BRIEF REPORT

Pregnancy in the Sixth Decade of Life

Obstetric Outcomes in Women of Advanced Reproductive Age

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Context As a result of oocyte donation, women in their sixth decade of life are now able to conceive and carry pregnancies to term. However, little is known about pregnancy outcomes in this population.

Objective To describe pregnancy outcomes in women aged 50 years or older who conceived after in vitro fertilization with donor oocytes.

Design and Setting Retrospective analysis of cycles conducted at a US university assisted reproduction program during calendar years 1991-2001.

Patients Seventy-seven postmenopausal women with no chronic medical conditions (mean [SD] age, 52.8 [2.9] years; range, 50-63 years) who underwent 121 embryo transfer procedures (89 fresh and 32 frozen). Pregnancy outcomes were ascertained by chart review and telephone follow-up.

Main Outcome Measures Maternal and neonatal outcomes.

Results There were 55 clinical pregnancies for a total pregnancy rate of 45.5%. The live birth rate was 37.2%. Of the 45 live births, 31 were singletons, 12 were twins, and 2 were triplets, for which the mean (SD) gestational ages at delivery were 38.4 (2.1) weeks, 35.8 (2.8) weeks, and 32.2 weeks, respectively. Mean (SD) birth weights were 3039 g (703 g), 2254 g (581 g), and 1913 g, respectively. Apgar scores at 1 and 5 minutes were 8.2 (0.9) and 9.1 (0.5), respectively. Of singletons, 68% were delivered by cesarean, and all multiples were delivered by cesarean. Mild preeclampsia was noted in 25% of patients and severe preeclampsia in 10%. Gestational diabetes required diet modification in 17.5%, and 2.5% required insulin.

Conclusions Appropriately screened women aged 50 years or older can successfully conceive via oocyte donation and experience similar pregnancy rates, multiple gestation rates, and spontaneous abortion rates as younger recipients. During pregnancy, they appear at increased risk of preeclampsia and gestational diabetes. A majority can expect to deliver via cesarean. However, there does not appear to be any definitive medical reason for excluding these women from attempting pregnancy on the basis of age alone.

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IN VITRO FERTILIZATION (IVF) WITH donated oocytes has made pregnancy possible for many women whose infertility cannot be treated by any other means. Oocyte donation was initially developed as a therapy for young women with premature ovarian failure, rather than as a means of overcoming the age-related decline in fertility. However, the high success rates observed with oocyte donation among younger recipients were mirrored in women older than 40 years.[1] Several reports confirmed the efficacy of oocyte donation in the older group,[2-5] and subsequently it was demonstrated that pregnancies could be achieved in women older than 50 years.[6,7] Oocyte donation gradually became an important tool in the armamentarium of the fertility specialist. During 1998, the last year for which published data are available, 4783 cycles of oocyte donation were reported to the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry.[8]

One of the principal concerns regarding the application of this therapy to women of advanced reproductive age is the incidence of obstetric complications that may arise as a result of the advanced age of these new mothers. The increased incidence of underlying medical disease, decreased cardiovascular reserve, and diminished ability to adapt to physical stress that may accompany aging could combine to increase perinatal

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and maternal morbidity or even mortality. Retrospective population-based studies have suggested an increased risk of poor pregnancy outcome with advanced maternal age.[9] However, such reports are necessarily confounded by inconsistencies in prenatal surveillance, preexisting medical conditions, and access to appropriate health care. In contrast, when patients of advanced maternal age were followed and delivered their infants in a modern tertiary care center, no increase in adverse outcome was noted.[10] Furthermore, few published series address obstetric and neonatal outcomes in this group.[11-13] Therefore, the purpose of this investigation was to describe the obstetric outcomes of women older than 50 years whose pregnancy was the result of IVF with donor oocytes.

METHODS

All cases of oocyte donation in which the recipient was older than 50 years conducted at the Assisted Reproductive Technologies Program of the University of Southern California during calendar years 1991-2001 were included. This study was approved by the institutional review board of the Keck School of Medicine of the University of Southern California. Outcomes of cycles were ascertained by clinic and hospital chart review and telephone follow-up, if necessary. Up to 9 of the pregnancies and their outcomes have previously been reported.[12-14]

Patients

A total of 77 postmenopausal women aged 50 to 63 years (mean [SD], 52.8 [2.9] years) underwent IVF with donor oocytes. Patient characteristics are summarized in TABLE 1.

Precycle screening included history and physical examination, pelvic examination, and Papanicolaou testing. A normal endometrial cavity was required and its presence confirmed by a hysterosalpingogram and/or a hydrosonogram. Recipients were also required to provide documentation of a normal mammogram, chest x-ray, electrocardiogram, complete blood cell count, chemistry panel, lipid panel, and thyroid-stimulating hormone level. Cardiovascular reserve was confirmed by a treadmill stress test. Per California state law, all recipients underwent infectious disease screening. A semen analysis was obtained from male partners.

All recipients completed a biopsy cycle to assess endometrial response to exogenous estrogen and progesterone. The hormone replacement regimen has previously been described[1-3] and consisted of oral estradiol and intramuscular or transvaginal progesterone.

All couples underwent a psychosocial consultation prior to initiation of therapy. The purpose of this screening was to identify potential issues regarding unequal genetic participation in the anticipated offspring, adjustment to parenthood at an advanced age, and disclosure to the child of his or her genetic background.

Exclusion criteria comprised any chronic medical condition including hypertension and clinically significant findings in any of the screening criteria.

Donors

Donors were young women who were either self-designated (relatives or friends), or anonymous and compensated, and each was matched 1:1 to each recipient. The mean (SD) age was 27.5 (2.6) years (range, 22-33 years).

All donors underwent psychological screening prior to stimulation. Medical screening included history and physical examination, pelvic examination, and Papanicolaou testing. Infectious disease screening similar to that of recipients, chemistry panels, complete blood cell counts, and lipid panels were also obtained. Controlled ovarian hyperstimulation was achieved with standard pituitary down-regulation with leuprolide acetate and ovarian stimulation with human menopausal gonadotropins or recombinant follicle-stimulating hormone. Oocytes were retrieved by transvaginal ultrasound-guided follicle aspiration. When supernumerary embryos were available, they were cryopreserved for potential future transfer.

Pregnancies were diagnosed by rising β-human chorionic gonadotropin levels 9 days after embryo transfer. Clinical pregnancies were defined by ultrasound evidence of a gestational sac. Data were analyzed by analysis of variance and the Fisher exact test.

Table 1. Characteristics of Recipients (N = 77)

Characteristic	Mean (SD)	Range
Age, y	52.8 (2.9)	50-63
Gravidity	1.2 (1.7)	0-6*
Parity	0.8 (1.2)	0-4*

*None of the prior pregnancies was the result of in vitro fertilization or other assisted reproductive technologies.

Table 2. Pregnancy Data

	No.	Clinical Pregnancy, No. (%)	Deliveries, No. (%)
Fresh transfers	89	38 (42.7)	31 (34.8)
Frozen transfers	32	17 (53.1)	14 (43.8)
Total	121	55 (45.5)	45 (37.2)

RESULTS

During this 11-year period, 89 oocyte retrievals resulted in a total of 121 embryo transfers (89 fresh and 32 frozen). The mean (SD) number of oocytes obtained per donor was 17.5 (8.4), and the mean number of fertilized oocytes was 9.3 (5.3). The mean number of fresh embryos transferred during the study period was 3.7 (2.2), and the mean number of frozen embryos transferred was 3.6 (1.4). The number of embryos transferred during 1 cycle gradually decreased over time from up to 5 embryos in the 1990s to 2.2 embryos on average in 2001.

Pregnancy Data

There were 55 clinical pregnancies for a clinical pregnancy rate of 45.5% (55/121). Of the 77 women in the series, 42 (54.5%) had live births. Three women carried 2 consecutive pregnancies. A total of 42 donors provided oocytes for the 45 deliveries. In 26 cases (58%), the delivery was the mother's first. The total live-birth rate in this cohort, combining fresh and frozen cycles, was 37.2% (45/121). Pregnancy data are detailed in TABLE 2.

Among the 3 women who carried 2 consecutive pregnancies, all 3 were in their 50s during both pregnancies, each used the same donor to achieve both

Table 3. Neonatal Outcomes

Outcome	No. of Patients	Gestational Age, Mean (SD) [Range], wk	Birth Weight, Mean (SD) [Range], g
Singletons	31	38.4 (2.1) [30.6-41.6]	3039 (703) [1108-4233]
Twins	12	35.8 (2.8) [30.0-40.0]*	2254 (581) [1222-3070]*
Triplets	2	32.2 [31.3-33.0]*	1913 [1165-2500]*

*$P<.001$ compared with singletons.

pregnancies, and 1 of the 3 women experienced preeclampsia during both pregnancies.

Neonatal Data

Of the 45 live births, there were 31 singletons, 12 twins, and 2 triplets delivered. The multiple gestation rate was 31.1% (14/45). The mean (SD) Apgar scores at 1 and 5 minutes were 8.2 (0.9) (range, 6-10) and 9.1 (0.5) (range, 8-10), respectively. TABLE 3 summarizes the neonatal outcomes with respect to gestational age and birth weight at delivery. The mean gestational ages and birth weights of the multiple gestations were significantly less than those of singletons.

Patient Outcomes

Of all live births, 78% (35/45; 95% confidence interval [CI], 63%-89%) were delivered by cesarean. Of singletons, 68% (21/31; 95% CI, 47%-82%) were delivered by cesarean, 6% (2/31; 95% CI, 1%-21%) by vacuum-assisted vaginal delivery, and 26% (8/31; 95% CI, 12%-42%) by normal spontaneous vaginal delivery. Of multiples, 100% (14/14; 95% CI, 75%-100%) were delivered by cesarean ($P<.02$) compared with singletons. The cesarean delivery rate was not related to age or prior parity within this cohort.

Perinatal data were ascertained in 40 of the deliveries. The incidence of mild preeclampsia in this cohort was 25% (10/40; 95% CI, 11%-47%); the incidence of severe preeclampsia was 10% (4/40; 95% CI, 3%-23%). There were no episodes of eclampsia. Among women younger than 55 years, preeclampsia was noted in 26% (8/30; 95% CI, 14%-46%) compared with 60% (6/10; 95% CI, 26%-86%) of those aged 55 years or older. The incidence of preeclampsia was similar among women experiencing their first delivery (34.8% [8/23]; 95% CI, 21%-47%) compared with that of women who were multiparous (35.2% [6/17]; 95% CI, 21%-47%).

Gestational diabetes required diet modification in 17.5% (7/40; 95% CI, 7%-33%) of patients, and 2.5% (1/40; 95% CI, 1%-8%) of patients required insulin. As with preeclampsia, gestational diabetes was more common among women aged 55 years or older (40% [4/10]; 95% CI, 10%-67%) compared with those younger than 55 years (13% [4/30]; 95% CI, 6%-32%).

One patient who was carrying a singleton experienced premature rupture of membranes at 29 weeks and was hospitalized for 10 days until delivery; 1 patient required delivery of twins at 30 weeks' gestation for acute onset of severe preeclampsia; 1 patient underwent hysterectomy for a placenta accreta; and 1 patient received a blood transfusion after a cesarean delivery for placenta previa. There were no neonatal or maternal deaths.

COMMENT

We have previously reported that recipient age does not appear to play a substantial role in the efficiency of oocyte donation, suggesting that endometrial receptivity is unaltered by age.[1-3] The menopausal uterus is not only receptive to implantation with adequate steroid replacement, but also appears capable of supporting the gestation throughout the term of pregnancy. However, controversy remains whether children conceived as a result of IVF experience a higher risk of being born earlier or at a lower birth weight. Schieve et al[15] conducted a recent population-based study comparing infants born after IVF with general population-based controls. Despite the gestational age of singletons at delivery being similar between the 2 study groups (39.1 vs 39.5 weeks, respectively), the risk of a low-birth-weight infant in the IVF group was 2.6 times that of the general population. Interestingly, there was no difference in the percentage of low-birth-weight infants born to women aged 20 to 29 years compared with women older than 45 years. In our cohort, the mean gestational age and weight of singletons, twins, and triplets observed appears to be similar to those historically reported in spontaneous pregnancies in younger gravidas.[16-18]

As with other reports of pregnancy outcomes after assisted reproduction,[1-8] we observed high multiple gestation rates. Multiple gestations increase both maternal and neonatal morbidity rates, and it would seem prudent to limit the number of embryos transferred in this group.[19] With higher per-embryo implantation rates observed with blastocyst transfers,[20,21] it may be reasonable to offer women older than 50 years the option of single blastocyst transfer to diminish the risk of multiple gestations.

Data with respect to obstetric outcome in this age group are extremely limited. Narayan et al[11] reported a notable lack of maternal and neonatal complications in 7 women older than 50 years who had conceived naturally. A prior series from our institution reported obstetric outcomes of 17 viable pregnancies in women older than 50 years using oocyte donation.[12] Perinatal and neonatal profiles were similar to those observed in the current series.

Because of our screening criteria, no patients had glucose intolerance or hypertension prior to conception. Nevertheless, we observed a high incidence of gestational diabetes and pregnancy-associated hypertension in this group. Furthermore, the incidence of both complications appeared to be markedly increased in women older than 55 years compared with those aged 50 to 54 years. While neither difference was statistically significant, the trend toward higher complication rates with advancing age appeared to be strong and should be evaluated in larger series.

According to data from the National Center for Health Statistics in 1998, hypertension associated with pregnancy was identified in 3.7% of 146 320 pregnancies that ended in a live birth.[22] In another investigation, the incidence of pregnancy-associated hypertension was 9.6% in women older than 40 years compared with 2.7% in younger gravidas 20 to 30 years of age.[23] The observed rate of 35% in the current study represents an approximate 10-fold increase compared with younger gravidas and at least a 3-fold increase when compared with women older than 40 years. This exaggerated rate may be partly due to the influence of donated gametes, which are immunologically foreign to the recipient. Salha et al[24] reported that preeclampsia was diagnosed in 18.1% of women who received donated gametes compared with 1.4% in age-matched controls. Preeclampsia is also more common among primigravidas,[16] who represented more than half of our patients (26 of 45 deliveries).

An analogous increase in the rate of gestational diabetes with increasing maternal age was reported by Mestman.[25] In that series, the incidence of gestational diabetes was reported to be 3.7% in women younger than 20 years, 7.5% between the ages of 20 and 30 years, and 13.8% in women older than 30 years. In the current series, 17.5% of women had gestational diabetes managed by diet, and 2.5% had their diabetes controlled by insulin. This suggests that the trend toward higher rates of gestational diabetes with age continues after 50 years of age and represents a 2- to 5-fold increase in incidence compared with younger women.

We observed an unusually high operative delivery rate in this series. This may be a consequence of the high-risk nature of these pregnancies. A recent series comparing IVF pregnancies with natural conceptions in young women[26] reported the cesarean delivery rate to be more than doubled in the IVF group; among singletons, cesarean delivery was 1.75 times more likely after IVF than after natural conceptions. The high operative delivery rate may also represent a separate phenomenon; it is possible that the older uterus may be less efficient in effecting normal labor and vaginal delivery. Our experience suggests that even carefully screened, healthy women older than 50 years who opt for oocyte donation should be advised of an increased incidence of operative intervention at the time of delivery.

To our knowledge, this report represents the largest single cohort of women completing pregnancies in their sixth decade of life. Within the constraints imposed by the limited power of this study, pregnancy and successful delivery may be expected in healthy women in their 50s. In spite of a marked increase in gestational diabetes and pregnancy-associated hypertension in this carefully screened population of women, favorable maternal and neonatal outcome may be expected with contemporary obstetric surveillance and management. Women who choose to become mothers in this age group may expect a high rate of cesarean delivery. On the basis of these data, there does not appear to be any definitive medical reason for excluding these women from attempting pregnancy on the basis of age alone.

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Acquisition of data: Paulson, Boostanfar, Saadat, Mor, Tourgeman, Slater, Francis, Jain.
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