



Comparison of Obstetric Outcomes Between IVF cycles with Donor Oocyte and Spontaneous Conception Pregnancies: A Retrospective Cohort study

Yadav Vikas ^{1*}, Malhotra Neena ², Mahey Reeta ², Singh Neeta ², Kriplani Alka ²

1- Department of Obstetrics and Gynecology, School of Medical Sciences and Research, Sharda Hospital, Sharda University Campus, Uttar Pradesh, India

2- Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background: Oocyte donation has facilitated couples to achieve pregnancy in conditions like diminished ovarian reserve, premature ovarian failure, and inheritable disorders. However, it is unclear whether pregnancy complications are due to oocyte donation per se or due to confounding factors such as maternal age or the allogenic fetus. In this retrospective comparative cohort, an attempt was made to evaluate and compare multiple obstetric and perinatal outcomes.

Methods: The present study comprised all women in the age range of 20-45 years who conceived from oocyte donation (n=102) between 1/12/2011 to 30/09/2017. Control group consisted of spontaneous conception cases (n=306) in ratio of 1:3 with no previous medical or surgery comorbidity. Obstetric and perinatal outcomes were compared between two groups.

Results: Mean maternal age was significantly higher in the donor oocyte IVF group (group 1; 35.13 years) as compared to spontaneous conception group (group 2; 31.75 years). Parity between the two groups was comparable. Pregnancy induced hypertension (PIH) was seen in 33.33% of cases in group 1 as compared to 7.18% in group 2. Moreover, gestational diabetes mellitus was seen in 34.31% of cases in group 1 as compared to 9.47% in group 2 (p=0.001). By the same token, there was significant difference in perinatal outcomes between the two groups.

Conclusion: Oocyte donation should be treated as an independent risk factor for miscarriage, hypertensive disorder, and gestational diabetes mellitus in pregnancy.

Keywords: Bleeding in first trimester, Gestational diabetes mellitus, Oocyte donation, Pregnancy induced hypertension.

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Introduction

Oocyte donation is a well-established method for the treatment of infertility in women (1). In vitro fertilization (IVF) has resulted in birth of more than 3 million children worldwide (2). While advances in early IVF improved the technology for treating women with tubal disease, those with premature ovarian failure had no effective fertility treatments until 1983. Oocyte donation was introduced in 1984 which allowed wom-

en with ovarian insufficiency to become pregnant (3). Oocyte donation has helped couples to achieve pregnancy in situations where the female partner has diminished ovarian reserve, premature ovarian failure, and surgical menopause (4). Though estimates and statistics from India are not available, with increased availability and accessibility of technologies, certainly more couples are availing themselves of the benefits of assisted reproductive

* Corresponding Author:
Yadav Vikas, Department
of Obstetrics and
Gynecology, School of
Medical Sciences and
Research, Sharda Hospital,
Sharda University Campus,
Uttar Pradesh, India
E-mail:
vikiyadav1789@gmail.com

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techniques using oocyte donation for above conditions. While women attempting pregnancy with donor oocytes are in advanced age for the obvious indications, the implications of pregnancy are far reaching in terms of obstetric and neonatal outcomes. Advanced maternal age is associated with pregnancy complications including hypertensive disorders, gestational diabetes, preterm labor, and fetal growth restriction (5, 6). The most common complication noted in pregnancies after donor oocyte IVF is pregnancy induced hypertension, affecting 16 to 40% of women (7-10). Some researchers have proposed that it is not maternal age but the allogenic fetus that may predispose women to maternal hypertensive disorders, fetal growth restriction (FGR), abnormalities in placentation, and gestational diabetes mellitus (11-16). Considering these conflicts on the results of pregnancy and neonatal outcome, an attempt was made to analyze our data in this regard in order to enable us counsel affected women. In this retrospective comparative cohort study, multiple obstetric and perinatal outcomes including abortion, preterm labor, antepartum hemorrhage, intrahepatic cholestasis of pregnancy (ICP), gestational diabetes mellitus, preeclampsia, fetal growth restriction, and fetal birth weight were evaluated and these variables between donor oocyte conception group and spontaneous conception group were compared.

Methods

The present study was a retrospective comparative cohort comprised of all women between the ages of 20-45 years who conceived from oocyte donation (n=102) between 1/12/2011 to 30/09/2017. The period was chosen in view of the modifications in regulations of third party reproduction which have been implemented by the Indian Council of Medical Research (ICMR) since 2010 (17). For control group, obstetric and perinatal profiles were taken from hospital database. The ICMR prohibits the use of oocytes donated by a relative or a known friend of either the wife or the husband. Considering the proposed allogenic theory which was suggested to be a reason for adverse perinatal outcome, women who underwent IVF with donor oocytes using siblings as donors prior to this period were all excluded. Out of 102 who conceived from oocyte donations, 76 had poor ovarian reserve (AMH <0.9 ng/ml), 11 had premature ovarian failure, and 15 were in advanced maternal age. Obstetric and perinatal outcomes were

compared with all women who had spontaneous conception (n=306). Patients were selected in the same time period in a ratio of 1:3. They were recruited retrospectively from hospital and their data were recorded at first antenatal visit between 6-9 weeks. All cases had no previous known medical or surgical comorbidity. Obstetric and perinatal profile of these patients was also retrieved from hospital database. All selected oocyte donors were in the age group of 21-30 years with mean age of 25 ± 4.42 years.

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 gonadotrophins starting from day 2 or 3 of menstruation using recombinant FSH (Gonal-F injection, Merck Serono Specialties Pvt. Ltd., Italy and Gonal-F, Merck Serono Ltd., India) at doses depending on the donor's age, BMI, ovarian reserves including AMH levels and antral follicle counts assessed prior to the start of cycle. GnRH antagonist (cetorelix 0.25 mg/day, cetrotide, Merck Serono Specialties Pvt. Ltd., Italy and Gonal-F, Merck Serono Ltd., India) was started from the sixth day of stimulation. Ovulation trigger was given when ≥ 3 follicles reached a diameter of 18 mm using recombinant hCG (ovitrelle injection, 250 micrograms, Merck Serono Ltd., India). Transvaginal oocyte retrieval was done after 34-36 hr under ultrasound guidance. The retrieved oocytes were inseminated with the male partner's sperm. The resultant embryos were frozen or transferred to the recipient if her endometrial lining was deemed ready after estrogen priming (endometrial thickness of ≥ 8 mm).

Endometrial preparation of recipients: Oocyte recipients underwent down-regulation and daily subcutaneous injection of GnRH agonist 0.5 mg (Lupride injection, Bayer Zydus Pharma Ltd., India) was started on the 21st day of preceding menstrual cycle. Endometrium was prepared with daily administration of estradiol valerate 4 mg from day 1 of bleeding and increased to 6 mg from day 8 of the cycle until the endometrium reached a thickness of ≥ 8 mm. Progesterone (Susten 100 injection, Sun Pharma, India) was started on the day of oocyte retrieval and continued until 14 days after embryo transfer. Embryo transfers were done on day 3 or day 5 depending on the embryo grading and the recipients' endometrial preparation. As per our institute protocol, two good quali-

ty embryos were transferred on day 3 or day 5. In cases where the endometrium was not prepared despite hormone therapy, the embryos were frozen and subsequently transferred in frozen embryo transfer (FET) cycle. The progesterone replacement was done in the form of micronized progesterone (Susten 100 Injection, Sun Pharma, India).

Pregnancy follow-up: Pregnancy was achieved when beta-hCG levels increased 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 obstetric parameters compared in both groups included first trimester bleeding, miscarriage, pre-eclampsia, oligoamnios, gestational diabetes mellitus, antepartum hemorrhage, preterm delivery, fetal growth restriction (FGR), intrahepatic cholestasis of pregnancy (ICP), mode of delivery, and postpartum complications. The neonatal outcomes including birth weights, Apgar scores, NICU stay, and congenital anomaly were compared in two groups.

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

Age matched subgroup analysis was done to compare the incidence of pregnancy induced hypertension and gestational diabetes mellitus between donor oocyte and spontaneous conception

group.

Statistical analysis: Data was presented in numbers and percentages. Statistical analysis was performed with chi-square test for categorical variables. The mean values were compared via student's t-test. Continuous outcomes (estimated gestation age and birth weight) were compared using student's t-test and linear regression; dichotomous outcomes were analyzed by logistic regression. To control for confounding variables, further analysis was performed using multivariable logistic regression model. The $p < 0.05$ was considered statistically significant.

Results

During the study period of 1/12/2011 to 30/09/2017, 102 women with donor oocyte conception were compared with 306 spontaneous conception women during the same period. Mean maternal age was significantly higher in the donor oocyte IVF group as compared to spontaneous conception group. Parity between the two groups was comparable. The number of women in the advanced age (>35 years) was higher in the donor group (Table 1). Regarding the obstetric events in two groups, a significantly higher incidence of miscarriage was observed in donor oocyte IVF group compared to spontaneous conception group ($p=0.001$). Bleeding in first trimester was likewise significantly higher in donor IVF group as compared to spontaneous conception group ($p=0.001$) (Table 2). The incidence of PIH was significantly high in donor oocyte IVF group as compared to spontaneous conception group ($p=0.001$). Subgroup analysis was done to compare PIH and GDM outcome in donor oocyte group and spontaneous conception group. Using multiple logistic

Table 1. Demographic profile of the study groups

Outcome	Group 1 donor IVF No. (%) n=102	Group 2 low risk patients No. (%) n=306	p-value
Mean age (years)	35.13±5.03	31.75±4.47	p=0.001
≤30	26 (25.49)	192 (62.74)	
31-40	61 (59.80)	86 (28.10)	
≥41	15 (14.70)	28 (9.15)	
Obstetric history			p=0.437
Primigravida	72 (70.6)	228 (74.5)	
Multigravida	30 (29.4)	78 (25.5)	

Table 2. Comparison of obstetric outcome of all pregnancies in two groups

Outcomes	Group 1 donor IVF No. (%) n=102	Group 2 low risk patients No. (%) n=306	p-value and significance
Obstetric events			
Early onset OHSS *	2 (1.96)	0 (0)	p=0.062
First trimester bleeding	21 (20.58)	14 (4.57)	p=0.001
Miscarriage	28 (27.45)	18 (5.88)	p=0.001
Anemia *	4 (3.92)	68 (22.22)	p=0.001
Preeclampsia	34 (33.33)	22 (7.18)	p=0.001
Oligoamnios	3 (2.94)	8 (2.61)	p=0.99
GDM *	35 (34.31)	29 (9.47)	p=0.001
APH *	11 (10.78)	7 (2.28)	p=0.001
Preterm delivery	56 (54.90)	19 (6.20)	p=0.001
ICP *	14 (13.72)	14 (4.57)	p=0.002
Abnormal presentation	5 (4.90)	8 (2.61)	p=0.326
Postpartum hemorrhage	7 (6.86)	5 (1.63)	p=0.013
Mode of delivery			
Vaginal	8 (7.84)	208 (67.97)	p=0.001
Spontaneous	8 (7.84)	168 (54.9)	
Induced	0	40 (13.07)	
LSCS	94 (92.15)	98 (32.02)	p=0.001
Elective	31 (30.39)	82 (26.79)	
Emergency	63 (61.76)	16 (5.22)	

GDM: Gestational diabetes mellitus; OHSS: Ovarian hyperstimulation syndrome. APH: Antepartum hemorrhage; FGR: Fetal growth restriction. ICP: Intrahepatic cholestasis of pregnancy

regression analysis, age class adjusted PIH incidence was compared between the two groups (Table 3) which was significantly higher in donor oocyte group as compared to spontaneous conception group ($p=0.001$), even after removing age as a confounder.

Gestational diabetes was found to be more prevalent in donor oocyte IVF group as compared to spontaneous conception group ($p=0.001$). Using

multiple logistic regression analysis, age class adjusted GDM incidence was compared between two groups (Table 4) which was significantly higher in donor oocyte group as compared to spontaneous conception group ($p=0.001$), even after removing age as a confounder (Table 3).

There was significant difference in the incidence of oligoamnios, antepartum hemorrhage, preterm delivery, intrahepatic cholestasis of pregnancy

Table 3. Age adjusted odds ratio for PIH and GDM by logistic regression analysis

Outcome	Variables	Adjusted odds ratio	p-value
PIH	Age	1.12	0.001
	Donor (ref)	1.00	
	Spontaneous conception	0.24	
	GDM		
GDM	Age	1.17	0.001
	Donor (ref)	1.00	
	Spontaneous conception	0.32	

Table 4. Comparison of perinatal outcome of all pregnancies in two groups

Outcome	Group 1 donor IVF (n=102) No. (%) n=120 fetuses	Group 2 low risk patients (n=302) No. (%) n=309 fetuses	p-value
Fetal outcome			
Mean birth weight	2480.96±625.89	2788.70±608.68	p=0.001
Twins	18 (15)	7 (2.26)	p=0.001
Apgar <8	26 (21.66)	9 (2.91)	p=0.001
SFD	17 (14.16)	18 (5.82)	p=0.005
LFD	5 (4.16)	5 (1.61)	p=0.151
Hyperbilirubinemia	12 (10)	4 (1.29)	p=0.001
Respiratory distress	26 (21.66)	6 (1.94)	p=0.001
Hypoglycemia	4 (3.33)	4 (1.29)	p=0.228
Still birth	0	3 (0.97)	p=0.563
Congenital anomaly	2 (1.66)	4 (1.29)	p=0.676

SFD: Small for date baby. LFD: Large for date

(ICP), fetal growth restriction (FGR), post partum hemorrhage, and mode of delivery among the two groups ($p=0.001$) as shown in table 2.

The value of mean birth weight, Apgar score, incidence of SFD, hyperbilirubinemia, and respiratory distress as perinatal outcomes (Table 4) were significantly higher in donor oocyte group as compared to spontaneous conception group ($p=0.001$).

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 the number of couples desirous of donor oocytes increases, it becomes necessary to evaluate obstetric, perinatal, and neonatal complications of the procedure. 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 caesarean section.

The present study showed an increased risk of GDM and PIH among women with donor oocyte pregnancies as compared with spontaneous conception pregnancies. When logistic regression

analysis was done for age-class matching, there still existed significantly higher incidence of PIH and GDM in donor oocyte pregnancies as compared to spontaneous conception pregnancies.

Studies on obstetric outcomes in donor oocytes pregnancies (8, 18) have shown an increased risk of preterm labor, preeclampsia, and cesarean delivery. However, another study (19) failed to find any association of adverse outcomes with conception after oocyte donation. A study on the Danish cohort (20) suggested an increased risk of preeclampsia and preterm labor in donor oocyte pregnancies as compared with spontaneous conception pregnancies. In our study, the results showed significant association between oocyte donation and FGR, antepartum hemorrhage, preterm labor, and cesarean delivery rate. This might be explained by the small sample size which is a significant limitation of the study. Increased cesarean rate in donor oocyte group was due to the preference of most of the patients in donor oocyte IVF group, opting for elective cesarean. Advanced maternal age is associated with a significantly increased risk of perinatal complications (21); therefore, it is necessary to eliminate bias caused by maternal age and other risk factors. Levron et al. (12) 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 (16) found an increase in

gestational hypertension in a subset of patients when controlling for multiple gestation and parity. However, age was a confounder in this study. The present findings are consistent with a few studies reporting high complication rates with donor oocyte pregnancies independent of recipient's age, parity, and the age of the donor (22-28). Obstetric complications in pregnancy after oocyte donation might be explained on the basis of immunologic theory (29). Parental sharing of human leukocyte antigen 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 process.

Limitation of the study was our small sample size. In our study, only a single control group of all spontaneously conceived patients was included. In fact, a control group including IVF patients with their own oocytes could have been recruited. The strength of this study was the homogeneity of the obstetric care and having 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 results 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 (32) and this should be part of the counseling service provided for the couple while they set out to proceed with donor oocyte IVF cycle. Obstetricians and pediatricians need to be aware of the increased pregnancy risks, which should be managed appropriately during the pregnancy, delivery, and puerperium period (33).

Conclusion

Donor oocyte IVF has proven to be an effective alternative for infertility treatment. Oocyte donation should be treated as an independent risk factor for miscarriage, hypertensive disorder, antepartum hemorrhage, preterm delivery, and gestational diabetes mellitus in pregnancy. Women should be informed of the risks and donor oocyte pregnancies should be managed in high risk ob-

stetrics clinics. Our study provides useful information for counseling couples who are considering the use of donor oocyte to achieve pregnancy.

Conflict of Interest

The authors declare that they have no conflict of interests.

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