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Factors associated with clinical outcome in an embryo recipient cycle at a public In-vitro fertilization centre

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Abstract

Background: Several factors influence the outcome of embryo recipient cycles. Knowledge of these factors will help in patient care.
Objective: To determine factors associated with outcome in embryo recipient cycles.
Materials and Methods: A retrospective analysis of all embryo recipient cycles from January 2015 to December 2017 in public tertiary hospital based assisted reproductive program. Primary outcome measure was clinical pregnancy. Comparative analysis of baseline demographic and clinical/treatment variables was made between cycles that resulted in clinical pregnancy and those that did not.
Results: Overall 155 embryo recipient cycles were reviewed and there were 52 clinical pregnancies [33.5%]. The mean age was 42.9± 4.3. The mean age, type and duration of infertility did not influence the cycle outcome. The mean endometrial thickness did not differ significantly between the two groups [9.2±1.5 vs 8.8±1.9], but pregnancy rate was higher with endometrial lining greater than ⩾ 8mm (OR 0.36, *p =0.02*). Good quality embryos 37% (50/135) resulted in more clinical compared to poor ones 10% (2/20), (OR 5.29 p= 0.016). Over 70% of embryo transfer process was easy. The pregnancy rate was significantly higher with easy transfer 38.4% (43/112) compared to 20.9% (9/43) of difficult transfers, (P=0.039, OR, 2.35; 95%Cl 1.03-5.59).
Conclusion: Embryo quality and transfer difficulties are principal determinants of outcome in embryo recipient cycles. Recipients' midcycle endometrial thickness of at least 8mm may positively influence cycle outcome. Therefore, these factors must be fully evaluated and optimized before treatment is initiated.

Key words: donor oocyte, in-vitro fertilization, embryo recipient, pregnancy, infertility.

Introduction

Invitro fertilization(IVF) using donor oocyte is a common treatment for a wide range of infertility scenario including menopausal women or advanced female age, premature ovarian failure (POF), genetic disorders and recurring failure of IVF. Donor oocyte treatment is used to circumvent the aforementioned infertility conditions as it permits optimization of oocyte quantity and quality from the fertile donor, while preparation of the infertile recipient endometrial receptivity is done. High live birth rate has been reported in embryo recipient cycles of IVF treatment.[1,2]

Despite these reports the need for improved implantation/pregnancy rate of replaced embryos still remains. The exact cause of this failed implantation or pregnancy is unknown, but may be influenced by several factors like age of oocyte donor and of recipient, stimulation regimens, laboratory conditions, transfer techniques, embryo quality, the uterus and endometrial receptivity of the recipient or in the ability of the embryo to invade the endometrium properly.[1-4] Age has been reported as a significant contributor to IVF success, with decline in fertility as age increases.[3,5] Oocytes from healthy, young, fertile donors provide a consistently high-

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quality gamete and thus eliminates the decline in fertility attributed to aging of the ovaries and depletion of primary oocytes.[5,6] The recipients' age have also been reported by some authors to adversely affect outcome however, others have not observed this relationship.[5-8] Other recipient's characteristics like endometrial thickness and pattern, previous pregnancies, uterine pathology have been implicated as predictors of success in oocyte donation cycles.[2,4,8,9] Noyes, et al found embryo quality clearly plays a prominent role in all assisted reproduction, including donor oocyte cycles.[10]

The prevailing culture, socio-economic state and health seeking behavior in sub-Saharan African setting as ours provides a suitable environment where women delay need for infertility treatment until an advanced age thus warranting oocyte donation. Donor oocyte treatment is increasingly being used by older women to achieve childbirth. Our experience is that of an increase in clients accessing donor programs, so we undertook an analysis of embryo recipient cycles in an attempt to elucidate factors associated of successful cycle outcome. This knowledge will be useful in patient counseling and management.

Materials and methods

Our center is a leading tertiary public health institution IVF unit with aim to provide low cost IVF, affordable to vast majority of our population. Informed written consent was obtained for all IVF and donor oocyte related procedure and approval for this study was obtained from the ethics and research committee of the hospital.

We evaluated retrospectively all first treatment attempt fresh embryo recipient cycles (n=155) from January 2015 to December 2017. All donors were anonymous and aged between 19-26 years. Every donor underwent pre-procedure hormonal assay, screening for genotype, HIV, HBsAg, and HCV. Every recipient underwent a pre-procedure laboratory test, hysterogram or transvaginal ultrasound scan.

During the study period the unit protocol for IVF treatment was stimulation using the long agonist protocol and a day 3 embryo transfer policy. Oocyte donors and ovulatory recipients were batched with oral contraceptives (OCP) from follicular phase of previous cycle. Down regulation with subcutaneous dose of 500 μg/d buserelin was started in the luteal phase (day 17-21) of the pre-treatment cycle. Ovarian stimulation was commenced on the third day of menses for the donors by administration of human menopausal gonadotropin (HMG,150-300 IU/d), daily dose of HMG was adjusted with vaginal sonographic monitoring, when at least three follicles reached 18mm in diameter, 10000 IU of HCG was administered, and retrieval of oocyte was achieved after 34 hours.

In the recipients, oral estrogen was started at the beginning of their menstrual cycle and they were maintained on estrogen (Progynova®) at a dose of 8 to 12mg daily adjusted according to sonographic appearance and thickness of the endometrium. Endometrial thickness was defined as the thickest diameter in the longitudinal plane of the uterus as measured by transvaginal ultrasound (Shenzhen mindray® biomedical electronic co. Ltd, Shanghai. model:DP 6600). Endometrial thickness as recorded

Table 1: Association between age and pregnancy outcome

Age of recipient	Total n(%)	Clinical pregnancy n(%)	Miscarriage n(%)	Live births n(%)
<35	3(1.9)	1(33.3)	0	1(33.3)
35-39	16(10.3)	5(31.3)	1(6.3)	4(25)
40-44	58(37.4)	21(36.2)	4(6.9)	17(29.3)
45-49	65(41.9)	23(35.4)	6(9.4)	17(26.1)
50-54	11(7.1)	2(18.1)	0	2(18.1)
>55	2(1.3)	0	0	0
Total	155	52(33.5)	11(7.1)	41(26.4%)
P value		0.769		

Table 2: Comparison of baseline cycle parameters between pregnant and none pregnant group

Variables	Total n[155] (%)	Clinical Pregnancy yes n[52]	Clinical Pregnancy no n[103]	X^2 test	Odds ratio	95%cl	P value
Age mean±SD	42.9±4.3	41.8±4.5	43.3±4.1				0.473
<35	3(1.9)	1	2				
35-39	16(10.3)	5	11				
40-44	58(37.4)	21	37				
45-49	**65**(41.9)	23	**42**	2.55			0.769
50-54	11(7.1)	2	9				
>55	2(1.3)	0	2				
Infertility duration mean		11.6±5.4	10.4±5.7				0.705
Mean FSH		25.6±22.1	26.7±26.0				0.329
Type of infertility							
Primary	34(21.9)	15(44.1%)	19				
Secondary	121(78.1)	37(30.6%)	84	2.18	1.79	0.82-3.91	0.139
Previous delivery Yes	40(25.8)	17(42.5%)	23				
No	115(74.2)	35(30.4%)	80	1.94	1.69	0.80-3.55	0.164
Uterine fibroids Yes	62(40)	17(27.4%	45				
No	93(60)	35(37.6%)	58	1.74	0.63	0.31-1.26	0.187
Cause of infertility							
Female	43(27.7)	16	27				
Male	46(29.7)	18	28	2.07			0.356
Combined	66(42.6)	18	48				
Endometrial thickness mean		9.2±1.5	8.8±1.9				0.209
Fertilization method	116(74.8)	41(35.3%)	75				
IVF	39(25.2)	11(28.2%)	28	0.67	1.39	0.63-3.08	0.414
ICSI							
Embryo quality							
Good	135(87.1)	50(37.0%)	85			1.18-	
Poor	20(12.9)	2(10.0%)	18	5.71	5.29	23.78	0.016
Embryo transfer							
Easy	112(72.3)	43(38.4%)	69				
Difficult	43(27.7)	9(20.9%)	34	4.25	2.35	1.03-5.39	0.039
Mean Number of embryos transferred		2.8±1.3	3.0±1.3				0.589

Table 3: Comparative analysis of pregnancy at each millimeter measure of endometrial thickness.

Endometrial thickness[mm]	Total n[155] (%)	Clinical Pregnancy yes n[52]	Clinical Pregnancy no n[103]	X^2 test	Odds ratio	95%Cl	P value
Range		6.8-13.2mm	5.7-15.30mm				
<7	14(9.0)	1(7.1%)	13				
7-7.9	24(15.5)	6(25%)	18				
8-8.9	42(27.1)	18(42.9%)	24				
9-9.9	34(21.9)	14(41.2%)	20				
10-10.9	16(10.3)	5(31.3%)	11	8.98			0.254
11-11.9	16(10.3)	4(25%)	12				
12-12.9	6(3.9)	3(18.8%)	3				
=13	3(1.9)	1(33.3%)	2				
Endometrial thickness[mm]							
<8	38(24.5)	71(8.4%)	31				
=8	117(75.5)	45(38.5%)	72	5.17	0.36	0.15-0.89	0.023

on recipient cycle on day of hCG administration for the donor was retrieved for analysis. On the day of oocyte retrieval for the donor, progesterone administered trans-vaginally was added to the recipients' medications and oral estradiol was continued. Fertilization was done either by invitro technique [IVF] or intracytoplasmic sperm injection [ICSI] as appropriate. The resultant embryos were rated in the laboratory according to their morphologic characteristics and blastomere number on day 2 after oocyte retrieval. Grade 1(excellent), the best rated embryos, included those with at least five to six cells and no blastomere fragmentation. Grade 2 (good) had at least four to five cells and 5-20% fragmentation. Grades 3 and 4 (reasonable and poor) consisted of any number of cells with 30% to 50% fragmentation.[11] All embryos were transferred trans-cervically in the lithotomy position with the Wallace catheter with ultrasound guidance 3 days after retrieval. The number of embryos transferred per recipient varied according to the number of good quality embryos available but usually not more than 5 embryos could be transferred. Transfers were rated as easy, moderate, or difficult with respect to specific information about the use of instruments, bleeding, and other technical aspects. Easy transfers required no instrumentation. Moderate transfers included the use of a malleable Wallace stylet, mild cervical traction, as well as double transfers necessitated by retained embryos. Difficult transfers involved the use of strong counter traction, probing, or dilation of the cervical canal and bleeding. Estrogen and progesterone supplementation was continued until a negative pregnancy test or for 12 weeks if a pregnancy had resulted. Clinical pregnancy was defined as a gestational sac visualized on vaginal ultrasonography.

Data analysis was done using SPSS statistical package version 20 with comparative significance determined at $P< 0.05$.

Results

One hundred and fifty-five fresh embryo recipient cycles were reviewed and there were 52(33.5%) clinical pregnancies. The clinical pregnancy rate was 33.5%, of these, 11[7.1%] had spontaneous miscarriages and 41 eventuated in live births (26.5%). The mean age was 42.9± 4.3. When evaluating the relationship between recipient age

and pregnancy outcome, there was no apparent difference between the two groups [41.8±4.5 vs 43.3±4.1]. Comparing both group across age interval, pregnancy rates ranged from a high of 36.2% and 35.4% in the recipient group aged 40 to 44 and 45 to 49 years respectively to a low of 18.1% in the recipients ⩾ 50 years but this was not significant. (see Table 1).

The type of infertility, previous delivery and presence or not of uterine fibroids did not influence the pregnancy outcome. There was no statistically significant difference in the duration of infertility and mean basal FSH level between the two groups [11.6±5.4 vs 10.4±5.7 and 25.6±22.1 vs 26.7±26.0 respectively]. Both groups had similar causal factors for infertility with combined female and male factors being majority [44.37% and 28.87%]. The mean endometrial thickness of all recipients was 8.9±1.8 mm and there was no significant difference in endometrial thickness between the two groups. (see table 2).

There was no significant difference in the method of fertilization and number of embryo transferred between the two groups. Transfer of optimal quality embryos (excellent/good; 135 total) resulted in the higher clinical pregnancy rates of 37% (50/135) rates, compared with poor quality embryos (20) transferred with pregnancy rate of 10% (2/20). The quality of embryo transferred significantly influenced pregnancy rate with 5 times odds of pregnancy when good quality embryos are transferred compared to poor ones [p= 0.016]. Over 70% of embryo transfer process was easy with only 27.7% difficult transfers. The pregnancy rate was significantly higher with easy transfer 38.4% (43/112) compared to 20.9% (9/43) of difficult transfers. The odds of getting pregnant was twice when transfer was easy compared to a difficult transfer, p=0.039.

Further analysis of endometrial thickness across the group interval is shown in table 3; a higher pregnancy rate 42.9%[18/42] was observed for thickness 8-8.9mm and 9-9.9mm 41.2%[14/34] in comparison to the lowest pregnancy rate 7.1%(1/14) observed in cycles where the endometrial thickness was measured at < 7mm;[actual endometrial thickness of 6.8mm]. Overall majority 75.5%(117) had endometrial thickness greater than or equal to 8mm while 24.5% (38) had endometrial thickness less than 8mm. Cycles where the endometrial lining measured greater than 8mm had the greatest chance for pregnancy (odds ratio 0.36) compared to where the endometrial thickness was < 8 mm (*p =0.02)*.

Discussion

Among the clinical factors influencing the outcome of embryo recipient in an oocyte donation cycle, quality of transferred embryos and ease of trans-cervical transfer were found to be significantly associated with clinical pregnancy.

Although reports have implicated advanced recipient age from 45 years onwards, as clearly associated with a poorer outcome in oocyte donation cycles,[5,6] our data did not support this notion, as there was no significant difference in pregnancy rate across age group however most pregnancy occurred in the 45-49 age range. Also the miscarriage rate and live birth rate was not affected by age. One of the oldest recipients at age 52yrs had (although not significantly so) pregnancy success and a live birth. Age has been severally reported to impact on success of various IVF programs including recipient cycles; the key factor identified here being the decline in ovarian function with age.[12,13] In recipient cycles however, the use of oocyte from healthy young fertile donors helps control for most age-related factors; lending credence to the fact that uterine aging lags behind ovarian age.[7,8] This may also be explained by our observation that most clients using donor oocyte are within the age range of 40-50 years, with only a few young women with premature ovarian failure (POF) seeking same treatment. In our study only 3(1.9%) were less than 35yrs of age, largely from POF and resistant ovaries. Contrary to the foregoing, researchers have documented a decline in both embryo viability and, to an extent, uterine receptivity in women above the age of 40 years.[8,13]

Uterine factors have been reported as the principal recipient-related contribution to achieving pregnancy with donated eggs.[9,10,14] These uterine factors relates to the endometrium, myometrium and cervix. Endometrial thickness has been reported to be predictive of pregnancy outcome in IVF cycles.[9] Measurement of endometrial thickness in the late follicular phase of a woman's cycle is often used to assess endometrial readiness in IVF and

embryo recipient cycles. A thicker endometrial lining has been associated with a greater chance for pregnancy.[15] In addition, some researchers have noted an absolute endometrial thickness below which pregnancies may not occur.[9,10,14] Our study corroborates these previous reports with endometrial thickness being higher for the pregnant group and significantly higher pregnancy when endometrial thickness is ⩾ 8mm. This study further suggests that an endometrial thickness of less than 7mm is associated with a relatively poor chance for pregnancy. Noteworthy is that some previous studies,[4,10,16] have recorded pregnancy for thin endometrium of ≤ 6mm with eventual live birth, thus making it difficult to recommend canceling or cryopreserving embryos in cycles where thin endometrium is discovered. However, one may suggest that if that patient does not achieve pregnancy, the endometrium should be evaluated further to rule out underlying pathology, specifically intrauterine synechiae, before a subsequent attempt. Endometrial pattern has also been reported to be somewhat prognostic of pregnancy outcome in IVF cycles.[15] We did not analyse endometrial pattern in this study.

Furthermore in this study the presence or not of uterine fibroids, which are common structural uterine abnormality did not influence pregnancy, however, we did not document the location of the fibroid which may be more important in this regard. Several studies have investigated the effect of uterine fibroids on implantation and pregnancy rate in IVF with varying results.[14,17] Zenke and colleagues observed in their study that most patients with uterine fibroids elected to have at least one ET without surgery with an understanding that, should implantation fail or pregnancy abort, then myomectomy would be advisable before future transfers.[2] This suggestion may be useful in our setting where the incidence of fibroid is high.

Despite its apparent simplicity, ET has been regarded as the most elusive and least understood step in ART.[18] Some studies identified route of transfer, with ZIFT and GIFT as better predictors of success than transcervical ET.[19] In this study all recipients had transcervical embryo transfer, difficult ETs had a negative impact on IVF-ET outcome as was observed in this study with more of the difficult transfers in the non pregnant group. This corroborates previous reports that identified difficult ET as a major cause of failure in IVF and embryo recipient cycles.[2,20,21] From the foregoing it may become necessary in IVF programs, for all patients to undergo a simple trial transfer with a rigid catheter early in the evaluation to detect cervical stenosis or tortuosity. If passage is difficult, then a prior cervical dilation or hysteroscopic evaluation may be helpful.

Embryo quality, particularly when only poor quality embryos are available for transfer, appears to be predictive of negative IVF outcome.[2,10,20,21] We observed that better quality embryo was associated with increased positive outcome. The finding that quality of embryo influences recipient cycle outcome tends to support the hypothesis that subtle variations in sperm quality also influence the outcome of ART.[10,22] Although we did not undertake a detailed sub-analysis of semen characteristics, there was however no difference in the extent of male factor infertility or fertilization technique between the two groups; suggesting that sperm quality may not have played significant role in influencing cycle outcome.

In conclusion, the key recipient-related factors associated with success in embryo recipient cycles were embryo quality and transfer difficulties. Summarily cycles that resulted in pregnancy had better quality embryos transferred and easier ETs procedure than the non pregnant group.

This study is however limited by the small sample size and limited number of predictive variables analysed. Other potentially important variables include endometrial pattern and configuration, markers of secretory endometrial transformation, sub-endometrial and endometrial blood flow, location of uterine fibroids, performing dummy or trial ET before the actual procedure, removing cervical mucus before ET, cervical flushing and reflux, site of deposition and direction of flow of the microdroplet containing the embryos, and characteristics of sperm used for fertilization. Careful examination of these variables is likely to identify additional predictors of success with donor oocyte cycles. In addition prospective randomized controlled clinical trial will further contribute to predicting useful factors in the success of oocyte donation cycles.

Donor oocytes are being used more and more.

Optimizing embryo transfer challenges before treatment is initiated and ensuring good quality embryos by astute gamete recruitment and treatment is recommended in order to improve outcome for embryo recipients' cycle.

Conflict of interest: none

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