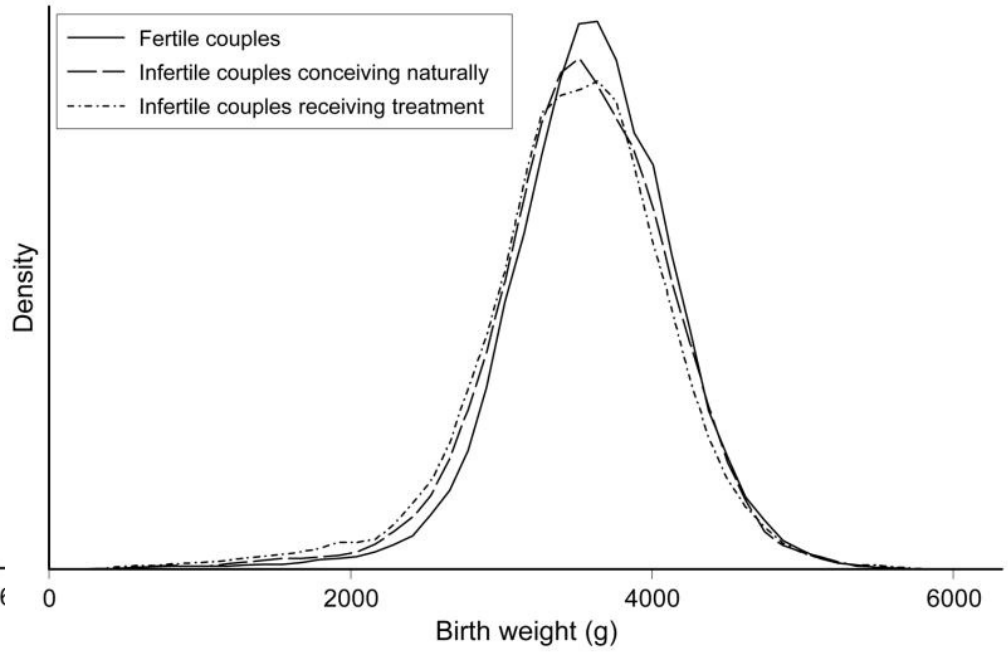
Comparison of IVF (n=2239) and spontaneous pregnancies (n= 6343) in subfertile women : IVF does worse!

The poor perinatal outcome in this database could not be explained by subfertility and suggests that other factors may be important in the known association between assisted conception and poor perinatal outcome.

However:

Effect of time-to-pregnancy and/or infertility treatment on birth weight (Zhu et al., 2007, Danish National Birth Cohort (1997–2003), 51,041 singletons born of fertile couples (time to pregnancy ≤12 months), 5787 born of infertile couples conceiving naturally (time to pregnancy >12 months), and 4317 born after any treatment.):

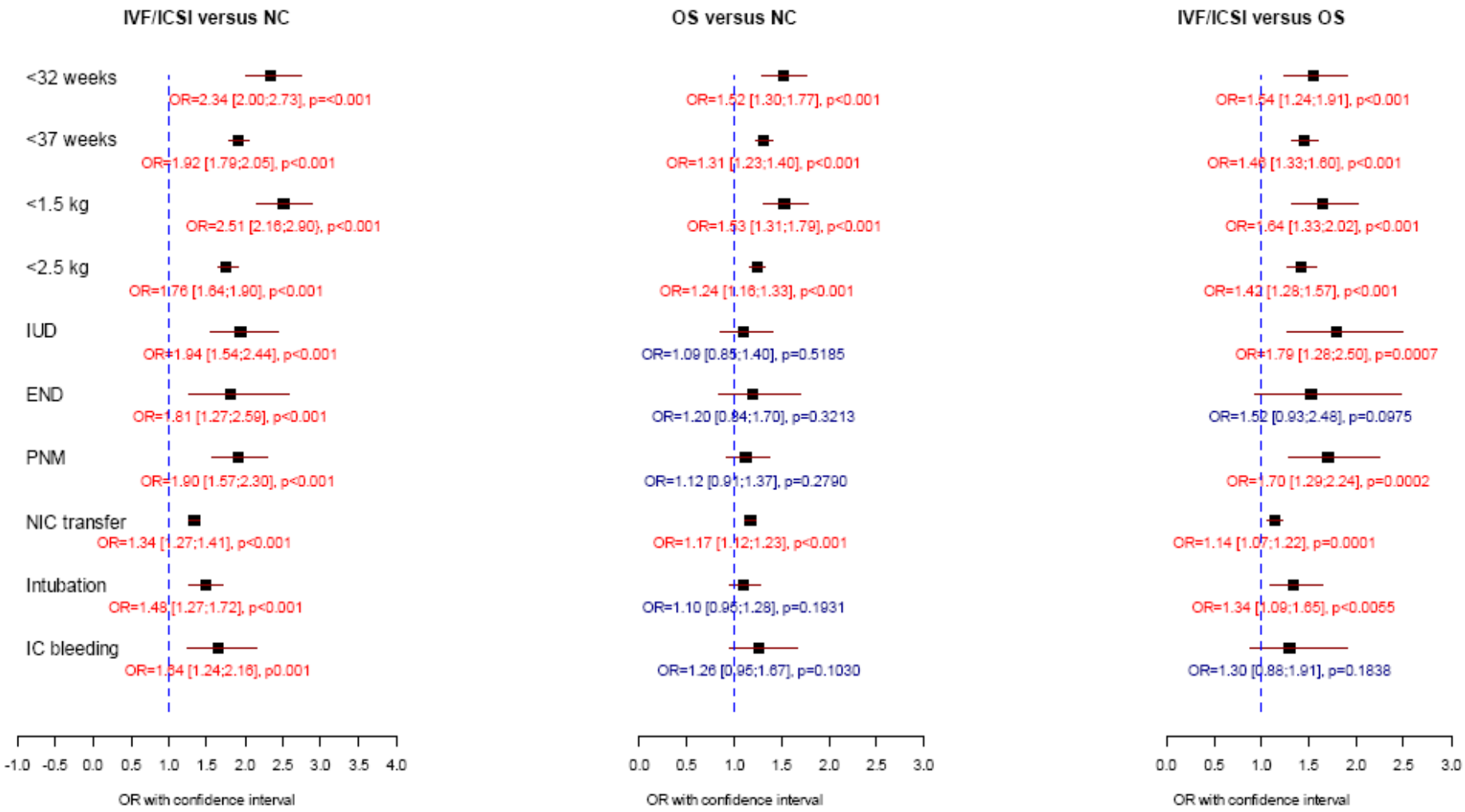




Ombelet et al., in preparation

- 12 years population-based registry (642,613 singletons)
- IVF/ICSI singletons had a significantly worse outcome when compared to OS and NC for almost all investigated perinatal parameters.
- OS singletons were also significantly disadvantaged for birthweight and prematurity when compared to NC.
- The outcome of twin pregnancies was similar for the three groups unless only unlike-sex
- twins were studied separately. Among this subgroup, IVF/ICSI carried a higher risk for low birth weight when compared to NC. OS unlike-sex twins were at increased risk for low birth weight and perinatal mortality when compared to NC.

Comparisons for singletons (Ombelet et al., in preparation)



(OR = odds ratio with 95 % confidence intervals, OS = ovarian stimulation, NC = natural conception, IUD = intrauterine death, END = early neonatal death, PNM = perinatal mortality, NIC transfer = transfer to the neonatal intensive care unit, IC bleeding = intracranial bleeding)

Conclusion

Worse pregnancy outcome following ART increases with complexity of the treatment.

This can still be the result of both patient and treatment dependent factors.

Only a RCT comparing different treatments in the same patient population can answer this question.


AND NOW FOR
SOMETHING
COMPLETELY
DIFFERENT

Pregnancies after donor insemination

- Smith et al., 1997: Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility.
- Kyrou et al., 2009: Is the use of donor sperm associated with a higher incidence of preeclampsia in women who achieve pregnancy after intrauterine insemination?

Graeme N. Smith, MD, PhD,[a] Mark Walker, MD,[b] Julie L. Tessier, MD,[a] and Kenneth G. Millar, MB[a]

Kingston, Ontario, Canada

	Insemination type		
	Donor (n = 37)	*Partner (n = 44)*	*Significance*
Age at conception (yr)	31.6	31.8	$p = 0.87$
Male infertility	25	16	$p = 0.0002$
Ovulation induction	18	43	$p = 0.0001$
Cycles	2.5	2.4	$p = 0.85$
Operative delivery*	21	14	$p = 0.01$
GA (wk)	39.1	38.0	$p = 0.06$
Birth weight (gm)	3200	3099	$p = 0.52$
Male/female fetuses	17:20	18:26	$p = 0.64$
Twins	3	5	$p = 0.72$

Three cases of mild preeclampsia were found in the partner insemination program and nine cases of preeclampsia (five severe, four mild) in the donor insemination program (relative risk 1.85, 95% confidence interval 1.20 to 2.85).

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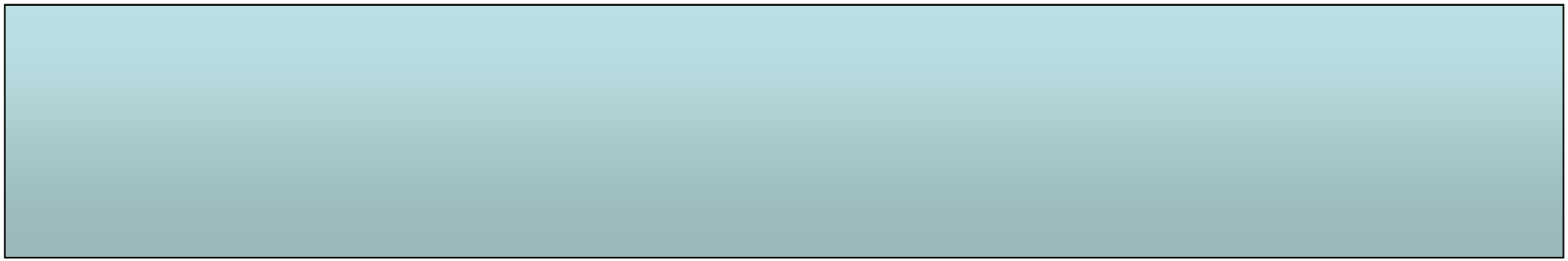

Dimitra Kyrou, M.D., Efstratios M. Kolibianakis, M.D., Ph.D., Paul Devroey, M.D., Ph.D., and Human Musavi Fatemi, M.D., Ph.D.

713 pregnancies (438 after donor insemination and 275 after partner IUI).

The incidence of preeclampsia in pregnancies resulting from donor sperm was higher than in the partner insemination group: 10.9% (48/438) versus 7.2% (20/275), respectively. Logistic regression was performed controlling for the following parameters: type of sperm, number of previous cycles, and number of babies.

The variables that significantly predicted the risk of preeclampsia were the type of sperm used for insemination and the number of previous IUI cycles performed.

The fewer cycles that were performed, the higher the incidence of preeclampsia that was observed. Thus these data support the hypothesis that there is a protective effect of prolonged exposure to sperm on the incidence of preeclampsia.

And what about the ectopics?

- Case reports:
- Plotti et al., 2008: Bilateral ovarian pregnancy after intrauterine insemination and controlled ovarian stimulation.
- Hypothesis: risk for ectopic pregnancy increases after controlled ovarian hyperstimulation!
  - Fernandez et al., 1991: Ovulation induction alone was associated with an increased risk of ectopic pregnancy (adjusted odds ratio = 3.98; 95% confidence interval 1.10-14.30). These results suggest that hormonal factors may be involved in the development of ectopic pregnancy.

American Journal of Epidemiology

Vol. 157, No. 3
Printed in U.S.A.
DOI: 10.1093/aje/kwf190

Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-based Study in France

Variables	Controls (n = 1,683)		Cases (n = 803)		Crude OR*	95% CI*	p value†
	No.	%	No.	%			
Previous use of oral contraceptive							
No	298	17.8	209	26.5	1		<0.001
Yes	1,377	82.2	581	73.5	0.6	0.5, 0.7	
Previous use of intrauterine device							
No	1,460	87.2	637	80.6	1		<0.001
Yes	215	12.8	153	19.4	1.6	1.3, 2.0	
Ovulation induced with clomiphene citrate							
No	1,632	97.4	762	95.1	1		0.003
Yes	43	2.6	39	4.9	1.9	1.2, 3.0	
History of infertility							
No	1,475	89.0	543	69.2	1		<0.001
<1 year	47	2.8	35	4.5	2.0	1.3, 3.2	
1–2 years	58	3.5	64	8.2	3.0	2.1, 4.3	
>2 years	77	4.7	143	18.2	5.0	3.7, 6.8	

Conclusions

IUI: lower birth weights are related to the infertility (but there may also be a treatment effect)

Increased risk for ectopic pregnancy < Stimulation? Infertility in se?

Donor inseminations: more preeclampsia !