Original Article

Comparison of Obstetric Outcomes of Pregnancies after Donor-Oocyte *In vitro* Fertilization and Self-Oocyte *In vitro* Fertilization: A Retrospective Cohort Study

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ABSTRACT

Aims: The aim of this study is to evaluate and compare multiple obstetric and perinatal outcomes between donor-oocyte *in vitro* fertilization (IVF) and self-oocyte IVF group. **Settings and Design:** This study was done in a tertiary care center with ART unit. This was a retrospective comparative cohort study. **Materials and Methods:** The present study comprised all women between 20 and 45 years who conceived from oocyte donation (*n* = 78) between December 1, 2010, and December 31, 2016, and compared with all women who underwent self-oocyte IVF (*n* = 112). The process involved controlled ovarian stimulation and retrieval of the donor oocytes, preparation of recipient endometrium, and pregnancy management. Obstetric and perinatal outcomes were compared. **Statistical Analysis Used:** Chi-square test was used for categorical variables. Analysis for confounding variables was performed using multivariable linear and logistic regression analysis. **Results:** Baseline characteristics between the two groups were comparable. Miscarriage, first-trimester bleeding, pregnancy-induced hypertension (PIH), and gestational diabetes mellitus were significantly higher in donor-oocyte IVF group compared to self-oocyte cycles (*P* = 0.001). Using multiple logistic regression analysis, age class adjusted PIH incidence was significantly higher in donor-oocyte group as compared to self-oocyte group (*P* = 0.010). There was no significant variation in perinatal outcomes between the donor- and self-oocyte IVF cycles (*P* > 0.05). **Conclusion:** Oocyte donation should be treated as an independent risk factor for PIH.

KEYWORDS: *First-trimester bleeding, gestational diabetes mellitus, oocyte donation, pregnancy-induced hypertension*

INTRODUCTION

Oocyte donation has facilitated couples to achieve pregnancy in situations where the female partner has diminished ovarian reserve, premature ovarian failure, inheritable genetic disorders, and surgical menopause.[1] The practice of egg donation began in the early 1980s when the first pregnancy was reported and the numbers have steadily increased since then mostly in the last decade.[2] In the United States until 2012, over 20,000 women attempted oocyte donation, and the number is increasing.[3] While such figures may not be available from the nation, with increasing availability and accessibility, certainly more couples are availing the benefits of assisted reproductive techniques using oocyte donation for the above conditions. While women attempting pregnancy with donor oocytes are advanced in age for the obvious indications, the implications of pregnancy are far reaching in terms of obstetric and neonatal outcome.[4]

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Advanced maternal age is associated with pregnancy complications including hypertensive disorders, gestational diabetes, preterm labor, and fetal growth restriction (FGR).[5,6] The most common complication noted in pregnancies after donor-oocyte *in vitro* fertilization (IVF) is pregnancy-induced hypertension (PIH), ranging from 16% to 40% of women.[7-10] However, few available studies report conflicting evidence about the risk of hypertensive disorders in donor-oocyte pregnancies particularly after adjusting for maternal age.[11,12] It is unclear whether pregnancy complications and obstetric risks are due to oocyte donation *per se* or due to confounding factors such as maternal age. Some researchers have proposed that it is not maternal age but the allogenic fetus that may predispose women to maternal hypertensive disorders, FGR, abnormalities in placentation, and gestational diabetes mellitus (GDM).[11,13-17] Considering these conflicts on the results of pregnancy and neonatal outcome, we planned to analyze our data in this regards so as to enable us counsel our women likewise. In a retrospective comparative cohort study, we aimed to evaluate and compare multiple obstetric and perinatal outcomes including abortion, preterm labor, antepartum hemorrhage, intrahepatic cholestasis of pregnancy (ICP), GDM, preeclampsia, FGR, and fetal birth weight and compare these variables between self-oocyte conception group and donor-oocyte conception group. The outcome of this study provides important information for women considering using donor oocytes as a treatment for infertility.

MATERIALS AND METHODS

The present study was a retrospective comparative cohort study comprising all women between the age groups of 20 and 45 years who conceived from oocyte donation (*n* = 78) between December 12, 2010, and December 31, 2016, and compared with all women who underwent self-oocyte IVF (*n* = 112) in the same time period. In both the groups, up to two good-quality embryos were transferred. However, in women with advanced age (>38 years) and those with poor-grade embryo, a maximum of three embryos were transferred. In donor-oocyte IVF group out of 181 patients, 78 were urinary pregnancy test (UPT) positive – 43.1%. In self-oocyte IVF control group out of 402 patients in the given time period, 112 were UPT positive – 27.86%.

Until 2010, altruistic oocyte donations were permitted wherein younger sibling was most favored oocyte donor for financial and social reasons. The national guidelines prohibit the use of oocytes donated by a relative or a known friend of either the wife or the husband.[18] Neither the clinic nor the couple shall have the right to know the donor identity and address, essentially maintaining anonymity between donors and recipients. Considering the proposed allogenic theory which was suggested to be a reason for adverse perinatal outcome, we excluded women who underwent IVF with donor oocytes using siblings as donors before this period. Obstetric and perinatal outcomes were compared with all women who had conceived UPT positive with self-oocyte (*n* = 112) during the same period at the center for assisted reproductive techniques (ART) of the institute, with all babies followed in the neonatal division. All oocyte donors selected were in the age group of 21–30 years with a mean age of 25 ± 4.42 years with at least one living issue from the previous conception.

The process involved controlled ovarian stimulation and retrieval of the donor oocytes, preparation of recipient endometrium, and pregnancy management. All donors were stimulated by antagonist protocol. Ovarian stimulation was done with gonadotropins starting from day 2 or 3 of menstruation, with recombinant follicle-stimulating hormone in dosages depending on the donor's age, body mass index, ovarian reserves including anti-Mullerian hormone levels, and antral follicle counts assessed before the start of cycle. GnRH antagonist cetrorelix 0.25 mg/day was started from the 6th day of stimulation. Ovulation trigger was given when ≥3 follicles reached a diameter of 18 mm with recombinant human chorionic gonadotropin (hCG), 250 µg. Oocyte retrieval was done after 34–36 h transvaginally under ultrasound guidance. The retrieved oocytes were inseminated or injected with the male partner's sperms. The resultant embryos formed were frozen or transferred to the recipient if her endometrial lining was deemed prepared after estrogen priming (endometrial thickness of ≥8 mm).

Endometrial preparation of recipients

Oocyte recipients underwent downregulation with GnRH agonist injection lupride 0.5 mg subcutaneous daily from mid-luteal phase (day 21) of the preceding menstrual cycle. Endometrium was prepared with estradiol valerate 4 mg daily from day 1 of bleeding and increased to 6 mg per day from day 8 of the cycle until the endometrium reached a thickness of ≥8 mm. Progesterone injection micronized progesterone 100 mg IM was started on the day of oocyte retrieval of donor and continued until 14 days after embryo transfer. Embryo transfers were done on day 3 or day 5 depending on the embryo grading. In cases where the endometrium did not agree despite hormone preparation, the embryos were frozen and subsequently transferred in frozen embryo transfer cycle. The progesterone replacement was done in the form of micronized progesterone 100 mg im.

Pregnancy follow-up

Pregnancy was defined by rising beta-hCG levels done after 16 days of the embryo transfer and was further confirmed by ultrasonographic visualization of gestational sac at 6 weeks. Estrogen was tapered and stopped once fetal heart activity was documented and progesterone support continued until 10–12 weeks of gestation. During pregnancy, both groups were followed up in antenatal clinic of our institute.

The obstetrical parameters compared in both groups included outcomes such as first-trimester bleeding, miscarriage, preeclampsia, oligoamnios, GDM, antepartum hemorrhage, preterm delivery, FGR, ICP, mode of delivery, and postpartum complications. The neonatal outcomes such as birth weights, Apgar scores, neonatal intensive care unit stay, and congenital anomaly were compared in two groups.

Definitions

- Miscarriage: Bleeding, expulsion of the fetus, or disappearance of cardiac activity *in utero* before 20-week gestation
- Preeclampsia: Blood pressure ≥140/90 mmHg with proteinuria after 20-week gestation
- Gestational diabetes mellitus: Carbohydrate intolerance first recognized during pregnancy
- Preterm delivery: Delivery before 37-week gestation
- FGR: Birth weight <10th percentile for the gestation age.

Fetal outcomes such as mean birth weight, Apgar score <8, stillbirth rate, and small for date/large for date fetus and early neonatal complications such as hyperbilirubinemia, respiratory distress, hypoglycemia, and congenital anomaly were also compared.

Age-matched subgroup analysis was done using logistic regression analysis to compare the incidence of PIH and GDM between donor- and self-oocyte groups.

Statistical analysis

Data were presented in numbers and percentages. Statistical analysis was performed with Chi-square test for categorical variables. We compared the mean through *t*-test. Continuous outcomes (estimated gestation age and birth weight) were compared using *t*-test and linear regression; dichotomous outcomes were analyzed by logistic regression. Further analysis was performed, if indicated, to control for confounding variables using multivariable linear and logistic regression analysis. $P < 0.05$ was considered statistical significant. Odds ratios and 95% confidence intervals were established as well as multiple logistic regression.

RESULTS

During the study period December 1, 2010–December 31, 2016, 78 women with donor-oocyte conception were compared with 112 women conceiving after ART using self-oocyte during the same period. Baseline characteristics [Table 1] between the two groups were comparable. Although there were a higher number of women in the advanced age (>35 years) in the donor group, the difference did not meet statistical significance. Obstetric events compared between the two groups [Table 2] suggested a significantly higher incidence of miscarriage in donor-oocyte IVF group compared to self-oocyte cycles ($P = 0.002$). First-trimester bleeding was likewise significantly higher in donor-oocyte IVF group as compared to self-oocyte IVF group ($P = 0.004$). The incidence of PIH was significantly high in donor-oocyte IVF group as compared to self-oocyte IVF group ($P = 0.001$). Using multiple logistic regression analysis, age class adjusted PIH incidence was compared between two groups [Table 3] which was significantly higher in donor-oocyte group as compared to self-oocyte group ($P = 0.010$), even after removing age as a confounder.

Subgroup analysis was done to compare PIH outcome in singleton and multiple pregnancies in self- and donor-oocyte group, as shown in Table 4. Gestational diabetes was found to be more in donor-oocyte IVF group as compared to self-oocyte IVF group ($P = 0.001$). However, when regression analysis model was used for age-matched results, it was not significant (NS, $P = 0.234$). There was no statistical difference in the incidence of early-onset ovarian hyperstimulation syndrome, anemia, oligoamnios, antepartum hemorrhage,

Table 1: Demographic profile of the study group (donor-oocyte recipients) and control group (self-oocyte conception)

Outcome	Group 1 Donor-oocyte IVF (*n*=78), *n* (%)	Group 2 Self-oocyte IVF (*n*=112), *n* (%)	*P* and significance
Mean age (years)	35.78±5.32	32.96±3.90	
≤30	19 (24.3)	50 (44.6)	0.396 (NS)
31-34	21 (26.9)	34 (30.3)	
35-40	26 (33.3)	22 (19.6)	
≥41	12 (15.3)	6 (5.3)	
Obstetric history			
Primigravida	55 (70.5)	90 (80.3)	0.05 (NS)
Multigravida	23 (29.5)	22 (19.6)	0.05 (NS)
Previous abortions	15	22	

NS=Not significant, IVF=*In vitro* fertilization

Table 2: Comparison of obstetric outcome of all pregnancies of donor-oocyte recipients with self-oocyte conception

Outcome	Group 1 Donor-oocyte IVF (*n*=78), *n* (%)	Group 2 Self-oocyte IVF (*n*=112), *n* (%)	*P* and significance
Obstetric events			
Early-onset OHSS*	1 (2)	2 (2)	0.05 (NS)
First-trimester bleeding	12 (21.4)	6 (6)	0.101 (NS)
Miscarriage	22 (28.2)	12 (10.7)	0.002 (S)
Anemia*	1 (2)	2 (2)	0.05 (NS)
Preeclampsia*	19 (34)	9 (9)	0.001 (S)
Oligoamnios*	1 (2)	4 (4)	0.665 (NS)
GDM*	19 (34)	15 (15)	0.007 (S)
APH*	7 (12)	7 (7)	0.305 (NS)
Preterm delivery*	32 (56)	40 (40)	0.064 (NS)
ICP*	112 (22)	12 (12)	0.109 (NS)
FGR*	4 (8)	8 (8)	0.05 (NS)
Abnormal presentation*	2 (4)	2 (2)	0.05 (NS)
Postpartum complication*	3 (6)	6 (6)	0.05 (NS)
Mode of delivery			
Vaginal	0	8 (8)	0.052 (NS)
Spontaneous	0	5 (5)	
Induced	0	3 (3)	
LSCS	6 (100)	92 (92)	0.052 (NS)
Elective*	22 (39.3)	48 (48)	
Emergency*	34 (60.7)	44 (44)	0.045

*Total donor-oocyte pregnancy=56, *Total self-oocyte pregnancy=100. GDM=Gestational diabetes mellitus, OHSS=Ovarian hyperstimulation syndrome, APH=Antepartum hemorrhage, FGR=Fetal growth restriction, ICP=Intrahepatic cholestasis of pregnancy, LSCS=Lower segment cesarean section, IVF=*In vitro* fertilization, S=Significant, NS=Not significant

Table 3: Adjusted odds ratio and 95% confidence limits for pregnancy-induced hypertension incidence between two groups

Variables	Adjusted OR	*P*	95% CI Lower	95% CI Upper
1. Age group				
Group 1#	1.00		0.71	5.41
Group 2&	1.96	0.195		
2. Group 1	1.00			
Group 2	3.68	0.010	1.36	9.93

1=Age<35 years' age group, 2=Age >35 years' age group, #Donor-oocyte IVF group, &Self-oocyte IVF group. IVF=*In vitro* fertilization, OR=Odds ratio, CI=Confidence interval

preterm delivery, ICP, FGR, abnormal presentation, mode of delivery, and postpartum complications among the two groups (*P* > 0.05 NS), as shown in Table 2.

Perinatal outcome [Table 5] including mean birth weight, Apgar score, respiratory distress, and congenital anomaly did not suggest any significant variation between the donor- and self-oocyte IVF cycles (*P* > 0.05).

DISCUSSION

Donor-oocyte IVF has now been proven to be a successful option of ART for many women with diminished ovarian reserve, advanced age, genetic disorders, and those with repeated IVF failures due to poor oocyte quality. As more couples are desirous of donor oocytes to treat infertility, obstetric, perinatal, and neonatal complications need to be evaluated. To assess risks, one needs to have a carefully constructed control group, but unfortunately, most prior analysis of donor-oocyte IVF pregnancies have been handicapped by the lack of an appropriate comparison group. Infertility, ART procedures, parity, multiple gestations, and advanced maternal age may all confer independent risks and can confound the analysis. To date, studies addressing these issues have been largely limited to case series. These studies have had varying results, with some showing increased risk for preeclampsia, gestational diabetes, and cesarean section.

The present study showed an increased risk of GDM and PIH among women with donor-oocyte pregnancies as compared with self-oocyte pregnancies. When logistic regression analysis was done for age-class matching, there still existed significantly higher incidence of PIH in donor-oocyte pregnancies as compared to self-oocyte pregnancies. However, no significant difference in the incidence of GDM was noted when the two groups were age matched.

Studies on obstetric outcomes in donor-oocyte pregnancies[8,19] have shown an increased risk of preterm labor, preeclampsia, and cesarean delivery. However, another study[20] failed to find any association of adverse outcomes with conception after oocyte donation. A study on the Danish cohort[21] suggested an increased risk of preeclampsia and preterm labor in donor-oocyte pregnancies as compared with pregnancies after autologous IVF. By contrast in our study, the results did not show any significant association between oocyte donation and FGR, preterm labor, or cesarean delivery rate. This might be explained by the small sample size which is a significant limitation of the study. Advanced maternal age is associated with a significantly increased risk of perinatal complications;[9] therefore, it is necessary to eliminate bias caused by maternal age and other risk factors. Levron *et al*.[14] recently showed that oocyte donation was independently associated with a higher rate

of hypertensive disease of pregnancy after adjustment for maternal age and parity. Wiggins and Main[17] found an increase in gestational hypertension in a subset of patients when controlling for multiple gestation and parity. However, age was confounder in this study. The present findings are consistent with a few studies reporting high complication rates with donor-oocyte pregnancies independent of recipient age, parity, and the age of the donor.[17,22-28] Obstetric complications in pregnancy after oocyte donation might be explained on the basis of immunologic theory.[29] Parental human leukocyte antigen sharing is thought to have a role in the etiology of preeclampsia.[30] Fetus is allogenic to the gestational carrier in donor-oocyte pregnancies.[31] One study[30] has reported increased immune activity and fibrinoid deposition at the maternal-fetal interface of donor-oocyte pregnancies, representing a host versus graft rejection-like process.

Limitation of the study was our small sample size. In our study, we had only single control group of all IVF self-oocyte conceived patients. We lacked the control group which could come from spontaneously conceived patients and thus were unable to compare our results with the general population.

The strength of this study includes the homogeneity of obstetric care and the ability to have an appropriate control group for the donor-oocyte IVF study population. The close matching of the control group for infertility, parity, and plurality is a unique feature of this study and makes the result more compelling. The multiple logistic regression analysis also addresses well the maternal age.

On the one hand, assisted reproductive technology using oocyte donation has enabled women at advanced age or with ovarian failure to achieve pregnancy, while on the other hand, conception after oocyte donation can subject them to a higher risk of maternal morbidity and mortality,[31] and this should be part of counseling the couple while they set out to donor-oocyte IVF cycle. Obstetrician and pediatrician need to be aware of the increased pregnancy risks, which should be managed appropriately during the pregnancy, delivery, and puerperium period.[32]

CONCLUSION

Donor-oocyte IVF has proven to be an effective form of infertility treatment. Oocyte donation should be treated as an independent risk factor for hypertensive disorder in pregnancy. Women should be informed of the risks, and donor-oocyte pregnancies should be managed in high-risk obstetric clinics. Our study provides useful

Table 4: Pregnancy-induced hypertension outcome based on plurality between two groups

Plurality	PIH number of cases (%)	*P* and significance
Self-oocyte IVF (*n*=100)		
Singleton (*n*=70)	4 (5.7)	Singleton
Twins/higher (*n*=30)	5 (16.7)	(self vs. donor)
		0.001 (S)
Donor-oocyte IVF (*n*=56)		
Singleton (*n*=37)	14 (38)	Twins/higher
Twins/higher (*n*=19)	5 (26)	(self vs. donor)
		0.698 (NS)

IVF=*In vitro* fertilization, PIH=Pregnancy-induced hypertension, S=Significant, NS=Not significant

Table 5: Comparison of perinatal outcome of all pregnancies of donor-oocyte recipients with self-oocyte *in vitro* fertilization

Outcome	Group 1	Group 2	*P* and significance
	Donor-oocyte IVF (*n*=56) *n* (%) (*n*=66) fetuses	Self-oocyte IVF (*n*=100) *n* (%) (*n*=140) fetuses	
Fetal outcome			
Mean birth weight	2462.04±660.248	2440.13±747.263	0.137 (NS)
Twins	18 (32)	30 (21.4)	0.0651 (NS)
Triplets/higher gestation	0	5 (3.5)	0.179 (NS)
APGAR <8	15 (27.2)	35 (25)	0.05 (NS)
SFD	3 (4.5)	10 (7.1)	0.556 (NS)
LFD	6 (9)	20 (14.3)	0.05 (NS)
Hyperbilirubinemia	3 (4.5)	2 (1.4)	0.05 (NS)
Respiratory distress	14 (24)	30 (21.4)	0.05 (NS)
Hypoglycemia	1 (1.5)	5 (3.6)	0.667 (NS)
Still birth	0	3 (2.1)	0.503 (NS)
Early neonatal death	0	4 (2.9)	0.308 (NS)
Congenital anomaly	1 (1.5)	4 (2.9)	0.05 (NS)

SFD=Small for date baby, LFD=Large for date, IVF=*In vitro* fertilization, NS=Not significant

information for counseling couples who are considering the use of donor oocyte to achieve pregnancy.

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Conflicts of interest

There are no conflicts of interest.

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