

Blastocyst Transfer

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One of the most common consequences of Assisted Reproductive Technologies (ART) is high order pregnancies. It is well recognized that as the number of fetuses increases, so does the expense and the risk to the mother and babies. Therefore, the ultimate goal of ART is a normal single intrauterine pregnancy that ends with the uneventful delivery of a healthy infant.

It was once a common practice, among reproductive specialists, to transfer more than one embryo to increase the chance of establishing a pregnancy. Intrauterine Inseminations are often performed when several follicles are present.

"Transferring three or more embryos is a misleading practice", says Dr. Sonja Kristiansen, Medical Director of the Infertility Center of Houston. She points out that the latest national statistics reveal that the probability of pregnancy increases when up to three embryos are transferred. However, when more than three are transferred success rates are not improved but the probability of high order pregnancies (triplets or quadruplets) increases greatly.

Under standard IVF culture conditions, approximately 10 to 40% of fertilized eggs will progress to maturity where a pregnancy can be established. "The challenge for the in-vitro fertilization team is to choose the embryos most likely to result in the delivery of a normal baby", adds Dr. Michael Allon, Practice Director of the Infertility Center of Houston. Therefore accurate selection enables the clinician to transfer fewer embryos, leading to a high pregnancy rate, without the unwanted complications of multiple births.

Over the past several years, embryo culture techniques have improved, enabling us to culture for five to seven days after retrieval. Normally, by this time the embryos have reached a stage of development called the blastocyst. This extended culture time enables nature to select the "strongest" embryos those most likely to produce a pregnancy therefore fewer can be transferred.

"Blastocyst culture is the latest important advance in IVF technology. It is exciting to be able to offer patients this promising state-of-the-art technique. It provides us the ability to increase pregnancy success versus the risk of multiples for IVF couples when we assist them in their quest for parenthood," explains Dr. Kristiansen.

What is Blastocyst Culture and Transfer?

A blastocyst is an embryo that has developed in culture for at least five days after fertilization and has divided into two different cell types. The surface cells are termed the trophectoderm and will eventually become the placenta and the inner cell mass will

become the fetus. A healthy blastocyst should hatch from its shell (zona pellucida) by the end of six days or earlier and begin to implant within the lining of the uterus.

In the early years of human IVF, embryos were transferred to the uterus between 24-48 hours (Day-1 or Day-2 transfer) after fertilization. Later, some laboratories started to grow the embryos for three days before transfer.

This was a more physiological approach since it is known that under in-vivo conditions the embryos reach the uterine cavity around the end of the third day following fertilization. Three day old embryos have usually developed to the 4- to 8-cell stage.

Since we cannot determine the viability of each embryo at this stage, and given the high embryonic loss at this stage, it was common to replace many embryos to compensate for those that would not implant.

This practice yields adequate pregnancy rates, however, it often resulted in high order pregnancies. Because of the danger to the babies and the mother, in addition to the social and economic stresses that the care and nursing of the newborns represent, high order pregnancies remained an unwanted serious obstetrical complication.

Usually, two blastocyst stage embryos are transferred compared to four or five day-3 embryos. This dramatically reduces the probability of multiple pregnancies with higher pregnancy rates in many cases.

Let us use a hypothetical case to illustrate our point. A patient has 13 oocytes harvested. With our current rates of fertilization, about 10 will become embryos (80%). At this point, it is not possible to determine which of these 10 are most likely to implant and develop into a baby.

By day three, 7 of the 10 embryos may be developing into healthy 4- to 8-cell embryos. The others may have slowed or stopped their development and their prognosis is not favorable. In this example, we are left with seven embryos that still look like they may have excellent potential.

However, we cannot determine based on their appearance, which ones are the best to transfer on day 3. Further culture for two additional days in the blastocyst culture medium allows the natural selective process to continue.

Thus, after 5 days of growth in the laboratory, only 4 or 5 of the original ten embryos may remain viable and we can now identify the best embryos to transfer. Embryos transferred at the blastocyst stage have made it through key metabolic developmental processes and typically offer a greater chance of implanting.

Disadvantages of blastocyst transfer.

There is the risk of canceled transfer due to failure of embryos to develop to blastocysts. A higher number of 1-cell embryos are needed to assure an adequate number of

blastocysts to select for fresh transfer. The risk of no supernumerary embryos for cryopreservation if in vitro development is poor.

Under common conditions about 40% of the fertilized oocytes should develop to the blastocyst stage. However, in certain cases embryo development is severely compromised and there would be no embryos to transfer. In order to limit this risk, blastocyst transfers may be offered to patients less than 40 years of age or those who are recipients of donor oocytes.

Candidates for blastocyst transfer will have the embryo transfer five days after egg harvest. The IVF laboratory staff will evaluate the embryos on the morning of the next day after egg retrieval. If there are less than four high quality embryos, the embryo transfer will be rescheduled for day 3.

The Infertility Center of Houston- Experience in Blastocyst Culture

"Two important factors limit the number of embryos that will develop to blastocysts," points out Dr. Jose J. Hernandez, Laboratory Director of the Infertility Center of Houston. First, the inherent health of any embryo will dictate its ability to continue to grow and divide. Several eggs may initially fertilize, but only a few will progress to the four-cell stage, fewer to the eight-cell stage, and even fewer will develop into blastocysts.

Simply put, this self-selection can be viewed as survival of the fittest. The second growth limiting factor was the culture systems. As early as 1993, Dr. Hernandez started cultivating embryos in vitro to the blastocyst stage.

He understood that the dynamic process of embryo development required more than the "one size fits all," culture media that had been used prior to this point. Therefore, from the beginning, he started using what today is called "sequential media". He understood that before embryo metabolic activity takes over, maternal nutrients stored in their cytoplasm are used.

Therefore, he used medium that would facilitate their development in vitro during their first 3 days in culture. Followed by culture for two additional days in a more complex medium that is suited to this stage of development. Therefore, from the oocyte harvest onward, the embryos are exposed to specific media designed to meet the nutritional requirements of each stage of development.

Refinements in technique promises to maximize safety and success rates.

The ability to grow embryos to the blastocyst stage of development in the laboratory, rather than the traditional three days, allows embryologists to determine with greater certainty which embryos are really the best in terms of their potential for implantation.

The Infertility Center of Houston is constantly looking for alternatives to improve IVF success rates through refinements of clinical and laboratory techniques. "Blastocyst culture and the new generation of embryo transfer catheters, in addition to refinements

in the ovarian stimulation protocols have played an important role in our impressive pregnancy success rates", concur Drs. Allon and Kristiansen.

The transfer of high-grade blastocysts has resulted in implantation rates between 40% and 50%. With the transfer of only two blastocysts, Drs. Kristiansen and Allon have achieved pregnancy rates as high as 80% in some cases.

These high implantation and pregnancy rates are due, in large part, to the blend of medical expertise and experience in the clinical and laboratory settings to take advantage of nature's selection of those embryos that have the highest chances of producing a pregnancy.

Can we use blastocyst culture and transfer for everyone?

Patients who have less than four embryos developing normally by 48 hours after fertilization derive little benefit from blastocyst culture, since little can be gained in further embryo self selection.

The blastocyst culture conditions do not improve the health or viability of an individual embryo, which is not otherwise able to develop for 5 days in vitro and then implant; rather it allows embryos capable of sustained growth to continue in culture and reach their maximum inherent capability.

There are currently many unresolved issues regarding blastocyst transfer. Blastocyst transfer has a number of risks, and accordingly, is not appropriate for every couple. In a small percentage of patients, none of the embryos develop to the blastocyst stage and gradually degenerate. This results in a complete loss of all embryos.

There are many other unanswered questions. Will blastocyst transfer improve pregnancy rates for patients with specific conditions, such as age, clinical history, etc., but not for others? Is there a combination of factors (number of embryos for transfer and their inherent quality) to consider achieving an acceptable pregnancy rate? Which patients are the most appropriate for blastocyst transfer?

Our criteria to choose Day-3 vs. Day-5 (Blastocyst transfer)

Allowing the embryos to develop an additional two days in the laboratory gives us more discriminatory power to select the embryos with the highest developmental potential. In addition, replacing the embryos five to six days after fertilization allows the embryos to arrive in the uterus at a more physiologic time (with natural conception the embryo does not implant until about six days after fertilization).

Blastocyst transfer may be of particular benefit for patients who develop many good quality embryos and want to limit their risk of a multiple pregnancy by transferring fewer embryos with higher potential for implantation.

The decision to perform blastocyst culture and transfer is based on several factors including patient age, the number of eggs retrieved, previous IVF success, and perhaps

most important, the embryo grade on day 1 of culture. Blastocyst culture and transfer has significant advantages for younger patients, egg recipients who receive eggs from younger donors, high responders (many eggs retrieved), or patients with previous IVF success.

We encourage you to discuss the possibility of blastocyst transfer with your infertility team.