Guest Article

Blastocyst Transfer—A Way Head

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The last 2 decades have witnessed many technological advances especially in Assisted Reproductive Technologies. The initial euphoria and enthusiasm was to produce more good quality oocytes and use more powerful drugs and innovate better protocols, but accumulating evidence and experience has made us reconsider our aims and made us more conservative.

The essence of advances in contemporary ART is to maximize success and minimize complications. The concept of blastocyst transfer aims at

- Maximizing success
- Selecting the embryos with implantation competence
- Minimizing multiple births
- Synchronizing embryo and endometrial development
- Test of quality control in the laboratory

In 1998 Dale et al were the first to suggest that the uterus is more hostile and provides a different, more acidic milieu for the embryo compared to the oviduct. There is more nutritional and homeostatic stress for the 2-8 cell embryo in the uterus at a higher acidic pH as compared to the fallopian tubes. Optimizing culture media enables these young embryos to reach the blastocyst stage before their eventual transfer into the uterus.

A pioneering study by Gardner et al in 1998 clearly revealed a superior pregnancy rate of 71% with day 5 transfer as compared to 66% with day 3 transfer.

Evaluate Effectiveness of Blastocyst Culture & Transfer Prospective randomized trial

	Day 3	Day 5
No. of ET	3.7	2.2
Imp. Rate	30.1	50.5
Preg.rate	66%	71%

The study group in 2 consecutive studies was limited to those patients who had previously exhibited a good response to HMG (Gardner et al, 1998, Schoolcraft et al, 1999). There was a need to evaluate a heterogenous group including poor and moderate responders.

This study stimulated ART clinics the world over to embrace this new technique which has yielded significantly superior results.

1. Reduction in the rate of multiple births.
   Worldwide, IVF is responsible for the birth of around 25,000 twins. Twins are associated with a greater risk of neonatal deaths, malformations and prematurity. When blastocyst transfer is done only one or two good quality blastocysts are transferred as compared to more embryos during conventional ET (D3). Thus the incidence of iatrogenic IVF higher order multiple pregnancies is reduced thereby seldom requiring embryo reduction, an inherently risky procedure.
2. It enables us to select embryos for transfer which are capable of implantation. In the process of

embryonic growth the best healthy embryos grow rapidly and reach the blastocyst stage while poor quality embryos grow slowly or get arrested at an early stage. This allows us to screen and select the best embryos for transfer based on their growth and not just on morphological appearance. It is a process of natural selection in which only the best embryos survive and suboptimal embryos are automotically eliminated before transfer.

3. Synchronizing embryo and endometrial development

   The transfer of blastocyst on day 5 offers the clinician an opportunity to modify the endometrium and make it more receptive before embryo transfer. By studying endometrial growth and vascularity the optimal time for ET can be decided, and suitable modifications can be made prior to transfer.

4. Successful blastocyst culture is a measure of quality control for the IVF lab.

   Stringent quality control and meticulous preparation of sequential culture media are the cornerstone towards achieving a good harvest of blastocysts. The percentage of embryos that reach the blastocyst stage in a given IVF lab is an indication of the capability and efficiency of that ART unit.

   At our clinic, we were encouraged by the superior results of blastocyst transfer and convinced that it would improve pregnancy rates. A study with sequential blastocyst transfer was done between Feb 99 — Dec 99 as shown in the table below.

Fertility Clinic — Results
Feb'99 — Dec'99

· Subjects selected for study	143
· Embryos allowed to grow blastocyst	416
· Embryos which grew into blastocyst	199 (47.83%)
· Grade I	- 146
· Grade II	- 53
· Morula Stage	- 147
· Embryo arrested or degenerated — 70	

The patients selected formed a heterogenous group and the results were encouraging as shown below.

Fertility Clinic
Feb'99-Dec'99

· Clinical pregnancies	- 47
· Gr. I blastocyst	- 47.05% (40/85cycles)
· Gr. II blastocyst + Morula	- 14.81% (4/27 cycles)
· Morula transfer only	- 9.67% (3/31 cycles)

This study was continued from Jan 2000 to July 2000.

Fertility Clinic — Results
(Jan'2000 — July'2000)

· Subjects selected for study	122
· Embryos allowed to grow into blastocyst	383
· Embryos which grew into blastocyst	213 (55.6%)
· Grade I	- 148
· Grade II	- 65
· Morula Stage	- 75
· Embryos arrested or degenerated	- 95

Results
Fertility Clinic (Jan'2000-July'2000)

· Clinical pregnancies	- 36
· Gr. I blastocyst	- 39.76% (31/78 cycles)
· Gr. II blastocyst + Morula	- 13.04% (3/23 cycles)
· Morula transfer only	- 14.3% (3/21 cycles)

We evaluated the number of multiple pregnancies in this study.

Multiple Pregnancy

	Feb'99-Dec'99	Jan'2000-July'2000
Clinical Pregnancies	47	36
· Single pregnancy	35	29
· Twin pregnancy	8	7
· Triplets	4	-

A greater percentage of these pregnancies were singleton pregnancies.

We also tried growing frozen — thawed embryos to blastocyst stage before transferring them and obtained better results (17.3%)

Frozen — thawed ET
Fertility Clinic Feb'99-Dec'99

· No. of patients		- 23
· Embryos		- 94
· Grade I	-20	
· Grade II	- 17	
· Morula	- 40	
· Slow growth	- 17	
· Clinical pregnancies	- 4 (17.3%)	

In the study period Feb 99 — Dec 99, 106 patients underwent conventional IVF with transfer on day 2 or day 3, for the reasons mentioned below.

Conventional IVF
(Feb 1999-Dec1999)

· No of patients		106
Recagon trial patients	48	
Poor responders	26	
No. of patient where embryos <5	12	
No. of patient where embryos did not reach to blastocyst	20	
· Clinical pregnancies		23 (23%)

The results of conventional IVF were as follows.

Fertility Clinic Feb'99-Dec'99
Conventional IVF — ET D3

· Patients	106
· Oocytes obtained	1276
· Oocytes fertilized	718 (56.26%)
· Oocytes cleaved	616 (85.83%)
· Embryos transferred	411
· Transfers not done	6
· Clinical pregnancies	23 (23%)

This study convincingly revealed a superior pregnancy rate of 47.5% with sequential blastocyst transfer as compared to conventional IVF-ICSI (23%). Our study shows that sequential transfer has significantly improved our results. We have the security of conventional results with advantages of the newer techniques and the confidence to upgrade our services to blastocyst transfer. The transfer of a single grade I blastocyst will give the best result.

The advent of new techniques has raised several issues, which need to be resolved such as:

- Will blastocyst transfer improve pregnancy rate in all couples?
- Which group of patients are likely to benefit the most?
- How many blastocysts should we transfer?
- How many couples will not have blastocyst for transfer if we culture to day 5?

A study by Pantos et al (1999) revealed that women greater than 40 years of age had a lower rate of blastocyst formation, pregnancy rate and implantation rate than those less than 40 years.

Success rates for the development of viable Human Blastocyst, Pregnancy & Implantation Decline significantly in women ≥ 40 yrs old.

· Patients undergoing IVF treatment — 293

Blastocyst development rate.
- Women > 40 yrs - 22%
- Women < 40 yrs - 44.6%

Pregnancy rate
- Women > 40 yrs - 21.1%
- Women < 40 yrs - 44.6%

Implantation rate
- Women > 40 yrs - 8.9%
- Women < 40 yrs - 19.9%

Thus older patients are less likely to benefit from blastocyst transfer. Gardner et al (2000) in a recent study demonstrated a pregnancy rate of 70% with transfer of only one top scoring blastocyst, which incidentally had a 50% twinning rate. He concluded that atleast one top scoring blastocyst must be transferred to achieve good results.

TOWARDS SINGLE BLASTOCYST TRANSFER (n=107)

	2 top scoring blastocysts	Single top scoring blastocyst
Imp. Rate	70%	50%
Preg. Rate	87%	70%
Twinning	61%	50%

Clinicians and embryologists are now trying to crystallise this knowledge and improve their

Efforts are trying to improve in the following directions developing better culture media to minimize toxic stress, bringing about a reduction in apoptotic index by TGF & IgF and removing fragments from embryos. They are also assessing the importance of macromolecules and trying to identify viable embryos on day 2.

Ongoing research in the above directions and breakthroughs in these fields will enable clinicians to achieve the best result. With existing available information Eg. blastocyst culture and transfer may be the gold standard till we have better technology tomorrow.

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