Perinatal outcome, health, growth, and medical care utilization of 5- to 8-year-old intracytoplasmic sperm injection singletons

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Objective: To evaluate short- and long-term health in intracytoplasmic sperm injection (ICSI) singletons.
Design: Follow-up study.
Setting: University medical center, assessments between March 2004 and May 2005.
Patient(s): Singletons born between June 1996 and December 1999 after ICSI in the Leiden University Medical Center laboratory were compared with matched singletons born after IVF and natural conception.
Intervention(s): Mode of conception.
Main Outcome Measure(s): An examiner blinded to the conception mode of the child assessed congenital malformations and growth. Information on pregnancy, perinatal period, birth defects, general health, and medical consumption was obtained through questionnaires.
Result(s): Outcomes of children conceived by ICSI and IVF (n = 81/81, preterm infants excluded) were comparable or even more positive for ICSI. Perinatal outcomes were poorer after ICSI than natural conception: prematurity: P=.014; low birth weight: odds ratio = 7.4, 95% confidence interval (CI) [0.9; 62.5]; mean birth weight: Δ = 186 g, 95% CI [21; 351]. The ICSI mothers had more pregnancy complications (n = 33 vs. 18) and in-hospital deliveries (prevalence ratio 1.36, 95% CI 1.17; 1.48). No further differences were found between ICSI and natural conception children on congenital malformations, health, growth, and medical consumption (n = 87/85, preterm infants included).
Conclusion(s): No adverse health outcomes were identified in ICSI singletons up to age 5–8 years compared to IVF and natural conception singletons, besides poorer perinatal outcomes after ICSI versus natural conception. (Fertil Steril® 2008;89:1133–46. ©2008 by American Society for Reproductive Medicine.)

Key Words: ICSI, in vitro fertilization, pregnancy complication, birth weight, preterm birth, congenital abnormality, health care, health, growth, consumption

Intracytoplasmic sperm injection (ICSI) is an invasive method of artificial reproduction. Besides the mechanical damage that may occur due to the injection, fertilization may take place with oocytes and spermatozoa of lesser quality because natural selective barriers are circumvented (1–4). To evaluate the potential of negative consequences of the ICSI procedure, ICSI offspring is closely monitored on a wide range of outcome measures, for example, chromosomal aberrations (5), birth defects (6), perinatal outcome (7, 8), and development (9). Although the technique was introduced in 1992 (10), follow-up studies have not reached beyond the age of 5 years except for one project (11, 12).

Received December 12, 2006; revised April 23, 2007; accepted April 24, 2007.
Supported by the Leiden University Medical Center, Leiden, The Netherlands.
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In the present study we focus on pregnancy and perinatal outcome, congenital malformations and dysmorphic features, general health, growth, and medical care utilization up to age 5–8 years. By assessing this wide scope of outcomes in one defined group of children (born after ICSI, IVF, or natural conception [NC]) we aim to minimize selection and information bias. In addition, in reviewing the literature, general health, growth, and medical care utilization of ICSI children appear not to have been studied widely beyond the perinatal period into school-age (11, 13, 14). We differentiate two research questions. First, we assessed the potential negative effect of ICSI as compared to IVF on the various outcome measures. Both ICSI and IVF children have a background of parental subfertility, maternal hormonal stimulation, fertilization in vitro, and an increased risk of prematurity and low birth weight. The fertilization procedure differs. Second, we investigated the overall effect of ICSI compared to NC to answer the future parents' question: will the health outcome of my child differ if it is born after ICSI instead of NC, given similar parental characteristics up to the time of conception?

MATERIALS AND METHODS

The Institutional Review Board approved the study design. The investigators have no conflicts of interest to declare. Of all participants, at least one of the parents signed for informed consent. Data collection was carried out between March 2004 and May 2005.

Selection and Matching

Singletons conceived by ICSI and born between June 1996 and December 1999 after fertility treatment in the Leiden University Medical Center were invited. Exclusion criteria were: oocyte or sperm donation, cryopreservation of the embryo, and selective embryo reduction with medical indication. Identical inclusion criteria were used in the selection of children conceived by IVF who were matched person-to-person to ICSI participants for gender, socioeconomic status, gestational age (preterm/term), maternal age at the time of pregnancy (±3 years), and birth date (closest). Socioeconomic status low, medium, or high was ascribed using the zip code/socioeconomic status indicator of Statistics Netherlands (15), based on home price and income. If no match was available within the maternal age range of ±3 years, larger deviations were permitted.

Regular preschools and primary schools with zip codes that indicated social class distributions similar to the ICSI cohort assisted in the recruitment of naturally conceived singletons. We applied group matching on socioeconomic status, gender, and birth date. The composition of the NC control group from regular schools was reasonable as only one ICSI child attended special education.

Data Collection

Three detailed questionnaires were filled out by the parents: [1] general information, [2] pregnancy and birth, and [3] health of the child. Parental educational level was indexed according to the SOI register (standard education classification) of Statistics Netherlands (16). The parents were requested to bring the "baby book" (given to all mothers at the infant welfare center, where growth and other parameters are measured) or the obstetric data form to guide them through questions on birth parameters. Information on the incidence of vanishing twins in ICSI and IVF pregnancies and on the time of vanishing was retrieved from obstetric records. As a part of the questionnaire on child's health we used the World Health Organization/Region survey (17–19) to assess airway symptoms. Outcome consisted of prevalence and severity of the following symptom clusters and diagnoses: shortness of breath, wheeze, asthma, cough and phlegm, cough, runny/congested nose, and pneumonia. The questions covered the full history of the child as well as the past 12 months only.

In a physical examination, congenital malformations and dysmorphic features were reported by an investigator who was blinded to the mode of conception. A clinical geneticist, also blinded for conception mode, categorized the malformations in major malformations and minor malformations/dysmorphic features.

We examined three dimensional vision with a stereo test, using a Polaroid 3D Vectograph (Stereo Optical Co. Inc., Chicago, IL). Growth of the child was assessed by measuring height and weight on a calibrated balance, and head circumference using a nonstretching measuring tape.

The use of three detailed questionnaires resulted in missing values. The number of missing values was referred to in the tables by various symbols as explained in the legends.

Definitions

International definitions were followed for preterm (gestational age <37 weeks), very preterm (gestational age <32 weeks), low birth weight (<2,500 g), very low birth weight (<1,500 g), and small for gestational age (birth weight for gestational age < -2SD) (20).

Other definitions include: gestational hypertension: hypertension without proteinuria developing in the latter part of pregnancy in a previously normotensive woman; preeclampsia: onset of hypertension and proteinuria after 20 weeks of gestation or proteinuria superimposed on chronic hypertension; gestational diabetes: glucose intolerance of variable degree with onset or first recognition during pregnancy; ovarian hyperstimulation: combination of ovarian enlargement due to multiple ovarian cysts and an acute fluid shift out of the intravascular space.

Congenital malformations and dysmorphic features were studied on the basis of the Q-codes (Q0-99) of the ICD10 and on the textbook by Aase (21). Major malformations were defined to cause functional impairment or to require surgical correction. Complexity of the malformation and rarity of occurrence were also considered.

Statistics

Statistical analysis was performed with the SPSS 11.0 for Windows package (SPSS Inc., Chicago, IL). Continuous data were analyzed with an independent *t*-test if a normal distribution was likely and with a Mann-Whitney test if the distribution was skewed. Categorical data were analyzed using Pearson's χ^2 test. We performed linear and logistic regression analysis to adjust for confounders. Statistical significance was reached if $\alpha < 0.05$. Differences in continuous data were presented as a mean difference and 95% confidence interval (95% CI). Differences in categorical data (2 x 2) were expressed in terms of odds ratios (OR) and 95% CI if the prevalence of the outcome was <10% in at least one group. If the prevalence exceeded 10% in both groups the prevalence ratio (PR) and 95% CI was given, as the OR would overestimate or underestimate the relative risk in that situation (22). *P* values were provided for categorical data with more than two categories. Multitesting correction was not performed; instead, data were interpreted with caution and in the light of previous literature.