Does underlying infertility aetiology impact on first trimester miscarriage rate following ICSI? A preliminary report from 1244 singleton gestations

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BACKGROUND: We evaluated the impact of using ICSI for assisted fertilization on first trimester survival rates of singleton gestations among an unselected infertile population. METHODS: The 1244 singleton gestations achieved by ICSI were segregated according to underlying infertility aetiology, with 55.0\% having male factor, 3.6\% endometriosis, 4.3\% polycystic ovarian disease, 9.1\% tubal factor, 24.3\% unexplained and 3.3\% other. None of the patients had coexisting infertility factor. RESULTS: The survival rate of all ICSI singleton gestations during the first trimester was 72.2\%. There were no differences in early pregnancy loss (EPL) rate by infertility factor. Among patients undergoing ICSI because of male factor, there were no differences in EPL using ejaculated or non-ejaculated sperm. Regardless of aetiology, women aged >40 years had significantly higher EPL (42.1\%). CONCLUSION: Our preliminary results demonstrate that first trimester miscarriage rates of ICSI gestations are not affected by underlying infertility aetiology but are affected by maternal age.

Key words: ICSI/infertility/miscarriage/pregnancy

Introduction

Human reproduction is not efficient, with the majority of conceptions being lost very early in gestational life (Macklon et al., 2002). Implanted embryos may undergo developmental arrest at any point during early gestational life, and spontaneous abortion rates among natural conceptions are notoriously difficult to measure. Pregnancies achieved by the use of assisted reproduction technologies, however, are easier to follow than those conceived spontaneously, offering the opportunity to observe early gestational life ultrasonographically. Miscarriage significantly reduces the initial success and efficacy of assisted reproduction treatment, as well as increasing the psychological burden on patients. Couples who are planning assisted reproduction pregnancies should be informed of the potential hazards of these methods, enabling them to be aware of any potential risk factors that may cause miscarriage. Moreover, women who are candidates for assisted reproduction technology have characteristics that may predispose them to an increased risk of miscarriage (Ezra and Schenker, 1995). Thus, information about the presence and the extent of excess risk of miscarriage in assisted reproduction pregnancies would be useful for assessing their outcomes and for counselling of these patients.

Several studies have assessed miscarriage rates in in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) pregnancies as well as the origin of spermatozoa utilized for assisted fertilization is considered in this regard (Coulam et al., 1996; Govaerts et al., 1998; Orvieto et al., 2000; Wennerholm et al., 2000; Schieve et al., 2003). Miscarriage rates have been also documented in groups of patients with a specific aetiology of infertility, such as polycystic ovarian syndrome (PCOS) or male factor (Mercan et al., 1998; Wang et al., 2004). On the other hand, it is of importance to note that miscarriage rates among patients who conceived by assisted reproduction treatment have not been segregated by multiplicity of the gestation.

At present, almost half of fresh embryo transfers result from ICSI (Human Fertilisation and Embryology Authority, 2000) and ICSI has become a routine laboratory service. However, the use of testicular sperm and the micromanipulation of gametes have raised questions about the safety of this procedure. It is therefore necessary to clarify whether ICSI should be used for all \textit{in vitro} inseminations.

Since chromosomal abnormalities (mostly aneuploidy) have been reported to account for 50–75\% of miscarriages during the first trimester of gestation (Goddijn and Leschot, 2000; Philipp et al., 2003), one measurable outcome to evaluate the safety of ICSI can be the rate of miscarriage among ICSI pregnancies. Conceivably, an increased rate of pregnancy loss may indicate an abnormal outcome related to ICSI as a technique. However, miscarriage rates have not been
extensively assessed in a general infertile population (regardless of male factor) undergoing assisted reproduction treatment with ICSI. It is therefore important to document the survival rate of implanted gestations following ICSI and to compare these rates relative to underlying aetiology of infertility. In this study, we report the first trimester survival rates of singleton gestations achieved by ICSI from patients with different types of infertility.

Materials and methods

Patients

The database of the German Hospital at Istanbul was retrospectively evaluated to identify all singleton gestations conceived by ICSI during the period from 1997 to 2002. Among the 8417 patients who underwent ICSI, 2186 (25.9%) were diagnosed as singleton gestations following embryo transfer. We excluded from this study all patients who were subsequently followed up outside the hospital and those who had monochorionic or heterotopic pregnancies or frozen–thawed embryo transfer. Couples having coexisting infertility factors or women with a history of recurrent pregnancy loss were excluded from the study, as were couples known to have structural or numerical chromosomal aberrations.

The remaining gestations were categorized according to the underlying aetiology of infertility. Male factor cases were diagnosed according to the standards of the World Health Organization; tubal factor cases were diagnosed by either hysterosalpingogram or laparoscopy; PCOS was diagnosed by irregular menses, reversed FSH:LH ratio and sonographic appearance of ovaries; and all endometriosis cases were stage ≥II according to the American Fertility Society classification. Infertility was defined as unexplained if comprehensive evaluation failed to reveal any apparent cause.

Pregnancy was diagnosed as the presence of an intrauterine implanted embryo, defined as a gestational sac as defined by transvaginal ultrasonogram following ICSI and embryo transfer. A gestational sac was defined by the presence of an intrauterine hypoechogenic area of ≥8 mm and covered by a double echogenic rim with a visible yolk sac (diameter ≥2 mm), as identified by a 6 MHz vaginal probe (Apio 80, Powervision and Corevision; Toshiba Corp., Japan).

A miscarriage was defined as the cessation or lack of detection of cardiac activity in the gestational sac or the inability to detect a previously defined gestational sac after vaginal bleeding during the 10 weeks following embryo transfer. Gestations with trophoblast regression but without sonographic evidence of pregnancy were not considered as miscarriages.

All patients underwent scanning by transvaginal ultrasonogram 3 weeks (18–22 days) after embryo transfer. None of the gestations evaluated started as a multiple type followed by subsequent vanishing of embryos.

All patients continued to receive progesterone, 100 mg i.m., as luteal phase support for 8 weeks after embryo transfer. In our centre, the method for assisted fertilization was ICSI, which was used in all patients regardless of their aetiology of infertility.

All couples were thoroughly informed about the treatment procedures, and written informed consent was obtained from all patients. The treatment protocols were approved by the ethics committee of the German Hospital at Istanbul.

Statistical analyses were performed using the χ²-test, Fisher’s exact test, analysis of variance with Bonferroni’s post hoc test, and multivariate logistic regression analysis, where applicable. P < 0.05 was considered statistically significant.

Results

Among the 2186 singleton gestations achieved by ICSI in our hospital during the period from 1997 to 2002, 1244 (56.9%) met the inclusion criteria for this study. When we diagnosed infertility factors among the recruited couples, we found that 684 (55.0%) were due to male factor, 113 (9.1%) to tubal factor, 45 (3.6%) to endometriosis, 54 (4.3%) to PCOS, 41 (3.3%) to other factors (hyperprolactinaemia, hypogonadotropic hypogonadism, myoma uteri, uterine dysconfiguration, genital tuberculosis, or secondary infertility), and 302 (24.3%) were unexplained. The mean age of the women was 32.1 ± 4.3 years, and the mean age of their spouses was 36.6 ± 3.8 years.

During the first trimester, 234 (18.8%) patients experienced pregnancy loss. Miscarriage rate was significantly higher in women aged >40 years than in younger women (42.1 versus 17.6%; OR, 3.1; 95% CI, 2.0–5.7; P < 0.0001).

Multivariate logistic regression analysis demonstrated that miscarriage rates in singleton gestations did not differ according to underlying infertility factor (P > 0.05) (Table I). However, when the infertility categories were divided according to age (<35 versus ≥35 years), older patients with male factor, unexplained factor and tubal factor had significantly increased rates of miscarriage compared with younger patients. In contrast, the survival rates of gestations among the remaining infertility categories were not affected by age (Table II).

Among patients with male factor infertility, there was no difference in miscarriage rates when surgically retrieved sperm (15/81, 18.5%) or ejaculated sperm (115/604, 19.0%) were used for ICSI. Miscarriage rates also did not differ in patients undergoing assisted reproduction treatment with ICSI because of female factor (18.7%) (Figure 1).

Discussion

Several studies have reported miscarriage rates in ICSI pregnancies (Table III), and have compared rates in IVF and spontaneous pregnancies. Whereas most have found no significant differences in early miscarriage rates, one study found that the early pregnancy loss rate was significantly lower in ICSI (11%) than in IVF (24%) pregnancies (Orvieto

Table I. Miscarriage rates of gestations by infertility factor

<table>
<thead>
<tr>
<th>Infertility Factor</th>
<th>n</th>
<th>Age (years)</th>
<th>No. of miscarriages (%)</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male factor</td>
<td>685</td>
<td>32.02 ± 4.9</td>
<td>130 (18.9)</td>
<td>0.74</td>
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<tr>
<td>Unexplained</td>
<td>303</td>
<td>31.61 ± 4.8</td>
<td>55 (18.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>114</td>
<td>32.34 ± 4.7</td>
<td>20 (17.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>46</td>
<td>32.32 ± 4.1</td>
<td>11 (23.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>PCOS</td>
<td>54</td>
<td>30.8 ± 4.7</td>
<td>13 (24.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Others</td>
<td>42</td>
<td>31.59 ± 5.3</td>
<td>6 (14.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Total</td>
<td>1244</td>
<td>32.08 ± 4.3</td>
<td>235 (18.8)</td>
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</tbody>
</table>

Multivariate logistic regression.

aMean ± SD.

OR = odds ratio; CI = confidence interval; PCOS = polycystic ovarian syndrome.
et al., 2000). Although there are no randomized data on miscarriage rates following ICSI and IVF (van Rumste et al., 2004), early pregnancy and perinatal outcomes of ICSI gestations appear not to be different from those of IVF gestations (Tarlatzis and Bili, 2000; Wennerholm et al., 2000; Kozinszky et al., 2003). In addition, no clinical effects of ICSI severe enough to cause a miscarriage during the first trimester have been reported (ASRM/SART, 2002).

It has been suggested that offspring from ICSI carry an increased rate of chromosomal aberrations (Bonduelle et al., 2002). Those abnormalities, however, seem to be related to the underlying parental risk of abnormality and not to the ICSI procedure itself. Although patients undergoing assisted reproduction treatment have a higher rate of miscarriage than do fertile patients, these differences in loss rates are not completely understood and may originate from predisposing factors that are more prevalent in patients suffering from infertility (Ezra and Schenker, 1995).

We recently reported that prenatal karyotypes of fetuses in pregnancies achieved by ICSI for male factor infertility did not differ from fetal karyotypes in pregnancies achieved by ICSI for non-male factor infertility (Jozwiak et al., 2004). Furthermore, IVF and ICSI pregnancies that aborted during the first trimester showed no significant differences in the incidence of embryonic anomalies (Causio et al., 2002).

In the majority of reports, ICSI procedures have been performed in cases of male factor infertility, which may eventually pose a risk to the offspring. Therefore, we studied segregated gestations according to male and female factor infertility, with the latter category consisting of infertility aetiologies depending on women as a single group. Male factor infertility was further subdivided into groups in which ejaculated sperm and non-ejaculated sperm were used.

The impact of sperm origin and quality on miscarriage rates was assessed among ICSI pregnancies and compared to those of IVF pregnancies. No differences in miscarriage rates have been reported in patients undergoing ICSI for male factor or IVF for non-male factor (Mercan et al., 1998), and semen origin was found not to affect the miscarriage rate in both sets of patients (Palermo et al., 2000). We also found that sperm origin did not have any impact on the early survival rate of gestations. In contrast to our findings, the miscarriage rate has been reported to be higher in gestations using surgically retrieved sperm than in those using ejaculated sperm (Anderson et al., 2002), although others have reported similar results for both groups (Wennerholm et al., 2000; Goker et al., 2002).

To our knowledge, our study is the first in which miscarriage rates in a relatively large number of singleton ICSI pregnancies have been segregated according to male and non-male factor infertility. Our results confirm that first trimester survival rates of singleton gestations did not differ when patients with non-male factor infertility underwent ICSI. We also found that the survival rates of gestations

| Table II. Outcome of gestations by infertility factor and maternal age |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Age < 35 years  | Age ≥ 35 years  | Or 95% CI       | P               |
|                | No. of         | No. of          | No. of          | No. of          |
|                | pregnancies     | miscarriages (%)| pregnancies     | miscarriages (%)|
| Male factor    | 461             | 65 (14)         | 224             | 65 (29.0)       |
| Unexplained    | 210             | 27 (12.8)       | 93              | 28 (30.1)       |
| Tubal factor   | 73              | 8 (10.9)        | 41              | 12 (29.2)       |
| Endometriosis  | 30              | 6 (20.0)        | 16              | 5 (31.2)        |
| PCOS           | 41              | 9 (21.9)        | 13              | 4 (30.7)        |
| Others         | 29              | 3 (10.3)        | 13              | 3 (23.0)        |
| Total          | 844             | 118 (13.9)      | 400             | 117 (29.2)      |

Fisher’s exact and χ²-tests.

OR = odds ratio; CI = confidence interval; PCOS = polycystic ovarian syndrome; NS = not significant.

<table>
<thead>
<tr>
<th>Table III. Miscarriage rates in ICSI pregnancies</th>
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<tr>
<td>Author</td>
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<tr>
<td>Wisanto et al. (1995)</td>
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<td>Coulam et al. (1996)</td>
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<td>Wennerholm et al. (2000)</td>
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<td>Tummers et al. (2003)</td>
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<td>Wang et al. (2004)</td>
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</table>

*IVF and ICSI pregnancies were mixed. EPL = early pregnancy loss.
achieved by ICSI among non-male factor patients did not differ from those of IVF pregnancies (Winter et al., 2002). miscarriage rates among individuals with different causes of infertility have not been assessed thoroughly. Miscarriage rates in a subgroup of patients with infertility factor have been and are being reported in most studies addressing assisted reproduction technology as a part of the outcome. Although individuals with PCOS are prone to have miscarriages (Reindollar, 2000), recent studies have demonstrated that this adverse effect is related not only to the condition itself but to coexisting obesity (Wang et al., 2004). While we found that the miscarriage rate was highest among PCOS pregnancies, it did not differ significantly from that of the other groups, primarily because of the relatively small size of our PCOS group. We also confirmed that miscarriage rate was not higher in patients with endometriosis than in the general infertile population (Matorras et al., 1998; Kortelahti et al., 2003). Similarly, we found that the miscarriage rate in ICSI patients with unexplained infertility did not differ from that in the general infertile population, a result previously observed in patients with unexplained infertility undergoing IVF (Isaksson et al., 2002). In agreement with previous studies, we observed an increased risk of miscarriage with increasing maternal age (Fretts et al., 1995; Abdalla et al., 1993; Andersen et al., 2000). Indeed, we found that almost half of women aged >40 years aborted prior to the second trimester. Similarly, a 50% miscarriage rate has been reported in women aged >40 years undergoing ICSI (Nikolettos et al., 2000), and the delivery rate is only 12% in this group of women (Osmanagaoglu et al., 2002). Therefore, prior to assisted reproduction treatment, the likely pregnancy outcome of these individuals should be considered, and couples should be informed accordingly. The current study differs in two ways from similar studies evaluating miscarriage rates in ICSI pregnancies. The earlier studies used the demonstration of a fetal heartbeat to define pregnancy. This method, however, may miss a significant number of implanted embryos following transfer, which would have been detected by the presence of a gestational sac, even in the absence of cardiac motion. In other words, this method may underestimate the lifespan of earliest stage implanted embryos, which would have been detected by ultrasonographic visualization. We recently demonstrated vanishing embryos in multiple gestations by using the presence of a gestational sac as a landmark (Ulug et al., 2004), indicating that this approach would better evaluate the intrauterine fate of implanted ICSI embryos. In contrast to most other studies evaluating miscarriage rates in ICSI pregnancies, we evaluated miscarriage rates only in singleton gestations. Most of the earlier studies assessing early pregnancy loss in ICSI pregnancies did not account for multiple fetuses and defined abortion as the total miscarriage of the pregnancy. During early gestational life, a significant number of multiple gestations can have spontaneous reductions, which should be considered in calculations of abortion rates (Ulug et al., 2004). In addition, the survival rates of singleton gestations differ from those of multiple gestations during the first trimester (Sebire et al., 1997; Tummers et al., 2003). In conclusion, we have shown that first trimester miscarriage rates in singleton gestations achieved by ICSI were not affected by the underlying infertility factor, but were affected by maternal age. Our results also demonstrated that ICSI did not pose additional risk for miscarriage when utilized as a regular assisted fertilization method for infertile couples undergoing assisted reproduction treatment.

References


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