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Maternal and child outcome after in vitro fertilization – a review of 25 years of population-based data from Sweden

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Abstract

Objective. To summarize data on deliveries after in vitro fertilization (IVF) performed in Sweden up to 2006. *Design.* Cohort study of women and children, conceived after IVF, with comparisons of deliveries after IVF before and after 1 April 2001. *Setting.* Study based on Swedish health registers. *Population.* Births registered in the Swedish Medical Birth Register with information on IVF from all IVF clinics in Sweden. *Methods.* Results from the second study period are summarized, and outcomes between the two periods are compared. Long-term follow-up is based on data from both periods. *Main outcome measures.* Maternal and perinatal outcomes, long-term sequels. *Results.* Some maternal pregnancy complications decreased in rate, notably pre-eclampsia and premature rupture of membranes. The rate of multiple births and preterm births decreased dramatically, with a better neonatal outcome, including reduced neonatal mortality. No difference in outcome existed between IVF and intracytoplasmic sperm injection or between the use of fresh and cryopreserved embryos, but children born after blastocyst transfer had a slightly higher risk for preterm birth and congenital malformations than children born after cleavage stage transfer. An increased risk for cerebral palsy, possibly for attention deficit and hyperactivity disorder, for impaired visual acuity and for childhood cancer was noted, but these outcomes were rare also after IVF. An increased risk for asthma was demonstrated. No effect on maternal cancer risk was seen. *Conclusion.* A marked decrease in multiple births was the main reason for better pregnancy and neonatal outcome and may also have a beneficial effect on long-term results, notably cerebral palsy.

Abbreviations CI, confidence interval; ICD, international classification of diseases; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OR, odds ratio; RR, risk ratio; SGA, small for gestational age

Introduction

Even though most pregnancies after in vitro fertilization (IVF) have a normal outcome, an increased risk for a number of obstetric and neonatal complications exists, such as preterm delivery and congenital malformations. These appear to depend only slightly on the IVF technique used, but seem mainly to relate to the subfertility status of the parents and notably the mother. One exception is the high rate of multiple births, which was due to the transfer back of two or more embryos. During the past 25 years, some important changes in IVF technology have occurred. In 1992, intracytoplasmatic sperm injection (ICSI) was introduced, which opened up the treatment of male infertility. Other new techniques were freezing of embryos followed by transfer of thawed embryos, increase of culture time with transfer of blastocyst stages, and a trend towards single embryo transfer. During the period, changes in the selection of couples

for IVF may also have occurred because of the increasing access to IVF facilities, which permits treatment of less severe subfertility cases.

In order to evaluate possible changes with time of IVF, there should ideally be access to national data comprising both a large number of IVF pregnancies and an adequate amount of background material for comparison. The presence of national health registers in Sweden makes it possible to perform such analyses and to compare changes over time in delivery outcome and also to conduct long-term follow-up of women who delivered after IVF and their children. In 2005, a series of articles was published on outcome after IVF during the years 1982–2001 (1). A new set of data was collected for IVF up to and including 2006, and articles on specific problems have been published or are in press (2–10). Here we summarize results from the second study period, compare outcomes between the two periods and describe long-term follow-up, based on data from both periods.

Material and methods

Methodological issues in studies of delivery outcome after IVF were extensively discussed by Nygren et al. (1), to which the reader is referred. Pregnancies after IVF which ended with a delivery were reported from all IVF clinics in Sweden, and further information was obtained by linkage with national health registers as specified below. In principle, data collection was made in the same way during the study periods, but more detailed IVF data were obtained for the second period (Table 1). It was then possible to analyze some new features, such as the effect of blastocyst transfer and vanishing twins.

The first study was based on embryo transfers from 1982 to 31 March 2001 and therefore deliveries up to and including 2001. The second study was based on embryo transfers from 1 April 2001 to the end of 2006 and therefore including some deliveries in 2007. The first study analyzed data from 13 261 women who had IVF and gave birth to 16 280 infants. The second study analyzed data from 14 126 women who gave birth to 15 570 infants. The numbers were thus similar for the two periods.

Table 1. Available information on IVF pregnancies, obtained from the IVF clinics.

	Years of embryo transfer	
Variable	1982–2001	2002–2006
Maternal identification	Yes	Yes
Date of embryo transfer	Year, month	Date
IVF clinic	Yes	Yes
IVF method	Yes	Yes
Blastocyst transfer	No	Yes
Number of transferred embryos	No	Yes
Number of sacs at early ultrasound	No	Yes
Date of early ultrasound	No	Yes

Delivery outcome was studied using the Swedish Medical Birth Register (11), which contains medical data on the pregnancy, delivery and pediatric examination of the newborn. Information on indication for IVF was not available. Supplemental information on congenital malformations was obtained from the Birth Defects Register (previously Register of Congenital Malformations) and the Patient Register on hospitalized children (12). Long-term follow-up was carried out using the Swedish Cancer Register (13), the Patient Register (14) and the Prescribed Drug Register (15). Small for gestational age (SGA) as a measure of intrauterine growth retardation was based on sex- and parity-specific standard graphs derived from the Medical Birth Register (16).

Analyses were performed using the Mantel–Haenszel technique. Risk estimates were in most cases made as odds ratios (ORs) with 95% confidence intervals (95% CI) according to Miettinen's method. Two ORs were compared based on the Mantel–Haenszel variances. When the expected number of outcome was below 10, risk ratios as observed over expected numbers were used instead, with 95% CI from Poisson distributions.

A special study was made of the risk for asthma in children born after IVF compared with other children. Asthma was identified by five or more prescriptions for anti-asthmatic drugs after the age of two years, based on data in the Swedish Prescribed Drug Register (15) from 1 July 2005 up to and including April 2010. Adjustment was made for the following maternal characteristics: year of delivery, maternal age, parity, smoking in early pregnancy and body mass index. Children whose mothers were born abroad or with either parent of non-Swedish citizenship were excluded.

The study was performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was required.

Results

The percentage of ICSI among all IVF increased considerably over time and is now around 50%. The use of cryopreserved embryos also increased to about 10%, and the proportion of single embryo transfers is at present about 70%.

The median age for women having their first child after IVF decreased from 34 to 32 years, while among all women who gave birth it increased from 25 to 28–29 years. The length of the reported involuntary childlessness decreased slightly. Maternal smoking decreased markedly in both groups.

Pregnancy complications

In our previous study (17), we verified that a number of maternal complications during pregnancy occurred at a higher rate than expected after IVF in comparison with the general

Table 2. Some pregnancy complications after IVF.

Pregnancy complication	First period		Second period	
	Odds ratio	95% CI	Odds ratio	95% CI
Pre-eclampsia	1.63	1.53–1.74	1.31	1.22–1.40
Placental abruption	2.17	1.74–2.72	1.82	1.53–2.17
Placenta previa	3.65	3.15–4.23	4.18	3.64–4.81
Premature rupture of membranes	2.54	2.34–2.76	1.63	1.49–1.79
Cesarean section	2.04	1.97–2.12	1.43	1.37–1.48

Note: Odds ratio with 95% confidence intervals (95% CI) was estimated after adjustment for year of birth, maternal age, parity and smoking in early pregnancy. Estimates for the first (17) and second study periods are compared.

population, namely pre-eclampsia, placental abruption, placenta previa and premature rupture of membranes. There was also an increased rate of cesarean sections. For some of these outcomes, a decline with time was found (2). Table 2 compares the ORs for each condition between the two periods; for all conditions except placenta previa, the OR was lower during the second than during the first period. For placental abruption, the decline may be random (z=1.21, p=0.19).

There was a sharp decline in multiple births after IVF during the years 2002–2006 (2). In 2002, the rate had gone down to 21%, from a maximum of over 30% in 1991. It continued to decrease, and reached 6% (95% CI 5.1–6.9%) in 2006. During these years, there were only 11 triplet deliveries after IVF.

The decline in the rate of multiple births was a result of the increasing rate of single embryo transfer. Among embryo transfers made in 2002, single embryo transfer represented 25%, in 2003 54%, in 2004 70%, in 2005 74% and in 2006–2007 75%. In only six instances, three embryos had been transferred (2002–2003).

Among 195 pregnancies, two sacs were identified by ultrasound in early pregnancy but only one infant was born; the phenomenon called 'vanishing twin'. They represent 16.5% of the 1 183 pregnancies where two sacs were identified. An unpublished analysis of these cases showed no deviations from other singletons with respect to preterm birth, low birthweight, intrauterine growth retardation or congenital malformations.

Among all twins born in 2001–2007 after IVF, there were 728 pairs with the same sex of both twins and 692 pairs with different sex of the twins. An estimate based on Weinberg's differential rule (18) suggests that 36 twin pairs (95% CI 25–50) were monozygotic; the expected number from the population was 61, adjusted for year of birth and maternal age, risk ratio = 0.60, 95% CI 0.42–0.82. There were thus significantly fewer than expected monozygotic twin pairs, which contrasted with the excess noted in the previous analysis of the years 1982–2001; an adjusted OR of 3.0 (95% CI 1.4–3.5) based on an estimated number of monozygotic twins of 148.

The decline in twinning will directly affect rates of preterm birth, low birthweight and intrauterine growth retardation (SGA), which all declined sharply (2). After embryo transfer during 2002–2006, the average percentage of preterm births (<37 weeks) was 14.5% against the population average of 6.2%. It declined from 23.2% in the 2002 cohort to 10.9% in the 2006 cohort. The average percentage of low-birthweight infants (<2500g) was 11.7, declining from 18.7 to 8.4%, and the population average was 4.3%. The average percentage of SGA infants was 5.1%, declining from 7.3% to a minimum (in 2005) of 3.7%. The population average was 2.3%.

In one study, we compared the outcome among unlike-sexed and therefore dizygotic twins after IVF with that of such twins in the population (3), using the total IVF material from 1982 to 2007. We found evidence for a worse neonatal outcome in the former group, with a significantly higher rate of very preterm births (<32 weeks) and of neonatal jaundice.

Neonatal characteristics

Among singleton births, changes in rates of preterm birth, low birthweight or SGA were less marked than among all IVF infants. The crude rates had gone down during the whole observation period (2), but there was no further certain decline during 2002–2007. The average preterm rate after IVF was 7.5%, against the population rate of 5.1%; the average low-birthweight rate was 5.3%, against the population rate of 3.1%; and the average SGA rate was 3.3%, against the population rate of 2.1%. For all outcomes, the risks were thus about 50% increased compared with the population. This was to a large extent due to maternal characteristics. If adjustment was made for year of birth, maternal age, parity, smoking, body mass index and number of previous miscarriages, the odds ratio for preterm birth was 1.32 (95% CI 1.22–1.47), for low birthweight 1.34 (95% CI 1.23–1.47), and for SGA 1.16 (95% CI 1.03–1.27). If adjustment was also made for known period of unwanted childlessness as a proxy for subfertility, all odds ratios were close to 1.0; preterm birth 1.01 (95% CI 0.90–1.12), low birthweight 0.98 (95% CI 0.86–1.11), and SGA 0.89 (95% CI 0.77–1.03).

Table 3. Odds ratios for neonatal conditions in all infants and in singletons, comparing infants born after IVF with other infants, for the time period 2001–2006.

	All infants		Singletons	
Neonatal condition	Odds ratio	95% CI	Odds ratio	95% CI
Apgar <7 at five minutes	1.27	1.31–1.44	1.04	0.89–1.22
Cerebral bleeding	1.66	1.19–2.33	1.11	0.70–1.77
Neonatal convulsions	1.08	0.74–1.58	1.04	0.68–1.57
Respiratory diagnoses	1.63	1.52–1.77	1.19	1.08–1.31
Mechanical ventilation	2.68	2.03–3.54	1.64	1.10–2.45
Continuous positive airway pressure	2.20	1.90–2.53	1.37	1.11–1.68
Sepsis/pneumonia	1.20	1.01–1.43	1.08	0.89–1.32

Note: Odds ratios were adjusted for year of birth, maternal age, parity, smoking in early pregnancy, body mass index and number of previous miscarriages.

Over the total observation time, a decline could be observed in the rate of cerebral bleeding, convulsions, respiratory diagnoses, use of continuous positive airway pressure or mechanical ventilation and of sepsis/pneumonia (2). To a large extent, this was due to the declining rate of multiple births, and changes among singletons were hardly noticeable.

For infants born after IVF during the second study period, the odds ratios for the various neonatal conditions are shown in Table 3. For all variables except neonatal convulsions, an increased odds ratio was seen when all infants were studied. When the analysis was restricted to singletons, all ORs decreased and only those related to respiratory diagnoses, mechanical ventilation and continuous positive airway pressure remained significant.

There was a weak decline in stillbirth rates during the observation period (2). For the second study period, the OR for stillbirth (after adjustment for year of birth, maternal age, parity, smoking, body mass index and previous miscarriages) was 0.94 (95% CI 0.73–1.20), similar to the adjusted OR for the first period of 1.06 (95% CI 0.85–1.33).

The total risk for early neonatal death declined markedly during the total observation period (2), while the risk for singletons remained relatively unchanged. For the second period, the adjusted OR was 2.22 (95% CI 1.89–3.10) for all infants and 1.79 (95% CI 1.17–2.75) for singletons.

A small risk increase for any congenital malformation was seen after IVF. For the second period, the OR was 1.23 (95% CI 1.14–1.32), and for the first period 1.42 (95% CI 1.32–1.52), but follow-up times differed. There was only a relatively weak decline in the congenital malformation rate during the observation period (2). Some malformations showed a specifically high risk in the first period. For some of them, a risk increase of the same magnitude remained during the second period: any or major cardiovascular defect and limb reduction defects. For others, a risk increase remained, but the risk estimate was significantly lower for the second period than for the first: neural tube defects, cardiac septum defects and esophageal atresia. For a third group of malformations, a risk was seen during the first but not during the second period: orofacial clefts, small bowel atresia, anal atresia and hypospadias (7).

During the second period, the use of International Classification of Diseases, 10th Edition (ICD-10) made it possible to study cases coded as syndromes (ICD Q87) and compare their occurrence after IVF with that in the population. The risk for a syndrome defined in this way was doubled, but based on only 14 cases. In the total material, seven children were identified with syndromes which at least sometimes are due to imprinting errors: Prader–Willi (n=4), Silver–Russell (n=2) and Beckwith–Wiedemann (n=1) (7).

Long-term follow-up

In a previous study (19), we showed that children born after IVF required more hospital care than other children, at least up to the age of eight years. Excess use was found for conditions associated with central nervous system damage, including cerebral palsy, congenital malformations, infections, asthma and accidents. In order to study long-term effects on some specific conditions, we conducted new studies on the following five different outcomes: cerebral palsy (4), attention deficit hyperactivity disorder (5), poor visual acuity (10), asthma and cancer (6). Table 4 summarizes data from the three published studies and adds data on asthma.

A follow-up study of the occurrence of maternal cancer after IVF treatment and delivery compared with other women who had given birth showed an increased risk for most cancer types before the IVF, but a lower risk for breast and cervix cancer (mainly cancer in situ) and a normal rate of most other cancers after IVF (9). The only exception was an increased risk for ovarian cancer, but this was seen already before IVF was performed.

Differences in outcome according to IVF method used

Very few differences were found between outcomes after different types of IVF techniques and notably between standard

Table 4. Odds ratios at long-term follow-up of children conceived after IVF.

Outcome	Reference	Number	Odds ratios	95% CI
Cerebral palsy	4	138	1.96	1.66–2.31
Attention deficit hyperactivity disorder	5	212	1.18	1.03–1.36
Poor visual acuity	10	25	1.55	1.04–2.32
Asthma	Present study	1388	1.28	1.21–1.35
Cancer	6	53	1.42	1.09–1.87

IVF and ICSI. We could not verify the postulated difference in congenital malformation rates after cryopreserved ICSI compared with fresh ICSI or cryopreserved standard IVF (7). In contrast, we found some evidence for a higher malformation rate and possibly also a higher rate of preterm birth after blastocyst transfer than after early cleavage transfer (8).

Discussion

It is important to monitor effects of medical interventions. This is usually done with some kind of epidemiological approach. In most instances, no specific effect is expected, but a number of short-term and long-term outcomes are studied in order to identify deviations which could be the result of the intervention. Related to IVF, most concern has been directed to the offspring, but maternal complications and long-term effects of the hormonal treatments, usually given before IVF, have also caused concern. As many outcomes are studied, the problem with multiple testing is important. Findings in one epidemiological study are seldom conclusive, even in the presence of statistical significance, but have to be repeated in separate studies or by continued observation.

Our studies of the outcome after IVF comprise data for 25 years (embryo transfers made from 1982 to 2006). We have divided the material into two periods of different lengths but with approximately the same number of cases. This gives an opportunity for comparisons and studies of change over time. There can be many explanations for a difference in risk for a specific outcome between the periods. One is that the risk has genuinely changed, but one should consider the possibility that the estimated ORs could be randomly high or low. Straightforward statistical tests may not help because of the multiple testing situation. One can use pregnancy complications as an example. A number of pregnancy complications were studied during the first period, and some were statistically significantly increased among women who have had IVF. They may genuinely have been increased or they may have randomly high as a consequence of multiple testing. When these outcomes were studied again during the second period, and a lower OR was found, this may have been due to a decline in the risk or due to a more adequate estimate of a true and unchanged lower risk. Most of these outcomes have shown a decreasing occurrence in the total population, but by using ORs, the IVF pregnancies were compared with non-IVF pregnancies and therefore such background trends were eliminated.

The majority of outcomes studied have shown a similar pattern, with a decline in risk, such as pre-eclampsia, premature rupture of membranes, cesarean section, preterm birth, low birthweight, SGA, early neonatal death and some congenital malformations. Some have remained with an unchanged risk increase, such as placenta previa and some congenital malformations.

There was, however, a clear-cut and easily understandable decrease in the multiple birth rate as a consequence of the agreement to reduce the number of transferred embryos. A lower rate of multiple births could easily explain the large decline in many neonatal outcomes. The idea that a reduction of the number of multiple births would be beneficial has been challenged (20,21). One argument has been that IVF twins had a better outcome than ordinary twins. This statement was, to a large extent, based on comparisons between IVF twins (who are mainly dizygotic) with other twins (a large proportion being monozygotic). We compared unlike-sex twin pairs (who are dizygotic) after IVF with such twins conceived spontaneously and found evidence that the former had more neonatal problems than the latter (3). The strong decline of the twinning rate while the neonatal outcome became markedly better supports the opinion that single embryo transfer is beneficial.

Among singleton infants, relatively small changes occurred, and these changes were more difficult to evaluate. If genuine, they could be the result of a change in case mix, for instance women with less pronounced subfertility (decreasing period of unwanted childlessness) problems were included during the second period compared with the first period (2). Indications for IVF were not registered in the present study. Mounting evidence supports the idea that a major cause of the problems lies in parental and notably maternal subfertility, which was illustrated in the present study of preterm birth, low birthweight and SGA, where the risks disappeared after adjustment for years of unwanted childlessness as a proxy for subfertility. Other possibilities were advances in IVF methodology or obstetric treatment of women after IVF. During the observation period, major changes in IVF technology had taken place, most notably by the introduction and spreading of ICSI techniques. Our analyses so far had not identified any major differences between standard

IVF and ICSI with respect to delivery outcome, so that was probably not an explanation for the noted effects. The only possible effect of a technical modification was the indicated increased risks seen after blastocyst transfer (9), but these findings are preliminary and motivate further studies.

The decline in preterm birth rates will affect neonatal morbidity, which is strongly linked to prematurity. Among the neonatal diagnoses studied during the second period, only respiratory problems were increased among singletons. Other neonatal morbidity appeared to be linked to twinning, and a further reduction of multiple births will most likely diminish the total risk further. The risk for early neonatal death remains elevated also among singletons.

Some specific outcomes are worth further comments. Our data for the whole study period and for the two periods separately indicated no signs of an increased risk for intrauterine death in pregnancies after IVF. This is in contrast to the recent study from Denmark (22), where a marked increase in stillbirth risk was claimed. We cannot explain the discrepancy between the two studies, but it seems unlikely that the IVF technique by itself increases the risk for stillbirth.

Monozygotic twinning has repeatedly been described to occur at an increased rate after IVF (23–27), and this was found in data from the first study period (28). In the data from the second study period, no indications of an increased monozygotic twinning rate were found. There has been some discussion on the cause of monozygosity after IVF, and zona pellucida manipulation has been suggested (24), but in other studies this could not be verified (such as 25,27). The decline in monozygosity rate in our material is unexplained. It is of some interest that it has occurred in parallel with the decline in the risk for certain congenital malformations which are thought to be linked to the origin of monozygotic twinning, such as spina bifida, esophageal, small gut and anal atresia (29). In a recent study (30), a specific increase after IVF was described in a group of malformations called 'blastogenesis birth defects', which contains most of the above-mentioned conditions and includes monozygotic twins. Whatever the cause of monozygosity after IVF may be, it may have declined in strength at the same time as the rate of dizygotic twinning declined.

Many of the neonatal morbidities found after IVF increased the risk for early neonatal death, but also for late sequelae. One would therefore expect long-term effects on the development of children born after IVF. This was also seen. An increased risk of cerebral palsy exists, but was strongly linked to multiple births. In our analysis (4), we found some evidence that the risk for cerebral palsy declined when the rate of multiple births went down, but it is still too early to draw firm conclusions. A moderate increase in the risk of attention deficit hyperactivity disorder was noted (5), but this condition is difficult to study epidemiologically, and an important component in its etiology is genetic. Twinning seemed not to increase the attention deficit hyperactivity disorder risk and, if the risk is present at all, it may remain basically unchanged. Poor visual acuity was also demonstrated, mainly a result of cerebral damage (10). A much more common effect was that on asthma, where many perinatal factors have been shown to act as risk factors, including cesarean section. Finally, a weak increase in the cancer risk among children after IVF was identified (6). Possible intermediary factors could be preterm birth and neonatal asphyxia. All outcomes except for asthma are of low prevalence, and a moderate risk increase still represents only a low absolute risk for a child born after IVF.

A concern has repeatedly been expressed that the hormone treatments associated with IVF could increase the risk for maternal cancer. We found no evidence for such an effect (9). It is true that the risk for ovarian cancer was higher after IVF than among the control women, but even before the IVF, an increased risk for ovarian cancer was seen. This indicates an association between ovarian pathology, leading both to infertility and the need for IVF, and to an increased risk for ovarian cancer. The hormonal treatments taking place at IVF did not seem to increase cancer risk, at least not in premenopausal women. The lower risks for breast and cervical cancers are difficult to explain, but may be a result of more intensive screening and therefore identification and treatment of precancerous conditions, or to less use of oral contraceptives.

Conclusions

The 25 year survey of delivery outcome after IVF in Sweden verified the presence of a number of deviations, but also that most of them have declined in rate, mainly as a result of the lower rate of multiple births after the agreement to reduce the number of eggs transferred. Other factors may have contributed, such as changes in patient mix or IVF methodology. It is yet unclear whether there will also be a positive effect on long-term sequelae. We found little evidence for a difference in outcome between standard IVF and ICSI or between fresh and cryopreserved embryos used for transfer.

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References

1. Nygren K-G, Finnström O, Källén B, Otterblad Olausson P. Population-based Swedish studies after *in vitro* fertilisation. Acta Obstet Gynaecol Scand. 2007;86:774–82.

2. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Trends in delivery and neonatal outcome after *in vitro* fertilisation in Sweden: data for 25 years. Hum Reprod. 2010;25:1026–34.
3. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Selected neonatal outcomes in dizygotic twins after IVF versus non-IVF pregnancies. BJOG. 2010;117:676–82.
4. Källén AJB, Finnström OO, Lindam AP, Nilsson EME, Nygren K-G, Otterblad Olausson PM. Cerebral palsy in children born after in vitro fertilization. Is the risk decreasing? Eur J Paediatr Neurol. 2010;14:526–30.
5. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Is there an increased risk for drug treated ADHD in Swedish children born after in-vitro fertilization? Eur J Paediatr Neurol. Jan 31, 2000 [Epub ahead of print].
6. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Cancer risk in children conceived by in vitro fertilization. Pediatrics. 2010;126:e270–6. Avilable online at: http://www.pediatrics.org/cgi/content/full/126/2/270.
7. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Congenital malformations in infants born after in vitro fertilization in Sweden. Birth Def Res (Part A). 2010;88:137–43.
8. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Blastocyst versus cleavage stage transfer in in vitro fertilization: differences in neonatal outcome? Fertil Steril. 2010;94:1680–3.
9. Källén B, Finnström O, Lindam A, Nilsson E, Nygren K-G, Otterblad Olausson P. Malignancies among women who gave birth after in vitro fertilization. Hum Reprod. 2011;26:2253–8.
10. Tornqvist K, Finnström O, Källén B, Lindam A, Nilsson E, Nygren KJ, et al. Ocular malformations or poor visual acuity in children born after in vitro fertilization in Sweden. Am J Ophthalmol. 2010;150:23–6.
11. National Board of Health and Welfare. Centre for Epidemiology. The Swedish Medical Birth Register – a summary of content and quality. Available online at: http://www.socialstyrelsen.se/Publikationer2003/2003-112-3 (accessed May 12, 2010).
12. National Board of Health and Welfare. Centre for Epidemiology. Registration of congenital malformations in Swedish health registers. Available online at: http://www.socialstyrelsen.se/Publikationer2004/2004-112-1 (accessed May 12, 2010).
13. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register – a sample survey for year 1998. Acta Oncol. 2009;48:27–33.
14. National Board of Health and Welfare. Statistics of diseases and surgical treatments of patients. Available online at: http://www.socialstyrelsen/register/halsodataregister/patientregistret/inenglish (accessed May 12, 2010).
15. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register – opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16:726–35.
16. Källén B. A birth weight for gestational age standard based on data in the Swedish Medical Birth Registry, 1985–1989. Eur J Epidemiol. 1995;11:601–6.
17. Källén B, Finnström O, Nygren K-G, Otterblad Olausson P. In vitro fertilisation in Sweden: obstetric characteristics, maternal morbidity and mortality. BJOG. 2005:112:1529–35.
18. Fellman J, Eriksson AW. Weinberg's differential rule reconsidered. Hum Biol. 2006;78:253–75.
19. Källén B, Finnström O, Nygren K-G, Otterblad Olausson P. In vitro fertilization in Sweden: child morbidity including cancer risk. Fertil Steril. 2005;84:605–10.
20. Gleicher N, Barad D. The relative myth of elective single embryo transfer. Hum Reprod. 2006;21:1337–44.
21. Gleicher N, Barad D. Twin pregnancy, contrary to consensus, is a desirable outcome in infertility. Fertil Steril. 2009;91:2426–31.
22. Wisborg K, Ingerslev HJ, Henriksen TB. IVF and stillbirth: a prospective follow-up study. Hum Reprod. 2010;25:1312–16.
23. Edwards RG, Mettler L, Walters DE. Identical twins and in vitro fertilization. J In Vitro Fert Embryo Transf. 1986;3:114–17.
24. Sills ES, Moomjy M, Zaminovic N, Veel LL, McGee M, Palermo GD, et al. Human zona pellucida micromanipulation and monozygotic twinning frequency after IVF. Hum Reprod. 2000;15:890–5.
25. Schachter M, Raziel A, Friedler S, Strassburger D, Bern O, Ron-El R. Monozygotic twinning after assisted reproductive techniques: a phenomenon independent of micromanipulation. Hum Reprod. 2001;16:1264–9.
26. Alikani M, Cekleniak NA, Walters E, Cohen J. Monozygotic twinning following assisted conception: an analysis of 81 consecutive cases. Hum Reprod. 2003;18:1937–43.
27. Elizur SE, Levron J, Shrim A, Sivan E, Dor J, Shulman A. Monozygotic twinning is not associated with zona pellucida micromanipulation procedures but increases with high-order multiple pregnancies. Fertil Steril. 2004;82:500–1.
28. Källén B, Finnström O, Nygren K-G, Otterblad Olausson P. In vitro fertilization (IVF) in Sweden: infant outcome after different IVF fertilization methods. Fertil Steril. 2005;84:611–17.
29. Ericson A, Källén B. Congenital malformations in infants born after IVF: a population-based study. Hum Reprod. 2001;16:504–9.
30. Halliday JL, Ukoumunne OC, Baker HWG, Breheny S, Jaques AM, Garrett C et al. Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies. Hum Reprod. 2010;25:59–65.