# Childbirth after IVF treatment in Sweden 1982–2001

Socialstyrelsen

The Board classifies its publications into different types of document. This report is a *Research report*. This means that it contains knowledge and analyses based on scientific methods. The authors themselves are responsible for contents and conclusions.

Artikelnr 2006-112-1

Publicerad www.socialstyrelsen.se, maj 2006

# Foreword

One of the principal functions of the Centre for Epidemiology (EpC) at the Swedish National Board of Health and Welfare is, to analyse and report on the national population's state of health. EpC is responsible for several nation wide registers of medical data.

This report presents results from several studies focusing on births after in vitro fertilisation (IVF) in Sweden. The investigation covers IVF procedures in Sweden from 1982 up to and including procedures performed before April, 2001. In all 13,261 women giving birth to 16,280 infants born after IVF were included. Some of the results have been published in a series of original articles.

The study was carried out by Professor Bengt Källén of the Tornblad Institute at the University of Lund and medical expert at the Centre for Epidemiology. Petra Otterblad Olausson, PhD, Head of Unit for Health Registries at the Centre for Epidemiology has also participated. Professor Orvar Finnström, Associate professor KG Nygren and Associate professor Ulla-Britt Wennerholm contributed to the original articles.

Stockholm May, 2006

Professor Måns Rosén, Director
Centre for Epidemiology
Swedish National Board of Health and Welfare

# Content

# Introduction

The present report summarizes the analysis of the outcome after in vitro fertilization (IVF) in Sweden. Previous reports have been published for the period 1982–1995[1] and for the period 1982–1997[2]. Based on these reports and an update for 1998–2001, a number of scientific papers have been published[3–8]. The number of IVF pregnancies has increased considerably and the proportion of them which have been made using intracytoplasmic injection (ICSI) has increased markedly. This method is now used in nearly half of all IVF procedures. Various modifications have been introduced, notably the use of frozen embryos and also the use of epididymal or testicular sperms for ICSI and other modifications of the IVF technology have been made. This is the main reason for a continued follow-up of IVF pregnancies.

## Literature review

A very large number of studies have been published world-wide on the outcome of pregnancies after IVF procedures and a number of relatively recent reviews are available[9–12]. Findings are relatively consistent for singleton births after IVF: a doubling of the mortality, a doubling of the risk for preterm birth (<37 weeks), a 70–80 per cent increase in the risk for low birth weight (<2500g), and a 50 per cent increased risk for small-for-gestational age (SGA). An increase in risk for congenital malformations of 30–40 per cent has been reported[9–12].

The high rate of multiple births after IVF is well known. Studies comparing twins born after IVF with naturally conceived twins usually find no major differences but in a review and meta-analysis[13], an increased risk for preterm birth after IVF was noticed.

Many of the original articles are based on small samples of IVF pregnancies from single IVF centres and the power to detect deviations in rare outcomes is low. A number of large scale studies are available. The largest data come from US[14,15] based on a large register of pregnancies after artificial reproductive techniques (ART) compared with national data. Thus, 62 551 infants singleton infants born after ART during the years 1996–2000 were studied[14]. Other large studies come from the the early MRC Working Party on Children Conceived by In Vitro Fertilizations[16], the Finnish Medical Birth Registry[17], the French FIVNAT study[18], and an early study based on Swedish data[1]. Studies of outcome among twin pregnancies after IVF, comparing with naturally conceived twins, were based on Danish IVF and health registers[19].

Many articles compare outcome after standard IVF and intracytoplasmic sperm injection (ICSI) and basically find no major differences.

In many analyses, crude comparisons have been made without consideration to the special parental characteristics related to infertility and treatment with IVF. An important question is if the deviations in pregnancy outcomes,

seen after IVF, is the result of the IVF technique or is due to confounding from parent characteristics. This line of thought was developed in some studies[20].

Literature on specific problems in the outcome will be discussed in association with the findings of the present study.

The present report is based on a study of delivery outcome after IVF procedures in Sweden from 1982 (when the first Swedish baby was born after IVF) up to and including births after IVF procedures performed before April 1, 2001. Some of the results have been published in a series of original articles[3–8].

## Methodological problems

The first problem is to identify women who have had IVF. This can be done in different ways. Sometimes all women treated at one IVF centre have been followed – this allows a high degree of detail on, for instance, IVF techniques used and clinical characteristics of the infertile couple, but the number of cases will often be relatively low. In order to increase numbers, collaboration between many centres can be made using identical protocols, or a central register of treated women can be formed. As always when large registers are built up, one has to expect some loss of cases and also a lower degree of details of the individual cases.

The next problem is to obtain information on the outcome of the pregnancies. This is often done by an individual follow-up, based on medical records, interviews or questionnaires. An alternative is to use central health registers for outcome data. This method will increase the probability that the outcome data will not be biased by the fact that the woman had an IVF. On the other hand, outcome data in central registers are usually not perfect and in order to ascertain malformations, often multiple sources are needed.

The third problem is to get adequate controls to compare with. Such controls are non-IVF births. They may either be selected in a case-control fashion or be taken from registers and then removing known IVF cases. If ascertainment of IVF cases is not complete, some (unidentified) IVF cases will be mixed with the true controls, but if ascertainment of IVF is good, such an admixture will play a very small role. It can be debated whether as controls should be used women with fertility problems who had achieved a pregnancy without IVF, either spontaneously or after other treatments like ovarian stimulation. They will not be perfect controls because they have got pregnant without IVF but will at least to some degree reduce the possible influence of the subfertility status itself on pregnancy outcome.

This is associated with the basic problem of the aim of the study. As pointed out by Mitchell[20], there are two separate issues involved. One is whether the IVF pregnancy increases the risk for an unwanted pregnancy outcome and therefore represents a hazard for the woman and her baby and contributes to the burden of health care in the society. The other question is whether the IVF procedure itself carries a risk or if the fact that the couple needs an IVF can explain anomalies in pregnancy outcome. In order to answer the first question, the adequate control material is made up of any non-IVF pregnancy (spontaneous or achieved by other means than IVF). In order

to answer the second question, either comparison should be made with women who have had infertility problems but achieved a pregnancy without IVF, even though – as pointed out above – these women are not perfect controls. In a register study, adjustment can be made for subfertility, e.g., as years of unwanted childlessness, if such data are available.

The fourth problem is a question of numbers. If relatively common phenomena are studied (e.g., multiple births) even small data sets can give adequate information. If we suppose that 20 per cent of all IVF pregnancies result in the birth of twins, that estimate from a series of 100 IVF births with have a 95% confidence interval of 13–29 per cent, an obvious increase over the background incidence of perhaps 1–2 per cent. With 1,000 IVF births the confidence interval will be 18–23 per cent and with 10,000 IVF births 19–21 per cent.

If a less common condition is studied, e.g., the presence of a major congenital malformation occurring in 3 per cent of the infants, a registered rate of 4 per cent (33% increase) among 100 IVF children will have a 95% confidence interval of 1–10 per cent, among 1000 children 2.9–5.4 per cent, and among 10,000 children 3.6–4.4 per cent – only the latter can thus demonstrate that the rate was actually increased. The problem will not be solved by making a very detailed study of the children with respect to congenital malformations – the number of cases will nevertheless decide the accuracy of the registered rate. It is of course also important that the outcome is registered in an identical way among IVF children and control children – to compare rates obtained by detailed follow up of IVF children with rates in routine registers of congenital malformations is of course neither efficient, nor recommendable.

The same is true for follow up of relatively rare effects on psychological or neurological development. To study in great detail (e.g., using psychological tests or clinical neurological evaluations) 100 IVF children can only reveal a very strong effect. A much higher statistical power is obtained using outcome registers (when available) even though the registration of the outcome may be incomplete. It is, however, necessary that the registration of the outcome is not biased by the fact that an IVF was performed.

## Aim of the study

The aim of this study is to compare delivery outcome after IVF with the outcome among all births. Such outcomes refer both to the children born and to the treated women and refer both to events during pregnancy, at delivery, during the neonatal period, and a follow-up period studying various aspects of morbidity. By identifying the effect of various confounders, including period of unwanted childlessness as a measure of subfertility, we tried to separate effects due to characteristics of the treated women from possible effects of the IVF procedure itself.

# Materials and Methods

## Data collection of women undergoing IVF

In 1994 the Medical Birth Register (MBR)[21] began registering information on treatments for subfertility, including information on IVF. In order to supplement with data from years before 1994, information was requested from all 17 IVF clinics in Sweden on women who had given birth after IVF treatment (or when the outcome of pregnancy was unknown). It later appeared, however, that the register information on IVF (obtained by midwife interviews at the first visit to the antenatal care centre) was grossly inadequate (only about 50 per cent reported) why data collection from IVF clinics was continued also after 1994. It occurred separately for three periods: 1982–1994, 1994–1997, and 1997–2001. Minor changes were made in the data collection method, notably between the first and second collections.

All Swedish IVF clinics were asked by the National Board of Health and Welfare to list all women who had IVF treatments resulting in births or when pregnancy outcome was not known. The identification number of each woman was given (everyone living in Sweden gets a unique identification number which is widely used in society and in all health care), the IVF method, and the date of embryo transfer (ET). The following IVF methods were defined:

Standard IVF: fresh stimulated, fresh unstimulated, cryopreserved (frozen) embryo

ICSI: fresh ejaculated sperm, fresh epididymal sperm, fresh testicular sperm, frozen embryo from ejaculated sperm, other sperm, or unspecified sperm.

In a few instances, other or unspecified IVF methods were stated.

Data collection occurred up to April 1st, 2001. This date was chosen to make sure that all infants conceived during the study period should be born before the end of 2001.

## Register analysis

The files with identification numbers of women who had undergone IVF were linked with the Medical Birth Register (MBR)[21], using the date of embryo transfer to identify the relevant pregnancy. All reported women could not be identified in the MBR. Some had incorrect or incomplete identification numbers, all of which could not be corrected after contact with the reporting clinics. Some were non-Swedish women who gave birth abroad and these were not included in the study. Some births are not registered in the MBR (a few per cent are missing every year) – such missing cases could be identified from the official statistics of Statistics Sweden but were not in-

cluded in the analysis because all comparisons were made using data from the MBR.

The MBR is based on reports from all delivery units in the country and consists of three parts: one related to antenatal care, one to delivery, and one based on information from the paediatric examination of the newborn.

The study group was thus defined as women who had undergone IVF with deliveries that could be identified in the MBR. A total of 13 261 deliveries were identified in this way with 16 280 infants born. The distribution according to IVF method is seen in Table 1.

This means that pregnancies ending in a spontaneous or induced abortion were not included in the study. For stillbirths, the Swedish definition of 28 completed weeks was applied.

In order to get further information on infants and women, linkage was performed with further central health registers. The Register of Congenital Malformation (RCM)[22] supplied further information concerning possible malformations in the infants born. This register which is a surveillance register is built from special reports from delivery units on relatively severe malformations. An infant can have a malformation diagnosis in this register but not in MBR (and vice versa). The diagnostic accuracy is larger in RCM than in MBR – the former is based on verbatim descriptions, the latter on ICD codes. Foetuses aborted after foetal diagnoses are reported to RCM but registration of identification numbers are not allowed why this material could not be analyzed from the point of view of IVF.

Further information on congenital malformations was obtained from the Hospital Discharge Register (HDR)[22] by linkage of the infant identification numbers in MBR to the HDR. Linkage was performed up to and including 2002.

HDR[23] was used for further purposes. One was to supplement neonatal diagnoses in MBR with such diagnoses from HDR. The reason for this is that some neonatal diagnoses had not been reported from the neonatal wards to the delivery units (which report to MBR) and could in this way be supplemented. Another reason was that using hospitalization information, severe morbidity of the children could be followed up to the end of 2002. The third reason was to study maternal morbidity during pregnancy and the year after delivery – for this study, maternal identification numbers were used to identify maternal hospitalizations.

***Table 1:*** *Number of women undergoing IVF and number of infants born by these women according to IVF method.*

| Method | Women | Infants |
|---|---|---|
| Standard IVF, all | 9 060 | 11 283 |
| Fresh stimulated | 8 067 | 10 116 |
| Fresh unstimulated | 103 | 112 |
| Frozen | 890 | 1 055 |
| ICSI, all | 4 155 | 4 955 |
| Fresh ejaculated sperm | 3 549 | 4 248 |
| Fresh epididymal sperm | 109 | 146 |
| Fresh testicular sperm | 126 | 151 |
| Frozen ejaculated sperm | 305 | 343 |
| Frozen other sperm | 28 | 33 |
| Frozen sperm, unspecified | 38 | 43 |
| Other or unspecified | 46 | 64 |
| Total | 13 261 | 16 280 |

Both children and mothers were studied using the Swedish Cancer Register[24]. Children were followed from birth up to the end of 2002; mothers were searched for cancer diagnoses both before and after the IVF delivery. In the study of maternal cancer, each woman entered only once even if she had more than one IVF pregnancy.

Survival of children and mothers was studied using the Swedish Cause of Death Register.

In studies of all outcomes, comparisons were made with corresponding outcomes among all deliveries in Sweden 1982–2001, registered in the MBR (n=2 039 943).

## Statistical methods

Descriptions of outcomes can be made as percentages with their errors. In order to evaluate these against the expected outcome in the absence of IVF, comparisons with non-IVF pregnancies can be made. Comparisons of, for instance, cancer rates, can be made as crude odds ratios which will be close to risk ratios because both exposure (IVF) and outcome (e.g., cancer) are rare events. The necessity to evaluate whether possible differences are the result of the IVF process or rather caused by other factors which are associated both with IVF and with outcome (confounders), various adjustments have to be made. It is possible to use different statistical methods to reach that goal. The most common method, logistic regression, is built on modelling – in standard cases only as linear regressions – which sometimes is very complex. To take an example: maternal age and parity co-vary in the effect of infant birth weight, but the form of regression of maternal age differs according to parity. Another method, which we used, is the Mantel–Haenszel technique. This is based on chi-square analyses and the greatest draw-back is if information is lost because "control" data are lacking in cer-

tain strata (e.g., maternal age <20, parity 3, smoking ≥10 cigarettes per day). As in our study, IVF pregnancies are compared with non-IVF-pregnancies, it is rather unlikely to find a stratum with IVF pregnancies but without non-IVF pregnancies, why this draw-back is of little consequence.

We studied the characteristics of women who have undergone IVF in order to identify deviations in their characteristics which could affect the outcomes studied and which therefore had to be taken into consideration.

# Results

## Use of IVF in Sweden 1982—2001

The first infant conceived after IVF in Sweden was born in 1982. Figure 1 shows the number of women who gave birth after IVF (and were identified in MBR) up to and including 2001. The graph is divided into deliveries after standard IVF and after ICSI. The very marked increase in the use of ICSI, beginning in 1993, is evident and in the years 2000–2001, nearly as many deliveries occurred after ICSI as after standard IVF. In the total material, ICSI represents 30 per cent of all infants born after IVF.

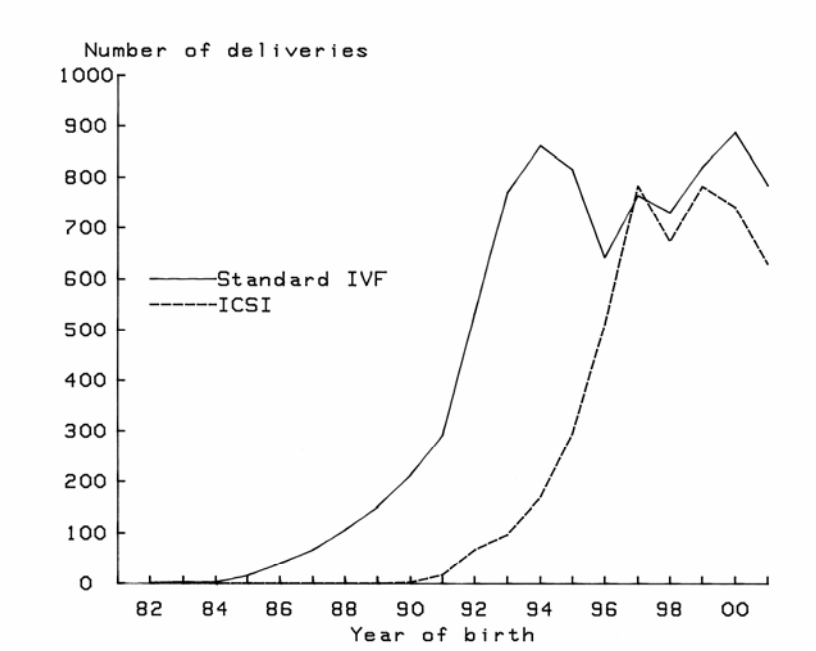


***Figure 1**: Number of deliveries after standard IVF and after ICSI during the years 1982—2001.*

The annual distribution of deliveries divided after the number of infants per birth is shown in Table 2:

***Table 2:*** *Annual distribution of deliveries according to year of birth and number of infants in birth. Rates per 10 000 deliveries are also given.*

| Year | Singletons | Twins | Triplets | Quadruplets | Total | Per 10000 |
|---|---|---|---|---|---|---|
| 1982 | 1 | 0 | 0 | 0 | 1 | 0.1 |
| 1983 | 2 | 1 | 0 | 0 | 3 | 0.3 |
| 1984 | 3 | 0 | 0 | 0 | 3 | 0.3 |
| 1985 | 14 | 1 | 1 | 0 | 16 | 1.7 |
| 1986 | 31 | 7 | 2 | 0 | 40 | 4.0 |
| 1987 | 58 | 9 | 0 | 0 | 67 | 6.5 |
| 1988 | 87 | 15 | 3 | 1 | 106 | 9.6 |
| 1989 | 112 | 32 | 6 | 1 | 151 | 13.3 |
| 1990 | 162 | 43 | 8 | 3 | 216 | 17.8 |
| 1991 | 204 | 90 | 15 | 1 | 310 | 25.4 |
| 1992 | 420 | 148 | 29 | 1 | 598 | 49.4 |
| 1993 | 604 | 231 | 32 | 0 | 867 | 75.2 |
| 1994 | 761 | 256 | 15 | 0 | 1 032 | 94.5 |
| 1995 | 846 | 246 | 16 | 0 | 1 108 | 110.2 |
| 1996 | 872 | 267 | 11 | 0 | 1 150 | 123.3 |
| 1997 | 1 194 | 349 | 5 | 0 | 1 548 | 176.7 |
| 1998 | 1 085 | 311 | 7 | 0 | 1 403 | 166.2 |
| 1999 | 1 209 | 387 | 5 | 0 | 1 601 | 189.1 |
| 2000 | 1 270 | 354 | 5 | 0 | 1 629 | 185.2 |
| 2001 | 1 148 | 261 | 3 | 0 | 1 412 | 158.5 |
| Total | 10 083 | 3 007 | 163 | 7 | 13 261 | |

The maximum percentage of deliveries after IVF is thus 1.9 per cent (in 1999).

## Characteristics of women undergoing IVF

There are 17 IVF clinics in Sweden which have been active during the study period. Nine of them are public and eight private. Among all deliveries, 42 per cent were the results of a treatment in a public clinic. Many of the private clinic treatments were performed after referral from the public health system. There were some restrictions in public health care: women over 38 years usually did not get IVF and if the couple had a previous child together, IVF was not given. No such general restrictions existed in private clinics.

A total of 12 186 women gave birth to the 16 280 identified IVF infants. If a woman had more than one IVF delivery, one was randomly selected. The analysis of the characteristics of women undergoing IVF was restricted to the 12 160 where the IVF method was known. Comparisons were made between women undergoing standard IVF and women undergoing ICSI.

Differences in maternal characteristics may arise in different ways: women with certain characteristics may have an increased risk for infertility (e.g., high age, certain diseases), women with certain characteristics may, when having fertility problems, be differently apt to search medical advice

or to accept the IVF treatment, and women who are infertile and want to have an IVF may change her life style (e.g., drug use, smoking).

A first analysis was made of maternal age, parity, and smoking in early pregnancy (Table 3).

***Table 3:*** *Maternal age, parity and smoking among women giving birth after IVF. Odds ratio (OR) with 95% confidence interval (95%CI).*

| | Standard IVF vs. population | | | ICSI vs. population | | | ICSI vs. standard IVF | |
|---|---|---|---|---|---|---|---|---|
| | N | OR | 95%CI | N | OR | 95%CI | OR | 95%CI |
| **Maternal age** | | | | | | | | |
| —19 | 0 | 0.00 | – | 1 | 0.01 | – | | – |
| 20–24 | 60 | 0.03 | 0.02–0.03 | 83 | 0.09 | 0.07–0.10 | 2.32 | 1.63–3.29 |
| 25–29 | 1 074 | 0.23 | 0.22–0.25 | 829 | 0.44 | 0.40–0.47 | 1.70 | 1.52–1.89 |
| 30–34 | 3 663 | 2.18 | 2.09–2.28 | 1 657 | 1.95 | 1.83–2.07 | 0.95 | 0.88–1.04 |
| 35–39 | 3 158 | 6.49 | 6.24–6.75 | 1 096 | 4.17 | 3.90–4.46 | 0.73 | 0.66–0.79 |
| 40–44 | 375 | 3.34 | 3.03–3.69 | 161 | 3.09 | 2.66–3.60 | 0.85 | 0.49–1.04 |
| 45+ | 2 | 0.47 | – | 1 | 0.48 | – | | – |
| **Parity** | | | | | | | | |
| 1 | 5 481 | 5.09 | 4.88–5.31 | 2 878 | 6.66 | 6.23–7.11 | 1.18 | 1.07–1.31 |
| 2 | 2 217 | 0.63 | 0.60–0.66 | 784 | 0.42 | 0.39–0.46 | 0.90 | 0.81–1.00 |
| 3 | 496 | 0.22 | 0.20–0.24 | 132 | 0.15 | 0.13–0.17 | 0.80 | 0.64–0.99 |
| 4+ | 138 | 0.11 | 0.09–0.12 | 34 | 0.07 | 0.05–0.10 | 0.65 | 0.42–0.97 |
| **Smoking** | | | | | | | | |
| Unknown | 597 | | – | 317 | | – | | – |
| None | 6 750 | 1.00 | reference | 3 255 | 1.00 | reference | 1.00 | reference |
| <10 | 678 | 0.94 | 0.87–1.01 | 186 | 0.73 | 0.63–0.84 | 0.83 | 0.68–1.00 |
| 10+ | 307 | 0.72 | 0.62–0.83 | 70 | 0.60 | 0.48–0.75 | 0.78 | 0.56–1.05 |
| Any | 985 | 0.88 | 0.82–0.94 | 256 | 0.66 | 0.58–0.75 | 0.80 | 0.65–0.94 |

For maternal age and parity, each group is compared with all other groups, for smoking with non-smokers. Each variable adjusted for year of birth and the other two variables.

It can be seen that the maternal age effect differs between standard IVF and ICSI – women who had ICSI were more often below 30 than women with standard IVF. The highest occurrence of IVF was seen in the age class 35–39 years for both types of treatment. As expected, IVF is performed in excess at first parity, more marked after ICSI than after standard IVF. Women who had IVF smoked less than expected and this was more pronounced for women who had ICSI than women who had standard IVF.

The fact that women who had IVF smoked less than other pregnant women are probably the result of an active choice because of the problems to get pregnant. It is interesting that this phenomenon is weaker for women who had standard IVF than for women who had ICSI in spite of the similar couple subfertility status. One possible explanation is that smoking increases the risk for female subfertility.

Maternal education level was obtained by linkage with the Swedish Education Register and refers to educational level in 2002. There is a correlation between maternal education and use of IVF (Table 4) with increasing use of

IVF with education level. There is no significant difference between women who had ICSI and women who had standard IVF.

***Table 4:*** *Education level among women giving birth after IVF. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Standard IVF vs. population | | | ICSI vs. population | | | ICSI vs. standard IVF | |
|---|---|---|---|---|---|---|---|---|
| | N | OR | 95%CI | N | OR | 95%CI | OR | 95%CI |
| 1 | 86 | 0.63 | 0.51–0.78 | 30 | 0.44 | 0.31–0.63 | 0.71 | 0.45–1.12 |
| 2 | 580 | 0.78 | 0.71–0.85 | 229 | 0.63 | 0.55–0.72 | 0.94 | 0.78–1.13 |
| 3 | 3 992 | 1.00 | reference | 1 883 | 1.00 | reference | 1.00 | reference |
| 4 | 462 | 1.17 | 1.05–1.29 | 264 | 1.31 | 1.15–1.39 | 1.05 | 0.88–1.25 |
| 5 | 2 976 | 1.40 | 1.33–1.47 | 1 332 | 1.30 | 1.21–1.39 | 0.96 | 0.87–1.05 |
| 6 | 60 | 1.46 | 1.10–1.93 | 38 | 1.92 | 1.40–2.64 | 1.29 | 0.82–2.02 |

Education level: 1 = compulsory school <9 years, 2 = compulsory school 9 (10) years, 3 =gymnasium education, 4 = post-gymnasium education <2 years, 5 =post-gymnasium education 2 years or more, 6 = graduate studies. Swedish gymnasium is approximately equivalent with upper secondary school in UK and senior high school in the US. Adjustment only for year of birth.

This table shows that both for standard IVF and ICSI, use of the techniques follows maternal education level. Part of this could be due to differences in maternal age distribution between women of different educational levels: high educational levels may postpone their pregnancies longer than low educational levels and with increasing age, the risk for infertility increases and therefore the risk for IVF. Older women may also seek medical help after a shorter period of involuntary childlessness than younger women. Adjustment for maternal age at delivery removed the educational level effect, but if adjustment was instead made for age at the reported beginning of the period of unwanted childlessness, the effect remained. The association is thus complex and difficult to dissect. We therefore did not try to compensate for possible differences in educational level which have, in Sweden, rather small impact on delivery outcome.

Little is known from the literature on the association between maternal educational level and the use of IVF – most likely this differs between different populations.

There was a marked geographical variation in the use of IVF in Sweden as can be seen from Table 5.

***Table 5:*** *Risk to have a delivery after IVF in different Swedish counties. Odds ratio (OR) with 95 % confidence interval (95%CI). Each county is compared with all other counties and adjustment is made for year of birth, maternal age, parity, and smoking habits.*

| | Any IVF | | ICSI vs IVF | |
|---|---|---|---|---|
| **County** | **OR** | **95%CI** | **OR** | **95%CI** |
| Stockholm | 0.70 | 0.67–0.73 | 0.66 | 0.60–0.74 |
| Uppsala | 0.93 | 0.84–1.03 | 0.95 | 0.74–1.21 |
| Södermanland | 1.35 | 1.20–1.51 | 0.97 | 0.75–1.26 |
| Östergötland | 0.81 | 0.73–0.90 | 1.05 | 0.82–1.35 |
| Jönköping | 0.88 | 0.78–0.99 | 1.70 | 1.31–2.20 |
| Kronoberg | 1.27 | 1.11–1.46 | 1.07 | 0.80–1.42 |
| Kalmar | 0.79 | 0.68–0.92 | 1.32 | 0.89–1.94 |
| Gotland | 0.99 | 0.76–1.27 | 0.24 | 0.12–0.49 |
| Blekinge | 0.95 | 0.80–1.13 | 0.76 | 0.52–1.12 |
| Skåne | 1.20 | 1.13–1.26 | 0.96 | 0.85–1.03 |
| Halland | 1.22 | 1.10–1.36 | 1.43 | 1.14–1.80 |
| Västra Götaland | 1.19 | 1.13–1.24 | 1.66 | 1.49–1.85 |
| Skaraborg | 1.62 | 1.41–1.86 | 1.73 | 1.23–2.42 |
| Värmland | 1.35 | 1.21–1.50 | 0.69 | 0.54–0.87 |
| Örebro | 1.26 | 1.13–1.40 | 0.88 | 0.69–1.13 |
| Västmanland | 0.88 | 0.77–1.01 | 0.81 | 0.59–1.12 |
| Kopparberg | 1.59 | 1.44–1.76 | 0.69 | 0.54–0.89 |
| Gävleborg | 1.15 | 1.02–1.29 | 0.96 | 0.72–1.28 |
| Västernorrland | 0.77 | 0.67–0.90 | 1.07 | 0.77–1.47 |
| Jämtland | 0.86 | 0.72–1.03 | 1.12 | 0.75–1.67 |
| Västerbotten | 0.65 | 0.56–0.76 | 0.66 | 0.47–0.92 |
| Norrbotten | 0.93 | 0.82–1.06 | 1.04 | 0.78–1.38 |

There is thus a significant variation between counties in the use of IVF and also a variation in the proportion of the two main types of IVF. The risk of having a delivery after IVF varies from 0.65 (Västerbotten) to 1.62 (Skaraborg) and the risk to have an ICSI versus a standard IVF from 0.24 (Gotland) to 1.73 (Skaraborg). Within Skaraborg county, the risk for standard IVF is itself also increased: 1.36 (95%CI 1.15–1.61).

Even though adjustment had been made for some maternal characteristics, population differences may still explain part of the variation. Another likely explanation is the access to an IVF clinic and the therapeutic traditions of the county health care.

Various further maternal characteristics are described in Table 6. Maternal BMI was recorded only from 1992 onwards and only in about 80 per cent of cases.

***Table 6:*** *Some maternal characteristics among women giving birth after IVF. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| Variable | Standard IVF vs. population | | | ICSI vs. standard IVF | | | ICSI vs. population | |
|---|---|---|---|---|---|---|---|---|
| | N | OR | 95%CI | N | OR | 95%CI | OR | 95%CI |
| **BMI when known (1992–2001)** | | | | | | | | |
| <19.8 | 392 | 0.74 | 0.67–0.82 | 196 | 0.76 | 0.66–0.88 | 1.02 | 0.84–1.25 |
| 19.8–25.9 | 4 290 | 1.00 | reference | 2 077 | 1.00 | reference | 1.00 | Reference |
| 26+ | 1 516 | 1.13 | 1.07–1.20 | 911 | 1.33 | 1.23–1.44 | 1.14 | 1.02–1.27 |
| **Work situation when stated** | | | | | | | | |
| None | 1 221 | 0.67 | 0.62–0.71 | 573 | 0.73 | 0.66–0.82 | 0.94 | 0.86–1.03 |
| Whole day | 5 194 | 1.00 | reference | 2 408 | 1.00 | reference | 1.00 | reference |
| Part day | 1 405 | 0.82 | 0.77–0.87 | 586 | 0.94 | 0.86–1.08 | 0.96 | 0.85–1.09 |
| **Non-Swedish nationality in parents** | | | | | | | | |
| None | 7 523 | 1.00 | reference | 3 427 | 1.00 | reference | 1.00 | reference |
| Any parent | 809 | 0.61 | 0.55–0.64 | 401 | 0.66 | 0.60–0.74 | 0.92 | 0.80–1.06 |
| Mother | 388 | 0.57 | 0.52–0.64 | 183 | 0.62 | 0.53–0.72 | 0.90 | 0.74–1.10 |
| Father | 254 | 0.79 | 0.70–0.90 | 135 | 0.81 | 0.68–0.96 | 0.97 | 0.76–1.23 |
| **Previous miscarriage** | | | | | | | | |
| Both | 167 | 0.46 | 0.39–0.53 | 83 | 0.59 | 0.48–0.73 | 0.90 | 0.67–1.20 |
| None | 6 489 | 1.00 | reference | 3 192 | 1.00 | reference | 1.00 | reference |
| 1 | 1 371 | 1.12 | 1.06–1.18 | 492 | 0.89 | 0.81–0.98 | 0.73 | 0.64–0.82 |
| 2 | 327 | 1.16 | 1.03–1.29 | 114 | 0.97 | 0.80–1.17 | 0.67 | 0.53–0.85 |
| 3+ | 145 | 1.23 | 1.03–1.44 | 30 | 0.61 | 0.43–0.88 | 0.40 | 0.26–0.60 |

Non-Swedish parents had a lower rate of IVF pregnancies than Swedish parents. IVF was more common among women with overweight and less common in lean women compared to women with a normal BMI. For overweight women, the effect was more pronounced for standard IVF than for ICSI. It has been reported[25] that obesity also lowers the pregnancy rate after IVF and results in an increased risk of early pregnancy losses (before week 6). Fewer women than expected did not work or worked only part time in early pregnancy after IVF – there was no difference between standard IVF and ICSI. After adjustment for maternal education, the effect of part time work disappeared, however, but the association between IVF and no work outside home persisted (OR = 0.80, 95%CI 0.71–0.89).

Women who had standard IVF had an increased rate of previous miscarriages but this was not seen for women who had ICSI.

IVF women thus differ from other pregnant women from a number of aspects. These may appear as confounders in the analysis of delivery outcome. In order to investigate the impact of such factors, preterm birth among singletons were studied. An increased risk for preterm birth among singletons is a well known effect of IVF (see below).

The risk for preterm birth among singletons born after IVF compared with other infants, adjusted only for year of birth, was OR = 1.72 (95%CI 1.58–1.91) when the analysis was restricted to women with a known BMI. If adjustment was made also for maternal age, parity, and smoking habits, the

OR decreased to 1.45 (1.30–1.61). If further adjustment was made also for BMI, nationality, and number of previous miscarriages, only a slight further change occurred: OR = 1.43 (95%CI 1.29–1.59).

In the further study, year of birth, maternal age, parity, and smoking habits were regarded as confounders of importance. In some analyses, the number of years of unwanted childlessness (when stated) was added as a proxy for the subfertility status of the couple.

## Maternal drug use in early pregnancy

Table 7 presents an analysis of maternal drug use in early pregnancy as reported at the first antenatal care centre visit (usually week 10–12) for part of the study period when this information was available.

***Table 7:*** *Use of drugs in early pregnancy, July 1 1995–2001, among women giving birth after IVF. Odds ratio (OR) estimates association between IVF treatment and maternal use of drug, adjusted for year of birth, maternal age, parity, and smoking, with 95% confidence intervals (95%CI).*

| | Number of women using specific drug | | | |
|---|---|---|---|---|
| **Drugs used** | **IVF** | **Population** | **OR** | **95%CI** |
| Any drug | 3 457 | 149 424 | 2.81 | 2.68–2.95 |
| **Drugs specifically used at IVF:** | | | | |
| Progesterone | 1 147 | 1 508 | 22.9 | 21.7–24.6 |
| Estrogens | 49 | 131 | 11.4 | 8.85–14.8 |
| ovulation stimulation* | 204 | 1 508 | 7.99 | 7.03–9.08 |
| gonadotrophin releasing drugs* | 73 | 172 | 17.5 | 14.3–21.3 |
| bromocriptine* | 21 | 295 | 3.49 | 2.24–5.43 |
| folic acid | 530 | 6 962 | 4.09 | 3.74–4.48 |
| all drugs except the above listed ones | 2 869 | 143 358 | 2.14 | 2.04–2.25 |
| among them, ATC drugs | 2 226 | 141 095 | 1.43 | 1.36–1.51 |
| **Specific drugs or drug groups:** | | | | |
| *Drugs used for chronic diseases* | | | | |
| Insulin | 43 | 1 657 | 2.07 | 1.52–2.81 |
| antiepileptics | 11 | 1 373 | 0.61 | 0.33–1.13 |
| drugs used at intestinal inflammation | 22 | 966 | 1.57 | 1.02–2.42 |
| antihypertensive drugs | 35 | 1 826 | 1.16 | 0.82–1.63 |
| Thyroid hormone | 125 | 4 962 | 1.75 | 1.46–2.10 |
| antiasthmatics | 249 | 19 463 | 1.39 | 1.22–1.58 |
| systemic corticosteroids | 48 | 2 102 | 1.71 | 1.29–2.28 |
| *Drugs directly related to pregnancy* | | | | |
| multivitamins | 161 | 5 835 | 1.39 | 1.18–1.63 |
| Vitamin B–12 | 29 | 1 208 | 1.36 | 0.94–1.99 |
| E-vitamin | 10 | 76 | 5.36 | 2.76–10.4 |
| calcium | 20 | 548 | 2.15 | 1.37–3.38 |
| iron | 59 | 2 885 | 1.64 | 1.26–2.14 |
| antihistamines for NVP | 270 | 20 874 | 1.28 | 1.13–1.45 |
| metoclopramide | 16 | 879 | 1.71 | 1.02–2.85 |
| *Psychopharmacological drugs* | | | | |
| neuroleptics, sedatives | 31 | 3 504 | 0.67 | 0.47–0.96 |
| bensodiazepines | 6 | 1 007 | 0.42 | 0.18–1.00 |
| antidepressive drugs | 38 | 4 124 | 0.59 | 0.42–0.81 |
| SSRI | 19 | 2 874 | 0.40 | 0.26–0.63 |

| | Number of women using specific drug | | | |
|---|---|---|---|---|
| **Drugs used** | **IVF** | **Population** | **OR** | **95%CI** |
| *Drugs used for infections* | | | | |
| antibiotics | 212 | 18 501 | 1.14 | 0.99–1.31 |
| nitrofurantoin | 52 | 2 058 | 1.93 | 1.46–2.54 |
| peroral decongestive drugs | 28 | 2 107 | 0.96 | 0.65–1.41 |
| local nose preparations | 101 | 5 336 | 1.24 | 1.01–1.52 |
| Cough medicines | 44 | 2 684 | 1.21 | 0.89–1.64 |
| *Analgesics and anti-inflammatory drugs* | | | | |
| NSAID | 67 | 7 726 | 0.58 | 0.45–0.73 |
| opiates | 35 | 2 159 | 1.44 | 1.02–2.02 |
| ketobemidon+spasmolytics | 24 | 67 | 13.7 | 8.29–22.8 |
| mild analgesics | 695 | 41 117 | 1.41 | 1.30–1.53 |
| drugs for migraine | 17 | 1 531 | 0.65 | 0.40–1.05 |
| *Other drugs* | | | | |
| drugs for stomach ulcer | 51 | 4 018 | 0.89 | 0.67–1.18 |
| Antacids | 35 | 2 260 | 1.09 | 0.77–1.54 |
| heparin-related drugs | 38 | 424 | 5.73 | 4.18–7.85 |
| thrombocyte aggregation inhibitors | 52 | 447 | 5.75 | 4.31–7.88 |
| antihistamines for allergy | 109 | 8 345 | 0.97 | 0.80–1.17 |

* These obviously referred to treatment before or in association with the in vitro fertilization procedure.

Note that the table gives number of women using a drug or a group of drugs and as each woman may use many drugs, the sum of the number of women using individual drugs will be larger than the total number of women. NVP = nausea and vomiting in pregnancy, NSAID = non-steroid anti-inflammatory drugs. SSRI = selective serotonin re-uptake inhibitors.

Any drug use was nearly three times more common in women who had IVF than in other women. To some extent this was due to the use of drugs in association with the IVF procedure but also disregarding those, an excess of drug use existed. This referred both to drugs directly related to pregnancy and to some drugs taken for chronic diseases. The excess use of insulin, drugs used at intestinal inflammation, thyroid hormone, and anti-asthmatic drugs may indicate increased risks for subfertility, at least at some of these conditions. Psychopharmacological drugs were used less often among women after IVF than among other women. An increased use of certain other drugs (e.g., nitrofurantoin) could be an effect of the early contact with health care among IVF women – drug use is recorded at the first antenatal care visit.

# Neonatal outcome after IVF

## Multiple births after IVF

Table 2 shows the number of twin, triplet, and quodruplet deliveries different years. Figure 2 plots the percentage of twin deliveries during the observation period (with the first seven years added because of low numbers). There is an initial increase in twinning rate which reaches a maximum in 1991 (29%) and then declines to 18.5 per cent in 2001. This decline resulted in a reduction of the rate of preterm births. In 1991, the odds ratio for preterm birth (after adjustment for maternal age, parity, smoking, and years of involuntary childlessness) was 4.63 (95%CI 3.62–5.92) but in 2001 the cor-

responding OR was 1.33 (95%CI 1.12–1.57). The risk was thus reduced with 72 per cent.

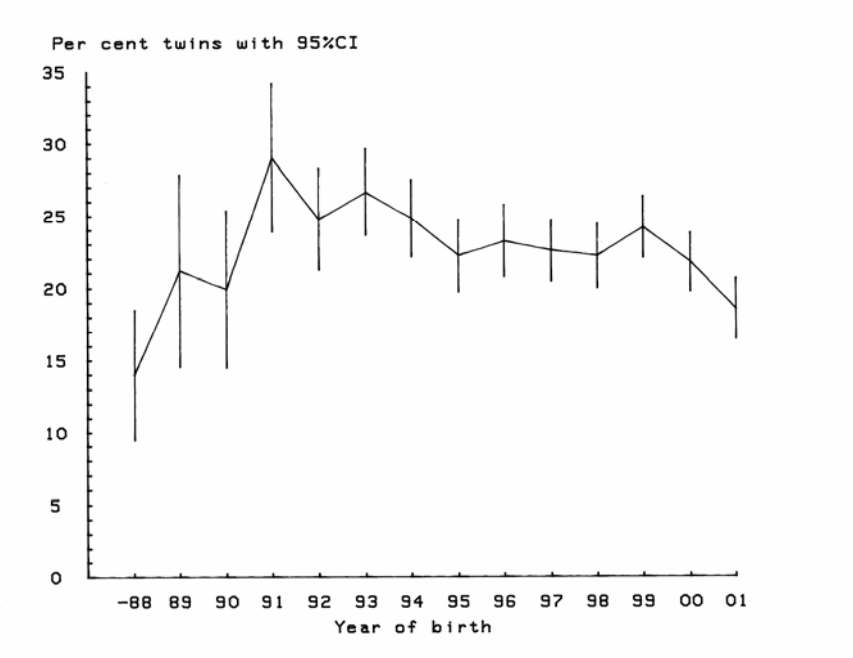


***Figure 2:*** *Percentage of twin deliveries after IVF during the observation period.*

Triplets occurred most frequently during the years 1991–1996 and quadruplets only between 1988 and 1992. The total triplet set rate is 1.2 per cent and only seven quadruplet sets occurred.

Towards the end of the observation period, the rate of multiple births in this data set is below that reported for the year 2000 from European IVF registers with a 24 per cent rate of twins, 2 per cent of triplets, and 0.04 per cent of quadruplets[26]. This is mainly the consequence of an agreement among the Swedish IVF clinics to reduce the number of embryos transferred from three to two. A later recommendation has been made to mainly use one-embryo transfers. Studies from the Nordic countries[27–29] and the Netherlands[30] indicate an adequate pregnancy rate and a very low rate of multiple births after single embryo transfer.

The total number of analyzable twin pairs (when the sexes of both twins were known) is 2676. Among them, 1412 were like-sexed and 1264 unlike-sexed. Using Weinberg´s law, the number of monozygotic twin pairs can be estimated to 2676–2*1264=148. When this number was compared with the similarly calculated rate in the total population, adjusting for year of birth and maternal age, we found an increased risk for monozygotic twinning, OR = 2.99 (95%CI 2.54–3.52). The increased risk for monozygotic twinning after IVF has been described repeatedly[31,32], but the explanation to the phenomenon is uncertain. Zona pellucida manipulation or hatching has been implicated[33,34] but the association is unclear[35]. One study[36] found 81 monozygotic twin pairs among 4305 pregnancies following assisted conception (1.9%) which is a higher rate than that found by us (1.3%). An increased risk for monozygotic twinning has been described after ovarian stimulation also in the absence of IVF[37].

Table 8 presents twinning risks after different IVF methods.

***Table 8.*** *Comparison of different IVF methods. Per cent twin deliveries and odds ratio (OR) for twinning with 95% confidence intervals (95%CI) after adjustment for year of birth and maternal age.*

| IVF method | Per cent twins | OR | 95%CI |
|---|---|---|---|
| Standard fresh IVF | 24.4 | 1.00 | reference |
| Standard frozen IVF | 18.1 | 0.69 | 0.58–0.83 |
| Fresh ICSI | 22.1 | 0.87 | 0.79–0.97 |
| Frozen ICSI | 11.4 | 0.49 | 0.37–0.67 |

Standard fresh IVF thus had the highest twinning rate among the four groups. This could either be the result of the number of embryos transferred or of different efficiency in implantation and survival of implanted embryos. No individual information is available on the number of embryos transferred at each IVF event in the studied population but a register exists at the National Board of Health and Welfare on the IVFs performed during the period 1994–2000 where the number of transferred embryos is given together with the IVF technique for all IVFs performed. Table 9 shows these data.

***Table 9:*** *Comparison of different IVF methods. Per cent of treatments with two or three embryos transferred and odds ratios (OR) with 95% confidence intervals (95%CI) using standard fresh IVF as a reference and with adjustment for year of transfer and IVF clinic.*

| | Two embryos transferred | | | Three embryos transferred | | |
|---|---|---|---|---|---|---|
| IVF method | Per cent | OR | 95%CI | Per cent | OR | 95%CI |
| Standard fresh IVF | 80.1 | 1.0 | reference | 9.2 | 1.0 | reference |
| Standard frozen IVF | 81.3 | 0.96 | 0.89–1.03 | 8.1 | 1.04 | 0.93–1.17 |
| Fresh ICSI | 71.6 | 0.53 | 0.49–0.58 | 11.7 | 0.75 | 0.65–0.88 |
| Frozen ICSI | 71.9 | 0.43 | 0.38–0.48 | 8.5 | 0.52 | 0.43–0.62 |

The lower twinning rate after ICSI than after standard fresh IVF is thus explainable by a lower rate of transfer of two or three embryos. This cannot, however, explain the lower rate of twinning after standard frozen IVF and here the explanation may be a less good survival of the transferred embryos than after standard fresh IVF.

## Infant sex after IVF

The normal sex ratio (number of males/number of females) is 1.06 for singletons and 1.03 for infants born in multiple births. After standard IVF, a significantly high sex ratio was found: 1.13 (1.09–1.17) but for infants born after ICSI the sex ratio was significantly low: 0.94 (0.89–1.00). There was no statistically significant difference in sex ratios among singletons and infants born in multiple births, neither after standard IVF, nor after ICSI. In a previous report[38] in the literature, a low sex ratio was found after ICSI and a

high after standard IVF but none of them differed significantly from the normal sex ratio.

The low sex ratio after ICSI is reasonable as no selection for X or Y carrying sperm is made and a ratio of 1:1 should be expected. The observed ratio of 0.94 is only marginally below that ratio. The high sex ratio after standard IVF is more difficult to explain. It has been postulated that during normal pregnancy, a very early excess death of female conceptuses would explain the normal male excess[39]. This process could be enforced in the IVF environment – but then one would expect the same phenomenon after ICSI which is thus not seen.

## Preterm birth, low birth weight, and growth retardation among singleton IVF births

Information on gestational duration exists for 10 062 singleton births after IVF (99.7%), on birth weight for 10 004 (99.1%), and on small-for-dateness for 9 983 infants (99.0%).

Preterm birth (<37 completed weeks) was found in 9.6 per cent of the IVF singletons compared with 5.3 per cent among all singleton infants born and very preterm birth (<32 weeks) in 1.9 per cent against 0.7 per cent. Low birth weight (<2500g) was found in 7.3 per cent compared with 3.5 per cent among all singleton infants, and very low birth weight (<1500g) in 1.8 per cent compared with 0.6 per cent. Small for gestational age (SGA, gestational length specific birth weight <2 standard deviations below normal weight) was found in 5.1 per cent against 2.8 per cent in all singletons infants born.

Table 10 shows the effect of various adjustments on the odds ratio for preterm birth and gives data for three different periods.

Thus most of the increased risk for preterm birth among singletons is due to confounding of maternal age, parity, subfertility, and smoking.

There is a marked reduction of the odds ratio with time. The trend is statistically significant (p=0.01). During the last period, the increased risk is no longer statistically significant.

***Table 10**: Odds ratio (OR) with 95% confidence interval (95%CI) for preterm birth (<37 weeks) among singletons born after IVF compared with all other singleton infants after various adjustments and for three time periods.*

| Adjustments or period | OR | 95%CI |
|---|---|---|
| Only year of birth | 1.98 | 1.85–2.11 |
| Year of birth, maternal age, parity | 1.58 | 1.48–1.69 |
| Year of birth, maternal age, parity, known period of childlessness | 1.21 | 1.10–1.34 |
| Year of birth, maternal age, parity, known period of childlessness, smoking | 1.23 | 1.11–1.36 |
| 1982–1990 | 1.89 | 1.41–2.54 |
| 1991–1995 | 1.24 | 1.06–1.45 |
| 1996–2001 | 1.13 | 0.98–1.30 |

Table 11 compares the odds ratios for short gestational length, low birth weight, and SGA.

***Table 11:*** *Odds ratio (OR) with 95% confidence interval (95%CI) for very preterm, preterm, very low birth weight, low birth weight, and SGA with only adjustment for year of birth and with adjustment for year of birth, maternal age, parity, smoking, and years of known unwanted childlessness (total adjustment).*

| | | Adjustment | | | |
|---|---|---|---|---|---|
| | | Year of birth | | Total | |
| **Outcome** | | **OR** | **95%CI** | **OR** | **95%CI** |
| Gestational duration | <32 weeks | 2.68 | 2.33–3.08 | 1.22 | 0.98–1.51 |
| | <37 weeks | 1.98 | 1.85–2.11 | 1.23 | 1.11–1.36 |
| Birth weight | <1500g | 3.06 | 2.66–3.53 | 1.24 | 0.98–1.56 |
| | <2500g | 2.31 | 2.15–2.49 | 1.21 | 1.08–1.35 |
| Small for gestational age | | 2.09 | 1.91–2.28 | 1.09 | 0.96–1.24 |

The effect on gestational duration was smaller than that on birth weight when adjustment was only made for year of birth – this agrees with an increased risk for SGA. When "total" adjustment was made, the effects on gestational duration and birth weight were similar and no residual effect on SGA was seen.

The crude odds ratios found are in the same order of magnitude as those described repeatedly in the literature[9–11]. They are, however, much reduced when the various confounders are taken into consideration and notably the confounding by subfertility status. The remaining, moderately high odds ratios may at least to some extent be explained by residual confounding.

In Table 12, different IVF methods are compared using fresh standard IVF as a reference.

***Table 12:*** *Comparison between different IVF methods of odds ratio (OR) for preterm birth (<37 weeks) and low birth weight (<2500g) among singletons with 95% confidence intervals (95%CI) after adjustment for year of birth, maternal age, parity, smoking, and years of known unwanted childlessness.*

| | Preterm birth | | Low birth weight | |
|---|---|---|---|---|
| **IVF method** | **OR** | **95%CI** | **OR** | **95%CI** |
| Standard fresh IVF | 1.00 | reference | 1.00 | reference |
| Standard frozen IVF | 0.69 | 0.50–0.95 | 0.49 | 0.02–0.75 |
| Fresh ICSI | 0.96 | 0.80–1.15 | 0.97 | 0.79–1.19 |
| Frozen ICSI | 0.97 | 0.55–1.38 | 0.99 | 0.59–1.66 |

Outcome after standard frozen IVF appears better than after fresh standard IVF but no difference is seen between ICSI and IVF.

## Low Apgar score after IVF

Information on Apgar score at 5 minutes existed for 15 965 infants born after IVF. An Apgar score <7 at 5 minutes occurred in 2.6 per cent of the IVF infants while in the population that figure was 1.3 per cent. This was to a large extent due to multiple births. Among singleton births, the rate was 1.8 per cent among IVF infants and 1.3 per cent in the population. The OR, only adjusted for year of birth, was 1.29 (95%CI 1.11–1.50) for singleton infants but when adjustment was made also for maternal age, parity, smoking, and years of involuntary childlessness, the OR decreased to 0.77 (95%CI 0.62–0.97). For multiple births, the corresponding OR was 0.85 (95%CI 0.67–1.07). The low Apgar score is apparently due to maternal characteristics. When singleton infants born after different IVF methods were compared using standard fresh IVF as a reference, the OR was significantly low for standard frozen IVF (OR = 0.26, 95%CI 0.09–0.78) but close to 1.0 for fresh ICSI (OR=1.05, 95%CI 0.73–1.50) and for frozen ICSI (OR=0.98, 95%CI 0.42–2.31).

The low odds ratio for low Apgar score after frozen standard IVF is thus compatible with the lower risk for preterm birth.

## Stillbirth rate and infant mortality after IVF

Among the infants born after IVF, 195 died before one year of age: 1.2 per cent. Among them, 81 were stillborn. Table 13 shows the odds ratios for death after various adjustments.

***Table 13:*** *Deaths among infants conceived after IVF compared with all infants born. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Stillbirths | | Neonatal deaths | | Stillbirth +infant death | |
|---|---|---|---|---|---|---|
| **Adjustments made** | **OR** | **95%CI** | **OR** | **95%CI** | **OR** | **95%CI** |
| Year of birth | 1.37 | 1.10–1.71 | 2.92 | 2.36–3.61 | 1.72 | 1.48–1.99 |
| Year of birth, maternal age, parity, and smoking | 1.06 | 0.85–1.33 | 2.71 | 2.18–3.37 | 1.49 | 1.28–1.73 |
| Year of birth, maternal age, parity, smoking, childlessness | 1.04 | 0.75–1.45 | 1.38 | 0.96–2.00 | 1.13 | 0.90–1.43 |

Death rate was thus increased but this was mainly explainable by characteristics of the IVF mothers. Only for neonatal deaths did an increased risk remain which was close to statistically significant. The total death risk is slightly lower than that usually stated in the literature[9–11].

There was no statistically significant difference in death risk according to IVF method used but the OR for standard frozen IVF was non-significantly low (OR = 0.57, 95%CI 0.28–1.16) compared with standard fresh IVF.

The relatively small material of infants born after standard frozen IVF thus showed slight advantages over infants born after standard fresh IVF:

less risk for preterm birth, for low birth weight, low Apgar score, and possibly death. A possible explanation is a selection of embryos used for transfer.

## Neonatal diagnoses after IVF

A number of neonatal diagnoses were studied: cerebral haemorrhage, neonatal convulsions, and respiratory problems including use of mechanical ventilation or CPAP, neonatal sepsis. Table 14 shows the results.

For all conditions, increased risks were seen. When the material was divided into singletons and multiple births no marked differences were seen between IVF infants and other infants within each group with the exception of respiratory problems and use of CPAP which was increased in both. For the other conditions, the crude increased risk was thus a consequence of the high rate of multiple births among IVF infants.

Table 15 compares the risk of these diagnoses among infants born after standard IVF and after ICSI.

***Table 14:*** *Neonatal complications among infants born after IVF. Odds ratio (OR) with 95% confidence intervals (95%CI) adjusted for year of birth, maternal age, parity, and smoking habits.*

| | IVF infants | | Population | | |
|---|---|---|---|---|---|
| **Diagnosis** | **No.** | **o/oo** | **o/oo** | **OR** | **95%CI** |
| Cerebral haemorrhage | 40 | 2.5 | 1.12 | 3.35 | 2.48–4.53 |
| Singletons | | | | 0.79 | 0.35–1.79 |
| Multiples | | | | 1.31 | 0.88–1.95 |
| Neonatal convulsions | 45 | 2.8 | 1.56 | 1.39 | 1.02–1.89 |
| Singeltons | | | | 1.36 | 0.93–1.97 |
| Multiples | | | | 0.81 | 0.44–1.48 |
| Respiratory problems | 1 388 | 8.5 | 2.99 | 2.51 | 2.37–2.65 |
| Singletons | | | | 1.26 | 1.15–1.43 |
| Multiples | | | | 1.29 | 1.19–1.41 |
| Mechanical ventilation | 77 | 0.5 | 0.17 | 2.72 | 2.18–3.40 |
| Singletons | | | | 1.42 | 0.95–2.12 |
| Multiples | | | | 0.97 | 0.71–1.32 |
| Use of CPAP | 317 | 1.9 | 0.40 | 3.38 | 3.03–3.76 |
| Singletons | | | | 1.49 | 1.19–1.85 |
| Multiples | | | | 1.17 | 1.00–1.36 |
| Neonatal sepsis* | 144 | 1.3 | 0.40 | 1.48 | 1.23–1.78 |
| Singletons | | | | 1.01 | 0.77–1.31 |
| Multiples | | | | 1.02 | 0.76–1.38 |

*Identified exclusively for the period 1996–2001 when ICD-10 was used.

***Table 15.*** *Neonatal complications among infants born after IVF according to IVF method. Odds ratio (OR) with 95% confidence intervals (95%CI) adjusted for year of birth, maternal age, parity, and smoking habits. z compares the two ORs with p-values.*

| | Standard IVF | | ICSI | | | |
|---|---|---|---|---|---|---|
| **Diagnosis** | **OR** | **95%CI** | **OR** | **95%CI** | **Z** | **p-value** |
| Cerebral haemorrhage | 3.23 | 2.32–4.50 | 4.08 | 2.04–8.18 | 0.59 | 0.34 |
| Neonatal convulsions | 1.27 | 0.87–1.86 | 1.57 | 0.93–2.66 | 0.64 | 0.33 |
| Respiratory problems | 2.68 | 2.12–2.86 | 2.03 | 1.81–2.27 | 4.2 | <0.001 |
| Mechanical ventilation | 2.85 | 2.22–3.67 | 2.27 | 1.44–3.59 | 0.9 | 0.28 |
| Use of CPAP | 4.35 | 3.85–4.91 | 3.02 | 2.43–3.76 | 2.8 | 0.01 |
| Neonatal sepsis | 1.55 | 1.22–1.97 | 1.35 | 1.05–1.79 | 2.9 | 0.01 |

Both for respiratory problems, use of CPAP, and neonatal sepsis, the risk thus appears larger after standard IVF than after ICSI. This comparison is, however, confounded by differences in multiple births. Therefore, the odds ratio for ICSI vs standard IVF was studied after adjustment for number of infants in the birth (Table 16).

***Table 16.*** *Effect of IVF method and of twinning on neonatal diagnoses. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Effect of IVF method | | Effect of twinning | |
|---|---|---|---|---|
| **Diagnosis** | **OR[a]** | **95%CI** | **OR[b]** | **95%CI** |
| Cerebral haemorrhage | 1.53 | 0.79–2.95 | 2.36 | 1.18–4.71 |
| Neonatal convulsions | 1.24 | 0.61–2.14 | 0.77 | 0.29–2.06 |
| Respiratory problems | 0.88 | 0.76–1.02 | 3.52 | 2.98–4.15 |
| Mechanical ventilator | 0.93 | 0.46–1.89 | 2.80 | 1.32–5.92 |
| CPAP | 0.80 | 0.58–1.09 | 5.39 | 3.81–7.63 |
| Neonatal sepsis | 0.99 | 0.68–1.44 | 2.15 | 1.42–3.27 |

[a] Adjusted for year of birth, maternal age, parity, smoking, and number of infants in birth.

[b] Adjusted for year of birth, maternal age, parity, smoking, and IVF method.

The only condition when the OR approached but did not reach statistical significance was for respiratory problems and possibly the use of CPAP. If, instead, the effect of twinning independent on IVF method was studied, high odds ratios were obtained with the exception for neonatal convulsions.

In conclusion, definitive increases in the risk for various neonatal diagnoses are seen among infants born after IVF but they seem basically independent of IVF method used and seem to a large extent be due to the high rate of multiple births even though respiratory problems and perhaps also neonatal convulsions occurred in excess also in singletons. Some reports in the literature have compared neonatal diagnoses after different types of IVF procedures, but little is published on comparisons with infants born after spontaneous conception.

## Congenital malformations after IVF

The presence of congenital malformations among infants born after IVF was studied at two different levels.

The analysis was first restricted to conditions registered in the Medical Birth Register. Those diagnoses refer to the newborn period and the registration of malformations is known to be incomplete but there is little reason to believe that the recording of a congenital malformation is influenced by the fact that the mother had been treated with IVF.

In the Medical Birth Register, some malformations are regarded as less significant and to be rather unevenly registered: preauricular appendix, patent ductus at preterm birth, single umbilical artery, undescended testicle, congenital hip (sub)luxation, and minor skin malformations (mainly nevus). The analysis was also made with exclusion of these conditions, leaving what has been called "weeded" malformations. There were 811 IVF infants with any congenital malformation in the Medical Birth Register (5.0%) and the population rate was 4.0 per cent. Among the malformed IVF infants, 535 had a "weeded" malformation (66%), among all malformed infants 59 per cent had a "weeded" malformation. The crude odds ratio for any congenital malformation is 1.26 and for a "weeded" malformation 1.46.

Table 17 summarizes this analysis and shows the results of various adjustments.

***Table 17:*** *Risk for a congenital malformation as registered in the Medical Birth Register among infants born after IVF compared with other infants after various adjustments. Odds ratio (OR) with 95% confidence interval (95%CI).*

| | All malformed | | "Weeded" | |
|---|---|---|---|---|
| **Adjustments** | **OR** | **95%CI** | **OR** | **95%CI** |
| Year of birth | 1.42 | 1.32–1.52 | 1.52 | 1.29–1.66 |
| Year of birth, maternal age, and parity | 1.33 | 1.24–1.43 | 1.44 | 1.32–1.57 |
| Singletons | 1.30 | 1.20–1.41 | 1.39 | 1.26–1.53 |
| Multiple births | 1.02 | 0.91–1.15 | 0.96 | 0.76–1.21 |
| Year of birth, material age, parity, years of known childlessness | 1.05 | 0.95–1.16 | 1.12 | 0.99–1.28 |
| Year of birth, maternal age, parity, years of known childlessness, smoking | 1.04 | 0.93–1.16 | 1.12 | 0.98–1.27 |
| Singletons | 1.07 | 0.95–1.21 | 1.11 | 0.95–1.29 |
| Multiples | 0.86 | 0.70–1.05 | 0.94 | 0.73–1.19 |

There is thus a nearly 50 per cent increase in the risk of a congenital malformation in infants born after IVF but this risk is explained by the maternal factors age, parity, smoking, and known years of unwanted childlessness where the latter factor is the strongest one. The increase is seen for singleton births but not for multiple births. The explanation to the latter finding is probably that the majority of twin pairs after IVF are dizygotic but in the population only a little more than half are dizygotic and a congenital malformation risk associated with twinning is mainly coupled to monozygosity. The crude risk increase is of the same order of magnitude as that described in the literature[11–12].

A more complete ascertainment of congenital malformations can be made with the use of two other national health registers: the Register of Congenital Malformations and the Hospital Discharge Register. In this way, the number of IVF infants identified with a congenital malformation increased from 811 to 1 344 (8.3%). Among them, 531 had rather minor conditions and thus 813 (5%) had a severe malformation. The total risk of infants in the population with malformations identified this way is 4.6 per cent. It is possible to compare various IVF methods with respect to the risk for congenital malformations using this more complete material (Table 18). In this table, a number of minor and clinically little significant conditions have been excluded.

For many IVF methods only few cases occurred and the confidence intervals are huge. The only method which appeared to carry a reduced risk for congenital malformations is fresh un-stimulated standard IVF but this is based on only 112 infants among which 3 had a congenital malformation. There is no sign of a different risk after ICSI compared with standard IVF. This finding is in agreement with the literature[11–12].

***Table 18:*** *Infants with a congenital malformation identified according to IVF method used. Odds ratios (OR) with 95% confidence intervals (95%CI) comparing each specific IVF method with fresh stimulated standard IVF as reference. Adjustment for year of birth, maternal age, and number of infants in birth.*

| | Number of infants | | | | | |
|---|---|---|---|---|---|---|
| **Method** | **Malformed** | **Total** | **Per cent** | **95%CI** | **OR** | **95%CI** |
| **Standard IVF** | | | | | | |
| Fresh stimulated | 829 | 10 116 | 8.2 | 7.7–8.7 | 1.00 | reference |
| Fresh un-stimulated | 3 | 112 | 2.7 | 0.6–7.6 | 0.30 | 0.10–0.88 |
| Frozen | 81 | 1 055 | 7.7 | 6.1–9.5 | 0.94 | 0.74–1.21 |
| **ICSI** | | | | | | |
| Ejaculated sperm | 371 | 4 248 | 8.7 | 7.9–9.6 | 1.08 | 0.94–1.25 |
| Epididymal sperm | 10 | 135 | 7.4 | 3.6–13.2 | 0.95 | 0.49–1.87 |
| Testicular sperm | 11 | 147 | 7.5 | 6.8–13.0 | 0.93 | 0.49–1.75 |
| Frozen ejaculated sperm | 28 | 343 | 8.2 | 5.5–11.6 | 0.99 | 0.66–1.49 |
| Frozen other sperm | 3 | 33 | 9.1 | 1.9–24.3 | 0.98 | 0.38–4.11 |
| Frozen unspecified | 5 | 43 | 9.1 | 3.9–25.1 | 1.30 | 0.50–3.36 |
| Other or unspecified | 3 | 48 | 6.3 | 1.3–17.2 | 0.76 | 0.24–2.40 |
| **All ICSI vs all standard IVF** | | | | | | |
| Standard IVF | 913 | 1 283 | 8.1 | 7.6–8.6 | 1.00 | reference |
| ICSI | 428 | 4 949 | 8.6 | 7.9–9.5 | 1.00 | 0.74–1.36 |

For some specific malformations or groups of malformations, prevalence figures were obtained also for the total population with inclusion of all three sources of cases. This made it possible to specifically calculate the risk for these conditions among infants born after IVF (Table 19).

Increased risks were seen for some conditions: neural tube defects (anencephaly, spina bifida), orofacial clefts, cardiac defects, all types of atresia (choanal, oesophageal, small gut, anal), and hypospadias. It should be noted

that these risk increases refer to the over-all increase of 50 per cent for all types of congenital malformations.

***Table 19:*** *Observed (Obs.) and expected (Exp.) numbers of infants with specific groups of malformations (excluding 56 infants with chromosome anomalies). Expected numbers were calculated with adjustment for year of birth. Odds ratios (OR) with 95% confidence intervals (95%CI) are given. When the expected numbers are low, observed/expected ratios (RR) are given with exact 95%CI, based on Poisson distributions.*

| | Number of infants | | | | |
|---|---|---|---|---|---|
| | Among IVF | | Population | | |
| **Group of malformations** | **Obs.** | **Exp.** | **Obs.** | **OR/RR** | **95%CI** |
| Anencephaly (RR) | 5 | 0.6 | 78 | 7.6 | 2.5–7.7 |
| Spina bifida | 20 | 4.1 | 586 | 5.1 | 3.4–7.8 |
| Encephalocele (RR) | 0 | 0.7 | 70 | 0.0 | 0.0–5.3 |
| Any neural tube defect | 25 | 7.4 | 734 | 4.8 | 3.3–6.9 |
| Hydrocephaly without NTD | 13 | 7.5 | 954 | 1.7 | 1.0–3.0 |
| Orofacial clefts | 68 | 28.5 | 3 623 | 2.4 | 1.9–3.1 |
| Cardiovascular defects (except PDA and SUA) | 262 | 51.7 | 19 249 | 1.7 | 1.5–2.0 |
| Major cardiovascular defects | 50 | 24.2 | 3 888 | 2.1 | 1.6–2.8 |
| VSD or ASD without major cardiovascular defect | 156 | 61.1 | 6 338 | 2.6 | 2.2–3.1 |
| Choanal atresia (RR) | 7 | 1.5 | 159 | 4.6 | 1.9–9.5 |
| Oesophageal atresia | 18 | 4.7 | 452 | 4.0 | 2.6–6.3 |
| Small gut atresia | 19 | 3.3 | 315 | 6.4 | 4.2–9.6 |
| Anal atresia | 23 | 5.2 | 533 | 4.7 | 3.2–6.9 |
| Abdominal wall defects[1] | 8 | 4.5 | 431 | 1.8 | 0.9–3.6 |
| Craniostenosis | 16 | 10.8 | 1 019 | 1.5 | 0.9–2.5 |
| Limb reduction defects | 14 | 9.7 | 1 022 | 1.5 | 0.9–2.5 |
| Hypospadias | 75 | 44.5 | 4 216 | 1.7 | 1.4–2.1 |

[1] Only 1987–2001. Before 1987, ICD codes could not with certainty identify an abdominal wall defect.

ASD = atrium septum defect, NTD = neural tube defect, PDA = patent ductus arteriosus, SUA = single umbilical artery, VSD = ventricular septum defect.

The risk for specific congenital malformations after standard IVF and after ICSI was not significantly different except for hypospadias (Table 20). Adjustment was only made for year of birth because other putative confounders are similar for standard IVF och ICSI.

Eighteen children born after standard IVF (n=10) or ICSI (n=8) had multiple malformations (at least three major malformations) or defined syndromes. Among the latter there was one Goldenhaar syndrome, one Saethre-Chotzen syndrome, one Prader-Willi syndrome, one Russel-Silver syndrome, one Larsen syndrome, and one Zellweger syndrome. The latter child was born after standard IVF, the other five after ICSI. Among the infants with multiple malformations, three had oesophageal atresia, six anal atresia, and one of them had both conditions.

***Table 20:*** *Comparison of the risk for specific congenital malformations among infants born after standard IVF or ICSI. Odds ratios (OR) compare the risk after ICSI with that after standard IVF. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| Group of malformations | IVF | ICSI | OR | 95%CI |
|---|---|---|---|---|
| Neural tube defect (NTD) | 17 | 7 | 1.29 | 0.43–3.38 |
| Hydrocephaly excluding NTD | 8 | 5 | 2.64 | 0.54–2.64 |
| Orofacial cleft | 50 | 18 | 0.83 | 0.45–1.53 |
| Cardiovascular defect (exept PDA and SUA) | 180 | 81 | 0.78 | 0.58–1.04 |
| Choanal atresia | 3 | 4 | 1.40 | 0.42–11.5 |
| Alimentary tract atresia | 34 | 22 | 1.26 | 0.67–2.36 |
| Abdominal wall defect | 3 | 5 | 2.53 | 0.52–12.2 |
| Craniostenosis | 10 | 6 | 1.40 | 0.42–4.64 |
| Limb reduction defect | 11 | 3 | 0.48 | 0.13–1.84 |
| Hypospadias | 46 | 29 | 1.94 | 1.09–3.44 |
| Chromosome anomaly | 40 | 17 | 0.72 | 0.38–1.36 |
| Malformed infants without chromosome anomaly | 873 | 411 | 0.98 | 0.84–1.11 |

In the literature there is little evidence for a risk increase (over the basic risk increase for any congenital malformation) for specific congenital malformations. The most discussed conditions refer to imprinting diseases[41–42], notably Beckwith-Wiedemann and Angelman syndromes. In one study[43], 4 among 16 children born after IVF and with Angelman syndrome showed imprinting defects against 4 per cent of all children with Angelman syndrome. The authors also found an increased risk after hormonal stimulation alone or more than 2 years of infertility. Another study[44] demonstrated genomic imprinting defects in disruptive spermatogenesis. In a Danish study[45], no infants with an imprinting disease was identified among 6 052 IVF infants. In the present study, no case of Beckwith-Wiedemann or Angelman syndromes was found, but one infant with Prader-Willi and one with Russel-Silver syndrome which have both been associated with imprinting errors.

Neural tube defects (anencephaly and spina bifida) showed a clear-cut excess. Part of this excess could be due to a reluctance to abort a diagnosed twin with anencepahly but this can hardly explain the increased risk of spina bifida. Neural tube defects have been associated with low folic acid levels, but women undergoing IVF more often used folic acid than other women (see above). A specific association between IVF and neural tube defects may exist.

Marginally increased risks were seen for orofacial clefts and for cardiac defects. Among the latter, the highest risk was for infants with ventricular or atrial septum defects, not associated with major cardiac defects, but was also seen for infants with major cardiac defects.

There is a marked increased risk for various types of alimentary tract atresia (oesophageal, small gut, and anal atresia) and also of choanal atresia. Some of the multi-malformed infants had two or more of these conditions

and show some resemblances to the VATER association, thought to arise very early in development. It has been suggested that the over-risk for these malformations which also occur in excess with monozygotic twinning may be due to a factor, common both for the malformations and for the monozygotic twinning.

An increased risk for hypospadias has been reported before[46] but the specific association with ICSI is not generally recognized. It was found in two previous studies of IVF infants born in Sweden[47,48] but not in two other studies[38, 49]. The possible specific association between ICSI and hypospadias has been tentatively explained by a genetic link between paternal subfertility and infant hypospadias. The varying results in different studies could at least to some extent be due to different use of ICSI.

In the literature, a number of cases of gross malformations have been described in infants or foetuses conceived after IVF[50–54], e.g., limb-body-wall defects and bladder or cloacal exstrophy. Such cases were not found in our study – if they occurred they may have been identified at prenatal diagnosis and aborted. One case of conjoined twinning was found in the Swedish material[48].

## Long-time morbidity and mortality among children born after IVF

Long-time morbidity among children was studied as the risk to be hospitalized compared with that of all children born. The over-all risk for hospitalization, only adjusted for year of birth, was 1.97 (95%CI 1.90–2.03). After adjustment also for maternal age, parity, and smoking, the risk increased to 2.09 (95%CI 2.02–2.16) and after further adjustment for years of involumtary childlessness the risk decreased to 1.73 (95%CI 1.61–1.81). The risk was elevated but lower when the analysis was restricted to term infants: 1.44 (95%CI 1.36–1.52).

In a rather small study[55], no difference in health care utilization was found when 95 IVF children and 79 naturally conceived children were followed. A large study from Finland[56] found a higher incidence of various diseases when IVF singletons were compared with other singletons but not when IVF twins were compared with other twins. The latter finding was also supported in a large Danish study[57] where a higher hospitalization rate was found for IVF twins than for IVF singletons but no difference between IVF twins and other twins.

When the risk increase for different child ages was studied, it remained elevated up to the age of 8 (Figure 3).

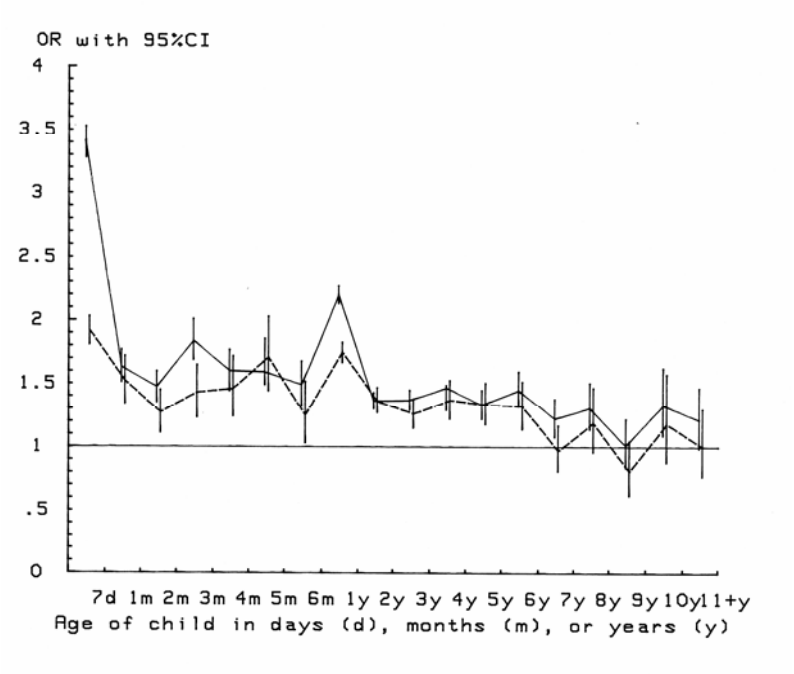


***Figure 3:*** *Risk for hospitalization at different ages among children conceived by IVF compared with other children. Broken line shows risk after adjustment for years of unwanted childlessness.*

A number of specific diagnoses were studied (Table 21).

***Table 21:*** *Discharge diagnoses among children born after IVF (any type) compared with all children born. Adjustments only for year of birth. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Number of IVF children | | OR (95%CI) | |
|---|---|---|---|---|
| **Diagnosis** | **All** | **Term** | **All** | **Term** |
| *CNS effects* | | | | |
| Mental retardation | 17 | 6 | 1.23 (0.76–1.98) | 0.68 (0.31–1.50) |
| Cerebral palsy | 37 | 9 | 1.89 (1.37–2.60) | 0.88 (0.46–1.70) |
| Epilepsy | 70 | 29 | 1.52 (1.30–1.92) | 0.92 (0.64–1.33) |
| Behavioural problems | 37 | 17 | 1.57 (1.14–2.17) | 1.10 (0.68–1.17) |
| – any of these | 118 | 45 | 1.49 (1.24–1.78) | 0.87 (0.65–1.17) |
| Convulsions | 401 | 277 | 1.36 (1.20–1.53) | 1.28 (1.14–1.44) |
| *Congenital malformations* | | | | |
| *Infections* | 599 | 336 | 1.94 (1.79–2.11) | 1.60 (1.43–1.78) |
| Sepsis | 43 | 27 | 1.51 (1.12–2.05) | 1.41 (0.97–2.06) |
| Pneumonia | 449 | 270 | 1.21 (1.10–1.33) | 1.04 (0.92–1.17) |
| Appendicitis | 64 | 45 | 1.30 (1.02–1.67) | 1.31 (0.97–1.67) |
| Upper respiratory tract | 891 | 581 | 1.25 (1.17–1.34) | 1.15 (1.06–1.25) |
| *Asthma/bronchitis* | 816 | 445 | 1.27 (1.18–1.37) | 0.97 (0.88–1.07) |
| *Accidents* | 2 234 | 1 345 | 1.56 (1.49–1.64) | 1.29 (1.21–1.36) |

A number of conditions were more common among IVF children than among other children, including an increased risk for various signs of CNS damage. This seemed to be mainly an effect of preterm births. Neonatal convulsions also occurred in excess and this remained among term infants.

Most follow-up studies have been limited in size and found no or little difference in the mental or neurological development of IVF children compared with naturally conceived children. A Swedish study of part of the present material[58] found an increased risk for habilitation among IVF children, notably for cerebral palsy and also when the analysis was restricted to singletons. There was little difference between IVF twins and spontaneous twins which agrees with a large study from Denmark[59] while another large Danish study[45] found an 1.8 times increase in the risk for cerebral palsy among singleton IVF children against other singletons. The latter studies were based on a psychiatric register and a hospital discharge register. Another Swedish study, also register-based and based on part of the present material, described an increased use of hospitalization among IVF children and an increased risk for cerebral palsy and epilepsy, but not of mental retardation[60].

The findings in the large register studies are reasonable as it is well known that preterm birth (and therefore also twinning) is a risk factor for cerebral palsy and, as described above, are typical results of IVF. The absence of an effect in small studies is probably a question of low power to evaluate low frequency events.

The increased risks seen for various infections may also to a large extent be due to preterm births but some effects remained significant or near significant among term infants. A contributing factor may be increased parent anxiety when the child was conceived after IVF. The increased risk for asthma disappeared when only term infants were studied and the increased risk for accidents was reduced in term children. There may exist a proness for accidents at minor brain damage[61].

## Cancer among children born after IVF

Only 29 children born after IVF had been reported to the Swedish Cancer Register. From the general population, 21.4 were expected, adjusted for year of birth. The odds ratio is then 1.41 (95%CI 0.98–2.03). After adjustment also for maternal age, parity, and smoking it is 1.35 (95%CI 0.93–1.97). There is no difference in risk among children born after standard IVF (odds ratio 1.36) and those born after ICSI (odds ratio 1.39). Table 22 summarizes these children.

The only condition which is in clear excess is Langerhan´s histiocytosis. The risk ratio is 5.6 (95%CI 1.8–13.0).

Most studies on cancer risk in IVF children have found no excess risk[62,63]. The only finding of a specific cancer risk after IVF is the report from the Netherlands[64] of an excess of retinoblastoma: five cases were identified and judged from the population rate, this was a clear excess but no formal epidemiological study was made. We found only one case of retinoblastoma which agrees with the expected number but obviously this may be a randomly low value.

***Table 22:*** *Tumor diagnoses reported to the Cancer Register among children born after IVF. Expected numbers are calculated on the basis of all cases reported to the register after adjustment for year of birth.*

| | Number | | Number after | |
|---|---|---|---|---|
| **Diagnosis** | **observed** | **expected** | **IVF** | **ICSI** |
| Acute lymphatic leukemia | 8 | 5.6 | 4 | 4 |
| Myeloid leukaemia central nervous system | 1 | 0.1 | 1 | 0 |
| Malignancy | 8 | 4.2 | 4 | 4 |
| Retinoblastoma | 1 | 0.8 | 1 | 0 |
| Hepatoblastoma | 1 | 0.4 | 1 | 0 |
| Medullary thyroid cancer | 1 | 0.1 | 1 | 0 |
| Sarcomas | 2 | 2.2 | 2 | 0 |
| Langerhan´s histiocytosis | 5 | 0.9 | 4 | 1 |
| Laryngeal in situ carcinoma | 1 | 0.01 | 1 | 0 |
| Benign testicular teratoma | 1 | 0.3 | 1 | 0 |
| Total | 29 | 21.4 | 20 | 9 |

There are thus two specific conditions which may be somehow related to IVF: retinoblastoma (sometimes a result of an imprinting error), and histiocytosis. Both observations are based on small numbers and may be random findings and are anyway very low frequency events in the order of magnitude of 1 per 15 to 20 000 births for both conditions. In an earlier study of cancer development in Sweden after IVF[60], two of the five histiocytosis cases were identified among 3 975 children (0.35 expected at that time) and the three further cases have later appeared among 12 305 children. There is no obvious explanation to the possible excess of Langerhan´s histiocytosis and it may still be an effect of multiple testing.

## Maternal morbidity during and after pregnancy after IVF

During pregnancy, women who had undergone IVF were more often hospitalized than other pregnant women. Using the Hospital Discharge Register, we identified 3 427 hospitalizations among the 13 261 IVF pregnancies (26%) against 187 641 hospitalizations among 1 543 112 deliveries in the population (12%). The odds ratio, adjusted for year of birth, maternal age, parity, and smoking, was 2.78 (95%CI 2.67–2.89). There were 0.45 hospitalization events among the IVF pregnancies (1.72 events per hospitalized woman) while the corresponding figures for the population were 0.12 per woman and 1.22 per hospitalized woman. Table 23 shows the results for some selected pregnancy diagnoses.

Among women who got pregnant after IVF, 320 (2.4%) were hospitalized for hyperstimulation.

***Table 23:*** *Some selected diagnoses for which women were hospitalized during pregnancy. Numbers and odds ratios, adjusted for year of birth, maternal age, parity, and smoking. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | IVF | | Population | | | |
|---|---|---|---|---|---|---|
| **Diagnosis** | **Number** | **Per cent** | **Number** | **Per cent** | **OR** | **95%CI** |
| *Early pregnancy bleeding* | 275 | 2.1 | 9 549 | 0.5 | 4.59 | 4.08–5.15 |
| standard IVF | 201 | 2.4 | | | 4.67 | 4.09–5.33 |
| ICSI | 74 | 1.5 | | | 3.76 | 3.01–4.69 |
| Singletons | 181 | 1.8 | 9 160 | 0.5 | 4.11 | 3.56–4.75 |
| Multiples | 94 | 3.0 | 389 | 1.5 | 2.33 | 1.75–3.08 |
| *Ovarian torsion* | 10 | 0.08 | 152 | 0.01 | 10.6 | 5.69–19.7 |
| Singletons | 1 | 0.01 | 149 | 0.01 | – | |
| Multiples | 9 | 0.28 | 3 | 0.01 | – | |
| *Thromboembolic disease* | 9 | 0.07 | 487 | 0.02 | 2.20 | 1.13–4.27 |
| Singletons | 3 | 0.03 | 474 | 0.02 | – | |
| Multiples | 6 | 0.19 | 13 | 0.05 | – | |
| *Sepsis/pneumonia* | 5 | 0.04 | 911 | 0.05 | 0.58 | 0.25–1.39 |
| Singletons | 3 | 0.09 | 897 | 0.05 | – | |
| Multiples | 2 | 0.06 | 14 | 0.05 | – | |

The increased risk for early pregnancy bleeding after IVF has been described repeatedly[65–66]. Other complications are rare. The rate of ovarian torsion, 0.75 per 1000 pregnancy, is similar to that described previously[67].

Delivery diagnoses studied are shown in Table 24 and Table 25 presents the odds ratios for each diagnosis, adjusted for year of birth, maternal age, parity, and smoking.

***Table 24****: Diagnoses given to women at delivery.*

| **Diagnosis** | **IVF** | **%** | **Population** | **%** |
|---|---|---|---|---|
| Preeclampsia | 978 | 7.4 | 55 728 | 2.8 |
| Placental abruption | 79 | 0.6 | 8 664 | 0.3 |
| Placenta praevia | 179 | 1.3 | 5 269 | 0.3 |
| Retained placenta | 137 | 1.0 | 24 085 | 1.2 |
| Bleeding in association with vaginal delivery | 1 036 | 7.8 | 140 297 | 7.1 |
| Premature rupture of membranes | 580 | 4.4 | 28 626 | 1.4 |
| Primary inadequate contractions | 749 | 5.6 | 57 192 | 2.8 |
| Secondary uterine inertia | 1 725 | 13.0 | 144 009 | 7.1 |
| Thromboembolic complication | 6 | 0.04 | 587 | 0.03 |

***Table 25:*** *Diagnoses given at delivery among women pregnant after IVF compared with all women who gave birth. Odds ratio (OR) with 95 % confidence interval (95%CI).*

*Comparision of singleton and multiple births*

| | **All** | | **Singletons** | | **Multiples** | |
|---|---|---|---|---|---|---|
| **Number of births** | **13,261** | | **10,087** | | **3,174** | |
| **Diagnosis** | **OR** | **95%CI** | **OR** | **95%CI** | **OR** | **95%CI** |
| Preeclampsia | 1.63 | 1.53–1.74 | 1.22 | 1.12–1.33 | 0.96 | 0.85–1.09 |
| Placental abruption | 2.17 | 1.74–2.72 | 1.87 | 1.41–2.47 | 1.47 | 0.91–2.37 |
| Placenta praevia | 3.65 | 3.15–4.23 | 3.84 | 3.26–4.53 | 1.77 | 1.14–2.75 |
| Retained placenta | 1.07 | 0.90–1.27 | 1.19 | 0.99–1.43 | 0.60 | 0.34–1.06 |
| Bleeding in association | 1.40 | 1.38–1.50 | 1.24 | 1.15–1.34 | 1.05 | 0.89–1.24 |
| Premature rupture of membranes | 2.54 | 2.34–2.76 | 1.47 | 1.29–1.67 | 0.99 | 0.86–1.13 |
| Primary inadequate contractions | 1.06 | 0.98–1.14 | 0.97 | 0.89–1.06 | 1.04 | 0.86–1.26 |
| Secondary uterine inertia | 0.93 | 0.88–0.98 | 0.88 | 0.83–0.93 | 1.01 | 0.89–1.16 |
| Thromboembolic complication | 1.21 | 0.53–2.74 | 0.87 | 0.27–2.78 | 1.28 | 0.23–7.23 |

*Comparison of standard IVF and ICSI*

| | **Standard IVF** | | **ICSI** | |
|---|---|---|---|---|
| **Number of births** | **9,063** | | **4,162** | |
| **Diagnosis** | **OR** | **95%CI** | **OR** | **95%CI** |
| Preeclampsia | 1.64 | 1.51–1.78 | 1.58 | 1.42–1.76 |
| Placental abruption | 2.29 | 1.74–2.72 | 1.61 | 0,91–2.85 |
| Placenta praevia | 3.60 | 3.01–4.31 | 3.78 | 2.95–4.78 |
| Retained placenta | 0.99 | 0.79–1.24 | 1.21 | 0.93–1.58 |
| Bleeding in association with vaginal delivery | 1.38 | 1.27–1.50 | 1.43 | 1.28–1.60 |
| Premature rupture of membranes | 2.75 | 2.49–3.05 | 2.18 | 1.89–2.51 |
| Primary inadequate constractions | 0.97 | 0.89–1.06 | 1.01 | 0.86–1.26 |
| Secondary uterine inertia | 0.94 | 0.88–1.07 | 0.90 | 0.83–0.98 |
| Thromboembolic complication | 1.65 | 0.61–4.48 | 0.00 | – |

Table 25 shows that for a number of pregnancy diagnoses (notably preeclampsia, placental abruption, placenta praevia, bleeding in association with a vaginal delivery, and premature rupture of membranes), the odds ratio was increased in pregnancies after IVF and there were no major differences between standard IVF and ICSI. Odds ratios were higher in singleton pregnancies than in twin or higher order pregnancies. An increased risk for pregnancy hypertension[65–66] and placenta previa[65] has been described in the literature, not only among women who had IVF but also among untreated subfertile women[67].

In order to see how much of the increased risk for preterm birth after IVF was due to the increased risk for preeclampsia, placental abruption, and placenta praevia, the odds ratio was determined after exclusion of pregnancies with one or more of these diagnoses. The odds ratio for preterm birth was then only slightly reduced: from 1.71 (95%CI 1.60–1.82) to 1.66 (95%CI 1.52–1.81).

Table 26 shows the risk for a caesarean section after an IVF pregnancy, divided into singleton and multiple births.

***Table 26:*** *Caesarean section after IVF compared with all deliveries and divided according to standard IVF and ICSI and according to years of birth, maternal age, and parity. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Singletons | | | Multiple births | | |
|---|---|---|---|---|---|---|
| **Group** | **Number** | **OR** | **95%CI** | **Number** | **OR** | **95%CI** |
| All | 2 472 | 1.38 | 1.32–1.43 | 1 750 | 1.19 | 1.09–1.29 |
| *IVF method:* | | | | | | |
| standard IVF | 1 611 | 1.43 | 1.35–1.52 | 1 204 | 1.24 | 1.13–1.37 |
| ICSI | 851 | 1.28 | 1.18–1.38 | 546 | 1.08 | 0.94–1.23 |
| *Year of birth:* | | | | | | |
| 1982–1990 | 132 | 1.84 | 1.51–2.24 | 83 | 1.49 | 1.02–2.17 |
| 1991–1995 | 700 | 1.50 | 1.37–1.64 | 593 | 1.35 | 1.17–1.56 |
| 1996–2001 | 1 630 | 1.31 | 1.23–1.38 | 1 074 | 1.09 | 0.98–1.21 |
| *Maternal age:* | | | | | | |
| – 24 years | 19 | 1.67 | 1.03–2.71 | 18 | 1.62 | 0.75–3.49 |
| 25 – 29 years | 303 | 1.73 | 1.52–1.96 | 294 | 1.08 | 0.91–1.29 |
| 30 – 34 years | 917 | 1.35 | 1.25–1.45 | 836 | 1.29 | 1.14–1.45 |
| 35 – 39 years | 1 023 | 1.32 | 1.25–1.45 | 553 | 1.12 | 0.95–1.31 |
| 40 – years | 200 | 1.30 | 1.09–1.56 | 49 | 1.09 | 0.51–2.36 |
| *Parity* | | | | | | |
| 1 | 1 957 | 1.32 | 1.25–1.39 | 684 | 1.06 | 0.92–1.22 |
| 2 | 413 | 1.57 | 1.41–1.75 | 814 | 1.20 | 1.06–1.36 |
| 3 | 70 | 1.90 | 1.46–2.49 | 203 | 1.41 | 1.14–1.75 |
| 4+ | 22 | 1.99 | 1.27–3.13 | 49 | 1.55 | 1.02–2.37 |

A risk increase for caesarean section is clearly seen, more pronounced for singleton births than for multiple births. It is slightly higher for standard IVF than for ICSI. There was a decline in likelihood with time and with maternal age and an increasing likelihood with parity. The higher caesarean section rate in IVF pregnancies has been described repeatedly in the literature.

There was no increased risk for instrumental delivery among vaginal deliveries after IVF. The OR, adjusted for year of birth, maternal age, parity, and smoking was 1.02 (95%CI 0.95–1.08) for singleton births and also 1.02 (95%CI 0.86–1.22) for multiple births.

Table 27 describes the use of delivery induction in pregnancies where delivery did not start with a caesarean section (most of which were elective).

***Table 27:*** *Induction of labour after IVF compared with all deliveries and divided according to standard IVF and ICSI and according to years of birth, maternal age, and parity. Deliveries starting with a caesarean section are excluded. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | **Singletons** | | | **Multiple births** | | |
|---|---|---|---|---|---|---|
| **Number of births** | **8208** | | | **1948** | | |
| **Group** | **Number** | **OR** | **95%CI** | **Number** | **OR** | **95%CI** |
| All | 1 278 | 1.37 | 1.29–1.46 | 561 | 1.08 | 0.96–1.21 |
| *IVF method* | | | | | | |
| standard IVF | 754 | 1.33 | 1.23–1.44 | 347 | 1.02 | 0.89–1.18 |
| ICSI | 516 | 1.42 | 1.29–1.56 | 212 | 1.18 | 0.98–1.42 |
| *Year of birth:* | | | | | | |
| 1982–1990 | 10 | 1.73 | 0.87–3.43 | 6 | 1.08 | 0.35–3.35 |
| 1991–1995 | 364 | 1.53 | 1.36–1.71 | 157 | 0.94 | 0.76–1.16 |
| 1996–2001 | 896 | 1.32 | 1.22–1.42 | 405 | 1.15 | 1.00–1.33 |
| *Maternal age* | | | | | | |
| – 24 years | 16 | 1.89 | 1.13–3.16 | 4 | 0.48 | 0.13–1.81 |
| 25 – 29 years | 186 | 1.60 | 1.37–1.87 | 106 | 1.07 | 0.83–1.37 |
| 30 – 34 years | 542 | 1.44 | 1.31–1.58 | 273 | 1.12 | 0.94–1.32 |
| 35 – 39 years | 457 | 1.23 | 1.11–1.37 | 174 | 1.03 | 0.82–1.27 |
| 40 – years | 69 | 1.20 | 0.91–1.58 | 11 | 2.12 | 0.68–6.60 |
| *Parity* | | | | | | |
| 1 | 1 010 | 1.33 | 1.25–1.43 | 210 | 1.07 | 0.88–1.31 |
| 2 | 212 | 1.62 | 1.40–1.87 | 266 | 1.14 | 0.96–1.35 |
| 3 | 28 | 1.00 | 0.67–1.48 | 74 | 0.92 | 0.68–1.25 |
| 4+ | 20 | 2.05 | 1.24–3.37 | 18 | 1.13 | 0.62–2.08 |

The likelihood for an induction of delivery was thus increased after IVF but only in singleton pregnancies. Among singletons, there was a decline in likelihood with period and with increasing maternal age. There was no clear-cut difference between standard IVF and ICSI.

Exclusion of pregnancies with a diagnosis of premature rupture of the membranes did not change the odds ratios for induction. In preterm births, the OR was 1.19 (95%C% 0.94–1.51), for births in weeks 37–38 it was 1.56 (95%CI 1.34–1.81) and for births in weeks 39–41 it was 1.55 (95%CI 1.43–1.68).

We studied some selected diagnoses for women who had been hospitalized within 60 days after delivery. Table 28 summarizes the findings. Only for postpartum bleeding was a significant difference seen between IVF pregnancies and other pregnancies. There was no significant difference between standard IVF and ICSI or between singleton births or multiple births.

***Table 28:*** *Discharge diagnoses at hospitalizations occurring before 60 days after delivery. Odds ratios (OR) adjusted for year of birth, maternal age, parity, and smoking, with 95 % confidence intervals (CI).*

| Diagnosis | IVF | Population | OR | 95%CI |
|---|---|---|---|---|
| *Puerperal infection* | 92 | 5 618 | 1.23 | 0.99–1.51 |
| Singletons | 59 | 5 468 | 1.01 | 0.78–1.32 |
| Multiples | 33 | 150 | 1.25 | 0.80–1.95 |
| Standard IVF | 55 | 5 618 | 1.28 | 0.98–1.66 |
| ICSI | 36 | | 1.12 | 0.81–1.56 |
| *Thrombo-embolic disease* | 7 | 463 | 1.77 | 0.84–3.71 |
| *Postpartum bleeding* | 55 | 2 987 | 2.02 | 1.51–2.65 |
| Singletons | 35 | 2 893 | 1.63 | 1.15–2.30 |
| Multiples | 20 | 94 | 1.41 | 0.76–2.61 |
| Standard IVF | 37 | 2 987 | 1.92 | 1.39–2.66 |
| ICSI | 18 | | 2.15 | 1.35–3.42 |
| *Mastitis* | 59 | 3 287 | 1.24 | 0.96–1.62 |
| Singletons | 44 | 3 224 | 1.16 | 0.86–1.57 |
| Multiples | 15 | 63 | 1.26 | 0.66–2.41 |
| Standard IVF | 36 | 3 287 | 1.29 | 0.92–1.80 |
| ICSI | 23 | | 1.13 | 0.74–1.72 |

## Cancer among women who had IVF

In order to study cancer risk, the 12,186 women who had a birth after IVF were compared with all women who had given birth during the observation period (1982–2001) and were born the same years as the IVF women (1943–1979, a total of 1 098 456) by a search in the Swedish Cancer Register. We made adjustments for the year of birth of the woman, the year of the first IVF pregnancy (for IVF women) or the year of the first delivery after 1981 (for the group of comparison), and the parity at that delivery.

We identified a total of 614 women who had given birth after IVF and were registered in the Cancer Register – 412 were registered before their first IVF delivery and 202 after it. Table 29 summarizes the results.

***Table 29.*** *Number of women with cancer before the end of 2002 among women who had an infant born after IVF and among all women who gave birth, Cancers before and after the first IVF delivery. Odds ratio (OR) with 95 % confidence interval (95%CI).*

| | Cancer before delivery | | | | Cancer after delivery | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of women with cancer | | | | Number of women with cancer | | | |
| **Cancer type** | **IVF** | **all women** | **OR** | **95%CI** | **IVF** | **all women** | **OR** | **95%CI** |
| All types | 412 | 22 541 | 1.13 | 1.02–1.25 | 202 | 46 170 | 0.79 | 0.69–0.91 |
| Breast | 2 | 183 | 0.29 | – | 35 | 7 183 | 0.76 | 0.54–1.06 |
| Cervix | 334 | 17 659 | 1.02 | 0.92–1.13 | 78 | 26 362 | 0.63 | 0.50–0.79 |
| Uterine body | 0 | 5 | 0 | – | 1 | 197 | 2.56 | – |
| Ovary | 12 | 252 | 2.70 | 1.49–4.91 | 12 | 1 075 | 2.08 | 1.15–3.76 |
| Chorion epithelioma | 4 | 1 093 | 0.25 | 0.10–0.63 | 2 | 920 | 0.25 | 0.07–0.88 |
| Malignant melanoma | 20 | 657 | 1.21 | 0.76–1.93 | 17 | 2 182 | 1.32 | 0.79–2.20 |

Most studies in the literature have found no increased cancer risk after IVF when compared with the risk in the general population[69–70]. We have chosen to compare the cancer risk with that after non-IVF pregnancies because pregnancy itself may affect cancer risk. An increased risk during the year following IVF treatment has been described[69,71] which can hardly be due to the treatment. An increased ovarian cancer risk among infertile women has been described irrespective of treatment[72]. We found an increased ovarian cancer risk in women both before and after IVF treatment.

## Maternal mortality after IVF

Among the women who gave birth after IVF treatment, 33 had died before the end of 2002. The OR for death, adjusted for the year of birth of the woman, date of first IVF pregnancy, parity at that pregnancy, and smoking was 1.06 (95%CI 0.75–1.50). Table 30 gives the causes of death.

***Table 30:*** *Causes of death for 33 women who had given birth after IVF and died before the end of 2002.*

| Cause of death | Number |
|---|---|
| Malignant tumour | 15 |
| Cardiovascular disease | 4 |
| Pulmonary embolus | 1 |
| Cardiac arrest during caesarean section | 1 |
| Asthma | 2 |
| Pneumonia | 1 |
| Metabolic disease | 1 |
| Alcohol-related death | 1 |
| Accidents | 4 |
| Suicide | 3 |

The woman who died during caesarean section did so in a pregnancy after a standard IVF which was not included in the present analysis because it ended before 28 completed weeks and the stillborn foetus was therefore not legally a child.

In an earlier study[73], a reduced mortality risk was described but comparison was then made with the mortality risk in the total population and the effect was judged to be a "healthy patient" effect. Our comparison was made with women who gave birth during the observation period and this effect was therefore minimized.

# General discussion and conclusions

There is no question that pregnancies occurring after IVF are burdened with an increased risk for maternal and infant morbidity. This has been described repeatedly in nearly all studies based on large enough number of cases and is clearly observable also in the data which are presented in this report. Thus, an approximate doubling of the rate of preterm births among singletons was found, a 70 per cent increase in perinatal mortality, and a 50 per cent increase in congenital malformation rate which agrees with results in the literature.

What does such an effect mean? It can be looked upon from two points of view: the individual risk for the woman who gets pregnant after IVF to get a complication and/or a damaged child, and the contribution of IVF to the occurrence of such outcomes in the population. In order to compare these effects, one can calculate the absolute risk for a woman who has become pregnant after IVF to have for instance a preterm or malformed baby and the proportion of preterm, dead, or malformed infants in the population which are the result of IVF pregnancies. The latter figure will give an estimate of the impact by IVF on the population and the health care resources.

Among women giving birth after IVF during the years 2000–2001 (when 1.9 per cent of women who gave birth conceived after IVF), 7.3 per cent had a singleton infant born before week 37 and 1.5 per cent before week 32. Thus, 92.7 per cent of the singleton infants were term. Among all singleton infants born before week 32 these years, 3 per cent were after IVF. The corresponding figure for singleton infants born before week 37 was 2 per cent. Neither the individual risk, nor the contribution to the population was thus very large.

Contrary to this, the probability for a woman to have a twin delivery after IVF was 20 per cent and a triplet delivery 0.3 per cent. Twenty-two per cent of all twin pairs and 20 per cent of all triplet sets in the population were conceived after IVF. It has repeatedly been stated in the literature that birth outcome after IVF twin deliveries does not differ from spontaneous twin deliveries but in such comparisons, a distinction between monozygotic and dizygotic twin pairs were often not made and problems are more common at monozygotic than at dizygotic twinning. After IVF, the majority of twin pairs are dizygotic, even if an increased risk also for monozygotic twinning has repeatedly been shown and was seen also in our study. Recently, another twin complication has been reported after IVF conceptions: monochorionic dizygotic twinning[74]. The rate of dizygotic twinning was reduced in Sweden after an agreement among IVF clinics to restrict the number of transferred embryos to a maximum of two[3]. A change to single embryo transfer implemented in 2002 in Sweden is expected to further reduce twinning rate and therefore also maternal and infant complications.

The death rate among infants born after IVF is increased. However, for the years 2000–2001, 99.6 per cent of women who conceived by IVF had at

least one surviving infant to take home. The corresponding figure for the population is 99.7 per cent.

There is an increased risk for an infant to have a congenital malformation compared to spontaneously conceived infants, but the absolute risk is low. If restricted to severe malformations we can estimate that the risk increase is from perhaps 2 per cent to about 3 per cent. For the individual woman this risk increase is negligible and among all infants born with such malformations in the years 2000–2001, those conceived after IVF will represent only eight per cent.

The effects of IVF on maternal and infant morbidity could be due to the IVF procedure or be the result of the fact that the parents of children conceived by IVF may differ from other parents and these differences could explain the differences in outcome. In many studies in the literature, some obvious such confounders have been taken into consideration like maternal age and parity. As shown in the present analysis, the IVF women show a number of other characteristics which distinguish them from other women giving birth. Some of these characteristics may be direct consequences of the infertility status (e.g., the low smoking rate, working situation, and the low use of psychoactive drugs), other may be related to the cause of infertility (like previous miscarriage, high BMI, chronic diseases). When such factors are of importance for the outcome, they should be taken into consideration in the analysis because they will appear as confounders.

The most important such confounder is the subfertility state itself. This has often been pointed out in the literature, and it has been suggested that analyses should be based on matching of women having IVF with women with fertility problems but conceiving spontaneously. Another way to handle this problem is to adjust for subfertility in the analysis, e.g., as done in some previous studies[1] and in the study presented here, using the stated length of involuntary childlessness as a measure of subfertility. Any such analysis will probably not be completely effective because one will compare couples who have tried a certain period to conceive without success and therefore were treated with IVF with couples who spontaneously or after other treatments conceived after the same length of period of subfertility. Some residual confounding of subfertility can still remain. In the present analysis it was repeatedly shown that the factor “years of unwanted childlessnes” was the most important confounder present and for many outcomes completely or nearly completely removed the effects of IVF. There are many published studies which demonstrate sub-optimum neonatal outcome at maternal subfertility also in the absence of IVF[37, 68, 75].

Like in the main part of the literature on the subject, only small differences were seen in the outcome after ICSI and standard IVF. The characteristics of the women undergoing ICSI and IVF to a large extent were similar even though some differences existed (e.g., rate of previous miscarriages). If ICSI was solely made because of paternal subfertility, one would perhaps have expected larger differences between the two groups. ICSI is, however, sometimes used also at female infertility (e.g., if repeated efforts with standard IVF have not resulted in pregnancy). Another factor of importance may be that at paternal subfertility, the probability for a conception may be lower if also the woman is subfertile than if she has a normal fertility.

When adjusted for the most important confounders, the risk for preterm birth among singletons was markedly reduced and during the last 5 years of observation was no longer statistically significant while it was significant in the beginning of the period. This could indicate changes in medical care or changes in the selection criteria of couples who get IVF.

Basically there is little or no difference in neonatal outcome after standard IVF and ICSI which agrees with most information in the literature. There is a tendency that outcome is better after frozen than after fresh standard IVF which probably is due to a selection phenomenon as good access to eggs is needed in order to freeze embryos for a later IVF attempt.

Most of the negative effects on the neonate appear to be related to the high rate of multiple births and after adjustment for twinning, no significant difference remains between ICSI and standard IVF.

Much interest has been paid to the increased risk of congenital malformations in infants conceived by IVF. This effect is seen also in our material but disappears completely after adjustment for among other things years of involuntary childlessness. The general moderately increased risk for a congenital malformation is therefore a result of maternal (and perhaps paternal) characteristics and not a consequence of the IVF procedure itself and hardly differs between standard IVF and ICSI. There are, however, a few conditions which seem to occur in excess after IVF. Among those can be mentioned neural tube defects, orofacial clefts, cardiac defects, atresia of different parts of the alimentary tract, and possibly hypospadias which is the only malformation more prevalent after ICSI than after standard IVF. Even though the risk for infant spina bifida appears five times increased, the absolute risk for a woman with an IVF pregnancy to have an infant with spina bifida is low (about 1.2 per 1 000) and should be of little concern but may suggest a need for intensified prenatal screening for a neural tube defect. The same is true for the other malformations with a specific risk increase.

In the literature, a number of severely malformed infants born after IVF have been described. In the present material, few such cases were seen. An explanation may be that such foetuses have been identified by prenatal diagnosis and aborted – no information on such occurrences exists in this data set. Even though fetuses aborted after prenatal diagnoses are reported to the Register of Congenital Malformations, Swedish law prohibits that the specific individual can be identified and therefore information on IVF cannot be obtained.

Another rare outcome of little practical but much theoretical interest is the imprinting errors, apparent as specific congenital syndromes or cancers. Most discussed are two conditions: Beckwith-Wiedemann and Angelman syndromes. Neither was identified among the 16 280 infants which were studied in the present investigation but two other conditions which may be related to imprinting errors were found: Prader-Willi and Russel-Silver sydromes. If actually imprinting errors occurred in these two children is not known. Another imprinting error has been linked to the development of retinoblastoma. This rare eye tumour has been associated with IVF[64]. The observation has not been verified and we found only one such case which is close to the expected rate. This does not exclude an association. Again it is possible that an increase in the rate of imprinting errors is not the result of

the IVF procedure but associated with the underlying male subfertility[44] and therefore mainly associated with ICSI.

The other specific cancer type which could possibly be associated with IVF is histiocytosis. This has only been reported from the Swedish material and may well be a result of multiple testing. Against it speaks the fact that the association was first observed on the earlier part of the material and was verified on the later part. It is still possible that it is a random finding and the low rate (3 per 10 000) anyway should be of little concern for the woman who has had an IVF. If the association is true, however, it may be of interest in the investigation on the aetiology of this rare condition.

Infants born after IVF show a higher hospitalization rate than other infants, also years after birth. This is rather expected as it is known that preterm birth and multiple births are associated with an increased morbidity, not only in the neonatal period but also later. The increased risk for hospitalization was seen for all diagnoses studied and seemed to be strongly linked to preterm birth as the odds ratios were reduced and most of them became non-significant when the study was restricted to term infants. The three exceptions were: convulsions, congenital malformations, and accidents. The analysis is, however, complicated by the fact that parents of children conceived after IVF may be more anxious and more prone to seek medical help than other parents also for less severe medical problems.

Also maternal obstetric complications were more common than expected after IVF. Most of these have already been described in the literature and there is some evidence that they are associated with the underlying subfertility status.

In conclusion, without any doubt pregnancies after IVF represent risk pregnancies both for the mother and the infant. The individual risk is usually not very high but the contribution to the burden of health care in society may nevertheless be important. This fact appears to be little associated with the IVF procedure itself or which type of IVF procedure has been used but seems to be related to the subfertility state of the woman (and sometimes man). The only direct effect of the IVF procedure is that on the rate of multiple births. This can effectively be counter-acted by the nowadays introduced recommendation of single embryo transfer and it will be interesting to follow how this rule in practice will affect multiple birth rate and related complications. Up till now no certain advantage or disadvantage can be seen with the different IVF techniques but as technology develops, continued surveillance should be made, based on large numbers.

# References


1. Bergh T, Ericson A, Hillensjö T, Nygren K–G, Wennerholm U–B. Deliveries and children born after in vitro fertilisation in Sweden 1982–1995: a retrospective cohort study. Lancet 1999; 354: 1579–1585.
2. Barn födda i Sverige efter provrörsbefruktning 1982–1997 (Children born in Sweden after in vitro fertilization 1982–1997). Socialstyrelsen. EpC–rapport 2000:1. Stockholm 2000.
3. Källén B, Finnström O, Nygren K G, Otterblad Olausson P. Temporal trends in multiple births after in vitro fertilisation in Sweden: a register study. BMJ 2005; 331: 382–383.
4. Källén B, Finnström O, Nygren K G, Otterblad Olausson P. In vitro fertilization (IVF) in Sweden: Infant outcome after different IVF methods. Fertil Steril 2005; 84: 611–617.
5. Källén B, Finnström O, Nygren K G, Otterblad Olausson P. In vitro fertilization (IVF) in Sweden: Risk for congenital malformations after different IVF methods. Birth Defects Res (Part A) 2005; 73:162–169.
6. Källén B, Finnström O, Nygren K G, Otterblad Olausson P. In vitro fertilization in Sweden: child morbidity including cancer risk. Fertil Steril 2005; 84: 605–610.
7. Källén B, Finnström O, Nygren K G, Otterblad Olausson P. In vitro fertilization in Sweden: maternal characteristics. Acta Obst Gynecol Scand 2005; 84: 1185–1191.
8. Källén B, Finnström O, Nygren K G, Otterblad Olausson P, Wennerholm U-B. In vitro fertilisation in Sweden: obstetric characteristics, maternal morbidity and mortality. BJOG 2005; 112: 1529–1535.
9. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: A meta-analysis. Obstet Gynecol 2004; 103: 551–563.
10. Helmerhorst FM, Perquin DAM, Donker D, Kerise MJNC. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004; 328: 261–264B.
11. Bower C, Hansen M. Assisted reproductive technologies and birth outcomes: overview of recent systematic reviews. Reprod Fertil Develop 2005; 17: 329–333.
12. Hansen M, Bower C, Milne E, de Klerk N, Kurinczuk JJ. Assisted reproductive technologies and the risk of birth defects – a systematic review. Human Reprod 2005; 20: 328–338.
13. McDonald S, Murphy K, Beyene J, Ohlsson A. Perinatal outcome of in vitro fertilization twins: a systematic review and meta-analysis. Amer J Obst Gynecol 2005; 193: 141–152.
14. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med 2002; 346: 731–737.
15. Schieve LA, Ferre C, Peterson HB, Macaluso M, Reynolds MA, Wright VC. Perinatal outcome among singleton infants conceived through assisted reproductive technology in the United States. Obstet Gynecol 2004; 103: 1144–1153.
16. MRC Working Party on Children Conceived by In Vitro Fertilisation. Births in Great Britain resulting from assisted conception, 1978–1987. BMJ 1990; 300: 1229–1233.
17. Gissler M, Silverio MM, Hemminki E. In-vitro fertilization pregnancies and perinatal health in Finland 1991–1993. Human Reprod 1995; 10: 1856–1861.
18. FIVNAT. Pregnancies and births resulting from in vitro fertilization: French national registry, analysis of data 1986–1990. Fertil Steril 1995; 64: 746–756.
19. Pinborg A, Loft A, Schmidt L, Andersen AN. Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. Hum Reprod 2003; 18: 1234–1243.

20. Mitchell AA. Infertility treatment – more risks and challenges (Editorial). N Engl J Med 2002; 346: 769–770.
21. National Board of Health and Welfare, Centre for Epidemiology The Swedish Medical Birth Registry – a summary of content and quality. http://www.sos.se/FULLTEXT/112/2003-112-3/2002-112-3.pdf.
22. National Board of Health and Welfare, Centre for Epidemiology. Registration of Congenital Malformations in the Swedish Health Registers. http://www.socialstyrelsen.se/Publicerat/2004/5120/2004-112-1.htm.
23. National Board of Health and Welfare, Centre for Epidemiology. The Swedish Hospital Discharge Register. http://www.sos.se/epc/english/ParEng.htm
24. National Board of Health and Welfare, Centre for Epidemiology Cancer incidence in Sweden 2002. http://www.sos.se/FULLTEXT/42/2003-42-11/2003-42-11.pdf
25. Fedorcsak P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, Omland AK, Abyholm T, Tanbo T. Impact of overweight and underweight on assisted reproduction treatment. Human Reprod 2004; 19: 2523–2528.
26. Nyboe Andersen A, Gianaroli L, Nygren KG et al. Assisted reproductive technology in Europe, 2000. Results generated from European registers by ESHIRE. Human Reprod 1004; 19: 490–503.
27. Tiitinen A, Unikilakallio L, Halttunen M, Hyden-Granskog C. Impact of elective single embryo transfer on the twin pregnancy rate. Human Reprod 2003; 18: 1449–1453.
28. Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, Bergh C. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. N Engl J Med 2004; 351: 2392–2402.
29. Thurin Kjellberg A, Carlsson P, Bergh C. Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis. Human Reprod 2006: 21: 210–216.
30. Lukassen HGM, Braat DD, Wetzels AMM, Zielhuis GA, Adang EMM, Scheenjes E, Kremer JAM. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. Human Reprod 2005; 20: 702–708.
31. Edwards RG,Mettler L, Walters DE. Identical twins and in vitro fertilization. J In Vitro Fert Embryo Transfer 1986; 3: 114–117.
32. Wright V, Schieve LA, Vahratian A, Reynolds MA. Monozygotic twinning associated with day 5 embryo transfer in pregnancies conceived after IVF. Human Reprod 2004; 19:1831–1836.
33. Sills ES, Moomjy M, Zaninovic N, Veek LL, McGee M, Palermo GD. Human zona pellucida micromanipulation and monozygotic twinning frequency after IVF. Human Reprod 2000; 15: 890–895.
34. Schieve LA, Meikle SF, Peterson HB, Jeng G, Burnett NM, Wilcox LS. Does assisted hatching pose a risk for monozygotic twinning in pregnancies conceived through in vitro fertilization? Fertil Steril 2000; 74: 288–294.
35. Elizur SE, Levron J, Shrim 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: 500–501.
36. Alikani M, Cekleniak NA, Walters E, Cohen J. Monozygotic twinning following assisted conception: an analysis of 81 consecutive cases. Human Reprod 2003; 18: 1937–1943.
37. Källén B, Otterblad Olausson P, Nygren KG. Neonatal outcome in pregnancies from ovarian stimulation. Obstet Gynecol 2002; 100: 414–419.
38. Bonduelle M, Liebaers I, Deketelaere V, Derde M-P, Camus M, Devroey P, Van Steirteghem A. Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999). Human Reprod 2002; 17: 671–694.
39. Boklage CE. The epigenetic environment: secondary sex ratio depends on differential survival in embryogenesis. Human Reprod 2005; 20: 583–587.

40. Leslie GI, Gibson FL, McMahon C, Tennant C, Saunders DM. Infants conceived using in-vitro fertilization do not over-utilize health care resources after the neonatal period. Human Reprod 1998; 13: 2055–2059.
41. Maher ER, Afnan M, Barratt CL. Epigenetic risks related to assisted reproductive technologies: Epigenetics, imprinting, ART and iceberg? Human Reprod 2003; 18: 2508–2511.
42. Gosden R, Trasler J, Lucifero D, Faddy M. Rare congenital disorders, imprinted genes, and assisted reproductive technology. Lancet 2003; 361: 1975–1977.
43. Ludwig M, Katalinic A, Gross S, Sutcliffe A, Varon R, Horsthemke B. Increased prevalence of imprinting defects in patients with Angelman syndrome born to subfertile couples. J Med Genet 2005; 42: 289–291.
44. Marques CJ, Carvalho F, Sousa M, Barros A. Genomic imprinting in disruptive spermatogenesis. Lancet 2004; 363: 1700–1702.
45. Lidegaard Ø, Pinborg A, Nyboe Andersen A. Imprinting diseases and IVF: Danish national IVF cohort study. Human Reprod 2004; 20: 950–954.
46. Silver, RI, Rodriguez R, Chang TS, Gearhart JP. In vitro fertilization is associated with an increased risk for hypospadias. J Urol 1999; 161: 1954–1957.
47. Wennerholm U-B, Bergh C, Hamberger L, Lundin K, Nilsson L, Wikland M, Källén B. Incidence of congenital malfomrations in children born after ICSI. Human Reprod 2000; 15: 944–948.
48. Ericson A, Källén B. Congenital malformations in infants born after IVF: a population-based study. Human Reprod 2001; 16: 504–509.
49. Lie RT, Lyngstadaas A, Ørstavik KH, Bakketeig LS, Jacobsen G, Tanbo T. Birth defects in children conceived by ICSI compared with children conceived by other IVF methods; a meta-analysis. Int J Epidemiol 2005; 34: 696–701.
50. Shanske AL, Pande S, Aref K, Vegarich C, Brion L, Reznik S, Timortritsch IE. Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) in triplet pregnancies after IVF och CVS. Birth Defects Res Part A 2003; 67: 467–471.
51. Merlob P, Fisch B. Neonatal outcome and congenital malformations in children born after IVF. Human Reprod 2002; 17: 3004–3005.
52. Wood HP, Trock BP, Gearhart JP. In vitro fertilization and the cloacal-bladder exstrophy-epispadias complex: is there an association? J Urol 2003; 169: 1512–1515.
53. Hirokawa S, Uotani H, Futatami T, Sasaki Y, Ogawa J, Sakai M, Tsukada K. A case of body stalk anomaly arising in the second baby of a triplet pregnancy aftet in-vitro fertilization and embryo transfer. Pediatr Surg 2003; 19: 223–225.
54. Fujimori K, Shiroto T, Kuretake S, Gunji H, Sato A. An omphalopagus parasitic twin after intracytoplasmic sperm injection. Fertil Steril 2004; 82: 1430–1432.
55. Leslie GI, Gibson FL, McMahon C, Tennant C, Saunders DM. Infants conceived using in-vitro fertilization do not over-utilize health care resources after the neonatal period. Human Reprod 1998; 13: 2055–2059.
56. Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Jarvelin MR. Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. Human Reprod 2003; 18: 2328–2336.
57. Pinborg A, Loft A, Schmidt L, Greisen G, Rasmussen S, Andersen AM. Hospital care utilization of IVF/ICSI twins followed until 2–7 years of age: a controlled Danish national cohort study. Human Reprod 19: 2529–2536, 2004.
58. Strömberg B, Dahlquist G, Ericson A, Finnström O, Köster M, Stjernqvist K. Neurological sequelae in children born after in-vitro fertilisation: a population-based study. Lancet 2002; 359: 461–465.
59. Pinborg A, Loft A, Schmidt L, Greisen G, Rasmussen S, Andersen AM. Neurologic sequelae in twins born after assisted conception: controlled national cohort study. BMJ 2004; 329: 311–314B.

60. Ericson A, Källén B. Hospital care utilization of infants born after IVF. Human Reprod 2002; 17: 929–932.
61. Hellgren L, Gillberg C, Gillberg IC. Children with deficits in attention, motor control and perception (DAMP) almost grown up: general health at 16 years. Dev Med Child Neurol 1993; 35: 881–892.
62. Bruinsma F, Venn A, Lancaster P, Speirs A, Healy D. Incidence of cancer in children born after in-vitro fertilization. Human Reprod 2000; 15: 604–607.
63. Klip H, Burger CW, Kraker J de, Leeuwen FE van: Risk of cancer in the offspring of women who underwent ovarian stimulation for IVF. Human Reprod 2001; 16: 2351–2458.
64. Moll AC, Imhof SM, Cruysberg JRM, Schouten-van Meeteren AYN, Boers M, Leeuwen FE van. Incidence of retinoblastoma in children born after in-vitro fertilisation. Lancet 2003; 361: 309–310.
65. Tan SL, Doyle P, Campbell S, Beral V, Rizk B, Brinsden P, Mason B, Edwards RG. Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. Am J Obst Gynecol 1992; 167: 778–784.
66. Ochsenkühn R, Strowitzki T, Gurtner M, Strauss A, Schulze A, Hepp H, Hillemanns P. Pregnancy complications, obstetric risks, and neonatal outcome in singleton and twin pregnancies after GIFT and IVF. Arch Gynecol Obstet 2003; 268: 256–261.
67. Gorkemli H, Camus M, Clasen K. Adnexal torsion after gonadotrophin ovulation induction for IVF or ICSI and its conservative treatment. Arch Gynecol Obstet 2002; 267: 4–6.
68. Thomson F, Shanbhag S, Templeton A, Bhattacharya S. Obstetric outcome in women with subfertility. BJOG 2005; 112: 632–637.
69. Venn A, Watson L, Bruinsma F, Giles D, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilization. Lancet 1999; 354: 1586–1590.
70. Gauthier E, Paoletti X, Clavel-Chapelon F and the E3N group. Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study. Human Reprod 2004; 19: 2216–2221.
71. Lerner-Geva L, Geva E, Lessing JB, Chetrit A, Modan B, AMIT A. The possible association between in vitro fertilization treatments and cancer development. Int J Gynecol Cancer 2003; 12: 23–27.
72. Kashyap S, Moher D, Fung MFK, Rosenwaks Z. Assisted reproductive technology and the incidence of ovarian cancer: A meta-analysis. Obstet Gynecol 2004; 103: 785–794.
73. Venn A, Hemminki E, Watson L, Bruinsma F, Healy D. Mortality in a cohort of IVF patients. Human Reprod 2001; 16: 2691–2696.
74. Miura K, Niikawa N. Do monochorionic dizygotic twins increase after pregnancy by assisted reproductive technology? J Human Genet 2005; 50: 1–6.
75. Ghazi HA, Spielberger C, Källén B. Delivery outcome after infertility – a registry study. Fertil Steril 1991; 55: 726–732.