RESEARCH ARTICLE

A Retrospective Study of Recipient-related Predictors of Success in an Oocyte Donation Program

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ABSTRACT

Introduction: Prior to the era of *in vitro* fertilization, no options for conception were available to women with primary ovarian insufficiency, decreased ovarian reserve, or genetically transmittable diseases. Oocyte donation (OD) has been used in such women for almost 30 years. It also offers an opportunity to study the participation of the uterus in the process of human embryo implantation.

Aim: To identify recipient variables that may have a significant impact on the pregnancy outcome of an OD program.

Materials and methods: The present study was conducted at Madras Medical Mission Hospital, Chennai, India. We retrospectively evaluated 192 patients and 283 embryo transfer cycles as a result of OD over a period of 5 years. Rates of implantation, clinical pregnancy, ongoing pregnancy, miscarriage, and live birth were calculated for different age groups, endometrial thickness (ET), indications of OD, fresh and frozen embryo transfers (FET), type of subfertility, past history of endometriosis, and body mass index (BMI) of the recipients. Data evaluation was mainly done by Chi-square analysis, and receiver operating characteristic (ROC) curves were made for age and ET.

Results: The results of this study showed a clinical pregnancy rate (CPR) of 37.1%, implantation rate (IR) of 19.3%, miscarriage rate of 20.4%, ongoing pregnancy rate (OPR) of 32.2%, and live birth rate (LBR) of 26.6%. Significant association was seen between age of recipient and OPR (p = 0.014), and also between fresh embryo transfers, CPR, OPR, and LBR (p < 0.05). The ROC curves showed a significant association of LBR with age of recipient.

Conclusion: Although no single or combined recipient variable(s) could be identified as predictor(s) of pregnancy, significant association was found between OPR, LBR, and recipient's age and also between fresh embryo transfers with CPR, OPR, and LBR.

Keywords: Age, Endometrial thickness, Oocyte donation, Pregnancy outcome.

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INTRODUCTION

Infertility secondary to absent or irreversibly abnormal oocyte development was once considered to be an absolute barrier to a woman's fertility. *In vitro* access to human oocytes and transfer of the resulting embryos into the uterus of another woman is one of the ways by which such women can be helped.

Oocyte donation had been introduced in 1983 to allow women with ovarian insufficiency to become pregnant.[1] In 1984, the delivery of the first baby was reported as a result of OD. The success of the technique broadened its indications to repeated *in vitro* fertilization (IVF) failure, advanced maternal age, or inheritable disease,[2] and today OD is well established worldwide. The rapidly increasing number of women in older age groups pursuing donor egg therapy raises questions about the relationship between oocyte and recipient age. The popularity of egg donation is evidenced by rapidly increasing demand for the services. In India itself, absolute doubling in the egg donation cycles has been noted for a duration of 3 years period from 2007 to 2009.[3]

Success of OD is influenced by multiple factors, including the age of the oocyte donor and recipient, the embryo quality and reproductive status, and endometrial receptivity of the recipient. Donor's age is of prime importance because oocyte age is one of the primary contributors of IVF outcome.[4] It has also been reported that recipient's age is inversely related to the success of OD.[5,6] However, Noyes et al[7] suggested that the age of recipient is not necessarily a poor prognosticator for the success of OD cycle. Endometrial thickness and pattern have been implicated as predictors of success in OD cycles.[8,9]

Implantation rate is considered to be one of the most sensitive and accurate variable and should serve as the

basis of assessment and comparison for studies of uterine receptivity.[10] The current study aims to identify recipient-related variables that may predict the pregnancy outcome and optimize the results of an OD program.

MATERIALS AND METHODS

This was a retrospective study of 192 recipients and 283 embryo transfer cycles that resulted from OD, from June 1, 2009 to May 31, 2014 at the Institute of Reproductive Medicine, Madras Medical Mission Hospital, Chennai, India. All regulations regarding OD were observed as per the Indian Council of Medical Research guidelines. All the cycles had an anonymous egg donor aged between 21 and 31 years. No oocyte sharing between two recipients was done in the study. All recipients had embryo transfers only in cleavage stage in this study. A complete medical and past reproductive history of all donors was reviewed and ovarian reserve was assessed by baseline ultrasound for antral follicle count.

All recipients, their partners, and all donors were tested for blood group, human immunodeficiency virus, syphilis, and hepatitis B and C, and were also subjected to a psychological evaluation. Recipients above 40 years were referred for medical fitness to a physician before starting the treatment. Donors were stimulated with recombinant follicle-stimulating hormone from day 2/3 of their menstrual cycle using either long agonist or fixed antagonist protocol. Trigger was given only when at least three follicles of 18 mm were visualized on ultrasound and oocyte retrieval was scheduled 35 h after the trigger. In all recipients, a mock cycle with estrogen priming for mid-cycle ET was done and hysteroscopy was done only if indicated.

Donors and recipients were synchronized. Cycling recipients were given oral contraceptive pills in the previous cycle. Hormone replacement therapy was started on the second day of the cycle, and if patient was down-regulated confirmation was done for the same by serum E2 levels on day 2. Increasing doses of estradiol valerate were given orally starting with 2 mg twice a day for the first 4 days of the cycle, followed by 2 mg thrice a day for the next 4 days. Dose was increased maximum up to 2 mg four times a day, i.e., 8 mg/day only if ET was less than desired on 10th/11th day. Noncycling recipients were started on hormone therapy without any downregulation. After a minimum of 11 to 12 days of priming with estrogen if ET was appropriate, recipients were advised administration of intravaginal micronized progesterone at the dose of 400 mg, two times a day. In case of fresh embryo transfer cycles, progesterone was started beginning from the day of donors' oocyte retrieval. Embryos were replaced on day 3 of progesterone supplementation.

Each anonymous donor was matched phenotypically with the potential recipients. The match of a specific donor with a specific recipient was based on chronology of completion of requirements and similarities of physical features. Mature oocytes were classified as metaphase II at the time of aspiration. Intracytoplasmic sperm injection was performed for all. The resultant embryos were rated in the laboratory according to their morphologic characteristics and blastomere number, on day 2/3 after oocyte retrieval. In the current study only good quality embryos were transferred. All the patients were given similar luteal support and 16 days after the embryo transfer, serum beta-human chorionic gonadotropin assessment was done and if positive, transvaginal ultrasonography was performed 1 week later to confirm the presence of a gestational sac. Estrogen and progesterone supplementation was continued until a negative pregnancy test, or if a pregnancy had resulted, through 10 to 12 weeks of pregnancy.

Outcomes of interest included IR, CPR, OPR, LBR, and miscarriage rates (MRs) for each variable. The IR was calculated by dividing the number of gestational sacs seen on the first trimester ultrasound by the number of embryos transferred. Clinical pregnancy was defined by visualization of an intrauterine gestational sac with cardiac activity in the first trimester. Ongoing pregnancy in this study was considered to be a pregnancy which continued beyond 12 weeks. Live birth was defined as delivery of a live-born infant at or after 26 weeks gestation and miscarriage was defined as a clinical pregnancy ending before 26 completed weeks of gestation. Data were analyzed mainly by using Chi-square analyses with comparative significance determined at $p < 0.05$ and ROC curves were made for finding the association of age and ET with occurrence of live birth and miscarriage.

RESULTS

The CPR in this study was 37.1%; IR was 19.3%; MR was 20.4%; OPR was 32.2%; and LBR was 26.6%. The results were very much similar to Indian data provided by NARI (National ART Registry of India) report of 2009[3] and which has also been included in the world report published by International Committee for Monitoring Assisted Reproductive Technology.

Recipient Age

The recipient's age ranged from 22 to 45 years and the mean age in this study was 35.5 ± 5.69 (Graph 1). Across all age group, an average of 2.8 embryos was transferred.

The data of pregnancy outcome with recipient's age are shown in Table 1. The pregnancy rates (PRs) were highest in the recipients in <30 years cohort, and least in

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Table 1: Association of age with pregnancy outcome

Age group	IR	CPR	OPR	MR	LBR
≤30 years	56/252 = 22.2%	31/68 = 45.5%	28/68 = 41.1%	4/31-1 = 13.3%	26/68-1 = 38.8%
31–35 years	52/274 = 18.9%	28/74 = 37.8%	25/74 = 33.7%	5/28-4 = 20.83%	18/74-8 = 27.2%
36–40 years	67/325 = 20.6%	30/87 = 34.48%	22/87 = 25.2%	7/30-6 = 29.1%	16/87-7 = 20%
≥41 years	28/201 = 13.9%	16/54 = 29.6%	16/54 = 29.6%	4/16-3 = 30.7%	11/54-4 = 22%
p-value	0.091	0.106	0.014	0.057	0.170

Table 2: Association of ET with pregnancy outcome

ET (mm)	IR	CPR	OPR	MR	LBR
<8	24/195 = 12.3%	11/54 = 20.3%	9/54 = 16.6%	3/10 = 30%	8/52 = 15.3%
8–9	96/495 = 19.39%	50/133 = 37.5%	44/133 = 33.08%	9/42 = 21.4%	32/121 = 26.4%
>9	83/362 = 22.9%	44/96 = 45.8%	38/96 = 39.5%	7/39 = 17.9%	31/90 = 34.4%
p-value	0.402	0.356	0.951	0.113	0.977

Table 3: Association of indication of OD with pregnancy outcome

Indication of OD	Implantation rate	CPR	OPR	MR	LBR
POF/POI	65/218 = 29.8%	33/61 = 54 %	28/61 = 45.9%	6/25 = 24%	22/53 = 41.5%
POR	125/707 = 17.6%	66/188 = 35.1%	58/188 = 30.8%	12/54 = 22.2%	44/188 = 23.4%
Genetic	7/34 = 20.5%	4/9 = 44%	3/9 = 33.3%	1/4 = 25%	3/9 = 33.3%
Previous poor egg quality	6/93 = 6.45%	2/25 = 8%	2/25 = 8%	0%	1/25 = 4%
p-value	0.213	0.154	0.063	0.439	0.381

POF: Premature ovarian failure; POI: Primary ovarian insufficiency; POR: Poor ovarian responder

recipients ≥41 years, but were not statistically significant, except the OPR (p = 0.014).

Endometrial Thickness

Embryo transfer in this study was done only if ET was between 6 and 13 mm. The pregnancy outcomes at various ET are shown in Table 2. There was a rising trend of pregnancy outcomes with ET > 9 mm, although statistically not significant (p > 0.05).

The ROC curves were made for finding the association of age and ET with occurrence of live birth and miscarriage. Age appeared as a significant predictor of live birth, while ET failed to show an ability to predict whether live birth will occur or not. The ROC curves failed to show an ability to predict whether miscarriage will occur or not.

Indication of OD

The most common indication for OD was poor ovarian reserve (Graph 2). The pregnancy outcomes for various indications of OD are shown in Table 3. The recipients who had egg donation in view of premature ovarian failure had higher PRs in comparison to the others, but the difference was not statistically significant (p > 0.05).
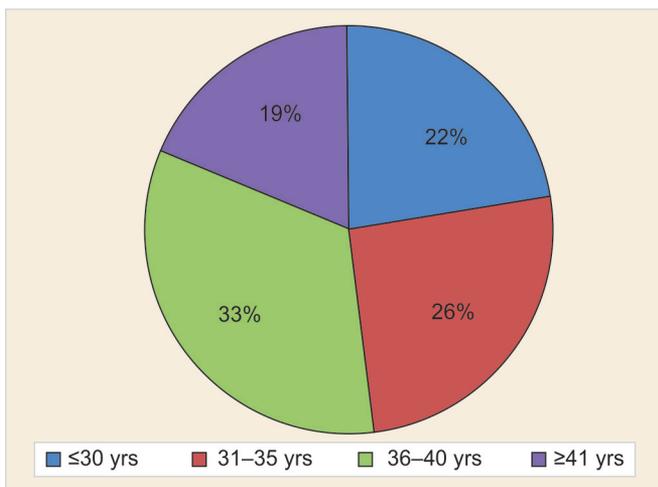
Graph 1: Age distribution (n = 192)
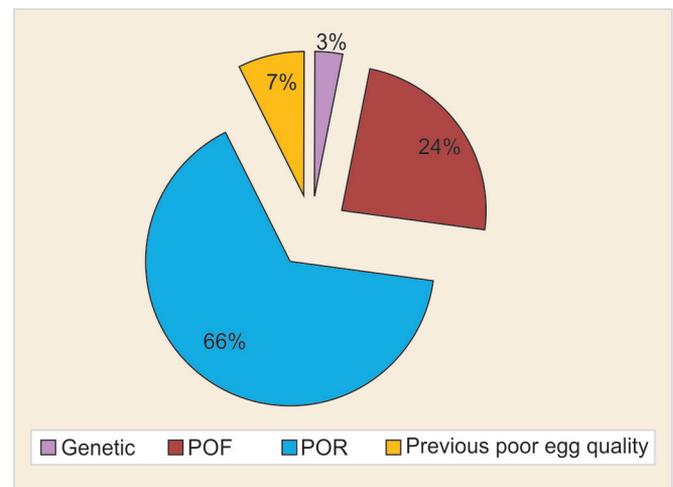
Graph 2: Indication of OD (n = 192)

Fresh or Frozen Embryo Transfers

The pregnancy outcomes, as shown in Table 4, were calculated for two groups depending on whether they had fresh or FET; 52% had fresh embryo transfer and 48% had FETs in this study, and the fresh embryo transfer cycles had significantly higher CPR, OPR, and LBR (p < 0.05).

Endometriosis

Out of 192 subjects, only 38 recipients (20%) had endometriosis. The pregnancy outcomes of patients with endometriosis in Table 5 show that the presence of endometriosis in oocyte recipients did not alter the prognosis of OD cycles (p > 0.05).

Type of Subfertility

Among all the recipients, 74% had primary and 26% had secondary subfertility. Pregnancy outcomes, as shown in Table 6, have no significant association with the type of subfertility (p > 0.05).

Body Mass Index

An average BMI in this study is 26.09 ± 4.54. The World Health Organization 2004 classification of BMI was used.

The majority (45.8%) of the recipients were in the overweight category, and BMI did not show any significant effect on the pregnancy outcomes in this study (p > 0.05), as shown in Table 7.

DISCUSSION

Predictors

Age

There has been some controversy regarding the issue of whether uterine receptivity declines with advancing age. Paulson et al[11] found no age-related decline in endometrial receptivity. However, Yaron et al[6] found a lower PR and a higher MR in older recipients. The largest study to date examining the relationship between recipient age and pregnancy outcomes from donated eggs was published by Toner et al[12] and had concluded that PR and IR did not vary until the patient reached the "late forties" and decreased significantly thereafter. Similarly, a large retrospective study conducted by United States National Registry on recipients of donor oocyte treatment cycles between 2008 and 2010 concluded that donor oocyte recipients have stable rates of pregnancy outcomes before age 45, after which there is a small but steady and significant decline.[13] A significant decline in the IR associated

Table 4: Association of fresh and frozen transfers with pregnancy outcome

Type of embryo transfer	IR	CPR	OPR	Miscarriage rate	LBR
Fresh	133/554 = 24.0%	65/147 = 44.2%	55/147 = 40.1%	10/55 = 18.1%	48/127 = 37.8%
Frozen	70/498 = 14.06%	40/136 = 29.45	32136 = 23.5%	9/30 = 30%	23/116 = 19.8%
p-value	0.059	0.010	0.003	0.107	0.005

Table 5: Association of pregnancy outcome with endometriosis

Endometriosis	IR	CPR	OPR	MR	LBR
Yes	28/262 = 10.6%	17/69 = 24.6%	14/69 = 20.2%	2/12 = 16.6%	12/64 = 18.7%
No	175/790 = 22.1%	88/214 = 41.2%	77/2.14 = 35.9%	17/74 = 22.7%	69/199 = 23.0%
p-value	0.311	0.145	0.419	0.484	0.773

Table 6: Association of type of subfertility with pregnancy outcome

Type of subfertility	IR	CPR	OPR	MR	LBR
Primary	158/770 = 20.5%	86/204 = 42.1%	75/204 = 36.7%	12/66 = 18.18%	61/184 = 33.1%
Secondary	45/282 = 15.9%	19/79 = 24.0%	16/79 = 20.2%	7/17 = 41.1%	10/77 = 12.9%
p-value	0.404	0.435	0.463	0.315	0.520

Table 7: Association of pregnancy outcome with BMI

BMI, kg/m^2	Implantation rate	CPR	OPR	MR	LBR
<18.5	9/48 = 18.7%	5/13 = 38.4%	3/12 = 25%	2/12 = 25%	1/12 = 8.33%
18.5–24.9	63/391 = 16.1%	35/105 = 33.3%	28/98 = 28.8%	9/98 = 9.1%	22/98 = 22.4%
25–29.9	107/470 = 22.7%	52/127 = 40.9%	47/117 = 40.1%	7/117 = 40.1%	35/117 = 29.9%
>30	24/143 = 16.7%	13/38 = 34.2%	13/36 = 36.1%	1/36 = 2.7%	13/36 = 36.1%
p-value	0.234	0.105	0.218	0.232	0.125

with increasing recipient's age has also been reported by many other authors.[5,10] Histologic, ultrastructural, and biochemical changes like subepithelial extracellular matrix deposition, stromal angiosclerosis become more common with age.[12,14]

Embryo IRs also decline in a linear fashion, from 29% in women <34 years to approximately 5% at age 42.[2] Borini et al[5] found reduced PRs in patients over the age of 40. The abnormal endometrial receptivity in aging subjects may be due to decreased levels of progesterone receptors, but oocyte senescence is felt to be primarily responsible. However, demised endometrial receptivity may also play a role.[15] Results of several clinical studies concerning ovum donation have shown that there is a decline in conception rate with increasing recipient age. A similar decline was noted in the present study in recipients beyond 41 years, but it was not statistically significant.

There has been no conclusive evidence of age-related histological changes in the endometrium. Navot et al[15] and Abdalla et al[8] found no difference in either the PR or MR between younger and older patients. Similarly, in this study, the pregnancy outcome had no significant difference between various age groups.

Endometrial Thickness

The measurement of ET and its echogenic pattern is an easy, noninvasive technique that has been used to assess endometrial receptivity. It is generally accepted that a thin endometrial stripe on transvaginal ultrasound is associated with a reduced embryo implantation potential,[16] while some authors have even reported an adverse effect of an increased ET.[17]

The echogenic pattern of the endometrium has also been suggested to be a predictor of pregnancy outcome by some,[18,19] and of no benefit by others in characterization of uterine receptivity in IVF patients.[16] The value of ET and echogenic pattern is still undetermined as prognostic factors of implantation. In this study, we evaluated the pregnancy outcomes at different ET, and no significant difference was noted.

Noyes et al[7] retrospectively analyzed 343 oocyte recipient cycles, and found that CPR and LBR were significantly lower when ET was <8 mm than when ET was >9 mm. However, in a large study of 3,089 recipient cycles, no specific ET significantly determined cycle prognosis in terms of PR, IR, or MR. Even a thin endometrium (<6 mm) had good PR and IR, without an increased MR.[20] Garcia-Velasco et al[21] performed a matched pair analysis of 365 recipients with discordant outcome and found that ET measured on cycle day 15 or 16 was not a significant finding. Pregnancies and live birth have been

reported to occur even at ET of 4 mm.[7,22] Oocyte donation cycles provide a unique model to eliminate confounding variables that typically occur when comparing groups of patients undergoing autologous IVF.

In summary, research suggests that ET may not be as helpful in predicting success as previously thought. The exact limit below which implantation is unlikely to occur has been hard to define. There is some debate about "how thin is too thin," as well as "how thick is too thick." In the current study, PR was maximum in cycles where the ET measured >9 mm, but results were not statistically significant. No pregnancies occurred in cycles where ET was <6.5 mm in this study.

The recent meta-analysis by Kasius et al[23] indicates that ET has a limited capacity to identify women who have a low chance to conceive after IVF. The frequently reported cut-off of 7 mm is related to a lower chance of pregnancy, but occurs infrequently. The use of ET as a tool to decide on cycle cancellation, freezing of all embryos, or refraining from further IVF treatment seems to be not justified. Further research is needed to investigate the real independent significance of ET in IVF.

Indication for Oocyte Donation

Oocyte donation is an invaluable therapeutic option for a growing list of indications, yielding excellent results. A retrospective analysis of 54 recipients with either premature ovarian failure or physiological menopause, undergoing OD between 2000 and 2007 at Monash IVF, concluded that OD in both premature ovarian failure and physiological menopause was highly successful and cumulative PR is an important statistic parameter, which can be used to inform women seeking this technique. High rates of complications, in conjunction with individual risk-factor analysis, need to be considered when counseling postmenopausal women about OD.[24]

In the current study, the most common indication for OD was poor ovarian reserve. The recipients who had egg donation in view of premature ovarian failure had highest PRs as reported by Ameratunga et al,[24] but the difference in this study was not statistically significant.

Fresh and Frozen Embryo Transfers

Frozen embryo transfers in IVF cycles have shown better PRs than fresh embryo transfer according to the systematic review done in 2013.[25] This could be explained by a better embryo-endometrium synchrony achieved with endometrium prepared cycles. Because all the trials in this meta-analysis included potentially normal or high-responder patients, these results should not be extrapolated to all types of patients undergoing artificial reproductive technique (ART).

In ART, the highest PRs are obtained in fresh OD cycles. In these cycles, the endometrium is artificially primed and the embryos are, therefore, transferred to an environment that had not suffered the effects of the supraphysiologic hormonal levels that occur during controlled ovarian hyperstimulation (COH).[25] Similarly in this study also the fresh embryo transfers had significantly better pregnancy outcome when compared to frozen cycles. Although the oocytes are of the same quality, some studies of shared oocyte cycles found significantly higher PRs in recipients compared with oocyte donors, and this may be related to a superior quality of ER.[26,27] Similarly, in FETs, endometrial priming may be achieved with the use of E2 and P, and the endometrial development can be controlled more precisely than in cycles of COH with gonadotropins.[28,29] To date, with the advances of the embryo cryopreservation techniques, the quality of the frozen embryos and their potential of implantation are similar to that observed with fresh embryos.[30,31] Although in most of the studies comparing fresh and frozen transfers the best-quality embryos are chosen for the fresh transfer, the results are similar between the two types of treatments.[32]

Endometriosis

A systematic review indicated that PRs are lower in women undergoing IVF treatment with endometriosis than in women with tubal infertility.[33] It has to be noted that endometriosis does not adversely affect PRs in some large databases.[34] To investigate possible mechanisms for reduced PRs in endometriosis patients, data from donor egg IVF programs can be analyzed to dissect out the influence on embryo implantation and pregnancy of ovarian/oocyte and uterine factors, depending on whether endometriosis is present in the donor or recipient.

A study analyzing a cohort of 170 oocyte donors reported no significant effects but a trend for reduced PRs in recipient cycles if the donor had endometriosis and a trend for reduced IRs in recipients with endometriosis, suggesting a potential mild effect of endometriosis on both the uterine environment and the quality of the oocyte.[35] In conclusion, more studies are needed to provide adequate power to address the question whether endometriosis-associated subfertility is related to reduced oocyte quality or to reduced endometrial receptivity.

In this study, the pregnancy outcome was not affected by the presence of endometriosis in the recipients. Other studies have also shown a similar result.[34,36] Endometriosis may be relevant in the context of a natural cycle, but its possible negative impact seems to be overcome by standard endometrial priming protocols used in OD cycles.

Type of Subfertility

The pregnancy outcome in this study had no significant association with type of subfertility. A review of literature did not reveal any studies of comparison between type of subfertility and pregnancy outcome in egg donation cycles.

Body Mass Index

Obesity is associated with adverse reproductive outcomes including subfertility and increased risk of miscarriage.[37] Obese women who conceive naturally are at increased risk of adverse pregnancy outcomes, and those who conceive with the assistance of IVF face similar risks in pregnancy as women who conceive naturally.[38,39] There has been a long-standing debate about which components of the reproductive process are affected most by obesity. Whereas some have focused on adverse effects of obesity on oocyte quality, others have focused on the endometrium.[40] A number of studies have evaluated associations between obesity and adverse reproductive outcomes in women undergoing donor oocyte IVF and embryo transfer as a way to separate out the effects of obesity on the oocyte *vs* the endometrium and implantation. Taken alone, these studies are limited by sample size.

In the present study, no significant association was found between the BMI and pregnancy outcomes. The pooled results of studies in the systematic review and meta-analysis on IVF outcomes in obese donor oocyte recipients in 2012 had shown that obesity is not associated with decreased embryo implantation or clinical pregnancy and also there was no effect on miscarriage and LBRs. However, it is difficult to apply the results of this work to women conceiving naturally or through IVF using their own oocytes. A prospective study of obesity and its associations with outcomes in natural and ART conceptions will be helpful in moving this forward.[41]

Other recipient-related variables that have adverse affect on pregnancy outcome in OD program include chemotherapy, radiotherapy, Asherman's syndrome, hydrosalpinx, fibroid uterus, endometrial patterns, serum estradiol levels on day of transfer, and difficulty during embryo transfer. One of the limitations of this study is that the above-mentioned variables have not been evaluated. In addition, the effect of donor variables and pregnancy complications in recipients has also not been studied.

CONCLUSION

In this study, age of the recipients was associated with a significant decline in OPR (p = 0.014). The rates of clinical pregnancy, ongoing pregnancy, and live births were significantly higher in fresh embryo transfer cycles (p < 0.05). Endometrial thickness was not a useful predictor of success in OD cycles. However, in this study,

ET > 9 mm before transfer resulted in better pregnancy outcome, although not statistically significant. According to the interpretation of the ROC curves, age appeared as a significant predictor of live birth. As the age increases, the chance of occurrence of live birth decreases, while ET (endometrium thickness) failed to show an ability to predict whether live birth will occur or not and similarly ROC curve interpretation failed to show an ability to predict whether miscarriage will occur or not.

No other recipient variables have shown any significant association with the pregnancy outcome in OD program. Furthermore, large prospective studies would be optimal to confirm the relationship between recipient variables and ART outcomes.

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