CLINICAL REVIEW

A Primary Care Approach to the Infertile Couple

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Background: **Approximately 20% of reproductive age couples have difficulty conceiving or maintaining an established pregnancy. The family physician is in a unique position to provide patient education, begin initial evaluation, make appropriate referrals, and offer ongoing counseling and support to couples who experience problems with fertility.**

Methods: **And extensive clinical review was conducted based on a MEDLINE search, the Cochrane database of systematic reviews, and other supporting evidence.**

Results: **Major physiologic influences affecting live birth rates include age, coital frequency, and duration of infertility. Male factor is associated with approximately 40% of these cases and should be addressed early in the evaluation.**

Conclusion: **Many conditions once considered untreatable can now be routinely corrected. As managed care programs expand coverage to include infertility services, primary care providers will be asked to participate in the initial phase of this care. This article offers a practical approach. (J Am Board Fam Pract 2001;14:33–45.)**

Family physicians are frequently the first clinicians consulted by patients concerned about potential infertility. Because of the anxiety that often accompanies early attempts to conceive, it is important for providers to have accurate knowledge about what represents normal fecundity, when a couple's fertility should be investigated, and the availability of various treatment options. Establishing a good referral network of specialists is essential in dealing with difficult cases and in helping couples achieve successful pregnancies.

Methods

Using MEDLINE, the Cochrane database of systematic reviews, and other supporting evidence, we undertook an extensive review of the published literature, applying the key words "infertility" and "habitual abortion."

Aspects of Fertility

Fecundability is the ability to achieve a recognized pregnancy within one menstrual cycle.[1] Many mathematical models exist to describe fecundability in so-called normal populations. For example, the interconceptual period of Hutterite women, a religious group refusing access to birth control, is often compared with other populations.[2] Other models are based on observations of fertile women undergoing artificial donor insemination for treatment of male azoospermia and on otherwise healthy women seeking routine gynecologic care.[3,4] From these studies, probability of conception curves have been constructed and provide a basis for deciding when extensive investigation is warranted or when a proposed therapy is efficacious. Only one in five (20%) couples actively trying to conceive will be successful in a given month. Yet, the other 80% can be reassured by the knowledge that more than 85% will become pregnant within the first year.[3,4]

Once couples are able to conceive, a live birth is anticipated. Unfortunately, many pregnancies result in spontaneous abortion. The ability to deliver a liveborn is affected most by maternal age.[5–8] The risk of having a clinically recognized spontaneous abortion increases from approximately 10% for those younger than 30 years, to 18% for those in their late 30s, to 34% for those in their early 40s.[9] Women older than 35 years are more likely to have difficulty with chromosomal nondisjunction and associated aneuploidy. Depending on the karyotype

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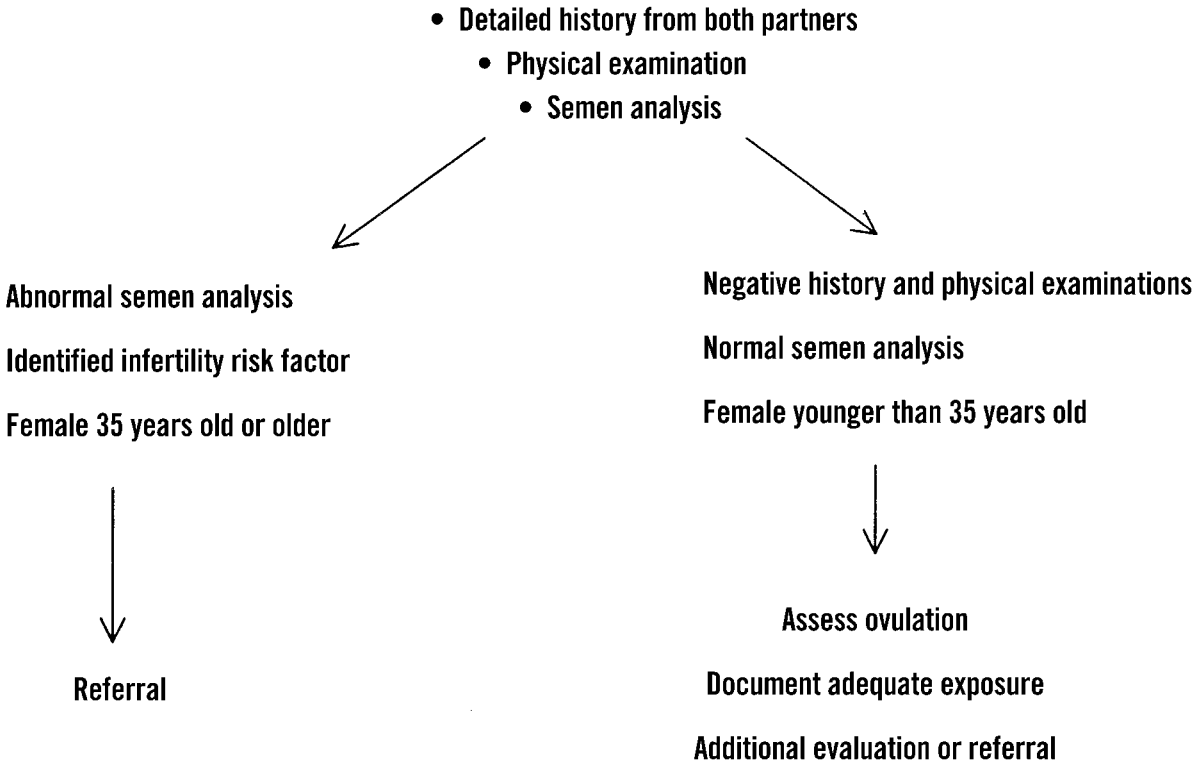

Figure 1. Initial screening evaluation.

of the conceptus, these patients can give birth to genetically compromised infants or experience stillbirth, miscarriage, and failed implantations.[7]

Genetics aside, the older patient has had more time to develop pelvic adhesions secondary to untreated pelvic infection or occult endometriosis.[6] Additionally, this group is at increased risk for ovulatory dysfunction and associated luteal phase abnormalities.[8] Coital frequency often decreases with age, potentially enhancing the contribution that timing of intercourse makes in cases of infertility.[5] By the time a woman is 35 years old, the quoted live birth rate for her age-group is one-half that of the younger population. The likelihood of a successful outcome in these women is lower even if actual pathologic conditions are diagnosed and treated.

The length of time a couple has been attempting to conceive has an independent impact on prognosis, especially for those couples with normal findings on evaluation. Couples with infertility spanning 4 or more years tend to have a poor prognosis.[9]

Local referral patterns clearly affect the respective infertility diagnoses encountered in a particular setting. Examining diagnoses of couples undergoing infertility investigation shows that male factor causes are found up to 40% of the time.[10] Among women, pelvic conditions (endometriosis, tubal disease, pelvic adhesions, etc) account for 30% to 40% of cases, while ovulatory dysfunction and cervical factors each contribute another 10% to 15%. A smaller percentage (5%) relate to other causes, such as hypothyroidism, immunologic factors, and luteal phase defect. Roughly 10% remain unexplained even after thorough investigation.[10]

Knowledge of these factors and their relative contribution to the problem of infertility will help the family physician begin a directed screening evaluation of affected couples in the ambulatory setting. Women older than 35 years or those at high risk for infertility based on medical history should be promptly evaluated as soon as the question of infertility arises. On the other hand, young couples with normal medical histories who have been trying to conceive for less than 1 year can be observed for an appropriate time based on anticipated fecundability rates. For these patients, a screening semen analysis and documentation of ovulation can be initiated as a means of reassurance

Table 1. Important History and Physical Findings.

Type of Problem	Specific Indicators
Sexual techniques	Vaginal lubricants
	Douching after coitus
	Poor timing related to actual fertile period
Sexual dysfunction	Incomplete penetration:
	Male: erectile dysfunction, premature ejaculation
	Female: vaginismus, chronic vaginitis
	Frequency of intercourse <2 times a month
Pelvic mechanical problems	Exposure to sexually transmitted disease
	Pelvic inflammatory disease or endometriosis
	Previous pelvic or abdominal surgery
	History of induced abortion or postpartum complications
	Intrauterine device use
	Severe dysmenorrhea or chronic pelvic pain
	Exposure to tuberculosis
	Enlarged or irregular shaped uterus
	Cervical hood or history of in utero exposure to diethylstilbestrol
	Chronic vaginal discharge
	Scant menses
Endocrine problems affecting fertility	History of abnormal puberty
	Abnormal menstrual cyclicity (outside the 24- to 35-day range)
	History of amenorrhea
	Abnormal basal body temperature charts (monophasic or luteal phase <10 days)
	History of nonpuerperal galactorrhea
	Abnormal pattern of hair growth
	Acne
	History, signs, or symptoms of thyroid, adrenal, or other systemic disorder
Potential genetic problems	Known or suspected hereditary disease in patient or family
	Consanguinity
	Two losses or one pregnancy with documented anomalies
	Birth defects
	Unexplained mental retardation
	Advanced maternal age
	Teratogen exposure
	Ethnic groups at special risk

Adapted from Blankstein et al.[11]

or, in the case of abnormal results, to recognize those in need of early referral (Figure 1).

Step 1: The Screening Evaluation

A complete medical, reproductive, and sexual history should be the initial step in the evaluation of couples complaining of infertility, focusing on eliciting historical signs or symptoms associated with infertility (Table 1). Many clinicians find the use of preprinted educational material and questionnaires helpful in this regard. Both partners should be interviewed separately, as well as jointly, to elicit important facts that one partner might not wish to reveal to the other. Complete records of any past investigation or treatment for infertility should be obtained and subsequently reviewed with the couple.

The aim of the physical examination is to look for evidence of systemic disease, genetic abnormalities, or androgen dysfunction in either partner.[11] In women, a breast examination should be done to assess for the presence of occult galactorrhea or abnormal breast masses. Pelvic examination should be directed toward detecting signs of hyperandrogenism (eg, enlarged clitoris); vaginitis or pelvic infection; or congenital anomalies (eg, absent va-

gina or uterus, longitudinal or transverse vaginal septum, cervical changes consistent with in utero diethylstilbestrol exposure). Parametrial thickness, detection of uterosacral ligament nodularity, and uterine mobility should be noted on bimanual examination, because abnormalities in these areas can indicate past pelvic inflammatory disease or endometriosis.[9]

The examination should not be limited to female reproductive organs. A detailed skin examination can reveal signs of androgen excess, such as hirsutism, seborrhea, acne, and acanthosis nigricans.[12] Vitiligo or other forms of depigmentation can suggest autoimmune systemic disease.[13] Documentation of body composition (weight, height, body mass index) and blood pressure measurements should also be reviewed, as obesity is often associated with androgen excess.[14]

In the male partner, an attempt should be made to look for endocrine stigmata consistent with hypogonadism and associated undermasculinization, including gynecomastia, immature secondary sexual characteristics, and small testes.[15] Location and condition of the urethral opening and prepuce should be noted. The scrotum should be palpated for content, consistency, and tenderness. The testes should be carefully measured by stretching the scrotal skin over both testicles, defining their contour separate from the epididymal head by palpation, and estimating the testicular size. The testes of an adult male should be greater than 10 mL in volume by orchidometer, which corresponds to a palpable longitudinal axis of 4 to 5 cm and an anteroposterior diameter of 2 cm.[16] Scrotal hernias, hydroceles, or lymphoceles, if present, should be noted. Cysts, tenderness, or thickening in the epididymis and vas deferens can suggest inflammatory or infectious causes. Evaluating the patient in an upright standing position and having him perform a Valsalva's maneuver will help make scrotal varicosities obvious.

Initial laboratory investigation of the female partner generally includes a complete blood count, urinalysis, Papanicolaou smear, vaginal wet mount, appropriate cultures should infection be suspected, and an assessment of ovulation. In the ambulatory setting, the latter can be accomplished by charting basal body temperature, obtaining a serum progesterone approximately 7 days after expected ovulation, or using commercially available urinary luteinizing-hormone-surge ovulation predictor kits.[17]

Table 2. Basic Semen Analysis: Summary of Lower International Normal Values.

Characteristic	Value
Volume	2–6 mL
Sperm count	≥20 × 106/mL
Motility	≥40.0%
Forward progression	≥3.0
Morphology	≥40% normal

Ovulation that occurs at reasonable intervals is critical for successful conception to take place. Women with oligo-ovulation or whose menstrual cycles are less than 24 days or longer than 35 days require further evaluation.

An initial semen analysis should be obtained from the male partner early in the infertility evaluation, before any invasive tests are done on the woman (Table 2). Once a determination about semen adequacy is made, a directed evaluation can be undertaken. If the semen analysis is satisfactory, the remainder of the screening evaluation will center on the female partner.

Step 2: The Directed Investigation

Male Partners With Unsatisfactory Findings on Semen Analysis

Although the period of abstinence necessary to obtain an optimal semen specimen has been the subject of debate, 2 to 4 days is usually recommended.[18] An abnormal initial sperm count necessitates that more than one sample be analyzed to determine a trend. If there has been a history of febrile illness or major physiologic or psychologic stress within the previous 3 months, one full cycle of spermatogenesis (approximately 72 days) should be allowed before repeating the analysis.[18]

To diagnose male factor infertility, the semen analysis should be standardized and performed according to the guidelines of the World Health Organization.[18] Unfortunately, the predictive value of the semen analysis is limited, even when properly performed, and reliable tests for sperm function do not yet exist.[19] Most andrologic disorders are treated empirically.[20]

Based on treatment approach, male factor infertility can be divided into the following six categories: genetic causes, gonadotropin deficiency, anatomic defects, infections, immunologic causes, and idiopathic causes.

Genetic

It has been estimated that 30% of male factor infertility is genetic. Affected men frequently have azoospermia or oligospermia associated with low motility and a predominance of abnormal forms. Genetic disorders include chromosomal aneuploidy and mutations in the genes associated with spermatogenesis, which can be inherited or arise from new mutations. Klinefelter syndrome (47,XXY) is encountered in approximately 1 in 700 to 1,000 newborns, representing the most common numerical chromosome anomaly in infertile men.[21] Classic Klinefelter syndrome arises from meiotic nondisjunction of the X chromosome. These patients usually have small firm testes, low serum testosterone levels, and azoospermia. If gonadotropin levels are elevated in a male partner with sperm counts consistently less than 10,000,000/mL, karyotyping should be done to rule out Klinefelter syndrome.[22]

Other more recently recognized genetic abnormalities associated with male factor infertility include translocations, inversions, Y chromosome-specific deletions, androgen receptor gene mutations, and cystic fibrosis (CFTR) gene.[21]

Gonadotropin Deficiency

Men who are hypothalamic or have pituitary dysfunction are frequently hypogonadal and have azoospermia or oligospermia and low motility. Serum follicle-stimulating hormone, luteinizing hormone, and testosterone levels are low in these men, and the testes are usually small and soft. Beyond the genital examination, a finding of anosmia might be encountered in hypogonadal men who have had gonadotropins suppressed from puberty (Kallman syndrome).[23] In hypogonadal men treatment with GnRH or gonadotropin therapy can be successful after several months of therapy.[19] Consequently, if signs and symptoms of hypogonadism are present, an endocrine investigation should include a thyroid-stimulating hormone measurement to rule out subclinical hypothyroidism, total and free testosterone and gonadotropin measurements to assess testicular-pituitary-hypothalamic function, and a prolactin measurement to screen for occult hyperprolactinemia.[11]

Anatomic Defects

Absence or obstruction of the ejaculatory ducts, testicular maldescent, retrograde ejaculation, and varicocele have been associated with infertility. Affected men have normal follicle-stimulating hormone, luteinizing hormone, and testosterone levels. They have normal testicular volume but abnormal semen findings. If there is azoospermia or severe oligospermia, and the patient has normally functioning gonads based on gonadotropin and testosterone levels, the male genital tract could be obstructed. Checking the semen for the absence of fructose can determine whether the patient's ejaculatory duct is absent or obstructed.[18]

Congenital bilateral absence or atrophy of the vas deferens is found both in men with cystic fibrosis and in those men with an isolated Wolffian duct anomaly.[21] Azoospermic men with the isolated anomaly have a 60% increase in mutations for the CFTR gene. Identification of these mutations becomes clinically relevant in such cases when pregnancy through assisted reproduction is contemplated, because cystic fibrosis is the most common autosomal recessive disorder with a carrier frequency of 1:20.[21]

Retrograde ejaculation occurs when the lumbar sympathetic nerves are injured through surgery or disease process. A urine specimen should be scanned for spermatozoa in those men suspected of having retrograde ejaculation, particularly those with diabetes.[19] Alpha-adrenergic agonists, anticholinergics, and imipramine have been used to reverse the condition. When medical therapy fails, spermatozoa can be recovered for use with assisted reproduction technologies either by electrovibration or by surgery.[19]

Some 3% to 6% of men will have undescended testes at birth.[19] It is preferable that such malposition be corrected within the first year of life, as germ cell degeneration and dysplasia start in early infancy.[19] Because of the push to early correction, few such cases will be encountered in the infertility setting.

Varicoceles are believed to cause decreased fertility as a result of hypoxia, stasis, increased pressure, increased catecholamines, and increased temperature in the testicle.[19] Varicoceles are the most frequent physical finding in subfertile men, although they are often not detected on routine physical examination and can require referral for ultrasound evaluation.[24] Varicocelectomy has become the most frequent operation for male infertility.[19,20] Unfortunately, it remains highly questionable whether this clinically invasive procedure

results in better outcomes than observation alone. Currently, it appears that surgery should be recommended for those men with scrotal pain or swelling but not for improvement of pregnancy rates.

Infection

Symptomatic bacterial infection or venereal disease of the male genital tract should be treated to avoid subsequent obstruction of the efferent ducts. Further evaluation of the ejaculate after prostatic massage might be indicated if the semen analysis suggests infection. If the patient has a history of urethritis, both partners should have genital specimens cultured and receive antibiotic therapy based on identification of a specific organism. Male patients have traditionally been screened for gonorrhea, chlamydia, mycoplasma, and *Ureaplasma* organisms, and some clinics routinely screen for any anaerobic bacterial infection, particularly when leukocytes are found in sperm on semen analysis. The importance of asymptomatic genital tract infections, however, remains ambiguous. Incidental leukocytes in sperm found on semen analysis has a high spontaneous resolution rate without treatment.[19,20] Additionally, few randomized controlled studies have been done to clarify the influence of antibiotic treatment on subsequent pregnancy rates in asymptomatic men. When studies using pregnancy as an outcome parameter are considered, no significant differences have been found between those groups on antibiotic therapy and those under observation alone.[19,20] Thus, the practice of obtaining routine cultures in asymptomatic men should be questioned.

Immunologic Infertility

This condition is diagnosed when antisperm antibodies are found in the seminal fluid and no other cause of infertility has been detected. Immunologic testing for antisperm antibodies should be considered when there is evidence of poor sperm motility or agglutination on semen analysis or a history of serious scrotal trauma. Men who have had a vasectomy with subsequent vasovasostomy are at particular risk for antisperm antibody formation, which might hamper subsequent fertilization attempts.[25] Concentrations of antisperm immunoglobulin G or immunoglobulin A above 50% gave been associated with greatly reduced pregnancy rates, and concentrations above 90% virtually exclude the chance of spontaneous pregnancy. Until recently, immunosuppressant medications, such as glucocorticoids, have been used to treat immunologic infertility. Unfortunately, severe side effects, such as muscle wasting, aseptic necrosis of the femoral heads, infection, and gastritis, can override any potential benefit.[19,20] Affected men should be referred for assisted reproduction. Intracytoplasmic sperm injection, a technique that microinjects a single spermatozoa or spermatocyte into each oocyte obtained from follicular aspiration during in vitro fertilization cycles, is a highly successful method of treatment for these patients.[25,26]

Idiopathic Infertility

Unexplained male infertility probably has many underlying causes. Various treatment regimens have been used, including gonadotropin-releasing hormone, gonadotropins, testosterone, bromocriptine, clomiphene citrate, vitamin C, and vitamin E, to name a few. Unfortunately, not one of these approaches used empirically has been shown to improve pregnancy rates in subfertile men.[19,20]

When the semen analysis is consistently abnormal, therapy can be directed at correcting the underlying disorder while completing the female evaluation. Artificial insemination by donor sperm will be required when the male partner has frank testicular failure as documented by azoospermia with castrate-level gonadotropin levels.[26] On the other hand, unsatisfactory sperm counts secondary to hypogonadotropic hypogonadism can self-correct once the primary endocrine disorder is addressed.[19,20,27]

Treatment with timed intrauterine insemination in an ovulation-induction cycle can be offered to many couples with male factor infertility.[19,20,28] In vitro fertilization might be required, however, particularly if fewer than 1,000,000 motile spermatozoa or high antisperm antibody titers are discovered.[19,20,25,26] Many conceptions in this group have resulted from oocyte micromanipulation with intracytoplasmic sperm injection (ICSI).

Women With Amenorrhea

Once pregnancy is ruled out, the evaluation of a woman with amenorrhea is directed toward determining whether she is estrogen deficient, because one of several covert conditions can exist in the hypogonadal patient. Hypogonadism can be ruled out immediately and inexpensively in the office if there is evidence of endogenous estrogen produc-

tion on a vaginal cytologic sample (more than 15% superficial cells with small, pyknotic nuclei and large amount of cytoplasm). Hypogonadism is suggested by the predominance of parabasal cells. Smaller parabasal cells, which have a nuclear to cytoplasmic ratio of 50:50, suggest hypogonadism.[29]

Response to a progestational challenge test (10 mg of medroxyprogesterone acetate daily for 13 days orally, or a single intramuscular injection of 100 mg progesterone in oil) also will be indicative of the adequacy of endogenous estrogen.[9,29] If enough circulating estrogen is present to proliferate the endometrial lining, exposure to progesterone will induce the lining to undergo secretory maturation and induction of menstrual bleeding.[9] At the same time, thyroid-stimulating hormone and prolactin levels should be measured to assess for systemic disorders that adversely affect ovulatory function.

Failure to bleed after this challenge suggests that the patient might be hypogonadal, and serum gonadotropin levels should be measured. If the gonadotropins are elevated to castrate levels on two separate occasions, ovarian failure is diagnosed.[30] Women younger than 36 years in whom ovarian failure is discovered should have a karyotype investigation to rule out the presence of occult Y chromosomal material or evidence of sex chromosome mosaicism. Women with a Y chromosome are at increased risk for the development of gonadal ridge tumors and require gonadectomy.[31] Those without Y material but with chromosomal mosaicism (eg, 45,X/46,XX; 45,X/46,X,i(Xq)) can have occult renal or cardiac abnormalities or autoimmune conditions that might not become manifest until later in adulthood.[32] These women are sterile and should be encouraged to consider fertility treatment through oocyte or embryo donor programs.[33]

If the patient appears to have functioning gonads based on both clinical examination and normal gonadotropins, failure to withdraw to progestogen challenge could be secondary to endometrial scarring (Asherman syndrome).[34] In this situation, giving a priming dose of estrogen and repeating the progestational challenge will clarify whether an end-organ problem exists. Failure to respond to this combination suggests a uterine cause of amenorrhea; a hysterosalpingogram or hysteroscopy will confirm the diagnosis.

A hypogonadal woman with abnormally low gonadotropins could be suffering from pituitary insufficiency, an occult craniopharyngioma, severe hypothyroidism, or an expanding pituitary tumor. If the fasting prolactin level is elevated to more than 100 ng/mL, and the patient gives no history of excessive breast stimulation or psychoactive medication usage, pituitary studies by magnetic resonance imaging or computed tomography are indicated.[35,36] Alternatively, lower elevations of prolactin might indicate compression or injury to the tuberoinfundibular stalk and should not be ignored.[37] In some patients, more extensive provocative endocrine testing might be indicated depending on the clinical history and screening laboratory results. It is imperative that these women receive a thorough evaluation of their endocrine status before attempting ovulation induction. Patients with amenorrhea secondary to hyperprolactinemia will usually begin ovulatory cycles once normal prolactin levels are established with the use of bromocriptine.[35] Most hypogonadal patients with suppressed gonadotropins are able to conceive successfully when managed with exogenous gonadotropin therapy.

Women With Presumptive Ovulation

If the woman has a history of normal menstrual cycles, and no abnormalities are found during the physical examination, a presumed diagnosis of ovulation is reasonable. In these cases, the workup should be directed at documenting ovulatory cycles, tubal patency, endometrial receptivity, and hospitable cervical mucus. Most of these procedures require specific and appropriate timing within the menstrual cycle (Table 3), and it is helpful to sequence them rapidly within 3 to 4 months so that therapy can be initiated if needed. Although referral to a reproductive specialist might be warranted at this point for invasive procedures, the family physician should remain informed of the patient's progress and be available to provide ongoing support of the couple, as well as to facilitate referral for second opinion, assisted reproduction, or specialized reproductive surgery in appropriate cases.

Women With Chronic Eugonadal Anovulation, Irregular Ovulation, or Signs of Androgen Excess

For women who are clinically anovulatory (based on history, basal body temperature charts, urinary luteinizing hormone ovulation predictor kit, or

Table 3. Timing of Screening Evaluation.

Test	Phase of Cycle	Expected Normal Results
Hysterosalpingogram	Early follicular phase	Tubal patency, normal uterus
Laparoscopy, hysteroscopy	Early follicular phase	Normal pelvis and endometrium
Postcoital test	Just before the midcycle luteinizing hormone surge	Mucus with good spinnbarkeit More than 10 motile sperm per high-power field
Serum progesterone	Mid luteal phase	Luteal assay range defined by kit
Endometrial biopsy	Late luteal phase	Late secretory endometrium

Adapted from Speroff et al.[9]

properly timed luteal progesterone level) serum prolactin and thyroid-stimulating hormone levels should be measured. Therapy can then be directed to correct the hormonal imbalance as indicated. Additionally, if physical signs suggesting androgen excess are found, serum total testosterone and dihydroepiandrostendione sulfate (DHEAS) levels should be determined to rule out ovarian and adrenal androgen-producing tumors, particularly if rapid masculinization within several months has occurred.[9] A presumptive diagnosis of polycystic ovarian disease can be made if the results of these tests fall within tumor range (testosterone $>$ 200 ng/dL or DHEAS $>$ 700 μg/dL), excluding other causes of anovulation.[9] Acute, rapid virilization, however, requires a full investigation even if the testosterone and DHEAS concentrations are less than cutoff levels described.

In selected patients, additional screening for elevated 17-hydroxyprogesterone can also be useful in ruling out late-onset adrenogenital syndrome (congenital adrenal hyperplasia).[38] Congenital adrenal hyperplasia is caused by a specific adrenal enzyme defect inherited in an autosomal recessive fashion. The 21-hydroxylase defect is the most common and, when inherited in the severe form, can result in newborn ambiguity with or without severe salt wasting. It has been estimated that from 1% to 5% of women with hirsutism have late-onset congenital adrenal hyperplasia. Little or no manifestation of the condition is evident before puberty. As the adrenal glands become more active at puberty, progressive hirsutism and disordered menses soon occur. At the clinical level patients with late-onset congenital adrenal hyperplasia are clinically indistinguishable from other patients with eugonadal anovulation and androgen excess.

Management of the ovulatory dysfunction is frequently treated the same in both groups. The genetic carrier status, however, is higher in certain populations, making preconceptual counseling and testing appropriate, because the homozygous condition is the most frequent form of genital ambiguity and the most frequent endocrine cause of neonatal death.[9] It has been estimated that 1 in 3 eastern European Jews, 1 in 4 Hispanics, 1 in 5 Slavs, and 1 in 9 Italians are heterozygous carriers.[9] Screening with blood 17-hydroxyprogesterone level has become the primary form of assessment. Affected individuals will have levels many times higher than normal. Routine screening is recommended for at-risk populations, for patients with pedigrees containing unexplained neonatal death, or for those with genital ambiguity.

Eugonadal anovulation will most often be managed with ovulation induction through use of drugs like clomiphene citrate. Pregnancy success rates are high when ovulatory dysfunction is the only infertility factor.[39]

Recurrent Pregnancy Loss

Today, 1 in 5 women in the United States gives birth to her first baby when she is older than 35 years.[40] These women are at increased risk for aneuploid conceptions and hence have lower take-home baby rates.[41] Unfortunately, more than one clinical loss is not that unusual in this age-group.

Most pregnancy loss occurs in the first trimester and is associated with random genetic events.[42] Habitual abortion has been classically defined as three or more consecutive losses, but the chance of a successful live birth after three consecutive losses remains hopeful at 55% to 60%.[9,43] These odds are improved up to 70% when habitual abortion occurs following at least one normal liveborn.[9]

It is best to customize the clinical approach to a couple with recurrent pregnancy loss based on the woman's age and level of anxiety, rather than to the number of previous miscarriages, as most evalua-

Table 4. Habitual Abortion Considerations.

Genetic	Consider pedigree
	Offer karyotype and genetic counseling
Environmental	Eliminate tobacco, alcohol, caffeine, occupational toxins, stress
Endocrine	Rule out luteal phase insufficiency, thyroid disease, diabetes
Anatomic	Consider cavity study to rule out septate uterus, partial Asherman syndrome, incompetent cervix, leiomyomata
Infectious	Cultures often inconclusive
	Consider antibiotic treatment?
Immunologic	Consider antiphospholipid and lupus screening
	Refer for more complex testing as indicated

tions will result in normal findings. Obtaining a family pedigree from both partners should be a first step.[44] Clinical testing should be aimed at detecting causes that can be documented (Table 4). In approximately 8% of couples with recurrent loss, one partner will be found to carry a balanced chromosomal translocation.[44] Karyotyping of both partners is particularly important if the couple has had a malformed fetus or liveborn in addition to recurrent losses. Couples should be informed that normal parental karyotyping does not exclude genetic causes, since many losses result from undetectable single-gene defects. If the karyotype is abnormal, referral for genetic counseling is indicated. In most situations, there is a 50% chance of normal offspring in subsequent pregnancies, although gamete donor therapy can be offered as an alternative.[45]

Failed or faulty implantation and embryonic growth secondary to a suboptimal endometrium has been postulated as a cause of recurrent pregnancy loss. Treatment approaches traditionally have been directed at progesterone supplementation or ovulation induction.[46–48]

Other causes of recurrent loss include müllerian anomalies (eg, septate uterus), intrauterine synechiae (Asherman syndrome), and antiphospholipid syndrome, or other immune causes.[49–51] More commonly, subclinical thyroid disease and uncontrolled diabetes mellitus can also be associated with pregnancy loss.[52,53] Contrary to common belief, no conclusive evidence exists linking endometriosis with an increased risk of spontaneous abortion.[9]

Environmental factors, such as heavy smoking and alcohol and coffee consumption, have been associated with an increased risk of recurrent abortion.[54] The association of early pregnancy loss with caffeine use has been controversial. The safety of low levels of caffeine intake (less than 5 cups of coffee per day) has recently been supported through measurement of maternal serum paraxanthine levels and correlation with rates of spontaneous abortion in women who were part of the National Collaborative Perinatal Project.[55] In this study, only very high serum paraxanthine concentrations (equivalent to more than 6 cups per day) were associated with an increased abortion risk. Based on available evidence, it is therefore safe to reassure women about low-to-moderate caffeine intake in the first trimester.

Anesthetic gasses, certain dry-cleaning fluids, isotretinoin (Accutane), and petrochemical occupational exposures have also been implicated.[56,57] Infectious agents, such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Toxoplasma gondii*, *Listeria monocytogenes*, *Mycoplasma hominis*, herpesvirus, and cytomegalovirus, have been associated with recurrent loss, but causation has not been substantiated.[9] Treatment, if rendered, has been largely empirical.[20]

Therapy Considerations

There are few absolutes when dealing with the infertile couple. Therapy should be directed at shifting the couple's fecundity curve toward that of the normal population in their age-group. Interpretation of the literature regarding intervention-specific prognosis must be done cautiously. It is insufficient to look at the pregnant versus nonpregnant percentages, particularly if repetitive treatment cycles are considered. Life table analysis studies are more appropriate when comparing repetitive treatment cycles, because this approach adjusts for patient dropout rates and conceptions that occur during early treatment cycles.[58]

Choice of therapy often comes down to issues of efficacy, cost, ease of use, and side effects. An estimated 28% of all couples seeking reproductive assistance will have normal findings on evaluation, making the unexplained group a more common finding in recent years. Empiric therapy options become important in these situations, as few couples want to be observed after several years of trying unsuccessfully to conceive. In epidemiologic terms, couples with unexplained infertility who are cared for without treatment have a cumulative

pregnancy rate of 60% to 70% within 3 years, with some variation in rates by age and duration of infertility.[59,60] There have been no large, randomized clinical trials investigating the efficacy of empiric therapy in this group, although generally anticipated per-cycle pregnancy rates for this group are 5% for timed intercourse, 10% for superovulation with intrauterine insemination, and 15% to 25% for assisted reproduction therapies.[61] These rates must be adjusted downward for older women and will be influenced negatively as the duration of infertility increases. It is important for both patients and providers to remain realistic about prognosis, considering that even if every diagnosed problem were corrected, conception is not likely to occur at a higher rate than Mother Nature normally allows.

Counseling

There is no evidence that infertile couples have higher levels of psychopathology compared with fertile couples, and most cope well with excellent compliance through difficult and sometimes lengthy evaluation and treatment efforts.[62] Yet, throughout this process it is not unusual for patients to experience some level of frustration, sadness, loss of control, and other depressive symptoms.[63] Infertility, for these couples, is a life crisis.[64] Early in the evaluation, either partner might feel guilt or shame regarding his or her contribution to the diagnosis that renders the couple infertile. As treatment begins, couples can experience cycles of hope and despair with each passing menstrual cycle. As the duration of treatment lengthens, psychological distress is likely to increase. In some cases, patients might become obsessed with their infertility, "making a career out of pursuit of pregnancy."[66] This obsession is detrimental to other aspects of their lives, from which marital and sexual problems frequently result. Additional behaviors associated with infertile couples include the avoidance of family functions in which other children are present and unrealistic optimism regarding their prognosis in light of appropriately delivered information to the contrary.

How well couples cope with the psychological stress of infertility depends on many factors, including age at diagnosis, basic personality structure, coping styles and defense mechanisms, preexisting mental health diagnoses, family and friend support, and motivations for seeking pregnancy in the first place.[66] Beyond these issues, one of the most important factors in determining how well a couple copes with infertility evaluation and treatment is the skill level of the providers who care for them.

Psychological support is critical for all families who are confronted with a diagnosis of infertility. It should be emphasized from the initial office visit that infertility is a couple-family problem, and the discussion should not focus entirely on medical diagnosis and treatment. For the family physician involved in the care of these patients, information regarding past mental health problems, coping styles, partner and family support, and basic personality structure is often known. This knowledge is valuable in the early stages of counseling, while assessing the personal and family aspects of the diagnosis. As partners often differ in their response to what they are told, the impact of the information will likely be felt differently. The family physician can provide or refer patients for counseling to improve communication between partners throughout this process.

Anyone counseling patients regarding infertility must first be familiar with the causes, workup, and treatment options available to couples who are experiencing difficulty achieving pregnancy. An initial assessment of their response to the diagnosis and a discussion of the implications of evaluation and treatment should take occur. At the outset, anticipatory guidance should be provided regarding the expected emotional responses the couple can experience and the symptoms that might occur while on specific hormonal and other treatment regimens. The couple should be reassured that the feelings each partner might experience are normal. Patients should be encouraged from the beginning to attend to their own personal care needs, including nutrition, rest, exercise, and work schedules. Tips on how to deal with family and friends, as well as how to respond in public gatherings, can be helpful for couples who do not raise this as an issue themselves. It is important to differentiate between the common dysphoria that occurs among infertile couples and true dysfunction that can result during the process of an infertility evaluation.[62] The family physician should be prepared to assist in referral to appropriate counseling resources should a more formal support mechanism be required.

Finally, it is important to recognize that an often-neglected goal of counseling couples is to help them deal with ending unsuccessful therapy. This decision can be particularly difficult for the unexplained infertile group, because there is no obvious pathologic condition on which to base the decision to end therapy. Couples need to be able to share their feelings in a safe environment so they can make the right personal decision about stopping therapy or initiating adoption procedures. Support groups, such as those organized by RESOLVE, Inc, can be helpful in this regard. Patients considering adoption must prepare for the rigors of social agency evaluation and can become disappointed early in the process. An alternative is private adoption.[67–69]

Ethics, Insurance, and the Law

The concept of patient autonomy would dictate that the role of providers is to offer medically appropriate technology to the infertile patient without making judgments about who should be a parent and how this should happen. In other words, it is each person's right to choose whether and how to procreate. That chosen, where does the money come from?

On 26 July l990 the Americans with Disabilities Act (ADA) was signed into law. This law prohibits "discrimination based on disability in employment, programs and services provided by state and local governments, goods and services provided by private companies, and in commercial facilities."[70] The ADA has a primary focus on employment issues. Under this act fairness in providing health insurance coverage is required. The Supreme Court has ruled that procreation is a major life activity. Infertility limits one's participation in this major life activity. Can infertility be classified as a disability? If so, can employer-sponsored health insurance benefits be compelled to provide coverage for infertility? Additionally, can infertile patients undergoing treatment compel employers to give reasonable accommodation for frequent office visits and so on?

Since the enactment of the ADA, the law's application to health insurance issues has been a dynamic area of jurisprudence. Many lawsuits have been filed by women who say that employers have illegally refused to reduce their hours or failed to provide insurance coverage for infertility services. Many of these cases have been settled out of court. In a recent Supreme Court decision, Bragdon v Abbott, the court confirmed the viewpoint that reproduction constitutes a major life activity under the ADA.[70] It is hoped that more test cases will expand access to infertility therapy.

Summary

The initial evaluation of a couple that is unable to conceive can be easily and effectively conducted in an ambulatory, primary care setting. As more couples are seeking reproductive assistance, primary care providers will frequently be asked to participate in the early stages of this treatment. Many conditions once considered untreatable can now be routinely corrected, typically in conjunction with a referral specialist. Throughout the process, the family physician is in a unique position to provide patient education and ongoing psychosocial support to these couples.

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