



EMBRYO TRANSFER

Essential reading prior to your planned procedure

In order to assist you in understanding the various factors underlying our recommendation for which and how many embryos to transfer during your planned procedure, we have prepared the following background information sheet about embryo assessment. Finally, we attach the guidelines of the American Society for Reproductive Medicine regarding the number of embryos to transfer.

Cleavage stage transfer

Embryos that are transferred on day 3 (and sometimes on day 2) following egg retrieval are referred to as being in the cleavage stage. After 3 days, normal embryos will usually have undergone 3 cell divisions, developing to 2, 4 and then 8 cells. However, individual cells do not always divide at the same instant in time. Three cell divisions can therefore present as either 6, 7 or 8 cell embryos, and that is what we need to see in order to call the embryo normal. We have occasionally seen healthy pregnancies from 5 cell or even 4 cell embryos (we know because these were the best available on the day of transfer) but the chance for pregnancy in these embryos is lower. We would not recommend transfer of an embryo that has less than 4 cells on day 3.

When the transfer is on day 2, the embryos are expected to be 3 or 4 cells to be considered of good quality.

We also grade the embryos using a letter system to describe the appearance of the individual cells within each embryo. The scoring system takes into account the size and shape of each cell, how well defined they are, whether or not and to what degree they are fragmented, and the appearance of the cytoplasm, or water component, within the embryo. The system grades embryos from A to E, but it is rare for our embryologists to assign an A, so at the Genesis lab a B quality embryo is considered good. Other embryos selected for transfer may be C or somewhere in between, what we call B/C. Embryos that appear particularly excellent may be given an A or A/B grade. D quality embryos are highly fragmented and not suitable for transfer. An E is assigned when the embryo development has arrested. These also cannot be transferred because they are not viable.

Although, using our scoring system, an 8B embryo would be considered top quality, in reality most pregnancies occur from 6, 7 or 8 cell embryos with grades of either B, C or B/C.

If transferred on day 2, the embryos most likely to result in pregnancy will be 3 or 4 cells with grades of either B, C or B/C.

If you are having your embryo transfer at the cleavage stage (Day 2 or 3), please refer to the attached sheet and then continue with to the information about embryo freezing.

Blastocyst Transfer

After the cleavage stage, the embryo progresses through the morula stage (reaching about 100 cells, generally on day 4) and then on to become a blastocyst, where it will have expanded and grown to several hundred cells. Most patients are aware that having a blastocyst transfer significantly raises the chance that pregnancy will occur. While generally true, the difference has more to do with embryo quality than it does with the actual timing of the transfer (either day 3 or day 5). Blastocyst transfer is most useful as a technique for distinguishing the best embryos when many good quality embryos are present on day 3 (i.e. greater than 2). Embryos that look normal on day 3 may stop growing or significantly slow their growth over the following two (and occasionally three days). The ones that undergo the most expansion are more likely to be healthy and therefore have a higher chance of implanting. If the best embryos for transfer is an obvious choice by day 3, then there is no reason to delay and the transfer is performed on that day.

If you are having a blastocyst transfer, then it is likely that you had sufficient embryo number and quality on day 3 to make waiting to day 5 (and occasionally day 6) the better choice for you. At this stage, we still need to distinguish between varying degrees of blastocyst quality. To do this, we first assign a number to the embryo based on its degree of expansion. Numbers 1 through 5 are used, with 1 being an early blastocyst, 4 being a fully expanded blastocyst and 5 indicating that the blastocyst shell has opened up and hatching of the blastocyst is occurring.

Two additional components of the blastocyst are graded, each using an A, B, C system. The first letter grade is assigned to the inner cell mass, which is the part of the embryo that becomes the actual fetus. The second letter reflects the state of the trophectoderm, which is the part of the embryo that will develop into the placenta and membranes. Grades of A or B for either component are both good and reflect the embryo's suitability for transfer or cryopreservation (freezing). If available, we prefer to transfer embryos with an expansion grade of 2 or above. All of these grades of embryos can lead to healthy pregnancy, either at the time of fresh transfer or at some later date, after thawing. As a general rule, cryopreservation of embryos is done at the blastocyst stage, either on day 5 or 6. Grade 1 embryos may be cryopreserved if they are AA quality.

Number of embryos to transfer

While choosing which embryos are suitable for transfer, and on which day, is usually obvious and based on accepted laboratory criteria, the decision regarding the number of embryos to transfer is not always clear. Nevertheless, it is potentially the most consequential. Also, it occurs at the culmination of the IVF procedure, when every patient's particular history, social as well as financial circumstances and other factors may influence the decision. Before reaching a final decision about the number of embryos to transfer, we suggest that you read the attached ASRM guidelines and then consider the following:

The optimal number of babies to have with each pregnancy is one. This is what nature intended the uterus to hold safely. Each additional fetus that grows during the course of a pregnancy poses risk to the mother (including ovarian hyperstimulation syndrome) and, perhaps of greater importance, to the other fetus or fetuses sharing the womb. Not surprisingly, the complication rate for multifetal pregnancies is always higher than for singleton pregnancies. Even twin pregnancies carry with them more danger than singletons, and this includes both neonatal outcome and long term child health. At GENESIS, we encourage you to follow the guidelines that will optimize your chance of having a healthy singleton pregnancy. Needless to say, triplet and higher order pregnancies should be avoided at all costs. While it may not be something that you feel strongly about on the day of your transfer, we would prefer it take you three tries to conceive one baby than one try to conceive three. The physical and psychological risks such complicated pregnancies pose, as well as the significant financial burden that they present, must be considered.

The above notwithstanding, it is not uncommon for your physician to recommend that two or more embryos be transferred. Such decisions are generally based on your age. As women age, their embryos are much more likely to have genetic defects that prevent implantation, regardless of the embryo grade. It is therefore common to recommend that multiple embryos be transferred because, in women of advanced reproductive age, multifetal pregnancy is rarely an issue.

As a general rule, the more healthy embryos that are available for transfer, the less we would want to transfer. This is because the availability of many embryos usually reflects many healthy eggs at the source; this, in turn, makes it more likely that each individual embryo is healthy and likely to implant. When there are many embryos that are suitable freezing on the day of the transfer (usually day 5), it is best to transfer only one if you are less than 35 years old. This technique avoids the chance of multifetal pregnancy while assuring that, if pregnancy does not occur, enough frozen embryos will be available for future tries. Remember that the scientists will only freeze the highest quality embryos, so if you need to move eventually to frozen embryo transfer, this will also offer you a high chance of conception. It should also be remembered that high quality blastocysts are at higher risk for splitting, which leads to monozygotic (identical) twinning, another reason why transfer of two blastocysts should be avoided in these types of situations. In contrast, when there are very few embryos, one may give serious consideration to transferring more than the guidelines may suggest. If the egg yield from the retrieval procedure has been low, and/or when the stimulation has been difficult, prolonged or required high

doses of gonadotropins, the main concern is the genetic normality of the embryos available. In such situations, we may recommend assisted hatching of the embryos and then transfer of all available embryos on day 3.

Of course, it is not possible to predict, based on our visual assessment of the embryos, whether they are genetically competent to implant and grow into a healthy baby. This is why embryos that look perfect may lead to negative outcomes and, conversely, why embryos that appear suboptimal often will grow into beautiful babies.

Of course, there are many determinants of success from the IVF cycle. We hope that your embryo transfer procedure will be the beginning of a healthy pregnancy. Should you not conceive, please schedule an appointment with your physician so that he or she can review the essential elements of your treatment cycle and help you plan the next logical step.

TABLE 1				
Recommended limits on the numbers of embryos to transfer.				
Prognosis	Age			
	< 35 yrs	35–37 yrs	38–40 yrs	41–42 yrs
Cleavage-stage embryos^a				
Favorable ^b	1–2	2	3	5
All others	2	3	4	5
Blastocysts^a				
Favorable ^b	1	2	2	3
All others	2	2	3	3

^a See text for more complete explanations. Justification for transferring one additional embryo more than the recommended limit should be clearly documented in the patient's medical record.

^b Favorable = first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.

Practice Committee Number of Embryos Transferred. Fertil Steril 2009.

Embryo Cryopreservation

The last part of the embryo transfer procedure is the decision regarding any embryos that are not transferred. In general, these are the steps that are followed:

If you have your transfer on Day 3 and there are viable embryos left over, these will be extended in culture up to 3 more days. Embryos that become a well developed blastocyst will be frozen on Day 5 or Day 6.

If you have your transfer on Day 5, non-transferred blastocysts that are fully developed will be frozen on that same day. Any additional embryos that fully develop on Day 6 will be frozen on that day.

Beyond Day 6, all embryos that are not chosen for cryopreservation will be discarded. On this or the following day you should receive a call from our nursing department letting you know if any embryos have been frozen. If not, please call us the next day. If you have embryos that have remained in extended culture and you have not been given a status report on them within a week of your egg retrieval procedure, please call the IVF Nursing office so that we can report to you the final results.

Please note that if you have no embryos cryopreserved this does not determine that you will not become pregnant with this particular embryo transfer. For that you will need to stay on your medications and come for your planned pregnancy test.

Reference:

Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Guidelines on number of embryos transferred. *Fertility and Sterility* 2009; 92: 1518-1519.