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Birth defects in infants conceived by intracytoplasmic sperm injection: an alternative interpretation

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Abstract

Objective: To test the hypothesis that liveborn infants conceived by intracytoplasmic sperm injection are at an increased risk of having a major birth defect.

Design: Reclassification of the birth defects reported in infants born after intracytoplasmic sperm injection in Belgium and comparison with prevalence estimated in Western Australian population by means of same classification system.

Setting and subjects: 420 liveborn infants who were conceived after intracytoplasmic sperm injection in Belgium and 100 454 liveborn infants in Western Australia delivered during the same period.

Main outcome measures: Estimates of birth prevalence of birth defects and comparisons of odds ratios between cohort conceived after intracytoplasmic sperm injection and Western Australian infants.

Results: Infants born after intracytoplasmic sperm injection were twice as likely as Western Australian infants to have a major birth defect (odds ratio 2.03 (95% confidence interval 1.40 to 2.93); $P = 0.0002$)

and nearly 50% more likely to have a minor defect (1.49 (0.48 to 4.66); $P = 0.49$). Secondary data-led analyses, to be interpreted with caution, found an excess of major cardiovascular defects (odds ratio 3.99), genitourinary defects (1.33), and gastrointestinal defects (1.84), in particular cleft palate (5.11) and diaphragmatic hernia (7.73).

Conclusions: These results do not confirm the apparently reassuring results published by the Belgian researchers of intracytoplasmic sperm injection. Further research is clearly required. Meanwhile, doctors practising intracytoplasmic sperm injection should bear this alternative interpretation in mind when they counsel couples and obtain informed consent for the procedure.

Introduction

Intracytoplasmic sperm injection, the selection and injection of a single spermatozoon into an oocyte, is probably the most important development in assisted reproduction since the birth of the first "test tube baby" in 1978. This procedure offers, for the first time, real

prospects of genetic parenthood for men with profound oligospermia and, by means of testicular biopsy and epididymal aspiration, even for those men with azoospermia. There are, however, several theoretical concerns about the safety of intracytoplasmic sperm injection and potential risks for the offspring.¹⁻³ These concerns can be categorised broadly into four groups: the risks of using sperm that potentially carry genetic abnormalities, the risks of using sperm with structural defects, the potential for mechanical and biochemical damage and of introducing foreign material into the oocyte, and the risks associated with overcoming processes of natural selection by injecting a single spermatozoon.

This procedure was developed by a group at the Brussels Free University.⁴ This group had the foresight to institute, at the outset, follow up of the infants conceived by intracytoplasmic sperm injection at their centre. Their findings represent the first substantive data set available with which we can start to investigate the concerns about the procedure. As their number of infants has increased, they have published their findings in a series of papers.⁵⁻⁹ To date, they have closely examined 76% of the 420 infants born alive between April 1991 and September 1994 after intracytoplasmic sperm injection at their centre and have collected some information about the remainder.⁹ They classified birth defects as follows: "Malformations that generally cause functional impairment or require surgical correction were defined as major, and the remaining malformations were considered minor." They concluded that the prevalence of major birth defects in liveborn infants of 3.3% was "within the expected range."⁹

As the Belgian group did not have any specific data for comparison, they used published data from elsewhere in the world to compare with their findings. However, the problem with these comparisons is that different definitions of what constitutes a major birth defect were used in the comparison data. For example, the Belgian group cited data for births after in vitro fertilisation from the Australian National Perinatal Statistics Unit.^{9 10} However, this unit uses the five digit British Paediatric Association's ICD-9 system to classify birth defects and registers only those birth defects diagnosed by 28 days of age.^{10 11} This classification system has a much broader definition of what constitutes a major defect than does the classification used by the Belgian group. It is therefore possible that the Belgian group underestimated the comparative prevalence of major birth defects in their cohort of infants.

The aim of our study was to test the hypothesis that the infants born alive after intracytoplasmic sperm injection in Belgium are at an increased risk of having a major birth defect. To do this we reclassified the Belgian data according to the methods used by the Western Australian Birth Defects Registry and then compared the results with population data from the registry.^{12 13}

Methods

The Western Australian Birth Defects Registry receives notifications of birth defects diagnosed in Western Australian children aged up to 6 years.^{12 13} Notifications of birth defects diagnosed in spontaneous abortions,

terminations of pregnancy, and stillbirths are also received, although they were not included in our analysis as the comparison was with only live births after intracytoplasmic sperm injection. Multiple sources of notification are used, and data, which have been validated on several occasions, are available for births from 1980 onwards.¹⁴⁻¹⁷ For the purposes of the registry, birth defects are defined as abnormalities probably of prenatal origin and include structural, chromosomal, genetic, and biochemical defects.¹² Each defect (up to a maximum of 10 defects per child) is coded according to the five digit British Paediatric Association's ICD-9 system and is also coded as major or minor according to a method devised by the Centers for Disease Control in the United States.^{11 18}

A list of the birth defects reported by the Belgian group in the 420 infants born alive after intracytoplasmic sperm injection was given to the coding officer at the Western Australian Birth Defects Registry, who does all the registry's coding and has done so since 1989.⁹ The coding officer, who was not aware of the Belgian categorisation of the defects, coded the defects as major, minor, or not included, according to the registry criteria. When there was insufficient information available to classify the defect according to the registry criteria—for example, patent ductus arteriosus—the least severe classification was chosen (see footnotes to table 1).

Statistical analysis

We compared the reclassified Belgian data with the prevalence of birth defects diagnosed by the age of 1 year that were reported to the Western Australian Birth Defects Registry for liveborn infants delivered in 1991-4 inclusive. The primary analysis compared the birth prevalence of major and minor defects overall. Comparisons of the occurrence of system specific defects were carried out as secondary data-led analyses. We calculated birth prevalence and the odds ratios for birth prevalence (and their 95% confidence intervals) using the methods of Clayton and Hills.¹⁹ We calculated two tailed P values using the standard χ^2 test for association.

Results

Table 1 details all the birth defects (major and minor) observed in the infants born alive after intracytoplasmic sperm injection in Belgium, together with the classification of the defects according to both the Belgian and Western Australian systems of classification. Under the Belgian classification system, 14 of the 420 infants (3.33% (95% confidence interval 1.99% to 5.55%)) were defined as having major birth defects and 84 (20.0% (16.4% to 24.1%)) were regarded as having minor defects. Under the Western Australian classification, 31 of the 420 infants (7.38% (5.04% to 10.31%)) were classified as having major defects and three (0.71% (0.23% to 2.19%)) were classified as having minor defects.

During 1991-4, there were 100 454 live births in Western Australia, of which 2.7% were multiple births.²⁰ The infants were born to mothers with a mean age of 27.9 years (range 12-49 years). In this period, 3800 liveborn infants were notified as having major defects diagnosed by the age of 1 year. This represents a birth

Table 1 Birth defects observed in 420 liveborn infants conceived by intracytoplasmic sperm injection in Belgium classified according to Belgian classification⁹ and to classification of Western Australian Birth Defects Registry

Birth defects (No of children affected)	Belgian classification	Registry classification
Holoprosencephaly (1)	Major	Major
Pierre Robin syndrome + pseudarthrogryposis + brain stem pathology (1)	Major	Major
Preaxial polydactyly (1)	Major	Minor
Hypospadias + unilateral cryptorchidism (1)	Major	Major
Scrotal hypospadias + bifid scrotum + micropenis + bilateral cryptorchidism (1)	Major	Major
Cleft palate + renal cysts (1)	Major	Major
Cleft palate (1)	Major	Major
Fallot's tetralogy (1)	Major	Major
Diaphragmatic hernia (1)	Major	Major
Hypospadias (1)	Major	Major
Femur-fibula-ulna syndrome (1)	Major	Major
Trisomy 21 (1)	Major	Major
Situs inversus + ventricular septal defect (1)	Major	Major
Soft tissue syndactylism 3rd and 4th fingers (1)	Major	Minor
Atrial septal defect type II (7)	Minor	Major
Atrial septal defect type II + inguinal hernia (1)	Minor	Major
Atrial septal defect type II + patent ductus arteriosus (1)	Minor	Major
Ventricular septal defect + preauricular tag (1)	Minor	Major*
Ventricular septal defect + congenital angioma (1)	Minor	Major
Ventricular septal defect + sacral dimple (1)	Minor	Major
Patent ductus arteriosus (6)	Minor	Major or NR†
Tricuspid valve insufficiency (1)	Minor	NR
Coronal hypospadias (1)	Minor	Major
Cryptorchidism (1)	Minor	Major
Inguinal hernia (7)	Minor	NR
Hydrocoele (7)	Minor	NR
Renal duplication (1)	Minor	Major
Epicanthal folds (2)	Minor	NR
Pre-auricular tag (1)	Minor	NR
Ear pit (1)	Minor	NR
Unilateral simian crease (3)	Minor	NR
Bilateral simian crease (1)	Minor	NR
Clinodactyly 5th finger (1)	Minor	Minor
Overriding toes (2)	Minor	Minor
Metatarsus adductus (1)	Minor	Major or NR‡
Angioma of nose (1)	Minor	Major
Major angiomas (1)	Minor	Major
Angioma (20)	Minor	Major, minor, or NR§
Congenital naevus (20)	Minor	Major, minor, or NR§
Cutis marmorata congenita (1)	Minor	Major, minor, or NR¶
Pilonidal sinus (1)	Minor	NR
Umbilical hernia (10)	Minor	NR
Pyloric stenosis (2)	NR	Major
Total:		
Major (%)	14 (3.33%)	31 (7.38%)
Minor (%)	84 (20.0%)	3 (0.71%)

NR=Not registered as birth defect under the classification system.

*Ventricular septal defects: coded as minor if they are specified by notifier as trivial or are now closed, otherwise coded as major.

†Patent ductus arteriosus: isolated ductus is coded as major if still patent at 3 months of age in a child born at term or at 6 months in a child born preterm. If ductus is ligated in a full term infant or in a preterm infant over 2 months chronological age, it is also coded as major. Isolated ductus not meeting the above criteria is not registered in registry classification. A ductus in the presence of other congenital heart disease is always included.¹⁷ The six patent ductus arteriosus in the Belgian data were assumed to be not eligible for registration and were not included in the total number of major defects in the registry classification.

‡Metatarsus adductus: coded as major if treated by splinting or surgery, if not treated would not be registered. The single case was assumed not to have been treated and was therefore not eligible for registration and not included in the total number of major defects in the registry classification.

§Angioma and congenital naevus: included in the registry classification if they are multiple or >4 cm²; they are coded as minor unless they are disfiguring or require extensive surgery, in which case they are coded as major. If they do not meet the above criteria they are not registered. The 40 angiomas and congenital naevi were assumed to be not eligible for registration and were not included in the total number of major or minor defects in the registry classification.

¶Cutis marmorata congenita: included in the registry classification when it is diagnosed as cutis marmorata telangiectasia congenita and is defined as major or minor depending on the extent and severity; neonatal cutis marmorata is not registered. The single case was assumed to be not eligible for registration and was not included in the total number of major or minor defects in the registry classification.

prevalence of 3.78% (95% confidence interval 3.67% to 3.90%) for major birth defects, compared with the prevalence of 7.38% in the infants born after intracytoplasmic sperm injection. The prevalence odds ratio for this comparison was 2.03 (1.40 to 2.93; $P=0.0002$), indicating that the infants born after intracytoplasmic

sperm injection were twice as likely to have a major birth defect diagnosed as were the Western Australian infants. We recalculated the figures for the infants born after intracytoplasmic sperm injection assuming that the three ventricular septal defects not associated with other cardiac defects were trivial and therefore not

classified as major (see footnotes to table 1). This gave a prevalence of 6.67% (4.64% to 9.49%) and a prevalence odds ratio of 1.82 (1.24 to 2.67; $P = 0.0023$).

During 1991-4, 484 of the Western Australian infants were notified as having a minor defect diagnosed by 1 year of age, which represents a birth prevalence of 0.48% (0.44% to 0.53%). Compared with the prevalence of 0.71% in the infants born after intracytoplasmic sperm injection, this gave a non-significant prevalence odds ratio of 1.49 (0.48 to 4.66; $P = 0.49$).

Table 2 compares the birth prevalence of major cardiovascular, genitourinary, and gastrointestinal defects (according to the Australian classification) in the infants born after intracytoplasmic sperm injection and the Western Australian infants. The former infants showed a greater prevalence of major cardiovascular defects than did the Western Australian infants (3.33% (1.99% to 5.55%) *v* 0.67% (0.62% to 0.72%)), representing a fivefold excess risk (odds ratio 5.12 (2.99 to 8.77); $P < 0.0001$). Even after excluding the three infants with ventricular septal defects that may have been trivial, there was still evidence of a fourfold excess risk (odds ratio 3.99 (2.18 to 7.30); $P < 0.0001$).

The infants born after intracytoplasmic sperm injection also showed a slightly greater prevalence of major genitourinary defects than did the Western Australian infants (1.43% *v* 1.08%), representing a non-significant 30% excess risk (odds ratio 1.33 (0.59 to 2.98); $P = 0.489$).

Overall, the infants born after intracytoplasmic sperm injection showed a greater prevalence of major gastrointestinal defects than did the Western Australian infants (0.95% *v* 0.52%), with a non-significant associated odds ratio of 1.84 (0.68 to 4.94; $P = 0.23$). However, two of these infants with such birth defects had a cleft palate, giving a prevalence of 0.48% (0.12% to 1.88%) compared with only 0.09% (0.07% to 0.11%) in the Western Australian population. This suggests that the infants born after intracytoplasmic sperm injection had a fivefold excess risk of cleft palate (odds ratio 5.11 (1.26 to 20.80); $P = 0.023$). One of the infants born after intracytoplasmic sperm injection had a diaphragmatic hernia, giving a prevalence of 0.24% (0.03% to 1.67%) compared with a prevalence of 0.031% (0.02% to 0.04%) in the Western Australian infants (odds ratio 7.73 (1.05 to 56.76); $P = 0.044$).

Discussion

The findings of our reclassification and reanalysis are rather less reassuring than the conclusions published by the Belgian researchers, who reported no increase in the prevalence of birth defects in infants born after intracytoplasmic sperm injection.⁹ Our results suggest that these infants were twice as likely to have a major birth defect as was the general population of Western Australian infants born during the same period—a result unlikely to be due to chance. Furthermore, our estimate was a conservative one as it excluded all six infants with a patent ductus arteriosus on the basis that there was insufficient information to determine whether they met the criteria of the Western Australian Birth Defects Registry to be included as major defects (see footnotes to Table 1). The same was true for the 20 infants with angiomata and the 20 infants with congenital naevi. Three infants with ventricular septal

Table 2 Prevalence of major birth defects (according to classification system of Western Australian Birth Defects Registry) observed in 420 liveborn infants conceived by intracytoplasmic sperm injection in Belgium compared with population figures from the registry

Birth defects	No (%) of infants affected	
	Belgian data (n=420)	Registry data (n=100 454)
Cardiovascular defects		
Fallot's tetralogy	1	
Situs inversus + ventricular septal defect	1	
Atrial septal defect type II	8	
Atrial septal defect type II + patent ductus arteriosus	1	
Ventricular septal defects + non-cardiac defects	3	
Total	14 (3.33%)	672 (0.67%)
Genitourinary defects		
Cryptorchidism + hypospadias	1	
Scrotal hypospadias + bifid scrotum + micropenis + bilateral cryptorchidism	1	
Hypospadias	1	
Coronal hypospadias	1	
Cryptorchidism	1	
Renal duplication	1	
Total	6 (1.43%)	1080 (1.08%)
Gastrointestinal defects		
Cleft palate + renal cysts	1	
Cleft palate	1	
Pyloric stenosis	2	
Total	4 (0.95%)	521 (0.52%)

defects were classified as having major defects, as such defects would always be defined as major according to the registry criteria unless they were notified as being "trivial." Excluding these three infants reduced the odds ratio estimate to just less than two, but this had no impact on the substantive conclusions.

Potential for confounding and bias

Our reclassification of the Belgian data produced results for the two infant populations that were more appropriate for comparison than had been the case before. However, we recognise that the vigilance in terms of diagnosing birth defects would not necessarily have been the same in the two populations. The Belgian research group have closely examined 76% of their infants at 2 months of age, and it is therefore possible that they diagnosed defects which would not otherwise have come to medical attention in the first year of a child's life, if ever. However, all the defects defined as major according to the Western Australian criteria would, with the possible exception of the ventricular and atrial septal defects, have either been visibly obvious at birth—such as cleft palate—or so clinically serious—such as Fallot's tetralogy—that it is unlikely that they would not have been diagnosed in the general course of events. Most ventricular and atrial septal defects would also probably have been detected during the course of the routine child health surveillance that is in place in Western Australia. It seems unlikely, therefore, that differential vigilance in surveillance would account entirely for the excess of major defects seen in the infants born after intracytoplasmic sperm injection in Belgium.

There is also little reason to believe that the Western Australian population of infants has an unusually low prevalence of major birth defects compared with European populations; indeed, the prevalence of birth defects in Western Australia is

generally higher than that reported from registers in Europe.²¹ Furthermore, 17% of the mothers who delivered in Western Australia in 1991-4 had been born in Europe, and control data collected for another study showed that in 1981-5 only 9% of infants did not have at least one parent, grandparent, or great grandparent born in Europe.^{20 22}

Birth defects are known to occur more often in infants from multiple pregnancies, but this is largely confined to monozygous multiples.^{23 24} Excess numbers of defects seen in dizygous multiples tend to be positional in origin—such as talipes—and probably relate to the reduced space in the uterine cavity. Nearly half (48%) of the 420 infants born after intracytoplasmic sperm injection were multiple births, whereas only 3% of the Western Australian births were multiple.⁹ However, this is unlikely to account for the excess of major birth defects seen in the infants born after intracytoplasmic sperm injection as, although not stated, nearly all of the multiples are likely, by the nature of their conception, to have been dizygous or trizygous.

The overall mean maternal age for the infants born after intracytoplasmic sperm injection was 32.1 years, while it was 27.9 years for the Western Australian infants; a difference almost certainly due to the history of infertility of the couples treated by intracytoplasmic sperm injection.^{9 20} Chromosomal defects are known to increase in incidence with increasing maternal age, and gastroschisis increases with decreasing maternal age. Otherwise, there is little relation between maternal age and the risk of birth defects.

Conclusions

No single system for classifying birth defects can be regarded as the gold standard, although the British Paediatric Association's classification is widely used by many registries around the world. However, the issue here is not which is the best classification system but that, in comparing two sets of data, the data must be classified with the same system. The Belgian researchers chose to use their own classification system and then compared the results with data that had been classified with more inclusive systems. While the Belgian classification has some pragmatic value in that it classifies as minor those defects that do not affect function or require surgery, this could lead us to ignore the potential underlying aetiological aspects—namely, what are the findings telling us about the effects of intracytoplasmic sperm injection and the causes and effects of the types of male infertility treated with this procedure? Both of these are vital questions if we wish to advance our knowledge and understanding of the physiology of fertilisation and embryonic development, and the causes of male infertility.²

Our reanalysis of the Belgian data suggests that infants born after intracytoplasmic sperm injection may experience an excess of major birth defects. While these findings do not exclude the possibility of other teratogenic influences, parental infertility and the procedure of intracytoplasmic sperm injection are the two exposures that all the infants born after intracytoplasmic sperm injection in Belgium had in common. These findings clearly require confirmation in further data sets of all pregnancy outcomes, not just live births, and they presently raise more questions than they answer.

Key messages

- Reports of data from Belgium concluded that there was no increase in the occurrence of major birth defects among infants conceived by intracytoplasmic sperm injection
- However, the Belgian researchers used a narrow definition of what constituted a major birth defect, and they might have underestimated the comparative prevalence of major defects
- We reclassified the birth defects in the infants born after intracytoplasmic sperm injection using a standard classification system and compared the results with data from Western Australia that were classified with the same system
- We found that the infants born after intracytoplasmic sperm injection were twice as likely to have a major birth defect and nearly 50% more likely to have a minor defect
- Further research is required to elucidate these results, but, meanwhile, they should be born in mind when counselling infertile couples about intracytoplasmic sperm injection

Our results also suggest that there may be an excess occurrence of major cardiovascular, gastrointestinal, and genitourinary defects generally—and cleft palate and diaphragmatic hernia specifically—in infants born after intracytoplasmic sperm injection. These particular findings must be interpreted with caution as they arose from multiple significance testing in the absence of a primary hypothesis and are mainly based on small numbers. However, we report them as they raise additional hypotheses and emphasise the need for continued surveillance of birth defects in the Belgian cohort and the instigation of systematic surveillance of birth defects in other cohorts of infants conceived by intracytoplasmic sperm injection, together with the collection of appropriate data for comparison.

Clearly, further research is required to elucidate these apparently discrepant results and their implications. Meanwhile, the results from this reanalysis have important implications for counselling couples, providing information, and obtaining informed consent before performing intracytoplasmic sperm injection. These findings are unlikely to deter many would-be recipients or practitioners, nor do we believe they necessarily should. They are, however, of value, as it is vital that couples embarking on this procedure have realistic expectations of the outcome.

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Commentary: Major defects are overestimated

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After reclassification of birth defects according to the system used by the Western Australian Birth Defects Registry, Kurinczuk and Bower's reanalysis of our data suggests that the 420 live born infants conceived by intracytoplasmic sperm injection were twice as likely to have a major birth defect as the general population of Western Australia. This result is considered unlikely to be due to chance.

For the cardiac malformations in particular, we think that the authors overestimate the number of major malformations. They do not take into account the fact that these malformations were found as part of an ultrasound research screening programme for the infants conceived by intracytoplasmic sperm injection. Kurinczuk and Bower made conservative estimates about the patent ductus arteriosus in six children, since we had given insufficient information to determine whether they should be included as major defects according to Australian criteria. In fact, none of the cases of patent ductus arteriosus reported as a minor anomaly was still patent at 3 months of age when the child was born at term or at 6 months of age when the child was born prematurely.

Most of the atrial septal defects were foramen ovale with small shunts, detected very early after birth by routine ultrasound examination, done for the purposes of our study. On further follow up (within several months) there was no evidence of shunt, which begs the question of whether they should even be considered as a minor malformation in the first place. For completeness of our reports, however, we mentioned them in the list of minor malformations, but we cannot agree at all that they might be categorised as major malformations.

With regard to the three ventricular septal defects, these may certainly be considered minor in the two cases where they closed spontaneously before 1 year of age. The third case had regressed at 2 months of age,

but an additional examination at 1 year of age will allow a correct classification.

Kurinczuk and Bower conclude that the observation of two out of 420 children with cleft palate suggests that there might be a fivefold excess risk for cleft palate after intracytoplasmic sperm injection. We consider this a premature conclusion. Overall, the authors observed an excess of gastrointestinal defects in the infants born after intracytoplasmic sperm injection compared with the Australian population, including (in their classification) a higher number of cleft palates (two children). These two children were two non-identical twins. No family history of cleft palate was documented. The fact that the two cleft palates occurred in the same pregnancy suggests an environmental or genetic problem rather than a problem related to the procedure itself.

Genitourinary malformations were found in excess in the infants born after intracytoplasmic sperm injection compared with the Australian population; this is what we might expect, since we know that some of the fathers had a genitourinary malformation and that some of these malformations can be transmitted to offspring. In one case the son had, indeed, exactly the same form of hypospadias (with two meatus) as his father.

Recalculating the prevalence of major cardiac defects without the nine cases of atrial septal defects would give a figure of 1.1% (5/420). This is not significantly different from the 0.67% observed in the Western Australian population (odds ratio 1.786 (95% confidence interval 0.74 to 4.33)). Recalculating the prevalence of all major malformations without the cases of atrial septal defects gives a figure of 5.23% (22/420), which is higher than the 3.78% observed in the Western Australian population but is not significantly different (odds ratio 1.406 (0.91 to 2.16)). However, the number of infants born after intracytoplasmic sperm injection that have been studied is still small.

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