chapter 7

Treatment of Infertility

CONTENTS

Box

Figures

Chapter 7

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Sophisticated new technologies, such as in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT), have recently been developed for the treatment of infertility. In addition to these new reproductive technologies, great progress has been made in the treatment of infertility with traditional medical and surgical approaches, such as drug therapy and reproductive-tract microsurgery and laser surgery. Although noncoital reproductive technologies have received much attention, the more traditional approaches currently account for the overwhelming majority of infertility treatments.

MEDICAL TREATMENTS

In this section, all nonsurgical procedures and practices are considered medical treatments. Artificial insemination and cryopreservation are considered separately.

Female Infertility

Medical treatments for female infertility administered by a health care provider can range from advice that assists a couple in pinpointing the time of ovulation to complex regimens of fertility drugs.

As described in chapter 6, the initial patient history and physical examination are important tools in identifying possible infertility problems or suspected factors contributing to it. Evaluating and maintaining good general health and nutrition can contribute significantly to reproductive function, Yet even in the case of robust general and psychological health, a fully functioning reproductive system may be lacking. As is true with all diagnostic procedures, infertility treatments can be a source of considerable anxiety about pain and outcome; the psychological well-being of the couple is a principal factor to consider during treatment (see box 7-A).

Ovulation Induction

Female infertility is often related to problems with the complex biological events surrounding ovulation. Disorders of ovulation include conditions such as amenorrhea (absence of menstruation), Oligomenorrhea (scanty or infrequent menstruation, usually cycles longer than 35 days), or luteal phase defects (LPD) (failure of the endometrial lining of the uterus to develop properly after ovulation). The complete absence or irregularity of the menstrual cycle is the most obvious indicator of ovulatory dysfunction. In this case, further testing is needed to determine the exact site of the ovulatory problem—hypothalamus, pituitary, ovary, or elsewhere. Only when the origin of the dysfunction has been identified can appropriate treatment be administered.

It is not unusual, however, even in the presence of apparently normal and regular menstrual periods, for there to be underlying ovulatory failure, Ovulatory dysfunction without menstrual irregularity becomes apparent only after examination of basal body temperature (BBT) charts, serum progesterone levels, and endometrial biopsies. Although a number of therapeutic agents treat ovulatory dysfunction, the most commonly used are compounds known as fertility drugs. These include clomiphene citrate, human gonadotropins (human menopausal gonadotropin, follicle-stimulating hormone, human chorionic gonadotropin), gonadotropin releasing hormone, bromocriptine, glucocorticoids, and progesterone. The etiology of the dysfunction determines which treatment to use.

Clomiphene Citrate.—The most commonly prescribed fertility drug is clomiphene citrate ***(CC).*** Clomiphene is a nonsteroidal estrogen-like compound that binds to estrogen receptors in the body. Although its mode of action in inducing ovulation remains unclear, it most likely blocks the actions of the natural estrogens in the hypothalamus (36).

Box 7-A.—Psychological Effects of Undergoing Treatment

The emotional effects of medical and surgical treatments for infertility are often a problem, particularly for women. Clomiphene citrate, for example, may prolong the menstrual cycle and thus falsely increase the hope of a pregnancy. Other drugs cause weight gain, nausea, acne, hot flashes, and mood swings.

Some fertility drugs create a risk of multiple conceptions. Although many couples welcome twins after a period of infertility, the increased risk of miscarriage, birth defects, low birth weight, and complications during delivery are worrisome, and some couples hesitate at the thought of raising several children at once.

Many people find themselves nervous about surgery, fearing both the procedure and their future efforts to achieve pregnancy once the procedure is over. Those who take time away from work for surgery and recovery will need to decide whom to tell and how much to tell about the reason for the surgery, and how to manage lost income as well as expenses not covered by insurance.

A couple using artificial insemination must adjust to achieving pregnancy noncoitally. The clinical atmosphere surrounding the insemination can be unsettling, and the man must produce a semen specimen while the woman waits. It is not uncommon for the male to be temporarily impotent. The woman is often concerned that she may not be ovulating on the day of the insemination, despite efforts to use home ovulation test kits accurately. Since about 50 percent of infertility clinics do not do inseminations on weekends, some couples feel frustrated that they have missed a potential insemination because of the rigidity of the clinic's schedule.

Couples using IVF must accept its relatively low success rate and high cost; tolerate the medication prescribed for the woman; be able to travel to the clinic; bear the expense of lost work time, travel, and hotel stays; endure the anxiety of waiting to see whether fertilization occurs; and wait two anxious weeks to see if pregnancy ensues.

Some couples using artificial insemination by donor are put off by the thought of the woman carrying another man's baby. Together, they must decide whether they will tell others about the insemination. They may wonder whether their love for a child conceived with donor sperm will be any different than that for a child conceived in traditional fashion.

Couples hiring surrogate mothers are still so few that little has been written about their experiences. Nevertheless, all the problems experienced with artificial insemination by donor are likely to be present in analogous form. In addition, during the 9 months of pregnancy the couple will probably worry about whether the baby will ever really be turned over to them. Even if this happens, they may well worry whether complications will arise later, should the baby's biological mother ever regret her participation.

Infertile couples may also have difficulty making major decisions or changes in their lives. Job changes may not take place because the medical insurance is needed or a pregnancy is expected at any time. A new house may not be bought or a vacation may be skipped because of the expense and uncertainty of infertility. A couple's life can become controlled by infertility treatment.

SOURCE: Office of Technology Assessment, 1988

It may also affect the function of the pituitary and ovaries **(35,66,75).** The end result 'is increased gonadotropin secretion and stimulation of the ovary. Clomiphene's use is primarily indicated for patients with oligomenorrhea caused by mild dysfunction of the hypothalamus or pituitary or by other conditions (66). To induce ovulation, this drug is usually given on the fifth day after the onset of menses and continued through day nine. With this regimen, ovulation is expected between days 14 to 18 of the cycle.

Gonadotropin.—In more severe cases of ovulatory dysfunction resulting from pituitary or hypothalamic shutdown, human gonadotropins can be administered to stimulate the ovary directly (36). This can be accomplished with either human menopausal gonadotropin (hMG) or human follicle-stimulating hormone (hFSH). These potent stimulators of ovarian function are extracted from the urine of menopausal women. They are usually used if an individual fails to respond to clomiphene citrate or other compounds.

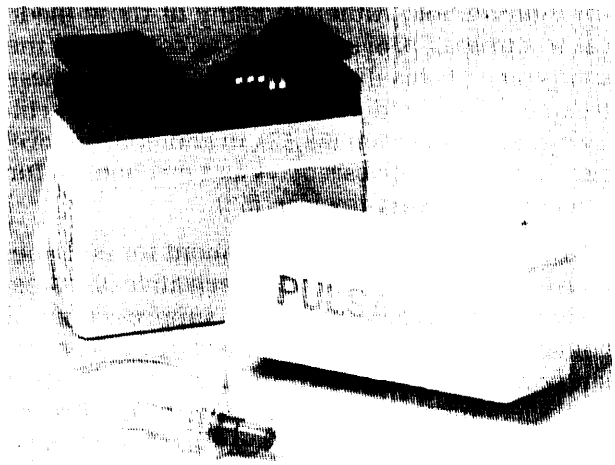
Administration regimens for gonadotropins can vary considerably depending on the nature of the ovulatory dysfunction, the other medications being given concurrently, and the preference of the individual clinician. Because these hormones bypass the endogenous gonadotropin control system and act directly on the ovary, careful monitoring of their potent effects on the ovary must accompany their administration. This is accomplished by daily measurements of the amount of estrogen produced by the ovary under the influence of these compounds, and by monitoring the growth of ovarian follicles with ultrasound (52). As the ovarian follicles containing the ova (eggs) develop under the influence of these two hormones, ultrasound (and estrogen measurement) allows the physician to determine if the follicles are large and mature enough for ova release.

The actual release of the ovum is brought about by injection of an additional hormone, human chorionic gonadotropin (hCG), which is similar to luteinizing hormone (LH). The high hCG levels resulting from the injection mimic the actions of the natural LH ovulatory surge, causing rupture of the follicle and release of the ovum.

Gonadotropin Releasing Hormone.—In cases of severe hypothalamic dysfunction with intact pituitary and ovarian function, induction of ovulation with gonadotropin releasing hormone (Gn-RH) has been successful (76). Gn-RH is the hormone released from the hypothalamus that in turn causes the secretion of gonadotropins from the pituitary gland. In cases of hypothalamic dysfunction, Gn-RH release is impaired or absent. With the ***use of a*** portable infusion pump, Gn-RH can be administered in such a way that it mimics the natural release pattern (see figure 7-1), This promotes secretion of gonadotropins from the pituitary, follicle development, and subsequent natural ovulation. Although officially only available for ovulation induction in clinical trials at present, this approach of mimicking endogenous hormone patterns may become more widely used upon approval by the Food and Drug Administration.

Bromocriptine. –Bromocriptine is commonly used in cases of infertility associated with oversecretion of prolactin. Prolactin, a hormone responsible for normal milk production, can also disrupt regular ovulatory function. In women with hyperprolactinemia (high levels of prolactin, often caused by a hormone secreting tumor) or transient elevations of prolactin, daily administration of bromocriptine can lower blood prolactin levels. Bromocriptine is a synthetic compound that interferes with the pituitary's ability to secrete prolactin. Ovulation usual]y returns after 6 to 12 weeks of daily treatment (66).

Figure 7.1 .—Portable Infusion Pump



Infusion pump is worn continuously and delivers gonadotropin releasing hormone intermittently either subcutaneously or intravenously.

SOURCE: Ferring Laboratories, Inc., Suffern, NY, 1988

Glucocorticoids. -Ovulatory dysfunction is often present in patients with adrenal disorders. Treatment of the adrenal condition with synthetic glucocorticoids (one class of hormones naturally produced by the adrenal glands) alone or in combination with other drugs can result in resumption of ovulatory cycles (17). This treatment can also be effective for the amenorrhea associated with polycystic ovaries (24).

Progesterone.—Luteal phase defect can also be treated with drugs, depending on the etiology, Treatment with progesterone, the hormone normally secreted in large quantities by the ovary after ovulation, can be an effective treatment for this condition (47).

Other Drug Therapies

Endometriosis can be treated with a variety of pharmaceutical agents. Even in severe cases, drug

therapy is usually recommended prior to surgical intervention. Although many of these medical treatments prove effective in combating the symptoms of this disorder, the efficacy of these treatments for endometriosis-associated infertility remains uncertain (33,53). In addition, the precise role endometriosis plays as a mechanism for infertility remains unclear (53).

The most popular drug treatment for endometriosis is danazol, a synthetic derivative of testosterone. This compound acts to suppress normal gonadotropin secretion and thereby cyclic ovarian hormone production, and has a direct effect on the endometrium (5). The end result of these multiple actions is to produce a hormonal state, similar to that of chronic anovulation, that causes regression of endometriosis tissues (25). Danazol taken daily for periods of 4 to 6 months or longer is the usual course of treatment. After this time, evidence of endometriosis is often reassessed by laparoscopy.

Other drug therapies include progestogens, estrogens, Gn-RH blockers, or combinations of these compounds.

Uterine and Cervical Infections

Infections of the male and female reproductive tract have been increasingly recognized as a major contributory factor of infertility. Although infectious organisms such as gonorrhea have long been associated with severe reproductive tract disorders, micro-organisms such as chlamydia and mycoplasma are now also associated with reproductive-tract infections that lead to infertility. These infections are associated with pelvic inflammatory disease and cervical or uterine factors in infertility.

Treatment of chlamydia, gonorrhea, and mycoplasma is usually accomplished with a 7- to 10-day regimen of antibiotics such as tetracycline, erythromycin, or doxycycline. Adequacy of treatment must be verified by followup laboratory cultures 3 to 6 weeks after treatment (59).

Immunological Disorders

The role of antibodies to sperm and semen in the etiology of infertility has received increased attention. A number of studies have shown an increased incidence of sperm antibodies in both the male and female partners of infertile couples compared with normal fertile couples (60). These antibodies are most likely responsible for abnormal sperm and cervical mucus interactions that inhibit or prevent fertilization from taking place.

A number of treatments for this condition have been used. When the antibodies to the sperm appear in the female partner only, condom therapy may be beneficial. Use of condoms for 6 months has been reported to reduce the quantity of sperm antibodies in the female (31), This may lead to normal sperm-mucus interaction when use of a condom is discontinued during subsequent fertile periods. However, this practice is no longer widely used. Glucocorticoid therapy is also effective in

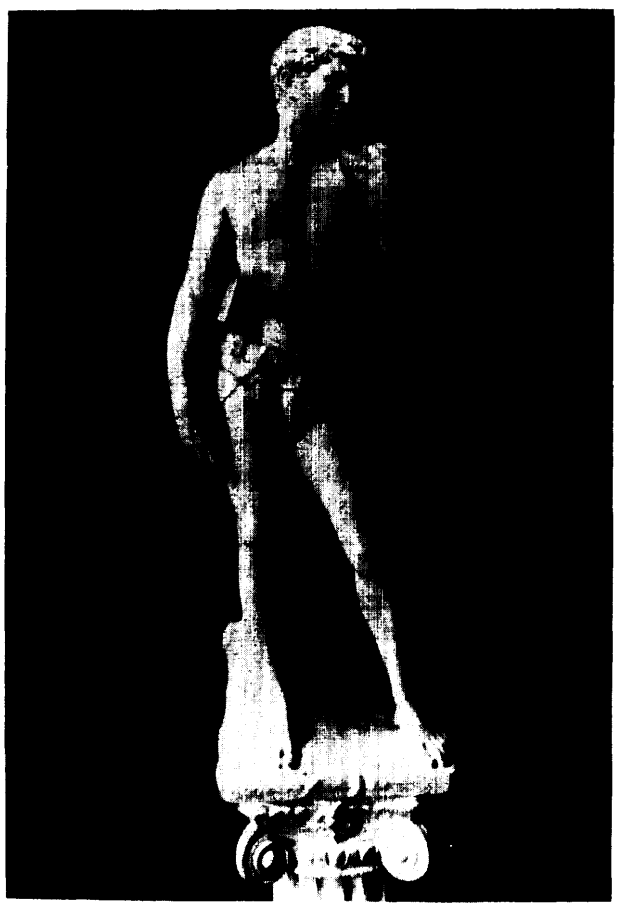


Photo credit: ***Repro-Med*** *Systems, Inc., Middletown, NY*

Water-cooled scrotal jacket.

suppressing the production of these antibodies in both the male and female. It has been reported that once antibody levels have been reduced, pregnancy rates increase (37). In addition to the above procedures, which act to reduce the production of sperm antibodies, intrauterine insemination with the husband's washed sperm, donor insemination, IVF, or gamete intrafallopian transfer may be appropriate.

Sexual Dysfunction

Several sexual dysfunction conditions are associated with infertility in the female. The most common is vaginismus, a condition in which penile entry into the vagina is impossible or extremely difficult because of an involuntary contraction of the muscles around the outer third of the vagina. This condition can be caused by past sexual assault, previous traumatic pelvic examinations, anxiety, painful intercourse due to chronic vaginitis or lubrication disorders, or other psychological and organic problems. If an organic cause can be treated or ruled out, and the condition continues, then treatment for this disorder usually entails simple, passive dilatation of the vagina with associated desensitization techniques. This treatment is effective in nearly all patients, allowing normal intercourse to commence or resume (23).

Male Infertility

Medical treatment for male infertility is not as extensive as treatment for female infertility. Although a number of characteristics of semen and sperm can be assessed by semen analysis, the treatment of abnormalities remains elusive.

Environmental Factors

Environmental factors appear to be closely associated with some forms of male infertility. Excessive heat to the testes and exposure to toxic chemicals (e.g., in the workplace) have been associated with reduced sperm production and viability (72). Routine cooling of the scrotum, as with a water-cooled scrotal jacket, may increase sperm quality (78).

Hormone Therapy

Hormone therapy in male infertility is most beneficial in cases of gonadotropin deficiency. Human menopausal gonadotropin administered in combination with human chorionic gonadotropin for periods of up to 6 months can be an effective treatment for some types of azoospermia. Clomiphene citrate and tamoxifen can stimulate natural gonadotropin secretion, thereby increasing stimulation of the testes and subsequent spermatogenesis. Long-term treatment with gonadotropin releasing hormone delivered by portable infusion pumps has been reported to induce spermatogenesis in patients with hypothalamic deficiencies (73).

Testolactone, a drug that reduces the production of estrogen, has also been used for treatment of male infertility, although its efficacy in such treatment has been challenged (14). Numerous other kinds of drugs have been administered in cases of male infertility, including testosterone (low and high doses), corticosteroids, triiodothyronine, kinin-releasing agents, anti-prostaglandins, and vitamins C and E (45). Overall, the efficacy of drug and hormonal therapy in the majority of male infertility patients remains unclear.

Reproductive Tract Infections

Although infections of the reproductive tract are less common in the male than in the female, a patient's semen should be cultured in the laboratory to screen for the presence of a wide range of micro~organisms. Infections such as gonorrhea, chlamydia, mycoplasma, and others can be treated with appropriate antibiotics, depending on the patient's medication sensitivity. Prostatitis (inflammation of the prostate gland) can also be treated with antibiotic regimens for periods as long as several months.

Sexual Dysfunction

Sexual dysfunction as a contributing factor of infertility may be present in as many as 5 percent of infertile couples (56). Male patients with organic impotence may respond to hormone therapy, surgery to restore blood flow to the penis, or drug therapy that directly induces erections. In addition, erection and ejaculation may be induced by electrical or vibratory stimulation such as used

76-580 - 88 - 5 : QL 3

in spinal cord injury patients (see box 1O-A in ch. 10). Psychogenic impotence and premature ejaculation can be treated successfully with psychotherapy and behavior modification. Retrograde ejaculation can be treated with drugs or surgery depending on the etiology of the condition.

SURGICAL TREATMENTS

Female Infertility

Many different surgical procedures are used in the treatment of various disorders of the female reproductive tract. Only the procedures most commonly and widely used in the treatment of infertility are discussed here. These procedures can be roughly divided into two categories, traditional surgery (macrosurgical) and microsurgery. Traditional reproductive surgery techniques usually refer to surgery on large, easily visualized structures; microsurgical techniques entail fine, delicate surgical procedures performed with the aid of a microscope or other magnifying apparatus. Although some conditions may indicate the use of one approach over the other, there is often overlap between these approaches for any given treatment.

All these procedures are performed under general anesthetic and, with the exception of the use of the laparoscope, involve laparotomy. Laparotomy involves a larger incision in the abdominal wall than laparoscopy, to allow direct visualization of the reproductive structures.

Traditional Surgery

Infection, previous surgery, peritonitis, and pregnancy complications can all lead to adhesions, occlusion, and scarring of the female reproductive tract.

Adhesions are abnormal fibrous connections made between structures of the female reproductive tract that are not otherwise joined. These often occur in the ovary or fallopian tubes after inflammation or damage. This condition can impair fertility by severely restricting the movement of the fallopian tubes, thereby hindering ovum pickup from the ovary and transport toward the uterus. Removal of adhesions (adhesiolysis) is accomplished by electrocautery devices, dissection, or lasers, In the case of lasers, this maybe accomplished via the laparoscope, although this approach is not common. Once adhesions are removed, tubal and ovarian motility can be greatly improved (64).

Pelvic inflammatory disease can often lead to a narrowing or occlusion of the distal end (closest to the ovary) of a fallopian tube—the ampulla and fimbria. A salpingostomy attempts to recreate the normal fallopian tube opening and fimbria function when complete occlusion has occurred. A fimbrioplasty corrects partial restriction, occlusions, or adhesions of the finger-like appendages of the fimbria so that normal movement can resume. These procedures are usually performed without magnification, although the microsurgical approach is likely to improve success. In addition, the carbon dioxide laser may be of some use in these procedures (46,62).

A surgical approach may also be warranted in cases of endometriosis that either do not respond to drugs or are severe. Endometrial tissue (implants) throughout the abdominal cavity can be removed by excision or cauterization. Recent attempts have employed the laser to vaporize implants. Again, as with distal tubal surgery, microsurgical techniques may greatly improve removal of endometrial tissue that may otherwise go undetected (53).

Microsurgery

The development of new and better microsurgical techniques in recent years has greatly improved the success of tubal surgery. The most common tubal microsurgical procedures involve excision and repair of scarring or damage at various points along the fallopian tubes. This is critical to ensure proper ovum transport down the fallopian tubes and passage of sperm in the opposite direction,

Scarring to the inside of the fallopian tube is most difficult to treat successfully since this condition usually involves not only narrowing or occlusion of the tube but also damage to the mil-

lions of cilia lining the tract. Extensive damage to these cilia, which help propel the ovum toward the uterus, severely impairs ovum transport.

With the aid of a microscope, fine surgical instruments, and much practice, a skilled microsurgeon can locate and excise the damaged portion of the tube. The two ends of the tubes are cleared of any material and then the inside of the tube (lumen) is rejoined and sutured together. Special care must be taken for proper alignment of the ends of the tube. Using this basic approach, various sections of the fallopian tubes can be repaired. Because the diameter of the tubes varies at different locations, however, removal of large lengths can make joining a larger diameter section to a much smaller diameter section technically difficult. In addition, depending on the extent and location of damage or scarring, the difficulty and success rate varies. Overall, the greater the length of fallopian tube left, the higher the rate of success at attaining pregnancy (63).

Success rates for these procedures depend largely on the skill and training of the individual surgeons. The overall success rate for this treatment of infertility should continue to improve as more surgeons become proficient at reproductive microsurgical techniques.

In Vitro Fertilization

In vitro fertilization is a highly sophisticated infertility treatment that involves obtaining mature oocytes through surgical procedures such as laparoscopy or through nonsurgical procedures such as ultrasound-guided oocyte retrieval. These mature oocytes are produced by natural ovulatory cycles, or, more commonly, by ovulation induction with fertility drugs such as clomiphene citrate, human menopausal gonadotropin, gonadotropin releasing hormone, and others.

Protocols for ovulation induction vary among IVF practitioners. Development of follicles under the influence of fertility drug stimulation is usually monitored by ultrasound imagery (see figure 7-2) and blood estrogen levels. Eggs are collected by aspiration of the fluid inside the follicles via laparoscopy or nonsurgically with ultrasound-guided aspiration techniques. Once the oocytes are collected, their maturity is assessed microscopically, and fertilization of mature eggs is attempted with washed sperm. If available, at least 50,000 motile sperm per oocyte are added to the culture dish to achieve fertilization. The sperm and oocytes are incubated for about 18 hours. Oocytes are then examined to see if fertilization has occurred (evidenced by the presence of pronuclei). The fertilized oocytes then cleave, usually within 35 hours after insemination, and the resulting embryos are transferred back to the uterine cavity at the 2-to 16~ell stage (see figure 7-3). After transfer, progesterone or hCG administration maybe given to supplement the natural luteal phase hormonal environment. If implantation occurs, small increases in hCG can be measured within a few days.

Figure 7-2. -Ultrasonogram of Developing Follicles

Ultrasound is routinely used to monitor the growth and development of follicles under the influence of fertility drug stimulation. The black areas represent f luid-filled follicles that contain the maturing oocyte. The size of a follicle can be estimated from sonogram.

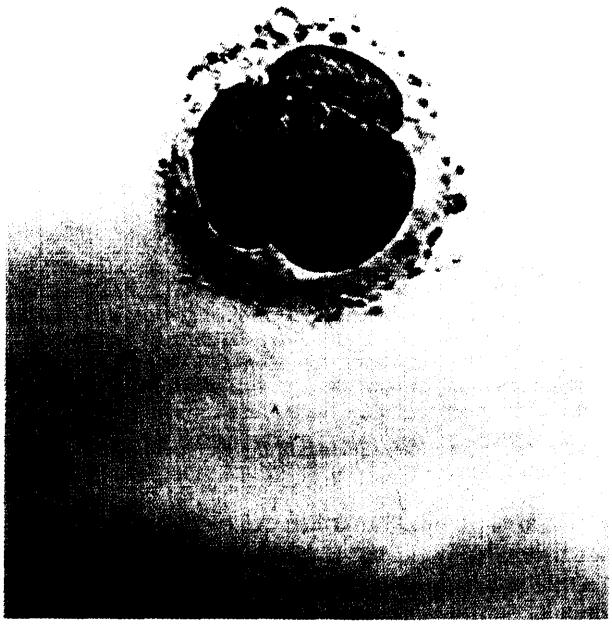
SOURCE: IVF Program, Medical College of Virginia, Richmond, VA, 1987.

IVF treatment is indicated in a number of disorders including tubal disease unresponsive to therapy, endometriosis, cervical mucus abnormalities, oligospermia, idiopathic infertility, and any combination of these disorders. The success rate for IVF varies considerably among programs (see chs. 8 and 15).

Gamete Intrafallopian Transfer

Gamete intrafallopian transfer is an infertility treatment method that directly transfers sperm

Figure 7-3.—Multicellular Embryo



Human embryo developing in vitro before transfer to female reproductive tract or cryopreservation.

SOURCE: ©Reprinted with permission. A.A. Acosta and J.E. Garcia, "Extracorporeal Fertilization and Embryo Transfer," *Infertility: Diagnosis and Management,* J. Aiman (cd.) (New York, NY: Springer Verlag, 19S4).

and oocytes into the fallopian tubes. As a consequence, fertilization can take place within the fallopian tubes. This technique relies on both medical and surgical procedures (3).

Development of follicles is accomplished by the administration of either clomiphene citrate or human menopausal gonadotropin or both. Thirty-six hours before GIFT is to take place, hCG is administered to the patient to precipitate ovulation of the mature follicles. The oocytes are collected by aspiration of the developed follicles through laparoscopy. Approximately 2.5 hours before the procedure, a semen sample is collected, prepared by washing and swim-up techniques, and treated with antibiotics. After evaluation of both the sperm and oocytes, one or two oocytes are loaded into a catheter. Next an air bubble is introduced into the catheter, followed by 100,000 motile sperm, The catheter is then threaded through the operating channel of the laparoscope into the end of the fallopian tubes for a short distance (1.5 centimeters). The contents of the catheter are gently emptied into the fallopian tube and, if possible, the procedure is repeated for the other fallopian tube. Subsequently the patient usually receives daily progesterone treatment for up to 8 weeks.

In some instances of male infertility, when small numbers of sperm are available, a variation of this procedure may be employed. Oocytes retrieved after ovulation induction may be fertilized in the laboratory as with IVF. The resulting embryo(s), however, are placed in the fallopian tubes rather than directly in the uterus.

Treatment with gamete intrafallopian transfer may be indicated in infertility related to a number of factors including endometriosis, premature ovarian failure, unexplained infertility, poor oocyte pickup by the fimbria due to adhesions, and oligospermia (3)32). Recent reports of success with GIFT are described in chapter 15.

Tubal Ovum Transfer

A less common technique with some similarities to IVF and gamete intrafallopian transfer is the tubal ovum transfer method (also known as low tubal ovum transfer). This approach uses similar ovulation induction and oocyte retrieval protocols as IVF and gamete intrafallopian transfer. However, the oocytes are transferred past a blocked or damaged section of the fallopian tube, to an area closer to the uterus. The couple then engages in intercourse or artificial insemination is performed. In this manner, the oocytes overcome the barrier created by disease or damage to the fallopian tubes and fertilization can occur within the female reproductive tract.

Embryo Lavage and Transfer

Embryo lavage (also known as ovum transfer, uterine lavage, or flushing) involves the retrieval of a fertilized ovum from the uterus by means

of a specially designed catheter. After carefully monitoring a menstrual cycle to determine the point of ovulation, artificial insemination is performed on a fertile donor woman. Several days later a specially designed catheter is inserted into the female reproductive tract and the fertilized ovum is literally flushed out and retrieved. The ovum is then transferred to a waiting recipient whose cycle has been synchronized in such a way that the uterine lining is prepared for implantation (lO)ll).

Male Infertility

Repair of Varicocele

Varicocele is the presence of a dilated varicose vein in the testes. This condition occurs in between 10 and 20 percent of all men and approximately 20 to 40 percent of infertile men. Varicoceles are most often found in the left testis, probably because of the anatomical differences between the blood supply to left and right testes. In some cases, however, there may be a right testis varicocele (55).

The mechanism by which a varicocele depresses male fertility remains unclear but it has been suggested that the increased scrotal blood flow may raise scrotal temperature and adversely affect spermatogenesis. Regardless of the exact mechanism, repair of varicoceles can increase the quality and quantity of the ejaculate. The surgical procedure is relatively simple. Usually, under general anesthetic, a small incision is made in the groin, the spermatic cord is located, and the spermatic vein is isolated from the spermatic artery and vas deferens. The varicose spermatic vein is tied off above the varicosity, taking care not to include or damage the artery or vas deferens. Ahernative approaches to this procedure include insertion of a small balloon to occlude the vein or injection of substances that will block the veins. In some cases the varicocele may reappear due to either recollateralization or failure to ligate all branches of this vein during prior surgery (55).

Improvement in semen quality after this procedure can take 3 months or longer. Reports of the effectiveness of this procedure vary widely (22,61). of the individuals who do show improved semen analysis, a smaller percentage have partners who eventually become pregnant. Although this procedure remains one of the oldest and simplest treatments for male infertility at the moment, its efficacy for improving male fertility remains controversial.

Microsurgery

A number of other conditions contribute to infertility in the male that can be effectively treated with surgery. Only the most frequently performed procedures are discussed here. These conditions result in blockage of sperm transport through the delicate ducts of the male reproductive tract. These obstructions can arise in the epididymis, vas deferens, or ejaculatory ducts for a variety of reasons, including inadvertent damage during previous surgery or vasectomy, infections, or failure to develop as a result of a birth defect.

Reconnection or reanastomosis of the vas deferens (also known as vasovasostomy or vasectomy reversal) is a delicate operation that must be performed by a skilled microsurgeon. Portions of the vas deferens are cut away until two clean ends are obtained. To ensure that all obstruction of the duct has been removed, small samples of fluid are taken from the testicular end of the vas and examined for sperm. This procedure is continued until the presence of large numbers of sperm confirm no further occlusion between the testis and the vas deferens. The two ends are then carefully aligned and sutured together. The success of this procedure is greatly influenced by the skill of the surgeon (62).

The other location in the male reproductive tract where blockage or occlusion is likely to occur is the epididymis. Blockage here most often is a result of infection and inflammatory reaction. Because the epididymis is such an extensive duct (approximately a 20-foot-long coiled tube), pinpointing the location of the obstruction can be difficult. However, by carefully excising portions of the epididymis until sperm are observed, the occlusion can be eliminated. Once sperm are present, the end of the vas deferens is connected to the patent epididymal duct (62).

ARTIFICIAL INSEMINATION

Artificial insemination is one of the oldest forms of infertility treatment, having been performed in the nineteenth century. Even though more sophisticated infertility treatment techniques have been developed since these early reports, artificial insemination continues to be one of the simplest and most successful infertility procedures.

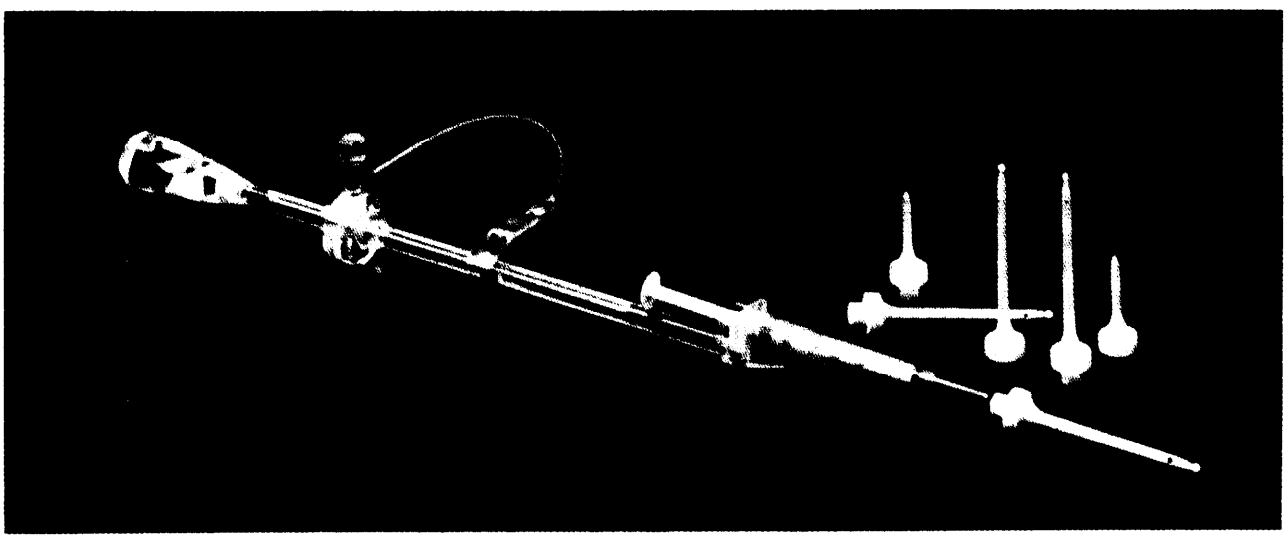
The practice of artificial insemination is usually classified as using the husband's sperm for insemination or using donor sperm. In each case the sperm can be placed either within the cervical canal or directly into the uterus. In addition, an approach that places sperm directly into the body cavity (peritoneum) has been successful in treating infertility. All inseminations are performed around the time of either drug-induced or natural ovulation.

Intracervical

Intracervical insemination involves placing sperm in or near the cervical canal of the female reproductive tract by means of a syringe or catheter (see figure 7-4). Protocols vary among practitioners but multiple inseminations during each fertile period are usually performed to increase the likelihood of conception.

The optimum time for insemination is the period just prior to or during ovulation, before basal body temperature rises. Cervical mucus is most receptive to sperm at this time. Approximately 48 hours before the expected BBT rise, sperm are collected from the husband or donor by masturbation into a clean, sterile container. In some cases, sperm are collected after the couple has had intercourse using a condom. In these instances, the condom should be void of lubricants and spermicides. The collected semen is allowed to liquefy and a semen analysis performed. Usually, within 1 to 2 hours after collection, part of the semen sample is loaded into a syringe with a flexible tip and placed in the cervix. The remaining sperm are placed in a special cervical cup that fits over the cervix. This cup remains in place for 6 to 8 hours to retain the sperm within the cervical canal and is then removed by the patient. Similar procedures are employed when frozen donor sperm are used. Intracervical insemination with the husband's sperm

Figure 7=4.—Device Used for Artificial insemination



Artificial insemination is usually performed with a syringe similar to the device shown.

SOURCE: Zygotek Systems, Inc., Springfield, MA, 19S8.

is usually indicated in cases where the male fails to deposit sperm in the female reproductive tract.

Intrauterine

Intrauterine insemination differs from intracervical by the location of sperm deposition in the female reproductive tract. In instances where cervical mucus is hostile to sperm, it is often advantageous to bypass the cervix and place sperm directly in the uterine cavity. Washed sperm are used with intrauterine insemination,

Direct Intraperitoneal Insemination

One technique for infertility treatment involves the same methods of ovarian stimulation and sperm preparation as IVF and gamete intrafallopian transfer. However, 35 hours after hCG is administered to precipitate ovulation, a sample containing at least 6 million sperm is injected directly into the body cavity between the uterus and the rectum. It appears that at least 500,000 motile sperm are needed for fertilization to occur with this method, If ultrasound shows that the follicles have not ruptured 24 hours after the first insemination, then the sperm injection is repeated. In the initial reports based on a small sample, this relatively simple technique produced a pregnancy rate of 14 percent per treatment cycle (26).

Sperm Preparation

Sperm Washing

Sperm washing is performed to separate viable sperm from the other components of the semen such as prostaglandins, antibodies, and possibly micro-organisms. This can also work to concentrate the viable sperm into a smaller volume for insemination. The basic approach involves diluting the semen sample with various tissue culture media containing albumin or serum, which somehow helps maintain sperm motility. This mixture is then centrifuged at low speed to separate out sperm (2). The concentrated sperm are resuspended in appropriate solutions for artificial insemination, IVF, or gamete intrafallopian transfer.

Swim-up Techniques

The swim-up technique is employed to concentrate only the highly motile sperm in the semen sample. This is usually accomplished by layering a solution containing proteins (albumin) or other substances over the semen or washed sperm sample. During a short time the most motile sperm in the sample will literally ‘(swim up” into the top layer, leaving behind most of the abnormal and nonmotile sperm. Motility of the sample used for insemination can be increased severalfold, thereby increasing the likelihood of successful fertilization (2),

Drug Treatment

Disorders of motility may sometimes be improved by addition of chemicals such ***as*** caffeine, arginine, or kinins to the semen sample, but the efficacy and safety of these procedures is unclear (7). Other drug treatments of the ejaculate most notably include treatment of the sample with antibiotics to eliminate possible bacterial infection (2).

CRYOPRESERVATION

Gametes

Sperm

Spallanzani’s 1776 report of sperm survival after freezing in snow was the first step to modern cryopreservation of sperm in both humans and animals (41). It was only after the discovery that glycerol, acting as a cryoprotectant, was effective in preserving sperm’s survivability during freezing that successful insemination of women with previously frozen and thawed sperm was accomplished (9). Since then many laboratories have successfully frozen sperm to be used in subsequent insemination. Large-scale operations of semen collection and cryopreservation have become a major part of the animal husbandry industry. For humans, sperm banks and programs now exist around the world from which donor sperm can be purchased for insemination.

Techniques for sperm cryopreservation differ among laboratories. Most facilities now use cryo - protecting agents such as glycerol, and they freeze sperm in straws or ampoules in liquid nitrogen (41). Although some loss of sperm or sperm motility during freezing is expected, this can vary greatly depending on characteristics of original sample, freezing technique, and cryoprotectant.

Oocytes

Three births have been recorded in Australia and West Germany from oocytes that were frozen and thawed. Freezing oocytes is not widely practiced, however, in IVF programs at present. Although the technique is similar to freezing sperm and embryos, different characteristics of the unfertilized oocyte make it extremely susceptible to cryopreservation damage (71). Much additional work is needed before oocyte freezing is a viable procedure in infertility treatment.

Embryos

Cryopreservation of embryos is increasingly practiced in IVF programs around the world. This approach presents several advantages. If multiple eggs are retrieved and fertilized during an IVF cycle, then any embryos not transferred during that cycle would be available for transfer during subsequent cycles without additional fertility drug stimulation and egg retrieval. Another aspect of cryopreservation of embryos is the ability to reduce the risk of multiple pregnancies by transferring only one embryo at a time. However, this transfer protocol reduces the chances of pregnancy as well.

The techniques for freezing embryos differ in several respects among laboratories. The major differences involve the substance used to protect the embryo from damage by freezing (the cryoprotectant), and the stage at which the embryo should be frozen to ensure maximum survivability upon thawing (7 I). In addition, the length of time the embryos remain frozen also varies. One recent study suggests freezing embryos at the earlier, l-cell to 4-cell stages is optimal (70)71). Conflicting reports make it unclear whether the length of time an embryo is frozen is a factor on post-thawing success (70)71).

RISKS OF INFERTILITY TREATMENTS

As in most areas of medical practice, there are potential risks associated with certain procedures used in infertility treatment. These risks can generally be divided into several categories: risks involved with drug treatments; risks associated with surgical procedures; and risks of pregnancy complications including miscarriage, ectopic pregnancy, and multiple gestations. Risks of some of the most commonly used treatments are discussed in this section.

Drug Treatments

Female

Risks related to ovulation induction with various fertility drugs have been widely investigated. Clomiphene citrate can result in subadequate cervical mucus, impaired tubal motility, abnormal sperm transport, and Iuteal phase defect (58), Although some reports have suggested that CC may contribute to an increased incidence of early pregnancy loss (2.5 times more likely than in spontaneously conceived gestations) (29), other reports have found no such increase (1,42).

Treatment with CC may increase the risk of ectopic pregnancy (16). This increased risk may be due to alterations in tubal motility, to a higher incidence of damaged tubes in infertile women (who tend to get placed on drugs such as CC), or to the increased number of ova released after ovulation induction, raising the number of opportunities for a tubal implantation (15).

Multiple gestation is another risk of CC and other drugs used to induce ovulation, increasing the risk of pregnancy complications including prematurity, gestational diabetes mellitus, toxemia, and placental abnormalities. The incidence of multiple gestations after CC use has been reported to range from 8 to 13 percent (58).

Other risks of CC treatment include hyperstimulation of the ovary (ovarian enlargement), moler

intrauterine pregnancies, vitamin B_{12} deficiency, and possible premature aging of the ovary from repeated stimulations (38).

A number of the risks described for CC use may also be applicable to ovulation induction with human menopausal gonadotropins. As reported for CC, hMG treatment maybe associated with luteal phase defect (21). Risk for ovarian hyperstimulation syndrome (OHSS) is more prominent with hMG than CC administration (20). Severe OHSS can include ovarian enlargement (which may be massive), abdominal distension, increased blood viscosity, and coagulation abnormalities, leading to thromboembolism and death (49)57). OHSS is largely the result of excessive hMG administration and can usually be avoided by careful monitoring of blood estrogen levels. OHSS appears to be associated with the administration of hCG (57); if estrogen levels become too high, therefore, hCG can be withheld.

Ectopic pregnancy rates of 2.7 percent (30) and 3.1 percent (48) have been reported in hMG-induced pregnancies, similar to the incidence with CC administration. Multiple pregnancies are more commonly encountered after hMG therapy than after CC. The incidence of twin and higher order pregnancies has been reported to range from 11 percent to 42 percent of hMG-induced gestations (58),

Other drugs used in infertility treatments carry risks of side effects as well. Many individuals taking bromocriptine for hyperprolactinemia experience side effects such as nausea, hypotension, hair loss, and headache (19). More serious complications of therapy have occasionally been reported, including pleuropulmonary fibrosis, which occurs with some regularity in patients on bromocriptine for extended periods of time, as in the treatment of Parkinsonism (58). Psychosis has been reported to have been induced by bromocriptine (69), ostensibly due to effects on central neurotransmitters. Of particular concern are reports of stroke and myocardial infarction in young, apparently healthy women on moderate doses of bromocriptine. It is believed that these complications may be due to an increase in coagulability of blood (18).

As with other drugs used to induce ovulation, gonadotropin releasing hormone carries some risks. Hyperstimulation of the ovary has been reported using Gn-RH. However, this risk appears to be less likely than with CC or hMG ovulation induction (58).

The hormone that has become most widely used in the suppression of endometriosis is danazol. Most women taking this drug experience bloating and weight gain (12). Additional possible side effects include muscle cramps, flattening of the breasts, hot flushes, oily skin, depression, acne, and hirsutism (12). Other infrequent complications that have been reported include thrombocytopenia, hepatotoxicity, hepatitis, and hepatocellular carcinoma (58).

There is no evidence that danazol therapy can cause persistent reproductive toxicity after the drug is stopped; however, inadvertent administration of danazol during pregnancy can cause masculinization of female fetuses (40).

Male

A number of different agents that are used to induce ovulation have also been used in an attempt to optimize semen quality in infertile or subfertile men. These include androgens, CC, hCG, hMG, Gn-RH, glucocorticoids, and a variety of other agents.

The rationale for giving androgens is to temporarily suppress the activity of the testes, Subsequent withdrawal of the androgens then might be accompanied by a rebound increase in spermatogenesis. Androgens administered to some men may suppress sperm production altogether with no subsequent rebound. It is unclear, however, if this is a complication of the drug treatment or of the primary testicular disorder for which the therapy was given (58).

The use of CC in oligospermic men is based on the anti~estrogenic activity of this drug. There have been occasional reports of serious adverse effects of this therapy, including a case of pulmonary embolism (13) and two cases of testicular ***germ cc]]*** tumors after therapy (51). The occurrence of such isolated cases may be coincidental and cannot be interpreted as indicating a risk of the therapy. It is considered unlikely that CC poses a significant health risk for men (58).

Glucocorticoids have been used in men to reduce the development or activity of sperm antibodies. Glucocorticoids, given chronically, maybe associated with adrenal suppression, osteoporosis, impaired glucose tolerance, psychosis, and other complications. Men receiving glucocorticoids for sperm antibodies develop such complications as readily as any other patient (54).

Side effects and potential complications of bromocriptine, used to treat male infertility, are similar for men and women.

Surgery

Female

The complications of general anesthesia, including drug reactions, cardiac depression, hypotension, aspiration, and death, do not appear to be different for infertility surgery than for surgery in general. Surgical complications such as injury to bowel, excessive blood loss, and infection are possible with any intra-abdominal operation (58).

Because surgery may cause scar tissue of its own, much effort has gone into developing procedures to prevent postoperative pelvic adhesions. However, adhesions and scarring remain potential consequences of reproductive tract surgery.

The complication of tubal surgery of greatest concern is ectopic pregnancy. A number of investigators have reported ectopic pregnancy rates after tubal surgery ranging from 4 to 38 percent (58).

Use of lasers at laparotomy for tubal reconstructive surgery may be associated with complications specific to the laser, such as inadvertent reflection of the laser beam resulting in damage to other tissues or in the starting of fires in the surgical drapes. The incidence of documented injury from laser surgery in the abdomen has been reported to be less than 0.5 percent **(18).**

Laser laparoscopy is an acceptably safe tool for the treatment of endometriosis, although intra-abdominal bleeding may require the use of traditional cautery for control. Based on the limited number of reports available, serious complications do not appear to occur more often than in laparoscopies in general (58).

Male

The major risk of male genital tract surgery such as reversal of vasectomy is operative infection and bleeding. The major complication of varicocele ligation is postoperative hydrocele, a collection of fluid in the scrotum. The fluid collection maybe due to inadvertent destruction of lymphatic drainage vessels during the procedure (68).

Testicular atrophy was also at one time a complication of varicocele ligation, occurring in as many as **14** percent of cases. Improvements in surgical technique appear to have eliminated this complication (28).

Artificial Insemination

The major risk of artificial insemination by donor is transmission of disease from the donor to the recipient, including chlamydia, gonorrhea, cytomegalovirus (a potential cause of fetal illness), hepatitis B virus, and human immunodeficiency virus (38)58). The risk appears to be less after intracervical insemination than after intrauterine insemination (67).

In Vitro Fertilization

IVF can involve a number of procedures that each have risks and possible complications. Ovulation induction for IVF often involves several fertility drugs (CC, hMG, Gn-RH, hCG) used in combination and carries the risks described previously.

Many IVF cycles demonstrate features of luteal phase deficiency (8,27). It has been proposed that aspiration of the follicle to obtain the ovum may damage the follicle or may remove too many granulosa cells, which impairs subsequent luteal phase function. Experience with human IVF cycles suggests that the agents used to hyperstimulate the ovary are more likely than aspiration to be responsible for luteal dysfunction (74).

Several oocyte retrieval methods employing ultrasound-guided aspiration have been developed (44). Since the aspirating needle may traverse the bladder, blood in urine is seen with regularity after this procedure (38,58). It is likely that ultrasound-guided aspiration of follicles will replace laparoscopy in many programs due to comparable re-

suits and lower cost, fewer discomforts, and less risk with the nonoperative approach (34).

obtaining multiple oocytes leads to the possibility that more embryos will be generated than can be transferred in a given IVF cycle. The cryo - preservation of excess embryos for use in future cycles is being considered an important option in more and more programs. Thawing of frozen embryos often fails to yield viable embryos. Long-term effects to individuals born after embryo cryopreservation remain to be fully investigated.

As the number of embryos transferred per cycle increases, so does the incidence of multiple gestations. Several complications attributable to the embryo transfer procedure have been reported. The catheter used to introduce the embryos into the uterus may result in trauma to the endometrium (50). The transferred embryos may implant in the fallopian tube. The first IVF pregnancy was, in fact, a tubal pregnancy (65). Some programs report an ectopic pregnancy rate of 2 to 3 percent (39); however, a review of the experience of a number of programs reported that **10** percent of IVF pregnancies are extrauterine (6). The placement of the catheter high in the uterus may predispose to ectopic pregnancies. One study reported a 17-percent ectopic rate with high placement as opposed to a 2-percent ectopic rate when the catheter was place in the middle of the cavity (77).

The miscarriage rate for infertility patients is generally higher than that for the normal population. Although rates as high as one in three have been reported for some infertility patients, determination of these risks remains a complex undertaking (see ch. 15).

Preterm delivery is more common in pregnancies after IVF than in spontaneous pregnancies (4,43). This is partly due to the high incidence of multiple gestations, although an increased prematurity rate is also seen in births of one infant.

KNOWING WHEN TO STOP

> When you absolutely cannot have children, it's called sterility. When it seems to be taking an awfully long time but you still hope, it's called infertility.
>
> Infertility is worse.
>
> Katherine Bouton
> ***Ms.,*** April 1987

Current estimates indicate that even appropriate therapy will assist only 50 percent of infertile couples to achieve a pregnancy. Couples often ask how to know when to quit trying medical treatments. Their uncertainty is complicated by prevalent social assumptions that anything is possible if one works hard enough, that "where there is a will there is a way." In addition, the lack of information about idiopathic infertility in particular contributes to the fear of stopping too soon and perhaps omitting what would have been a successful treatment.

Medical indications for stopping treatment are not yet well developed because:

- selected reproductive technologies have only recently proliferated and instances of overuse have not been well documented;
- the current high costs of diagnosing and treating infertility cause many couples to exhaust their personal resources well before they have exhausted available treatments; and
- existing services for infertile couples may not help the couple to know when the stress associated with continued diagnosis and treatment is excessive.

Infertile couples who can afford to continue treatment may assume that infertility specialists will tell them when to stop, but in their desire to help infertile couples to conceive, physicians may not often enough pause to consider if a particular couple should stop trying.

It may be helpful for infertile couples to ask themselves:

- Is further treatment worth the pain, expense, and disruption?
- Is adoption or childfree living becoming an acceptable option?
- Is treatment costing so much that other goals are sacrificed?

- If it is not yet time to stop, when will it be?

New information about infertility and overuse of certain reproductive technologies may help to make this decision, but knowing when to stop will continue to be an individual matter for every infertile person and couple.

SUMMARY AND CONCLUSIONS

A variety of traditional and more recently developed medical and surgical treatments for infertility exist. Treatments often involve both members of a couple, each of whom may have a condition that causes subfertility. Medical treatment can range from instruction of the couple in the relatively simple methods of pinpointing ovulation to more complex treatments involving ovulation induction with fertility drugs followed by artificial insemination. Surgical treatments also span a wide spectrum of complexity, from ligation of testicular veins for varicocele repair to delicate microsurgical repair of reproductive tract structures in males and females.

As is true for the diagnostic procedures described in chapter 6, far fewer procedures exist for the treatment of male infertility than for female infertility. This underscores the lack of basic knowledge about male reproductive physiology and the paucity of approaches to treat dysfunctions of this system.

Although sophisticated noncoital reproductive technologies such as IVF or gamete intrafallopian transfer offer some hope to some infertile couples who could not otherwise be successfully treated, improvements of more traditional infertility treatments such as ovulation induction, traditional surgery and microsurgery, and artificial insemination continue to make these treatments the most widespread and successful approaches. It is also important to note that even complex and sophisticated treatment of one partner will be of no benefit if the other partner suffers from undiagnosed infertility. Therefore, as with diagnostic technologies, the couple as a unit is properly considered as the infertility patient.

Even as infertility treatments become more sophisticated and complex, basic knowledge of the male and female reproductive process remains lacking. Further research stands as a prerequisite in order for dramatic improvements in infertility treatment to occur.

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