Understanding the Medical Procedures and Terminology Surrounding Reproductive Technology

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Assisted reproductive technology (ART) has become one of the most exciting areas in medicine, providing opportunities for family building that have never before been possible and creating in its wake complex medical, legal, social, and ethical issues for both medicine and society (Seibel MM, et al., 1993). A seemingly endless array of techniques and procedures has been developed, each a slight variation of another. However, confusion often results because each technique is usually referred to by a descriptive acronym (Table 1.1). This chapter is intended to explain the various procedures performed in reproductive technology. Because the majority of procedures are based on either in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT), these two procedures will be described first.

IN VITRO FERTILIZATION (IVF)

In vitro fertilization involves the removal of one or more eggs, also called oocytes, from a woman's ovary just before ovulation. The egg is placed with sperm for 48–72 hours, during which time fertilization and division occur. The fertilized egg is then transferred into the woman's uterus using a thin catheter (Seibel MM, 1988).

There are several variations that can occur during an IVF cycle. The first has to do with whether or not medications are used to stimulate egg maturation. At the beginning of each menstrual cycle, approximately twenty or more eggs begin to mature. However, usually only one of those eggs is selected to ovulate. If the woman receives no medication during the first half of her IVF cycle, it is called a natural cycle, and only one mature egg can be anticipated from the retrieval. Success rates using one egg can rival those obtained in medicated cycles among women who are less than 35 years of age. With increasing age, however, results decrease. Natural cycles reduce the cost of the cycle by eliminating the need for medi-
ication. They also eliminate the risk of multiple births and the need for freezing "extra" fertilized eggs (Seibel MM, et al., 1995).

Medicated cycles use one or a combination of fertility drugs to increase the number of mature eggs available for retrieval (Seibel and Blackwell, 1994). The most commonly used drugs are human menopausal gonadotropins (HMG), which contain equal amounts of the pituitary hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and purified FSH, which is a purification of HMG. Both of these medications stimulate follicle growth. Many centers combine HMG and FSH with another type of medication called gonadotropin-releasing hormone (GnRH) agonists. The GnRH agonists help to control the rate of follicle development and prevent the woman from ovulating on her own.

Whether or not medications are used to stimulate follicle growth, a final injection of human chorionic gonadotropin (HCG) is given to complete the final stages of egg maturation and to time ovulation. The egg retrieval is usually performed approximately 34 hours after the HCG injection, a few hours before the egg would be released. The egg retrieval can be performed either by laparoscopy (Figure 1.1) or by ultrasound-guided retrieval. Because ultrasound retrievals can be performed under local anesthesia with mild sedation, they are generally the method of choice. Variations of ultrasound retrieval include transabdominal-transvesicle, transurethral-transvesicle (Figure 1.2), and transvaginal (Figure 1.3). The names describe the path the needle takes to reach the follicle; through the abdominal wall and bladder, through the urethra and bladder, and through the back wall of the vagina.

Once the egg is retrieved, the next step is fertilization. This occurs by preparing the sperm
and placing them together with the egg, usually in a petri dish within an incubator. Alternatively, the sperm and egg (gametes) may be placed into a 3-mL culture tube with a screw cap, covered in a protective plastic sheath, and inserted into the vagina like a suppository (Figure 1.4). This is called intravaginal culture (IVC) (Ranoux C, Seibel MM, 1989). Two days later, the culture tube is removed from the vagina, and the eggs are examined.

As with eggs fertilized in a petri dish, eggs that are fertilized intravaginally are placed in a thin catheter and transferred into the uterus. The embryo transfer (ET) is usually performed through the cervix (Figure 1.5). If the cervix is narrow or twisted, making embryo transfer difficult, a transuterine transfer (TUT) can be performed by placing a needle through the vagina and anterior wall of the uterus directly into the uterine lining (endometrium) and passing the catheter through the needle directly into the endometrium, bypassing the difficult cervix. If the fertilized egg implants, pregnancy follows as it would normally.

**GAMETE INTRAFALLOPIAN TRANSFER (GIFT)**

Both sperm and eggs are called gametes. Under natural conditions the ovulated egg is released into the fallopian tube. Following intercourse, the sperm begin reaching the fallopian tube within minutes, and if the egg is present, fertilization occurs. The fertilized egg then migrates to the uterus, where it implants and grows.

The GIFT procedure attempts to mimic this natural event by removing the egg from the ovary just before ovulation and placing it together with sperm into the fallopian tube, where it is hoped that fertilization will occur (Figure 1.6). In contrast to IVF, the GIFT procedure requires that there be at least one patent fallopian tube. In addition, if pregnancy does not occur, it is impossible to determine whether or not the sperm and egg fertilized.

As with IVF, there are several variations of GIFT. Although some centers do perform ultrasound-guided oocyte retrieval for GIFT followed by transcervical tubal cannulation and...
FIGURE 1.3. Ultrasound-Guided Oocyte Retrieval (Transvaginal Approach). The needle can be seen entering a follicle between the two parallel biopsy guide lines. (a) Schematic drawing; (b) Ultrasound view.
intratubal transfer of gametes (Jansen R, et al., 1988), the majority of centers continue to perform GIFT via laparoscopy because the catheter is difficult to see by ultrasound, making the procedure technically difficult. As a result, GIFT success rates using ultrasound guidance are generally lower.

Pronuclear Stage Tubal Transfer (PROST), Tubal Embryo Transfer (TET), and Zygote Intrafallopian Transfer (ZIFT)

PROST, TET, and ZIFT are all variations of GIFT that differ in one major respect. Instead of transferring sperm and an unfertilized egg into the fallopian tube, the three procedures above describe the transfer of a fertilized egg (Figure 1.7a, b). Therefore PROST, TET, and ZIFT all require IVF to be performed initially to achieve fertilization, followed in one or two days by a laparoscopy to transfer the fertilized eggs into the patient's fallopian tube.

Gamete Uterine Transfer (GUT)

Gamete uterine transfer is a simplified version of GIFT. The major difference between GUT and GIFT is that the unfertilized egg and sperm are placed into the uterus, not the fallopian tube (Figure 1.8). Therefore patent fallopian tubes are not required. Its main advantage is that the entire procedure can be performed by ultrasound, and laparoscopy is unnecessary. Following an ultrasound-guided egg retrieval, the previously collected and washed sperm are placed in a catheter and transferred directly into the uterine cavity. The procedure eliminates the need for incubation and subsequent transfer and therefore also eliminates most of the religious and personal objections to IVF.

Peritoneal Ovum and Sperm Transfer (POST)

Peritoneal ovum and sperm transfer is another variation of GIFT. The major difference between these two procedures is that the unfertilized egg and sperm are transferred via catheter through a needle into the patient's cul de sac using transvaginal ultrasound (Figure 1.9). In contrast to the GUT procedure, the patient must have normal fallopian tubes. As with GUT, the procedure does eliminate the need for laparoscopy, incubation, and subsequent transfer.

ARTIFICIAL INSEMINATION (AI)

Artificial insemination is the mechanical placement of sperm into the woman's repro-
ductive tract. If the husband’s sperm is used, the procedure is called homologous artificial insemination (AIH). If donor sperm is used, the procedure is called therapeutic donor insemination (TDI) (Loy RA, Seibel MM, 1990). To prevent confusion with the disease AIDS, the abbreviation AID is no longer used for artificial insemination with donor sperm. TDI is used when the man has too few sperm to achieve pregnancy or when he possesses an inherited condition that he does not wish to pass on to his children. In rare cases, TDI is used when the woman is Rh negative, the man is Rh positive, and the woman has become sensitized to a prior Rh positive baby, making the risk to a future Rh positive baby unacceptably high.

Several common insemination methods are performed with a catheter, and their names are usually descriptive of where the sperm are placed (Figure 1.10). Intracervical insemination (ICI) involves placement of the sperm in the upper vagina and lower cervix; intruterine insemination (IUI) involves washing the sperm and placing it into the uterus; and the least common procedure, transuterine intrafallopian tube insemination (TIFI), involves washing the sperm and placing it through the cervix into the fallopian tube (Figure 1.11).

Additional variations require a needle and include direct intraperitoneal insemination (DIFI), in which the washed sperm are placed into a catheter and threaded through a needle into the cul de sac after transvaginal egg retrieval (Figure 1.12), and direct intrafollicular insemination (DIFI), in which the transvaginal ultrasound is used to place sperm directly into
FIGURE 1.6. Schematic Drawing of Gamete Intrafallopian Transfer Illustrating (a) the Oocyte Retrieval and (b) the Gamete Transfer.
FIGURE 1.7a. A Fertilized Egg at the Pronuclear Stage. The two spheres are the male and female pronuclei.

FIGURE 1.7b. Illustration of Four Fertilized Eggs at Various Stages of Division.
FIGURE 1.8. Gamete Uterine Transfer (GUT).

FIGURE 1.9. Peritoneal Ovum and Sperm Transfer (POST).
the follicle without ever performing an egg retrieval. All methods of artificial insemination assume that the woman's fallopian tubes are patent and preferably normal.

ASSISTED FERTILIZATION

Assisted fertilization (also called micromanipulation) refers to a group of three procedures designed to aid the sperm in entering the egg (Van Steirteghem AC, et al., 1993). The first is zona drilling, in which a small hole is "drilled" in the zona pellucida or shell of the egg to allow the sperm easier access. This technique allows the sperm to be selected naturally. The second technique is called subzonal insemination (SUZI). In this procedure, approximately five sperm are selected and injected beneath the zona with the hope that one will achieve fertilization. The third procedure is called intracytoplasmic single sperm injection (ICSI) and involves the selection and placement of a single sperm directly into the egg. The ICSI procedure does prevent more than one sperm from entering the egg, but selecting which sperm to use and loading it into a micropipette are technically quite difficult. All of these procedures are performed when fertilization is poor or fails, with the hope that even a low sperm count will result in pregnancy (Figure 1.13). These procedures are no longer considered experimental, but genetic counseling is encouraged for couples choosing these techniques. Micromanipulation offers an alternative treatment to TDI for some couples.

Another micromanipulation technique is called assisted hatching. This procedure as-
SUMERS that for some couples, pregnancy does not occur because the zona is too thick for the embryo to break through and implantation is prevented. By creating an artificial break in the zona before transferring the fertilized egg into the uterus, some believe that implantation is aided (Zilberstein M, Selbel MM, 1994).

**SURROGATE**

A surrogate is a woman who is artificially inseminated with the sperm of a man who is not her husband. The surrogate carries the pregnancy, then turns the child over to the man after the delivery; his wife then adopts the child. Surrogates are usually needed only when a woman has had both of her ovaries and her uterus removed. A surrogate could be a friend, a relative, or a stranger identified for the sole purpose of becoming impregnated and carrying a pregnancy. Because the surrogate bears a child that is genetically half hers, this procedure incorporates many social, legal, and ethical issues. Both clear legal and psychological advice should be obtained in advance.

**GESTATIONAL CARRIERS**

A gestational carrier is a woman who carries another couple's child. In contrast to a surrogate, the gestational carrier does not use her own egg. In vitro fertilization is performed on the infertile couple, and the embryo is transferred into the gestational carrier. After the child is born, the gestational carrier turns the child over to the couple. The most common reason women need a gestational carrier is
that they have had their uterus removed but still have at least one working ovary. Alternatively, a woman may have a uterine condition that prevents her from carrying a pregnancy to term or a medical condition that would make pregnancy an undue risk. As with surrogates, a gestational carrier could be a friend, a relative, or a stranger identified for the sole reason of carrying a pregnancy that is not genetically her own. Clear legal and psychological advice should be sought in advance.

**EGG DONOR**

An egg donor is a woman who has an egg retrieval performed and allows her eggs to be used by another woman (a recipient) so that
the recipient can become pregnant. The donor's eggs are fertilized with the sperm of the recipient's husband. The recipient's uterine lining is hormonally prepared and synchronized with the donor's cycle, and the resulting embryo is transferred into the recipient, who carries the pregnancy. For egg donation to work, the recipient must have a uterus but does not need ovaries. The usual indications are premature menopause (before age 40) and genetic diseases the woman does not want inherited by her children. More recently, an increasing number of women nearing the end of their reproductive years (perimenopausal) or even in natural menopause are seeking egg donation (see Chapter 12).

Donors are usually divided into two categories: anonymous and known. However, I have listed three types of egg donors to reflect current trends: unknown, known, and well-known. Unknown or anonymous donors are women who never meet the recipient. Well-known donors are close friends or relatives who have known the recipient for a long time. Known donors—or, perhaps more appropriately, identified donors—are strangers who are found by the recipient for the sole purpose of providing eggs. They are not anonymous but have no preexisting relationship with the recipient. As with surrogacy and gestational carriers, legal and psychological support should be sought.

Patients requiring egg donation and who have ovarian failure (are menopausal) may initiate a cycle at any time using the protocol in Table 1.2. Patients receiving oocyte donation for purposes other than ovarian failure, or who have any remaining suggestion of ovarian function (occasional menses, etc.) should apply the protocol as follows. The recipient is asked to maintain a basal body temperature chart (BBT). On day 21 of the recipient's cycle, look for a BBT rise of at least 4 days and obtain a serum progesterone level. If ovulation is deemed to have occurred by either a sustained

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<th>TABLE 1.2. Cycle Initiation Protocol</th>
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<td><strong>Cycle Medication</strong></td>
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<td>1. Estradiol</td>
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*Day 6 is the day the donor begins gonadotropin treatment or the day before clomiphene citrate is initiated in partially medicated cycles.
**Day 14 is the day HCG is administered to the donor.

BBT rise or a progesterone value above 4 ng/ml, the recipient is given 3.75 mg of depo-lupron intramuscularly.

Once ovarian down-regulation has been documented by a serum estradiol value of less than 50 pg/ml and by a vaginal ultrasound examination demonstrating no significant ovarian cyst development, the replacement protocol is initiated as outlined for patients without ovarian function (see Table 1.2). The recipient must be down-regulated before the donor starts her ovarian stimulation. Either a fully medicated cycle using lupron and gonadotropins or a partially medicated cycle using clomiphene citrate (Seibel MM, 1995) may be employed.

Serum E2 levels may be determined on days 11 and 21 and serum progesterone on day 21 of the recipient cycle. No ultrasound is needed in the recipient, although ultrasound verification of endometrial thickness may be helpful in certain circumstances. Blood for serum progesterone should ideally be drawn 6 hours after progesterone injection.

In the event that initiation of the donor's cycle is delayed, the recipient should receive depo-lupron 3.75 mg for a second dose 21 to 28 days after the first dose. It should be possible to get the patient through her monitored cycle and into her replacement cycle by use of
two injections of depo-lupron. If the donor is close to beginning her gonadotropins (or clomiphene) and it is nearly time for another depo-lupron injection, the recipient should be switched to daily subcutaneous injections of 0.5 mg lupron which is continued until the donor receives HCG.

If egg donation is carried out in conjunction with a GIFT cycle, the protocol is the same as for an IVF cycle except that a progesterone dosage of 50 mg/day is administered on the day of the GIFT procedure and continued for 3 days. The progesterone dosage is increased to 100 mg/day on the fourth day following the GIFT procedure, and continued until pregnancy is established.

If the recipient becomes pregnant, progesterone in oil 100 mg/day is continued at 9:00 a.m., and one 400 mg progesterone vaginal suppository is administered at 9 p.m. daily, and the Estrace dosage is reduced to 2 mg daily. Treatment is discontinued 14 weeks following embryo transfer.

CONCLUSION

This chapter has defined the major procedures in assisted reproductive technology. I hope it will provide the reader with a better understanding of the chapters that follow. In addition, Appendixes 1-A through 1-J provide several short articles and letters to further clarify some of the major issues surrounding gamete donation.

REFERENCES