Background: As the number of older women attempting to conceive through donor oocyte-in vitro fertilization (DO-IVF) rises, their safety in pregnancy needs to be judiciously considered. Aims: This study aims to review the obstetric and perinatal outcomes of pregnancies achieved by DO-IVF.

Study Setting and Design: A retrospective study design conducted at a private health facility with services for assisted reproduction and gynecologic endoscopy.

Methods: A retrospective comparative study of all pregnancies achieved using DO-IVF and that using Self oocyte In-vitro fertilization (SO-IVF) treatment over a 3 years’ period was performed. Statistical Analysis: Comparative analysis of demographic variables, major obstetric, and perinatal complications was done with Chi-square test and Student’s t-test as appropriate. Regression analysis was done to determine a significant predictor variable for pregnancy and delivery outcome. The significance level was set at \( P < 0.05 \).

Results: A total of 343 completed IVF treatment cycles was reviewed; there were 238 DO-IVF and 105 SO-IVF cycles, with clinical pregnancy rate of 41.6% and 37.1%, respectively. The DO-IVF group was significantly older than the SO-IVF group (46.1 years vs. 34.1 years, \( P < 0.001 \)). Major obstetric complications identified, were hypertensive disorders in pregnancy (23.9%), preterm labor (16.7%), antepartum hemorrhage (11.6%). There was no statistically significant difference between the two groups in terms of obstetric complications and adverse maternal or perinatal outcomes. There were 97 (77.6%) singleton and 28 (22.4%) multiple pregnancies. Pregnancy complications were significantly associated with fetal plurality, \( P < 0.001 \). Multiple pregnancy had higher odds of experiencing adverse perinatal 4.96 (1.95–12.58) and maternal 7.16 (2.05–25.03) outcomes compared to singleton pregnancies, \( P < 0.001 \).

Conclusion: Key obstetric outcomes did not differ between DO or SO IVF achieved pregnancy. Even for older women, satisfactory outcomes can be expected for pregnancies achieved by DO-IVF. It is, however, instructive that for multiple pregnancies, obstetricians should institute appropriate surveillance strategies during pregnancy and delivery period and also to develop institutional capacity for quality neonatal care.

Keywords: Donor oocyte program, infertility, in vitro fertilization, maternal and perinatal care, multiple gestation, pregnancy and age

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INTRODUCTION

The utility of in vitro fertilization (IVF) treatment has rekindled the hope of motherhood for infertile women across all age groups. Particularly, older women with infertility now have a chance of achieving pregnancy through an oocyte donation treatment program. Advanced maternal age has been shown to impact on pregnancy and delivery outcome. [1,2] It has been established that fecundity declines with maternal age, also adverse pregnancy outcomes such as hypertension, diabetes, congenital anomalies, and miscarriages have been associated with advanced maternal age. [2-4] While the use of donor oocyte (DO) (IVF treatment) may mitigate the effect of oocyte quality on pregnancy outcome in older women, other age-related potential obstetric risk still remains. Some studies have suggested that DO achieved pregnancy is allogeneic to the gestational carrier with increased antigenic dissimilarity compared to autologous oocyte achieved pregnancies. [5,6] This increased immunological activity and fibrinoid deposition were noted to play a role in the etiology of pregnancy complications such as preeclampsia. [5,6] In addition, older women are more likely to have preexisting co-morbidities further complicating their pregnancy course and outcome common obstetric and perinatal complications reported in IVF achieved pregnancies in older women include pregnancy-induced hypertension, placenta previa, preterm labor, and gestational diabetes, also a higher rate of cesarean section delivery and obstetric hemorrhage have been observed. [4,7] Researchers have shown that use of DO IVF treatment with improved oocyte quality resulted in higher pregnancies and live birth rates compared to autologous oocyte treatment cycle. [3,4,6,8]

There exist a huge population of older women seeking pregnancy and childbirth through IVF. This is fostered by cultural and socio-economic reasons as well as the health-seeking behavior of most women in our environment. [8] The need to evaluate the pregnancy outcomes of these older women who are mainly recipients of oocyte donation program in an IVF treatment cycle becomes imperative. This would help treatment planning as well as patient counseling and education.

METHODS

This study sought to compare pregnancy and delivery outcomes between women who had IVF pregnancy with DO (DO-IVF or recipient group) and those with patient’s own (autologous) oocyte (SO-IVF or self-group).

Study design

A retrospective comparative study design.

Study setting and population

This comparative study was conducted at a health facility with services for assisted reproduction and gynecologic endoscopy. A 3 years (January 2017–December 2019) retrospective comparative study of all completed IVF-embryo transfer (IVF-ET) treatment cycle was undertaken. The study included all the patients who had confirmed clinical pregnancy following IVF-ET carried out between January 2017 and December 2019. These patients at the time of enrollment for IVF treatment had consented to use of anonymised data from their case files for research and educational purposes. All patients had prior evaluation and preparation as per standard protocol before treatment initiation. The same clinical and embryology team was involved in all IVF treatments using standard IVF protocols. [9]

During the study, the unit protocol for IVF treatment followed standard ovarian stimulation protocols; [9] all patients had oral contraceptive pills (for 3–4 weeks prior to the treatment cycle) for menstrual cycle synchronization and either the long agonist or antagonist protocol were the common prescribed stimulation methods. In the long agonist protocol down-regulation with gonadotropin-releasing hormone agonist as subcutaneous dose of Buserelin at 0.5 mg daily (Suprefact®; Sanofi, United Kingdom) which was started in the luteal phase (days 17–21) of the pretreatment cycle and with the onset of the menstrual cycle, the dose of buserelin was reduced to 0.25 mg daily till the day of trigger. Ovarian stimulation was commenced on the 3rd day of menses for 10–14 days with the administration of highly purified human menopausal gonadotropin (hMG) or recombinant follicle-stimulating hormone (FSH) at a daily dose of 150–375 IU, adjusted based on follicular response. Serial transvaginal ultrasonographic scan was done at interval from days 5 to 6 of stimulation to determine the numbers, size of follicles, and endometrial thickness. Whenever 2 or more follicles have grown to 18 mm or more, human chorionic gonadotrophin (hCG: 5000–10,000 IU) trigger was administered and oocyte retrieval was carried out at 35 h thereafter.

While in antagonist protocol, patients were commenced on hMG or recombinant FSH (150–375 IU) on day 3 of menstrual cycle for 10–14 days. Subcutaneous 0.25 mg daily GnRH antagonist (Cetrotide®; merckserono, Germany) was administered whenever the follicles have grown to 14 mm size usually around days 6/7 of stimulation and this was continued till the day of trigger to prevent premature LH surge. Intramuscular hCG or 2.5–3 mg of buserelin were administered subcutaneously for trigger whenever 2 or more follicles have grown.
to 18 mm or more. Oocyte retrieval was done by transvaginal needle aspiration under ultrasound guidance and was transferred immediately to the laboratory for oocyte screening, pickup, and treatment either by in vitro technique (IVF) or intracytoplasmic sperm injection.

Recipients of DOs had endometrial preparation with oral oestrogen (Progynova®) started at the beginning of their menstrual cycle at a dose of 8–12 mg daily adjusted according to sonographic appearance and thickness of the endometrium. Luteal support for all patients commenced after oocyte retrieval with progesterone (400 mg twice daily, cyclolest pessaries®) administered trans-vaginally. Embryos were transferred on days 3 or 5 of oocyte retrieval under transabdominal ultrasound guidance. The number of embryo(s) transferred was individualized based on available quality of embryos; 2 or 3 in most cases but usually not more than 4. The luteal phase support was continued with progesterone and pregnancy test was carried out 2 weeks after ET. Clinical pregnancy was defined as the presence of an intrauterine gestational sac using transvaginal ultrasound 28 days after ET.

Majority of the established pregnancies received obstetric/antenatal care at the private center and the public tertiary hospital in the city; while few patients had antenatal care at other standard health facilities under an obstetrician of their choice. Ethical approval was obtained from the ethics and research committee of the public referral tertiary institution; Approval number: ADM/E22/A/VOL.VII/14831113.

Data management

The case files and hospital records of deliveries of all patients who had achieved pregnancy by assisted reproductive technology during the study were retrieved for analysis. Pregnancy and delivery outcomes of all IVF patients were regularly updated on the hospital database through the case files and communication with the patient or attending obstetrician. Comparative analysis of pregnancy and delivery outcome was done between IVF achieved pregnancy with DO (DO-IVF or recipient group) and those with patient’s own (autologous) oocyte (SO-IVF or self-group). Data extracted for analysis included demographic characteristics, major obstetric complications such as early pregnancy loss, hypertension, diabetes, anemia, preterm labor, preterm premature rupture of membranes, antepartum hemorrhage, and postpartum hemorrhage. The mode of delivery, number of fetuses (plurality), gestational age at birth, birth weight, admission into special care baby unit (SCBU), and early neonatal death were also noted. The maternal and perinatal outcome was categorized as good/satisfactory or bad/adverse depending on the occurrence (or not) of debilitating or serious intrapartum or postpartum complications such as need for life-saving massive blood transfusion, cesarean hysterectomy, maternal mortality (maternal outcome) or admission to SCBU, severe neonatal morbidities or early neonatal death (perinatal outcome).

Statistical analysis

This was done using the statistical analysis was done using IBM, SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA) with Chi-square test for categorical variables and Student’s t-test for continuous variables. Regression analysis was done to determine a significant predictor variable for pregnancy and delivery outcome. Significance level was set at $P < 0.05$.

RESULTS

Overall there were 343 completed IVF treatment cycles. The clinical pregnancy rate (CPR) was 40.2% (138/343), miscarriage rate was 9.4% (13/138) with one (0.7%) being an ectopic gestation. There were 125 (36.4%) live births with 163 babies delivered (97 single, 18 sets of twins, 7 triplets, and 3 quadruplets). The analysis of outcome of treatment cycles is shown in Table 1: two groups, the DO (DO-IVF) and the self or autologous oocyte (SO-IVF) group were categorized for analysis; Out of the 343 IVF treatment cycles overwhelming majority 69.4% (238/343) were DO (DO-IVF) treatment cycles while 30.6% (105/343) used autologous oocyte (SO-IVF). In the DO-IVF group, 99 (41.6%) clinical pregnancies were established with 92 (38.7%) live births and 9 (9.1%) miscarriages while in the self-treatment cycles (self-group, SO-IVF) there were 39 (37.1%) clinical pregnancies, live birth rate and miscarriage rate of 31.4% and 10.2% respectively and there was no statistical difference.

Table 1: Summary of in-vitro fertilization treatment outcome in the study period

|                        | Total, n (%) | DO-IVF, n (%) | SO-IVF, n (%) | P     |
|------------------------|--------------|---------------|---------------|-------|
| Total treatment        | 343          | 238 (69.4)    | 105 (30.6)    |       |
| Clinical pregnancy     | 138 (40.2%)  | 99 (41.6)     | 39 (37.1)     |       |
| Miscarriage            | 13 (9.4%)    | 3 (7.7)       | 1 (2.6)       | 0.703 |
| Ectopic gestation      | 125 (36.4%)  | 92 (38.7)     | 33 (31.4)     |       |
| Livebirths             | 163          | 97 (78.0)     | 56 (64.5)     | 0.748 |
| Number of babies       |              |               |               |       |
| Single                 | 97 (78.0)    | 76 (78.0)     | 21 (43.5)     |       |
| Twins                  | 18 (12.8)    | 13 (13.2)     | 5 (10.2)      |       |
| Triplets               | 7 (5.0)      | 5 (5.0)       | 2 (4.1)       |       |
| Quadruplets            | 3 (2.1)      | 3 (3.1)       | 0 (0.0)       |       |

DO-IVF=Donor oocyte-in vitro fertilization,
SO-IVF=Self-oocyte-in vitro fertilization
Analysis of clinical characteristics is shown in Table 2; the mean age of the study population was 42.7 ± 6.8 years, the self-group was significantly younger than the recipient group (46.1 ± 4.3 vs. 34.1 ± 3.5, P < 0.001). Majority of the self-group were in the 30–39 age group (84.6%) while the recipient was mostly in the 40–49 age group (80.8%) (P < 0.001). Over 90% were nulliparous women. Among major pregnancy problems identified, hypertensive disorders in pregnancy (23.9%) and preterm labor (16.7%) were the most common. There was no statistically significant difference between the groups in terms of obstetric complications, P = 0.591. Majority (47.8%) delivered at term with mean gestational age at delivery was 36 ± 3.9 weeks for DO-IVF group and 36.5 ± 1.2 weeks for SO-IVF group, P = 0.470. There was no statistical difference in mean birth weight for DO-IVF group and SO-IVF group (2.96 kg vs. 3.0 kg). Majority (69.6%) of the babies were not admitted into SCBU and did not suffer early neonatal death (88.4%). Table 2 also shows analysis of maternal and perinatal outcome categorized as good/satisfactory or bad/adverse depending on the

| Variable                        | Total (n=138), n (%) | DO-IVF (n=99), n (%) | SO-IVF (n=39), n (%) | P   |
|---------------------------------|---------------------|----------------------|----------------------|-----|
| Age, mean±SD                    | 42.7±6.8            | 46.1±4.3             | 34.1±3.5             | 0.0001 |
| Age group                       | 27–57               |                      |                      |     |
| <30                             | 4 (2.9)             | 0                    | 4 (10.3)             | 0.0001 |
| 30–34                           | 17 (12.3)           | 0                    | 17 (43.6)            |     |
| 35–39                           | 20 (14.5)           | 4 (4.0)              | 16 (41.0)            |     |
| 40–44                           | 35 (25.4)           | 34 (34.3)            | 2 (5.1)              |     |
| 45-49                           | 46 (33.3)           | 46 (46.5)            | 0                    |     |
| 50-54                           | 10 (7.2)            | 10 (10.1)            | 0                    |     |
| 55-59                           | 6 (4.3)             | 5 (5.1)              | 0                    |     |
| Parity                          |                     |                      |                      |     |
| Nullipara                       | 127 (92.1)          | 89 (89.9)            | 38 (97.4)            | 0.322 |
| Primipara                       | 9 (6.5)             | 8 (8.1)              | 1 (2.6)              |     |
| Multipara                       | 2 (1.4)             | 2 (2.0)              | 0                    |     |
| Pregnancy complications         |                     |                      |                      |     |
| None                            | 72 (54.3)           | 55 (55.6)            | 18 (46.1)            | 0.591 |
| Hypertension                    | 33 (23.9)           | 23 (23.2)            | 10 (25.6)            |     |
| Preterm labor                   | 23 (16.7)           | 15 (15.2)            | 8 (20.5)             |     |
| Gestational diabetes            | 16 (11.6)           | 13 (11.3)            | 3 (7.7)              |     |
| Placenta praevia                | 1 (0.7)             | 0                    | 1 (2.6)              |     |
| Gestational age at birth, mean±SD (weeks) | 36.0±3.4            | 36.5±1.2             | 0.470                |
| Term (≥37)                      | 66 (47.8)           | 48 (48.5)            | 18 (46.1)            | 0.628 |
| Near term (36)                  | 27 (19.6)           | 17 (17.2)            | 10 (25.6)            |     |
| Preterm (<36)                   | 32 (23.2)           | 25 (25.3)            | 7 (17.9)             |     |
| Birth weight (kg), mean±SD      | 2.9±0.6             | 3.0±0.5              | 0.550                |
| SCBU admission                  |                     |                      |                      |     |
| Yes                             | 29 (21)             | 24 (24.2)            | 5 (12.8)             | 0.214 |
| No                              | 96 (69.6)           | 65 (65.7)            | 31 (79.5)            |     |
| ENND                            |                     |                      |                      |     |
| Yes                             | 3 (2.2)             | 2 (2.0)              | 1 (2.6)              | 0.864 |
| No                              | 122 (88.4)          | 89 (89.9)            | 33 (84.6)            |     |
| Maternal outcome                |                     |                      |                      |     |
| Satisfactory                    | 125 (90.6)          | 87 (87.9)            | 38 (97.4)            | 0.329 |
| Hysterectomy                    | 6 (4.3)             | 6 (6.1)              | 0                    |     |
| Massive obstetric hemorrhage    | 6 (4.3)             | 5 (5.1)              | 1 (2.6)              |     |
| Mortality                       | 1 (0.7)             | 1 (1.0)              | 0                    |     |

More than one complication may occur in one patient. SD=Standard deviation, SCBU=Special care baby unit, ENND=Early neonatal death, DO-IVF=Donor oocyte-in vitro fertilization, SO-IVF=Self oocyte-in vitro fertilization
occurrence (or not) of debilitating or serious intrapartum or postpartum complications. Majority 90.6% (125) had good maternal outcome. Adverse pregnancy and delivery outcome were minimal (9.4%) and not statistically different between the groups (DO-IVF vs. SO-IVF, \( P = 0.329 \)). One (0.7%) maternal mortality was recorded, a case of pulmonary thromboembolism on the 2nd day postcesarean section.

In Table 3, subanalysis of the association of pregnancy and delivery outcome with fetal plurality showed that pregnancy complications were significantly more common with increasing number of fetuses, \( P < 0.001 \). The mean gestational age at delivery for single, twin, triplet, and quadruplet gestation were 37, 35, 34, and 33 weeks respectively and the difference was significant, with majority of the multiple births being preterm <36 weeks gestation \( P = 0.001 \). Birth weight was significantly smaller with increase in number of fetuses, \( P < 0.001 \). The SCBU admission rate was higher (\( P < 0.001 \)) with increasing fetal number but there was no difference in the incidence of early neonatal death and in addition the fetal salvage was similar across the group. The incidence of adverse maternal outcome especially hysterectomy and massive obstetric hemorrhage was associated more with multiple gestation 28.6% (8/28) compared to singleton gestation 5.1% (5/97) \( P < 0.006 \).

Regression analysis to determine significant independent variable associated with pregnancy complications as well as adverse maternal and perinatal outcome is shown in Table 4; Maternal age, parity, and treatment group (DO-IVF or SO-IVF) did not influence the occurrence of pregnancy and delivery complications but fetal plurality was significantly associated with these outcomes (\( P < 0.001 \)). The odds of experiencing pregnancy complications, adverse perinatal and maternal outcomes were respectively 19.49 (4.24–89.61), 4.96 (1.95–12.58), and 7.16 (2.05–25.03) more likely with multiple gestation compared to singleton pregnancies, \( P < 0.001 \).

**Discussion**

This study demonstrated that DO treatment cycle is relatively common than self or autologous oocyte treatment, in addition, we observed higher clinical pregnancy and live birth rates in the DO IVF treatment cycles. These findings may suggest that a higher number of advanced-aged women who will require DO are accepting and accessing DO programs as a renewed hope for childbearing. This corroborates previous reports of increasing uptake of IVF by women who had hitherto delayed seeking orthodox treatment or infertility.\[10,11\] In addition, several reports have shown donor egg IVF to be a successful option of Assisted reproduction technique (ART) even for women of advanced age.\[11‑13\] Our CPR of 41.6% for DO IVF treatment is comparable to other studies where CPR of 33%–55% has been reported.\[12,13\] This is probably because the oocytes are derived from relatively young women with better fertility potential.

In this study, we compared the obstetric and perinatal outcomes of pregnancies after IVF-ET in older women who were mainly recipients of donated oocytes and those from relatively younger women who used autologous (self) oocytes. We observed comparable pregnancy complications in both groups, with hypertensive disorders in pregnancy

| Variable                        | Single (n=97) | Twins (n=18) | Triplet (n=7) | Quadruplets (n=3) | \( P \)   |
|---------------------------------|--------------|--------------|--------------|------------------|--------|
| Pregnancy complications         |              |              |              |                  |        |
| Yes                             | 41           | 16           | 6            | 3                | 0.0001 |
| No                              | 56           | 2            | 1            | 0                |        |
| Gestational age birth (weeks)   |              |              |              |                  |        |
| Mean±SD (range)                 | 36.8±1.4 (32‑39) | 35.4±0.7 (34‑37) | 34.4±0.7 (33‑36) | 33.7±1.5 (32‑35) | 0.001  |
| Birth weight (kg)               | 3.1±0.5      | 2.8±0.3      | 2.1±0.4      | 2.1±0.3          | 0.0001 |
| SCBU admission                  |              |              |              |                  |        |
| Yes                             | 18           | 6            | 6            | 3                | 0.0001 |
| No                              | 85           | 12           | 1            | 0                |        |
| ENND                            |              |              |              |                  |        |
| Yes                             | 2            | 0            | 1            | 0                | 0.156  |
| No                              | 105          | 18           | 6            | 3                | 0.006  |
| Maternal outcome                |              |              |              |                  |        |
| Satisfactory                    | 92           | 14           | 4            | 2                |        |
| Adverse                         | 5            | 4            | 3            | 1                |        |

SD=Standard deviation, SCBU=Special care baby unit, ENND=Early neonatal death
pregnancy complications, including placenta previa, placenta abruption, and placental adherence. Although we observed increased placenta abnormalities and associated adverse maternal complications with DO treatment group, it was not significantly different from the self-treatment group. Consistent with our study finding, Krieg et al.\(^3\) observed similar rates of maternal outcomes such as hypertensive disorders and placental abnormalities in women who conceived through DOs and those who used autologous oocytes. Krieg et al.\(^3\) speculated that the increased risk of obstetric complications observed may not necessarily be associated with the use of DOs but rather might be due to advanced maternal age, multiple gestation, or the IVF itself. Our study observed that multiple gestation was an independent significant predictor of increased odds for adverse pregnancy and delivery outcome.

Pregnancy complications such as preterm labor and pregnancy-induced hypertension were associated significantly with multiple gestation in this study. However, contrary to report\(^{[21,22]}\) associating perinatal complications especially preterm labor and delivery to be significantly higher in DO achieved IVF, we observed no significant difference in perinatal complications in both groups of women. This suggests that the gestational age and fetal plurality rather than the use of DO were the principal determinants of perinatal outcome. The effect of fetal plurality brings to fore the need for consideration of single ET (SET) or multifetal pregnancy reduction (MFPR) for women of advanced aged using DO. Howbeit, a previous study showed that despite recognizing the risks associated with higher-order multifetal pregnancy, infertile women still encourage transfer of multiple embryos and are less interested in SET or MFPR.\(^{[23]}\) Furthermore, the satisfactory perinatal outcome observed despite increased incidence of preterm low births refers the need for the availability of high-quality neonatal care in facilities caring for IVF pregnancies.\(^{[21,24]}\)

On the basis of increased risk for maternal complications including maternal death some researchers have recommended strict counseling and selection of women undergoing DO conception treatment especially at an advanced age.\(^{[25,26]}\) In this study, we observed that DO achieved pregnancies had comparable overall satisfactory obstetric and perinatal outcome with those of autologous oocyte treatment.

**Study limitation**

The small sample size limits the strength of the findings and recommendations from this study. Another limitation was analyzing obstetric outcomes of IVF pregnancies managed at different center with varied clinical protocols.
CONCLUSION

In the light of current evidence, pregnancy following DO IVF can be considered a safe experience even for older women, with obstetric and perinatal complications not different from the general population. The need for obstetricians to be aware of the increased pregnancy risks associated with multiple pregnancies in donor and autologous oocyte IVF is instructive to institute appropriate surveillance strategies during pregnancy and delivery period as well as develop capacity for quality neonatal care.

It is imperative that these older women using DOs should be managed as high-risk obstetric cases with individualized monitoring and management strategies to reduce complications and ensure successful live birth.

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Conflicts of interest
There are no conflicts of interest.

Data availability statement
Manuscript data is safely stored in our repository and authors are willing to share data upon reasonable request.

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