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# Pregnancy outcomes and maternal and perinatal complications of pregnancies following *in vitro* fertilization/intracytoplasmic sperm injection using own oocytes, donor oocytes, and vitrified embryos: A prospective follow-up study

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## ABSTRACT

**BACKGROUND:** Several global studies have assessed maternal and perinatal outcomes and complications with the type of embryo transfer (ET) following *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI). The present study assessed the incidence of maternal and perinatal outcomes and complications following IVF/ICSI associated with the type of embryo transferred. **METHODOLOGY:** A total of 2112 ETs were performed in 2092 female patients aged 21–50 years between January 1 and December 31, 2014 (Group A: Fresh ET using self-oocytes: 691; Group B: Fresh ET using donor oocytes: 810; and Group C: Thaw ET using vitrified-warmed embryos: 611). **RESULTS:** Incidence of clinical pregnancy rate, abortion rate, ectopic pregnancy rate, multiple pregnancy rate, live birth rate, and maternal complications was: Group A: 40.8%, 15.9%, 2.8%, 27.3%, 31.9%, and 17.7%; Group B: 50.2%, 21.8%, 1.6%, 32.5%, 36.9%, and 23.7%; and Group C: 42.9%, 25.2%, 1.1%, 31.3%, 29.6%, and 17.8%, respectively. Incidence of prematurity (<36 weeks of pregnancy), lower birth weight (<2500 g), perinatal mortality, and congenital abnormalities was as follows: Group A (29.52%, 36.2%, 5.22%, and 1.39%), Group B (42.58%, 46.2%, 4.6%, and 1.32%), and Group C (35.74%, 32.4%, 7.85%, and 0.94%), respectively. **CONCLUSION:** The higher incidence of the pregnancy outcomes in oocyte donation (OD) cycles can mainly be attributed to the younger age of oocyte donors. The higher incidence of complications in OD cycles could be due to advanced maternal age, different placentation, and immune tolerance.

**KEY WORDS:** Donor oocyte, *in vitro* fertilization/intracytoplasmic sperm injection, live birth, maternal complications, perinatal complications, self-oocyte, vitrified embryo

## INTRODUCTION

Infertility, a reproductive health condition prevalent among one in every four couples in the developing countries, is a neglected problem.<sup>[1]</sup> India alone accounts for 30 million couples of infertility of the total 48.5 million globally affected couples.<sup>[2,3]</sup>

Assisted reproductive technologies (ART) such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) have emerged as a promising treatment option for infertility. IVF/ICSI may involve the use of own oocyte, donor oocyte, or vitrified embryo.<sup>[4-6]</sup> However, these treatment options

have been reported to be associated with the risk of various maternal and perinatal complications which include hemorrhage,

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puerperal sepsis, preeclampsia, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preterm birth, low birth weight (LBW), small for gestational age (SGA), congenital abnormalities, and perinatal death.<sup>[5,7]</sup>

A woman's chances of having a pregnancy and a live birth when using IVF/ICSI are influenced by many factors, some of which are patient-related and outside a clinic's control (e.g., the woman's age or the cause of infertility). With the rise in the number of IVF/ICSI cycles carried out world over where clinics only present success rates in terms of pregnancy rates to couples who require IVF/ICSI, more robust data are required in terms of pregnancy outcomes (clinical pregnancy rates [CPRs], Clinical abortion rates [CAR], ectopic pregnancy rates [EPRs], multiple pregnancy rates [MPRs]), live birth rates (LBRs), maternal and perinatal complications associated with IVF/ICSI of each clinic, to inform such increasing number of couples who opt for IVF/ICSI. As per Society for ART (SART) register in 2013 across 467 clinics in the USA, a total of 160,554 IVF/ICSI cycles were performed, resulting in a total 135,423 embryo transfers (ETs). Among patients undergoing fresh ETs using own oocytes, CPR and LBR ranging from 6.9% to 54.3% and 2.9% to 47.4% were reported among different age groups. In thaw ET cycles using own oocytes, CPR and LBR ranging from 23.4%–54.2% and 14.2%–44.1% were reported among different age groups. In donor oocyte transfer cycles, patients undergoing fresh ETs, CPR and LBR were 66% and 55.9%, respectively, and in patients undergoing frozen – thawed ETs were 50.1% and 40.2%, respectively.<sup>[8]</sup>

The frequency and type of these complications may vary depending on the type of oocytes used, i.e., self-oocyte, donated oocyte, and vitrified embryo in IVF/ICSI. Several studies have compared the incidence of obstetric and perinatal complications associated with the type of oocyte used in the treatment.<sup>[7,9,10]</sup> A study by Liu *et al.* compared the obstetric and neonatal complications associated with the transfer of fresh, slow freezing, and vitrified embryos. The rate of preterm birth was reported to be less in the vitrified group (7.5%) as compared to fresh (9.2%) and slow freezing (7.8%) groups, respectively. Number of twin babies born was also less in vitrified group (382) and higher in fresh and slow freezing group, i.e., 734 and 1322, respectively. The rate of hyper-intensive disorders in vitrified, slow freezing, and fresh groups was 8.9%, 7.6%, and 9.5%, respectively.<sup>[7]</sup>

Another study compared the obstetric and perinatal outcomes in pregnancies with oocyte donation (OD) and standard IVF. The study reported an increased risk in pregnancies following OD such as first trimester bleeding (53% vs. 31%,  $P < 0.01$ ), PIH (31% vs. 14%,  $P < 0.05$ ), and perinatal mortality rate (3.3% vs. 0%) as compared to IVF.<sup>[4]</sup>

However, there is a lack of data on the incidence of these obstetric and perinatal outcomes following IVF/ICSI. This is the first study to gather the data on the incidence of maternal and perinatal outcome of pregnancy resulting from ET following IVF/ICSI using own oocytes, donor oocytes, and vitrified-warmed embryos.

## METHODOLOGY

### Study characteristics

This was a prospective observational study conducted at an infertility center. The study included all the patients who had a positive pregnancy test after ET carried out between January 1, 2014, and December 31, 2014, following IVF/ICSI. All the patients were provided a format of standard antenatal care (frequency of monitoring, medications, ultrasound monitoring, etc.) and were advised delivery at a well-equipped obstetric setup. All the pregnant subjects were under the obstetric care of an obstetrician of their choice either from the beginning or after 12 weeks as the obstetric care is not provided at the facility.

### Eligibility criteria

All the women who conceived following an ET during the study duration were included.

### Data collection

Two approaches were used to collect the data from the study patients:

- First, at the time of referral, each obstetrician was provided with a pro forma for pregnancy monitoring and to record the outcome of patient's pregnancy - both maternal and perinatal. The form was sent through the post and with the subject. In addition, the same was communicated to the respective obstetrician by telephone. They were requested to complete the form and send the same to our center within a month of abortion, ectopic pregnancy, or delivery
- In cases where obstetrician could not be contacted, the details regarding outcome were obtained from the subjects themselves through a phone call.

### Outcomes assessed

The study assessed the pregnancy outcome and frequency of several maternal complications and perinatal outcomes in the study patients. The pregnancy outcomes included were the CPR, CAR, EPR, LBR, MPR, and twin birth rate. The maternal complications including PIH; premature rupture of membranes (PROM); GDM; placental abnormalities, namely, placenta previa and abruption placentae; liquor abnormalities including oligohydramnios, polyhydramnios, and preterm labor were observed. The perinatal outcomes including prematurity, birth weight, still births, neonatal deaths, and congenital anomalies were recorded.

### Statistical analysis

Chi-squared test was used to assess and compare the frequencies of various maternal and perinatal outcomes of pregnancies following the transfer of self, donor, and vitrified-warmed embryos.

## RESULTS

### Patient profile

This prospective observational study included 2092 female patients aged 21–50 years who underwent 2112 ET (Group A: Fresh ET using self-oocytes; 21–42 years,  $n = 691$ , Group B: Fresh ET using donor oocytes; 22–50 years,  $n = 611$ , and Group C: Thaw ET using vitrified-warmed embryos: 21–50 years,  $n = 810$ ). The study design and disposition of the patients are presented in Figure 1.

### Outcomes in different groups

Table 1 enlists all the pregnancy outcomes assessed in this study. CPR was reported to be higher ( $P = 0.002$ ) in Group B ( $n = 307$ ; 50.2%), followed by Group C ( $n = 348$ ; 42.9%) and Group A ( $n = 282$ ; 40.8%). The rate of multiple pregnancies did not differ significantly between the treatment groups: Group A ( $n = 100$ ; 32.5%), Group C ( $n = 109$ ; 31.3%), and Group B ( $n = 77$ ; 27.3%). The CAR was higher ( $P = 0.017$ ) in Group C ( $n = 88$ ; 25.2%) in comparison to the Group B ( $n = 67$ ; 21.8%) and Group A ( $n = 45$ ; 15.9%).

The rate of ectopic pregnancies did not differ significantly in the three groups ( $P = 0.245$ ): Group A,  $n = 8$  (2.48%); Group B,  $n = 5$  (1.5%); and Group C,  $n = 4$  (1.1%). The LBR in the study was higher in Group B ( $n = 221$ ; 36.9%) in comparison to Group A ( $n = 221$ ; 31.9%) and Group C ( $n = 240$ ; 29.6%); however, it could not achieve statistical significance. The rate

of singleton and twin birth did not vary significantly among the three treatment groups. The percentage of singleton births among the three groups was higher in the Group A ( $n = 167$ ; 73.5%), followed by Group C ( $n = 180$ ; 72.2%) and Group B ( $n = 153$ ; 67.1%). The percentage of twin births was higher in the Group B ( $n = 75$ ; 32.8%), followed by Group C ( $n = 69$ , 27.7%) and Group A ( $n = 60$ ; 26.4%). Lower segment cesarean section was the mode of delivery in most of the study patients ( $N = 660$ : Group A,  $n = 203$ ; Group B,  $n = 221$ ; Group C,  $n = 236$ ). Vaginal delivery was reported in 48 patients (Group A,  $n = 25$ ; Group B,  $n = 7$ ; Group C,  $n = 16$ ).

### Maternal complications

Overall, the prevalence of maternal complications was 19.95%. The rate of maternal complications was highest in Group B (32.0%), followed by Group C (24.9%) and Group A (22.0%); however, difference was not statistically significant ( $P = 0.3687$ ).

Table 2 enlists the frequency and type of all the maternal complications observed. PIH was reported to be the most frequent maternal complication in Group B ( $n = 38$ ; 12.38%), followed by Group C ( $n = 26$ ; 7.47%) and Group A ( $n = 16$ ; 5.67%). Other frequent complications reported in the women during pregnancy were PROM ( $n = 50$ ; 5.33%) and oligohydramnios ( $n = 32$ ; 3.41%). Only one patient in the Group A had GDM. In the Group B and Group C, GDM was reported in 6 (2.7%) and 6 patients (2.2%), respectively. There was one maternal death in Group B due to acute renal failure 2 days post-LSCS done for severe PIH and twin pregnancy. Both babies are alive and well.

### Perinatal outcomes

The incidence of prematurity (<36 weeks of pregnancy) was highest in Group B (42.58%), followed by Group C (35.74%) and Group A (29.52%) [Table 3].

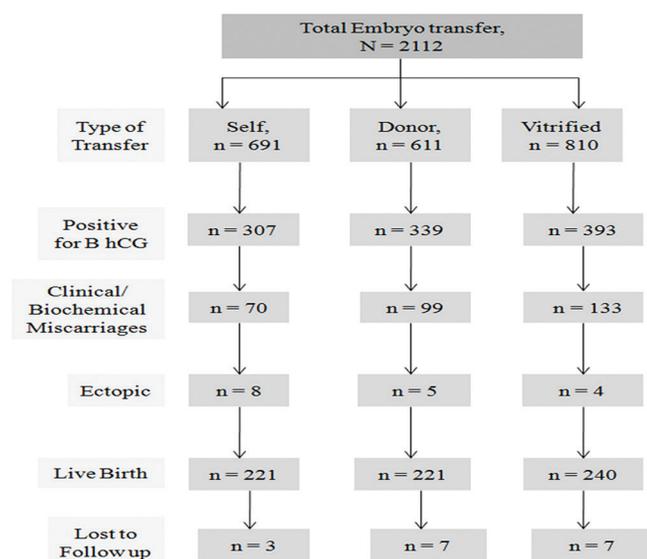


Figure 1: Study design and patient disposition

Table 1: Pregnancy outcomes assessed in the study

	Group A (%)	Group B (%)	Group C (%)	P
Age (years)	30.68±3.65	36.65±5.18	32.54±5.04	
Number of embryo transfer	691	611	810	
Clinical pregnancy	282 (40.8)	307 (50.2)	348 (42.9)	0.002
Clinical abortion	45 (15.9)	67 (21.8)	88 (25.2)	0.017
Multiple pregnancy	77 (27.3)	100 (32.5)	109 (31.3)	0.570
Ectopic pregnancy	8 (2.8)	5 (1.6)	4 (1.1)	0.245
Live birth rate	221 (31.9)	221 (36.1)	240 (29.6)	0.176
Single birth	167 (73.5)	153 (67.1)	180 (72.2)	0.271
Twin birth	60 (26.4)	75 (32.8)	69 (27.7)	0.271

Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw embryo transfer using vitrified-warmed embryos

Incidence of LBW (<2.5 kg) in Group A, Group B, and Group C was 43.20%, 55.11%, and 46.22%, respectively; of which 83.75% in Group A, 83.83% in Group B, and 70.06% in Group C belonged to LBW category (1.5–2.499 kg) [Table 4].

Perinatal death rate in the study was higher in Group C ( $n = 26$ ; 81.7/1000) in comparison to Group A ( $n = 16$ ; 55.0/1000) and Group B ( $n = 15$ ; 49.5/1000); however, the difference was not statistically significant among the three groups ( $P = 0.959$ ). The rate of stillbirths was 4.1% in Group A, 3.3% in Group B, and 6.2% in Group C [Table 5].

Congenital abnormalities [Table 6] were reported in 4 (1.39%) infants in Group A (pulmonary cyst, ventriculomegaly, tracheoesophageal fistula (TOF), cerebellar hypoplasia, hypertelorism, short femur, and Klinefelter's syndrome). One infant was born with

multiple congenital anomalies (TOF, cerebellar hypoplasia, short femur, hypertelorism) in Group A. In Group B, 4 (1.32%) infants had congenital abnormalities including transposition of great arteries, total anomalous pulmonary venous connection, anorectal malformation, and cardiac anomaly. In Group C, 3 (0.94%) infants had congenital abnormalities; they were TOF, ventriculomegaly, and hypoplastic nasal bone.

## DISCUSSION

This is the first prospective study to assess the pregnancy outcomes as well as incidence of maternal and perinatal outcomes in women undergoing IVF/ICSI treatment using self-oocyte, donor oocyte, and vitrified-warmed embryo.

The Japanese ART registry reports 190,613 ART treatment cycles in 2008 approximately 15% increase over 2007 reported treatments. All women used their own eggs or embryos and approximately 32% of all cycles used frozen thawed embryos. Of the 190,613 treatment cycles, 17.1% resulted in a clinical pregnancy and 10.7% resulted in a live birth delivery.<sup>[11]</sup>

The European register by the European Society of Human Reproduction and Embryology for 2010 reported outcomes of IVF/ICSI of more than 5 lakh cycles conducted in 31 countries. CPR of 33% for fresh ET cycles (both using own oocytes and donor oocytes) and 20.3% for thaw ET cycles were recorded. Overall MPR was reported to be 21.1%. Twin birth rate of 20.6% in IVF/ICSI and 12.5% in thaw cycles was recorded.<sup>[12]</sup>

In the present study too, CPR was found to be higher in fresh ET cycle using own oocytes and donor oocytes of 40.8% and 50.2%, respectively, compared to thaw ETs using vitrified-warmed oocytes, i.e., 42.9%. Overall, MPR

**Table 2: Maternal complications in patients undergoing different treatment types ( $P=1.000$ )**

Obstetric complications*	Group A (n=50)	Group B (n=73)	Group C (n=62)
GDM	1	6	6
PIH	16	38	26
APH	4	3	2
PPH	1	1	0
PROM	17	13	20
Polyhydramnios	2	2	1
Oligohydramnios	10	11	11
APLA	1	0	0
Jaundice	0	2	0
Pneumonia	0	2	2
Nephritis	1	0	0
Maternal death	0	1	0

\*Some patients had more than one complication. Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw embryo transfer using vitrified-warmed embryos, GDM=Gestational diabetes mellitus, PIH=Pregnancy-induced hypertension, APH=Antepartum hemorrhage, PPH=Primary postpartum hemorrhage, PROM=Premature rupture of membranes, APLA=Antiphospholipid antibodies

**Table 3: Prematurity rate following *in vitro* fertilization/intracytoplasmic sperm injection**

	Group A (n=227), n (%)	Group B (n=228), n (%)	Group C (n=249), n (%)	P
20-28 weeks	8 (3.52)	6 (2.63)	13 (5.22)	0.023
28.1-32 weeks	9 (3.96)	14 (6.14)	18 (7.22)	
32.1-36 weeks	50 (22.02)	77 (33.77)	58 (23.29)	
>36.1 weeks	160 (70.48)	131 (57.45)	160 (64.25)	
>40 weeks	0	0	0	

Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw embryo transfer using vitrified-warmed embryos

**Table 4: Birth weight of infants born with different treatment types ( $P=0.005$ )**

Birth weight (kg)	Group A (n=287), n (%)	Group B (n=303), n (%)	Group C (n=318), n (%)
Extremely LBW* (<1)	11 (3.8)	14 (4.62)	23 (7.23)
Very LBW (1-1.4999)	9 (3.1)	13 (4.2)	21 (6.6)
LBW (1.5-2.499)	104 (36.2)	140 (46.2)	103 (32.4)
LBW (2.5-3.999)	161 (56)	135 (44.6)	167 (52.5)
LBW (>4)	2 (0.69)	1 (0.33)	4 (1.25)

Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw Embryo transfer using vitrified-warmed embryos, LBW=Low birth weight

**Table 5: Perinatal death rate, stillbirth rate, and neonatal death rate comparison**

	Group A (n=16), n (%)	Group B (n=15), n (%)	Group C (n=26), n (%)	P
Still birth	12 (4.1)	10 (3.3)	20 (6.2)	0.959
Early NND	3 (1.04)	4 (1.32)	5 (1.57)	
Late NND	1 (0.34)	1 (0.33)	1 (0.3)	
Perinatal mortality/1000	16 (5.22)	15 (4.6)	26 (7.8)	

Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw Embryo transfer using vitrified-warmed embryos, NND=Neonatal death

**Table 6: Major congenital anomalies in patients undergoing different treatment types**

Congenital malformation	Group A, n=4 (1.39%)	Group B, n=4 (1.32%)	Group C, n=3 (0.94%)
Pulmonary cyst and cerebellar hypoplasia	1	-	-
Ventriculomegaly	1	-	1
Tracheoesophageal fistula	1	-	1
Hypertelorism and short femur, Klinefelter's syndrome	1	-	-
Transposition of great arteries	-	1	-
TAPVC	-	1	-
Anorectal malformation	-	1	-
Cardiac anomaly	-	1	-
Hypoplastic nasal bone	-	-	1

Group A=Fresh embryo transfer using self-oocytes, Group B=Fresh embryo transfer using donor oocytes, Group C=Thaw embryo transfer using vitrified-warmed embryos, TAPVC=Total anomalous pulmonary venous connection

was higher, i.e., 30.5%, being 27.3%, 32.55%, and 31.3% in Groups A, B, and C, respectively.

As per SART register in 2013 across 467 clinics in the USA, a total of 160,554 IVF/ICSI cycles were performed, resulting in 135,423 ETs. Among patients undergoing fresh ETs using own oocytes, CPR and LBR according to age group were: 54.3% and 47.4% (<35 years), 47.3% and 39.3% (35–37 years), 38.3% and 28.4% (38–40 years), 27.3% and 16.2% (41–42 years), 15.9% and 8.2% (43–44 years), and 6.9% and 2.9% (>44 years). In thaw ET cycles using own oocytes, CPR and LBR according to age group were: 54.2% and 44.1% (<35 years), 50% and 40.1% (35–37 years), 46.9% and 35.7% (38–40 years), 42.1% and 30.3% (41–42 years), 34.2% and 23.5% (43–44 years), and 23.4 and 14.2% (>44 years). In donor oocyte transfer cycles, the incidence of CPR and LBR in patients undergoing fresh ETs and frozen – thawed ETs was 66% and 55.9% and 50.1% and 40.2%, respectively.<sup>[8]</sup> In the present study, CPR and LBR in Group A were 40.8% and 31.9%, in Group B were 50.2% and 36.9%, and in Group C were 42.9% and 29.6%, respectively. The results of the study are comparable to SART data, CPR and LBR being highest in fresh ET cycles using donor oocytes.

Shen *et al.* in 2014 reported CPR, MPR, AR, and ER of 48.2%, 32.2%, 6.1%, and 2.5% in fresh ET cycle ( $n = 1150$ ) and 36.5%, 29.3%, 19%, and 3% in frozen-thawed ET cycles, thereby reporting the higher CPR in fresh ET cycles compared to frozen-thawed ET cycles, which is in accordance with the present study. AR in their study too was higher in frozen – thawed ET cycles compared to fresh ET cycles that too in agreement with the current study.<sup>[13]</sup>

Several studies in the past have reported a higher LBR following OD. A retrospective study by Remohí *et al.* reported accumulative pregnancy rate and LBRs to be 94.8% (confidence interval [CI] 90.6%–99.0%) and 88.7% (CI 88.1%–89.3%) following ovum donation.<sup>[14]</sup> The SART (2009) reported that the transfer of 9485 embryos with OD resulted in an LBR of 55.1%.<sup>[15]</sup> The study results were also in agreement with the findings of above studies as LBR ( $n = 221$ ; 36.9%) was higher in the Group B where fresh ET was done using donor oocytes. This is probably because the oocytes are derived from relatively young women with proven fertility.

Another study by Mirkin *et al.* reported CPR, AR, and MPR in OD cycles to be 47%, 19%, and 35%, respectively.<sup>[16]</sup> These results are comparable to present study which showed CPR (50.2%), AR (21.8%), and MPR (32.5%). A systematic review by Thomopoulos *et al.* reported an increased risk of PIH following ART. It concluded that the reduction of multiple gestations by using single ET techniques can be a therapeutic option for minimizing the hypertensive complications following assisted pregnancies.<sup>[17]</sup> An incidence of GDM is reported to be two times more in women with singleton pregnancies following ART as compared with the spontaneous pregnancies.<sup>[18]</sup>

Evangelia *et al.* in 2015 reported an increased incidence of PIH in OD cycles (15.8%) compared to self-oocyte cycles (9.5%). In the current study too, the frequency of PIH was reported to be higher in the Group B ( $n = 38$ , 16.6%) compared to Group A ( $n = 16$ , 7.04%).

The exact cause of maternal complications with OD is not known; the possibility is linked with advanced maternal

age, primiparity, and multiple pregnancies.<sup>[4]</sup> Abdalla *et al.* studied the obstetric outcome of pregnancies following OD in 232 patients. The study also reported an increased risk of PIH (23% of all deliveries) similar to the present study. The risk of postpartum hemorrhage was also higher in this study.<sup>[19]</sup>

Another study by Krieg *et al.* compared the maternal outcomes of women who conceived through donor oocytes with that of autologous oocytes in IVF. The study reported similar rates of hypertensive disorders, GDM, and placental abnormalities in both groups. This study speculated that the use of donor oocytes may not necessarily be associated with an increased risk of obstetric complications. The complications might be due to advanced maternal age, multiple gestation, or IVF itself.<sup>[20]</sup> In the current study, GDM was reported in six patients (2.6%) in Group B compared to only one patient (0.44%) in Group A. Overall, a higher incidence of PIH and GDM was observed as compared to other maternal complications.

The International Committee Monitoring ARTs World report, 2008–2010 included data from over 52 countries with 4,461,309 ART cycles resulting in 1,144,858 babies born. Delivery rate in fresh cycles per aspiration for IVF/ICSI was 19.8%, 19.7%, and 20% for the years 2008, 2009, and 2010, respectively, whereas in frozen-thawed ET cycles, they were 18.8%, 19.7%, and 20.7%, respectively. The risk of preterm birth is reported to be significantly higher in twins born (23%) after IVF as compared to the natural twins. LBW (<1000–2500 g) is another important outcome in newborns. The risk of LBW is increased due to prematurity resulting from multiple pregnancies, but the risk is even higher in singleton pregnancies and more evident in twins of IVF as compared to natural singletons and twins.<sup>[21]</sup> Although, previous studies have reported an increased risk of congenital abnormalities in children born after IVF/ICSI (30%–40%) as compared to natural conception.<sup>[22,23]</sup> A recent review by Fauser *et al.* reported a similar risk of birth defects in IVF and natural conception and a very low risk of genetic disorders in children born following assisted technologies. The review also concluded that the health of the children is independent of the ART and the differences observed might be due to maternal age.<sup>[24]</sup> The occurrence of congenital malformations in infants born after ART has also been linked to the cause of infertility and its determinants in the couples, medications used for ovulation induction and pregnancy maintenance.<sup>[17,25]</sup>

The perinatal mortality rate in fresh IVF/ICSI cycles using own oocytes was 22.8/1000 births, 19.2/1000 births, and 21/1000 birth for the years 2008, 2009, and 2010, respectively, whereas in frozen-thawed ETs, they were 15.1/1000, 12.8/1000, and 14.6/1000, respectively.<sup>[26]</sup>

In present study, perinatal death rate was 52.2/1000 births ( $n = 16$ ), 46/1000 births ( $n = 15$ ), and 78/1000 births ( $n = 26$ ) in Groups A, B, and C, respectively. The perinatal death rate was higher in the present study. However, of the total 16 deaths in the Group A, 50% babies were below 1 kg, and among 15 deaths in the Group B, 39.8% babies were below 1 kg, and among 26 total deaths in the Group C, 69.23% babies were below 1 kg; this could possibly be a contributing factor.

In the current study, the incidence of prematurity (<36 weeks of pregnancy) was highest in Group B (42.58%), followed by Group C (35.74%) and Group A (29.52%). The incidence of LBW (<2500 g) was higher in Group B (46.22%), followed by Group A (36.2%) and Group C (32.4%).

A systematic review (2004) of the studies comparing perinatal outcomes following assisted and natural conception concluded that singleton pregnancies following the assisted conceptions had adverse perinatal outcomes (very preterm birth, preterm birth, very LBW, LBW, SGA, cesarean section, admission to Neonatal Intensive Care Unit, and perinatal mortality) in comparison to the natural conception. All these studies have reported varied results on the association of adverse perinatal outcomes and assisted conceptions, but they lack in providing the accurate reasons for the association.<sup>[27]</sup>

Söderström-Anttila in his review stated that the perinatal complications in oocyte donated pregnancies are usually associated with GDM.<sup>[10]</sup> In the present study, GDM was reported in 6 patients with oocyte-donated pregnancies. However, we did not observe any perinatal complication in infants born to these patients. A retrospective study by Kato *et al.* demonstrated higher birth weight ( $3028 \pm 465$  vs.  $2943 \pm 470$  g,  $P < 0.0001$ ) of infants born following the transfer of vitrified embryos as compared to fresh ET.<sup>[28]</sup> Liu *et al.* reported birth weight to be higher in babies born from vitrified embryos (2587.4 g) as compared to the fresh (2494.4 g) or slow freezing (2538.8 g) transfer groups.<sup>[7]</sup> Another recent study by Roy *et al.* also reported improved perinatal outcomes in infants born following vitrified ET as compared to fresh ET including significantly higher birth weight (3296 g vs. 3441 g for fresh and vitrified-warmed groups), respectively.<sup>[29]</sup> Mascarenhas *et al.* in his study reported higher median birth weight in infants born in vitrified group (2587.4 g) as compared to the slow freezing (2538.8 g) or fresh (2494.4 g) transfer groups (vitrified vs. fresh:  $P = 0.0015$ ; vitrified vs. slow freeze:  $P = 0.049$ ).<sup>[3]</sup>

However, in the present study, the birth weight was not reported to be better in Group C.

Early studies on congenital malformations following IVF/ICSI reported inconsistent results. However, meta-analysis and systematic reviews done after 2000 and randomized control trials comparing congenital malformations between ART and spontaneous conceptions showed some evidence linking the two. An association of hypospadias with ICSI for male factor and imprinting genetic syndromes with IVF and ICSI has been well documented. What remains to be ascertained are the other systemic malformations such as cardiovascular, musculoskeletal, orofacial, and gastrointestinal defects.<sup>[30]</sup>

A case-control study conducted by Reefhuis *et al.* in 2009, which compared 13,586 cases with 5008 controls, found significant associations among singletons for the group of septal heart defects (odds ratio [OR] 2.1, 95% CI 1.1–4.0), cleft lip with/without cleft palate (OR 2.4, 95% CI 1.2–5.1), esophageal atresia (OR 4.5, 95% CI 1.9–10.5), anorectal atresia (OR 3.7, 95% CI 1.5–9.1), and an elevated OR (2.1) for hypospadias (95% CI 0.9–5.2). When the patterns among infants with multiple defects were studied, two phenotypes were relatively common among infants conceived using art; the vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal malformations and limb defects association and oculoauriculovertebral spectrum.<sup>[31]</sup>

Very little literature is available on the incidence of congenital malformations following oocyte donated pregnancies. In the present study, the incidence of congenital anomalies did not vary significantly between the three groups (Group A [1.39%], Group B [1.32%], and Group C [0.94%]). Even in the present study, the incidence of cardiac malformations, esophageal malformations, and anorectal malformations was reported to be higher. One infant was born with multiple congenital anomalies (TOF, cerebellar hypoplasia, short femur, hypertelorism) in Group A.

However, the current study has only followed children up to a month after the birth. Therefore, the studies with more follow-up periods are needed to be conducted to assess the long-term effects of IVF/ICSI involving the transfer of self, donor, and vitrified embryo. Further, a higher number of maternal complications in the Group C as compared with Group A might be due to the age and health of the donor and the recipient that could have affected the quality of the oocytes. Our study did not make a distinction among donor and self-oocytes in the vitrified embryo group. It is important that physicians examine a couple of factors before finalizing the type of ART treatment such as the cause of infertility, ovarian reserve, and maternal age. The continuous analysis of the patients with various diagnostic tests during the pregnancy is essential to prevent the occurrence of complications.

## CONCLUSION

Pregnancy outcomes and maternal and perinatal complications in pregnancies following IVF/ICSI in the present study are similar to developed countries. CPR and LBR are highest in OD cycles, as expected. This difference can mainly be attributed to the younger age of oocyte donors, which reduces the risk for aneuploidies. Furthermore, the incidence of maternal complications mainly PIH, GDM, prematurity, and LBW is higher in OD cycles, advanced maternal age possibly contributing as a confounding factor, although a different placentation and immune tolerance may contribute. This difference could possibly be nullified after adjusting for the subject's age. Furthermore, the incidence of multiple pregnancies was higher in egg donor cycles, which increases the incidence of these complications in Group B. No increase in the incidence of congenital malformation compared to the general population was recorded; however, data are available up to only 1 month after delivery.

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## Conflicts of interest

There are no conflicts of interest.

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