Factors influencing the obstetric and perinatal outcome after oocyte donation

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BACKGROUND: We evaluated interactions between perinatal outcome after oocyte donation and various maternal factors. METHODS: The study included 134 parturients after oocyte donation. Data were collected from medical files and personal interviews. Stepwise logistic regression analyses were used to evaluate associations between perinatal outcomes and selected maternal variables. RESULTS: Fifty percent of the women were >43 years old, 30.6% were >45 years and 67.9% were nulliparous. The rates of pregnancy induced hypertension (PIH), gestational diabetes and first and second trimester vaginal bleeding (STB) were 27.6, 23.9, 43.3 and 6% respectively, while 72% had Caesarean deliveries. The rates of preterm (PD), low birth weight (LBW), small for gestational age (SGA) deliveries and major malformations were respectively 14.9, 14.9, 7.6 and 2.2%. Using a logistic regression, PD was significantly associated with PIH, STB and maternal smoking. LBW deliveries were significantly associated with PIH, STB, nulliparity and maternal smoking. SGA babies were significantly associated with PIH. These perinatal outcomes were not associated with advanced maternal age or ovarian failure. CONCLUSIONS: There is a high risk of obstetric complications in singleton oocyte donation pregnancies, but the perinatal outcomes are favourable. Patients should be counselled about these risks and monitored for these complications during pregnancy.

Key words: first and second trimester bleeding/gestational diabetes mellitus/hypertensive disorders in pregnancy/oocyte donation/perinatal outcome

Introduction

Oocyte donation is a well-established method for the treatment of infertility in women (Remohi et al., 1997; Yaron et al., 1998). The high success rate of this procedure (Society for Assisted Reproductive Technologies, American Society for Reproductive Medicine, 2002) has led to its wide application in women with ovarian failure or dysfunction, at various ages and for various aetiologies. Oocyte donation is also offered to patients who repeatedly fail to conceive with standard IVF (Serhal and Craft, 1989).

Oocyte donation patients represent a unique parturient population because of the high incidence of advanced maternal age, often >45 years, and the high proportion of women with dysfunctional ovaries.

Most of the previous studies that have assessed the obstetric outcome after oocyte donation reported high rates of complications, such as pregnancy induced hypertension (PIH), gestational diabetes mellitus (GDM) and first trimester bleeding (FTB). However, these studies were based on a small number of women or were limited to only few obstetric or perinatal outcome measures (Serhal and Craft, 1989; Blanchette, 1993; Pados et al., 1994; Sauer et al., 1995, 1996; Remohi et al., 1997; Abdalla et al., 1998; Söderström-Anttila et al., 1998; Yaron et al., 1998). Moreover, very limited information is available regarding the risk factors affecting the perinatal outcome of these pregnancies.

The purpose of this study was to determine the obstetric and perinatal outcome of 134 singleton pregnancies following oocyte donation and to evaluate the interaction of these outcome variables with selected risk factors.

Patients and methods

We enrolled 170 consecutive women who conceived following oocyte donation at the Assuta IVF Unit in Tel-Aviv and who delivered between January 1995 and February 1999. In order to eliminate the confounding variable of multiple pregnancies, typically associated with a higher rate of obstetric and perinatal complications, we elected to restrict our study group to the 134 gestations with a singleton fetus. The steroid replacement regimen used was determined according to the preference of the individual attending.

Obstetric and perinatal data were collected in all cases through review of medical files and by detailed post-partum questionnaires and personal interviews. In particular, we recorded the maternal age (advanced maternal age was defined as an age at delivery >45 years), parity, smoking during pregnancy, previous uterine scar, extent of ovarian function at conception, PIH [classified according to the
American College of Obstetrics and Gynecology criteria (ACOG technical bulletin, 1996), GDM, FTB and second trimester bleeding (STB). Outcome variables included preterm delivery (PD) (delivery at <37 gestational weeks), low birth weight (LBW; <2500 g), small for gestational age [SGA, defined as a birth weight lower than the fifth percentile using the intrauterine curves of Alexander (Alexander et al., 1996)], Caesarean delivery, and need for admission to the neonatal intensive care unit (NICU).

Congenital malformations were classified according to Myrianthopoulos and Chung. (Myrianthopoulos and Chung, 1974).

Statistical analyses
Results are reported as mean ± SD, or n (%). Multiple stepwise logistic regression analysis was used to evaluate the association between a specific discrete perinatal outcome variable and the above mentioned demographic or obstetric variables. Odds ratios (ORs) and their 95% confidence interval (CI) were calculated. P < 0.05 was considered significant.

Results
The mean ± SD age of the women in the study was 41.3 ± 7.0 years (range 24–62). Advanced maternal age (>45 years) was present in 30.6% of the study population (41 women out of 134) and more than half of the women were >43 years old (50.7%). The age of 32 women was 46–49 years. The rates of women with ovarian failure, nulliparity, smoking and previous uterine surgery were 35, 67.9, 13.4 and 14.2% respectively. Indications for oocyte donation were as follows: (i) 80 women had functioning ovaries, but failed to conceive after several IVF cycles; 31 of them were <40 years old; (ii) 47 women had ovarian failure; among them, eight were classified as having primary amenorrhoea due to ovarian dysgenesis, five were classified as having amenorrhoea secondary to chemotherapy and/or irradiation treatment of a previous malignancy, 13 were diagnosed with premature ovarian failure (<40 years old) of unknown aetiology and 21 women were menopausal; (iii) in seven cases the indication for oocyte donation could not be clearly determined from the chart review.

The incidence of PIH was 27.6%. The women were further classified as having chronic hypertension (2.2%), gestational hypertension (10.4%), pre-eclampsia (5.2%) or severe pre-eclampsia (6.7%); 2.9% could not be classified. The rate of hypertension among women >45 years was 30%, non-significantly different from the 22% rate in women <45 years. The rates of GDM, FTB and STB were 23.9, 43.3 and 6% respectively. Among the women who developed GDM, 28.1% required insulin for adequate glycaemic control. Approximately 20% of the women had a spontaneous vaginal delivery. While 72% of the women had Caesarean deliveries, more than half of them were non-elective.

The mean ± SD length of gestation was 38.0 ± 2.6 weeks. The rate of PD, LBW and SGA were 14.9, 14.9 and 7.6% respectively. The mean birth weight was 2998 g. There were no cases of perinatal mortality, and the rate of major congenital malformations was 2.2%.

Table I depicts the ORs and 95% CIs for the factors associated with PD, LBW, babies born SGA, deliveries by Caesarean section and the need for NICU. PD was significantly associated with PIH, STB and maternal smoking. LBW deliveries were significantly associated with PIH, STB, nulliparity and maternal smoking. The delivery of an SGA baby was significantly associated with PIH. A stay in the NICU was significantly associated with GDM, STB and maternal smoking. These adverse perinatal outcomes were not significantly associated with advanced maternal age (>45 years) or ovarian failure. Caesarean delivery was associated with advanced maternal age, PIH, GDM and a previous uterine scar.

Discussion
The present study is one of the largest series of singleton pregnancies after oocyte donation reported to date. It includes a wide range of indications for oocyte donation and depicts a large number of obstetric and perinatal outcomes. Several studies have previously described the outcome of oocyte donation pregnancies (Tables II and III). However, these studies were smaller and were limited to specific age groups or to specific indications for oocyte donation. They often addressed a limited number of obstetric or perinatal outcomes and related to both singleton and multiple pregnancies.

In our study, limited by design to singleton pregnancies, we found that oocyte donation pregnancies were complicated by a high incidence of PIH, GDM, FTB and STB. Adverse perinatal outcomes were strongly associated with PIH, STB, GDM and maternal smoking, but not with age >45 years and ovarian failure.

FTB was the most frequently observed obstetric complication, presenting in 43.3% of our patients. Vaginal bleeding was reported to occur very frequently (12–15%) after oocyte donation (Pados et al., 1994; Abdalla et al., 1998; Söderström-Anttila et al., 1998). It has been suggested that FTB may be linked to early resorption of one or more fetuses in pregnancies that were multifetal early on (Shaw and Sauer, 1995). However, this seems unlikely in oocyte donation pregnancies since, first, transfer of only two oocytes per cycle has been reported to result in a high frequency (53%) of FTB (Söderström-Anttila et al., 1998) and second, IVF pregnancies (without oocyte donation) are associated with a low percentage of FTB (Tan et al., 1992; Söderström-Anttila et al., 1998). Another theoretical explanation is that the steroid replacement therapy received by the patient does not always provide the best endocrine environment for embryonic development. The aetiology for the high rate of FTB is yet to be explained. Nevertheless, the influence on pregnancy outcome seems limited and FTB was not associated with adverse perinatal effects.

In our series, there was no difference in the frequency of FTB between patients with ovarian failure and those with functioning ovaries; this finding is consistent with that of Söderström-Anttila et al. (Söderström-Anttila et al., 1998), but differs from the results reported by Pados et al (Pados et al., 1994).

The high rate of STB was unexpected since it has not been previously reported. Other authors reported rates of 5.8% (Pados et al., 1994) and 1% (Abdalla et al., 1998). In the series of Lipitz et al. in spontaneous pregnancies, STB was
Table I. Odds ratios (95% confidence intervals) for the factors associated with preterm delivery (PD), low birth weight (LBW), babies born small for gestational age (SGA), Caesarean section (CS) and admission to neonatal intensive care unit (NICU)

<table>
<thead>
<tr>
<th>Factor</th>
<th>PD</th>
<th>LBW</th>
<th>SGA</th>
<th>CS</th>
<th>NICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;45 years</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension disorders in pregnancy</td>
<td>4.79 (1.7–13.7)</td>
<td>NS</td>
<td>4.18 (0.7–23.1)</td>
<td>2.93 (0.8–10.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Second trimester bleeding</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Previous uterine scar</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant by multiple stepwise logistic regression analysis.

Table II. Comparison of demographic data and obstetric outcome in studies of singleton pregnancies after oocyte donation

<table>
<thead>
<tr>
<th>Number single/ mean maternal age (years) total</th>
<th>Mean maternal age (years) singleton</th>
<th>Age &gt;45 years</th>
<th>PIH</th>
<th>GDM</th>
<th>First trimester bleeding</th>
<th>Second trimester bleeding</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study (134/ 170)</td>
<td>41/41</td>
<td>30.6</td>
<td>27.6</td>
<td>23.9</td>
<td>43.3</td>
<td>6</td>
<td>72.3</td>
</tr>
<tr>
<td>Yaron et al., 1998b (104/155)</td>
<td>NG/NG</td>
<td>NG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Abdalla et al., 1998b (105/140)</td>
<td>NG/NG</td>
<td>NG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Söderström-Anttila et al., 1998b</td>
<td>39/49</td>
<td>33.5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>51</td>
</tr>
<tr>
<td>Remohi et al., 1997b (188/254)</td>
<td>NG/NG</td>
<td>NG</td>
<td>NG</td>
<td>NA</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Sauer et al., 1996b (45/74)</td>
<td>NG/NG</td>
<td>NG</td>
<td>NG</td>
<td>NA</td>
<td>NA</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Sauer et al., 1995b (10/17)</td>
<td>NG/NG</td>
<td>NA</td>
<td>100</td>
<td>20</td>
<td>0</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Pados et al., 1994b (44/52)</td>
<td>NG/NG</td>
<td>NG</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Salha et al., 1999b (3/39)</td>
<td>NG/NG</td>
<td>NG</td>
<td>28.2</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Serhal and Craft, 1989 (NG/21)</td>
<td>NG/NG</td>
<td>NG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NG</td>
<td>NG</td>
</tr>
</tbody>
</table>

Table III. Comparison of perinatal outcome in studies of singleton pregnancies after oocyte donation

<table>
<thead>
<tr>
<th>Perinatal mortality</th>
<th>Neonatal malformations</th>
<th>PD&lt;sup&gt;a&lt;/sup&gt; weight (g)</th>
<th>Mean birth</th>
<th>LBW&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SGA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Logistic regression for perinatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>0</td>
<td>2.2</td>
<td>14.9</td>
<td>2998</td>
<td>14.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Yaron et al., 1998b</td>
<td>0</td>
<td>NG</td>
<td>10.6</td>
<td>3022</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Abdalla et al., 1998b</td>
<td>NA</td>
<td>NA</td>
<td>13</td>
<td>NG</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Söderström-Anttila et al., 1998b</td>
<td>NA</td>
<td>5.1</td>
<td>13</td>
<td>3338</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Remohi et al., 1997b</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>3058</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Sauer et al., 1996b</td>
<td>0</td>
<td>NA</td>
<td>3218</td>
<td>NG</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Sauer et al., 1995b</td>
<td>0</td>
<td>NA</td>
<td>NG</td>
<td>3390</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>Pados et al., 1994b</td>
<td>1/44</td>
<td>NG</td>
<td>NG</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Present in only 1% of the women, and was associated with a fetal loss of 32% (Lipitz et al., 1991). It is known that STB, even of short duration, is associated with adverse fetal outcome (Yang and Savitz, 2001). In our series, STB was significantly associated with PD and LBW deliveries, and with an increased length of stay in the NICU.

The rate of chronic hypertension among our parturients was only 2.2%. However, hypertensive disorders in pregnancy were the second most frequently observed obstetric complication in our patients. This is consistent with previous reports showing rates varying between 23 and 38% (Serhal and Craft, 1989; Blanchette, 1993; Pados et al., 1994; Sauer et al., 1995b, 1996b, 1998b; Remohi et al., 1997b; Sauer et al., 1995b; Pados et al., 1994b; Abdalla et al., 1998b; Yaron et al., 1998b; Serhal and Craft, 1989).
et al., 1995, 1996; Abdalla et al., 1998; Söderström-Anttila et al., 1998; Yaron et al., 1998). This is in contrast with an incidence of PIH of 6–12% in the general population (Sibai et al., 1993; Gifford et al., 2000). It has been suggested that the increased rate of hypertension in oocyte donation pregnancies is related to advanced maternal age, nulliparity and ovarian failure (Pados et al., 1994; Yaron et al., 1998; ACOG practice bulletin, 2002). However, in our study, these were not independent risk factors for hypertensive disorders in pregnancy, which is consistent with others findings (Abdalla et al., 1998; Söderström-Anttila et al., 1998). Despite the multifactorial pathophysiology of PIH, more recent reports provide further support to the hypothesis that the development of PIH in oocyte recipients may be due to altered or inadequate immunoprotection of the feto-placental unit, due to the short duration of exposure to non-maternal antigens (Salha et al., 1999; Wang et al., 2002). The evidence that pre-eclampsia may be a disorder of the immunological mechanism involved in the normal feto-maternal host response includes several mechanisms, which indicate that exposure to paternal antigens is protective. In the oocyte recipient, immunological hyporesponsiveness can be explained either by an increased likelihood of human leukocyte antigen sharing between the mother and the two sets of paternal and donor oocyte histocompatibility antigens, or by an excessive antigenic load overwhelming the responder state, features that are more prominent in patients with ovarian failure. However, an article by Hall et al. does not support this theory, as, in their study which compared IVF pregnancies with donor sperm and with partner sperm, it was shown that long-term sexual cohabitation offers no protection from hypertensive disease of pregnancy (Hall et al., 2001). Nevertheless, hypertensive disorders in pregnancy were strongly associated with perinatal complications, such as PD, LBW and SGA deliveries. All of the complications noted above are well known to occur in hypertensive disorders in pregnancy regardless of its context (Cunningham et al., 2001; Ray et al., 2001).

GDM was seen in 23.9% of the women in this study, while the incidence of GDM in the general population is reported to be 2.5% (Xiong et al., 2001). Many diabetic women in our study (28.6%) required insulin for adequate glycaemic control. Advanced maternal age was not associated with a higher rate of GDM. Diabetes in pregnancy was associated with an increased rate of Caesarean deliveries and a greater rate of admissions to the NICU. The latter can probably be explained by the fact that infants born to a diabetic mother are more likely to be admitted to the NICU for blood sugar monitoring.

In spite of the high motivation of women who conceive through oocyte donation, in our series 13.4% of them smoked throughout pregnancy. As expected, smoking was associated with increased PD and LBW deliveries, and subsequently with more frequent stays in the NICU (Stillman et al., 1986; Voight et al., 1990).

Nulliparity was associated with LBW deliveries, which may be due to the fact that, in general, nulliparous women deliver children of lower birth weight than multiparous women (Seidman et al., 1988).

The rate of Caesarean deliveries was exceptionally high (72.3%), consistent with previous reports (Blanchette, 1993; Pados et al., 1994; Sauer et al., 1996; Abdalla et al., 1998; Söderström-Anttila et al., 1998; Yaron et al., 1998). The performance of the procedure was affected by the presence of PIH and GDM, advanced maternal age, and a previous uterine scar. All of the above-mentioned conditions are known risk factors for Caesarean delivery, but oocyte donation may represent an additional, independent risk factor (Dulitzki et al., 1998).

In terms of perinatal outcome variables, it may appear that the rate of PD was not significantly elevated, at 14.9%. This actually might not be entirely true, since in Israel, the rate of premature deliveries is much lower than in the USA, at ~7% (Melamed et al., 2000). Moreover, the rate of 7% in Israel is an overall one, including both singleton and multiple pregnancies, while this study, including only singleton pregnancies, should have led to an even lower rate than that in the general population. This would suggest that the rate of PD is high in singleton oocyte donation pregnancies, which is consistent with the recent finding that infants conceived with use of assisted reproduction technology, including IVF, are associated with a similarly high rate of prematurity even in singleton pregnancies (Bergh et al., 1999; Scheive et al., 2002).

Encouragingly, the rate of major congenital malformations was similar to that observed in the general population, which is in contrast with the recent finding that infants conceived with the use of IVF have twice as high a risk of congenital malformations as naturally conceived infants (Hansen et al., 2002). However, the power to detect any difference compared with the general population is very low in our study, due to the limited number of patients included.

A limitation of the present study is the lack of a control group. However, an appropriate control group would be difficult, if not impossible, to obtain because it would require the selection of spontaneously pregnant women at similar ages. An unbiased match is unlikely as fertility strikingly decreases with advancing age. Nevertheless, our study provides important risk estimates which should be made available to women electing to undergo oocyte donation.

In summary, our study, among the largest series of its type, revealed a high risk of obstetric complications in singleton oocyte donation pregnancies. Patients should be counselled about these risks prior to undergoing oocyte donation, and should be carefully monitored for these complications during pregnancy. Nevertheless, in spite of these obstetric complications, it appears from our study that the perinatal outcome is overall favourable.

References


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