

**Chapter 6**

# **Diagnosis of Infertility**

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# Diagnosis of Infertility

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Determining that there is a need for infertility treatment is often a difficult and somewhat arbitrary decision. Some professionals suggest that after 6 months of carefully timed unprotected intercourse or, more commonly, after a year of random attempts at conception, a couple seek some form of infertility evaluation (8)33).

Although a growing number of physicians are specially trained in infertility treatment, most such treatment is still carried out by the female partner's gynecologist (1). Since most women visit a gynecologist more frequently than their male partners seek medical treatment, the gynecologist usually serves as the first professional an infertile couple encounters in their attempt to conceive. As much as 80 percent of basic infertility treatment occurs with the personal gynecologist. In addition, the male partner may be referred to a urologist for basic infertility evaluation.

In cases of persistent infertility, however, patients increasingly are seeking out treatments by primary care physicians who specialize in infertility services, such as gynecologists and urologists who are often part of a group practice or infertility clinic. These are usually identified by one of the following means:

- referral by personal gynecologist or urologist to an associate in a group practice who is an infertility specialist;
- referral by gynecologist, urologist, or personal physician to the nearest medical school, large medical center, infertility clinic, or group practice;
- referral to a particular physician or clinic by organizations like Resolve (see box 6-A), a national infertile-couple support group that

maintains a referral service in its local chapters; or

- other methods, such as referral by other infertile couples, national or local medical societies or groups, advertisements, or media coverage of babies born from new reproductive technologies.

Since infertility problems can involve both men and women, infertility is best diagnosed and treated with a team approach, spanning several specialties in medicine such as gynecology, urology, andrology, endocrinology, and reproductive tract microsurgery. Many medical schools, large medical centers, and group practices have infertility treatment programs that employ, or have a close consulting relationship with, a variety of specialists. Because of the psychological aspects of undergoing treatment and accepting the results of these diagnostic procedures, some infertility programs make psychologists or counselors available to the patients (see table 6-1). Comprehensive infertility practices usually include:

- a gynecologist who specializes in reproductive endocrinology (hormonal control of reproduction) or reproductive tract surgery,
- a urologist or andrologist who specializes in male infertility conditions or reproductive tract surgery, and
- a genetic and psychological counselor.

Although the presence of these specialists does not guarantee the success of an infertility treatment program, and much successful infertility diagnosis and treatment is administered by personal gynecologists, the more complex the factors contributing to a couple's infertility are, the greater the chance they will benefit from a broad range of experts.

**Box 6-A.—Resolve, A Nationwide Support Network for Infertile Couples**

Trenton New Mexico Albany  
 Island New York City Portland  
 Rochester Ohio Tulsa Lancaster  
 Philadelphia Pittsburgh Nashville  
 Dallas Ft. Worth Utah Vermont  
 Washington, DC Milwaukee Appleton

**RESOLVE****WHEN YOU'RE WISHING FOR A BABY...**

Albany Northern California Orange  
 County Colorado Fairfield County  
 Hartford Ft. Lauderdale Miami  
 Tampa Boise Chicago Indiana Iowa  
 Louisville Ark-La-Tex Maine Maryland  
 Minneapolis St. Paul St. Louis  
 Michigan Nebraska Tenafly New  
 Brunswick Trenton New Mexico  
 Albany Ithaca Long Island New  
 York City Portland Rochester Ohio  
 Lancaster Philadelphia Pittsburgh  
 Nashville Dallas Ft. Worth Utah  
 Vermont Seattle Washington DC

SOURCE: Resolve, Inc., 5 Water St., Arlington, MA 02174.

Resolve, Inc., a nonprofit membership organization, was founded in Boston, MA, in 1973 by Barbara Menning. Menning was diagnosed infertile and found herself without emotional support and needing quality medical care. Meeting informally with friends and acquaintances who were also infertile, she began to write and speak about the issue.

By 1976, five groups in other parts of the United States had been formed, offering medical information and emotional support. In 1978, a small Federal family planning grant enabled Menning to rent office space, hire an assistant, and train family planning staff. By 1981, there were 35 affiliated, volunteer-run Resolve chapters across the United States. The Massachusetts office began to function as a clearinghouse for information and was responsible for the chapter network.

Today, 47 affiliated chapters offer monthly programs, telephone counseling, formal support groups, and medical information to infertile couples. The national office, financially supported by Resolve memberships and sale of literature, produces written medical information used by chapters and members, a national listing of specialists used by Resolve to refer patients to appropriate medical care, and information on programs that perform IVF or gamete intrafallopian transfer.

The staff of the national office are responsible for supervising chapters, initiating and responding to media inquiries, and providing public education on infertility to consumers and associated professionals. To date, Resolve has sponsored over forty 1-day conferences for infertile couples in major U.S. cities.

SOURCE: Office of Technology Assessment, 1988.

**PATIENT HISTORY**

A complete health history taken from both partners of an infertile couple is probably the single most important diagnostic tool the caregiver can employ. A complete patient history includes information about each partner's education, employment, personality, stimulant and substance use, medications and treatments, nutrition and diet, exercise, immunizations, medical history, surgical history, family history, psychological history, and sexual history.

Information obtained in this critical initial stage of the examination often provides important insights into the causes of a fertility problem. Clues derived from the details of an individual's personal, familial, and occupational background and the couple's sexual interaction can preclude the need for laboratory tests or complement their results. Questions, for example, about coital frequency and technique (e.g., use of vaginal lubricants) may indicate that these variables are the source of a

Table 6.1.—Counseling Opportunities

Mechanism of psychological support	Advantages	Disadvantages
<i>Infertility clinic:</i> Infertility clinic staff	No extra cost  Clinic staff familiar with in-house procedures, may be able to be sensitive to likely emotional reactions	May be distant from patient's home, thereby presenting logistical difficulties Patient may not wish psychological information in records Expressions of emotional needs usually limited to specific clinic procedures
Infertility clinic consultant	Counseling professional available when cases of extreme emotional distress are noted	Professional alerted only after the patient is clearly overwhelmed, thereby being more reactive than preventive in counseling response
Professional counselor on staff at infertility clinic for orientation and counseling when requested	Preventive approach that includes orientation to clinic procedures, possible emotional impact of diagnosis, and referral to appropriate support groups or community services	Emphasis is on initial visit with patient, but the responsibility for future or ongoing contact rests with the patient
Professional counselor on staff at infertility clinic for orientation and regular contact with all patients to monitor emotional coping with diagnosis and treatment	Preventive approach includes orientation to clinic, possible emotional impact of diagnosis and treatment, short-term counseling, referrals to community services, and offer of a clinic support group	May be perceived as intrusive, or unnecessary; patients may resent efforts to make counseling mandatory
<i>Community settings:</i> Counselors in community	Counselor can work cooperatively with other members of the medical team Sliding fee scales Located in patient's community	Waiting lists at many agencies Few counselors have in-depth knowledge about infertility
Community support group	Low or no cost Reduces feelings of isolation	individual needs may be submerged to group priorities
Telephone hot line	Offers privacy and anonymity	Counselors not likely to be knowledgeable about infertility
Counselors in private practice	Wait less lengthy than at community counseling agencies Patient chooses specific counselor	Costs may be high, although insurance may cover part or all
Religious leader	No cost Can address spiritual issues	Affiliation with religious institution may be necessary May be doctrinal objections to treatment chosen Few clergy knowledgeable about infertility

SOURCE Office of Technology Assessment, 1988

couple's inability to conceive. It is important, for instance, for the caregiver to ascertain whether the couple has experienced any form of sexual dysfunction (e.g., male impotence or erectile dysfunction), whether the couple engages in intercourse coincident with the woman's ovulation, and

whether either partner has successfully reproduced with the present or any previous mate.

The sexual history, like any other part of the health history, is taken to produce information that may bear on the couple's fertility problem

**(12).** When a sexually transmitted disease is suspected, patients must often describe sexual preference, numbers and regularity of sexual partners, and any symptoms of sexually transmitted disease

that partners may have exhibited. The information contained in a comprehensive sexual history may quickly pinpoint the source of fertility problems.

## PHYSICAL EXAMINATION

Physical examination seeks evidence of physiological or anatomical bases for infertility. Standard health parameters (e.g., height, weight) and cardiovascular and neurologic function (e.g., blood pressure, strength of pulse in lower extremities, reflexes, pelvic sensation) are measured and particular attention is paid to the genitals and any anatomical abnormalities.

### *Male*

The physical exam verifies the presence and structural adequacy of the various components of the genital tract (e.g., vas deferens, prostate, epididymis). Particular structural abnormalities associated with impaired fertility are sought (e.g., hernia, varicocele (varicose veins associated with the testes), or hypospadias (opening of the penis on the underside)). In addition, the size and volume of the testes are measured, as testicular atrophy is an indication of reduced sperm supply.

### *Female*

Although the gonads are not external in the female as they are in the male, secondary sex characteristics (i.e., breast development, hair and fat distribution) are observable and provide an important indication of hormonal secretion and response. Excessive facial or body hair, for instance,

may be the result of an excess of male hormones in a female.

A thorough pelvic examination, including palpation of structures throughout the genital tract, may identify infection, tumors, adhesions, or other abnormalities contributing to reproductive difficulties. Considerable information about internal pelvic structures can be obtained by means of palpation. An experienced physician can feel the size and shape of the uterus (which may have no bearing on fertility potential) and can check for the presence of any leiomyoma tumors (also known as fibroids), Leiomyomas, common in women over age 35, can sometimes interfere with implantation of the embryo or in rare instances cause miscarriage.

The pelvis is palpated for adhesions, rubbery bands of scar tissue that remain from previous infections or surgery. Adhesions that encapsulate the uterus, tubes, or ovaries can compromise the function of these organs. Small endometrial growths that are enough to cause infertility cannot, however, always be detected on manual exam. And there is no way to tell from a pelvic exam if the oviducts are open or closed. Overall, if the pelvic exam is normal, the probability of physical obstruction to pregnancy is reduced.

## TECHNOLOGIES FOR EVALUATION OF REPRODUCTIVE STATUS

The evaluation of the infertile couple is a complex, time-consuming process. Since some infertility can be attributed to idiopathic (unknown) causes, the diagnostic process can result in much frustration for both the physician and the patients. Most procedures are designed to evaluate the function of a single physiological or anatomical aspect of reproductive function. In some cases,

once an isolated abnormality is discovered, further diagnostic evaluation may not be pursued. This can be misleading if the infertility has more than one contributing factor.

In addition, a single determination of specific variables in the diagnostic evaluation can be misleading, since many of the physiological param-

ters assessed by these procedures, such as semen analysis and the postcoital test, can vary considerably over time.

A standard infertility workup (see box 6-B) may differ considerably from physician to physician, but the following procedures are most commonly followed:

- couple's history and physical exam,
- semen analysis,
- basal body temperature charts and other menstrual cycle mapping,
- cervical mucus evaluation,
- hormone assays,
- post-coital test,
- immunologic evaluation,
- endometrial biopsy,
- hysterosalpingogram,
- laparoscopy,
- hysteroscopy, and
- hamster-egg penetration assay,

### **Box 6-B.—Undergoing Diagnostic Procedures for Infertility**

Undergoing diagnostic procedures can often be unpleasant. Women are likely to feel probed and manipulated, and repeated trips to the physician's office may begin to affect personal and professional life. Men may need to supply several semen samples. Masturbation in a physician's office may feel ridiculous or embarrassing. Men may find the process of having sperm counted and scored disconcerting. In addition, men may suffer from a great deal of helplessness and guilt for being the one having a much less invasive diagnostic process.

A post-coital test involves visiting the physician within a few hours of timed intercourse so that the woman's cervical mucus can be examined to determine how sperm interact with the vaginal and cervical environment of the woman. The demands of the pending doctor's appointment may make sex unpleasant for either partner. The man must achieve erection and ejaculation on schedule, and the surrounding tension may result in temporary impotence. The same reaction may occur when a couple has charted the woman's basal body temperature to determine ovulation. Once again partners may feel pressured to have intercourse on a schedule unrelated to sexual desires. This problem presents itself as a midcycle pattern of sexual dysfunction. Both partners may dislike having to reveal the intimate details of their sex lives, particularly at a time when that has been disrupted and distorted by the needs of the diagnostic workup.

If a couple are told that their infertility is caused by a problem for which there is no treatment, their psychological response almost universally resembles that of mourning a death. A couple learning that there is a treatment are likely to feel relief and hope. However, these feelings may not be based on an accurate perception by the couple of what lies ahead. In addition, the couple may also feel apprehensive of the cost, the inconvenience, the discomfort, and the risks associated with many treatments. If their infertility is due to repeated miscarriages, rather than an inability to conceive, they may dread the prospect of risking the loss of more pregnancies.

The couple who receive a diagnosis of unexplained infertility enter a psychological limbo. For some, the diagnosis of idiopathic infertility begins a series of new visits to infertility specialists; for others, it begins mourning, denial, anger, and grief, without final acceptance. The couple may feel out of control, and with medical professionals also baffled as to the cause of their infertility, the couple enter what is often a lengthy period of intermittent mourning, and efforts to "try again."

Secondary infertility (the inability to conceive after having at least one biological child) engenders surprise, followed by frustration, as a couple once in control of reproduction find that fertility now eludes them. When such couples express sadness about their inability to conceive another child, their pain is often discounted by others as they are reminded that they are, in fact, already parents. Couples with secondary infertility may find themselves overly preoccupied with the child they have, as all their hopes rest on his or her accomplishments and good health.

### Diagnostic\* Female Infertility

There are essentially three types of diagnostic technologies to evaluate infertility in women: over-the-counter products, laboratory-based methods, and physician- and hospital-based methods and procedures. In addition to the well-known advances made in laboratory- and physician-based infertility treatment technologies, the market for patient-use products and devices distributed mostly over the counter has grown rapidly. These products increasingly allow informed infertile patients to use on their own some basic infertility diagnostics and treatment methods.

Not all the procedures described here would routinely be used in each diagnostic workup. If patient history, for example, indicated multiple episodes of a sexually transmitted disease, then investigation for tubal obstruction would be indicated, such as a hysterosalpingogram (an x ray of the uterus and fallopian tubes).

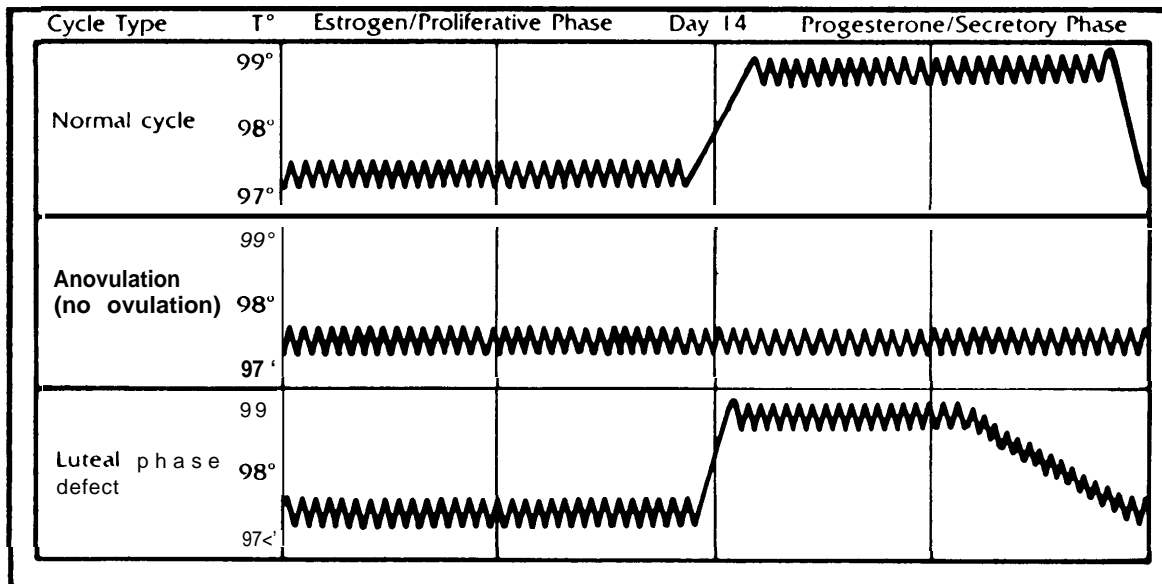
#### Basal Body Temperature

The recording of basal body temperature (BBT) is one of the oldest and most popular methods

for predicting ovulation. This procedure relies on the characteristic changes in basal (resting) body temperature during the menstrual cycle (see figure 6-1). These alterations in temperature are a result of changes in the hormonal output of the ovaries. During the preovulatory phase (usually 14 days in regular, average cycles) of a menstrual cycle, when estrogen levels are rising, the BBT remains at resting level, approximately 98.00 F. When ovulation occurs, estrogen levels decline and progesterone levels rise, which causes an upward shift in BBT to 98.40 F or higher, @here may also be a slight decrease in BBT immediately before the upward shift to 98.4° F. This small decline may coincide with ovulation.)

Since preovulatory temperature values may vary among women, it is the change in temperature rather than the absolute reading that is important. The BBT usually remains elevated throughout the remainder of the cycle, returning to 98.0° F at the onset of the next cycle (38). By taking body temperatures daily, the menstrual cycle can often be charted and subsequent ovulations pinpointed to within a 4- to 6-day period. If BBT does not increase during a cycle, this indi-

Figure 6-1.— Basal Body Temperature Charts



Typical basal body temperature patterns that indicate normal ovulation (top), ovulatory failure (middle), or ovulation with luteal phase defect (bottom).

SOURCE: J.H. Bellina and J. Wilson, *You Can Have A Baby* (New York, NY: Crown Publishers, Inc., 1955).



cates that ovulation has probably not taken place and progesterone levels remain low.

As part of the infertility workup, the BBT has the greatest value with women who have average length (28 days), regular cycles. Although some clinicians find the BBT to be an inaccurate indicator that the preovulatory surge of luteinizing hormone (LH) and ovulation have occurred (7), others find it useful for pinpointing 4 to 6 days during which ovulation is likely to occur during subsequent cycles (38).

Another way to predict ovulation is the calendar method, which relies on the regularity of a patient's cycle to indicate the period of fertility. After a woman has recorded the duration and days between her menstrual period over several consecutive cycles, she can get a general idea as to the timespan surrounding subsequent ovulations. This method relies heavily on the regularity of an individual's cycles, since no other indicators besides past history are employed to pinpoint ovulation. When used to predict the fertile period of a cycle for means of birth control, this method has a fairly high failure rate (8).

### Hormone Monitoring

Several ovulation prediction kits are currently sold over the counter. These kits measure, in a semiquantitative manner, the midcycle increase of LH, the hormone that causes ovulation under normal circumstances. The onset of the midcycle - LH increase precedes ovulation by an average of 32 to 36 hours (20). This change in LH secretion is quickly reflected in the urine, making measurement of urinary LH useful in clinical applications to approximate the time of ovulation (24).

Most of these kits employ the enzyme-linked immunosorbent assay procedure. Antibodies that bind LH are immobilized on a small dipstick pad or form a dry coating at the bottom of a test tube. These antibodies (either pad or coated test tube) are incubated with the urine specimen and an additional reagent. When LH is present in the urine, a specific antibody -LH-reagent complex will form. When treated with another reagent, this complex develops a characteristic color indicating the presence of LH in the urine. If LH levels are high, the color that develops will be intense compared with

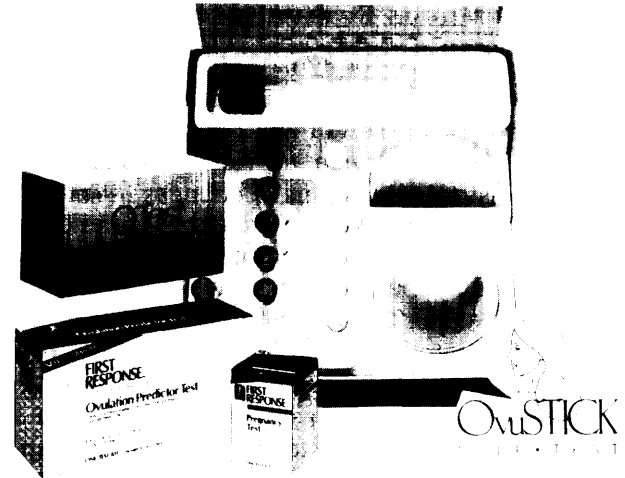


Photo credit: Office of Technology Assessment

Home diagnostic tests

a blank or reference indicator. In this manner, a qualitative prediction about the onset of the LH surge and the timing of ovulation can be made.

Measurement of another hormone, progesterone, as confirmation of ovulation, is quite routine in the infertility workup (17). This can be performed on a patient's blood or urine sample by laboratory personnel using complicated procedures such as radioimmunoassays to obtain a quantitative value, or in the physician's office or at home with rapid hormone test kits that provide semiquantitative values. Although observation of increased progesterone suggests that ovulation has occurred, failure to detect a rise of this hormone does not always indicate ovulatory failure but may suggest other hormonal problems such as luteal phase defect (50). In addition, failure of progesterone to increase to within the appropriate range may also signal a failure of ovulation. Furthermore, even in some instances where progesterone is in the ovulatory range, ovulation is not certain (49).

other hormonal tests may also be performed to evaluate the function of the other endocrine systems. These hormones include prolactin, thyroid hormones, adrenal hormones, and gonadotropin (LH and follicle-stimulating hormone (FSH)).

## Cervical Mucus Evaluation

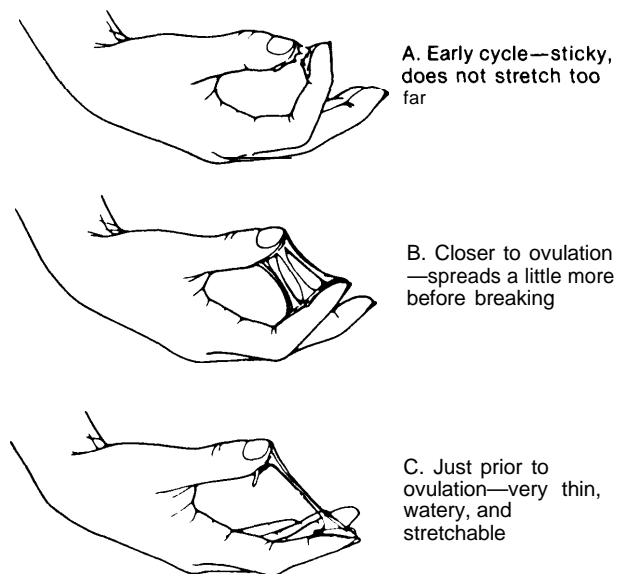
Another method for ovulation prediction relies on gross and microscopic examination of cervical mucus. As a result of changing levels of hormones during the cycle, cervical mucus undergoes consistent and dramatic changes in several of its physical properties. Under the influence of the high estrogen levels that precede ovulation, cervical mucus becomes thin, watery, salty, and stretchy (elastic). These first three characteristics can be evaluated by what is known as the fern test (see figure 6-2). When placed on a glass slide and allowed to dry, cervical mucus dries into a distinctive fern-like pattern. As ovulation approaches more ferning can be seen.

Likewise, the spinnbarkeit test evaluates the stretchiness of cervical mucus, which also increases under the influence of high estrogen levels. A small drop of mucus, obtained close to ovulation, is placed between two glass slides (or two fingers). When the slides are separated, the threading of the mucus that results should stretch 8 to 12 centimeters without breaking (see figure 6-2). If ovulation has already occurred, or there is ovulatory failure, then the mucus is scanty and thick.

In addition to these characteristics, cervical mucus should also be examined for the presence of cells or debris and proper pH (acidity or alkalinity), factors that can also affect fertility. The administration of fertility drugs such as clomiphene, for ovulation induction, can affect the characteristics of cervical mucus.

More sophisticated examination of the hormone-induced changes in the characteristics of these body fluids can contribute to ovulation prediction. One recently developed method relies on the documented changes in ion concentration (sodium and potassium) in saliva and vaginal mucus throughout the menstrual cycle (35). A handheld electronic device (CUE Fertility Monitor; Zetek, Inc., Aurora, CO) employs sensors that measure the electrical resistance of saliva and vaginal mucus. Because minute changes in the ion concentrations of these body fluids result in alterations of their electrical resistance, changes in electrical resistance of the saliva and vaginal mucus can

Figure 6-2.—Cervical Mucus Evacuation Tests



Two simple cervical mucus evaluation tests. Top panel shows the characteristic fern-like pattern (fern test) that results when pre-ovulatory cervical mucus dries on a glass slide. Bottom panel shows the characteristic stretchiness of cervical mucus during the pre-ovulatory period.

SOURCES: L. Speroff, R.H. Glass, and N.G. Kase, *Clinical Gynecologic Endocrinology and Infertility* (Baltimore, MD: Williams & Wilkins Co., 1978); S.J. Silber, *How Not To Get Pregnant* (New York, NY: Charles Scribner's Sons, 1987).

be used to predict ovulation, possibly up to 7 days in advance (2).

## Endometrial Biopsy

Endometrial biopsy involves microscopic examination of a sample of endometrial cells obtained

between days 22 and 25 (sometimes as late as day 26 or 27) of the menstrual cycle (assuming a regular, 28-day cycle). In the physician's office, a long hollow tube is passed through the cervix into the uterus and a small amount of tissue is scraped off the endometrium. By microscopic examination of these cells, the physician can date the endometrial lining in reference to the first day of the cycle. This dating of endometrial cells is accomplished by observation of the distinctive hormone-induced characteristics. The appearance of these cells changes daily under the influence of ovarian hormones (39).

During this stage of a normal menstrual cycle the endometrium is primed for implantation under the influence of progesterone, with the cells appearing secretory and spongy. If ovulation has not occurred or there is a luteal phase defect caused by inadequate progesterone secretion after ovulation, then the endometrial cells will not have the typical progesterone-induced appearance. If the characteristics of the endometrial cells can be dated to the appropriate day of the cycle (usually within 1 day), then normal ovulation and progesterone secretion have most likely occurred, suggesting normal ovulatory function.

### Ultrasonography

Use of ultrasound in infertility evaluation and treatment has become increasingly important. This technique uses high-frequency sound waves that are transmitted to one area of the body and echoed or reflected back by internal organs and structures. From the resulting patterns of transmission and reflection, detailed outlines of the female reproductive system can be obtained. Ultrasound is particularly useful in evaluating development of ovarian follicles during spontaneous or drug-induced cycles (16,34). If development of one or more follicles is monitored, and the subsequent collapse of these follicles after release of the ova can be visualized, then there is a good indication that ovulation has taken place. Ultrasound determination of ovulation is best used in combination with BBT, cervical mucus, or progesterone measurement. In some instances, ultrasound can be useful for visualization of growths or abnormalities in ovaries or the uterus. In addi-

tion, this technology is used in oocyte retrieval for in vitro fertilization (IVF).

### Hysterosalpingogram

The hysterosalpingogram (HSG) is a radiographic (x-ray) examination of the female reproductive tract. Radio-opaque dyes are slowly injected into the uterus while x rays are taken. As the uterus fills and the dye moves out into the interior of the fallopian tubes, the radiographs can pinpoint areas of occlusion, adhesions, growths, or abnormalities such as fibroids. In most cases of normal, healthy fallopian tubes, the dye fills the length of the tube and slowly spills out the far end into the body cavity (44). Some practitioners report therapeutic benefits from the use of oil-soluble rather than water-soluble dyes for HSG (15).

### Hysteroscopy

Hysteroscopy provides direct visualization of the interior of the uterus. The physician can evaluate directly any abnormalities that may be present in the uterus such as fibroids, polyps, a septum, or adhesions such as a web of scar tissue covering the uterine opening to the fallopian tubes. During hysteroscopy the uterus is expanded with injection of carbon dioxide gas or a liquid. This aids in visualization of tissue through the eyepiece of the hysteroscope, a long, narrow, illuminated instrument that is inserted through the cervix into the uterus. In addition to direct viewing, surgical procedures can also be performed by an experienced surgeon through the operating channel of the hysteroscope. These procedures include biopsies, removal of polyps, septums, scar tissue, fibroids, and removal of lost intrauterine devices. Some uterine and tubal abnormalities that do not appear with HSG or laparoscopy can only be detected by hysteroscopy (32).

### Laparoscopy

The laparoscope has become an essential tool in both the diagnosis and treatment of infertility (see figure 6-3). Laparoscopy, like hysteroscopy, allows direct visualization of the female reproductive tract through an illuminated long, narrow instrument. The laparoscope is inserted into the

**Figure 6-3.—Laparoscope in Use for Laser Surgery**

SOURCE: Martin M. Quigley, Cleveland Clinic, Cleveland, OH.

body cavity (usually through the umbilicus or naval) to view the outside (internal) surface of the uterus, ovaries, and fallopian tubes. To enhance the visualization of the peritoneal surface of these structures and assess patency of the fallopian tubes, a blue dye is often injected into the uterus and fallopian tubes, as in the HSG. To detect pelvic endometriosis, pelvic adhesions, and tubovarian adhesions, the laparoscope is usually necessary. As in the case of the hysteroscope, surgical procedures can be performed through the operating channel of the laparoscope, including lysis of pelvic adhesions and ablation of endometriosis (13,23). In addition to its diagnostic value, the laparoscope is frequently used to retrieve oocytes for IVF or gamete intrafallopian transfer.

### Post-Coital Test

A number of *in vivo* and *in vitro* procedures evaluate the interaction of sperm, semen, and cervical mucus. The oldest and most widely practiced of these techniques is the *in vivo* post-coital test

(also known as the Sims-Huhner test), which can be performed in a physician's office. Although this simple exam is widely used in infertility evaluation, there is lack of standardization and consensus on how to interpret the results (14).

This method evaluates sperm transport mechanisms within the female reproductive tract by directly examining under a microscope the interaction of sperm and cervical mucus. It should be performed as close to ovulation as possible, since cervical mucus is most conducive to sperm transport at that time. As ovulation approaches, the couple is asked to abstain from intercourse for several days prior to the planned test. One or two days before ovulation, the couple are instructed to have intercourse 2 to 4 hours before arriving at the physician's office (some physicians believe 6, 10, or even 24 hours after intercourse is a better indication of sperm transport). By means of a catheter, one to three samples of mucus are taken from different areas along the length of the cervical canal.

These specimens are evaluated for ferning pattern, spinnbarkeit, pH, cellularity, and debris, and for the number, motility, and quality of sperm present in the mucus sample. When examined under a microscope, a count of fewer than five motile sperm per field for mucus taken from the highest level of the cervical canal (internal os) indicates an abnormal post-coital test (37). Since inaccurate timing of this procedure is the most important cause of an abnormal result, negative post-coital tests should always be repeated. The presence of dead or nonmotile sperm can indicate a hostile cervical mucus or poor semen quality, which should be followed up by additional testing.

Several *in vitro* methods are also used to evaluate the quality of sperm-cervical mucus interaction. In a method devised by Kremer (25), cervical mucus collected around the time of ovulation is drawn up into a capillary tube (thin glass tubing) and the tube placed in a reservoir of the spouse's semen. Under normal conditions, the sperm can be observed penetrating the column of cervical mucus in one direction only when observed under low power through a microscope. If the sperm fail to move a set distance over a specified period of time, then subfertility may be suspected.

A variation on the Kremer method uses a commercially available preparation of small flat glass tubes filled with bovine cervical mucus (Pene-Trak™, Serono Diagnostics). Because of biochemical similarities between human and bovine cervical mucus, human sperm migrate up the Pene-Trak™ tube in a manner similar to their behavior when exposed to human cervical mucus. After a given period of time, the tube is examined under a microscope and the distance the sperm have penetrated the mucus column is measured. As with the Kremer method, failure of the sperm to move a minimal distance over a given period of time suggests an infertility problem (3,36). However, this test is not a substitute for human mucus in clinical testing (40).

### Sperm Antibody Evaluation

Antibodies to sperm maybe present in a significant portion of infertile couples. The exact extent or importance of these antibodies is unclear. However, some experts believe that antibodies can impair fertility by:

- impeding sperm penetration of cervical mucus,
- decreasing transport and viability of sperm in the oviducts,
- inhibiting sperm penetration of the ovum through blocking of possible receptor sites, or
- interfering with the normal postfertilization development of the fertilized ovum.

Antibodies are most readily diagnosed by examination of the postcoital test for sperm cervical mucus interaction, gelatin agglutination tests, sperm immobilization test, or the immunobead test (4). With improved sensitivity and better detection of minute quantities of sperm antibodies, diagnosis of immunological factors in infertility will most likely increase.

### **Diagnosics: Male Infertility**

Since less is known about male than female reproductive physiology, methods to diagnose and treat male infertility remain underdeveloped. The lack of comprehensive, standardized population data on various aspects of male infertility often results in a poor predictive value of test results. However, the present state of the art in male in-

fertility diagnostic tests can supply at least some information about the ability of an individual to impregnate a female partner. Until additional research and data analysis are conducted, the diagnosis and treatment of male infertility will remain difficult.

### **Semen Analysis**

The best diagnostic methods available to evaluate male infertility rely on the examination of a number of basic characteristics of sperm and seminal fluid (18). These parameters include the volume, pH, and viscosity of seminal fluid and the quantity, morphology, and motility of sperm in the sample. Basic sperm counts have been performed for many years as an index of male fertility, but recently developed tests can evaluate more subtle characteristics of the semen.

Since the evaluation of the semen has traditionally been subjective in nature, there is little standardization of diagnostic procedures. As a consequence, with the exception of total absence of sperm in the ejaculate, there remains less than total agreement over what constitutes a minimally adequate ejaculate necessary to achieve pregnancy (31,48). Introduction of computerized analysis may contribute to standardizing evaluation parameters and normal sperm characteristics between laboratories, and may provide objective criteria for measurements.

Since semen characteristics are subject to considerable fluctuation, semen analysis should be performed several times to ensure accurate evaluation of the ejaculate (46,48). The characteristics that can help in the diagnostic process include the following:

**Appearance:** The freshly collected semen sample should be whitish-gray in color. The presence of a bad odor or yellowish or red color may indicate infection or drug treatment (18).

**Volume: Average** semen volume ranges from 1.5 to 6 milliliters per ejaculate and varies depending on the period of abstinence between ejaculations. Even though smaller or larger semen volumes are often associated with infertility, the abnormal volume may not be the cause of the infertility but rather a symptom of some other condition. On the other hand, low semen volume may impair transport of sperm and high volume may dilute sperm density and decrease motility (18,31).

**Ejaculate pH:** Large deviations outside the normal pH range (7.2 to 7.8) can indicate inflammatory disorders of the prostate or seminal vesicles and may compromise fertility (18).

**Liquefaction and viscosity:** Usually the normal semen sample undergoes a transition from gel to liquid within 30 minutes of ejaculation. Liquefaction that does not occur or takes longer than 60 minutes may indicate prostatic disease and possibly trapped sperm contributing to infertility (18).

**Sperm concentration:** The concentration or count of sperm in the ejaculate is usually determined with the aid of a counting chamber such as a hemocytometer, a Makler chamber (30), or an automated device such as a Coulter counter or computer-assisted videomicrographic system. The actual number or concentration of sperm necessary to achieve pregnancy is still a matter of uncertainty. Statistical data and some clinical experience suggest that a sperm density of 20 million per milliliter is the lower limit of normal (29) but not the lower limit of fertility.

In general, 50 million to 60 million total sperm are usually necessary for fertilization (22). This assumes that the other characteristics of the sperm, such as motility and morphology, are good. However, men with sperm counts below this value may have reasonable chances for impregnation provided other characteristics of the ejaculate are normal (53). Since sperm density is a function of total semen volume as well as the number of sperm present, careful attention should be given to the natural fluctuation of semen volume and its influence on sperm counts.

**Sperm motility** Although motility of sperm has traditionally been a more subjective evaluation than sperm number, many investigators believe it to be the most important indicator of semen quality (18,31). In the simple slide technique, a small sample of the specimen is placed on a slide, coverslipped, and viewed under the microscope. The percent of motile sperm in several fields is determined and the motility itself rated on a +1 to +4 scale. Using this subjective analysis, 60 percent or more motility is considered normal. With the use of more objective techniques such as videomicrography, this figure may be lower (31).

Computer-assisted semen analysis involves a video camera and recorder integrated with a microscope. Images of sperm in the sample are digitized and sequential images are stored. Most commercial systems provide data on the percentage of motile sperm, the swimming speed or velocity, the percentage of progressively motile sperm and their swimming speed, the percent-

age of rolling sperm, and the percentage of straight-swimming sperm. Some systems offer information on other sperm parameters, such as lateral head displacement and linearity of motion.

Overall, computer-assisted analyses provide more objective information about sperm motility and swimming patterns. However, the accuracy of these systems may be low with samples having low sperm concentrations or large amounts of debris. At this time only a small number of the objective measures made possible by these systems has been correlated with infertility parameters (4). However, as these objective measures become more widely used and more information is collected, a better understanding of sperm characteristics may be achieved.

**Sperm morphology:** Morphological evaluation of human sperm is complicated by the great natural variation in shape and size. This makes it difficult to predict which forms are associated with infertility and which are within the normal range. Normal sperm have symmetrically oval heads with stout midpieces slightly longer than the heads. Also present are long, gradually tapering tails, 7 to 15 times longer than the heads. Ratios of these various parameters appear to be important predictors of fertility (4). Human semen always contains some abnormal or immature sperm forms but increased percentages of these types can decrease fertility. Analysis of sperm morphology has not found widespread use in clinical practice. However, with computer-assisted video micrographic systems, morphological characteristics may become better diagnostic tools.

**Fructose test:** Fructose is a sugar produced by the seminal vesicles and present in the normal ejaculate. When sperm are present in the semen sample, fructose is almost always present as well. However, in cases where no or few sperm can be observed in the sample, the absence of fructose suggests blocked or missing seminal vesicles or ejaculatory ducts. The presence of fructose in a sample with few or no sperm indicates functioning seminal vesicles with possible blockage further down in the epididymis or the vas deferens, or testes that are not producing sperm. Fructose is detected in the semen by the addition of chemical reagents and heat. Color change to orange-red indicates the presence of fructose (31).

**Agglutination and immunological disorders:** Immunological disorders, such as sperm antibodies or bacterial infections, can cause sperm to bind together, or agglutinate. This condition is observed microscopically and may be tail to tail, head to head, mixed, or agglutination with cellular debris

(18). The presence of antibodies can also be detected by sperm/cervical mucus interaction characteristics during the post-coital test. The importance of this parameter remains unclear.

**Infection screening:** As part of the evaluation of semen, routine cultures are also taken to detect the presence of micro-organisms such as ureaplasma, chlamydia, and others. The precise role of these infections in infertility is unclear.

### Hamster-Oocyte Penetration Test

The sperm/cervical mucus interaction tests evaluate sperm ability to navigate within the female reproductive tract. The hamster-oocyte penetration test examines sperm ability to penetrate the ovum once it has migrated into position. Usually, after capacitation for 18 to 20 hours, sperm are incubated with hamster eggs that have had their outer layer (zona pellucida) removed; normal human sperm usually penetrate these ova (52). If performed properly, there appears to be a correlation between the sperms' ability to penetrate the hamster and human oocytes. The reliability and significance of this test is controversial (10); however, further refinements and standardizations could make this an important diagnostic procedure for male infertility.

### Testicular Biopsy

In men with normal size testes, no sperm in the ejaculate (azoospermia), and normal FSH, a testicular biopsy may be performed to determine whether the underlying defect is failure or blockage of the sperm-conducting system or the absence of sperm production in the testes. The biopsy is performed under local or general anesthesia. A small sample of testicular tissue is removed through an incision in the scrotum. The tissue is placed in a fixing agent and examined by a pathologist microscopically (9). The physician examines the specimen to identify the sperm cells at different stages of development that indicate normal, ongoing production of sperm. The absence or small number of particular cell types can help identify the infertility factor.

### Radiography and other Methods

Lasography and vesiculography are diagnostic methods that employ radio-opaque dyes and x-ray examination of the sperm transport ducts. A

small incision is made in the scrotum and the vas deferens is exposed. Contrast dye is injected into the vas deferens or the ejaculatory duct and x rays are taken from various angles (see figure 6-4). This approach is particularly useful in pinpointing tubal obstruction in the male, since it gives an outline of the sperm transport system (48). Examination of the blood supply to the testis can also provide valuable diagnostic information in identifying varicocele. Venography or injection of contrast dye into the spermatic vein can verify a varicocele that may have escaped physical examination. Scrotal thermography, ultrasound, technetium scan, and Doppler test can also be useful for identification of varicocele and other vascular disorders of the male reproductive system (11,19).

Figure 64 Vasogram



## Endocrine Evaluation

Since sperm production is critically dependent on hormones produced by the testes, such as testosterone, and on hormones produced at other sites in the body, such as the gonadotropins (LH and FSH), the hormonal workup is an essential part of male infertility diagnostic procedures. Basic endocrinological tests include blood assay for LH, FSH, and testosterone. Other hormones that may be examined are prolactin, thyroid hormones, estradiol, and adrenocorticoids. In addition, in a few instances the competence of the pituitary/testicular system is assessed by the luteinizing hormone-releasing hormone (LH-RH, also known as Gn-RH) test. This involves injecting LH-RH and carefully monitoring the gonadotropin and testosterone response to this stimulation (26)31).

## Sexual Dysfunction

Sexual dysfunction should trigger a psychosexual evaluation by a trained psychologist or psychiatrist in the search for a cause for infertility. Physical examination of a patient who describes problems with impotence (erectile dysfunction) may include an assessment of erectile capacity. Determining the occurrence of erections during sleep (nocturnal penile tumescence, NPT) is considered one of the best means for distinguishing between physiologic and psychogenic causes of sexual dysfunction. NPT monitoring is best performed in the laboratory, where multiple sleep



Photo credit: DACOMED Corp., Minneapolis, MN

Penile rigidity monitor

characteristics can be recorded. The principle of the monitoring device is a strain gauge worn around the penis, which indicates changes in penile circumference during sleep. Erectile function has also been evaluated using ultrasound evaluation of the blood supply to the penis during drug-induced erection. (For additional discussion of impotence, see ch. 7.)

Retrograde ejaculation may be suspected when a patient fails to produce a semen sample or produces a small ejaculate. Diagnosis of this condition is most easily accomplished by observation of large numbers of sperm in the urine specimen taken soon after ejaculation. Full investigation of the etiology of this disorder may require a complete neurological assessment (18).

## Risks of Diagnostic Procedures

Tests and procedures performed in any specialty of medicine have certain known (and unknown) risks associated with them. Some infertility diagnostic and treatment procedures also fall into this category. Although some of these risks have been documented in the medical literature, others remain unknown or unreported.

Most procedures performed as part of an infertility workup have relatively minor risks associated with them. For example, endometrial biopsy is considered a generally safe procedure. Possible side effects of this procedure include pain, bleeding, and uterine cramping. More serious complications of this procedure, although uncommon, can result from accidental uterine perforation. In addition, if this biopsy is inadvertently performed during early pregnancy, spontaneous abortion is possible (21,47).

Hysterosalpingogram is often a painful procedure. In some cases severe pain may require administration of analgesics. The major risks of this procedure include the spread of micro-organisms from cervix to upper genital tract, the reactivation of dormant pelvic organ infections. However, infection occurs in only a small percentage of women after HSG, usually those with a previous history of this condition (21,44,47). Other possible complications include lung emboli and respiratory distress, which can have severe consequences. In addition, the risks associated with



small amounts of radiation exposure to the ovary are unknown (21).

It is not known if there is risk to the offspring from HSG inadvertently performed during early pregnancy. There is concern about radiation exposure of an early embryo; however, the dose of radiation from HSG is on the order of 1 rad or less. This amount of radiation appears unlikely to result in an increase in adverse pregnancy outcome (28). Whether or not HSG can dislodge an implanted blastocyst is uncertain but this possibility appears unlikely (47). In order to avert any theoretical risks to the early embryo, HSG is customarily performed prior to the anticipated time of ovulation.

Laparoscopy is a common procedure for both diagnosis and treatment of infertility. This procedure carries risks such as anesthesia complications, infection, or tissue damage, similar to those associated with other surgical procedures. The most common risk is post-surgical infection. Typical infection rates are two to three per thousand for laparoscopy. (6,41,42). Of these, most infections are superficial, involving the incisions in the abdominal wall, although more serious infections can occur.

Other risks associated with laparoscopy include injuries to intra-abdominal organs. These are associated in diagnostic procedures with introduction of instruments through the abdominal wall. In conventional laparoscopy, the initial step in the operation is the establishment of a space around the reproductive organs by placing two or three liters of gas (often carbon dioxide or air) into the peritoneal cavity. This gas lifts the abdominal wall off the internal organs permitting more space for insertion of instruments and a clearer view of the intra-abdominal contents. The placing of the gas is often accomplished with a long needle, placed into the abdomen. Misplacement of the needle into intestinal or blood vessels may be associated with severe injury to these organs and the need for major surgical repair (47).

In laparoscopic procedures where intra-abdominal surgery is also performed, another opportunity for internal organ injury exists—thermal injury to the intestine during cauterization of the fallopian tubes for sterilization. A final source of

complications during laparoscopy is the gas used to lift the anterior abdominal wall from the viscera. Gas-related shoulder discomfort after surgery is common, but serious complications are rare. Gas emboli may be associated with exceptionally large volumes or pressures of gas or with accidental injection of gas into a vessel.

Complications of hysteroscopy can include those attributable to the distending media and those associated with surgery, such as infection, anesthesia-related complications, or uterine *perforation*. Carbon dioxide used as the distending medium can cause hypercarbia, acidosis, and cardiac arrhythmias (43), although a review of 1,500 cases in which carbon dioxide was used showed no complications and there were no changes in pH, pCO<sub>2</sub>, or electrocardiogram in 40 monitored patients (27). The insertion of instruments into the uterus introduces the possibility of perforation of the uterus. Pelvic infection after hysteroscopy is unusual although the incidence of this complication appears to increase if surgical procedures are performed (5,51).

Since far fewer diagnostic tests exist to evaluate male infertility problems, the known risks of male infertility workup are fewer. For example, there are no known hazards associated with semen analysis, the most common and important diagnostic procedure for males. However, invasive techniques such as testicular biopsy can result in bleeding, infection, and possibly trauma to the testis causing transient decrease in function (47). Injection of radiologic contrast material into the vas deferens in lasography has been used to visualize portions of the male genital duct system. This procedure carries with it the possibility of injury to the vas or epididymis as well as exposure to x rays (45).

The degree of risks associated with any of these diagnostic procedures (as well as all medical procedures) are profoundly influenced by the skill with which they are performed. Relatively safe procedures can result in severe complications if performed by inexperienced and unqualified professionals. On the other hand, physicians with appropriate skill and training can provide safe and effective infertility workups, even if complicated

procedures are required. In addition, although certain risks to these procedures are known and can

be avoided, there may be additional unknown risks.

## SUMMARY AND CONCLUSIONS

Although an individual's reproductive capacity can be estimated with several methods, fertility is a product of the specific interactions of a couple. Evaluation of infertility, therefore, must consider the couple as a unit.

A thorough assessment of fertility extends beyond an evaluation of reproductive organs and reproductive cells (sperm and eggs). Physical examination of the infertility patient, for example, includes assessment of circulatory, endocrine, and neurologic function. Oral or written history-taking collects a broad range of medical and lifestyle characteristics that may influence reproductive health.

Examination of a male patient is simplified by the fact that his reproductive organs and germ cells (sperm) are readily accessible. However, this ease of accessibility is not accompanied by better and more varied infertility treatments in the male. This is due, in part, to a continued lack of knowledge about male reproductive physiology. Although semen analysis does permit evaluation of several aspects of male reproductive function and of semen quality and quantity, much uncertainty remains about what parameters can reliably differentiate sperm capable of fertilizing an egg from those that are not.

Female reproductive health can be estimated through a variety of indirect indicators (e.g., menstrual regularity, hormone levels, properties of

cervical mucus) and direct methods (e.g., tissue biopsy, laparoscopy, ultrasound imaging). These tests can often pinpoint easily treatable conditions or, in contrast, disorders so severe that successful pregnancy is highly unlikely. Even with the current sophisticated level of diagnostic technology, however, no fertility test can positively predict a woman's ability to conceive or maintain a pregnancy.

Present diagnostic methods are able to identify a factor contributing to infertility in the majority of cases. In cases of idiopathic (unexplained) infertility, diagnostic technologies have failed. Techniques that consider the interaction and compatibility of a couple as a unit (e.g., interaction between sperm and cervical mucus) provide some of the best predictors of a couple's ability to have a child. More basic and applied research are needed in this area. Until more is known about reproductive dysfunction, successful reproduction will remain the only absolute verification of a couple's fertility.

Like many medical procedures, some tests used in an infertility diagnostic workup have certain risks associated with them. These risks are often similar to those associated with other medical and surgical procedures and can depend on the skill and training of those performing the procedures.

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