IVF & ET

It's Not Just the Birds and Bees Anymore

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The high school biology teacher traditionally has been assigned the task of teaching human reproduction. The mechanics of the events in reproduction are relatively easy to understand and relate to students. Recent technological advances in cell culture and mechanical devices have changed all this. Doctors and scientists are now able to fertilize human ova outside the body (in vitro fertilization–IVF) and transfer them back into the mother (embryo transfer–ET). The resulting "test tube baby" phenomenon has prompted many biology teachers to search for current information about this new, interesting and exciting procedure.

The prcedures for IVF and ET in humans were developed in the late 1960s. The first successful full-term pregnancy and delivery was achieved in England with the birth of Louise Brown in the late 1970s. The procedure that brought about the conception of the world's first "test tube baby" consisted of five steps. In order of their occurrence, they are: (1) egg pick-up; (2) in vitro egg culture; (3) fertilization; (4) embryo growth and assessment; and, (5) embryo transfer.

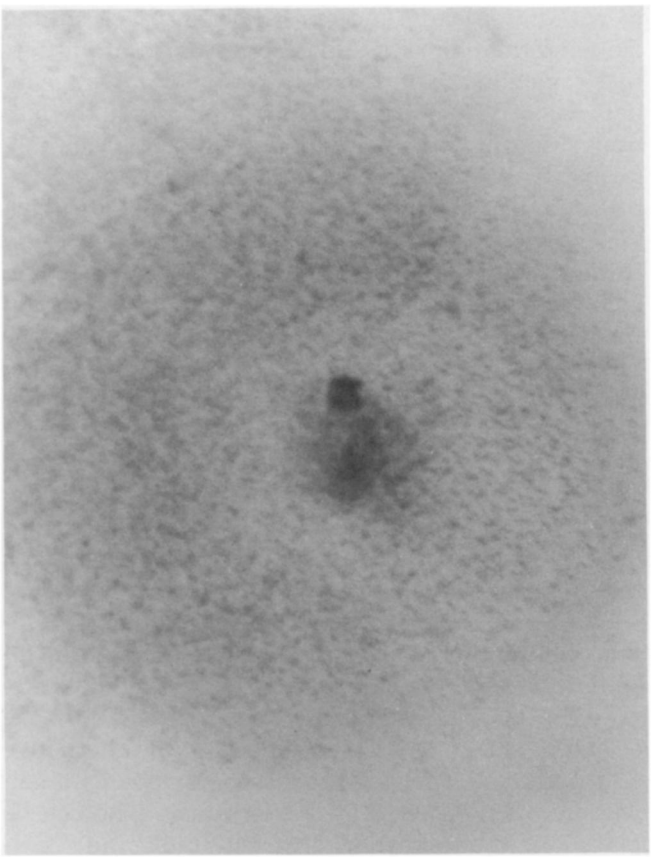
Egg Pick-Up

Egg pick-up can be accomplished by two different methods. The most widely used method, called a laparoscopy, involves the use of a fiber-optic viewing device called a laparoscope. This device contains a light source and a viewing ocular which enables the surgeon to view structures inside the body through a very small incision. A second method using a needle guided by ultrasound is still undergoing development and its usage is limited.

The laparoscopy is performed under general anesthesia. Normally three incisions are made into the abdominal cavity. The laparoscope is inserted through the uppermost incision and a pair of fine forceps is passed through the lowest incision. A Teflon-coated needle is inserted into a third incision made midway between the other two.

The surgeon is able to examine both ovaries with the laparoscope by manipulating them with the forcep. Once a ripe follicle is identified, the needle is passed through the wall of the follicle very slowly and carefully to avoid any possible damage to the egg or fluid leakage. After the needle has been inserted, the surgeon activates a vacuum-pressure device and aspirates the follicular fluid and the egg into a test tube. The egg itself is too small to be seen with the unaided eye, but it is usually covered with mucus and cells and will appear as a tiny white speck. The harvested egg is immediately examined by a trained specialist to determine if it has been damaged in any noticeable way.

If an egg is not recovered by aspirating the follicular fluid, the follicle can be flushed to try and dislodge the egg. Eggs obtained in this manner are less likely to be fully mature but they have been used successfully.



Photograph 1. Mature, preovulatory oocyte with fully expanded cumulus. (×240).

Once the egg has been collected, examined and found to be usable, it must be separated from the fluid and any blood clots that may have formed around it. When this is accomplished, the egg is ready for culture.

Egg Culture

The cleansed egg is placed into modified Ham's F10 medium that contains 7-10 percent fetal cord serum or maternal serum. The egg is then transferred to a suitable container with an appropriate amount of fluid and placed in an incubator that provides the egg with ideal temperature, humidity and CO concentration.

The egg is left undisturbed for 1-12 hours in order to reach a stage of maturation that would have occurred if the egg had been released naturally by the follicle.

Fertilization

The process of placing the sperm cells with the egg is known as insemination. About 50,000 of the most active, normal appearing sperm cells are placed in a test tube with the egg. The process of artificially placing a heavy concentration of sperm cells in close proximity to the egg makes it possible for fertilization by more than one sperm to take place. This would result in a fertilized egg that contains too many chromosomes and would not be viable. The number of sperm cells used for insemination has been reduced over the last few years from the original 500,000 to alleviate this potential problem. The test tube is returned to the incubator with the expectation that fertilization will take place.

Embryo Growth and Assessment

The physical growth and development of an IVF embryo is no different from that of a naturally-conceived embyro. The scientists that monitor the embryo use both the speed of its development and the physical appearance as an index of health. The cells that comprise the embryo should be regular in shape and about equal in size. For the embryo to be considered for ET, it should show rapid cell growth and no physical abnormalities. Embryos that have abnormal appearance or very slow growth are less likely to implant.

It is uncertain whether the embryo should be transferred at the 1, 2, 4, 8 or 16 cell stage. Pregnancies have developed when embryos consisting of only one cell were transferred. The sooner the embryo can be transferred, the less likely the chance that something will happen to it in the laboratory environment.

Photograph 2. Unfertilized oocyte with cumulus cells removed and sperm cells on surface of zona pellucida. (×700).

It is possible to transfer more than one embryo. In fact, up to four are routinely transferred. This increases the odds of having at least one embryo to implant. If more than one embryo implants and continues to develop, a multiple birth is possible. In the United States, because of moral and legal reasons, all fertilized, cleaving embryos are transferred to the donor's uterus.

It is possible to stop the development of the embryo by freezing it in liquid nitrogen. The embryo can later be thawed and transferred. This procedure is not generally accepted or practiced in the United States for human embryos. However, it is practiced very successfully in animal breeding programs.

Embryo Transfer

When the attending scientist determines that the embryo is at the proper stage of growth, the embryo and the patient are prepared for the transfer procedure. The transfer takes place in the operating room to minimize the risk of infection. The patient is not usually under any anesthesia but a tranquilizer may be given so that the patient is sufficiently relaxed for the procedure to proceed smoothly.

The preparation for the patient is simple. The doctor exposes the cervix and removes any excess fluid. The position and size of the uterus is evaluated in order to determine the best method of passing the catheter tube that will contain the embryo.

The embryo is brought to a room adjacent to the operating room. It is placed in a small drop of fluid and aspirated into a catheter tube about one millimeter in diameter. The embryo is now very vulnerable to a variety of conditions that could be detri-

mental. A sudden change in temperature, evaporation or physical damage could easily render the embryo nonviable. The transfer procedure must now occur as quickly as possible.

The scientist works with the doctor to pass the catheter tube through the cervix and a short distance into the uterus. This must be done very carefully to avoid any bleeding or stimulating any uterine activity. Either of these conditions could cause the transfer attempt to fail. The best catheter placement is not known for certain, but it is believed that the best location is where the Fallopian tube intersects the uterus. The location of this supposed best place is calculated by measuring the distance of the intersection from the cervix with the aid of ultrasound. The catheter is then inserted to this exact distance, assuring the best chance for success.

To deliver the embryo, the plunger of a small syringe attached to the end of the catheter is depressed. This expels the small amount of fluid containing the embryo into the uterus. The catheter is then withdrawn slowly to minimize the chance of making an artificial track in the uterine lining. A track might cause the embryo to move away from the site of deposition. Once the catheter is completely withdrawn, it is closely examined to assure that the embryo was indeed transferred.

This ends the intervention of science into the natural process of reproduction. The remaining nine months are no different than in any other pregnancy. The new individual formed by these advanced scientific methods is no different than if it had been conceived in the normal way.

One other aspect of this procedure is worth mentioning. The cost of the procedure is high. The cost for each attempt is about $5,000. The chance of achieving a full-term pregnancy is about 1 in 6.

As with any event that is covered by the national news media, IVF and ET will undoubtedly generate a great deal of interest and also a variety of questions from your students. We have already covered the technical aspects of the IVF procedure needed to answer their questions. But what about the clinical risks, ethical considerations, or legal problems that might interest your students? The remainder of this article will address such issues and provide you with relevant data to help answer questions that arise in your classroom discussion.

Clinical Risks

There are two main risks that the prospective mother faces in the IVF and ET procedures: (1) surgical complications and (2) an ectopic pregnancy (a pregnancy occuring outside the uterus). As of 1983, there has been only one patient experiencing surgical complications that were serious enough to be considered dangerous to the survival of the mother. This is an occurrence of only one in over 2,000 laparoscopies. This percentage is not unlike those experienced by patients undergoing laparoscopies for other purposes. The rate for ectopic pregnancy in the IVF & ET procedure is about 0.5 percent. This falls within the normal 0.3-3.0 percent range that occurs in natural pregnancies. It is clear from all the data available that the clinical risks of the IVF procedure are no greater than those for other surgical procedures.

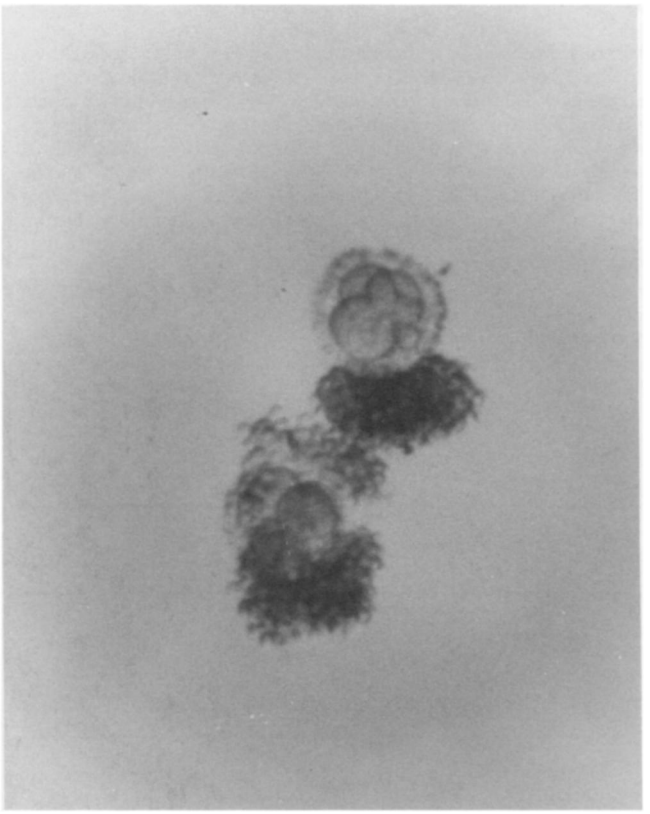
Since the embryo that is created in the IVF & ET procedure is subjected to a great deal of physical manipulation and handling, two main areas of concern arise: (1) the embryo may die of unknown causes or, (2) congenital abnormalities may be induced by the IVF & ET process. The death rate of IVF embryos may be higher than it is in natural pregnancy. This is because more than one embryo is harvested and fertilized in the IVF procedure and in the United States all fertilized embryos are placed back into the mother. Since the percentage of IVF & ET procedures that result in full-term pregnancies is still rather low, the percentage of embryos that die is quite high. Although the numbers seem to indicate that IVF loses a large number of embryos, nobody really knows how many are lost in natural pregnancies that last one month or less. With all the physical manipulations that the egg and sperm undergo in the IVF & ET procedure, it might seem likely that they are being damaged in some way. This does not seem to be the case. Although abnormalities of several IVF embryos have been reported, they do not seem to be related to the procedure or expressed in the resulting offspring. Out of about 125 IVF births, there has been only one serious abnormality evident in the child. This was a surgically corrected cardiac malformation. This does not mean that there will not be more defects expressed as the IVF children grow older.

All in all, there is no evidence to date to suggest that either the mothers or the children are at more risk than if they had been subjected to the natural reproductive cycle or a normal surgical procedure.

Ethical Considerations

The United States, Great Britian and Australia all have attempted to formulate policy regarding IVF and ET. A U.S. board, established in 1979, concluded that IVF and ET research is ethically acceptable providing that:

1. regulations regarding human subjects are complied with;
2. the purpose of the research relates primarily to safety and efficacy of IVF;
3. resulting embryos are not carried in the laboratory beyond the implantation stage;
4. the public is advised if the risk of producing abnormal offspring through IVF exceeds the



Photograph 3. Early cleavage stage human embryo (approximately 42 hours after insemination). (×240).

normal; and

5. all embryos that are transferred to the uterus are derived from married couples.

These recommendations were not changed by a new committee that began in 1980 and was terminated in 1983.

Although 25 states have laws that limit or forbid experimentation on a fetus and six seem to forbid the freezing of an embryo, Illinois is the only state that has undertaken the task of formulating its own policy specifically addressing IVF. The current law makes the doctor who undertakes the transfer the legal custodian of the embryo.

While the current research in the U. S. on IVF & ET conforms to the guidelines, the research in other countries may not. In September 1982, the Australians adopted guidelines that allowed for egg donations by a woman other than the intended mother. It also sanctioned research on the embryonic stages prior to implantation as long as the donors gave consent. The situation in England is similar. In November 1982, the British Medical Research Council sanctioned IVF research that is clinically relevant and involves no transfer of experimentally modified embryos for continued development *in vivo* with informed consent of the donors. They also allow the use of surplus embryos for experiments as long as they do not proceed beyond the implantation stage and are not stored frozen.

Legal Considerations

Most of the legal problems that arise in IVF research concern the status of the embryo. Is it a person? Does it have constitutional rights? In 1973, the first couple in the United States to attempt IVF had their embryo destroyed by a hospital supervisor who was afraid of the problems the research might cause the hospital. The couple sued the hospital and won $50,000. The courts did not believe the embryo to be a person possessing full legal rights. If it had, the doctor could have been charged with murder. If the courts had decided that the embryo was indeed a person and had full legal protection under the law, how many doctors and technicians would feel safe carrying a petri dish containing an embryo? If they accidently dropped the dish and caused the death of the embryo, they could be charged with murder.

What about embryos that no longer have parents? Such was the case of an Australian couple who had embryos frozen for a later transfer attempt. The couple unfortunately died before the transfer could take place. Should or could the embryos inherit the dead couple's estate? The court ruled that they could not.

The legal questions surrounding IVF & ET are very complicated and constantly changing. Some of the laws will probably have been changed by the time this article is published. It is virtually impossible to cover the full ramifications of the legal system on IVF research. This small amount of information should, however, alert you to the possible types of questions that your students might ask.

The information contained in this article should help you direct a meaningful classroom discussion on a very sensitive subject. This article has been assembled from the current research, articles and books. The field of IVF & ET is changing very rapidly, and for you as a teacher to keep abreast of all the new developments, it will require constant monitoring and updating.

Acknowledgement

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