

Neurological sequelae in twins born after assisted conception: controlled national cohort study

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Abstract

Objective To compare neurological sequelae in twins born after assisted conception with singletons after assisted conception and naturally conceived twins, and to assess neurological sequelae in children conceived after in vitro fertilisation (IVF) compared with intracytoplasmic sperm injection (ICSI).

Design Controlled, national register based, cohort study.

Participants Twins (n = 3393) and singletons (n = 5130) conceived by using assisted reproductive technologies and naturally conceived twins (n = 10 239) born in Denmark between 1995 and 2000. The children's age at time of follow up was 2-7 years.

Data sources Children were identified by cross linkage of the national medical birth registry and the national registry for in vitro fertilisation. Neurological and psychiatric diagnoses were retrieved from the national patients' registry and the Danish psychiatric central registry.

Main outcome measures Neurological sequelae, defined as cerebral palsy, mental retardation, severe mental developmental disturbances, and retarded psychomotor development. Further we made separate analyses on the specific cerebral palsy diagnosis.

Results The crude prevalence rates per 1000 of neurological sequelae in twins and singletons after assisted conception and in naturally conceived twins were 8.8, 8.2, and 9.6, and of cerebral palsy 3.2, 2.5, and 4.0, respectively. In twins after assisted conception compared with control twins, the odds ratios of neurological sequelae and specifically of cerebral palsy, adjusted for child sex and year of birth, were 0.9 (95% confidence interval 0.6 to 1.4) and 0.8 (0.4 to 1.6), respectively. The corresponding odds ratios for twins after assisted conception compared with singletons after assisted conception were 1.1 (0.7 to 1.7) for neurological sequelae and 1.3 (0.6 to 2.9) for cerebral palsy. The odds ratio of neurological sequelae in children conceived by ICSI was 0.9 (0.5 to 1.7) *v* children conceived by IVF.

Conclusions Twins from assisted conception have a similar risk of neurological sequelae as their naturally conceived peers and singletons from assisted conception. Children born after ICSI have the same risk of neurological sequelae as children born after IVF.

Introduction

In Denmark 5% of infants are the result of in vitro fertilisation (IVF) techniques (IVF and intracytoplasmic sperm injection, ICSI). The latest European data show that 39% of IVF infants are born as twins.¹ Several studies have shown that twin pregnancies are the main reason for the overall poorer neonatal outcome in pregnancies after assisted conception.²⁻⁵ However, the literature specifically addressing long term morbidity in twins after assisted conception is limited.⁶

To study the long term effects of IVF techniques on twins we established a database in Denmark with all singletons and twins born after assisted conception between 1995 and 2000. Our recent questionnaire study showed similar morbidity in twins after assisted conception and naturally conceived twins, but compared with singletons after assisted conception twins were more likely to have surgical interventions, special needs, and delayed speech development, whereas the prevalence of neurological sequelae was equal.⁷

We assessed prevalence rates of neurological sequelae in Denmark in a nationwide cohort of twins after IVF techniques and in two population based control groups of naturally conceived twins and of singletons conceived by IVF techniques. We also compared the roles of ICSI and conventional IVF in neurological sequelae in these children.

Methods

Participants

We used the Danish medical birth registry recording all births to identify women giving birth to twins and singletons from 1 January 1995 to 31 December 2000. A cross reference with the Danish registry for in vitro fertilisation enabled us to identify women who conceived naturally or after IVF. Using the linkage between the identification number of a mother in the civil registration system and her children in the medical birth registry, we identified every individual child in the three cohorts.

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Table 1 Mothers' and infants' characteristics in the three cohorts

	IVF-ICSI twins	Control twins	P value*	IVF-ICSI singletons	P value†
No of babies born alive	3393	10 239		5130	
No of stillborn babies‡	45 (13.1/1000)	123 (11.8/1000)	0.6	34 (6.6/1000)	0.002
Mean children's age at follow up in years (SD)	4.2 (1.7)	4.4 (1.7)	<0.001	4.1 (1.7)	0.12
Sex of babies:§					
No (%) of boys	1747/3352 (52.1)	5237/10 215 (51.3)	0.4	2700 (52.6)	0.6
No (%) of girls	1605/3352 (47.9)	4978/10 215 (48.7)		2430 (47.4)	
No (%) of twin pairs of the same sex	851/1676 (50.8)	3330/5103 (65.4)	<0.001	—	
Mean birth weight in g (SD)	2508 (615)	2540 (612)	0.01	3457 (629)	<0.001
Mean gestational age in weeks (SD)	35.9 (3.0)	36.1 (2.9)	0.02	39.3 (2.2)	<0.001
No of deaths per 1000 babies¶:					
Early neonatal, up to day 6	26 (7.6)	119 (11.6)	0.05	23 (4.5)	0.06
Late neonatal, day 7-28	4 (1.2)	22 (2.1)	0.3	3 (0.6)	0.4
Day 29-1 year	5 (1.5)	13 (1.3)	0.8	11 (2.1)	0.5
>1 year	1 (0.3)	4 (0.4)		0	
Total infant deaths	36 (10.6)	158 (15.4)	0.04	37 (7.2)	0.1
Mean maternal age at delivery in years (SD)	33.1 (3.7)	30.5 (4.5)	<0.001	33.8 (3.7)	0.001
No (%) of mothers aged <30 years	333/1668 (20.0)	2326/5119 (45.4)	<0.001	791/5128 (15.4)	<0.001
Odds ratio (95% confidence interval) of mothers aged <30 years v mothers >30 years	1	3.4 (2.9 to 3.8)	<0.001	0.7 (0.6 to 0.8)	<0.001
No (%) of women treated with:					
In vitro fertilisation	1262/1673 (75.4)	—		3456/4605 (75.0)	0.8
Intracytoplasmic sperm injection	411/1673 (24.6)	—		1149/4605 (25.0)	

*Differences of means of continuous parametric data were analysed with the use of Student's *t* test.

†Distributions between groups were compared by using Pearson's χ^2 analyses.

‡Stillborn children were not included in the cohorts and analyses.

§The sex was known for 3352 IVF or ICSI twins, 10 215 control twins, and 5130 IVF or ICSI singletons.

¶Children, who died were registered until 31 December 2000. After that point data from the Danish registry of causes of deaths were not updated. Children who died after delivery were included in the cohorts.

Outcome measures

We cross referenced the Danish patients' registry to identify all children diagnosed or treated in a hospital setting from birth until 31 December 2002.

We established a database with files from the different registries with each individual child in the three cohorts as the key variable and entered neurological and psychiatric diagnoses as outcomes. To ensure an accurate neurological diagnosis, all children were aged between 2 years and 7 years at time of follow up (31 December 2002). We allowed each child to be counted only once with a diagnosis code in each of three main diagnostic groups. See bmj.com for details of diagnosis codes and rankings.

Statistical analysis

We compared means and distributions between groups, and stratified for sex and year of birth to calculate odds ratios. We analysed twins as separate children and not as a pair. We performed two separate multiple logistic regression analyses to determine which variables independently predicted the dichotomous outcomes of neurological sequelae or not and of cerebral palsy or not. In all regression analyses we used the primary diagnosis of each child as the outcome variable. We performed three separate analyses, one for all three cohorts, a second for twins alone (IVF or ICSI and controls), and a third restricted to children conceived by IVF or ICSI, both singletons and twins (see bmj.com).

Results

Demographic data

We included 3393 twins conceived by IVF or ICSI, 10 239 naturally conceived twins, and 5130 IVF or ICSI singletons in the study (table 1). Since 41 IVF twins and 95 control twins were survivors of a stillborn

co-twin, the number of children in both twin cohorts was odd. The zygosity of the twins was estimated as 1.6% (26/1676) monozygotic IVF or ICSI and 31% (1557/5103) monozygotic control twin pairs. We adjusted all analyses for year of birth to account for the differences in average child age at time of follow up.

Neurological sequelae

We observed similar prevalence rates of neurological sequelae in IVF or ICSI twins and the two control groups. The crude prevalence of children with neurological sequelae was 8.8/1000 in IVF or ICSI twins, 9.6/1000 in control twins, and 8.2/1000 in IVF or ICSI singletons. The prevalence rates of the specific diagnoses cerebral palsy and mental retardation were also similar. Odds ratios of neurological sequelae, cerebral palsy, and mental retardation with and without adjustment for a child's sex and year of birth were the same in IVF or ICSI twins and both control groups. The odds ratios of neurological sequelae in ICSI compared with IVF children were 1.3 (95% confidence interval 0.6 to 3.0) for twins and 0.5 (0.2 to 1.2) for singletons. See bmj.com.

We identified one twin pair with neurological sequelae in 30 IVF or ICSI twins and six in 98 control twins, all of the same sex. The concordance rates were therefore 3.3% and 6.1%, respectively.

The role of zygosity

To account for the higher monozygotic rate among naturally conceived twins, we computed odds ratios of neurological sequelae in IVF or ICSI twins of the opposite sex compared with twins of the same sex (0.7, 0.3 to 1.4) and in control twins (1.0, 0.8 to 1.4).

To exclude the monozygotic twins we restricted our analyses to twins of the opposite sex. The odds ratios for neurological sequelae were 1.1 (0.6 to 2.3), mental retardation 1.1 (0.4 to 2.6), and cerebral palsy 1.3 (0.4

to 4.0) in twins of the opposite sex conceived by IVF or ICSI compared with control twins of the opposite sex.

Factors influencing the risk of neurological sequelae

We performed multiple logistic regression analyses for all children in the three cohorts and for twins alone to explore the effect of relevant confounders on the risk of neurological sequelae (table 2). Low birth weight or prematurity and male sex were strong risk factors for both outcome measures. After adjustment for low birth weight or prematurity, we observed that IVF and maternal age > 35 years had no independent effect on the risk of neurological sequelae, and neither had being a twin. In the analyses restricted to twins, IVF or ICSI twins had no greater risk of neurological sequelae than naturally conceived twins. We adjusted all data in the logistic regression analysis for children's year of birth.

To study the effect of ICSI, we performed regression analyses restricted to IVF or ICSI children. ICSI children had similar odds ratios as IVF children for neurological sequelae (0.9, 0.5 to 1.6) and cerebral palsy (0.8, 0.3 to 2.4). Also in these analyses male sex and low birth weight or prematurity independently affected the risk of both outcomes, and we found no difference between twins and singletons in the risk of any of the outcomes.

Discussion

Twins born after assisted conception have a similar risk of neurological sequelae as naturally conceived twins and singletons after IVF or ICSI. The risk of neurological sequelae in children born after ICSI and conventional IVF does not differ.

Limitations of the study

The study lacked data on the extent to which women in the group of naturally conceived twins had received ovarian stimulation with or without intrauterine insemination (IUI). Our questionnaire study showed that 17.3% of the control twin mothers conceived after ovarian stimulation with or without IUI.⁷ Recent papers have reported no influence of the stimulation procedure on neonatal outcome in singletons or in twins, so we assume that the risk of neurological sequelae in children conceived after ovarian stimulation without IVF is no greater than that of children conceived naturally.^{8, 9}

In accordance with two recent reports on mental development in ICSI children, we found a similar risk of neurological sequelae and cerebral palsy in ICSI and IVF children.^{10, 11}

As observations on twins are not fully independent, a potential risk exists of estimating the confidence intervals too narrowly. When considering our results, the concordance rates were one set of twins in 30 IVF or ICSI children, and six sets in 98 control twins, with neurological sequelae. Even though the concordance rates are low, if one twin is affected, then the other is more likely to be affected than would occur by chance.

Strengths of the study

The strengths of the study were the nationwide design which allowed us to assess the effect of confounding factors and evaluate the role of zygosity. The

Table 2 Multiple logistic regression analysis showing independent effects of being a twin infant, assisted conception (IVF and ICSI), maternal age ≥35 years, male sex, and low birth weight (<2500 g) (upper panel) or low gestational age (≤37 weeks) (lower panel) on the risk of neurological sequelae and cerebral palsy. Results are presented as odds ratios (95% confidence intervals), adjusted for child sex and year of birth

	Neurological sequelae		Cerebral palsy	
	All cases	Twins	All cases	Twins
Effects of birth weight				
Twin	0.7 (0.4 to 1.2)	—	0.6 (0.2 to 1.4)	—
Assisted conception	0.9 (0.6 to 1.4)	0.9 (0.6 to 1.4)	0.8 (0.4 to 1.5)	0.8 (0.4 to 1.5)
Low birth weight	2.3 (1.6 to 3.2)	1.9 (1.4 to 2.8)	4.4 (2.5 to 7.8)	3.0 (1.7 to 5.4)
Male sex	2.0 (1.4 to 2.8)	1.9 (1.3 to 2.8)	1.9 (1.1 to 3.2)	2.0 (1.1 to 3.5)
Maternal age ≥35 years	0.8 (0.6 to 1.2)	0.8 (0.5 to 1.4)	0.8 (0.4 to 1.5)	0.8 (0.4 to 1.7)
Effects of gestational age				
Twin	0.8 (0.5 to 1.3)	—	0.6 (0.2 to 1.4)	—
Assisted conception	0.9 (0.6 to 1.4)	0.9 (0.6 to 1.4)	0.8 (0.4 to 1.6)	0.8 (0.4 to 1.6)
Low gestational age	2.0 (1.4 to 2.8)	1.8 (1.2 to 2.6)	4.5 (2.5 to 8.1)	3.1 (1.7 to 5.7)
Male sex	1.9 (1.3 to 2.6)	1.8 (1.2 to 2.6)	1.8 (1.0 to 3.0)	1.9 (1.0 to 3.4)
Maternal age ≥35 years	0.8 (0.6 to 1.2)	0.8 (0.5 to 1.4)	0.8 (0.4 to 1.5)	0.8 (0.4 to 1.8)

compulsory Danish registries enabled us to trace all IVF or ICSI deliveries, identify and enrol all children and identify those with neurological sequelae diagnosed in a hospital setting. Moreover, the liberal access to assisted reproductive technologies, including reimbursement of the first three IVF treatments, makes Denmark the country with the highest number of performed IVF cycles per inhabitant in Europe. This is probably the reason why no fundamental differences exist in socioeconomic position between Danish IVF mothers and mothers who conceive spontaneously.⁷

Comparison with other studies

In most existing surveys the follow up period is too short or the sample size insufficient to draw firm conclusions.^{12, 13} However a Swedish register study had a sufficiently large sample size (2060 IVF twins) and found that IVF twins had a similar risk of neurological sequelae as their naturally conceived peers.¹⁴ In contrast to our results, they showed that the risk of neurological sequelae was higher in IVF twins than in IVF singletons. They did not, however, study the effect of ICSI. The crude prevalence of cerebral palsy per 1000 children in the Swedish study was higher than in our study. An overestimation of the prevalence of cerebral palsy in the Swedish study could have resulted from children being diagnosed by healthcare professionals other than doctors as well as from the shorter follow up period. The prevalence of cerebral palsy found in the IVF or ICSI singletons in our study was very close to the crude prevalence in eastern Denmark.¹⁵ It cannot be concluded that the rate of cerebral palsy in these singletons is the same as in the general population, as we relied on diagnoses recorded in a hospital setting. These problems, however, should not bias either study and do not explain the difference between their results.

Definition of neurological sequelae

To ensure the most objective classification of diagnoses we outlined the ranking system before data retrieval, and to keep a consistent recording of diagnoses we defined neurological sequelae as only the most severe neurological and psychiatric diagnoses. In the Swedish study the primary diagnosis, in case the child had more than one diagnosis, was chosen as the child's major

What is already known on this topic

Children born after assisted conception have a higher risk of neurological sequelae than naturally conceived children, mainly because of the higher frequency of twins

What this study adds

Twins born after assisted conception have a similar risk of neurological sequelae as naturally conceived twins and singletons born after assisted conception

The risk of neurological sequelae in children born after ICSI does not differ from that of children born after IVF

diagnosis. Another reason for the higher Swedish prevalence rates of cerebral palsy could be that the Swedish study comprised an earlier cohort of children and prenatal and neonatal care of IVF and twin pregnancies have improved since.

Our recent paper showed a marginally higher rate of admissions to neonatal intensive care units in IVF or ICSI twins (56.3%) than in naturally conceived twins (52.4%)¹⁶; the higher admission rate to intensive care in twins after assisted conception could have affected the prevalence of neurological sequelae favourably. By contrast, more intensive obstetric care in Denmark depends on chorionicity and not whether it is an assisted conception or not; monozygotic twins have an increased risk of morbidity and mortality and prenatal care of these pregnancies is more intense.

Potential biases

The prevalence rates of neurological sequelae were not underestimated in favour of IVF or ICSI twins because of higher mortality in these twins. Regarding IVF or ICSI twins versus singletons we observed no significant differences in mortality, and this could not bias the study (table 1). Excluding infant deaths from the denominator had negligible influence on the prevalence of neurological sequelae in the three cohorts. Consistent with an earlier survey, we found similar risks of neurological sequelae and cerebral palsy in twins of the same sex compared with twins of the opposite sex.¹⁷

Conclusion

The similar prevalence of neurological sequelae in twins and singletons born after assisted conception was reassuring. However recent studies have observed higher risks of other adverse outcomes, including a doubled stillbirth rate, all with familiar consequences and higher cost.^{2-5 7 16-17} The impact of our study should therefore not be a blind acceptance of dual embryo replacement in IVF but a well considered step towards elective single embryo transfer to the patients who are prone to having twins.

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Ethical approval: The trial was approved by the local research ethics committee and the Danish Data Protection Agency. A specific authorisation from the Danish Data Protection Agency was obtained to data retrieval from the Danish Psychiatric Central Registry.

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Endpiece

Qualities of a good surgeon

He is a good surgeon who possesses courage and presence of mind, a hand free from perspiration, tremorless grip of sharp and good instruments, and who carries his operation to success and to the advantage of his patient, who has entrusted his life to the surgeon. The surgeon should respect the absolute surrender and treat his patient as his own son.

Susrata, recognised as the father of Indian surgery, who wrote his treatise 2500 years ago

R K Choudhary, staff grade surgeon, Bishop Auckland