

In vitro fertilization (IVF) in Sweden: infant outcome after different IVF fertilization methods

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Objective: To compare infant outcome after different IVF techniques.

Design: A register study in Sweden of IVF infants compared with all infants born.

Setting: National health registers.

Patient(s): We studied 16,280 IVF infants, 30% of whom were conceived by intracytoplasmic sperm injection (ICSI).

Intervention(s): None.

Main Outcome Measure(s): Multiple births, infant sex, preterm birth, low birth weight, and small for gestational age among singletons, mortality, low Apgar score, neonatal diagnoses.

Result(s): Twinning was less frequent after frozen standard IVF (18.1%) and after ICSI (21.8%) than after fresh standard IVF (24.4%). The male/female ratio was significantly increased in infants conceived after standard IVF. No significant differences were seen between singleton infants conceived after different IVF methods with respect to preterm birth, low birth weight, or infant mortality, with the possible exception of frozen standard IVF, for which some of these rates were lower than after fresh standard IVF. Infants born after ICSI had an indicated lower risk of respiratory problems than infants born after standard IVF.

Conclusion(s): Little difference in outcome was seen after different IVF methods. The differences observed might be due to dissimilar characteristics of the treated women (e.g., because ICSI was mainly used in connection with male infertility). (Fertil Steril® 2005;84:611–7. ©2005 by American Society for Reproductive Medicine.)

Key Words: IVF, ICSI, multiple birth, preterm birth, mortality, neonatal diagnoses

The first infant in the world born after IVF was reported in 1978 (1), the technique of intracytoplasmic sperm injection (ICSI) was introduced in 1992, and the first pregnancy from a cryopreserved embryo occurred in 1993. Most studies have shown that infants born after IVF have a poorer perinatal outcome than naturally conceived infants (e.g., 2–6) although this seems largely to be due to multiple births and to confounding from maternal characteristics (2).

With the advancement and increasing use of new variants of IVF technique, the question arises whether these entail different hazards to the infant. Special interest has been paid to the ICSI technique when the suggested natural selection of sperm is bypassed. As reviewed by Retzlöff and Hornstein (7), no certain differences in congenital malformation rates between infants born after standard IVF or after ICSI have been demonstrated. The authors also point out the difficulties in conducting such analyses, notably when comparisons with naturally conceived infants are made.

For still more specific IVF techniques (e.g., ICSI with epididymal or testicular sperm), few data are available, and it is difficult to draw any firm conclusions.

In the present study, we used a large database of deliveries in Sweden after IVF and made comparisons with all infants born in Sweden, taking various putative confounders into consideration. The data set used includes that presented earlier (2), which contained infants born up to and including 1995 (n = 4,517) and relatively few ICSI infants (7.2%). Data for 1996–2001 have now been added (total n = 16,280, 30% ICSI). The study focuses on the risk for multiple birth, preterm birth among singletons, mortality, and neonatal diagnoses. In other communications, further safety aspects on IVF will be discussed, including the risk for congenital malformations.

MATERIALS AND METHODS

In vitro fertilization procedures have been performed in Sweden in 17 laboratories in hospitals or private clinics. The first child born after IVF was born in 1982. The National Board of Health and Welfare requested information from these laboratories on all women who had gone through IVF and were known to have given birth or who had a pregnancy with an unknown outcome. Each woman was identified with her personal identification number (PIN), which every person living in Sweden possesses and which is extensively

Received November 8, 2004; revised and accepted February 23, 2005. Supported by a grant from the K. and A. Wallenberg Foundation (KAW 2001-0124), Stockholm, Sweden (to B.K.).

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used in society and in all health care. A file was prepared with the PIN, a code for the laboratory where IVF was performed, year and month of ET, and the particular IVF method used. All IVF procedures performed before April 1, 2001 were included.

Infants born after IVF from 1982 to 2001 were identified by creating links between the above-mentioned file with the Medical Birth Register (8). This register covers nearly all deliveries in Sweden (a few percent are missing) and is based on copies of medical documents from antenatal care, delivery, and pediatric examination of the newborn. A current evaluation of the content of the register is available (9). The following variables were collected from the Medical Birth Register: year of birth, maternal age, parity, smoking in early pregnancy (reported at the first antenatal care visit, usually before the end of the first trimester), number of infants in birth, pregnancy duration, infant birth weight, Apgar score at 5 minutes, infant survival. Deaths after discharge from the neonatal unit were identified with linkage to the Cause of Death Register (10).

Neonatal diagnoses were obtained from the Medical Birth Register but were also identified (from 1987 onwards) from discharge diagnoses when the infant was hospitalized during the first week of life. Such discharge diagnoses were obtained from the Hospital Discharge Register (11) and were linked with use of the infant PIN. In spite of these efforts, some neonatal diagnoses are probably missing, but it is unlikely that this circumstance is linked to the presence or absence of IVF. Small for gestational age was based on the birth weight for gestational week graphs obtained from the Medical Birth Register (12).

Among live-born infants, certain neonatal diagnoses were studied: cerebral hemorrhage, convulsions, respiratory problems, and sepsis. These conditions were defined by the International Classification of Diseases (ICD) codes in the registers.

Cerebral hemorrhage was defined as 772.0 in ICD-8, 767.0 and 772.1-2 in ICD-9, and as P10, P11.0-P11.2, and P52 in ICD-10. (Sweden began using ICD-9 in 1987 and ICD-10 in 1997.) Neonatal convulsions were defined as 780.2 in ICD-8, 779.0 in ICD-9, and P90 in ICD-10. Respiratory problems were defined as 776.0-2 and 776.6-8 in ICD-8, 768.5-768.7, 769, and 770 in ICD-9, and P22-P23 in ICD-10. Neonatal sepsis was defined as 038 in ICD-9 and as A40, A41, and P36 in ICD-10. The ICD-9 has a poor ability to identify neonatal sepsis because no specific code is available among the codes for perinatal conditions.

Infants born after IVF and identified in the Medical Birth Register were compared with all infants born in Sweden during 1981–2001 and recorded in that register. A few percent of all infants born, according to the vital statistics kept by Statistics Sweden, were not registered in the Medical Birth Register. This can also be true for one of the infants in a multiple birth.

From an ongoing registration of all IVF procedures performed in Sweden (without individual identification), we estimated the number of transferred embryos in different types of IVF techniques. These data were available only for the years 1994–2000 (year of transfer).

Statistical Analysis

Statistical analysis was performed with the Mantel-Haenszel technique with adjustment for various putative confounders, as further specified. A risk was expressed as an odds ratio (OR) with its 95% confidence interval (95% CI) and was estimated with a test-based method (according to Miettinen). Two adjusted ORs were compared with two-tailed *z*-tests, with the χ^2 values from the adjusted ORs.

RESULTS

In Vitro Techniques Used

A total of 13,241 pregnancies were analyzed, with 16,280 infants registered. The distribution according to the IVF method used is shown in Table 1. Figure 1 shows the number of deliveries after standard IVF and ICSI, according to year of birth.

Multiple Births

Among the 13,241 deliveries, 3,006 were twin deliveries (23%). The frequency of monozygotic twins can be estimated with Weinberg's law, assuming that the number of dizygotic twin pairs is twice the number of unlike-sex twin pairs. Among the twin pairs, the sex of both twins was known in 2,676 pairs, and among them, 1,412 were

TABLE 1
Number of deliveries and infants, according to IVF technique used.

IVF method	Deliveries	Infants
Standard IVF		
Stimulated, fresh	8,067	10,116
Unstimulated, fresh	103	112
Frozen	890	1,055
Total	9,060	11,283
ICSI		
Ejaculated sperm	3,549	4,248
Epididymal sperm	109	146
Testicular sperm	126	151
Frozen ejaculated	305	343
Frozen other	28	33
Frozen unspecified	38	43
Total	4,155	4,955
Other or unspecified	26	33
Grand total	13,261	16,280

Källén. Infant outcome after IVF. Fertil Steril 2005.

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