The aged uterus: multifetal pregnancy outcome after ovum donation in older women

Michal J. Simchen, Adrian Shulman, Amir Wiser, Eran Zilberberg, and Eyal Schiff

Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Kfar Saba, Israel
Ramat Gan, and Meir Medical Center, Kfar Saba, Israel
Correspondence address. Tel: +972-3-5302169; Fax: +972-3-5302922; E-mail: michal.simchen@sheba.health.gov.il

BACKGROUND: We aimed to investigate whether multifetal pregnancies are at risk of more pregnancy complications in women of advanced age after ovum donation.

METHODS: Pregnancy outcome in women after ovum donation aged 40 and above was extracted. Labor and delivery data as well as antenatal records of women carrying twins were compared with those of singletons, as well as to a control group of all twin pregnancies delivered at Sheba Medical Center during 2007.

RESULTS: One hundred and twenty-five women after ovum donation aged ≥40 were studied. Of those, 42 women carried twin pregnancies and 83 carried singletons. The 42 women carrying twins comprised the study group and were compared with 417 control women with twins. Mean maternal age was 49.2 ± 4.3 years. Hypertensive complications (50%), diabetes in pregnancy (31%) and hospitalization in pregnancy (69%) were all extremely high in the study group. Mean gestational age at delivery was lower for the study group compared with controls (35.2 ± 2.3 versus 35.7 ± 2.6 weeks), with 35.7% of infants in the study group born ≤34 weeks gestation compared with 21.8% of controls, (OR: 1.99, 95% CI: 1.02–3.89). Mean birthweight was also significantly lower for study group infants compared with controls, with 77% of study infants born <2500 g compared with only 60% of controls (OR: 2.22, 95% CI: 1.3–3.77).

CONCLUSIONS: Pregnancy in advanced maternal age women after ovum donation carrying twins is associated with significant maternal and fetal complications, with increased risks of prematurity and lower birthweight. Possibly, the aged uterus is less suitable for carrying a multifetal pregnancy than a younger uterus. Therefore, the alternative of transferring a single, good-quality embryo should be the preferred option.

Key words: multifetal pregnancy / ovum donation / advanced maternal age / ED / egg donation

Introduction

With the rise in maternal age at first pregnancy over the last several decades, there has been increasing interest in the impact of advanced maternal age on pregnancy outcome. Several studies have focused on advanced maternal age, with the age cut-off defining ‘advanced maternal age’ being pushed upward progressively. Recently, we have published on maternal outcome over the age of 50 (Simchen et al., 2006), whereas others have also looked at the impact of pregnancy in the 6th decade of life on maternal as well as fetal outcome (Paulson et al., 2002; Salihu et al., 2003). Oocyte donation is now commonly used in menopausal women, despite their advanced chronological age. Pregnant women of advanced maternal age were found to have an increased risk of hypertensive and diabetic complications of pregnancy (Bianco et al., 1996; Dildy et al., 1996; Dulitzki et al., 1998), as well as an increased risk of Cesarean delivery (Bianco et al., 1996; Dulitzki et al., 1998; Callaway et al., 2005), whereas infants of women of advanced maternal age were found to be at an increased risk of intrauterine death (Fretts et al., 1995; Canterino et al., 2004; Jacobsson et al., 2004), as well as growth restriction and prematurity (Jolly et al., 2000; Simchen et al., 2006).

Multifetal pregnancy is a well-recognized risk factor for pregnancy complications and adverse pregnancy outcomes, including perinatal death, fetal growth abnormalities and premature delivery with its associated complications. It is also an independent risk factor for maternal complications such as hypertension and diabetes.

We hypothesized that women of advanced maternal age have an increased risk of complications when carrying a multifetal pregnancy.
In order to investigate this hypothesis, we examined pregnancy outcomes of twin pregnancies achieved with donor eggs in women over the age of 40. Thus, we hoped to isolate the contribution of the aging maternal ‘host’, specifically the intrauterine environment, on fetal outcome.

**Materials and Methods**

Detailed information on pregnant women who were at least 40 years of age or older at the time of delivery, who conceived after in vitro fertilization with ovum donation and whose pregnancy continued to delivery between 1999 and 2008 was extracted and reviewed. Data collected included maternal age, gravidity, parity, background medical information, gestational age at delivery, birthweight, birthweight percentile, number of fetuses, mode of delivery, complications of pregnancy (including diabetes, hypertension and post-partum complications, among others), indications for hospitalization prior to delivery.

We focused our study on women with twin pregnancies, in order to investigate whether maternal age (uterine age) contributes to fetal outcome with a growing number of fetuses. We compared maternal complications in women over 40 after ovum donation with twins to that of similar women carrying singletons. In addition, and specifically for comparison of fetal outcome, we utilized as controls all women carrying twins who gave birth at Sheba Medical Center during the year 2007 and 31 December 2007. Data were extracted from a computerized database. The information in this database is entered prospectively by the obstetrician or midwife responsible for the laboring woman’s medical care and includes maternal demographics, obstetrical history, labor and delivery events and immediate neonatal outcome.

Institutional research ethics board approval was obtained.

Small-for-gestational age (SGA) was defined as birthweight less than the 10th percentile for gestational age according to locally derived accepted tables corrected for multiplicity and gender (Dollberg et al., 2005). Low birthweight (LBW) was defined as birthweight of <2500 g, whereas very low birth weight (VLBW) was defined as birthweight of <1500 g.

Pregestational diabetes mellitus and gestational diabetes mellitus, as well as hypertensive complications of pregnancy, were defined according to the criteria of the American College of Obstetricians and Gynecologists (ACOG, 2001, 2002).

Statistical analysis was performed with SigmaStat 1.0 software (Jandel Engineering Ltd, Linslade, Bedfordshire, UK). Categorical data were compared using the Pearson χ² test and the Fisher exact test, as appropriate. Continuous variables were compared using the Student’s t-test when data were normally distributed and the Mann–Whitney rank-sum test or the two-sided non-parametric Wilcoxon test when not normally distributed. For birthweights, we computed means of twins’ weights per woman in order to compensate for interdependency of data of two twins of one pregnancy. OR and 95% CI were calculated when appropriate and considered significant if the confidence interval excluded unity. A P-value of <0.05 was considered statistically significant.

**Results**

Between January 1999 and December 2008, 125 women aged 40 and above gave birth following a pregnancy achieved with ovum donation. Of these 125 women, 83 women carried singleton pregnancies and gave birth to 83 live born fetuses, whereas 42 women carried twins. Of women with twins, one woman carrying twins suffered antenatal fetal loss of one fetus, resulting in 83 live born fetuses. Women carrying twins comprised our study group.

Mean maternal age in the study group was 49.2 ± 4.3 years (range 40–65 years). The frequencies of hypertensive complications of pregnancy and diabetes in pregnancy were extremely high in this group of pregnant, advanced age women (50% and 31%, respectively). This was similar to the rates of hypertensive and diabetic complications in advanced age women after ovum donation carrying singletons (Table I).

Overall, 29 out of 42 (69%) women required hospitalization for various reasons at some point during their pregnancy, significantly higher than the percentage of women carrying singletons who required in-patient stay (47%, P = 0.03). All deliveries but one (98%) in the study group were accomplished by Cesarean section. A summary of maternal characteristics is presented in Table I.

As our focus in this report lay in investigating whether pregnant egg recipients of advanced age carrying twins and their infants fare differently than women and infants of twin pregnancies in general, we compared pregnancy outcome to a control group of women carrying twins and giving birth at Sheba Medical Center, as outlined above.

Of the 83 twin pregnancies, 17 (20%) were monozygotic and 66 (80%) were dizygotic. Of these 125 women, 83 women carried singleton pregnancies and gave birth to 83 live born fetuses, whereas 42 women carried twins. Of women with twins, one woman carrying twins suffered antenatal fetal loss of one fetus, resulting in 83 live born fetuses. Women carrying twins comprised our study group.

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### Table I: Maternal characteristics: ovum recipient pregnant women aged ≥40 years and controls (women with twin pregnancies)

<table>
<thead>
<tr>
<th></th>
<th>Ovum recipient women with twins (n = 42)</th>
<th>Ovum recipient women with singletons (n = 83)</th>
<th>P-value (study twins versus study singletons)</th>
<th>Controls (n = 417)</th>
<th>P-value (study twins versus control twins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (years ± SD)</td>
<td>49.2 ± 4.3</td>
<td>49.3 ± 4.7</td>
<td>NS</td>
<td>31.6 ± 6.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (31%)</td>
<td>24 (29%)</td>
<td>NS</td>
<td>30 (7.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (50%)</td>
<td>35 (42%)</td>
<td>NS</td>
<td>38 (9.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>29 (69%)</td>
<td>39 (47%)</td>
<td>0.03</td>
<td>58 (13.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>41 (98%)</td>
<td>75 (89%)</td>
<td>NS</td>
<td>273 (65.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD, standard deviation; NS, not significant.
Pregnancy is opening up to many older women, with peri-/post-use of donor oocytes, the boundaries of reproductive age are continually being pushed upward. As a result, the possibility of achieving pregnancy is opening up to many older women, with peri-/post-menopausal pregnancies becoming an option. Several investigators have reported on pregnancy outcome in older women after ovum donation (Sauer et al., 1995, 1996; Yaron et al., 1998; Shulman et al., 1999; Paulson et al., 2002; Simchen et al., 2006). The findings presented in our study place an emphasis on the extremely high risk for pregnant women over 40 after ovum donation with regards to maternal complications such as hypertension and diabetes. Women with singletons as well as with twins demonstrated a significantly higher risk for hypertensive complications (40–50%) as well as diabetes in pregnancy (30%). This is most probably the result of the increased maternal age, as mean maternal age in our study group was 49 years, and has previously been reported by us (Simchen et al., 2006) as well as by others (Bianco et al., 1996; Dildy et al., 1996; Dulitzki et al., 1998). Nevertheless, it is interesting to note that the risk of spending time as in-patients, although very high for advanced age women with singletons, was significantly higher for women with twins, reaching almost 70%. This implies that a multifetal pregnancy takes its additional toll on the advanced age women. The increased risk of hospitalization should be specifically mentioned in counseling, especially when contemplating the possibility of twins.

Moreover, our findings in the present study highlight other concerns for women of advanced age in an ovum donation program carrying multifetal pregnancies. Specifically, the increased risks of lower birthweights and earlier delivery in older egg recipients carrying multifetal pregnancies warrant attention and specific counseling. The risks of delivering babies who will suffer consequences of significant prematurity are always in mind when contemplating twins or a higher order gestation, but this risk was found to be almost two times higher in egg recipients of advanced age, with over one-third of multifetal pregnancies terminating at or before 34 weeks gestation. Possibly, the aging uterus is less suited for this challenge than a younger uterus, highlighting the necessity of an appropriate uterine environment for adequately carrying to term more than one fetus. Shulman et al. (1999) reported reduced pregnancy rates in egg recipients after the age of 50 with increased miscarriage rates in recipients older than 45. This was postulated to be a result of uterine factors. Others have also reported on lower uterine receptivity with increasing age (Meldrum, 1993). Advancing maternal age was previously found to be associated with a higher risk of placenta-related complications (Ananth et al., 1996). Moreover, decreased blood flow to the placenta as well as uteroplacental underperfusion and placental infarcts have all been associated with increasing maternal age (Naeye, 1983). Studies utilizing three-dimensional sonography of the uterus and placenta have demonstrated this tool as a useful method for analyzing the placental vascular tree during gestation (Metzenbauer et al., 2001; Merce et al., 2004), impaired trophoblast invasion (Hafner et al., 2001) and an increased risk of LBW (Thame et al., 2001).

### Discussion

With the advance of assisted reproductive technologies as well as the use of donor oocytes, the boundaries of reproductive age are continuously being pushed upward. As a result, the possibility of achieving pregnancy is opening up to many older women, with peri-/post-menopausal pregnancies becoming an option. Several investigators have reported on pregnancy outcome in older women after ovum donation (Sauer et al., 1995, 1996; Yaron et al., 1998; Shulman et al., 1999; Paulson et al., 2002; Simchen et al., 2006). The findings presented in our study place an emphasis on the extremely high risk for pregnant women over 40 after ovum donation with regards to maternal complications such as hypertension and diabetes. Women with singletons as well as with twins demonstrated a significantly higher risk for hypertensive complications (40–50%) as well as diabetes in pregnancy (30%). This is most probably the result of the increased maternal age, as mean maternal age in our study group was 49 years, and has previously been reported by us (Simchen et al., 2006) as well as by others (Bianco et al., 1996; Dildy et al., 1996; Dulitzki et al., 1998). Nevertheless, it is interesting to note that the risk of spending time as in-patients, although very high for advanced age women with singletons, was significantly higher for women with twins, reaching almost 70%. This implies that a multifetal pregnancy takes its additional toll on the advanced age women. The increased risk of hospitalization should be specifically mentioned in counseling, especially when contemplating the possibility of twins.

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| Table II Pregnancy outcome for advanced age women after ovum donation (n = 42) compared with 417 controls |
|-----------------------------------------------|-----------------|-----------------|----------|
| **Gestational age at delivery (wks ± SD)**    | Study group (n = 42) | Control group (n = 417) | P-value |
| 35.19 ± 2.3                                   | 35.67 ± 2.6      | 0.039            |
| **Delivery ≤34 weeks**                        | 15 (35.7%)       | 91 (21.8%)       | 0.06    |
| **Mean birthweight (g)**                      | 2149 ± 474       | 2289 ± 585       | 0.02    |
| **Low birthweight < 2500 g**                  | 53/83 neonates (77.1%) | 503/834 neonates (60.3%) | 0.004  |
| **Very low birthweight < 1500 g**             | 6/83 neonates (7.2%)   | 78/834 neonates (9.4%) | NS     |
| SGA                                           | 14/83 neonates (16.9%) | 89/834 neonates (10.7%) | NS     |
| At least one SGA infant                        | 12 (28.6%)       | 83 (19.9%)       | NS     |

wks, gestational weeks; SD, standard deviation; SGA, small for gestational age, birthweight less than the 10th percentile corrected for multiplicity and gender (Dollberg et al., 2005); NS, not significant.
growth restricted, SGA infant among the study group neonates, highlight this possible utero-placental dysfunction.

As has recently been shown in several studies (Veleva et al., 2006, 13, 2009), elective single-embryo transfer is an option that does not decrease overall pregnancy rates in older or younger women. In fact, in view of the increased risks to both mothers and neonates in advanced age mothers with multifetal pregnancies, the alternative of transferring a single, good-quality embryo should be the preferred option.

Finally, the impact of uterine age on fetal outcome in multifetal pregnancies has not been addressed as such in the literature to date. The information obtained from our study can be used in counseling women of advanced age contemplating pregnancy with donor oocytes.

References


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