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THE RISK OF MAJOR BIRTH DEFECTS AFTER INTRACYTOPLASMIC SPERM INJECTION AND IN VITRO FERTILIZATION

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ABSTRACT

Background It is not known whether infants conceived with use of intracytoplasmic sperm injection or in vitro fertilization have a higher risk of birth defects than infants conceived naturally.

Methods We obtained data from three registries in Western Australia on births, births after assisted conception, and major birth defects in infants born between 1993 and 1997. We assessed the prevalence of major birth defects diagnosed by one year of age in infants conceived naturally or with use of intracytoplasmic sperm injection or in vitro fertilization.

Results Twenty-six of the 301 infants conceived with intracytoplasmic sperm injection (8.6 percent) and 75 of the 837 infants conceived with in vitro fertilization (9.0 percent) had a major birth defect diagnosed by one year of age, as compared with 168 of the 4000 naturally conceived infants (4.2 percent; $P < 0.001$ for the comparison between either type of technology and natural conception). As compared with natural conception, the odds ratio for a major birth defect by one year of age, after adjustment for maternal age and parity, the sex of the infant, and correlation between siblings, was 2.0 (95 percent confidence interval, 1.3 to 3.2) with intracytoplasmic sperm injection, and 2.0 (95 percent confidence interval, 1.5 to 2.9) with in vitro fertilization. Infants conceived with use of assisted reproductive technology were more likely than naturally conceived infants to have multiple major defects and to have chromosomal and musculoskeletal defects.

Conclusions Infants conceived with use of intracytoplasmic sperm injection or in vitro fertilization have twice as high a risk of a major birth defect as naturally conceived infants. (N Engl J Med 2002;346:725-30.)

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In vitro fertilization was introduced into practice with little formal evaluation of its effects on the health of the children conceived with this procedure. When intracytoplasmic sperm injection was introduced in 1992, earlier concern reemerged that infants conceived with the use of assisted reproductive technology might have an increased risk of birth defects.¹⁻⁴

In general, studies have not shown an increased risk of major birth defects in children conceived with either intracytoplasmic sperm injection or standard in vitro fertilization.⁵ Much of this research, however, has had methodologic problems, including inadequate sample sizes and a lack of appropriate data for comparison. Moreover, the definitions of major birth defects used for infants conceived with assisted reproductive technology were different from those used for infants conceived naturally; this difference may have led to an underestimation of the relative prevalence of birth defects among infants conceived with assisted reproductive technology.⁶

Treatment with assisted reproductive technology is provided by three private clinics in Western Australia. Treatment is regulated by the Human Reproductive Technology Act 1991, which established the statutory Reproductive Technology Register that contains information on all procedures performed with assisted reproductive technology in Western Australia since April 1993.⁷ We compared the prevalence of major birth defects among infants conceived with such procedures with that in a random sample of naturally

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conceived infants, using the same system of classification for all birth defects.

METHODS

Collection of Data

We used data from the Reproductive Technology Register to identify all pregnancies of at least 20 weeks' gestation resulting from intracytoplasmic sperm injection or standard in vitro fertilization treatment undertaken between 1993 and 1997 and all terminations of such pregnancies because of fetal abnormalities (regardless of the length of gestation). The three private clinics performed 719, 1191, and 2931 cycles of embryo transfer, respectively, during this period.

The Midwives' Notification System collects information on all infants delivered in Western Australia at 20 weeks' gestation or later.⁸ A random sample of 4000 infants born in Western Australia between 1993 and 1997 was selected after the exclusion of the infants conceived with assisted reproductive technology.

The Western Australian Birth Defects Registry collects information on birth defects occurring in liveborn and stillborn infants delivered in Western Australia, and on pregnancies terminated because of fetal malformations.⁹ For the purposes of the registry, birth defects are defined as abnormalities that are probably of prenatal origin, including structural, chromosomal, and genetic defects. The classification system of the British Paediatric Association, based on the *International Classification of Diseases, 9th Revision* (ICD-9), is used to code each defect, and all defects are classified as major or minor according to a method devised by the Centers for Disease Control and Prevention.⁹ Most minor defects (listed in Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>) are excluded from the registry; however, defects on the exclusion list that require treatment or are disfiguring are included. Approximately 90 percent of cases in the registry involve at least one major defect (with or without minor defects); the remainder involve minor defects only.⁹ Birth defects diagnosed prenatally and in children up to six years of age are included. Cases are reported by multiple statutory and voluntary sources with a high level of ascertainment and accuracy.¹⁰

Automatch (probabilistic matching software)¹¹ was used to link the records of the three registers. When linkage was complete, birth records were available for all infants in the study; records of birth defects were available for those for whom a link was found within the Birth Defects Registry.

To assess the potential effects of differential surveillance according to mode of conception, a list of all birth defects reported for each child was prepared without identification of whether conception was assisted or natural. An independent pediatrician examined the list and identified, on the basis of clinical experience, defects that might have been diagnosed because of closer surveillance and might not otherwise have been detected in a child less than one year of age.

Approval for the study was obtained from the appropriate institutional ethics committee.

Prevalence of Birth Defects

The prevalence of major birth defects diagnosed by one year of age was calculated for the intracytoplasmic-sperm-injection, in-vitro-fertilization, and natural-conception groups. We compared the groups by calculating odds ratios for major birth defects and exact 95 percent confidence intervals on the basis of prevalence. The use of these odds ratios rather than relative risks facilitated the comparison with the odds ratios that were subsequently calculated by logistic regression. Two-tailed P values were calculated with the use of SPSS software.¹²

Multiple logistic-regression analysis was used to assess the effect of maternal age and parity and the sex of the infant on the odds-ratio estimates. Generalized-estimating-equation analyses were per-

formed with the use of Stata software¹³ to examine the effect of potential correlations of risk between siblings in the data set.

Although our study dealt primarily with birth defects diagnosed at or after birth, it is possible that the rates of termination of pregnancy because of fetal anomalies might have differed between the assisted-conception groups and the natural-conception group and that investigating only births may have led to a biased result. We identified all terminations of pregnancy after the prenatal diagnosis of birth defects in the assisted-conception groups; there were four such terminations among the women who underwent in vitro fertilization and none among the women who underwent intracytoplasmic sperm injection. In Western Australia, there are 3.5 terminations of pregnancy because of fetal anomalies per 1000 total births. For the sake of comparison, we conducted a secondary analysis including 14 pregnancies that had resulted from natural conception and that had been terminated because of birth defects; these pregnancies were randomly selected from the Birth Defects Registry and added to the 4000 births for this analysis.

RESULTS

The study included 301 infants conceived with intracytoplasmic sperm injection, 837 infants conceived with standard in vitro fertilization, and 4000 naturally conceived infants. As compared with the mothers of the natural-conception group of infants, the women who had undergone treatment with assisted reproductive technology were, on average, older and less likely to have had a child previously (Table 1). They were more likely to be married or cohabiting, to be white, and to live in the metropolitan area of Perth. As compared with the infants in the natural-conception group the infants conceived with assisted repro-

TABLE 1. CHARACTERISTICS OF 4916 WOMEN WHO CONCEIVED WITH INTRACYTOPLASMIC SPERM INJECTION, WITH IN VITRO FERTILIZATION, OR NATURALLY.*

CHARACTERISTIC	INTRACYTOPLASMIC- SPERM-INJECTION GROUP (N=240)	IN-VITRO- FERTILIZATION GROUP (N=676)	NATURAL- CONCEPTION GROUP (N=4000)
Age — yr	32.6±4.0†	34.1±4.6†	28.2±4.4
Parity — no. (%)			
0	183 (76)†	454 (67)	1612 (40)
≥1	57 (24)	222 (33)	2388 (60)
Married or cohabiting — no. (%)	237 (99)†	664 (98)†	3564 (89)
Ethnic group — no. (%)			
White	230 (96)†	639 (95)†	3500 (88)
Aboriginal or Torres Strait Islander	1 (≤1)	3 (≤1)	220 (6)
Other	9 (4)	34 (5)	280 (7)
Place of residence — no. (%)‡			
Metropolitan Perth	197 (82)†	557 (82)†	2884 (72)
Rural area	43 (18)	119 (18)	1112 (28)
Unknown	—	—	4 (<1)

*Plus-minus values are means ±SD. Numbers of mothers do not match numbers of infants because of multiple births.

†P<0.001 for the comparison with the natural-conception group.

‡Data were missing for four mothers of infants in the natural-conception group.

ductive technology were more likely to be delivered by cesarean section, to have low birth weight, and to be born before term (Table 2). When only singleton infants were considered, low birth weight and delivery by cesarean section were significantly more common in both the in-vitro-fertilization group and the intracytoplasmic-sperm-injection group than in the natural-conception group, and preterm birth was significantly more common in the in-vitro-fertilization group than in the natural-conception group.

In a total of 26 of the infants conceived with intracytoplasmic sperm injection (8.6 percent [95 percent confidence interval, 5.7 to 12.4 percent]), 75 of the infants conceived with in vitro fertilization (9.0 percent [95 percent confidence interval, 7.1 to 11.1 percent]), and 168 of the naturally conceived infants (4.2 percent [95 percent confidence interval, 3.6 to 4.9 percent]), a major birth defect was diagnosed by one year of age ($P < 0.001$ for the comparisons between the natural-conception group and the assisted-conception groups). There were no significant differences in prevalence among the clinics (data not shown). When all the infants were considered, those conceived with assisted reproductive technology were more than twice as likely as naturally conceived infants to have a major birth defect diagnosed by one year of age (Table 3). The results were similar and remained significant when only singleton infants were considered, when the analyses were further restricted to singletons born at term (at least 37 weeks of gestation), and when the analyses were adjusted for maternal age and parity, the sex of the infant, and

correlation of the risk of birth defects between siblings (Table 3).

About two thirds of the major defects were diagnosed during the first week of life (Fig. 1), and more than 90 percent were diagnosed by six months of age. The defects in three infants in the natural-conception group (all renal defects), four infants in the intracytoplasmic-sperm-injection group (two with renal defects and two musculoskeletal defects), and one infant in the in-vitro-fertilization group (a musculoskeletal defect) were identified by the independent pediatrician as possibly having been diagnosed early because of close surveillance. When these infants were excluded from the analysis, the odds ratio for a major birth defect diagnosed by one year of age as compared with the natural-conception group was 1.8 (95 percent confidence interval, 1.1 to 2.9) in the intracytoplasmic-sperm-injection group and 2.2 (95 percent confidence interval, 1.7 to 3.0) in the in-vitro-fertilization group.

When pregnancies terminated because of fetal abnormalities were included in the analysis, the overall prevalence of major birth defects was 4.5 percent in the natural-conception group and 9.4 percent in the in-vitro-fertilization group; it was unchanged at 8.6 percent in the intracytoplasmic-sperm-injection group. When the nine infants with known inherited conditions and the seven with metabolic disorders were excluded from the analysis, the overall prevalence of birth defects was 8.0 percent in the intracytoplasmic-sperm-injection group, 8.5 percent in the in-vitro-fertilization group, and 4.0 percent in the natural-

TABLE 2. MODE OF DELIVERY AND CHARACTERISTICS OF INFANTS CONCEIVED WITH INTRACYTOPLASMIC SPERM INJECTION, WITH IN VITRO FERTILIZATION, OR NATURALLY.*

VARIABLE	ALL INFANTS					SINGLETONS ONLY				
	ICSI (N=301)	P VALUE	IVF (N=837)	P VALUE	NATURAL CONCEPTION (N=4000)	ICSI (N=186)	P VALUE	IVF (N=527)	P VALUE	NATURAL CONCEPTION (N=3906)
Delivered by cesarean section — no. (%)	95 (32)	<0.001	365 (44)	<0.001	816 (20)	48 (26)	0.05	183 (35)	<0.001	776 (20)
Male sex — no. (%)	165 (55)		454 (54)		2048 (51)	102 (55)		286 (54)		2000 (51)
Stillborn — no. (%)	2 (1)		17 (2)	<0.001	26 (1)	0		6 (1)		25 (1)
Birth weight — g	2847±799	0.02	2806±844	0.005	3345±592	3271±552	0.02	3182±686	<0.001	3368±571
Preterm delivery (<37 wk) — no. (%)	93 (31)	<0.001	265 (32)	<0.001	273 (7)	16 (9)		73 (14)	0.001	225 (6)
Multiple birth — no. (%)	115 (38)	<0.001	310 (37)	<0.001	94 (2)	—		—		—
Low birth weight — no. (%)										
<1500 g	18 (6)	<0.001	65 (8)	<0.001	51 (1)	2 (1)		19 (4)	<0.001	41 (1)
<2500 g	75 (25)	<0.001	188 (22)	<0.001	196 (5)	12 (6)		38 (7)	0.002	163 (4)
Gestational age — wk	37.0±3.3	0.004	36.7±3.8	0.002	39.0±2.1	38.6±2.2		38.0±3.0	0.03	39.1±2.0

*Plus-minus values are means ±SD. P values are for the comparisons with the natural-conception group and are not significant if not shown. ICSI denotes intracytoplasmic sperm injection, and IVF in vitro fertilization.

TABLE 3. PREVALENCE OF MAJOR BIRTH DEFECTS DIAGNOSED BY ONE YEAR OF AGE.*

GROUP	NO. OF INFANTS	PREVALENCE no. (%)	UNADJUSTED	ADJUSTED
			ODDS RATIO (95% CI)	ODDS RATIO (95% CI)†
All infants				
Natural conception	4000	168 (4.2)	1.0	1.0
Intracytoplasmic sperm injection	301	26 (8.6)	2.2 (1.3–3.3)	2.0 (1.3–3.2)
In vitro fertilization	837	75 (9.0)	2.6 (1.7–3.0)	2.0 (1.5–2.9)
All singletons				
Natural conception	3906	164 (4.2)	1.0	1.0
Intracytoplasmic sperm injection	186	18 (9.7)	2.4 (1.4–4.1)	2.2 (1.3–3.9)
In vitro fertilization	527	50 (9.5)	2.4 (1.7–3.4)	2.2 (1.5–3.2)
Term singletons‡				
Natural conception	3681	149 (4.0)	1.0	1.0
Intracytoplasmic sperm injection	170	15 (8.8)	2.3 (1.2–4.0)	2.2 (1.2–4.0)
In vitro fertilization	454	38 (8.4)	2.2 (1.5–3.2)	2.1 (1.4–3.2)

*CI denotes confidence interval.

†The odds ratios were adjusted for maternal age and parity, the sex of the infant, and correlation between siblings.

‡Term was defined as at least 37 weeks of gestation.

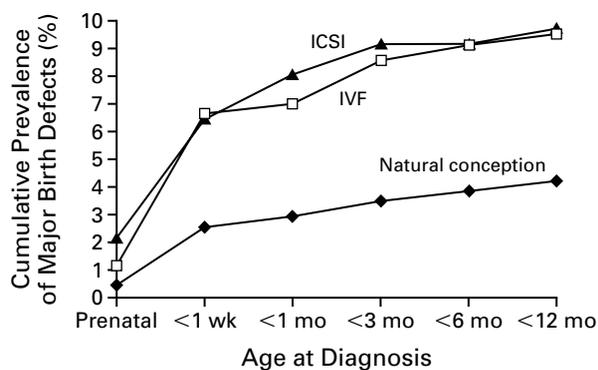


Figure 1. Cumulative Prevalence of Diagnosed Major Birth Defects in Singleton Infants, According to Age at Diagnosis. ICSI denotes intracytoplasmic sperm injection, and IVF in vitro fertilization.

conception group. The odds ratios for a major birth defect associated with assisted conception in these analyses remained similar to those calculated in the primary analysis (data not shown). All the infants in our study with unilateral undescended testis or hypospadias had undergone surgery and were therefore included in our primary analyses. Nevertheless, in some systems of classification of birth defects, these defects would be regarded as minor. When infants

with these conditions were excluded from the analysis, the odds ratio for a major birth defect was 2.5 (95 percent confidence interval, 1.6 to 4.0) in the intracytoplasmic-sperm-injection group and 2.2 (95 percent confidence interval, 1.6 to 3.0) in the in-vitro-fertilization group.

As compared with infants conceived naturally, a significantly greater proportion of those conceived with assisted reproductive technology had musculoskeletal and chromosomal defects (Table 4). Those conceived with in vitro fertilization, but not those conceived with intracytoplasmic sperm injection, had a significantly greater prevalence of cardiovascular, urogenital, and other defects. Some, but not all, of these findings persisted when the analysis was restricted to singletons (Table 4). We also compared the proportions of infants with multiple major defects, defined as two or more defects affecting different systems. Six of the infants conceived with intracytoplasmic sperm injection (2.0 percent), 13 of those conceived with in vitro fertilization (1.6 percent), and 20 of the naturally conceived infants (0.5 percent) had multiple major defects. Overall, the infants conceived with assisted reproductive technology were significantly more likely to have multiple major defects than the naturally conceived infants (odds ratio associated with intracytoplasmic sperm injection, 4.1 [95 percent confidence interval, 1.6 to 10.2]; odds ratio associated with in vitro fertilization, 3.1 [95 percent confidence interval, 1.6 to 6.3]). A complete list of the birth de-

TABLE 4. PREVALENCE OF MAJOR BIRTH DEFECTS ACCORDING TO THE ORGAN SYSTEM AFFECTED.*

TYPE OF MAJOR DEFECT	ALL INFANTS					SINGLETONS ONLY				
	ICSI (N=301)	P VALUE	IVF (N=837)	P VALUE	NATURAL CONCEPTION (N=4000)	ICSI (N=186)	P VALUE	IVF (N=527)	P VALUE	NATURAL CONCEPTION (N=3906)
	no. (%)		no. (%)		no. (%)	no. (%)		no. (%)		no. (%)
Any	26 (8.6)	<0.001	75 (9.0)	<0.001	168 (4.2)	18 (9.7)	<0.001	50 (9.5)	<0.001	164 (4.2)
Cardiovascular	4 (1.3)		15 (1.8)	<0.001	24 (0.6)	3 (1.6)		7 (1.3)		24 (0.6)
Urogenital	7 (2.3)		22 (2.6)	0.01	54 (1.4)	5 (2.7)		14 (2.7)	0.03	52 (1.3)
Musculoskeletal	10 (3.3)	0.004	28 (3.3)	<0.001	45 (1.1)	5 (2.7)		20 (3.8)	<0.001	44 (1.1)
Gastrointestinal	3 (1.0)		5 (0.6)		25 (0.6)	2 (1.1)		2 (0.4)		24 (0.6)
Central nervous system	0		3 (0.4)		6 (0.2)	0		2 (0.4)		6 (0.2)
Chromosomal	3 (1.0)	0.05	6 (0.7)	0.03	9 (0.2)	3 (1.6)	0.02	3 (0.6)		9 (0.2)
Metabolic	1 (0.3)		2 (0.2)		4 (0.1)	0		1 (0.2)		4 (0.1)
Other†	2 (0.7)		21 (2.5)	<0.001	25 (0.6)	2 (1.1)		15 (2.8)	<0.001	25 (0.6)

*If an infant had more than one major birth defect diagnosed by one year of age and the defects affected different organ systems, the infant appears more than once in the table. If an infant had two unrelated major defects affecting the same organ system, the infant appears only once in the table. P values are for the comparisons with the natural-conception group.

†Other major birth defects included major defects of the respiratory system, Klippel-Trénaunay-Weber syndrome, Holt-Oram syndrome, infantile Marfan's syndrome, and nonimmune hydrops fetalis, among others.

fects is provided in Supplementary Appendix 2 (available with the full text of this article at <http://www.nejm.org>).

Although minor birth defects were not the primary focus of this study, the Birth Defects Registry collects details of defects that would otherwise be considered minor but are disfiguring or require treatment (e.g., polydactyly). Such defects were diagnosed by one year of age in 1 infant in the intracytoplasmic-sperm-injection group (0.3 percent), 7 infants in the in-vitro-fertilization group (0.8 percent), and 25 infants in the natural-conception group (0.6 percent).

DISCUSSION

We found that infants conceived with assisted reproductive technology were more than twice as likely as naturally conceived infants to have major birth defects diagnosed during the first year of life and were also more likely to have multiple major defects. The increase in the risk of a major birth defect associated with assisted conception remained significant when only singleton or term singleton infants were considered, as well as after adjustment for maternal age and parity, the sex of the infant, and correlation between siblings. Furthermore, the estimates of the prevalence of defects reported to the registry by one year of age in the assisted-conception groups were well in excess of the 6 percent prevalence of major birth de-

fects reported by six years of age during the same period in the general population.⁹ The risk of birth defects was similar among infants conceived with in vitro fertilization and those conceived with intracytoplasmic sperm injection.

We designed our study to address the major methodologic problems of previous research. We used the same source of data and the same birth-defect classification system for all three groups of infants. Furthermore, data on birth defects were collected without reference to the mode of conception. There is nevertheless a risk of differential diagnostic vigilance, given that infants conceived with assisted reproductive technology may be more closely examined than naturally conceived infants, because of either the history of their conception or a clinical condition associated with prematurity or multiple birth. If so, major birth defects might have been diagnosed earlier in the assisted-conception groups. However, the results were essentially unchanged when we excluded defects that might be more likely to be detected with closer surveillance. We also found that the excess risk remained when only term singletons were considered.

Pregnancies that result from treatment with assisted reproductive technology may be more closely monitored than those that result from natural conception. However, detailed ultrasonographic examinations of fetal anatomy are performed at 16 to 20 weeks of

gestation in almost all pregnancies in Western Australia. Furthermore, the majority of the defects diagnosed prenatally in the infants in both the assisted-conception groups and the natural-conception group would have been clinically obvious at birth. We also minimized the likelihood of differential diagnostic vigilance by including defects diagnosed up to one year after birth, by which time most major defects are likely to have been detected; in Western Australia 70 percent of all major birth defects are diagnosed by one year of age.⁹ Increased diagnostic vigilance may also increase the rate of detection of more subtle defects; however, such vigilance is unlikely to explain the excess risk in the infants conceived with assisted reproductive technology, since the majority of the defects in this group were either visible (e.g., cleft lip and palate) or would have been clinically obvious at, or soon after, birth (e.g., tracheoesophageal fistula). Finally, although the likelihood of terminating a pregnancy because of fetal anomalies may vary with the mode of conception, the inclusion of pregnancies that were terminated because of birth defects had little effect on our findings.

An excess risk of major birth defects in infants conceived with assisted reproductive technology is plausible. Factors that may increase the risk of birth defects include the relatively advanced age of infertile couples; the underlying cause of their infertility; the medications used to induce ovulation or to maintain the pregnancy in the early stages; and factors associated with the procedures themselves, such as the freezing and thawing of embryos, the potential for polyspermic fertilization, and the delayed fertilization of the oocyte.¹⁴⁻¹⁷ Although older maternal age and low parity did not appear to explain our results, it is not possible to separate the excess risk that may be associated with infertility treatment from the excess risk related to the underlying causes of infertility.

Recent data have suggested that there is an increased risk of birth defects in infants conceived with in vitro fertilization¹⁸ or intracytoplasmic sperm injection,¹⁹ but these results might have been attributed to conditions associated with multiple and preterm birth.¹⁹ Our results cannot be explained by these factors, since they remained similar when we restricted our analyses to term singletons.

We found that there may be an excess occurrence of major cardiovascular, urogenital, chromosomal, and musculoskeletal defects associated with assisted conception. However, these findings regarding specific organ systems should be interpreted with caution, since they are based on small numbers of infants in each group. Although the prevalence of a specific defect is rarely reported for infants conceived with assisted reproductive technology, others have also sug-

gested that the prevalence of these defects is increased among such infants.^{6,16,19-21}

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