

*Controversy: Is IVF Associated with  
Increased Rate of Birth Defect*

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*In Vitro Fertilization as Associated  
with an Increase in Major Birth  
Defects*

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- **Patients**

- From 1989 through 2002
- Children conceived by IVF or IUI at the University of Iowa compared with a matched cohort of naturally conceived children.

**TABLE 1****Characteristics of couples in the IVF, IUI, and control groups.**

Characteristic	IVF (n = 864)	IUI (n = 270)	Controls (n = 6,374)
Maternal age (y) (mean ± SD)	→ 33.9 ± 4.6 <sup>a</sup>	→ 32.4 ± 4.3 <sup>a</sup>	→ 33.3 ± 4.3
Paternal age (y) (mean ± SD)	→ 36.1 ± 5.6 <sup>a</sup>	→ 34.2 ± 4.9	→ 34.6 ± 5.5
Parity (%)			
0	57 <sup>a</sup>	63.4 <sup>a</sup>	20
≥1	43 <sup>a</sup>	37 <sup>a</sup>	80
Maternal race/ethnicity (%)			
Caucasian	97.1	95.2	97.0
Black	0.2	0	0.7
Hispanic	0.9	1.9	1.3
Other	1.7	2.9	1.0
Paternal race/ethnicity (%)			
Caucasian	96.8 <sup>a</sup>	94.4 <sup>a</sup>	89.3
Black	0.9	0	1.2
Hispanic	1.0	3.0	8.3
Other	1.3	2.6	1.3
Married (%)	99.2 <sup>a</sup>	99.0 <sup>a</sup>	89.7
Maternal education (y) (median) <sup>b</sup>	16.0 <sup>a</sup>	16.0 <sup>a</sup>	14.0
Paternal education (y) (median) <sup>b</sup>	15.0 <sup>a</sup>	16.0 <sup>a</sup>	14.0
Maternal smoking (%)	1.9 <sup>a</sup>	4.7 <sup>a</sup>	13.3
Maternal alcohol use (%)	0.4 <sup>a</sup>	0.7 <sup>a</sup>	2.0

Note: All *P* values are for comparison with control group and are noted only if significant.

<sup>a</sup> *P* < .005.

<sup>b</sup> Education variable: values 13–16 = college (1–4 y).

Olson. Birth defects and infertility treatment. *Fertil Steril* 2005.

**TABLE 2****Characteristics of infants in the IVF, IUI, and control populations.**

Characteristic	IVF		IUI		Control (n = 8,422)
	(n = 1,462)	P	(n = 343)	P	
Mean gestational age (wk) (mean ± SD)					
All	36.5 ± 3.6	<.001	37.5 ± 3.9	.031	37.5 ± 3.0
Singletons	38.7 ± 2.2		38.7 ± 2.3		39.1 ± 1.9
Very low birth weight (<1,500 g)					
All	115 (7.9)	<.001	25 (7.3)	<.001	329 (3.9)
Singletons	12 (1.9)		7 (2.7)		37 (0.8)
Twins	62 (9.2)		9 (14.1)		210 (6.0)
Triplets/quadruplets	41 (28.3)		9 (60.0)		82 (25.6)
Low birth weight (<2,500 g)					
All	500 (34.2)	.002	72 (21.0)	<.001	2,011 (23.9)
Singletons	44 (6.8)		23 (8.7)		195 (4.3)
Twins	326 (48.5)		34 (53.1)		1,520 (43.3)
Triplets/quadruplets	130 (89.7)		15 (100)		296 (92.5)
Preterm delivery (<32 wk)					
All	129 (8.8)	<.001	23 (6.7)	.003	343 (4.1)
Singletons	10 (1.6)		6 (2.3)		36 (0.8)
Twins	70 (10.4)		8 (12.5)		237 (6.8)
Triplets/quadruplets	49 (33.8)		9 (60.0)		70 (21.9)
Multiple births					
Twins	672 (46.0)		64 (18.7)		3,512 (41.7)
Triplets/quadruplets	145 (9.9)		15 (4.4)		320 (3.79)
Male sex					
All	735 (50.3)		179 (52.2)		4,190 (49.8)
Singletons	330 (51.2)		132 (50.0)		2,309 (50.3)
Cesarean delivery					
All	706 (48.3)	<.001	114 (33.2)		3,152 (37.4)
Singletons	198 (30.8)		79 (29.9)		1,086 (23.7)

Note: Data are presented as n (%), unless otherwise noted. Data in this table are for descriptive purposes; no adjustments were made for confounding variables in the analysis. Statistical analyses were performed only for the "all infants" groups and not based on plurality. P values are for comparison with control group and are not significant if not shown.

**TABLE 3****Prevalence of major birth defects diagnosed by 1 year of age.**

Group	No. of infants	Prevalence (%)	Unadjusted OR (95% CI)	P	OR adjusted for plurality and/or parity	P
All infants						
Control	8,422	369 (4.4)	Reference		Reference	
IVF	1,462	90 (6.2)	1.44 (1.12–1.85)	.004	1.30 (1.00–1.67) <sup>a</sup>	.048 <sup>a</sup>
IUI	343	17 (5.0)	1.14 (0.70–1.87)	.593	1.11 (0.67–1.84) <sup>a</sup>	.679 <sup>a</sup>
All singletons						
Control	4,590	171 (3.7)	Reference		Reference	
IVF	645	38 (5.9)	1.62 (1.12–2.34)	.010	1.44 (0.98–2.12) <sup>b</sup>	.061
IUI	264	13 (4.9)	1.33 (0.75–2.37)	.324	1.19 (0.66–2.13) <sup>b</sup>	.568
All term singletons (≥37 wk)						
Control	4,285	148 (3.5)	Reference		Reference	
IVF	581	34 (5.8)	1.74 (1.18–2.56)	.006	1.57 (1.04–2.36) <sup>b</sup>	.031
IUI	231	12 (5.2)	1.53 (0.84–1.79)	.164	1.38 (0.75–2.57) <sup>b</sup>	.298

Note: Logistic regression with the GEE method accounting for correlation between infants from same mother.

<sup>a</sup> Adjusted for plurality and parity.

<sup>b</sup> Adjusted for parity.

Olson. Birth defects and infertility treatment. *Fertil Steril* 2005.

- Different treatments within the IVF category
  - *No significant differences in birth defect rates*
    - ZIFT VS ET
    - ICSI- VS non ICSI-
    - **Cryopreserved embryos VS fresh ones** (singletons)
  - A *higher incidence* in *twins* born after transfer of cryopreserved embryos as compared with twins conceived after the transfer of “fresh” embryos (OR 2.11, 95% CI 1.03–4.33,  $P = .041$ )

- **All infants**

- Multiple gestations were associated with a higher birth defect rate than singletons
- Triplets and other higher-order multiple gestations were associated with increased birth defects

- **Control**

- A statistically significant increase in defect rate was seen when twins were compared with singletons

- **IVF or IUI treatment**

- no difference in birth defects was seen in twins compared with singletons



**TABLE 4****Major birth defects by affected organ system.**

System	All infants (n = 10,227)					Singletons (n = 5,499)				
	Control (n = 8,422)	IVF (n = 1,462)	P	IUI (n = 343)	P	Control (n = 4,590)	IVF (n = 645)	P	IUI (n = 264)	P
CNS	50 (0.6)	9 (0.6)		1 (0.3)		15 (0.3)	2 (0.3)		1 (0.4)	
Cardiovascular	100 (1.2)	33 (2.3)	.002	5 (1.5)		45 (1.0)	16 (2.5)	.003	4 (1.5)	
Ear	29 (0.3)	8 (0.6)		2 (0.6)		12 (0.3)	4 (0.6)		2 (0.8)	
Eye	42 (0.5)	8 (0.6)		2 (0.6)		19 (0.4)	5 (0.8)		0 (0)	
Gastrointestinal	48 (0.6)	8 (0.6)		3 (0.9)		15 (0.3)	4 (0.6)		2 (0.8)	
Genitourinary	86 (1.0)	12 (0.8)		2 (0.6)		39 (0.9)	5 (0.8)		0 (0)	
Musculoskeletal	103 (1.2)	32 (2.2)	.007	9 (2.6)	.042	55 (1.2)	17 (2.6)	.006	7 (2.7)	0.08
Orofacial	43 (0.5)	10 (0.7)		4 (1.2)		27 (0.6)	6 (0.9)		3 (1.1)	
Respiratory	6 (0.1)	3 (0.2)		0 (0)		1 (0.02)	0 (0)		0 (0)	
Skin	19 (0.2)	4 (0.3)		0 (0)		12 (0.3)	4 (0.6)		0 (0)	
Syndrome	30 (0.4)	12 (0.8)	.026	1 (0.3)		17 (0.4)	7 (1.1)	.022	0 (0)	
Tumors	10 (0.1)	3 (0.2)		0 (0)		4 (0.1)	1 (0.2)		0 (0)	
Chromosomal	20 (0.2)	6 (0.4)		0 (0)		13 (0.3)	3 (0.5)		0 (0)	
Other	8 (0.1)	2 (0.1)		0 (0)		0 (0)	1 (0.2)		0 (0)	

Note: Data are presented as n (%). If a child had multiple defects in separate organ systems, the child appears more than once in the table. If a child had more than one unrelated defect affecting the same organ system, the child appears only once in the table. P values are comparisons with the control group. P values were not significant if not listed. Fisher's exact t-test was used. CNS = central nervous system.

- Analyzing the major birth defects of different gender
  - IVF
    - **Male infants** had an **8.03%** rate of major birth defects, compared with a **4.26%** rate in **female infants** (OR 1.96, 95% CI 1.23–3.12, *P*.004).
  - IUI or control
    - No increase in birth defects among male infants was noted

- The birth defect rate was increased after IVF when the analysis was limited to **term singletons**.
- Among IVF-conceived children, there was **no difference** in birth defect rates after intracytoplasmic sperm injection (**ICSI**) or after transfer of **cryopreserved embryos**.
- **Cardiovascular** and **musculoskeletal** defects and **known birth defect syndromes** were increased after IVF.

- *The cause of an increased rate of birth defects in children born after IVF is unknown*
- Among IVF-conceived children, there was **no difference** in birth defect rates after intracytoplasmic sperm injection (**ICSI**) or after transfer of **cryopreserved embryos**.

# Recent attention

1. Errors in genomic imprinting
  - Imprinting defects and impaired gametogenesis lined in men or induced with ovulation - inducing medications in women
    - reduced sperm concentrations and abnormal genomic imprinting in the spermatozoa (*Margues CJ. Lancet 2002;363:1700 -2*).
  - side effect of the infertility treatment
    - embryo culture media might predispose to imprinting defects in the embryo (*Edwards RG. Reprod Biomed Online 2003;7:131- 8. Niemitz EL. Am J Hum Genet 2004;74:599-609*).
2. A **genetic inherent** in one or both of the partners, leading to both **reduced fertility** and **subsequent birth defects**

*Children born after assisted fertilization  
have an increased rate of major congenital  
anomalies*

Reija Klemetti, M.H.Sc., Finland

*Fertil Steril 2005;84:1300 –7*

- *Patients*

- 1996 to 1998 in Finland
- Children from **IVF (n =4,559)**, **other ART (n= 4,467)**, and **controls (n = 27,078)**, a random sample of naturally conceived children).

- *Main Outcome Measures*

- Rate of major CAs.
- Children from IVF and other ART were compared with control children, both overall and by plurality, controlling for confounding factors by logistic regression.

**TABLE 1****Characteristics of IVF, other ART, and control mothers and children by multiplicity and gender.**

	<b>IVF</b>	<b>Other ART</b>	<b>Controls</b>
Mothers	n = 3,737	n = 4,188	n = 27,022
Age (y) (mean ± SD) <sup>a</sup>	33.9 ± 4.5	31.2 ± 4.6	29.8 ± 5.3
Age (y) <sup>b</sup>			
<25	2.2	8.3	19.7
25–29	17.3	34.1	32.2
30–34	40.6	37.2	31.4
35–39	30.1	16.4	13.5
40+	9.8	4.0	3.1
Married <sup>c</sup>	76.1	74.8	60.5
Parity <sup>b</sup>			
0	71.7	54.3	38.7
1	21.1	32.4	33.4
2	4.2	9.3	16.4
3+	2.4	3.3	10.1
Missing	0.6	0.7	1.4
Socioeconomic position <sup>b</sup>			
Upper white-collar	26.1	21.2	15.7
Lower white-collar	48.8	47.8	41.3
Blue-collar	12.8	13.9	16.6
Other	12.3	17.2	26.4
Place of residence <sup>b</sup>			
Southern Finland	44.8	38.6	40.6
Western Finland	33.4	38.3	34.4
Eastern Finland	9.9	9.5	10.4
Northern Finland	11.6	13.3	13.9
Missing	0.3	0.3	0.7
Children	n = 4,459	n = 4,467	n = 27,078
Singletons	64.3	87.9	97.8
Girls	32.7	42.8	48.6
Boys	31.6	45.1	49.3
Multiples	35.7	12.1	2.2
Girls	17.6	6.0	1.2
Boys	18.1	6.0	1.0

Note: Values are percentages, unless otherwise noted.

<sup>a</sup>  $P < .001$ , *t*-test.

<sup>b</sup>  $P < .001$  for all comparisons (IVF vs. other ART, IVF vs. controls, and other ART vs. controls),  $\chi^2$  test.

<sup>c</sup>  $P < .001$  (IVF vs. controls and other ART vs. controls), test for relative proportions.



TABLE 2

Prevalence of major congenital anomalies per 10,000 infant by the organ system affected.<sup>a</sup>

	Singletons						Multiples										
	IVF (n = 2,930)			Other ART (n = 3,926)			Controls (n = 26,489)			IVF (n = 1,629)			Other ART (n = 541)			Controls (n = 589)	
	n	/10,000	P <sup>b</sup>	n	/10,000	P <sup>b</sup>	n	/10,000		n	/10,000	P <sup>b</sup>	n	/10,000	P <sup>b</sup>	n	/10,000
Any	125	427	<.001	138	352	.022	756	285	70	430	.335	27	499	.836	31	526	
Central nervous system	9	31	.008	12	31	.003	31	12	9	55	.071	7	129	.006	0	0	
Eye, ear, face and neck	12	41	.009	6	15	.693	48	18	5	31	.583	1	18	.952	1	17	
Heart	44	150	.042	59	150	.021	287	108	33	203	.791	11	203	.840	13	221	
Other circulatory system	6	20	.740	12	31	.088	47	18	2	12	.790	0	0	.338	1	17	
Respiratory system	5	17	.284	5	13	.647	27	10	3	18	.496	0	0	.175	2	34	
Cleft palate and cleft lip	12	41	.034	14	36	.076	56	21	5	31	.904	0	0	.175	2	34	
Digestive system	14	48	.028	16	41	.083	67	25	5	31	.093	4	74	.836	5	85	
Urogenital system	35	119	<.001	26	66	.150	129	49	12	74	.789	4	74	.836	5	85	
Musculoskeletal system	34	116	.004	30	76	.588	182	69	20	123	.270	6	111	.441	4	68	
Skin, hair and nails	1	3	.533	2	5	.757	17	6	2	12	.395	0	0	NA	0	0	
Chromosomal anomalies	8	27	.304	7	18	.927	49	18	3	18	.496	2	37	.932	2	34	
Other congenital anomalies and the defects	12	41	.171	19	48	.020	71	27	9	55	.237	3	55	.381	6	102	

Note: NA = not applicable.

<sup>a</sup> n = number of children. If a child had a major malformation in more than one organ system, the child appears several times in the table. If the malformations affect the same organ system, the child appears only once in the table.<sup>b</sup> Test for relative proportions, control group as a reference group.

Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.

TABLE 3

Total risk of major congenital anomalies and risk according to organ system affected<sup>a</sup> by gender and multiplicity.

Multiplicity	Group	Risk									
		Girls			Boys			Total			
		n <sup>b</sup>	OR (95% CI)	OR <sup>c</sup> (95% CI)	n <sup>b</sup>	OR (95% CI)	OR <sup>c</sup> (95% CI)	n <sup>b</sup>	OR (95% CI)	OR <sup>c</sup> (95% CI)	
Singletons	Total	348	1.00	1.00	408	1.00	1.00	756	1.00	1.00	
	IVF	48	1.23 (0.90–1.66)	0.97 (0.69–1.36)	77	1.79 (1.40–2.30)	1.63 (1.23–2.15)	125	1.52 (1.25–1.84)	1.30 (1.05–1.61)	
	Other ART <sup>d</sup>	87	1.34 (1.02–1.74)	1.21 (0.88–1.67)	71	1.16 (0.80–1.50)	1.12 (0.86–1.46)	138	1.24 (1.03–1.49)	1.17 (0.97–1.41)	
	Heart	Control	128	1.00	1.00	136	1.00	1.00	264	1.00	1.00
	IVF	17	1.17 (0.71–1.95)	1.05 (0.62–1.78)	19	1.30 (0.80–2.11)	1.21 (0.73–2.00)	36	1.24 (0.87–1.75)	1.13 (0.79–1.62)	
	Other ART	29	1.57 (1.04–2.35)	1.52 (1.01–2.28)	24	1.17 (0.76–1.81)	1.17 (0.75–1.81)	53	1.36 (1.01–1.83)	1.33 (0.99–1.80)	
	Urogenital	Control	52	1.00	1.00	80	1.00	1.00	26	1.00	1.00
	IVF	9	1.53 (0.75–3.11)	1.47 (0.70–3.07)	22	2.57 (1.60–4.14)	2.46 (1.49–4.07)	31	2.14 (1.44–3.17)	2.05 (1.36–3.10)	
	Other ART	4	0.53 (0.19–1.46)	0.52 (0.19–1.45)	20	1.66 (1.02–2.72)	1.62 (0.99–2.65)	24	1.23 (0.79–1.90)	1.20 (0.78–1.87)	
	Musculoskeletal	Control	72	1.00	1.00	110	1.00	1.00	182	1.00	1.00
	IVF	11	1.35 (0.72–2.55)	1.26 (0.65–2.44)	23	1.95 (1.24–3.07)	1.75 (1.09–2.81)	34	1.70 (1.17–2.45)	1.55 (1.05–2.27)	
	Other ART	12	1.15 (0.62–2.12)	1.11 (0.60–2.05)	18	1.09 (0.66–1.79)	1.04 (0.63–1.72)	30	1.11 (0.76–1.64)	1.07 (0.73–1.58)	
	Multiples	Total	18	1.00	1.00	13	1.00	1.00	31	1.00	1.00
		IVF	26	0.55 (0.30–1.02)	0.45 (0.22–0.93)	44	1.13 (0.60–2.14)	1.31 (0.64–2.71)	70	0.81 (0.52–1.25)	0.80 (0.48–1.32)
		Other ART	7	0.44 (0.18–1.08)	0.41 (0.16–1.05)	20	1.59 (0.77–3.26)	1.56 (0.71–3.42)	27	0.95 (0.58–1.61)	0.91 (0.52–1.61)
Total		366	1.00	1.00	421	1.00	1.00	787	1.00	1.00	
Total	IVF	74	1.19 (0.93–1.54)	0.97 (0.73–1.28)	121	1.77 (1.44–2.17)	1.66 (1.31–2.10)	195	1.49 (1.27–1.75)	1.31 (1.10–1.57)	
	Other ART	75	1.26 (0.98–1.62)	1.15 (0.89–1.50)	91	1.30 (1.03–1.64)	1.26 (0.99–1.59)	166	1.28 (1.08–1.52)	1.21 (1.02–1.44)	

<sup>a</sup> Reference group (OR = 1) = control children. If a child had a major CA in more than one organ system, the child appears several times in the table. If the CAs affect the same organ system, the child appears only once in the table.

<sup>b</sup> n = number of malformed children.

<sup>c</sup> For all major CAs adjusted by age, parity, socioeconomic position, and region, and for some specific anomalies according to organ system adjusted only by age owing to the small number of cases.

<sup>d</sup> One other ART child excluded owing to missing gender status.

*Essoné. Assisted reproduction and congenital anomaly. Fertil Steril 2005.*

**The risk was only increased for boys, and the risk was decreased for multiple IVF girls**

**TABLE 4****Major genital anomalies (and all hypospadias) among singleton boys: number and rate per 10,000.**

	<b>IVF (n = 1,440)</b>	<b>Other ART (n = 2,014)</b>	<b>Controls (n = 13,339)</b>
Total			
No.	11	6	15
Rate	76	30	11
$p^a$	<.001	.036	
Hypospadias			
No.	7	3	10
Rate	15	7	4
$p^a$	<.001	.287	
All hypospadias <sup>b</sup>			
No.	11	8	38
Rate	76	40	29
$p^a$	.003	.390	

<sup>a</sup> Test for relative proportions, compared with controls.<sup>b</sup> Also includes glandular hypospadias.*Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.*

**TABLE 5**

**Drugs used by mothers of malformed and nonmalformed children.**

<b>Group</b>	<b>Malformed<sup>a</sup></b>	<b>Non-malformed</b>	<b>p<sup>b</sup></b>
<b>IVF<sup>c</sup></b>	<b>n = 179</b>	<b>n = 4,088</b>	
P	87	88	.736
FSH or hMG	59	63	.241
GnRH	55	62	.050
hCG	17	20	.286
E <sub>2</sub>	20	12	.003
<b>Other ART</b>	<b>n = 166</b>	<b>n = 4,301</b>	
Clomiphene citrate	81	86	.056
P	30	30	.896
FSH or hMG	14	11	.250
hCG	5	4	.598

Note: Values are percentages.

<sup>a</sup> At least one major congenital anomaly.

<sup>b</sup> Comparisons of malformed and nonmalformed groups, test for relative proportions.

<sup>c</sup> Two hundred ninety-two IVF children are excluded owing to the lack of information on drugs used.

*Klemetti. Assisted reproduction and congenital anomaly. Fertil Steril 2005.*

- **Conclusion**

- IVF was associated with an increased risk for major CAs among singleton boys and a decreased risk among multiple girls
- The risk after other ART was only slightly increased.

*Congenital abnormalities in children born after  
assisted reproductive techniques:*

*How much is associated with the  
presence of infertility and how much  
with its treatment?*

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*Fertil Steril 2005;84:1318 –9.*

- Couples with infertility might have **higher rates** of congenital abnormality, **whether they conceive after ART or spontaneously**.
  - Couples with infertility who conceive **spontaneously** have poorer perinatal outcomes than the general population (**Draper ES, *Lancet* 1999;353:1746 –9.**).
  - **Chromosomal abnormalities** are more frequent in men with **severe male factor infertility** who are referred for IVF/ICSI
  - **Unexplained female subfertility** also confers a higher risk of chromosomal abnormality

- Increased risk of congenital abnormality when compared with the general population
  - The treatment of ART with ICSI
  - Infertility itself
- Future
  - Research to answer these questions
  - Well counseling



*Do children born after assisted  
reproductive technology have a higher  
incidence of birth defects?*

Francois Olivennes, M.D.

Center for Reproductive Medicin, Hopital cochin, Paris, France

*Fertil Steril 2005;84:1325-6*

- Klemetti et al. (*Fertil Steril* 2005;84:1300 –7)
  - For IVF children
    - The odds ratio (OR) of CA - 1.3 (95% confidence interval [CI] 1.1–1.6).
    - increased risk among singleton boys
  - For other ART children
    - The OR of major congenital anomalies - 1.3 (95% CI 1.1–1.5)
  - Not explained by the maternal characteristics

- Hansen M (*Hum Reprod* 2005;20:328–38)
  - The pooled OR : 1.40 (95% CI 1.28–1.53) ~ 1.29 (95% CI 1.21–1.37).
  - The results were significant for major birth defects and for **singleton births only**.
  - a  $\geq 25\%$  increased risk of birth defects in ART children

- *Those studies therefore suggest that ART children could have a 25%–40% higher incidence of birth defects.*
  - The ART technique
    - technique itself (e.g., ICSI)
    - freezing/thawing
    - the culture media
    - the medications used in the ovarian stimulation or luteal phase support
  - The underlying causes of infertility

# *How to counseling*

- First , the overall rate of major malformations in the **control population is low (1%–3%.)**
  - A 30% increase puts this rate at **1.3%– 3.9%**
  - More than 95% of children are not carrying a malformation.
- Second, the classification of the malformation between major and minor
  - The type of malformation will of course play a major part in the information provided to patients.

*Thanks for your attention!!*