31. INFERTILITY AND ASSISTED REPRODUCTIVE TECHNOLOGIES

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I. **Infertility**
   A. **Definition.** Infertility is defined as the failure of a couple of reproductive age to conceive after at least 1 year of regular coitus without contraception. Primary infertility exists when a woman has never been pregnant. Secondary infertility occurs when a woman has a history of one or more previous pregnancies. Fecundability is the probability of achieving a pregnancy within one menstrual cycle. For a normal couple, this is approximately 25%. Fecundity is the ability to achieve a live birth within one menstrual cycle.
   B. **Incidence.** Recent data estimate that 10–20% of couples are infertile. In recent years, there has been an increasing demand for infertility services, especially in Western countries. The main reason for this is the tendency of women to delay childbearing because of career work. Other factors include an increase in the variety and effectiveness of assisted reproductive technology (ART) treatments, an increased public awareness of these treatments, an increase in tubal factor infertility as a consequence of sexually transmitted diseases, and a relative scarcity of babies placed for adoption because of effective contraception and increased availability of abortion services. In 1997 alone, 335 fertility clinics in the United States reported performing 71,826 ART treatment cycles that resulted in 17,054 deliveries of one or more living infants and a total of 24,582 babies born.
   C. **Differential diagnosis** (Table 31-1). The differential diagnoses of infertility encompass five principal categories: male factors, cervical factors, problems with the uterus or female pelvic organs or both, ovulatory problems, and unexplained causes. In addition, immunologic factors involving antiovarian or antisperm antibodies may adversely affect fertility by impairing fertilization, destroying gametes, and interfering with embryo cleavage or implantation. Their significance is controversial.

Differential diagnosis	%	Basic evaluation
Male factors	30	Semen analysis
Tubal/uterine/peritoneal factors	25	Hysterosalpingogram, laparoscopy, chromopertubation
Anovulation/ovarian factors	25	Basal body temperature chart, midluteal progesterone level, endometrial biopsy, luteinizing hormone testing
Cervical factors	10	Postcoital test
Unexplained infertility	10	All of the above

TABLE 31-1. DIFFERENTIAL DIAGNOSIS OF INFERTILITY

II. **Evaluation.** Successful reproduction requires proper structure and function of the entire reproductive axis, including hypothalamus, pituitary gland, ovaries, fallopian tube, uterus, cervix, and vagina. To assess this axis, the infertility evaluation comprises seven major elements:
- History and physical examination
- Semen analysis
- Sperm–cervical mucus interaction (postcoital testing)
- Testing for ovulation
- Evaluation of tubal patency
- Detection of uterine abnormalities
- Determination of peritoneal abnormalities

If these are properly coordinated, the evaluation can be completed in one menstrual cycle (Fig. 31-1). After the completion of the steps outlined in sec. **II.A**, sec. **II.B**, sec. **II.C**, sec. **II.D**, sec. **II.E**, sec. **II.F**, sec. **II.G** and sec. **II.H**, no abnormality or cause of infertility can be identified in 15% of couples. This group comprises a category known as “unexplained infertility.”

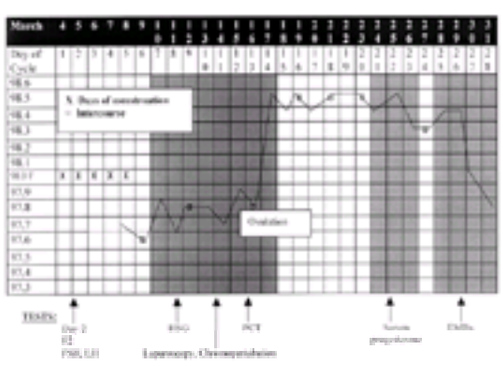

FIG. 31-1. Sample basal body temperature chart with complete infertility evaluation within one menstrual cycle. E2, estradiol level; EMBx, endometrial biopsy; FSH, follicle-stimulating hormone level; HSG, hysterosalpingogram; PCT, postcoital test.

A. **History and physical examination.** The initial assessment begins by obtaining an extended and complete history from both partners and performing a physical examination. A sexual history should include the frequency and timing of intercourse, as well as information regarding menstruation, impotence, dyspareunia, the use of lubricants, and sexually transmitted diseases.
B. **Semen analysis.** The semen sample should be collected after a period of abstinence of at least 48 hours and should be evaluated within 1 hour of ejaculation. The sample is obtained either by masturbation or by sexual intercourse with a silicone condom, as latex condoms are spermicidal. Normal parameters according to the World Health Organization are, per 1 mL volume: 20 million sperm or more, greater than 50% motility, greater than 30% normal morphology. If abnormalities are present, the patient should be referred to a urologist specializing in infertility to be evaluated for reversible causes of male-factor infertility.
C. The **postcoital test (PCT** or **Huhner test)** allows direct analysis of sperm and cervical mucus interaction and provides a rough estimate of sperm quality.
   1. The test is done between days 12 and 14 of a 28–30 day menstrual cycle (after 48 hours of abstinence) when there is maximum estrogen secretion. The mucus is examined within 2–8 hours.
   2. Because interpretation of the PCT is subjective, the validity of the test is controversial despite its long history of use. However, a finding of 5–10 progressively motile spermatozoa per high-power field and clear acellular mucus with a spinnbarkeit (the degree to which the mucus stretches between two slides) of 8 cm generally excludes a cervical factor. Fecundity rates do not correlate directly with number of motile sperm seen.
   3. The most common cause of an abnormal PCT is poor timing. Other causes include cervical stenosis, hypoplastic endocervical canal, coital dysfunction and male factors. The sample can also be assessed for pH, mucus cellularity, WBC, ferning. Clumping and flagellation of sperm without progression are often suggestive of antisperm antibodies.
D. The **basal body temperature (BBT) chart** (Fig. 31-1) is a simple means of determining whether ovulation has occurred. The woman's temperature is taken daily with a thermometer on awakening, before any activity, and is recorded on a graph. After ovulation, rising progesterone levels increase the basal temperature by approximately 0.4°F (0.22°C) through a hypothalamic thermogenic effect. Because the rise in progesterone may occur anytime from 2 days before ovulation to 1 day after, the temperature elevation does not predict the exact moment of ovulation but may establish that it has occurred. A temperature elevation that persists for less than 11 days is suggestive but not diagnostic of a luteal phase defect.
E. **Midluteal phase progesterone level** is another test to assess ovulation. A concentration greater than 3.0 ng/mL in a blood sample drawn between days 19 and 23 is consistent with ovulation, whereas a concentration greater than 10 ng/mL implies adequate luteal support. Luteal phase deficiency is diagnosed histologically, because the progesterone level does not indicate the cumulative response of the endometrium to progesterone during the luteal phase.
F. An **endometrial biopsy** evaluates the response of the endometrium to progesterone. The test is usually performed between days 24 and 26 of a 28 day menstrual cycle or 2–4 days before anticipated menstruation. The biopsy documents ovulation by histologic demonstration of decidualized stroma, allows for dating of the endometrium within 2–3 days, and assesses for endometritis. The date of the biopsy and the subsequent menstrual cycle are used to determine whether a luteal phase deficiency is present. Correlation of endometrial dating with the rise in BBT or luteinizing hormone (LH) surge or both is also helpful. A luteal phase defect may result from inadequate estrogen priming, progesterone secretion, or endometrial response. The risks of the procedure are minimal, but include infection, bleeding, interruption of pregnancy, and uterine perforation.
G. The **hysterosalpingogram (HSG)** assesses uterine and fallopian tube contour and tubal patency. It is performed in the early follicular phase, within 1 week of cessation of menstrual flow. This timing minimizes the chances of interrupting a pregnancy. The procedure is performed by injecting a radiopaque dye through the cervix. As more dye is injected, the dye passes through the uterine cavity into the fallopian tubes and peritoneal cavity. Permanent radiographic films are made under fluoroscopy to demonstrate patent or obstructed tubes. Nonsteroidal anti-inflammatory drugs may be given to prevent cramping. Prophylactic antibiotics (e.g., doxycycline, 100 mg orally twice daily) are advisable when the patient has a history of pelvic inflammatory disease or when hydrosalpinges are identified during the study. Cervical cultures for gonorrhea and *Chlamydia* infection should confirm negative results before instrumentation to avoid an iatrogenic peritonitis.
H. A **diagnostic laparoscopy** assesses peritoneal and tubal factors such as endometriosis and pelvic adhesions, and can provide access for simultaneous corrective surgery. Laparoscopy should be scheduled in the follicular phase, as with HSG, and is the final and most invasive step in the patient's evaluation, unless the HSG raised suspicion of abnormalities. Findings on HSG correlate with laparoscopic findings 60–70% of the time. Dye (usually a dilute solution of indigo carmine) should be instilled through the fallopian tubes (chromopertubation) during laparoscopy to visually document tubal patency. Hysteroscopy may also be included to ensure that no abnormalities were missed on the HSG.

III. **Treatment.** Before progressing to assisted reproductive technologies, an infertility patient should undergo treatment for reparable problems.
   A. **Anovulation.** The agents most commonly used to stimulate multiple ovarian follicles are clomiphene citrate (CC), human menopausal gonadotropins (hMG), and purified follicle-stimulating hormone (FSH). CC, a synthetic, nonsteroidal estrogen agonist-antagonist, increases the release of gonadotropin-releasing hormone (GnRH) and subsequent LH and FSH release. CC is useful in women with oligomenorrhea and amenorrhea with intact hypothalamic-pituitary-ovarian axes. If the patient is anovulatory, CC is often used before diagnostic procedures continue. Patients who are overweight and hyperandrogenic are the least likely to respond to CC. GnRH, hMG, FSH, and bromocriptine mesylate are used primarily in women who fail to respond to CC or who have hypogonadotropic amenorrhea or unexplained infertility. Prescription of these expensive drugs, which are used in the more complicated protocols for in vitro fertilization (see later), should be left to specialists trained in their use.
   B. **Hyperprolactinemia. Bromocriptine** is used to induce ovulation in patients with hyperprolactinemia. Bromocriptine is a dopamine agonist that directly inhibits pituitary secretion of prolactin, which restores normal gonadotropin release. The usual starting dose is 2.5 mg each bedtime to prevent dopaminergic side effects, which include nausea, diarrhea, dizziness, and headache. If oral administration cannot be tolerated, vaginal administration is recommended. A response is usually seen in 2–3 months, and 80% of hyperprolactinemic patients ovulate and become pregnant. CC is added if ovulation does not occur within 3 months after beginning treatment.
   C. **Thyroid problems** should be treated appropriately, as both hypothyroidism and hyperthyroidism may lead to infertility.
   D. **Hypothalamic-pituitary axis problems**, including extreme weight gain or loss, excessive exercise, and emotional stress, can all impact the secretion of GnRH from the hypothalamus and cause ovulatory dysfunction. These must be addressed by appropriate behavioral or psychological intervention.
   E. **Male factor infertility.** Although the gynecologist does not treat male patients directly, therapies to treat male factor infertility often involve hormonal manipulation in the female partner. The evaluation is analogous to that in the woman, with examination of the hypothalamic-pituitary-testicular axis, outflow tract, and testicular function. Toxins, viruses, sexually transmitted diseases, varicoceles, and congenital problems can all influence infertility. Fortunately, the initiation of intracytoplasmic sperm injection has revolutionized treatment of male infertility. As long as viable sperm can be retrieved by ejaculation, epididymal aspiration, or testicular biopsy, successful fertilization and pregnancy can be achieved. The current fertilization rate is 95% and the pregnancy rate is comparable to that of in vitro fertilization (IVF).
   F. **Endometriosis**, the ectopic growth of hormonally responsive endometrial tissue, may account for 15% of infertility in women; it is diagnosed and staged by laparoscopy. Endometriosis has a negative impact on fertility, and once diagnosed, it should be treated surgically before instituting infertility therapy. Laparoscopic resection or ablation of even minimal endometriosis may enhance fecundity in infertile women. If pregnancy fails to occur after surgical treatment, IVF or gamete intrafallopian transfer (GIFT) may be used. GnRH agonists, danazol, and continuous oral contraceptive pills may be used for the treatment of pain symptoms, but each will prevent pregnancy during its use.
   G. **Luteal phase defects** occur in both fertile and infertile women, and treatment is controversial. Nevertheless, in a couple with documented infertility, it is prudent to treat luteal phase deficiency with intramuscular or intravaginal progesterone until the luteoplacental shift occurs at 8–10 weeks gestational age.
   H. **Uterine factors** such as submucous leiomyomas, intrauterine synechia (Asherman's syndrome), and uterine deformities or septa cause approximately 2% of infertility. The mainstay of treatment for these conditions is surgical correction, usually via a hysteroscopic approach.
   I. **Infections** of the female and male genital tracts have been implicated as causes of infertility. *Chlamydia* infection and gonorrhea are the major pathogens and should be treated appropriately. *Ureaplasma urealyticum* and *Mycoplasma hominis* have also been implicated, however. If *U. urealyticum* and *M. hominis* are identified by culture, the patient should be treated with doxycycline, 100 mg by mouth twice daily for 7 days. This has been shown to increase the pregnancy rate in patients with primary infertility.
   J. **Tubal factor infertility** has become more prevalent with the increased incidence of salpingitis. The frequency of tubal occlusion after one, two, and three episodes of salpingitis is reported to be 11%, 23%, and 54%, respectively. Appendicitis, prior abdominopelvic surgery, endometriosis, and ectopic pregnancy can also lead to adhesion formation and damaged tubes. **Proximal** tubal obstruction is identified on HSG. Tubal spasm may mimic proximal obstruction, however, and obstruction should be confirmed by laparoscopy. Treatment consists of tubal cannulation, microsurgical tubocornual reanastomosis, or IVF. **Distal** tubal disease or distortion can be seen on HSG and laparoscopy. The success of corrective surgery (neosalpingostomy) depends on the extent of disease.

IV. **Assisted reproductive technologies.** Louise Brown, the first child successfully conceived by IVF, was born in 1978. Since then, several techniques have been developed that enhance our ability to overcome infertility. Among these are the ability to cryopreserve or freeze oocytes and use donor sperm and oocytes. Of all ART procedures nationwide, 29.5% resulted in pregnancy according to the 1997 National Fertility Clinic data. Over 50% of pregnancies resulted in single live

births whereas 25.9% resulted in twins and 5.3% in triplets or higher multiples. Miscarriages occurred in 14.5%, ectopic pregnancies in 0.3%, and stillbirths in 0.6%. The following types of procedures, listed in chronologic order of their development, are currently used.

A. In **gamete intrafallopian transfer**, extraction of oocytes is followed by the transfer of gametes (sperm and oocyte) into a normal fallopian tube by laparoscopy. GIFT requires general anesthesia and does not allow for visual confirmation of fertilization. If pregnancy does not occur, there is no way to determine if the cause is failure of fertilization or failure of implantation. The overall 1997 live birth/retrieval rate was 29.8%. (The statistics presented here are all for fresh, nondonor cycles.)
B. **Zygote intrafallopian transfer (ZIFT)** refers to the placement of embryos into the fallopian tube after oocyte retrieval and fertilization. It combines features of in vitro fertilization and GIFT. The overall 1997 live birth/retrieval rate was 28.0%.
C. **In vitro fertilization** refers to controlled ovarian hyperstimulation, ultrasonographically guided aspiration of oocytes, laboratory fertilization with prepared sperm, embryo culture, and transfer of the resulting embryos into the uterus through the cervix. Although most IVF procedures use fresh oocytes from the patient, transfer of frozen oocytes and transfer of "donor eggs" are also options. The overall 1997 live birth/retrieval rate was 27.7%. For patients undergoing IVF, the pregnancy success rate varies little by cause of infertility, with a success rate approximating the overall national rate in women with most diagnoses. The cumulative pregnancy rates increase as patients complete more cycles (after three cycles, 38%; after four cycles, 47%; after five cycles, 49%; and after six cycles, 58%). Frozen embryos yielded a live birth rate/transfer of 18.6% compared to 29.7% for fresh embryos (Table 31-2).

Diagnosis of patients undergoing IVF	Percentage of total cases	Live births per cycle (%)
Pelvic (or tubal) factor	27.9	24.2
Male factor	26.0	25.5
Endometriosis	14.6	24.5
Ovarian	12.6	22.6
Unexplained infertility	8.5	24.8
Other (immunologic or serious illness)	8	19.9
Uterine	2.2	18.9

Adapted from Figures 6 and 14 of the National Summary and Fertility Clinic Report, 1997.

TABLE 31-2. IN VITRO FERTILIZATION (IVF) SUCCESS RATES

D. In **intracytoplasmic sperm injection**, a single spermatozoon is injected into each oocyte, and the resulting embryos are transferred transcervically into the uterus. To date, no increased risk of congenital malformation has been seen. There is great concern, however, over the possibility of transmitting genetic defects to offspring during intracytoplasmic sperm injection, which may be responsible for infertility in the father.
E. **Indications for in vitro fertilization**
   1. **Tubal conditions**—large hydrosalpinges, absence of fimbria, severe adhesive disease, repeated ectopic pregnancies, or failed reconstructive surgical therapy.
   2. **Endometriosis** increasing as an indication for IVF, if other forms of treatment have failed.
   3. **Unexplained infertility**
   4. **Male factor infertility** low sperm count, low sperm motility, and abnormal morphology are associated with reduction in fertilizing ability.
   5. **Uterine malformations** related to diethylstilbestrol exposure.
F. **Controlled ovarian hyperstimulation and protocols for in vitro fertilization.** The agents most commonly used to stimulate multiple ovarian follicles are CC, hMG, and purified FSH. The particular products and protocols used may be tailored as the treatment proceeds to boost the chances of an adequate response and increase the pregnancy rate.
G. **Clomiphene-only** regimens are given on days 5–9 of the menstrual cycle. Response may be followed by BBT measurement, ultrasonography, and measurement of LH and estradiol levels. CC is inexpensive and has a low risk of ovarian hyperstimulation syndrome (OHSS). However, it creates a low oocyte yield (one or two per cycle) with frequent LH surges that lead to high cancellation rates in IVF cycles and low pregnancy yield. Most treatment regimens start with 50 mg/day for 5 days. If ovulation fails to occur, the dose is increased to 100 mg/day. The maximum dose is 250 mg/day. Human chorionic gonadotropin (hCG), 5000 IU to 10,000 IU, may be used to simulate an LH surge. Eighty percent of properly selected couples will conceive in the first three cycles after treatment. Potential side effects are vasomotor flushes, blurring of vision, urticaria, pain, bloating, and multiple gestation (5–7% of cases, usually twins).
H. **Clomiphene/hMG combinations** are used to increase the number of recruited follicles. The hMG and purified FSH are useful in patients who do not achieve pregnancy with CC and in patients with endometriosis or unexplained infertility. The hMG, which is a combination of LH and FSH, is given for 2–7 days after the clomiphene. This treatment is more expensive and can lead to life-threatening OHSS. Trade names for hMG include Humegon, Pergonal, and Repronex. Follicle maturation is monitored using sonography and serial measurement of estradiol levels. To complete oocyte maturation, hCG needs to be given once the follicles have reached 17–18 mm in diameter. Aspiration of follicles should be timed 35–36 hours after the hCG injection. The disadvantages of this protocol include premature luteinization, spontaneous LH surges that result in high cancellation rates, and multiple gestations.
I. **Gonadotropin-releasing hormone analogs/agonists (GnRHa)** are used via a flare-up protocol or a luteal phase protocol. The flare-up protocol causes an elevation of FSH in the first 4 days, which increases oocyte recruitment. After 5 days of administration, the GnRH agonist then down-regulates the pituitary to prevent premature luteinization and a spontaneous LH surge. The luteal phase protocol involves starting GnRHa administration on the seventeenth to twenty-first menstrual day. GnRHa increase the number, quality, and synchronization of the oocytes recovered per cycle and thereby improve the fertilization rate, the number of embryos, and the pregnancy rate. Successful ovulation rates are 75% to 85%. GnRHa are expensive and more complex to use, however, and can lead to OHSS.
J. **GnRH analogs/antagonists** are the latest addition to the fertility drug armamentarium. They block LH secretion without causing a flare-up effect. They are administered in a single dose on the eighth menstrual day or in smaller doses over 4 days. Because they block the periovulatory LH surge, fewer gonadotropins are required to stimulate ovulation, and side effects are decreased.
K. **Oocyte retrieval, culture fertilization, and transfer**
   1. The two major techniques of oocyte retrieval are ultrasonographically guided follicular aspiration and laparoscopic oocyte retrieval. The former is the most widely used technique. **Ultrasonographically guided oocyte retrieval** using a 17-gauge needle passed through the vaginal fornix is performed 34–36 hours after hCG injection. The procedure is done under heavy sedation. Potential complications include risk of bowel injury and injury to pelvic vessels.
   2. **Oocyte fertilization.** Sperm are diluted, centrifuged, and incubated before 50,000–100,000 motile spermatozoa are added to each Petri dish containing an oocyte. Fertilization is documented by the presence of two pronuclei and extrusion of a second polar body at 24 hours. At that stage, most embryos are cryopreserved for an unlimited period, with a survival rate of 75%.
   3. **Embryo transfer** is most commonly carried out 48–80 hours after retrieval at the four- to ten-cell stage. In general, no more than two embryos are transferred to limit the risk of multiple gestation and to optimize pregnancy rates. The actual number of embryos transferred depends on the individual's age and other risk factors for multiple pregnancy. It is common practice to supplement the luteal phase with progesterone given by vaginal suppository, beginning the day of oocyte release and continuing into the twelfth week of pregnancy.
   4. **Retrieval and pregnancy results.** Most programs have delivery rates of approximately 20% for women under the age of 40 years who are not affected by male factor infertility. The risk of ectopic pregnancy is 4% to 5%, and the risk of heterotopic pregnancies is less than 1%. Multiple gestation rate is approximately 30% (25% twins and 5% triplets). Summary of national data for 1997 showed that the average age of the woman was 35 years. A woman's chances of success with ART using her own eggs decrease at every stage as her age increases. The likelihood of implantation of a fertilized oocyte depends on the age of the oocyte donor, not that of the receiver; therefore, older women commonly use donor oocytes to improve chances of success.