

# Transfer of spontaneously hatching or hatched blastocyst yields better pregnancy rates than expanded blastocyst transfer

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## ABSTRACT

**CONTEXT:** Blastocyst stage embryo transfer (ET) has become routine practice in recent years. However, probably due to limitations of assisted hatching techniques, expanded blastocyst transfer (EBT) is still the preferred mode. Inexplicably, not much consideration has been given to spontaneously hatching/hatched blastocyst transfer (SHBT). **AIM:** This study aimed to investigate developmental potential of spontaneously hatching/hatched blastocyst against EBT in *in vitro* fertilization (IVF) cycles. **SETTINGS AND DESIGN:** Prospective study of 146 women undergoing their first IVF- ET cycle. **SUBJECTS AND METHODS:** On the basis of blastocyst status, women were classified into SHBT and EBT groups. Intracytoplasmic sperm injection cycles were excluded to remove male factor bias. Implantation rate (IR), clinical pregnancy rate, and live birth rate were the main outcome measures. **STATISTICAL ANALYSIS:** Graph-pad Prism 5 statistical package. **RESULTS:** SHBT group showed significantly higher blastocyst formation rate ( $53.3 \pm 17.5$  vs.  $43.1 \pm 14.5\%$ ,  $P = 0.0098$ ), top-quality blastocysts ( $71.8$  vs.  $53.7\%$ ,  $P = 0.0436$ ), IR ( $43.6$  vs.  $27.9\%$ ,  $P = 0.0408$ ), pregnancy rate ( $59.4$  vs.  $45.1\%$ ,  $P = 0.0173$ ), and live birth rate ( $36.8$  vs.  $22.8\%$ ,  $P = 0.003$ ) compared to EBT group. Multiple pregnancy rates remained comparable between the two groups. Implantation correlated strongly with top-quality blastocysts (Pearson,  $r = 0.4441$ ) in SHBT group, while the correlation was nonsignificant in EBT group. **CONCLUSION:** Extending culture of expanded blastocysts by a few hours to allow transfer of spontaneously hatching/hatched blastocysts gives higher implantation and pregnancy rates with no added risk of multiple gestations. Spontaneously hatching/hatched blastocysts have a better potential to implant and develop into a positive pregnancy.

**KEY WORDS:** Blastocyst transfer, expanded blastocyst, extended culture, implantation, *in vitro* fertilization, pregnancy outcome, spontaneously hatching/hatched blastocyst

## INTRODUCTION

Blastocyst stage embryo transfer (ET) has become almost routine practice since the advent of sequential culture media. It allows a natural selection of best embryo for transfer with minimal human interference. Blastocyst transfer (BT), therefore, results in high pregnancy rate while minimizing the risk of multiple gestation.<sup>[1,2]</sup> Current practice involves culture and transfer of expanded blastocysts. However, it has been observed that extended embryo culture often produces several expanded-stage blastocysts and, therefore, it is practically difficult to select the best blastocyst out of the many available for transfer.

Also, it has been observed that some blastocysts fail to hatch despite expansion of blastocoelic cavity and thinning of zona-pellucida (ZP).<sup>[3]</sup> Embryos that develop to expanded stage *in vitro* may fail to hatch *in vivo* upon transfer. Hence, *in vivo* hatching of blastocyst seems to be the current rate limiting step restraining the criterion of selection of expanded blastocyst for transfer. Assisted hatching (AH) techniques have been attempted to circumvent this problem. However, as per guidelines laid down by Committee of American Society for Reproductive Medicine (ASRM), the method has restricted use due to its conflicting and inconsistent results.<sup>[4]</sup> Discrepancies of AH techniques prompt toward use of an innate mechanism to allow *in vitro* hatching.

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Around a decade ago, few authors<sup>[5,6]</sup> reported high implantation and pregnancy rates with transfer of hatching/hatched blastocysts. Although the study<sup>[5]</sup> was limited by a small sample size ( $n = 6$ ) yet, the pertinent observation of both studies was that waiting till day 6 would allow only good-quality embryos to hatch. Surprisingly, however, no studies on spontaneously hatching/hatched blastocysts have since then been undertaken and transfer of expanded blastocyst is still an extensively followed practice.<sup>[1]</sup> Chances of success in assisted reproduction can be improved if embryo selection is based on naturally hatching status. Hence, a comparative study focusing on transfer of only *in vitro* spontaneously hatching/hatched blastocyst versus transfer of expanded blastocysts may not only aid in a better understanding of the implantation process per se, but also to evaluate comparative developmental and implantation potential of spontaneously hatching/hatched blastocyst as against expanded blastocyst transfer (EBT) in *in vitro* fertilization (IVF) cycles.

## SUBJECTS AND METHODS

In this prospective study, patients ( $n = 146$ ; mean age  $\pm$  standard deviation:  $30.6 \pm 3.9$  years) underwent fresh cycle of conventional IVF between April 2008 and March 2011. BT was provided to all patients during a single IVF cycle. Donor egg and intracytoplasmic sperm injection cycles were excluded to avoid bias due to male factor, since it has been reported that male infertility significantly reduces blastocyst production.<sup>[7]</sup> In case of severe male factor, donor sperm was used after obtaining written consent from the couple. Informed consent was sought from all patients for participation and our IVF center's institutional review board approved the protocol before beginning this study.

After downregulation with gonadotropin-releasing hormone (GnRH) agonist or using standard GnRH antagonist protocol, controlled ovarian hyperstimulation with recombinant follicle-stimulating hormone (FSH) (recagon, 200 IU/day) was started from day 2 of cycle. Injection human chorionic gonadotropin (hCG) (fertigyn, 5000 IU) was administered when at-least two lead follicles reached  $\geq 8$  mm diameter. Egg collection was done between 34 and 36 h after hCG injection. Micronized progesterone injection (susten, 100 mg daily) was given to provide luteal phase support. Sperm sample was prepared by swim-up/density-gradient method and insemination was done 4 h after egg collection. A single team of embryologists coordinated all procedures, thereby ensuring that the culture protocols and embryo assessment were standardized. In all cases, culture was extended to blastocyst stage when more than two zygotes or at-least two good-quality embryos were available at cleavage stage (day 3). Embryos were cultured in sequential

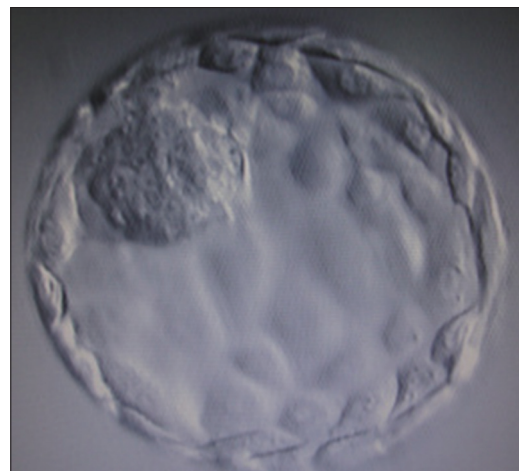
media (fertilization/cleavage/blastocyst media) in individual microdrops of 20  $\mu$ L: From day zero to day 1 in fertilization media, day 1 to day 3 in cleavage media and day 3 to -day 5/6 in blastocyst media and incubated at 37°C in benchtop incubator with a triple gas mixture (6% CO<sub>2</sub>, 5% O<sub>2</sub>, and 89% N<sub>2</sub>). Embryonic development was monitored daily and microphotographic images obtained at a specific time till day of transfer.

All 146 patients undergoing IVF with BT were sorted either into EBT or spontaneously hatching/hatched blastocyst transfer (SHBT) groups. Out of 73 women in each group, four patients in SHBT group and two patients in EBT group could not be offered BTs due to nonformation of blastocyst on account of arrest of embryos at eight-cell or morula stage or failure in hatching even on day 7 of extended culture. Hence, results were compared among 71 women in EBT group and 69 women in SHBT group.

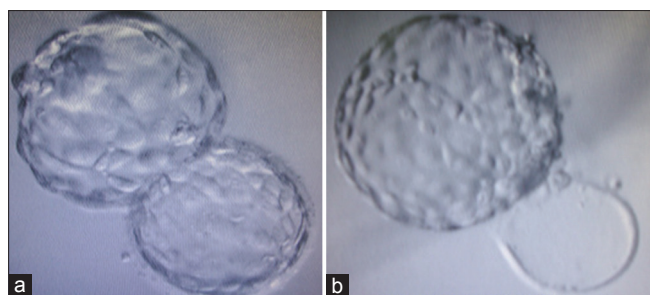
Group A ( $n = 71$ ): EBT group: Transfer of fully expanded blastocysts defined by presence of  $>50\%$  blastocoelic cavity with thinning zona, identifiable, compactly organized inner cell mass (ICM) and  $\geq 50$  trophoctodermal (TE) cells on day 5 of extended culture [Figure 1].

Group B ( $n = 69$ ): SHBT group: Transfer of partially hatched (TE cells emerging out of zona giving it a dumb-bell shaped appearance [Figure 2a] or completely hatched zona-free blastocyst [Figure 2b] on day six of extended culture.

Embryos were examined on morning of day 5 and the time of transfer of expanded blastocysts in EBT group was decided. Blastocysts in SHBT group were cultured further till sign of spontaneous hatching or completely hatched status was seen on morning of day 6. On day of transfer, all patients were offered either elective single blastocyst transfer (eSBT) or two blastocyst transfer (2BT). Final



**Figure 1:** Expanded blastocyst



**Figure 2:** (a) Hatching (dumb-bell shaped) blastocyst (b) Completely hatched (zona-free) blastocyst

decision on number of blastocysts transferred was taken by the couple.

All embryos were microphotographed before transfer and total time in hours from insemination to transfer was noted. Transcervical ET was performed using soft-tipped Cook's catheter in both groups. Immediately after transfer, catheters were flushed and media was examined microscopically to confirm absence of embryos.

On day of ET, endometrial thickness was measured and graded according to the endometrial pattern (multilayered or a nonmultilayered) visualized using transvaginal sonography. Endometrial thickness (centimeters) was derived from average measurements in each plane (longitudinal and transverse) of the distance between the endometrial-myometrial interfaces at the level of uterine fundus. Endometrial layers (pattern) reflected ultrasonologically discernible layers in the endometrium, ranging from one to four.<sup>[8]</sup>

Serum  $\beta$ -hCG on day 14 of ET indicated pregnancy outcome. Clinical pregnancy was confirmed by presence of gestational sac with positive cardiac activity.

### Embryo grading

Cleavage stage embryos were morphometrically graded by Veeck's criteria.<sup>[9]</sup> Blastocysts were graded as per Gardner's grading system<sup>[11]</sup> as follows:

1. Early blastocyst: Blastocoele <50% volume of embryo
2. Blastocyst: Blastocoele occupies  $\geq$ 50% volume of embryo
3. Full blastocyst: Blastocoele completely fills the embryo
4. Expanded blastocyst: Blastocoele volume larger than that of early embryo accompanied by thinning of ZP
5. Hatching blastocyst: Trophoctoderm starts herniating through ZP
6. Hatched blastocyst: Blastocyst completely escapes from zona.

For blastocysts graded as 3-6, development of ICM was assessed as follows: A-tightly packed, many cells; B-loosely grouped, several cells; and C-very few cells.

The trophoctoderm was assessed as follows: A-many cells forming a cohesive epithelium; B-few cells forming a loose epithelium; or C-very few large cells.

Morphologically, embryos in EBT group (grade 3 and 4) and SHBT group (grade 5 and 6) were classified as top quality when they reached at least fully expanded stage on day 5/6 or hatching/hatched status on day 6/7, with a distinct round or oval shape, compact ICM and trophoctoderm consisted of a high number of flat epithelium-like cells without dark granulation. For calculation purpose, top-quality embryos were regarded as grade 1, average quality as grade 2. Poor blastocyst morphology characterized by flat, irregularly shaped or fragmented ICM, presence of sparse granular or degenerated cells and trophoctoderm formed by fewer cells that had poor cell-to-cell attachment, was regarded as grade 3. By using this scoring system, blastocysts were selected for transfer. Excess number of blastocysts was cryopreserved. Mean grade of embryos was calculated as an average of number of embryos transferred.<sup>[10]</sup>

### Outcome measures

- 1) Implantation rate (IR):

$$\frac{\text{Total number of gestational sacs}}{\text{Total number of embryos transferred}} \times 100$$

- 2) Clinical pregnancy: Gestational sac with positive cardiac activity observed at ultrasound at around 6<sup>th</sup> week of amenorrhea was defined as confirmation of clinical pregnancy
- 3) Live birth rate:

$$\frac{\text{Total number of babies delivered}}{\text{Total number of embryos transferred}} \times 100$$

### Statistical analysis

Comparisons were made using unpaired Student's *t*-test, Chi-squared analysis, and Fisher's exact test, where appropriate.  $P < 0.05$  was considered statistically significant. Results are expressed as mean  $\pm$  standard deviation. Pearson's correlation coefficient (*r*) was evaluated to find correlation of blastocyst status and number with implantation rate (IR) in both groups. Biostatistical package Graph-pad prism (version 5.0) was used.

## RESULTS

No statistically significant difference in such variables as age, body mass index, infertility period, indications for treatment, mean baseline FSH level, number of days of stimulation or mean peak estradiol level on day of hCG was observed between the EBT and SHBT groups [Table 1].

**Table 1: Comparison of clinical data between EBT and SHBT groups**

Variables	Group A EBT (n=71) mean±SD	Group B SHBT (n=69) mean±SD	P value
Age (years)	31.0±4.1	30.5±3.6	0.4889
Infertility period (years)	7.6±4.5	7.6±4.0	0.9888
Body mass index (kg/m <sup>2</sup> )	23.8±3.9	23.9±4.5	0.8416
Indications for treatment			
Tubal factor	37	40	
Ovulatory dysfunction	13	11	
Endometriosis	10	09	
Unexplained factor	13	10	
Mean basal FSH (mIU/mL)	5.4±2.4	5.2±2.1	0.8245
Mean peak estradiol level (pg/mL)	2160±854	2210±860	0.7812
Mean days of stimulation	11.1±1.1	11.3±1.4	0.5223

EBT=Expanded blastocyst transfer; FSH=Follicle-stimulating hormone; SD=Standard deviation; SHBT=Spontaneously hatching/hatched blastocyst transfer

**Table 2: Comparison of embryological data between EBT and SHBT groups**

Variables	Group A EBT (n=71) mean±SD	Group B SHBT (n=69) mean±SD	P value
Mean no. of oocytes retrieved	12.4±6.1	14.1±7.6	0.1517
% fertilization	89.1±13.7	86.6±16.0	0.3179
% cleavage	90±11.5	86.3±15.4	0.1477
Total no. of BC formed and formation rate (%) on the day of transfer	350 (43.1±14.5)	400 (53.3±17.5)	0.0098**
Number of BC and mean no. of BC transferred	136 (1.9±0.05)	117 (1.7±0.05)	0.0156*
No. of top-quality BC transferred (%) (Gardner-schoolcraft scoring)	73 (53.7%)	84 (71.8%)	0.0436*
Mean grade of BC transferred	1.6±0.7	1.1±0.3	<0.0001***
Day of transfer	5.7±0.7	6.1±0.7	0.0027**
Hours after insemination	134±14.3	142.0±9.9	0.0017**
Endometrial thickness on the day of transfer (cm)	1.2±0.3	1.2±0.3	0.5734
Pattern of endometrium (grade)	3.95±0.18	4.0±0.11	0.2241

BC=Blastocyst; EBT=Expanded blastocyst transfer; SD=Standard deviation; SHBT=Spontaneously hatching/hatched blastocyst transfer, \*Significant, \*\*Highly significant, \*\*\*Extremely significant

Embryological data and ultrasonographic findings between the two study groups are represented in Table 2. Consistent with better quality blastocysts obtained in Group B, clinical pregnancy rate (CPR) and IR in group B (SHBT) was significantly higher than in group A (EBT) (CPR: 59.4% vs. 45.1%,  $P = 0.0173$  and IR: 43.6% vs. 27.9%,  $P = 0.0408$ , respectively). Multiple gestation

rates were comparable and did not differ significantly between the two groups (24.4% vs. 18.8%,  $P = 0.4777$ ). However, live birth rate was significantly much higher in SHBT group compared with EBT group [(43/117) 36.8% vs. (31/136) 22.8%,  $P = 0.003$ ]. The per-cycle live birth rate was much higher and differed significantly between the SHBT and EBT groups [62.32% (43/69) vs. 43.66% (31/71) respectively ( $P = 0.027$ )].

An extremely strong correlation of implantation with top-quality embryos was observed in SHBT group (Pearson  $r = 0.4441$ ), while it was nonsignificant in EBT group. Conversely, correlation of implantation with number of embryos was significant in EBT group (Pearson  $r = 0.2573$ ), whereas it was nonsignificant in SHBT group [Table 3].

## DISCUSSION

This is the first ever study involving exclusive transfer of spontaneously hatching/hatched blastocyst/s. Our results demonstrate that SHBT gives a distinct and significantly higher clinical pregnancy, embryo implantation, and live birth rate compared with EBT. Though an earlier study<sup>[5]</sup> had concluded that hatching of embryos by day 6 is a favorable prognostic factor for IVF outcome; it was a serendipitous finding since culture was extended till day 6 due to unavailability of best blastocyst for transfer on day 5 when most of the embryos were still in morula or early blastocyst stage. Another study<sup>[6]</sup> reported similar results with a larger sample group. However, both studies involved transfer of at least one hatching/hatched blastocyst along-with at least one nonhatched blastocyst rather than exclusive transfer of hatching/hatched blastocysts. Our results remove any ambiguity arising from earlier studies, clearly indicating that spontaneously hatching/hatched blastocyst and not expanded blastocyst should be the selection criterion and can be the most favorable prognostic factor for positive pregnancy outcome in assisted reproduction.

It has also been observed that the decisive morphometric characters described by Gardner *et al.*,<sup>[10]</sup> such as volume of blastocoeleic cavity, composition of ICM and number, and texture of trophoblastic cells (TE) that help to select the best embryo, generally do not appear by day 5 at pre-or early-blastocyst stage. Notably, our study for the first time reports that expanded blastocysts are formed only when the culture is extended beyond day 5. This additional time facilitates the slow growing day five morula/blastula stage embryos to develop into blastocysts and also facilitates compaction of ICM, increase in TE cells and enhancement in volume of blastocoeleic cavity resulting in thinning of ZP. Another interesting finding of this study is that 117 of the 400 blastocysts (>29%) formed in SHBT group, started

**Table 3: Correlation of implantation with number and grades of BCs (Pearson r)**

	Number of BCs transferred	Top class BCs transferred
Implantation in		
Group A (EBT)	0.2573*	0.1831 (NS)
Group B (SHBT)	0.1418 (NS)	0.4441***

BC=Blastocyst; EBT=Expanded blastocyst transfer; SHBT=Spontaneously hatching/hatched blastocyst transfer; NS=Not significant; \*Significant, \*\*\*Extremely significant

hatching, or were completely hatched by extending the culture just over 6 days, which is slightly higher than the 25% reported by Gardner *et al.*,<sup>[10]</sup> Thus, it may be assumed that over 70% blastocysts fail to hatch *in vitro* and get entrapped within the zona. Such blastocysts, if transferred, may also fail to hatch *in vivo*, hampering implantation and pregnancy rates.

It is noteworthy to mention that fast cleaving embryos do not necessarily extrapolate to blastocyst formation as about 70% of them are chromosomally abnormal and arrest before developing to the blastocyst stage.<sup>[11,12]</sup> Schiewe *et al.*,<sup>[13]</sup> observed that genetic abnormalities of the embryo, suboptimal culture conditions, and abnormalities of ZP may lead to failure in *in vivo* hatching and the implantation process becomes difficult or even impossible. Another study<sup>[14]</sup> concluded that about 35% of top class expanded blastocysts are aneuploid and may not succeed to hatch *in vivo* resulting in implantation failure. In the absence of preimplantation screening data, it is reasonable to assume that in both groups in our study, embryos that progressed to become blastocysts and subsequently implanted were genetically “normal.” This conjecture is further substantiated by reports stating that embryos selected for transfer on day 5 or day 6 will carry a lower risk of being aneuploid, thereby increasing a patient’s chances of achieving an ongoing pregnancy.<sup>[12]</sup> These findings again reinforce our predilection toward transfer of spontaneously hatching/hatched blastocyst over expanded blastocyst to avoid presumably aneuploid blastocysts and increase implantation rate.

A nonmultilayered endometrium consisting of homogeneous endometrial pattern (i.e., grade 4) characterized by either hyperechogenic or isoechogenic endometrium has been indicative of favorable endometrial response.<sup>[15]</sup> However, the nonsignificant difference in endometrial thickness and pattern in both EBT and SHBT groups vindicates our point that embryo quality is a major contributory factor for higher pregnancy and implantation rate. In addition, a significantly prolonged culture time in SHBT group apparently reduces uterine contractions at the time of ET contributing to successful implantation. This hypothesis is corroborated by findings stating that high frequency uterine contractility at the time of ET adversely affects implantation rates and pregnancy outcome in IVF.<sup>[16]</sup>

An extremely strong correlation of IR with top-quality blastocysts in SHBT group obtained in our study is authenticated by reports claiming that chances of success in assisted reproduction can be improved if embryo selection is based on hatching status.<sup>[6]</sup> The fact that number of embryos transferred really did not matter in SHBT group, emphasizes the relevance of quality over quantity. Therefore, transfer of fewer number of top quality blastocysts in SHBT group gave better pregnancy/live birth rates than EBT group where comparatively higher number of embryos was transferred. Mullin *et al.*,<sup>[17]</sup> recently reported higher implantation rates in patients who chose a single blastocyst transfer (eSBT) over double blastocyst transfer. No statistically significant difference in multiple pregnancy rates observed between the two groups in our study suggests that it may be prudent to transfer single hatching/hatched blastocyst and to avoid multiple pregnancy without compromising high implantation rates. The present study, thus, allows us to define new end points as regards time of transfer, number of blastocysts transferred, implantation rates, and IVF success.

## CONCLUSION

Our study confirms that extending blastocyst culture by few hours allows better developed, top-quality hatching/hatched blastocyst for transfer which subsequently improves implantation and pregnancy/live birth rates with no added risk of multiple pregnancies compared with EBT.


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