Original Article

One Plus One Is Better Than Two: Cumulative Reproductive Outcomes Are Better after Two Elective Single Blastocyst Embryo Transfers Compared to One Double Blastocyst Embryo Transfer

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Abstract

Aims: The aim of this study is to compare cumulative *in vitro* fertilization-intracytoplasmic sperm injection outcomes following two elective single embryo transfer (eSET) versus one double embryo transfer (DET) using blastocyst(s). **Settings and Design:** This was retrospective observational study. **Study Period:** The study was conducted during January 2015–December 2015. **Subjects and Methods:** Forty-one fresh + 25 frozen eSET versus 123 DET using self-oocytes and 68 fresh + 35 frozen eSET versus 184 DET using donor-oocytes were included in the study. All failing to achieve live birth after first eSET underwent frozen embryo transfer cycle with second blastocyst. Cumulative outcome after two eSET were compared with one DET. **Statistical Analysis Used:** The analysis was performed by Chi-square and *t*-test. **Results:** In self-oocytes group, higher but statistically nonsignificant cumulative clinical pregnancy rate (CPR) (58.5% vs. 57.7%, $P = 0.92$) and live birth rate (LBR) (48.7% vs. 44.7%, $P = 0.65$) with significantly lower multiple pregnancy rate (MPR) (4.2% vs. 45%, $P = 0.0002$) were obtained; whereas in donor-oocytes group, comparable cumulative CPR (73.5% vs. 65.7%, $P = 0.24$), significantly higher LBR (64.7% vs. 48.9%, $P = 0.02$) and significantly lower MPR (4% vs. 51.2%, $P = 0.00005$) were obtained after two eSET vs. one DET. In self-oocytes group, the incidence of prematurity (10% vs. 21.4%, $P > 0.05$) and low birth weight (25% vs. 45.6%, $P > 0.05$) were lower but statistically nonsignificant, whereas in donor-oocytes group, incidence of prematurity was lower but statistically nonsignificant (26.7% vs. 38.8%, $P > 0.05$) while of low birth weight was significantly lower (32.7% vs. 51.2%, $P = 0.0038$) after two eSET versus one DET. **Conclusion:** Cumulative LBR was higher with lower incidence of multiple births, prematurity and low birth weight after two eSET versus one DET using self- or donor-oocytes. Higher use of eSET improves reproductive outcomes in patients with good prognosis.

Keywords: *Blastocyst, donor-oocyte, elective single embryo transfer, live birth rate, multiple pregnancy rate, prematurity*

Introduction

Elective single embryo transfer (eSET) is defined as the transfer of single cleavage or blastocyst stage embryo from a larger cohort of available embryos. eSET is more beneficial in patients of a good prognosis: <35 years of age, more than one good quality embryo available for transfer, first or second treatment cycle, previous successful *in vitro* fertilization (IVF) cycle,

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recipients of embryos from donated eggs, previous living child.[1]

eSET lowers the risk of multiple gestations. Several complications have been associated with multiple births.[2] There is a higher incidence of hypertensive disorders, gestational diabetes, anemia, premature rupture of membranes, oligohydramnios/polyhydramnios, antepartum hemorrhage, postpartum hemorrhage, and operative deliveries in women bearing multiple pregnancies.[3,4] Furthermore, there is a higher incidence of prematurity and perinatal mortality in higher order births and more so with those conceived through ART.[5] The long-term health risks of prematurity are well recognized-mental and physical disability.[6]

A higher number of embryos are generally transferred to improve the implantation rate. Better culture media and culture conditions have permitted blastocyst culture, and this leads to a better embryo selection and increases implantation rates.

Single embryo transfer significantly reduces the risk of multiple pregnancy but may also decrease the chance of live birth following the first fresh IVF cycle. However, subsequent replacement of a single frozen embryo achieves a live birth rate (LBR) comparable with double embryo transfer (DET).[7]

Recognizing this issue, many European countries have enforced laws limiting the number of embryos transferred per cycle. In Belgium and Sweden it is mandatory to perform eSET for couples with good prognosis.[8] Globally, many developed countries have now shifted to policy of eSET since the onset of the new millennium.[1]

The health-care costs related to the maternal and perinatal complications arising in multiple pregnancies due to IVF-intracytoplasmic sperm injection (ICSI) cycles are also substantial and include both immediate costs due to maternal hospitalization, operative delivery, and neonatal intensive care as well as long-term costs due to chronic disability, rehabilitation, and special education.[9] This is all the more relevant in India, where insurance firms do not cover assisted reproductive techniques (ART). Thus, the added cost borne by the patient for two eSET cycles compared to one DET cycle to achieve a live birth seems justified.

With the rising number of births through ART, there is a need to regulate the number of embryos transferred in each embryo transfer cycle. Currently, most clinics are transferring an average of three embryos in each transfer cycle.[10] This has increased the incidence of multiple births, which, in turn, has increased the incidence of maternal and perinatal complications and thereby augmented the health care costs.

Many randomized and nonrandomized controlled trials have been conducted in the western world to assess the efficacy of eSET. With India conducting more than 120,000 IVF-ICSI cycles per year, there is a need to study efficacy of eSETin the context.[9] Hence, we carried out this study to compare cumulative pregnancy outcome until live birth and perinatal complications after two eSET and one DET.

Subjects and Methods

The present study was a retrospective observational study carried out over a period of 1 year (January 2015 to December 2015). This was conducted in compliance to the ethical principles of the Declaration of Helsinki (Brazil, 2013), International Council on Harmonization Good Clinical Practice (ICH-GCP) Guidelines (E6, 1996), Ethical Guidelines for Biomedical Research on Human Participants, (ICMR 2006), and other regulatory requirements.

All patients who underwent IVF-ICSI cycles using self- or donor oocytes between January 2015 and December 2015 and having at least two transferable blastocysts were included in the study.

According to the ICMR guidelines, IVF-oocyte donation was offered to the women who had following indications: Gonadal dysgenesis, premature ovarian failure, resistant ovary syndrome, advanced female age or poor responders to ovulation induction, carriers of recessive autosomal disorders and women who have attained menopause.

Cumulative outcomes were compared between the following groups: Group 1-two blastocyst stage eSET cycles (eSET): Two consecutive eSET from 1 stimulated cycle (first fresh and second frozen – if the first fails) and Group 2 - one blastocyst stage DET cycle (DET).

Patients underwent eSET due to:

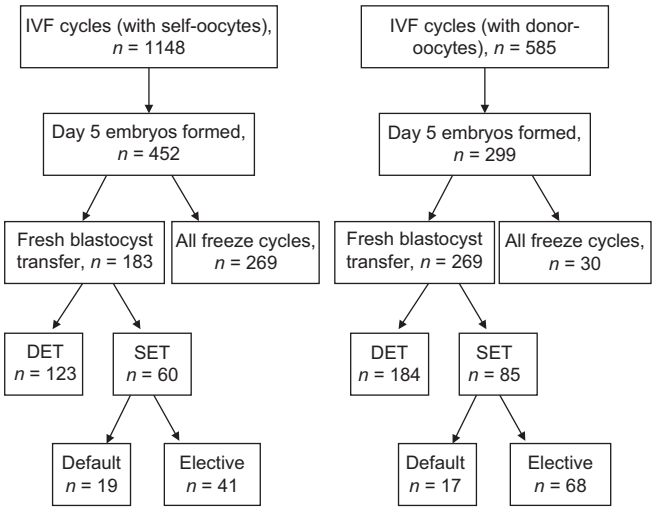
1. By choice (those who had a previous child)
2. Conditions where multiple pregnancy was not recommended
   a. Preexisting medical conditions-chronic hypertension, diabetes mellitus, heart disease
   b. Obstetric reasons-uterine anomalies such as the unicornuate uterus, history of myomectomy, history of preterm delivery, or second-trimester miscarriage– where a twin pregnancy was not preferred.
3. First IVF-ICSI cycle.

All patients who did not opt for blastocyst transfer or those having only one transferable blastocyst and

those who had an all freeze cycle due to premature progesterone elevation, the risk of OHSS or unfavorable endometrium were excluded.

A total of 183 patients using self-oocytes underwent fresh embryo transfer: 123 patients underwent double and 60 underwent single blastocyst transfer, of whom 41 were elective purposes and 19 were default (only single embryo formed). Two hundred and sixty-nine patients underwent fresh embryo transfer using donor-oocytes, 184 patients underwent double blastocyst transfer (DBT) and 85 underwent single blastocyst transfer, of whom 68 were elective and 17 were default (only single embryo formed) [Flowchart 1].

All patients undergoing stimulation and oocyte donors underwent stimulation on the flexible antagonist protocol. Baseline transvaginal sonography (GE Healthcare) was performed on the 2nd day of the menses to check the status of ovaries, antral follicle count (AFC), and thin endometrium (endometrial thickness <4 mm). Gonadotropin dosage was determined based on the patients' age, anti-mullerian hormone, AMH level, and body mass index. Patients were called for follicular monitoring scan after 5 days of stimulation and antagonist was started once the leading follicle measured >14 mm. Repeat scan was performed 2–3 days later, and recombinant hCG (Ovitrell 250 μg; Merck Serono) was administered as a trigger, when >3 follicle measured >17 mm. Serum progesterone was measured in all patients on the day of trigger administration. Segmentation of cycle was done (after triggering with gonadotropin-releasing hormone agonist [Decapeptyl 0.2 mg; Ferring]), if serum progesterone levels were higher than 1.5 ng/ml in fresh stimulations and >0.5 ng/ml in recipients or in patients in whom endometrium was unfavorable (polyp, <7 mm) or when patients were deemed to be at risk of OHSS (>15 follicles of >15 mm on day of trigger) were excluded from this study. Egg retrieval was performed 35 h after trigger. Embryo transfer was performed using one or two blastocyst stage good quality embryos. All patients received 800 mg vaginal micronized progesterone in two divided doses starting from the morning after egg retrieval.



Flowchart 1: Selection and exclusion of patients. DET: Double embryo transfer, SET: Single embryo transfer

All patients undergoing IVF-ICSI using donor-oocytes were treated with hormone replacement therapy (HRT) protocol. Estradiol valerate was started from the 2nd day of menses in increasing dose, 4 mg/day for 4 days and then 8 mg/day. When endometrial lining was ≥7 mm, serum progesterone level was measured. If serum progesterone level was <0.5 ng/ml, vaginal micronized progesterone 400 mg twice a day was added from the day of donor's egg retrieval. Embryo transfer was carried out after 5 days of progesterone administration.

Frozen embryo transfer was also performed in a similar HRT protocol.

Serum β-human chorionic gonadotropin (HCG) level (ECLIA method) was tested 14 days postembryo transfer. β-HCG >20 IU/L was considered as positive. In these patients, the first ultrasound was performed 1 week later, and clinical pregnancy was defined as the appearance of the gestational sac.

All pregnant patients were under the obstetric care of an obstetrician of their choice either from the beginning or after 12 weeks as we do not provide obstetric care. All 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.

Data collection was performed by two approaches:

1. At the time of referral, each obstetrician was provided with a form of pregnancy follow-up and to record the outcome of patient's pregnancy-both obstetric and perinatal. The form was sent through post or with the patient. In addition, the same was communicated to the respective obstetrician by telephone. They were requested to complete the form and send the same to the clinic within a month of abortion, ectopic pregnancy or delivery
2. In cases where obstetrician could not be contacted the details regarding outcome were obtained from the patient herself.

We assessed the pregnancy outcome and perinatal outcomes in the study patients. Our primary outcome was LBR and secondary outcomes were pregnancy rate (PR), implantation rate (IR), clinical PR (CPR),

clinical abortion rate, ectopic PR, multiple PR (MPR), maturity (in weeks) at birth, birth weight, and stillbirths.

Statistical analysis

For quantitative continuous variable student's *t*-test was used and for categorical variables Chi-square test was used. Mean age was reported as mean ± standard deviation being a descriptive study; with this sample size, we estimated 10% error to estimate the mean of the general population with confidence interval (CI) of 95%. Significance was set at $P < 0.05$. SPSS 16.0 (IBM Corporation, Chicago, IL, USA) was used to analyze the data.

Results

In self-cycles, 41 patients (25%) underwent the first cycle of eSET versus 123 patients (75%) underwent one cycle of DET. Mean age of patients of both groups were comparable (34.5 ± 4.27 versus 34.5 ± 3.39, $P = 0.074$). PR, CPR, and LBR were lower but not statistically significant following first fresh eSET versus one DET cycle (51.2% vs. 66.9%, $P = 0.272$; 43.9% vs. 57.7%, $P = 0.123$ and 39.02 vs. 44.7%, $P = 0.524$, respectively). IR was higher but not statistically significant following first fresh eSET versus one DET cycle (46.3% vs. 41.8%, $P = 0.592$). MPR was significantly lower in eSET group versus DET group (4.2% vs. 45%, $P = 0.009$). No significant difference was found in abortion rate and ectopic PR between two groups [Table 1a].

Out of 41 patients, 25 patients who did not achieve a live birth following first fresh eSET cycle underwent the second eSET with a frozen blastocyst. Cumulative outcome after two eSET cycles was compared with those 123 patients who underwent fresh DET in the same duration. Cumulative PR, CPR, and LBR were higher but not statistically significant following two eSET versus one DET (68.3% vs. 60.9%, $P = 0.4$; 58.5% vs. 57.7%, $P = 0.92$ and 48.7% vs. 44.7%, $P = 0.65$, respectively). IR was lower but not statistically significant following two eSET versus one DET cycle (37.8% vs. 41.8%, $P = 0.558$). Cumulative MPR was significantly lower after two eSET versus one DET (4.2% versus 45%, $P = 0.0002$). No significant difference was found in abortion rate and ectopic PR between 2 groups [Table 1b]. Only 78.5% delivered at term in DET group compared to 90% in e SET group, although the difference was not statistically significant. Furthermore, the incidence of babies with normal birth weight (>2.5 kg) was higher in those undergoing eSET (75%) compared to those undergoing DET (54.3%) but statistically nonsignificant. There were no congenital anomalies reported, and there was single perinatal mortality in both groups [Table 2].

Table 1a: Pregnancy outcomes in patients undergoing 1st elective single embryo transfer and double embryo transfer using self-oocytes

Parameters	eSET (1st), *n* (%)	DET, *n* (%)	*P**
Patients (*n*)	41	123	-
ET (*n*)	41	123	-
Mean age (years) (mean±SD)	34.5±4.27	35.0±3.39	0.074
PR	21/41 (51.2)	75/123 (60.9)	0.272
IR	19/41 (46.3)	103/246 (41.8)	0.592
CPR	18/41 (43.9)	71/123 (57.7)	0.123
MPR	1/18 (5.5)	32/71 (45)	0.009
CAR	2/18 (11.1)	13/71 (18.3)	0.466
EPR	0	2/71 (2.8)	0.544
LBR	16/41 (39.02)	55/123 (44.7)	0.524

*Chi-square test. DET=Double embryo transfer, eSET=Elective single embryo transfer, ET=Embryo transfer, PR=Pregnancy rate, IR=Implantation rate, CPR=Clinical pregnancy rate, MPR=Multiple pregnancy rate, CAR=Clinical abortion rate, EPR=Ectopic pregnancy rate, LBR=Live birth rate, SD=Standard deviation

In oocyte donation cycles, 68 patients (27%) who underwent eSET were older than 184 patients (73%) who underwent DET (41.04 ± 4.92 vs. 36.0 ± 4.88, $P = 0.00001$). PR, CPR and LBR were lower but not statistically significant following first fresh eSET versus one DET cycle (64.7% vs. 70.1%, $P = 0.411$; 57.3% vs. 65.7%, $P = 0.218$ and 48.5% vs. 48.9%, $P = 0.956$, respectively). IR was higher but not statistically significant following first fresh eSET versus one DET cycle (60.2% vs. 49.7%, $P = 0.109$). MPR was significantly lower after first eSET versus one DET (5.1% vs. 51.2%, $P = 0.00005$). No significant difference was found in abortion rate and ectopic PR between two groups [Table 3a].

Out of 68 patients, 35 patients who did not achieve a live birth following first fresh eSET cycle underwent the second eSET with a frozen blastocyst, using donor oocytes. Cumulative outcome after two eSET cycles was compared with those 184 patients who underwent fresh DET in the same duration. Cumulative PR and LBR were significantly higher following two eSET versus one DET (83.8% vs. 70.1%, $P = 0.002$ and 64.7% vs. 48.9%, $P = 0.02$, respectively). IR too was higher but not statistically significant following two eSET versus one DET cycle (50.48% vs. 49.72%, $P = 0.892$). Cumulative MPR was significantly lower after two eSET versus one DET (4% vs. 51.2%, $P = 0.00005$). No significant difference was found in CPR, abortion rate, and ectopic PR between two groups [Table 3b]. Only 61.2% delivered at term in DET group compared to 73.3% in eSET group; although, the difference was

Table 1b: Cumulative pregnancy outcomes in patients undergoing 1+1 elective single embryo transfer and double embryo transfer using self-oocytes

Parameters	eSET (2nd) frozen embryo transfer	Cumulative outcome (1+1 eSET) Group 1	DET Group 2	*P**
Patients (*n*)	25	41	123	-
ET (*n*)	25	66	123	-
PR	7	28/41 (68.3)	75/123 (60.9)	0.4
IR	6	25/66 (37.8)	103/246 (41.8)	0.558
CPR	6	24/41 (58.5)	71/123 (57.7)	0.92
MPR	0	1/24 (4.2)	32/71 (45)	0.0002
CAR	2	4/24 (16.6)	13/71 (18.3)	0.855
EPR	0	0	2/71 (2.8)	0.405
LBR	4	20/41 (48.7)	55/123 (44.7)	0.65

*Chi-square test. ET=Embryo transfer, PR=Pregnancy rate, IR=Implantation rate, CPR=Clinical pregnancy rate, MPR=Multiple pregnancy rate, CAR=Clinical abortion rate, EPR=Ectopic pregnancy rate, LBR=Live birth rate, DET=Double embryo transfer, eSET=Elective single embryo transfer

Table 2: Perinatal outcomes in patients undergoing 1+1 elective single embryo transfer and double embryo transfer using own oocytes

Perinatal complications	Group 1 (1+1 eSET), *n* (%)	Group 2 (DET), *n* (%)	*P**
Gestational age (weeks)			
20-28	1 (5)	0	0.09
28-32	0	0	-
32-36	1 (5)	12 (21.4)	0.093
36-42	18 (90)	44 (78.5)	0.257
Birth weight (kg)			
<1	1 (5)	0	0.043
1-1.5	0	3 (3.7)	0.156
1.5-2.5	4 (20)	34 (41.9)	0.069
2.5-4.5	15 (75)	44 (54.3)	0.092
>4.5	0	0	-
Congenital anomalies	0	0	-
Still birth	0	1 (1.2)	-
Early NND	1 (5)	0	-
Late NND	0	0	-
PNMR	1 (5)	1 (1.2)	0.27

*Chi-square test. NND=Neonatal death, PNMR=Perinatal mortality rate, DET=Double embryo transfer, eSET=Elective single embryo transfer

not statistically significant. The incidence of babies with normal birth weight (>2.5 kg) was significantly higher in those undergoing eSET compared to those undergoing DET (67.3% vs. 42.8%, $P = 0.0038$). There were no congenital anomalies reported and no statistically significant difference in perinatal mortality rate between the groups [Table 4].

Discussion

In the past, the implantation potential of embryos was lower due to suboptimal culture systems and poor embryo selection techniques. A higher number of embryos were frequently transferred to compensate for this to achieve higher PRs. With the advent of extended culture enabling blastocyst development and better embryo selection techniques such as morphological grading criteria and aneuploidy screening, better implantation rates have been achieved after transfer of a fewer number of embryos at every embryo transfer. However, transfer of even two embryos in the current era poses the patient at a substantial risk of twin pregnancy. With the rising proportion of twin deliveries, there is a higher incidence of preterm deliveries and low birthweight which in turn are associated substantial long-term health consequences, mental and physical disability among these children.[5,6] The shared goal of infertile couples and fertility specialists should be the birth of a healthy child, rather than a positive pregnancy test.

In the present study, all transfers were carried out at the blastocyst stage because this type of extended embryo culture would allow "selection" of better embryos having a higher implantation potential. All surplus good quality embryos were vitrified. Extended culture enabling blastocyst transfer and vitrification are two advances in ART that have significantly increased the number of live births per stimulated IVF cycle.[11,12] However, single embryo transfers result in a near null rate of multiple pregnancies, the risk is not completely avoided due to the risk of zygotic splitting.[13]

In this study, transferring one blastocyst using own oocytes did result in a lower rate of pregnancy and LBR compared to transferring two blastocysts on a single occasion (51.2% vs. 60.9%, $P = 0.272$) and (39.2% vs. 44.7%, $P = 0.524$) respectively, but the subsequent transfer of a single frozen blastocyst in these patients resulted in a higher cumulative PR (68.3% vs. 60.9%, $P = 0.4$) and LBR (48.7% vs. 44.7%, $P = 0.65$), although the difference was not statistically significant. This approach resulted in a significantly lower incidence of multiple pregnancies (4.2% vs. 45%, $P = 0.0002$).

Our results are comparable with Lukassen *et al*., who in a randomized controlled trial revealed that cumulative LBR following two fresh eSET cycles (41%) was similar to the rate following a single fresh DET cycle (36%), but the MPR was significantly lower following two fresh eSET cycles (0%) than single fresh DET (37%).[14]

Similar findings were observed in the largest (n = 661) and double-blinded multicenter randomized controlled trial conducted in 11 clinics in Sweden by Thurin *et al*. The LBR was (42.9%) in the double embryo transfer group (n = 331) as compared with (38.8%) in the single-embryo-transfer group (n = 330), rates of multiple births were 33.1% and 0.8%, respectively (P < 0.001). These results did not reveal equivalence of the two approaches in rates of live births, but they indicated that any reduction in the rate of live births with the transfer of single embryos is unlikely to exceed 11.6% points. However, 98% of embryo transfers were done with cleavage stage embryos in this trial, and cumulative outcomes were not compared.[15]

In a recent retrospective study published in 2016 in Korean patients, no significant difference was found in CPR and LBR between elective single blastocyst transfer (eSBT) and DBT, and the MPR was significantly lower in the eSBT group than in the DBT group.[16] Another recent study reporting on cost-effectiveness of SET vs DET also found SET to be less costly and more effective.[17]

In the oocyte donation cycles, PR and LBR following single eSET were lower than DET (64.7% vs. 70.1%, P = 0.411) and (48.5% vs. 48.9%, P = 0.956), respectively, although not statistically significant. However, cumulative PRs (83.8% vs. 70.1%, P = 0.002) and LBRs (64.7% vs. 48.9%, P = 0.02) were significantly higher after two eSET compared to DET, even though those undergoing eSET were significantly older compared to those undergoing DET. The MPRs were significantly lower (4% vs. 51.2%, P = 0.00005) in the eSET group vs. DET group. Our results are in line with a study conducted by Clua *et al*., a retrospective analysis of the outcome in 1139 recipient fresh cycles (1073 from DET and 66 from SET) with at least three available embryos for transfer was performed. The CPRs were similar after SET (45.5%, 30/66) and DET (57.1%, 613/1073), whereas the MPR was 0% and 39.5% for SET and DET, respectively.[18] Patients in ovum donation cycles are noted to have 40% MPR with double cleavage stage embryo transfer and 50% with DBT.[19]

In our study, prematurity rates were higher but statistically nonsignificant with DET group as compared with eSET group (21.4% vs. 10%, P = 0.09) when self-oocytes were used. In eSET group, 25% births weighed <2.5 kg compared to 45.7% in DET using self-oocytes (P = NS). In oocyte donation cycles also,

Table 3a: Pregnancy outcomes in patients undergoing 1st elective single embryo transfer and double embryo transfer using donor oocytes

Parameters	eSET (1st)	DET	*P**
Patients (*n*)	68	184	-
ET (*n*)	68	184	-
Mean age (years) (mean±SD)	41.0±4.92	36.0±4.88	0.00001
PR (%)	44/68 (64.7)	129/184 (70.1)	0.411
IR (%)	41/68 (60.2)	183/368 (49.7)	0.109
CPR (%)	39/68 (57.3)	121/184 (65.7)	0.218
MPR (%)	2/39 (5.1)	62 (51.2)	0.00005
CAR (%)	4/39 (10.2)	26/121 (21.4)	0.118
EPR (%)	1/39 (2.56)	1/121 (0.8)	0.395
LBR (%)	33/68 (48.5)	90/184 (48.9)	0.956

*Chi-square test. ET=Embryo transfer, PR=Pregnancy rate, IR=Implantation rate, CPR=Clinical pregnancy rate, MPR=Multiple pregnancy rate, CAR=Clinical abortion rate, EPR=Ectopic pregnancy rate, LBR=Live birth rate, DET=Double embryo transfer, eSET=Elective single embryo transfer, SD=Standard deviation

Table 3b: Cumulative pregnancy outcomes in patients undergoing 1+1 elective single embryo transfer and double embryo transfer using donor oocytes

Parameters	eSET (2nd) frozen embryo transfer	Cumulative outcome (1+1 eSET) Group 1	DET Group 2	*P**
Patients (*n*)	35	68	184	-
ET (*n*)	35	103	184	-
PR (%)	13	57/68 (83.8)	129/184 (70.1)	0.002
IR (%)	11	52/103 (50.48)	183/368 (49.72)	0.892
CPR (%)	11	50/68 (73.5)	121/184 (65.7)	0.24
MPR (%)	0	2/50 (4)	62/121 (51.2)	0.00005
CAR (%)	0	4/50 (8)	26/121 (21.4)	0.034
EPR (%)	0	1/50 (2)	1/121 (0.8)	0.516
LBR (%)	11	44/68 (64.7)	90/184 (48.9)	0.02

*Chi-square test. ET=Embryo transfer, PR=Pregnancy rate, IR=Implantation rate, CPR=Clinical pregnancy rate, MPR=Multiple pregnancy rate, CAR=Clinical abortion rate, EPR=Ectopic pregnancy rate, LBR=Live birth rate, DET=Double embryo transfer, eSET=Elective single embryo transfer

Table 4: Perinatal outcomes in patients undergoing 1+1 elective single embryo transfer and double embryo transfer using donor oocytes

Perinatal complications	Group 1 (1+1 eSET), *n* (%)	Group 2 (DET), *n* (%)	*P**
Gestational age (weeks)			
20-28	1 (2.22)	3 (3.2)	0.741
28-32	2 (4.44)	7 (7.5)	0.491
32-36	9 (20)	26 (27.9)	0.313
36-42	33 (73.3)	57 (61.2)	0.163
Birth weight (kg)			
<1	3 (6.5)	11 (7.8)	0.765
1-1.5	1 (2.17)	6 (4.28)	0.513
1.5-2.5	11 (23.9)	63 (45)	0.011
2.5-4.5	31 (67.3)	60 (42.8)	0.0038
>4.5	0	0	
Congenital anomalies	0	4 (2.8)	0.246
Stillbirth	1 (2.17)	6 (4.28)	-
Early NND	1 (2.17)	3 (2.14)	-
Late NND	0	1 (0.7)	-
PNMR	2 (4.34)	10 (7.14)	0.503

*Chi-square test. NND=Neonatal death, PNMR=Perinatal mortality rate, DET=Double embryo transfer, eSET=Elective single embryo transfer

we found higher incidence prematurity (<36 weeks) 38.8% with DET versus 26.7% with eSET (*P* = NS) and higher incidence low birth weight 57.2% with DET versus 32.7%% with eSET, difference being statistically significant (*P* = 0.0038). Even though statistical significance was not reached in most, trends were toward the better neonatal outcome.

A recent study by Ishihara *et al*. in Japan evaluated frozen and fresh single embryo transfer in a large cohort (*n* = 277,042) and considered neonatal and maternal outcomes. The authors found that single frozen blastocyst transfer was associated with 66% live birth per transfer, with 93% of these deliveries occurring at term, and that fewer than 4% were small for gestational age.[20] However, multiple embryo transfers were not included in the analysis for comparison.

In a meta-analysis conducted by Savasi *et al*., oocyte donation seems to be independently associated with a higher rate of pregnancy-induced hypertension and preeclampsia. Oocyte donation also seems to be associated with lower fetal birth weight.[21] However, after adjusting for obstetric complications, most studies report less pronounced differences in birth weight or no dissimilarities. In another meta-analysis conducted by Storgaard *et al*., which included results of 35 studies, the risks of preterm birth and low birth weight in singletons were AOR 1.75 (95% CI, 1.39–2.20) and 1.53 (95% CI, 1.16–2.01), respectively, in oocyte donation cycles.[22] Even in our study, better birth weights were seen in patients undergoing embryo transfer with self-oocytes compared to donor-oocytes. 90% deliveries occurred at term using self-oocytes compared to 73.3% using donor-oocytes and 75% weighed >2.5 kg using self-oocytes compared to 67.3% using donor-oocytes.

This finding of greater embryo to birth efficiency, significantly higher cumulative LBR in eSET group versus DET is not unexpected. Assuming that there exists some variation in cycle-to-cycle endometrial receptivity, as may be suggested by implantation defects associated with suboptimal endometrial thickness[23,24] and elevated serum progesterone in stimulated cycles[25] and inter-cycle variability in histology,[26] transferring embryos one at a time would minimize the potential for all embryos to be transferred to a nonreceptive uterus.

The major limitation of our study is its retrospective nature. Although similar studies have been performed in the past as discussed above, most of them are from the Western countries, and there is no such data from India. This is all the more relevant as the National ART Registry of India 2015, shows that 54.33% of patients with self-cycles and 54.6% patients with donor oocyte cycles had three or more embryos transferred per ET resulting in twin and higher order pregnancies in 32% in self and 38.4% in donor oocyte cycles, respectively. Through this study, we want to impress upon the fact that eSET is a viable alternative in selected patients and should be promoted in India also.

However, several challenges to application of eSET exist to date; mainly the patient's desire for higher success rate per cycle, patient's desire for twin pregnancy, financial considerations (additional cost of freezing and FET), laboratory culture conditions, inability to have blastocysts in all patients, especially with self-oocytes, embryo selection techniques and successful cryopreservation program. With adequate education of infertile couple about maternal and perinatal complications of twin pregnancy and long-term mental and physical health consequences of prematurity, eSET can be practiced for more and more couples. In addition, clinics should start portraying IVF success rates as cumulative live births per initiated cycle rather than per transfer to patients.

Conclusion

Better obstetric and perinatal outcomes are obtained following the elective transfer of a single blastocyst followed by one frozen blastocyst transfer compared to transfer of both at a time. The cumulative LBR is higher; there is a lower incidence of multiple pregnancies, prematurity and low birth weight. Recognizing the immediate and long-term consequences of low birth

weight and prematurity and thereby associated added health-care costs, shifting over to eSET policy in good prognosis patients and donor oocyte recipients, is certainly beneficial.

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Conflicts of interest

There are no conflicts of interest.

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