Birth defects in children born after ART

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Current understanding and management of health risks associated with IVF
ESHRE Special Interest Group: Safety and Quality in ART

Lübeck, January 18, 2008

ART children vs spontaneously concieved children Adverse perinatal outcomes

- Multiple birth x 10-20
- Very preterm birth and preterm birth in singletons x 2
- Very low birth weight and low birth weight in singletons x 2
- Birth defects?

Variability in the prevalence of birth defects

- Different real rates
- Different definition
- Different levels of ascertainment
- Different length of follow-up
- Different time periods

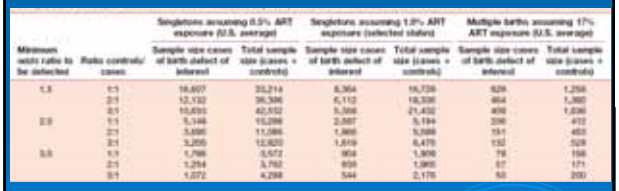
Birth defects in ART children vs spontaneously conceived children

The problem of sample size. Prospective follow up studies

Schieve et al, Fertil Steril, 2005

Birth defects in ART children vs spontaneously conceived children

The problem of sample size. Case-control studies



Schieve et al, Fertil Steril, 2005

Definition and classification of birth defects

- Anatomical defects or chromosomal abnormalities that are present at birth and are either fatal or significantly affect the individual´s function or appearance
- International Classification of Diseases (ICD 8, 9, 10)
- Major and minor birth defects

Birth defects
Literature search strategy

Pub Med, Cochrane databases
1978 - Nov 2007

- IVF
- In vitro fertili?ation
- ICSI
- Intracytoplasmic sperm injection
- Asssisted reproduction
- Assisted reproductive techn$
- Infertility treatment?
- Birth defect?
- Congenital malformation?
- Congenital abnormalit$
- Hospital$
- Follow-up
- Health and child
- Record linkage

Clinic or hospital based studies

Author	No of ART children	% children with birth defects ART	controls	Significance
Morin, 1989	83	2.4	1.1	No difference
Sutcliffe, 1995	91	3.3	2.4	No difference
Tanbo, 1995	355 singletons	2.0	1.7	No difference
Verlaenen, 1995	140 singletons	5.7	0	Significantly higher rate
Nassar, 1996	128	2.3	1.5	No difference
D´Souza, 1997	278	6.1	2.5	No difference
Fisch, 1997	100	8.0	1.9	No difference
Bowen, 1998	84	3.6	5.0	No difference
Koudstaal, 2000	307 singletons	2.3	2.3	No difference
Koudstaal, 2000	192 twins	3.6	2.6	No difference
Sutcliffe, 2001	208 ICSI, singletons	4.8	4.5	No difference
Zuppa, 2001	32 twins	6.2	1.3	No difference
Wang, 2002	1019 singletons	4.5	4.3	No difference
Isaksson, 2002	109	5.5	3.5	No difference
Zadori, 2003	262	1.9	1.2	No difference
Kozinszky, 2003	284 singletons	3.2	1.8	No difference
Kozinszky, 2003	150 twins	3.3	1.3	No difference
Merlob, 2005	278	9.1	4.9	Significantly higher rate
Bucket, 2007	432	8.8	NA	No difference

Population-based studies

Author	No of ART children	% with birth defects ART	controls	Significance
Beral, 1990	1,581	2.2	NA	No difference
Addor, 1998	82	6.1	2.4	No difference
Dhont, 1999	5,539	3.1	1.7	OR 1.8*
Westergaard, 1999	2,245	4.8	4.6	No difference
Anthony, 2002	4,224	3.2	2.7	OR 1.2*
Ludwig, 2002	3,372 ICSI	8.6	6.9	OR 1.25*
Hansen, 2002	837	9.0	4.2	OR 2.6*
Koivurova, 2002	304	6.6	4.4	No difference
Pinborg, 2004	3,393 twins	6.2	NA	No difference
Klemetti, 2005	2,930 singletons	4.3	2.9	OR 1.3*
	1,629 twins	4.3	5.3	No difference
Shevell, 2005	554	3.5	1.9	No difference
Källén, 2005	16,280	5.0	4.0	OR 1.3*

* Significantly higher

Systematic reviews and Meta-analyses

Birth defects in IVF/ICSI vs spontaneously conceived children

- Rimm *et al*, J Assist Reprod Genet, 2004
- McDonald *et al* , J Obstet Gynaecol, 2005
- Hansen *et al*, Hum Reprod, 2005

Meta-analysis of birth defects after ART

IVF/ICSI vs spontaneously conceived children

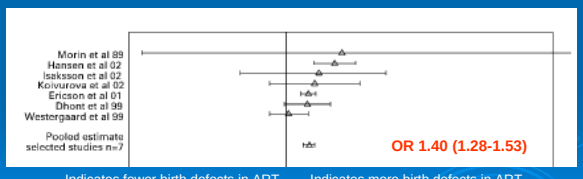
	No of studies	No of ART children	Plurality	OR/RR	95% CI
Rimm 2004	19	35,758	All	1.29	1.01-1.67
McDonald 2005	7	4,031	Singleton	1.41	1.06-1.88
Hansen 2005	7 25	16,038 28,638	All All	1.40 1.29	1.28-1.53 1.21-1.37

Meta-analysis Birth defects

IVF/ICSI vs spontaneously conceived children

Hansen et al, Hum Reprod, 2005,

7 reviewer-selected studies, 16,038 ART children



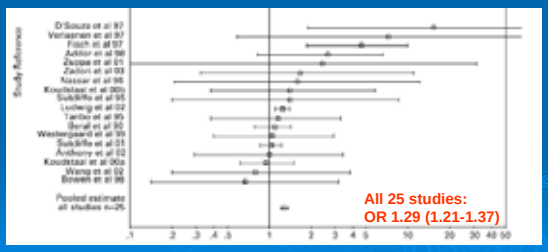
Indicates fewer birth defects in ART Indicates more birth defects in ART

Meta-analysis Birth defects

IVF/ICSI vs spontaneously conceived children

Hansen et al, Hum Reprod, 2005

18 remaining studies, 12,600 ART children



Indicates fewer birth defects in ART Indicates more birth defects in ART

Meta-analysis Birth defects

IVF/ICSI vs spontaneously conceived children

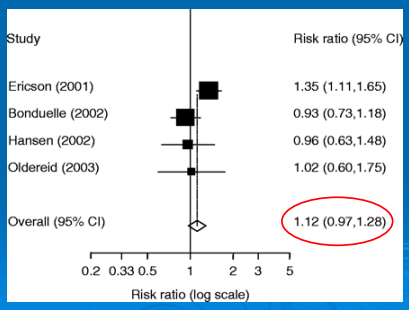
Hansen et al, Hum Reprod, 2005

	Reviewer selected studies (n=1-7)	All studies (n=5-19)
Major defects	2.0 (1.5-2.7)	1.3 (1.2-1.5)
Singletons + multiples	1.5 (1.4-1.6)	1.4 (1.3-1.5)
Singletons	1.4 (1.2-1.5)	1.3 (1.2-1.5)
Crude data	1.6 (1.5-1.7)	1.5 (1.4-1.6)
Adjusted/matched data	1.4 (1.3-1.5)	1.3 (1.2-1.4)
IVF only	1.9 (1.4-2.5)	1.9 (1.5-2.5)
ICSI only	2.0 (1.3-3.2)	1.3 (1.1-1.4)

Birth defects: IVF vs ICSI

	No of ICSI children	% ICSI children with birth defects	No of IVF children	% IVF children with birth defects	RR/OR	95% CI
Bonduelle 2002 Belgium	2889	4.2	2995	4.5	0.93	0.73-1.18
Hansen 2002 Australia	301	8.6	837	9.0	0.96	0.63-1.48
Oldereid 2003 Norway	553	3.1	1731	3.0	1.02	0.97-1.28
Ombelet 2005 The Netherlands	1655 singletons 1102 twins	2.1 3.2	3974 singletons 2901 twins	2.4 2.8	0.96 1.13	0.65-1.42 0.74-1.71
Källen 2005 Sweden	4949	8.6	11283	8.1	1.00	0.74-1.36

Meta-analysis of major birth defects IVF vs ICSI



Lie et al, Int J Epidemiology, 2005

Birth defects
The Swedish Population–based study

- Sweden, 1982-2001
- 16,280 ART children (30% ICSI) and > 2 000 000 controls
- Swedish Medical Birth Registry and Registry of Congenital Malformations, Hospital Discharge Registry

All birth defects	5% vs 4%	OR 1.26 (1.18-1.36)
Severe birth defects	3.3% vs 2.2%	OR 1.46 (1.39-1.65)

All birth defects, adjusted for year of birth, maternal age, parity, smoking, years of known childlessness OR 1.04 (0.93-1.16)
Singletons OR 1.07 (0.95-1.21)
Multiple births OR 0.86 (0.70-1.05)

Källen et al, Birth defects, 2005

BMJ **Infertility, infertility treatment, and congenital malformations: Danish national birth cohort**
Jin Liang Zhu, Olga Basso, Carsten Obel, Camilla Bille and Jorn Olsen

	Singletons born to fertile couples N=50,897 Group A	Singletons born to infertile couples N=5,764 Group B	Singletons born to infertile couples with infertility treatment N=4,588 Group C
All malformations	5.0%	6.0% B vs A: 1.20 (1.07-1.35)	6.7% C vs A: 1.39 (1.23-1.57) C vs B: 1.17 (1.00-1.36)

Group B vs A Increased rate of malformations in nervous, digestive and musculoskeletal system

Group C vs A Increased rate of malformations in nervous, digestive and musculoskeletal system and genital organs

Group C vs B Increased rate of malformations in genital organs

BMJ, 2006

BMJ

Infertility, infertility treatment, and congenital malformations: Danish national birth cohort

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Adj Hazard ratios of congenital malformations in singletons after different types of infertility treatment versus singletons born to fertile couple

Malformations	ICSI	IVF	IUI	Hormonal treatment
All	1.9*	1.4*	1.3*	1.3*
Genital organs	3.9*	2.2*	2.1*	1.4 (NS)
Nervous system	-	2.5*	1.4 (NS)	2.8*
Musculo-skeletal system	2.0*	1.6*	1.5*	1.2 (NS)

*Significantly higher

BMJ, 2006

Specific birth defects

The Swedish Population – based Study, 16,280 ART children
The Swedish Medical Birth Registry, The Swedish Registry of Congenital Malformations, The Swedish Hospital Discharge Registry

	Number of infants				
	Among IVF				
Group of malformations	Obs.	Exp.	Population Obs.	RR/OR	95% CI
Anencephaly (RR)	5	0.6	78	7.6	2.5–7.7
Spina bifida	20	4.1	586	5.1	3.4–7.8
Encephalocele (RR)	0	0.7	70	3.0	0.0–5.3
Any neural tube defect	25	7.4	734	4.0	3.3–6.9
Hydrocephaly without NTD	13	7.5	954	1.7	1.0–3.0
Orofacial clefts	68	28.5	3623	2.4	1.9–3.1
Cardiovascular defects (except PDA and SUA)	262	51.7	19249	1.5	1.5–2.0
Major cardiovascular defects	50	24.2	3888	2.1	1.6–2.8
VSD or ASD without major cardiovascular defect	156	61.1	6338	2.6	2.2–3.1
Choanal atresia (RR)	7	1.5	159	4.6	1.9–9.5
Esophageal atresia	18	4.7	452	4.0	2.6–6.3
Small gut atresia	19	3.3	315	6.4	4.2–9.6
Anal atresia	23	5.2	533	4.5	3.2–6.9
Any alimentary tract atresia	56	28.8	1302	1.9	1.5–2.5
Abdominal wall defects*	8	4.5	431	1.8	0.9–3.6
Craniostenosis	16	10.8	1019	1.5	0.9–2.5
Limb reduction defects	14	9.7	1022	1.5	0.9–2.5
Hypospadias	75	44.5	4216	1.7	1.4–2.1

Källen et al, Birth defects, 2005

Chromosomal aberrations in ICSI fetuses/babies

	No of tested ICSI fetuses/ babies	Abnormal de novo %	Inherited aberrations %	All aberrations %
In´t Veld 1995	15	33.3	0	33.3
Van Opstal 1997	71	12.7	0	12.7
Loft 1999	206	2.9	0.5	3.4
Wennerholm 2000	149	1.3	1.3	2.6
Aboulghar 2001	430	NA	NA	3.5
Ludwig 2002	830	NA	NA	3.3
Bonduelle 2002	1,586	1.6	1.4	3.0
Samli 2003	142	4.2	0	4.2
Jozwiak, 2004	1,136	1.2	0.3	1.5
All	4,565			2.7 (2.3-3.2)

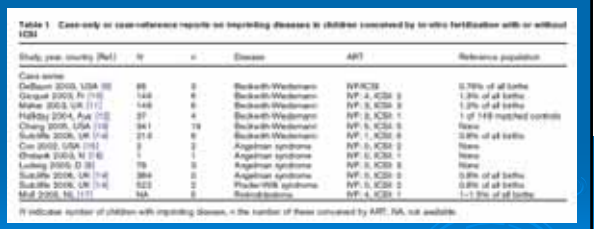
Prenatal diagnosis in ICSI fetuses

Bonduelle et al, Hum Reprod, 2002

	% Abnormal results in 1,586 samples	95% CI	Comparison general population
De novo	1.6	1.0-2.3	0.5% in prenatal tests (33.5 y)
Sex chromosome	0.6	0.3-1.2	0.2% in newborns *Nielsen 1991, Jacobs 1992*
Autosomal	0.95	0.5-1.6	0.45% in prenatal tests (33.5 y)
Inherited	1.4	0.9-2.1	0.3-0.4% in prenatal tests
All	3.0	2.2-3.9	0.8 -0.9% in newborns *Nielsen 1991, Jacobs 1992*

x 3

Imprinting disorders after ART



Lidegaard et al, Curr Opinon Obstet Gynecol, 2006

Imprinting disorders after ART

Two additional studies:

- Questionnaire survey: 220 children with AS, BWS and PWS:
  6.4% born after ART vs 2.1% in the Dutch population, RR 3.0
  (RR: AS 3.0, BWS 4.0, PWS 2.2)
  6.8% born after fertility problems vs 3.5% in the Dutch population, RR1.9
  Doornbos et al Hum Reprod, Sept 2007

- Questionnaire survey of 2,492 ART children in Ireland and England:
  1 BWS
  Conclusion: BWS post ART < 1%
  Bowdin et al Hum Reprod, Dec 2007

Conclusions (1)

- Data from population-based registry studies, systematic reviews and meta-analyses indicate a small but signficant increase (30-40%) in birth defects in children born after ART compared to the general population
- Some of the increase seems to be related to parental characteristics (age, parity, infertility) and multiple birth and preterm birth
- If the ART procedure is related to any increased risk is still not possible to answer

Conclusions (2)

- The prevalence of birth defects is similar after conventional IVF and ICSI
- Inherited and de novo chromosomal aberrations are increased after ICSI
- The absolute risk for any specific birth defect after ART is small
- There is continous need for monitoring the health of children born after ART

Thank You!