Human Reproduction Vol.16, No.3 pp. 504–509, 2001

# Congenital malformations in infants born after IVF: a population-based study

**A.Ericson[1] and B.Källén[2,3]**

[1]Epidemiological Center, National Board of Health, SE-106 30 Stockholm and [2]Tornblad Institute, University of Lund, SE-263 62 Lund, Sweden

[3]To whom correspondence should be addressed at: Tornblad Institute, Biskopsgatan 7, SE-223 62 Lund, Sweden. E-mail: embryol@embryol.lu.se

**The presence of congenital malformations in infants born after IVF was studied from a register consisting of practically all infants born in Sweden after IVF, 1982–1997 ($n$ = 9111). A further 64 infants were studied using only medical records. It is a nation-wide study and has a population-based control group ($n$ = 1 690 577) and relevant potential confounders have been taken into account. There was an excess of congenital malformations registered in the Medical Birth Registry ($n$ = 516, odds ratio = 1.47) but this excess disappeared when confounders were taken into consideration: year of birth, maternal age, parity, and period of unwanted childlessness (odds ratio = 0.89). For some specific conditions, an ~3-fold excess risk was seen: neural tube defects, alimentary atresia, omphalocele, and hypospadias (after intracytoplasmatic sperm injection). No excess risk for hypospadias was seen after standard IVF. Various explanations for these findings are discussed. It is postulated that the excess risk for alimentary atresia, like the excess risk for monozygotic twinning after IVF, is a direct consequence of the IVF procedure. The excess risk for hypospadias after ICSI may be related to paternal subfertility with a genetic background. The absolute risk for a congenital malformation in association with IVF is small.**

*Key words:* alimentary tract atresia/congenital malformations/hypospadias/IVF/neural tube defects

## Introduction

During the last few decades, IVF has become a major alternative in the treatment of infertile couples. In 1996, ~1.2% of all deliveries and 1.5% of all infants born in Sweden were the result of IVF and the percentage is increasing every year. Major concerns with the outcome of IVF pregnancies are related to multiple births and preterm deliveries but some authors have also discussed the possibility that there is an increased risk for congenital malformations (Lancaster, 1987).

Most such reports concern a limited number of pregnancies and estimates of malformation risks are often uncertain (Morin *et al*., 1989; Brandes *et al*., 1992; Bonduelle *et al*., 1995). Some studies are large enough to permit relatively certain determinations of malformation rates, but comparisons have often been made with population data from various types of registers while the identification of malformations in the infants born after IVF is the result of detailed follow-up. Thus a French study (FIVNAT, 1995) followed 6879 infants after IVF and found 2.8% with a malformation; this rate was compared with data from various registers of congenital malformations and was found not to deviate. A British study (MRC Working Party, 1990) described 1581 infants born after IVF or gamete intra-Fallopian transfer with national register data and also found a relatively low incidence of congenital malformations: 2.2–2.9% depending on follow-up time. Another English study (Rizk *et al*., 1991) described outcome of 1360 infants born after IVF and found no significantly increased risk for congenital malformations. A specific study has been published regarding infants born after intracytoplasmic sperm injection (ICSI) in Belgium: in the most recent report (Bonduelle *et al*., 1999) 1987 infants born after ICSI were analysed and no increase in the rate of congenital malformations was reported. A Danish registry (Westergaard *et al*., 1999) study, comparing outcome after IVF and matched control (matching including multiplicity), found 4.8% of children born after IVF and 4.6% of control children to have a congenital malformation.

A recent abstract (Lancaster *et al*., 2000) describes experiences from the Australian-New Zealand register of assisted conceptions which contains information on notified congenital malformations. They found 2.5% of infants among 4260 births or terminations after ICSI and similar in infants born after conventional IVF.

The registration of congenital malformations in general population registers is often incomplete and are therefore not suitable sources for background material.

A Swedish register study (Bergh *et al*., 1999) is one of the few studies which identified malformations in an identical way in the infants born after IVF (1982–1995) and in infants serving as controls and which is large enough to permit reasonably certain risk estimates. The total rate of infants with

any congenital malformation registered was 5.4% and the crude risk ratio (RR) after comparisons with the general population was 1.4 [95% confidence interval (CI) 1.3–1.5]. Specific information on infants conceived by ICSI has been reported (Wennerholm *et al*., 2000) from Sweden, based on 1139 such infants. An increased odds ratio (OR) for congenital malformations was found (1.75, 95% CI 1.19–2.58), apparently to a large extent due to multiple births even though a specific increase in the risk for hypospadias was seen.

We present a more detailed analysis of congenital malformations in infants born after IVF in Sweden and have extended the study material to infants born after procedures up to April 1, 1997.

## Materials and methods

The first delivery in Sweden after IVF treatment occurred in 1982. This procedure is at present or has been performed in 16 hospitals or clinics. These units reported to the National Board of Health all patients who had delivered after an IVF treatment. The delivery definition used is the birth of any living infant or a stillborn infant with a pregnancy duration of at least 28 completed weeks.

Using the unique personal identification number (assigned to each person living in Sweden and extensively used in society including in all health care), the outcome of the pregnancies and the presence of congenital malformations was identified from the Medical Birth Registry, a registry based on the medical records of antenatal care, delivery care, and the paediatric examination of the newborn (Cnattingius *et al*., 1990). The presence of a congenital malformation is represented in this register with the relevant ICD code. Further information was sought from the Swedish Register of Congenital Malformations (Källén, 1987) with auxiliary registers, especially the Child Cardiology Register which gets information from the child cardiology centres in Sweden on cardiac defects diagnosed before the age of 1 year, and the Cytogenetic Register which gets information from the cytogenetic laboratories on autosomal anomalies identified during the first year of life. In this way, the majority of congenital malformations can be identified.

The definition of a congenital malformation is a condition which is coded under Chapter 14 of ICD8 or 9 or under Chapter 17 of ICD10. Sweden began using ICD9 in 1987 and ICD10 during 1997. To these infants are added those which were specifically reported to the Register of Congenital Malformation or its auxiliary register. During 1996–1997, a total of 75 infants born after IVF treatment had not been reported to the Medical Birth Registry. Medical Records for these cases were sought and retrieved for 64 of the infants.

After addition of these cases, the survey included 9175 infants, 516 of which were identified as having a congenital malformation according to the above-mentioned definition (5.6%). Among them, 28 had no malformation diagnosis in the Medical Birth Register but were identified from the other registers or from the medical record scrutiny: six of them were not even reported to the Medical Birth Register. A further 23 infants (16 deliveries) had no information on the health of the infant in the available records or no medical records could be identified. These infants were searched in the Hospital Discharge Registry and three were identified with congenital malformations. They were followed in this register to the end of 1997 (up to 2 years after birth).

### *Statistical analysis*

The OR for having a congenital malformation, stratified for year of birth, maternal age (5 year group), parity (1–4+), number of infants in the birth, and length of period of involuntary childlessness (years) was estimated based only on conditions identified in the Medical Birth Registry. Mantel-Haenszel's technique was used and the 95% CI was estimated with a test-based method.

Comparisons between observed and expected numbers of specific malformations were made using exact Poisson distributions and expressed as RR. Expected numbers were calculated from the rates of each malformation in the population.

The proportions of malformed infants born after ICSI or the proportion of malformed infants born in multiple birth were compared with the corresponding proportions for all IVF infants using exact binomial distributions.

**Table I.** Odds ratios (OR) with 95% confidence intervals (95% CI) for being registered in the Medical Birth Registry in infants conceived by IVF compared with all infants after various stratifications.

| Stratification and subgroup | All | | Selected | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Only year of birth | 1.47 | 1.34–1.61 | 1.47 | 1.31–1.64 |
| Also maternal age and parity | 1.39 | 1.25–1.54 | 1.39 | 1.23–1.58 |
| Also number in birth | 1.18 | 1.06–1.32 | 1.19 | 1.04–1.36 |
| Singletons | 1.24 | 1.08–1.42 | 1.27 | 1.08–1.51 |
| Multiple births | 1.09 | 0.91–1.30 | 1.06 | 0.85–1.32 |
| Also known period of involuntary childlessness | 0.89 | 0.74–1.06 | 0.92 | 0.74–1.15 |
| Singletons | 0.88 | 0.70–1.11 | 0.90 | 0.68–1.20 |
| Multiple births | 0.90 | 0.67–1.21 | 0.96 | 0.66–1.38 |

'All' = all malformations; 'Selected' = malformations after removal of preauricular appendix, patent ductus arteriosus, undescended testicle, and unstable hip.

## Results

The sex ratio among the infants born after IVF treatment (1.10, 95% CI 1.05–11.4) was slightly but not significantly above the normal sex ratio of 1.06. There is a difference in sex ratio between infants born after standard IVF (1.14, 95% CI 1.09–1.20) and after ICSI (0.96, 0.88–1.04). These small deviations from the normal sex ratio will hardly influence the expected numbers of congenital malformations.

An OR for being entered in the Medical Birth Registry with a congenital malformation was determined after various stratifications (Table I). In the crude analysis (only stratifying for year of birth), a significantly increased OR was found. Stratification for maternal age and parity reduced it slightly but stratification for singleton/multiple birth reduced it markedly and when consideration was also taken of the (known) length of involuntary childlessness, the OR was even slightly below 1.0, similar for singletons and multiple births. In these calculations, many mild and variable conditions are included as well as others (such as patent ductus and undescended testicles) which are specifically related to preterm birth but also unstable hip which is more common in term births than in preterm births. Exclusion of these conditions (when present alone) and of the common and variable diagnosis of preauricular appendix did not change the OR substantially (Table I).

The OR is only 1.09 when the analysis is restricted to

**Table II.** Identified 'major' congenital malformation diagnoses irrespective of source, divided into standard IVF and ICSI.

| Malformation | IVF | ICSI | Total | Total no. of multiples |
|---|---|---|---|---|
| Anencephaly | 6 | 0 | 6 | 6 |
| Spina bifida | 6 | 0 | 6 | 3 |
| Microcephaly | 1 | 0 | 1 | 1 |
| Reduced brain tissue | 1 | 1 | 2 | 0 |
| Holoprosencephaly | 1 | 0 | 1 | 1 |
| Hydrocephaly | 6 | 1 | 7 | 5 |
| Other brain malformation | 2 | 1 | 3 | 2 |
| Microphthalmia | 1 | 1 | 2 | 0 |
| Cataract | 0 | 1 | 1 | 1 |
| Severe ear malformation | 2 | 1 | 3 | 2 |
| Transposition | 1 | 1 | 2 | 1 |
| Tetralogy of Fallot | 3 | 2 | 5 | 2 |
| Single ventricle | 1 | 0 | 1 | 1 |
| Hypoplastic left heart | 2 | 1 | 3 | 3 |
| Coarctation | 6 | 0 | 6 | 4 |
| Ebstein's anomaly | 1 | 0 | 1 | 1 |
| Pulmonary atresia | 2 | 1 | 3 | 1 |
| VSD | 34 | 7 | 41 | 19 |
| ASD | 11 | 2 | 13 | 9 |
| Other specific cardiac defect | 5 | 3 | 8 | 3 |
| Unspecified cardiac defect | 18 | 3 | 21 | 10 |
| Choanal atresia | 1 | 0 | 1 | 1 |
| Isolated cleft palate | 7 | 4 | 11 | 4 |
| Cleft lip/palate | 10 | 1 | 11 | 5 |
| Oesophageal atresia | 7 | 1 | 8 | 3 |
| Small gut atresia | 4 | 1 | 5 | 2 |
| Anal atresia | 5 | 4 | 9 | 5 |
| Pylorostenosis | 1 | 1 | 1 | 1 |
| Megacolon | 3 | 1 | 4 | 1 |
| Biliary tract malformation | 3 | 0 | 3 | 0 |
| Unspecified gut malformation | 0 | 2 | 2 | 2 |
| Hypospadias | 18 | 10 | 28 | 16 |
| Intersex | 1 | 0 | 1 | 0 |
| Other genital malformation | 5 | 2 | 7 | 5 |
| Kidney agenesis | 3 | 1 | 4 | 2 |
| Cystic kidney | 2 | 0 | 2 | 1 |
| Hydronephrosis/urethral malformation | 14 | 7 | 21 | 8 |
| Genu recurvatum | 1 | 0 | 1 | 0 |
| Varus foot deformity | 22 | 3 | 25 | 10 |
| Limb reduction | 5 | 0 | 5 | 3 |
| Arthrogryposis | 1 | 0 | 1 | 1 |
| Spine malformation | 1 | 0 | 1 | 1 |
| Tanatophoric dwarf | 1 | 0 | 1 | 0 |
| Diaphragmatic hernia | 1 | 0 | 1 | 0 |
| Abdominal wall defect | 3 | 4 | 7 | 3 |
| Incontinentia pigmentii | 1 | 0 | 1 | 1 |
| Conjoined twins | 0 | 1 | 1 | - |
| Zellweger syndrome | 1 | 0 | 1 | 0 |
| Tuberous sclerosis | 1 | 0 | 1 | 1 |
| Larsson syndrome | 1 | 0 | 1 | 1 |
| Nagel syndrome | 0 | 1 | 1 | 2 |
| Down's syndrome | 13 | 5 | 18 | 11 |
| Trisomy 13 | 0 | 1 | 1 | 0 |
| Trisomy 18 | 2 | 2 | 4 | 2 |
| Deletion chromosome 18 (q21.2) | 1 | 0 | 1 | 1 |
| Unspecified chromosome anomaly | 1 | 1 | 2 | 1 |
| Unspecified multiple malformation | 0 | 1 | 1 | 1 |
| Total no. of infants with any congenital malformation | 398 | 118 | 516 | 237 |

ICSI = intracytoplasmic sperm injection; VSD = ventricular septum defect; ASD = atrial septum defect.

**Table III.** Identified 'mild and variable' congenital malformation diagnoses irrespective of source, divided into standard IVF and ICSI

| Malformation | IVF | ICSI | Total | Total no. of multiples |
|---|---|---|---|---|
| Coloboma of eye | 2 | 0 | 2 | 1 |
| Preauricular appendix or branchial cyst | 14 | 7 | 21 | 10 |
| Unspecified ear malformation | 3 | 0 | 3 | 1 |
| Patent ductus arteriosus | 39 | 11 | 50 | 40 |
| Single umbilical artery | 5 | 0 | 5 | 3 |
| Nose malformation | 1 | 0 | 1 | 0 |
| Tongue tie | 2 | 0 | 2 | 2 |
| Meckel diverticle | 2 | 0 | 2 | 2 |
| Undescended testicle | 31 | 11 | 42 | 18 |
| Horse-shoe kidney | 1 | 0 | 1 | 1 |
| Skull/face anomaly | 3 | 1 | 4 | 0 |
| Sternocleido muscle anomaly | 1 | 1 | 2 | 1 |
| Unstable hip | 45 | 8 | 53 | 11 |
| Valgus foot deformity | 8 | 5 | 13 | 7 |
| Unspecified foot deformity | 3 | 2 | 5 | 0 |
| Polydactyly | 6 | 2 | 8 | 4 |
| Syndactyly | 5 | 4 | 9 | 4 |
| Cervical rib | 1 | 0 | 1 | 0 |
| Unspecified muscular anomaly | 3 | 1 | 4 | 1 |
| Unspecified skin anomaly, including nevus | 3 | 3 | 6 | 3 |

multiple pregnancies. As the majority of twins born after IVF treatments are dizygotic, the comparison was also made only with unlike-sexed twins in the population (which must be dizygotic). The OR after complete stratification then increased marginally to 1.10 (95% CI 0.71–1.71).

Tables II and III specify all identified congenital malformation diagnoses, irrespective of source. They have been grouped, somewhat arbitrarily, into 'major' (Table II) and 'mild and variable' (Table III) malformations. The tables show the number of diagnoses, which is larger than the number of infants with malformations.

Among all infants born after IVF, 18% were born after ICSI and 42% were born in multiple births. In order to see whether any specific congenital malformation occurred selectively more or less often in multiple births or after ICSI, the exact binomial 95% CI of the distributions seen in Table II were compared with those percentages. Only for hypospadias was a marginally significant excess seen for infants born after ICSI: 36% (95% CI 19–56%). No infant was born with a neural tube defect after ICSI, but this estimate has a 95% CI 0–26%, and thus includes the expected rate of 18% of ICSI.

Table IV lists infants with more than one major congenital malformation. Nine (nearly half of these infants) had one or more of the following intestinal tract atresias: oesophageal atresia, small bowel atresia, or anal atresia. In two of them, biliary tract malformations were also present.

Table V summarizes observed and expected numbers of some major groups of malformations. Statistically significant risk increases of ~3-fold are seen for neural tube defects, oesophageal, small bowel or anal atresia, and omphalocele. An ~50% increased risk is seen for hypospadias. Both the risk increase for omphalocele and for hypospadias show marginal statistical significance. When the risk for hypospadias in infants born after ICSI is calculated, however, the expected number is 3.4 and the observed number is 10, which gives an RR of 2.9 (95% CI 1.4–5.4). A corresponding calculation for infants

**Table IV.** Twenty infants with more than one major congenital malformation. All sources of information on malformations used

| |
|---|
| Anencephaly and horse-shoe kidney and intersex |
| Spina bifida and atrial septum defect |
| Spina bifida and omphalocele |
| Hydrocephaly and cleft lip/palate |
| Hydrocephaly and ventricular and atrial septum defect |
| Hydrocephaly and hypoplastic left heart syndrome |
| Microphthalmia and isolated cleft palate and polydactyly |
| Cleft palate and unspecified genital malformation |
| Cleft lip/palate and ventricular septum defect |
| Cleft lip/palate and unspecified heart defect |
| Oesophageal atresia and hydrocephaly |
| Oesophageal atresia and thumb aplasia |
| Oesophageal atresia and small gut atresia and biliary tract atresia |
| Oesophageal atresia and small gut atresia and kidney agenesis and genital malformation |
| Oesophageal atresia and anal atresia |
| Small gut atresia and biliary tract malformation |
| Anal atresia and kidney agenesis |
| Anal atresia and kidney agenesis and spine malformation |
| Anal atresia and kidney agenesis and limb anomaly |
| Omphalocele and cystic kidney and tetralogy of Fallot |

**Table V.** Observed and expected numbers of some large groups of major congenital malformations

| Congenital malformation | Observed | Expected | RR | 95% CI |
|---|---|---|---|---|
| Neural tube defects | 12 | 4.1 | 2.9 | 1.5–5.1 |
| Oro-facial clefts | 22 | 16.5 | 1.3 | 0.8–1.9 |
| Congenital heart defects | 93 | 82.6 | 1.1 | 0.9–1.4 |
| Oesophageal atresia | 8 | 2.3 | 3.5 | 1.5–6.9 |
| Small gut atresia | 5 | 1.6 | 3.1 | 1.0–7.3 |
| Anal atresia | 9 | 2.6 | 3.1 | 1.3–6.1 |
| Diaphragmatic hernia | 1 | 2.3 | 0.4 | 0.0–2.4 |
| Omphalocele | 7 | 2.1 | 3.3 | 1.3–6.9 |
| Hypospadias | 28 | 19.1 | 1.5 | 1.0–2.1 |
| Limb reduction defect | 5 | 4.9 | 1.0 | 0.3–2.4 |
| Down's syndrome | 18 | 20.2 | 0.9 | 0.5–1.4 |

RR = relative risk; CI = confidence interval.

born after standard IVF gives 18 observed and 15.7 expected, RR 1.1 (95% CI 0.68–1.81).

During the years 1993–1997, there were 498 593 deliveries in Sweden with 10 anencephalic infants and 7297 twin deliveries. Among the latter, one of the twins had anencephaly in six pairs. Four of these were among 1334 twin pregnancies after IVF. Corresponding figures for spina bifida are: 212 infants with spina bifida among singleton births (0.14 per 1000), and 12 among twins (0.16 per 1000). Among the 12 spina bifida twins, only two were born after IVF.

These data refer to infants born. We have no information on induced abortions performed because of the prenatal identification of a serious malformation. At the scrutiny of medical reports, mentioned above, one case was found when a fetus with a spina bifida and an Arnold-Chiari malformation had been identified in one of two twin fetuses and a feticide had been performed: this pregnancy was thus registered as a singleton pregnancy with a normal infant. Further such occasions may have occurred.

## Discussion

The present study is based on the majority of infants born after IVF in Sweden. Identification of cases was made from patient identities reported from the clinics performing the IVF. Ascertainment is not complete, which is, for instance, seen from the fact that some cases described in a report on infants born after ICSI performed in Gothenburg (Wennerholm *et al*., 2000) were not included in the present analysis, e.g. an infant with Goldenhar syndrome. Other observations also support the notion that ascertainment was incomplete—it can only be hoped that loss of cases is random. An advantage with the present study (except for its reasonably large size) is that the identification of congenital malformations in the infants does not rely on reporting from IVF clinics or detailed follow-up of children but is based on routine register data which makes it possible to compare infants born after IVF with all infants in the population.

Infants born after IVF have an increased risk for a congenital malformation. This risk increase, which is close to 50%, is an effect of the characteristics of the women undergoing IVF: age, parity, and period of involuntary childlessness. Involuntary childlessness of 4 years or more has previously been shown to increase the risk for a congenital malformation in the infant but the risk estimate was only a 17% increase of major malformations—in this study only few women had received IVF (Ghazi *et al*., 1991).

A specific risk increase was seen for a few malformation conditions, notably neural tube defects, alimentary tract atresia, omphalocele, and hypospadias. For other rather common conditions, such as oro-facial clefts, no significant increase was seen even though the upper confidence limit is close to 2. An association between the use of ovarian stimulation and the birth of infants with oro-facial clefts has been described (Long *et al*., 1992).

An association between neural tube defects and ovarian stimulation has been discussed for a very long time (Elwood *et al*., 1992; van Loon *et al*., 1992; Greenland *et al*., 1995) and the possibility that an increased risk exists after IVF has also been mentioned (Lancaster *et al*., 2000). In the present study we found 12 infants with neural tube defects, six with anencephaly and six with spina bifida. Among all infants with neural tube defects born in Sweden during 1996–1997, only 9% had anencephaly (seven among 77). Nine of the 12 neural tube defect infants identified after IVF were born in multiple births. In Sweden, the rate of anencephaly is about doubled in infants born as twins but no certain difference in spina bifida rate is seen between singletons and twins (Källén *et al*., 1994). Even if the percentage of twins among infants born after IVF is high (42%), the increased risk for anencephaly in twins only marginally changes the expected number of neural tube defects (from 4.1 to 4.4). The high number of multiple births may have another result, however. As most Swedish pregnant women have ultrasonography around week 16, anencephaly is nearly always detected. Those born (except for a very few cases where the religious conviction of the woman makes her unwilling to accept an induced abortion) are usually members of a twin pair, one infant with anencephaly and the other

normal. Twin pregnancies with an anencephalic twin are often interrupted; however, a woman who has had a long period of infertility followed by a successful IVF may be less apt to interrupt such a pregnancy than a woman with normal fertility.

A corresponding situation may also exist for spina bifida (where prenatal detection is less successful than for anencephaly). In this situation, however, a continued pregnancy may result in a surviving handicapped infant and therefore the pregnancy is more likely to be interrupted in a woman who had IVF treatment. We learned about one case where a selective feticide had been made after the identification of spina bifida in one of twin fetuses. The presence of three infants with spina bifida among singletons is slightly higher than expected (but this can obviously be random).

The second group of malformations which apparently occurs at an increased rate after IVF is alimentary atresia: oesophageal, small bowel, and anal atresia. Such an association has been reported previously (Lancaster, 1989). Among the 9111 infants, 19 had one or more of these malformations, 2 per 1000. This is a 2–3-fold higher rate than that found in Sweden in a previous study (Harris *et al*., 1995) and the present risk estimates for each one of these malformations is around 3. Among the 19 infants, nine had more than one atresia; in the previous Swedish population study this occurred in 4% of such infants (Harris *et al*., 1995). The risk for alimentary tract atresia in twins appears to be increased about three times but this seems to be mainly associated with monozygotic twinning and will therefore not much affect the expected number of infants born after IVF and with an atresia (Harris *et al*., 1995). The association between monozygotic twinning and this group of malformations suggests that at least some of the atresia malformations may be pathogenetically related to the monozygotic twinning process. This agrees with the suggestion in the literature that the VATER complex, where the presence of oesophageal and anal atresia are important components, may be due to a very early disturbance of embryonic development (Martínez-Frías *et al*., 1999). There is evidence in the literature (Sills *et al*., 2000) that monozygotic twinning is increased after IVF which is supported by the Swedish data. Among 1660 twin pairs 877 were like-sexed. Applying Weinberg's law, this means that 94 pairs should be monozygotic and the expected number from the population (stratified for year of birth and maternal age) is 36. The risk for monozygotic twinning is thus increased 2.6-fold (95% CI 1.5–3.8). The excess of monozygotic twins cannot in itself explain the increased rate of alimentary atresia but it is possible that a factor, associated with IVF, causes the increased risk for monozygotic twinning and also the increased risk for alimentary atresia. It is also suggestive that one set of conjoined twins (normal rate 1/75 000 births) occurred after IVF.

The increased risk for omphalocele which was observed may well be random even though formal statistical significance was reached.

Hypospadias, finally, is increased in infants born after ICSI but may not be so after standard IVF. It should be noted that the sex ratio after ICSI is even below the normal sex ratio and thus the risk increase for hypospadias is slightly underestimated. An increased risk of hypospadias after IVF has previously been described and then associated with progestogen treatment (Silver *et al*., 1999). It is doubtful if progestogen treatment causes hypospadias (Källén *et al*., 1992) and the present data suggest that the increased risk for hypospadias is specific for ICSI. Another explanation as suggested previously (Wennerholm *et al*., 2000) is a confounding by paternal subfertility which would explain the specific association with ICSI. An increased occurrence of testicular anomalies has been described in fathers of hypospadic boys (Sweet *et al*., 1974) but efforts to directly demonstrate an increased occurrence of parental subfertility at hypospadias have reached no conclusive results (Källén *et al*., 1991). A possible explanation is the transfer from father to son of a gene which causes testicular impairment as early as fetal stages, resulting in an increased risk for hypospadias. In the father, the same gene may cause subfertility.

Our data give little information on the presence of sex chromosome anomalies which have been associated specifically with ICSI. Such deviations are seldom detected in the routine examination of newborns and no systematic cytogenetic analysis of the offspring has been made.

In conclusion, the present study verifies an excess risk for a congenital malformation in infants born after IVF. The general excess risk seems to be explainable by maternal characteristics. For some specific conditions, a more marked risk increase is seen. For neural tube defects this may at least partly be an effect of attitudes to selective induced abortion, for hypospadias it may be an effect of confounding from paternal subfertility (perhaps on a genetic basis), and for alimentary atresia it may be associated with the same type of disturbance which increases the risk for monozygotic twinning. The latter may be a direct effect of the IVF procedure. The absolute risk for a serious malformation to occur after an IVF procedure is small.

## Acknowledgement

Collection of data on IVF was made by the Committee on In Vitro Fertilization, National Board of Health, Stockholm.

## References

Bergh, T., Ericson, A., Hillensjö, T. *et al*. (1999) Delivery and children born after in-vitro fertilisation in Sweden 1982–1995: a retrospective cohort study. *Lancet*, **354**, 1579–1585.

Bonduelle, M., Legein, J., Derde, M.-P. *et al*. (1995) Comparative follow-up study of 130 children born after intracytoplasmic sperm injection and 130 children born after in-vitro fertilization. *Hum. Reprod*., **10**, 3327–3331.

Bonduelle, M., Camus, M., Devos, A. *et al*. (1999) Seven years of intracytoplasmatic sperm injection and follow-up of 1987 subsequent children. *Hum. Reprod*., **14** (Suppl. 1), 243–264.

Brandes, J.M., Scher, A., Itzkovits, J. *et al*. (1992) Growth and development of children by *in vitro* fertilization. *Pediatrics*, **20**, 424–429.

Cnattingius, S., Ericson, A., Gunnarskog, J. *et al*. (1990) A quality study of a medical birth registry. *Scand. J. Soc. Med*., **18**, 143–148.

Elwood, J.M., Little, J. and Elwood, J.H. (1992) *Epidemiology and Control of Neural Tube Defects*. Monographs in Epidemiology and Biostatistics. Oxford University Press, Oxford, pp. 442–444.

FIVNAT (1995) Pregnancies and births resulting from *in vitro* fertilization: French national registry, analysis of data 1986–1990. *Fertil. Steril*., **64**, 746–756.

Ghazi, H.A., Spielberger, C. Källén, B. (1991) Delivery outcome after infertility—a registry study. *Fertil. Steril*. , **55**, 726–732.

Greenland, S. and Ackerman, D.L. (1995) Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil. Steril*., **64**, 936–941.

Harris, J., Källén, B. and Robert, E. (1995) Descriptive epidemiology of alimentary tract atresia. *Teratology*, **52**, 15–29.

Källén, B. (1987) Search for teratogenic risks with the aid of malformation registries. *Teratology*, **35**, 47–52.

Källén, B., Castilla, E.E., Kringelbach, M. *et al*. (1991) Parental fertility and infant hypospadias: an international case-control study. *Teratology*, **44**, 629–634.

Källén, B.A.J., Martínez-Frías, M.L., Castilla, E.E. *et al*. (1992) Hormone therapy during pregnancy and isolated. hypospadias: an international case-control study. *Int. J. Risk Safety Med*., **3**, 183–198.

Källén, B., Cocchi, G., Knudsen, L.B.K. *et al*. (1994) International study of sex ratio and twinning of neural tube defects. *Teratology*, **50**, 322–331.

Lancaster, P.A.L. (1987) Congenital malformations after in-vitro fertilization. *Lancet*, **18**, 1392–1393.

Lancaster, P.A.L. (1989) High incidence of selected congenital malformations after assisted conception. *Teratology*, **40**, 288 (Abstract).

Lancaster, P.A.L., Hurst, T. and Shafir, E. (2000) Congenital malformations and other pregnancy outcome after microinsemination. *Reprod. Toxicol*., **14**, 74 (Abstract).

Long, S., Robert, E., Laumon, B. *et al*. (1992) Épidemiologie des fentes labiales et palatines dans la région Rhone-Alps/Auvergne/Jura. A propos de 903 cas enregistrés enter 1978 and 1987. *Pédiatrie*, **47**, 133–140.

Martínez-Frías, M.L and Frías, J.L. (1999) VACTERL as primary, polytopic developmental field defects. *Am. J. Med. Genet*., **83**, 13–16.

Morin, N.C., Wirth, F.H., Johnson, D.H. *et al*. (1989) Congenital malformations and psychosocial development in children conceived by *in vitro* fertilization. *J. Pediatr*., **115**, 222–227.

MRC Working Party on Children Conceived by In Vitro Fertilization (1990) Births in Great Britain resulting from assisted conception, 1978–1987. *Br. Med. J*., **300**, 1229–1233.

Rizk, B., Doyle, P., Tan, S.L. *et al*. (1991) Perinatal outcome and congenital malformations in in-vitro fertilization babies from the Bourn-Hallam group. *Hum. Reprod*., **6**, 1529–1564.

Sills, E.S., Moomjy, M., Zaninovic, N. *et al*. (2000) Human zona pellucida micromanipulation and monozygotic twinning frequency after IVF. *Hum. Reprod*., **15**, 890–895.

Silver, R.I., Rodriguez, R., Chang, T.S. *et al*. (1999) *In vitro* fertilization is associated with an increased risk for hypospadias. *J. Urol*., **161**, 1954–1957.

Sweet, R.A., Schrott, H.G., Kirland, R. *et al*. (1974) Study of the incidence of hypospadias in Rochester, Minnesota 1940–1970, and a case-control comparison of possible etiological factors. *Mayo Clin. Proc*., **49**, 52–58.

van Loon, K., Besseghir, K. and Eshkol, A. (1992) Neural tube defects after infertility treatment: a review. *Fertil. Steril*., **58**, 875–884.

Wennerholm, U.-B., Bergh, C., Hamberger, L. *et al*. (2000) Incidence of congenital malformations in children born after ICSI. *Hum. Reprod*., **15**, 944–948.

Westergaard, H.B., Johansen, A.M.T., Erb, K. *et al*. (1999) Danish National In-Vitro Fertilization Registry 1994 and 1995: a controlled study of births, malformations and cytogenetic findings. *Hum. Reprod*., **14**, 1896–1902.

*Received on September 22, 2000; accepted on December 7, 2000*