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Female Infertility

Infertility is generally defined as one year of unprotected intercourse without conception.1 Some prefer the term ***subfertility*** to describe women or couples who are not sterile but exhibit decreased reproductive efficiency.

Approximately 85-90% of healthy young couples conceive within 1 year, most within 6 months.[2,3] Infertility therefore affects approximately 10-15% of couples and is an important part of the practice of many clinicians. Cycle ***fecundability*** is the probability that a cycle will result in pregnancy *and* ***fecundity*** is the probability that a cycle will result in a live birth.

Contrary to popular perception, the overall incidence of infertility has remained relatively unchanged over the past 3 decades. However, the evaluation and treatment of infertility have changed dramatically during that time. Three major developments have had the greatest impact. First was the introduction of *in vitro* fertilization (IVF) and other assisted reproductive technologies (ART). ART techniques have provided the means to study reproductive processes in new and more revealing ways and have markedly improved the prognosis for a great many infertile couples, particularly those whose infertility relates to severe tubal damage or male factors. Second, changes in population demographics have resulted in greater numbers of women attempting pregnancy at older ages when they are inherently less biologically fertile. Third, advances in ART and concerns about the age-related decline in fertility have combined to attract greater media attention and to raise public awareness of infertility and modern treatments. Consequently, infertile couples are now more likely to seek medical advice, evaluation, and treatment.

The Epidemiology of Infertility in the U.S.

The first U.S. census was in 1790. At that time, the crude birth rate was 55 per 1,000 total population; in 2007, it was 14.3 per 1,000,[4] representing nearly a 75% decline over the past 200-plus years. The crude birth rate in 2007 was 15% lower than in 1990 (16.7 per 1,000 population), but increased from 2002 (13.9 per 1,000), which was a record low for the nation.[5] The general fertility rate (births per 1,000 women aged 15-44) in 2007 was 69.5, 2% lower than in 1990 (70.9/1,000), 11% lower than in 1970 (87.9/1,000), and 35% lower than in 1950 (106.2/1,000) during the post-war "baby boom."[4,6,7] The general fertility rate in 2007 was the highest since 1990.

The overall long-term decline in U.S. birth and fertility rates has been attributed to several factors.

- Greater interest in advanced education and careers among women.
- Later marriage and more frequent divorce.
- Improvements in contraception and access to family planning services.
- Delayed childbearing.
- Decreased family size.

Attitudes towards women and among women in our society have changed dramatically in many ways over the past 30 years. Expanding opportunities have increased interests in advanced education and careers among women. U.S. census data indicate that in 1970, only 8.2% of women age 25 and older had completed 4 or more years of college; by 2001, that proportion had tripled (24.3%).[8] Women have represented the majority of college students in the U.S. since 1979. In recent years, the majority of bachelor's and more advanced degrees have been awarded to women. The proportion of U.S. women with infant children in the work force has steadily increased, from 31% in 1976 to 55% in 2000.[8] In 2006, 85% of all women ages 15 to 44 years were in the labor force.[9]

Greater focus on education and careers among women triggered other trends in modern society. Less frequent and later marriage and more frequent divorce were among the most striking. First marriage rates in the U.S. peaked after World War II, between 1945 and 1947 (143 per 1,000 single women aged 15-44), and declined about 15%

every 10 years and approximately 50% overall over the next 5 decades.[10] The median age at first marriage for women has risen steadily since 1960 (20.3 years) and reached an all-time high in 2007 (26.0 years). The probability of future marriage for women decreases as age increases: 84% at age 25, 72% at age 30, 52% at age 35, and 41% at age 40.[11] If and when women do marry, they also are more likely to divorce than in the past.[10,11,12] and [13] Divorce rates among women of reproductive age rose quickly after 1960 to more than double by 1980 (40 per 1,000 married women aged 15-44) and have declined only slightly over the last 30 years. The National Center for Health Statistics estimates that approximately one-third of new marriages among younger people will end in divorce within 10 years and 43% within 15 years. Once-married women also are increasingly less likely to remarry. Remarriage rates peaked in 1968 (166 per 1,000 divorces or widowed women aged 15-44) as divorce rates began to rise, but have since declined steadily by more than one-third, in parallel with first marriage rates.[10,11,12] and [13]

The post-war “baby boom” generation, those born between 1946 and 1964, was the first to be afforded the means to safely and effectively control their fertility. Expanding contraceptive options and access to family planning and legalized abortion services over the past 5 decades definitely have contributed to declining U.S. birth and fertility rates. Their effects have been direct, by reducing the number of unplanned pregnancies and births, and indirect, by helping women to avoid pregnancy until their education and career goals were met, and marriage and family become a priority.

The net result of all of these societal changes was a trend to delayed childbearing among American women. The mean age at first live birth has risen steadily, from 21.4 years in 1970 to an all-time high 25.2 years in 2004 (3.8 years and 18% higher). The percentage of first births occurring to women aged 30 or older increased more than 6-fold between 1970 and 2002.[14] Mean ages for all subsequent live births increased as well; the increase in mean age was greatest (3.6 years) for the second live birth (27.7 years), and lower for the third (2.5 years), fourth (1.6 years), and fifth births (0.4 years).[15] Between 1970 and 2007, birth rates fell for women ages 15-19 (68.3 vs. 42.5/1,000), 20-24 (167.8 vs. 106.4/1,000), and those 25-29 (145.1 vs. 117.5/1,000), and increased for women aged 30-34 (73.3 vs. 99.9/1,000), 35-39 (31.7 vs. 47.5/1,000), and those aged 40-44 (8.1 vs. 9.5/1,000).[4,7,16] Predictably, increasing age at first birth and declining fertility rates combined to result in fewer births per woman. At the height of the postwar baby boom, the U.S. total fertility rate (births by age 45) reached a modern high of 3.7 births per woman (1957). Thereafter, the total fertility rate declined to a low of 1.8 in 1976, rose slightly to 2.1 in 2001,[7] and has remained stable since.[4] The total fertility rates in some European countries are significantly lower (Italy, 1.33; Greece, 1.29; Spain, 1.32), and inadequate even to ensure replacement of the population.[17]

The larger number of women born during the postwar baby boom increased markedly the absolute numbers of women with impaired fertility. Over a 20-year interval, a large population of women was attempting pregnancy, often for the first time, when older and less biologically fertile. Whereas in the past many such women might have chosen to adopt, the availability of legal abortion services and society's increasing acceptance of single parenthood greatly reduced the number of infants available for adoption. Women were more likely to seek infertility services, and more likely to pursue the most aggressive forms of treatment, because they offered the greatest probability for success. Now, even the youngest “boomers” are over age 45 and have completed childbearing. In 2000, the median age of the U.S. population was 35.3 years and 16% of people were between the ages of 35 and 44, representing the largest 10-year age segment of the entire population. That same year, 14.2% of the population was 25-34 years of age, 13.9% was 15-24 years, and 14.6% was 5-14 years. ***Even barring any changes in the causes and prevalence of infertility, the absolute numbers of infertile women in the U.S. can be expected to decline in the years ahead.***

Trends in the incidence of infertility among U.S. women have been difficult to define confidently, partly due to

confusion over the use of two different measures—impaired fecundity, and infertility, which are defined differently, describe different populations, and can yield conflicting data.[18,19] However, evidence indicates that the incidence of infertility in the U.S. now is declining.[20] The earliest national estimate of infertility, from the 1965 National Survey of Family Growth (NSFG), was 11.2%. In 1982, 8.5% of married American women were infertile, and in 2002, 7.4% were infertile, representing a 10% decrease over the intervening 20 years.[20] Although the explanation is not entirely clear, the percentage of women ever treated for pelvic inflammatory disease also decreased steadily, from 17.1% in 1982 to 12.0% in 1988, to 8.2% in 1995, to 5.7% in 2002.[20] In a 2007 analysis of data derived from 25 population surveys sampling 172,413 women, the median international prevalence of infertility (12 months) among women ages 20-44 years was 9% (range 3.5% to 16.7%).[21]

The array of infertility services, and their availability, has increased dramatically over the last 25 years. Clinicians have become more aware of infertility and better trained to evaluate and treat its causes. The public too has a greater awareness of infertility and modern treatments, largely due to the increased media attention, good and bad, surrounding the advances and controversies relating to assisted reproductive technologies (ART). As infertility has become more visible, and more socially acceptable, couples have become less reluctant to seek evaluation and treatment.

According to data derived from the National Survey of Family Growth (NSFG) conducted in 1995, 9.3 million women ages 15-44 (15%) had ever received infertility services, an increase from 6.6 million women (12%) in 1982.[22] These data indicated that the demand

for infertility services increased during the 1980s and early 1990s, corresponding to the aging of baby boomers and the time when the availability of ART was rapidly expanding. Compared to the general population, women seeking infertility services were more likely to be older (aged 35-44 years; 43% vs. 36%) nulliparous (36% vs. 16%), married (79% vs. 64%), relatively affluent (61% vs. 51%), and to have health care insurance (83% vs. 74%).[22] Among those who received infertility services, 35% had used ovulation-inducing drugs and 1.6 % had undergone some form of ART. In the 2002 NSFG, 7.3 million women ages 15-44 reported ever having used infertility services, representing a significant decrease of approximately 20% since 1995.[23] Advice (74%) and testing (59%) were the most common types of services received, and nearly half reported receiving drugs to improve ovulation.[24]

Aging and Fertility

The effects of aging on female fertility are perhaps best revealed by the results of studies in “natural” populations wherein couples reproduce without voluntary restrictions;[25] the Hutterites in North America are a classic example. Contraception is condemned in the sect, which emigrated originally from Switzerland in the 16th century and settled ultimately in communal colonies in South Dakota in the late 19th century. Studies of fertility in the Hutterites illustrate how fertility declines with advancing age.[26] Whereas only 2.4% of Hutterite women were infertile, 11% bore no children after age 34, 33% were infertile by age 40, and 87% were infertile at age 45. Although revealing, these and other data derived from studies in natural populations may not reflect true biologic reproductive potential, for several reasons:

- Women who have children when young may be less inclined to conceive again in later life.
- Coital frequency often declines as age increases, reflecting decreasing desire or lack of a partner.
- The incidence of subclinical abortion is unknown.

- The cumulative impact of other diseases or conditions that can adversely affect fertility (e.g, pelvic infections, leiomyomata, endometriosis) is greater in older women.

Taken together, data from studies in the Hutterites and other natural populations suggest that fertility in women peaks between the ages of 20 and 24, decreases relatively little until approximately age 30 to 32, and then declines progressively. ***Overall, fertility rates are 4-8% lower in women aged 25-29 years, 15-19% lower in those aged 30-34, 26-46% lower in women aged 35-39, and as much as 95% lower for women aged 40-45 years***.[27,28] Variations in fertility rates among natural populations could reflect differences in genetic factors or socio-economic conditions at different times and in different places.

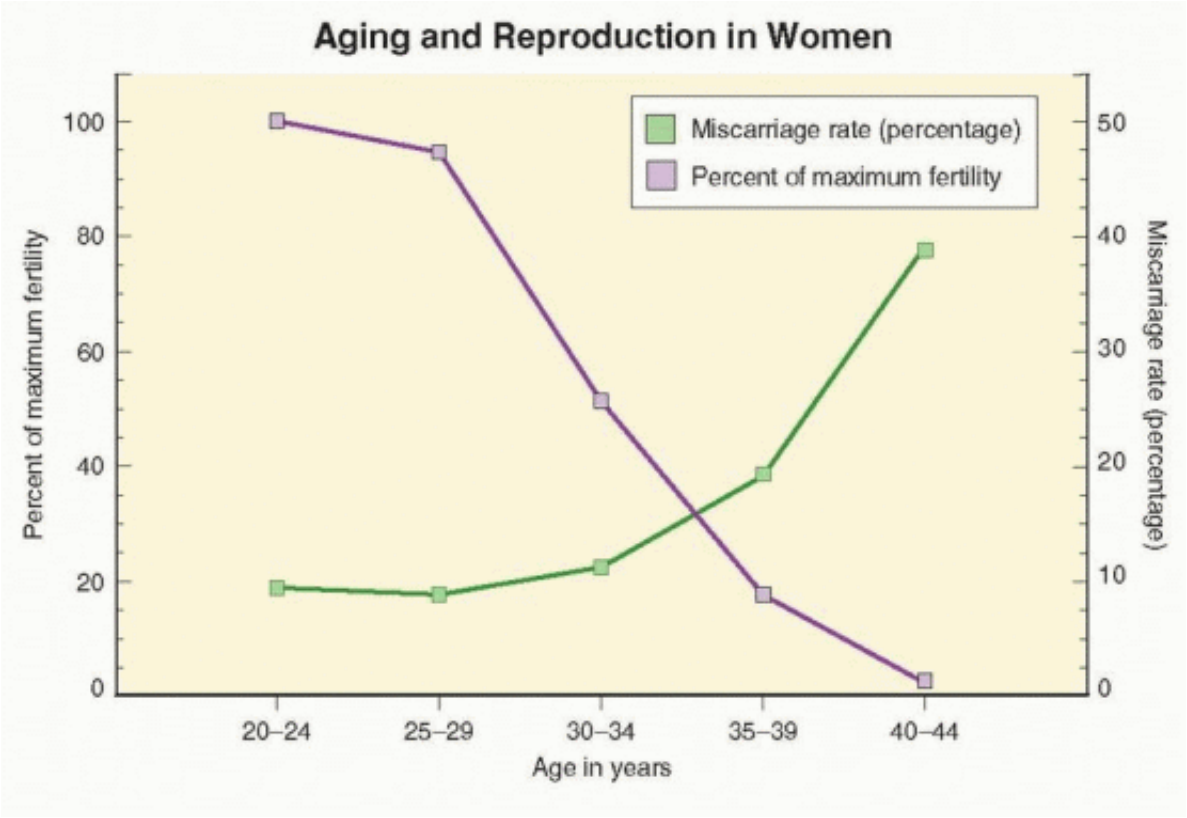
Other evidence for the adverse effect of aging on fertility derives from numerous studies of cumulative conception rates among women attempting pregnancy by artificial insemination with donor sperm. Data from donor insemination studies are informative because the women enrolled are less likely to have other infertility factors, and because carefully timed inseminations eliminate the confounding effects of decreasing coital frequency with increasing age. In a French study involving more than 2,000 women across up to 12 insemination cycles, conception rates were highest in those age 25 or younger (73%) and ages 26-30 (74%), 16% lower (62%) in women aged 31-35, and 27% lower in those over age 35 (54%).[29] An American donor insemination study yielded similar results, observing lower overall conception rates and a 2-fold higher number of inseminations per conception in women over age 35.[30] A Dutch study observed that the probability of a healthy live birth decreased by approximately 3.5% per year after age 30.[28] In a large British study of nearly 3,000 donor insemination cycles from a single center, cumulative conception rates

in women over age 30 were 20-35% lower than in younger women after 3 (17% vs. 21%), 6 (26% vs. 40%), and 12 insemination cycles (44% vs. 62%).[31]

Success rates achieved with ART also decline as age increases. The numbers of oocytes retrieved and embryos available are lower, embryo fragmentation rates are higher, and implantation rates are lower in older than in younger women.[32,33] Although ART pregnancy rates have increased steadily over the past 20 years for women in all age groups, annual reports derived from registry data collected by the Centers for Disease Control and Prevention (CDC) in the U.S. since 1989 demonstrate consistently that age is the single most important factor affecting the probability of success with ART. Pregnancy and live birth rates for ART cycles using fresh, non-donor eggs or embryos vary little for women under age 32, but thereafter decrease steadily in an almost linear fashion as age increases. Regardless whether success rates are calculated per cycle, per oocyte retrieval, or per embryo transfer, the result is the same. In the 2007 U.S. national summary, the live birth rate per embryo transfer was 45.9% for women under age 35, 36.9% for ages 35-37, 27.1% for ages 38-40, 16.0% for ages 41-42, and 8.4% for women aged 43-44 years.[34]

The age-related decline in ART live birth rates reflects not only decreasing fertility, but also increasing pregnancy wastage. Just as fertility decreases with increasing age, the incidence of clinically recognized miscarriage rises as age advances. ***Miscarriage rates in natural conception cycles are generally low before age 30 (7-15%) and rise with age, only slightly for ages 30-34 (8-21%), but to a greater extent for ages 35-39 (17-28%) and ages 40 and older (34-52%)***.[27,35,36] ***and*** [37] The same pattern is observed in pregnancies resulting from ART. In the 2007 U.S. national summary of IVF outcomes, miscarriage rates were below 15% for women under age 35, almost 30% at age 40, and over 50% for women age 44 and older.[34] Longitudinal studies of healthy young women wherein daily urine samples were monitored for the appearance of human chorionic gonadotropin (hCG) have revealed that true spontaneous miscarriage rates (also including clinically unrecognized “biochemical” pregnancies) are

substantially higher.[38,39] and [40] ***Up to 60% of all conceptions miscarry within the first 12 weeks of gestation and 20-40% of all early pregnancy losses go unrecognized***. Whether the incidence of occult early pregnancy loss also is higher in older women than young women has not been determined. If so, the relationship between true spontaneous miscarriage rates and age may be even more dramatic. Even if not, the overall miscarriage risk (recognized and unrecognized) in women over age 40 approaches or exceeds 75%.[39,41]



Physiology of Reproductive Aging

Established societal trends toward delayed childbearing and the age-related decrease in female fertility have focused a great deal of attention on the physiology of reproductive aging. Consequently, our understanding of the mechanisms that govern the pace of follicular depletion, the endocrinology of reproductive aging, and age-related changes in follicular dynamics and oocyte quality has advanced greatly over the past 20 years. We long ago recognized the changes in menstrual cycle characteristics that accompany advancing age, but now much better understand the mechanisms responsible for those changes. We long ago recognized that fertility declines as age increases, but now have measures of reproductive aging that help to guide our efforts to overcome its limitations. We know that we cannot prevent aging, but now can better help women to set and to realize their reproductive goals.

Follicular Depletion

During fetal life, germ cells rapidly proliferate by mitosis to yield approximately 6-7 million oogonia by 16-20 weeks of pregnancy.[42,43] and [44] From that point on, the germ cell population begins an inexorable decline mediated primary by gene-regulated apoptosis.[45] After entering the first meiotic division and becoming oocytes,

the number of germ cells falls to between 1 and 2 million at birth,[46] and to about 300,000 by the onset of puberty.[43,47] Over the next 35-40 years of reproductive life, only about 400 oocytes will ovulate, the rest being lost through atresia. By age 40, the size of the follicular pool declines to approximately 25,000, and at menopause, less than 1,000 follicles remain.[48,49,50] and [51]

Accurate modeling of the pattern of follicle depletion in the human ovary is important because the ability to measure reproductive aging or to predict the number of remaining follicles—to tell time on the biological clock—would help women make informed decisions about their reproductive plans.[52] However, for obvious reasons, accurate measures of the numbers of primordial follicles across a human female reproductive life span are difficult to obtain. The first attempt to define the age-related pattern of follicular depletion was based on an analysis of combined data from older morphometric studies and yielded a bi-exponential model of ovarian aging, describing a biphasic pattern of oocyte depletion, with a distinct increase in the rate of decline beginning at approximately age 37.5 years.[42,48,53,54] The biphasic model was widely accepted, despite the biological implausibility of an abrupt, population-wide, physiologic shift in the rate of follicular depletion.[55,56] The model still is cited frequently,[57,58] but subsequent work has demonstrated that a simpler, more biologically plausible, exponential[49,59] or power function[60] conforms best with available human data and current concepts regarding the mechanisms that govern the rate of follicular depletion.[52,61] ***The current working model describes a gradually increasing rate of follicular depletion in which the pace of decline increases as the number of follicles remaining decreases, supported by evidence that paracrine factors secreted by primordial follicles inhibit recruitment and regulate the size of the resting follicular pool.*** **[52,61,62]** ***and*** **[63]** The model describes the mean trajectory of follicular depletion, but leaves a great deal of population variation unexplained. Some of the variation among individuals doubtless relates to differences in the size of the initial follicular pool, which could be random but likely is genetically determined, and on lifestyle factors. The current model of reproductive aging still is evolving and does not yet have any real clinical utility because it cannot predict the reproductive lifespan for an individual woman.[52,60]

Endocrinology of Reproductive Aging

As the pace of follicular depletion increases during the latter reproductive years, but before any discernible change in menstrual regularity, serum follicle-stimulating hormone (FSH) levels begin to rise; luteinizing hormone (LH) concentrations remain unchanged. The subtle “monotropic” rise in circulating FSH concentrations is most apparent during the intercycle transition, when the corpus luteum regresses and menses begins, and could result from agerelated changes in the pattern of pulsatile gonadotropin-releasing hormone (GnRH) secretion, or from progressive follicular depletion and lower levels of feedback inhibition from ovarian hormones. The weight of available evidence supports the second explanation.[64,65]

A variety of studies in animals and women have identified changes in the patterns of hypothalamic-pituitary hormone secretion across the menopausal transition. In rodents, an age-related decrease in pulsatile GnRH and LH secretion and a loss of positive estrogen feedback have been observed, before the follicular pool is exhausted.[66,67,68] and [69] In nonhuman primates, pulsatile GnRH release increases during the perimenopause and the positive feedback response remains intact.[70] Studies in perimenopausal and postmenopausal women have yielded conflicting results. Whereas some have observed changes in sensitivity to estrogen feedback signals[71,72] or in LH pulse amplitude or frequency,[73,74,75,76,77] and [78] others have not.[79,80] and [81] The response to exogenous GnRH stimulation also is inconsistent.[77,82,83] On balance, these data suggest strongly that age-related changes in

pulsatile LH secretion and gonadotropin concentrations merely reflect changes in ovarian feedback signals and do not result from aging of the hypothalamic-pituitary axis.

The bulk of available evidence indicates that the progressive increase in FSH concentrations associated with reproductive aging results from a progressive decrease in the levels of feedback inhibition from the smaller cohorts of follicles recruited from a shrinking follicular pool. Circulating follicular phase inhibin B levels (derived primarily from smaller antral follicles) decrease as or even before FSH concentrations begin to increase.[64,84,85,86,87,88,89,90] and [91] Inhibin A levels also decline, but only in the later stages of reproductive aging, after the onset of menstrual irregularity.[88,92,93,94] and [95] Both inhibins selectively inhibit pituitary FSH secretion. Consequently, FSH levels rise progressively as inhibin production from smaller cohorts of aging follicles decreases, most noticeably in the early follicular phase. Whereas declining inhibin production also could reflect a decrease in the functional capacity of older follicles,[96] the observation that preovulatory follicular fluid inhibin concentrations are similar in young and older cycling women suggests that the number of remaining follicles is more important.[84] Ovarian steroid hormones do not play a major role. The initial rise in FSH levels precedes any measurable decrease in estradiol levels, by several years.[65,97] Follicular phase estradiol levels in older cycling women generally are similar to those in younger women, and often even higher.[84,98] Luteal phase estrogen and progesterone levels also do not seem to change consistently with advancing age.[64,86,88,99,100,101] and [102] Moreover, in sporadic ovulatory cycles in aging women, serum concentrations of estradiol and progesterone are comparable to those observed in younger women.[103]

As age and FSH levels increase, the follicular phase becomes shorter;[104,105] and [106] LH levels and luteal phase duration remain unchanged. As the follicular phase shortens, estradiol levels rise earlier, suggesting that higher FSH levels stimulate more rapid follicular development.[64] ***However, careful studies have shown that the earlier rise in estradiol levels results not from accelerated follicle growth, but from advanced follicular development at the beginning of the cycle and earlier selection of the dominant follicle***.[99,105,107] The earlier increase in follicular phase FSH level also frequently results in more than one dominant follicle,[108,109] and [110] explaining the higher prevalence of dizygotic twinning in older cycling women.[99, 108, 111]

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Reproductive aging already is quite advanced when the first clinical sign appears. Cycles remain regular, but overall cycle length and variability decrease gradually, reaching a nadir at an average age of 42 years,[104,112] when fertility is at or near an end. However, women generally take notice only when cycles become irregular, marking the beginning of the menopausal transition.[113] The menopausal transition begins at an average age of 46 years, but can arrive as early as age 34 and as late as age 54 years.[104,112,114,115] and [116] Thereafter, average cycle length and variability increase steadily as ovulations become less regular and frequent.[112] Regardless of age, the interval from loss of menstrual regularity to menopause is relative fixed, spanning approximately 5-6 years.[47,117,118] The age of menopause, recognized only in retrospect, averages 51 years, but ranges widely, between ages 40 and 60 years.[116,119,120,121,122,123] and [124] The variation in menopausal age is very similar across populations and generally follows a normal distribution that is slightly skewed to younger ages.[124,125] and [126]

Genetics of Reproductive Aging

Barring any disease that destroys or causes the removal of ovarian tissue and any important environmental insults, the total number of follicles at birth, and the age when the supply is exhausted, are genetically

determined.[47,127,128,129,130,131,132,133,134] and [135]

There is good correlation between menopausal age in mothers and daughters and between sisters, suggesting that genetic factors play an important role in determining menopausal age.[136,137] and [138] ***Approximately 10% of women become menopausal by the age of 45,[116,128] probably because they were endowed with a smaller than average ovarian follicular pool that is functionally depleted at an earlier age***. Pedigree analysis has revealed that the genetic features of early menopause (age 40-45) and premature ovarian failure (POF) are similar, suggesting a dominant pattern of inheritance through maternal or paternal relatives.[139,140] The same genetic factors that determine the age at menopause also likely determine the age of reproductive milestones preceding the menopause.[141] In natural populations, age at last birth varies as widely as the age at menopause, but occurs on average 10 years earlier.[47] Moreover, women who repeatedly respond poorly to exogenous gonadotropin stimulation also tend to have an earlier menopausal transition,[141,142,143] and [144] suggesting their poor response reflects an advanced stage of follicular depletion, beginning years sooner than would be anticipated normally.[141] Conversely, fertility in women destined for a later than average menopause may not decrease significantly until after age 40.

Genes affecting reproductive hormones (*FSH, FSHR, LH, LHR, CYP17, CYP19*) or involved in the initial growth of primordial follicles (*BMP15, GDF9, GPR3*) impact follicular function; mutations are rare in humans, but polymorphisms could influence the rate of follicular recruitment and depletion and thereby affect the length of reproductive life.[145] Variations in other genes encoding DNA binding proteins and transcription factors (*NOBOX, LHX8*) and RNA binding proteins (*NANOS*) expressed during oogenesis could affect germ cell formation; mutations causing POF have been identified in a few women.[146] Variations in other genes with links to POF also might affect the rate of follicular depletion in normal women (*ADAMts9, FOXL2*).[147,148] In a Dutch cohort study, common polymorphisms in the gene encoding the receptor for antimüllerian hormone (*AMHR2*) were associated with menopausal age,[149] implicating a decrease in AMH signaling that would weaken its paracrine inhibition of primordial follicle recruitment, leading to more rapid follicular depletion. Careful examinations of these and other candidate genes identified in genome-wide association studies likely will yield new insights and further our understanding of the mechanisms that govern reproductive aging.

The Aging Follicle and Oocyte

Whereas the number of remaining ovarian follicles steadily declines with increasing age, observations in stimulated cycles suggest that aging follicles also become progressively less sensitive to gonadotropin stimulation. As age increases, the total dose and duration of treatment required to stimulate multiple follicular development increase. The rate of rise and the peak in estradiol levels decrease, reflecting the smaller cohorts of follicles that can be recruited. However, the amount of estradiol secreted by the follicles that do emerge and grow to maturity appears comparable to that in younger women.[150] Although a decrease in exogenous hCG-induced ovarian androgen production can be demonstrated before the age of 30, circulating estradiol levels remain normal throughout and beyond the reproductive years, probably because rising FSH levels are able to compensate.[151] Studies of ovarian follicular development and preovulatory follicular fluid hormones in older and younger cycling women do not suggest any age-related decline in follicular function, once growth and development begins. Preovulatory follicles in older and younger women are similar in size and inhibin content, and follicular fluid progesterone levels and estrogen/androgen ratios are even higher in older than in younger women.[84]

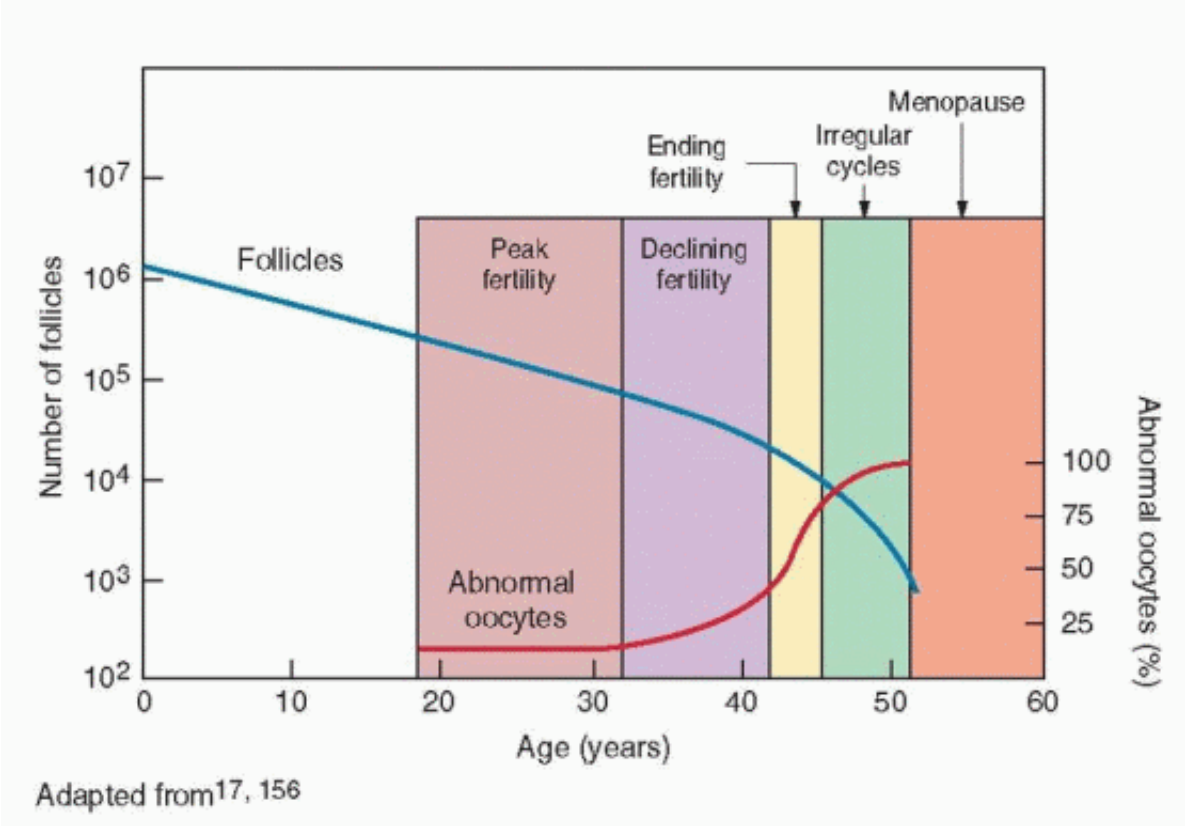
Older cycling women ovulate as regularly and more frequently than younger women. Their rising FSH levels apparently compensate quite effectively for any decrease in follicular sensitivity to gonadotropin stimulation. Preovulatory follicles in older cycling women get an earlier start, but grow at a normal pace and reach a normal size; their follicular fluid characteristics suggest they also are quite healthy. Why then does fertility in women decline progressively with age? ***The available evidence indicates that both the age-related decline in female fertility and the increase in risk of miscarriage can be attributed to an increase in the proportion of abnormal oocytes in an aging and shrinking follicular pool***.

As the number of follicles decreases, oocyte quality also declines (at least by age 31-32 years), primarily because of an increase in meiotic nondisjunction, resulting in an increasing rate of oocyte and embryo aneuploidy in aging women.[50,152,153] and [154] A wide variety of techniques has been used to study the chromosomal composition of human oocytes. The best available evidence, derived from detailed cytogenetic analysis of oocytes retrieved for IVF that failed to fertilize, suggests that the global rate of oocyte aneuploidy increases with advancing maternal age.[155,156] Oocyte aneuploidy results primarily from premature separation of sister chromatids during meiosis I (resulting in a single chromatid in place of or in addition to one or more whole chromosomes), or from whole chromosome nondisjunction during meiosis II.[156] The prevalence of both types of meiotic segregation errors increases progressively with age, but single chromatid events make the greatest contribution to the age-dependent increase in the prevalence of oocyte aneuploidy.[155,156,157,158] and [159]

The age-related decrease in the proportion of normal oocytes (23,X) and the corresponding increase in the proportion of aneuploid oocytes bear striking similarity to the age-related decrease in fertility and increase in the incidence of spontaneous miscarriage in women. Fertility and the prevalence of euploid oocytes decrease progressively with age. ***Miscarriage risk and the prevalence of aneuploid oocytes are relatively low and change little until approximately age 35 (about 10%), then increase progressively, reaching nearly 30% at age 40, 50% by age 43, and virtually 100% after age 45***.[155] These observations offer a logical explanation for the age-related increase in the prevalence of aneuploidy in spontaneous abortuses. Whereas at least half of all clinically recognized miscarriages exhibit an abnormal karyotype and the frequency of both euploid (normal) and aneuploid (abnormal) abortuses increases with maternal age, the probability that an abortus will be chromosomally abnormal increases with age, from less than 35% at age 20 to nearly 80% over age 42.[36] Trisomies are by far the most common abnormality observed, followed by polyploidies and monosomy X (45,X).

Studies of meiotic segregation have revealed that factors predisposing to nondisjunction relate to the disruption of chromosomal pairing and recombination.[160,161] Various mechanisms have been implicated, but all involve an age-dependent deterioration in cellular factors required for proper spindle formation and function.[162] Molecular investigations of chromatid cohesion and separation have implicated cohesins, a specific class of proteins that maintain cohesion between sister chromatids and oppose the splitting forces mediated by the microtubules of the meiotic spindle.[163,164,165] and [166] An age-related premature degradation or deficiency of cohesins may result in unstable bivalent chromatid structures and predispose to premature separation of sister chromatids before they align on the meiotic spindle. The smaller chromosomes appear more prone to premature chromatid separation, possibly because they have fewer of the chiasma that help to prevent such dissociation.[157,167,168] Other studies using high-resolution confocal microscopy to examine the meiotic spindle in human oocytes have revealed that abnormalities of the cleavage spindle microtubular matrix or chromosome alignment during meiosis II are four to five times more common in older cycling women (age 40-45) than in younger women (age 20-25).[50] These and other observations of cultured human oocytes collected from unstimulated ovaries further indicate that the meiotic competence of oocytes declines with age.[169] ***In sum, accumulated evidence strongly suggests that the***

primary cause of the age-dependent decrease in fecundability and increase in the incidence of miscarriage is an increasing prevalence of aneuploidy in aging oocytes resulting from disordered regulatory mechanisms governing meiotic spindle formation and function.



Aging and the Uterus

Aging does not appear to have any significant adverse effect on the uterus. Although the prevalence of benign uterine pathology (leiomyomata, endometrial polyps, adenomyosis) increases with age,[170,171] and [172] little evidence exists to indicate it has much overall impact on fertility in women.[173,174,175] and [176] Age also does not appear to adversely affect endometrial development or function in response to steroid stimulation.[177] The strongest evidence comes from comparing outcomes in nondonor and donor oocyte IVF cycles. Whereas early studies suggested that donor oocyte IVF pregnancy and delivery rates decreased modestly with the age of the recipient,[178,179] and [180] the bulk of more recent experience refutes those conclusions.[34,181,182]

In the national summary of ART success rates for the year 2007, live birth rates declined progressively with increasing age for nondonor egg cycles, as expected. In contrast, the overall live birth per transfer rate in donor egg IVF cycles was 55% and did not vary significantly with age of the recipient.[34] ***Live birth rates in donor egg IVF cycles relate to the age of the donor, not the age of the recipient.*** In one large series, miscarriage rates increased from 14% in women matched with egg donors ages 20-24 to 44% for women whose donors were over age 35.[183]

Aging and Male Fertility

The relationship between age and fertility in men is discussed in detail in Chapter 30 and summarized here. Modest

age-related decreases in semen volume, sperm motility, and morphologically normal sperm, but not sperm density, have been observed.[184] Semen characteristics generally do not accurately predict fertilizing capacity;[185,186,187] and [188] neither do endocrine parameters.[189,190] In studies of the effect of male partner age on pregnancy rates, female partner age and declining coital frequency with increasing age are obvious and important confounding factors. Among the few studies that have controlled for female age, pregnancy rates for men over 50 have been 23-38% lower than for men under age 30.[184] A British study that examined the effect of men's age on the time to conception (adjusting for the confounding effects of both partner's age and coital frequency) found that increasing men's age was associated with increasing time to conception and declining overall pregnancy rates; time to conception was 5-fold greater for men over age 45 than for men under age 25, and restricting the analysis to men with young partners yielded similar results.[191] Results of two studies that controlled for female partner age have suggested that male fertility may start to decline earlier, beginning in the late 30s.[192,193]

There are several possible biological mechanisms that might explain an age-related decline in male fertility. Sperm chromosomal abnormalities may increase in frequency with age and adversely affect early embryonic development.[194] There is at least some evidence to suggest that increasing male age may raise the risk of miscarriage in young women.[195] Average FSH levels in men increase during their 30s,[196] suggesting that age-related changes in the hypothalamic-pituitary-gonadal axis may begin during midlife.[197] The testes and prostate also exhibit morphological changes with aging that might adversely affect both sperm production and the biochemical properties of semen.[198] Whatever the mechanism, decreasing fertility with increasing male age in healthy couples suggests that normal sperm overproduction may not fully buffer the effects of increasing age.

On balance, the available evidence indicates that pregnancy rates decrease and time to conception increases as male age increases. However, because there is little or no overall vmeasurable decline in male fertility before age 45-50, male factors generally contribute relatively little to the overall age-related decline in fertility.

Ovarian Reserve Tests

Over the past 20 years, studies of the mechanisms involved in reproductive aging and its clinical consequences have stimulated efforts to measure “ovarian reserve,” generally describing the size and quality of the remaining ovarian follicular pool. A number of methods have now been described, all intended to predict fertility or to provide prognostic information regarding the likelihood of successful treatment in infertile women, recognizing that although the number and quality of oocytes decline with age, fertility varies significantly among women of similar age.

Like all screening tests, ovarian reserve tests are aimed at identifying individuals at risk for a disease, in this case a “diminished ovarian reserve” (DOR). ***It is important to emphasize that such tests cannot and do not establish a diagnosis of DOR; they only identify women more likely to exhibit a poor response to gonadotropin stimulation and to have a lower likelihood of achieving pregnancy with treatment.*** The value of a screening test depends on its validity, describing its ability to correctly categorize individuals as affected (sensitivity) or unaffected (specificity). The sensitivity and specificity of a screening test will vary with the chosen threshold value. A choice intended to maximize sensitivity minimizes the number of false-negative results (patients with DOR categorized as normal), but increases the number of false-positive results (patients with a normal ovarian reserve categorized as having DOR). Conversely, a threshold value that maximizes specificity minimizes false-positives, but increases false-negative results.

For measures of ovarian reserve, test threshold values should have high specificity for DOR, so as to decrease false-positive results (incorrectly categorizing a patient with a normal ovarian reserve as having DOR), thereby avoiding overly aggressive treatment or inappropriate recommendations to abandon treatment or pursue adoption or oocyte donation in women with a normal ovarian reserve. Treating women with unrecognized DOR (the consequence of maximizing specificity) is undesirable, but a less serious error.

The most important test characteristics of a screening test are its positive predictive value (PPV) and negative predictive value (NPV), which vary with the prevalence of the disease of interest (DOR) in the test population. PPV describes the probability that a woman with a positive test truly has DOR, and NPV is the probability that a woman with a negative test truly has a normal ovarian reserve. If the prevalence of DOR is low, as in young women, the PPV will be low, even if sensitivity and specificity are high. Conversely, if the prevalence of DOR is high, as in older women, the PPV will be high if a highly specific threshold value is chosen. ***If the purpose of ovarian reserve testing is to correctly identify women with DOR, it will be most useful in women at high risk for DOR. When applied in a low prevalence population, many women with a normal ovarian reserve will have a false-positive result and be categorized as having DOR.***

Ovarian reserve tests include both biochemical and ultrasonographic measures of the size and (by inference) the quality of the ovarian follicular pool. Biochemical tests include both basal measurements, such as FSH, estradiol, inhibin B, and antimüllerian hormone (AMH), and provocative tests, such as the clomiphene citrate challenge test. Ultrasonographic measures of ovarian reserve include the antral follicle count and ovarian volume. The clinical utility of any test of ovarian reserve is most easily and efficiently evaluated by examining the relationship between test results and IVF cycle characteristics and outcomes. Considering the costs, logistics, and risks involved with IVF, and the importance of accurate prognostication in counseling candidate couples, correlation with IVF outcome is arguably also the most clinically relevant measure.

Basal FSH and Estradiol Concentrations

Given that rising FSH levels are one of the earliest indications of reproductive aging in women, it was logical to think that the serum FSH concentration might serve as a useful ovarian reserve test. The basal FSH concentration is the simplest and still most widely applied measure of ovarian reserve.

Because serum FSH concentrations vary significantly across the cycle, the serum FSH concentration is best obtained during the early follicular phase (cycle day 2-4). FSH values

vary with the assay method; although values obtained with different assays correlate very well, absolute values can differ significantly. Values also vary with the reference standard, previously an international reference preparation of human menopausal gondotropin (IRPHMG), and now the World Health Organization Second International Reference Preparation (IRP 78/549).

Numerous studies have investigated the relationship between cycle day 3 FSH concentrations or FSH/LH ratios and IVF cycle outcomes, all observing that these measures correlate with the ovarian response to exogenous gonadotropin stimulation and, to a lesser extent, with the likelihood for success. As values increase, peak estradiol levels, the number of oocytes retrieved, and the probability for pregnancy or live birth steadily decline.[199,200,201,202,203,204] and [205] ***With current assays (using IRP 78/549), FSH levels greater than 10 IU/L (10-20 IU/L) have high specificity (80-100%) for predicting poor response to stimulation, but their sensitivity for identifying such women is generally low (10-30%) and decreases with the threshold value.***[206] Although most women who are tested (including those with DOR) will have a normal result, the test is still useful because those with abnormal results are very likely to have DOR. In a 2008 study, an FSH concentration above 18 IU/L had 100% specificity for failure to achieve a live birth.[207]

Because FSH levels can vary significantly, many clinicians prefer to repeat the test. Not surprisingly, consistently high values are associated with a poor prognosis, but a single elevated FSH concentration (>10 IU/L) does not have high specificity for predicting poor response to stimulation or failure to achieve pregnancy.[208] Serial testing in efforts to select the ideal cycle for treatment does not improve outcomes in women with fluctuating FSH concentrations.[209,210]

The basal serum estradiol concentration, by itself, has little value as an ovarian reserve test,[211,212,213] and [214] but can provide additional information that helps in the interpretation of the basal FSH level. An early elevation in serum estradiol reflects advanced follicular development and early selection of a dominant follicle (as classically observed in women with advanced reproductive aging), and will suppress FSH concentrations, thereby possibly masking an otherwise obviously high FSH level indicating DOR. When the basal FSH is normal and the estradiol concentration is elevated (>60-80 pg/mL), the likelihood of poor response to stimulation is increased and the chance for pregnancy is decreased.[215,216,217] and [218] When both FSH and estradiol are elevated, ovarian response to stimulation is likely to be very poor.

Clomiphene Citrate Challenge Test

The clomiphene citrate challenge test (CCCT) is a provocative and possibly more sensitive test of ovarian reserve that probes the endocrine dynamics of the cycle under both basal and stimulated conditions, before (cycle day 3 FSH and estradiol) and after (cycle day 10 FSH) treatment with clomiphene citrate (100 mg/d, cycle days 5-9).[219]

The smaller follicular cohorts in aging women produce less inhibin B and estradiol, resulting in less negative feedback inhibition on clomiphene-induced pituitary FSH release, causing an exaggerated increase in FSH concentrations.[85,220] Consequently, a frankly elevated cycle day 10 FSH concentration can identify women with DOR who might otherwise go unrecognized if evaluated with basal cycle day 3 FSH and estradiol levels alone.[221,222]

In studies evaluating CCCT results, stimulated concentrations of FSH, estradiol, and inhibin B have varied widely, limiting the value of the test.[223,224] and [225] A 2006 systematic review

of the predictive value of the CCCT over a range of day 10 FSH concentrations (10-22 IU/L) in women at low, average, and high probability of DOR concluded the test had 47-98% specificity and 35-93% sensitivity for predicting poor response to stimulation, and 67-100% specificity and 13-66% sensitivity for predicting treatment failure.[226] ***Overall, stimulated FSH levels have higher sensitivity but lower specificity than the basal FSH concentration.***[226]

Inhibin B

Inhibin B is secreted primarily during the follicular phase by the granulosa cells of smaller antral follicles, and might therefore be expected to have some value as an ovarian reserve test.[227] However, serum inhibin B concentrations increase in response to exogenous GnRH or FSH stimulation and vary widely across and between menstrual cycles.[213,228] ***Inhibin B is generally not regarded as a reliable measure of ovarian reserve.***

Although inhibin B levels are generally lower in women who respond poorly to exogenous gonadotropin stimulation than in those who respond normally,[229,230] even low threshold values (40-45 pg/mL) have only 64-90% specificity and 40-80% sensitivity for predicting poor response. Inhibin B has a relatively low PPV (19-22%) but a relatively high

NPV for detecting DOR in a general IVF population;[228,231] in a high prevalence population, the PPV of inhibin B can exceed 80%.[213] In most studies, inhibin B has had poor PPV for failed treatment.212, 213, 227, 232, 233

Antimüllerian Hormone

Antimüllerian hormone (AMH) is produced by the granulosa cells of preantal and small antral follicles, beginning when primordial follicles start development and ending when they reach a diameter of 2-6 mm.[234,235,236] and [237] Small antral follicles are likely the primary source because they contain larger numbers of granulosa cells and a more developed microvasculature.[238,239] Although it functions primarily as an autocrine and paracrine regulator of follicle development, AMH appears in measurable amounts in the serum.[240] The number of small antral follicles correlates with the size of the residual follicular pool and AMH levels decline progressively, becoming undetectable near the menopause.[241,242,243] and [244]

Because AMH derives from preantral and small antral follicles, levels are gonadotropin-independent and exhibit little variation within and between cycles. [245,246] ***and*** [247] In clinical studies, AMH has been assayed using two different commercial assay kits, and although the results they yield are highly correlated, their standard curves are not parallel and there is no applicable conversion factor; one comparative study observed that concentrations measured with one kit were more than 4-fold lower than those measured with the other.[248] Consequently, when applying results in clinical practice, it is important to know which assay method was used to measure AMH. Commercial assay kits yield consistent results with low interassay variation (<10%).[249]

The performance of AMH as a screening test of ovarian reserve has been examined in the general IVF population and in populations of women at low or high risk for DOR. Overall, lower AMH levels have been associated with poor response to ovarian stimulation and low oocyte yield, embryo quality, and pregnancy rates,[228,229,250,251] and [252] but studies correlating mean AMH levels with IVF outcomes have not yielded threshold values that can be applied confidently in clinical care.[211,229,231,250] ***In the general IVF population, low AMH threshold values (0.2-0.7 ng/mL) have had 40-97% sensitivity, 78-92% specificity,***

22-88% PPV and 97-100% NPV for predicting poor response to stimulation (<3 follicles, or <2-4 oocytes), but have proven neither sensitive nor specific for predicting pregnancy. [228,253,254] ***and*** [255] In women at low risk for DOR, values of 2.5-2.7 ng/mL have had 83% sensitivity, 82% specificity, 67-77% PPV, and 61-87% NPV for clinical pregnancy.[212,256] The higher threshold values decrease specificity, resulting in lower PPV because the prevalence of DOR was low. A study in women at high risk for DOR (involving older women, those with an elevated FSH, or history of poor response to stimulation) observed that an undetectable AMH had 76% sensitivity, 88% specificity, 68% PPV, and 92% NPV for three or fewer follicles.[229] A higher threshold value (1.25 ng/mL) had 85% sensitivity, 63% specificity, 41% PPV, and 57% NPV for cycle cancellation.[213]

AMH is a very promising screening test for DOR, but is likely to be more useful in a general IVF population or in women at high risk for DOR than in women at low risk for DOR. Low threshold values have good specificity for poor response to ovarian stimulation, but not for predicting pregnancy.

Antral Follicle Count

Reproductive aged women have an estimated 20-150 growing follicles in the ovaries at any one time, although only a few are large enough to be imaged (≥2 mm) by transvaginal ultrasonography.[257,258] and [259] Follicles of that size have reached a stage of development where they are responsive to FSH, which stimulates and supports more

advanced stages of development. ***Histologic studies have revealed that the number of small antral follicles in the ovaries is proportional to the number of primordial follicles remaining.***[260] ***Therefore, as the supply of primordial follicles decreases, the number of visible small antral follicles also declines.*** The antral follicle count (AFC; total number of antral follicles measuring 2-10 mm in both ovaries) thus provides an indirect but useful measure of ovarian reserve.[258,261,262,263] and [264]

AFC correlates with onset of the menopausal transition, indicating that it relates to the number of follicles remaining.[242] Some, perhaps as much as half, of the antral follicles that can be imaged are probably in the process of atresia, but there is no way other than observing their response to FSH stimulation to distinguish them from viable growing follicles.[17] However, AFC correlates well with oocyte yield in IVF cycles,[265] suggesting that gonadotroin stimulation can still rescue follicles that may be in the early stages of atresia.[266] Several studies have observed a relationship between the AFC and response to ovarian stimulation in IVF cycles. In the general IVF population, including women at low and high risk for DOR, an AFC threshold value of three to four follicles has high specificity (73-100%) for predicting poor response to ovarian stimulation and failure to conceive (64-100%), but relatively low sensitivity for both endpoints (9-73% for poor response, 8-33% for failure to conceive).[213,265,267,268,269,270,271] and [272] The PPV and NPV of AFC have varied widely in studies.

A low AFC has high specificity for predicting poor response to ovarian stimulation and treatment failure, making it a useful test, but low sensitivity limits its overall clinical utility.

Ovarian Volume

Not surprisingly, ovarian volume decreases with progressive follicular depletion.[273,274] However, the measure has high inter-cycle and inter-observer variability,[213,275,276] and [277] and because most studies of ovarian volume have excluded women with ovarian pathology such as endometriomas and polycystic ovary syndrome, results have limited generalizability.[274,278]

Ovarian volume (length × width × depth × 0.52=volume) generally correlates with the number of oocytes retrieved, but poorly with pregnancy.[267,272,279,280] and [281] A low ovarian volume (< 3mL) has high specificity (80-90%) and widely ranging sensitivity (11-80%) for predicting poor response to ovarian stimulation.[206] The PPV for poor response can be as low as 17% among women at low risk for DOR, and as high as 53% in women at high risk.[213] ***Overall, ovarian volume has very limited clinical utility as an ovarian reserve test.***

Other Tests of Ovarian Reserve

Numerous other provocative tests of ovarian reserve have been investigated, including exogenous FSH-stimulated estradiol, inhibin B or AMH levels[250,282,283,284,285] and [286] and GnRH agoniststimulated FSH, estradiol, inhibin B, or AMH concentrations.[250,282,287,288] and [289] In theory, the ovarian and endocrine response to FSH or GnRH agonist stimulation should provide the best estimate of the number of responsive follicles. ***However, a 2006 systematic review found no evidence that these more complex and costly tests predict response to ovarian stimulation or pregnancy any better than basal FSH, AMH, and AFC.***[206]

Combined Tests of Ovarian Reserve

Recognizing that no one test of ovarian reserve has 100% sensitivity and specificity, a number of investigators have examined the performance of varying combinations of ovarian reserve tests. Analysis is difficult, primarily because

of differences in chosen threshold values for specific tests. Moreover, because the different tests are highly correlated, using more than one measure in a prediction model does not necessarily improve its performance.[213,230,267] Complicated formulas also are generally not useful in clinical practice. One analysis combining AMH, inhbin B, AFC, and ovarian volume found that only AFC and AMH predicted response to stimulation and that the combination predicted outcome no better than the individual tests.[275] A meta-analysis of cohort studies investigating the performance of various combinations of tests concluded that models combining tests do not perform significantly better than individual tests such as the AFC.[290]

SUMMARY

Currently, there is no uniformly accepted definition of diminished ovarian reserve. A number of different measures have been developed, primarily for use in predicting success with IVF. The ideal ovarian reserve test should yield consistent results and be highly specific, to minimize the risk for incorrectly categorizing normal women as having a diminished ovarian reserve. Basal FSH is the most commonly used ovarian reserve test, but antral follicle count and antimüllerian hormone are promising predictors with significant potential advantages.

Ovarian reserve tests predict response to exogenous gonadotropin stimulation reasonably well, but whether the information gained truly affects outcomes is less certain. ***Although the planned amount of gonadotropin stimulation often is increased in predicted poor responders, those adjustments do not improve response predictably, probably because the small cohort of responsive antral follicles is the limiting factor and no amount of stimulation can increase that number appreciably.[291,292] and [293]*** Even in women

who previously exhibited a poor response to stimulation, changes in treatment regimens generally have not improved response or pregnancy rates in subsequent cycles.[292,294,295] and [296]

None of the ovarian reserve tests currently in use is an accurate predictor of pregnancy in IVF cycles, unless extreme abnormal threshold values are applied, which results in very low sensitivity for identifying women having a poor prognosis.[207] The tests are adequate for predicting poor response, which does have prognostic value, although not as much in young women as in older women.[297,298] and [299] Although ovarian reserve tests have become a routine element of pre-treatment evaluation for couples planning IVF, it can be argued that routine testing has limited clinical utility in the large majority of patients and can be misleading, especially in women at low risk for having a diminished ovarian reserve.[17]

Ovarian reserve tests also have become a routine element of the diagnostic evaluation for infertility. Advocates for the liberal application of ovarian reserve tests argue that abnormal tests can help to persuade older women to abandon plans to pursue aggressive, costly, and likely futile treatment, and can help to convince young women to do just the opposite, to take fullest advantage of a rapidly closing window of opportunity. Others more circumspect emphasize correctly that few young women will have an abnormal test, and some of those who do inevitably will be categorized incorrectly, leading to inappropriate counseling and treatment. ***The best overall strategy would seem to limit ovarian reserve testing to women at increased risk for having a diminished ovarian reserve and to apply highly***

specific threshold values to minimize the risk for a falsepositive result. In this context, ovarian reserve testing can best be justified for women with any of the following characteristics:[141,300,301,302] and [303]

- Age over 35.
- Unexplained infertility.
- Family history of early menopause.
- Previous ovarian surgery (ovarian cystectomy or drilling, unilateral oophorectomy), chemotherapy, or radiation.
- Smoking.
- Demonstrated poor response to exogenous gonadotropin stimulation.

Ovarian reserve tests always should be interpreted with caution. Rigid application of test results risks inappropriate recommendations for treatment, or for no treatment, and both must be avoided. An abnormal test result does not preclude the possibility of pregnancy. Except perhaps when grossly abnormal, test results should not be used to deny treatment, but only to obtain prognostic information that may help to guide the choice of treatment and best use of available resources. Although the probability of pregnancy may be low, many with abnormal test results will achieve pregnancy if afforded the chance. Ultimately, regardless of the prognosis, the success rate for any individual woman will be 0% or 100%.

Guiding Principles for Evaluation and Treatment of Infertility

From the beginning, the evaluation of infertility should focus on the *couple* and not on one or the other partner, regardless of past reproductive performance. Both partners should be encouraged to attend each visit during evaluation, whenever possible. Each can provide

information and perspective the other may not have or remember. Joint visits also help to ensure that both partners understand any information, options, and recommendations that may be offered and that each has the opportunity to have their questions addressed directly.

Clinicians caring for infertile couples should keep four basic goals in mind:

- To identify and to correct specific causes of infertility, when possible. With proper evaluation and treatment, the majority of women will achieve pregnancy.
- To provide accurate information and to dispel the misinformation commonly gained from friends and mass media.
- To provide emotional support during a trying time. In many couples, the inability to conceive results in feelings they have lost control over an important and very personal part of their lives, and the process of evaluation adds to that burden. Infertile couples often need the opportunity to express their concerns, frustrations, and fears, and support groups can help to meet that need. Group meetings can help couples to realize that their problem is not unique and to learn how others cope with similar problems. Whereas severe anxieties can have adverse effects on ovulatory function and coital frequency, there is no substantial evidence that the usual anxieties of couples trying to conceive cause or contribute to their infertility.
- To guide couples failing to conceive with other forms of treatment to alternatives, including IVF, the use of

donor gametes (oocytes or sperm), and adoption, and to help those who reject or fail treatment to come to closure.

Counseling must be an ongoing process during both evaluation and treatment. Regular visits to review and critique results and to outline recommendations for further evaluation and treatment help to ensure that all of the couple's medical, emotional, and financial needs and concerns are addressed effectively in a timely fashion.

Lifestyle and Environmental Factors

Understandably, all infertile couples are very interested in learning anything they might do to maximize the likelihood of achieving a successful pregnancy. Lifestyle choices and environmental factors influence fertility and deserve consideration and discussion when they are relevant. Over 35% of American women are obese and another 30% are overweight.[304] Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2 and overweight is defined as a BMI between 25 kg/m^2 and 30 kg/m^2. In women, obesity is associated with menstrual dysfunction, decreased fertility, and increased risks of miscarriage and obstetric and neonatal complications. In men, obesity is associated with abnormal semen parameters and can adversely affect fertility.[305]

Substance abuse is one of the few things over which the couple may have specific control, smoking being the most important. Many are not aware of the adverse effects smoking has on fertility and pregnancy outcome.[306] The couple's motivation to maximize their fertility presents a golden opportunity to educate those who smoke and to establish a smoking cessation strategy. Smoking has well-known adverse impact on pregnancy outcome, and evidence strongly suggests that fertility is lower in both men and women who smoke.[307,308,309,310] and [311] The prevalence of infertility is higher, fecundability is lower, and the time to conception is longer in smoking than in non-smoking women, and the effects of passive smoke exposure are only slightly less than those of active smoking by either partner.[312] The available data suggest that the adverse effects of smoking on fertility are dosedependent.[308,313,314] and [315] The mechanisms involved ay include accelerated follicular

depletion,[316,317] and [318] menstrual cycle abnormalities,[319] or gamete or embryo mutagenesis induced by toxins in cigarette smoke.[320,321,322,323] and [324] A causal relationship between cigarette smoking and female infertility has not been established. However, based on the results of a meta-analysis including 12 studies (overall OR for risk of infertility in women smokers versus non-smokers 1.60), and assuming a 25% prevalence of smoking in women of reproductive age, up to 13% of female infertility may relate to smoking.[310] Consequently, an active approach to prevention of infertility is justified, discouraging smoking and helping those who smoke to quit.[325]

Other forms of substance abuse also can adversely affect fertility. Marijuana inhibits the secretion of GnRH and can suppress reproductive function in both women and men.[326] In women, marijuana use can interfere with ovulatory function.[327] Cocaine use can impair spermatogenesis in men[326,328] and has been associated with a greatly increased risk of tubal disease in women.[327] Heavy alcohol consumption in women may decrease fertility;[329,330] and [331] in men, it has been associated with decreased semen quality and impotence.[332] Conflicting evidence suggests that moderate alcohol intake can reduce fecundability.[333,334] In both women and men, even modest amounts of alcohol consumption have been associated with lower pregnancy rates in IVF cycles.[335] Although moderate caffeine ingestion (≤250 mg daily; two standard beverages) appears not to have any adverse effects on fertility, higher levels of consumption may delay conception[311,336,337] or increase the risk of pregnancy loss.[338]

Other potentially harmful occupational and environmental exposures, although uncommon, may be identified. Exposures to perchlorethylene in the dry cleaning industry, toluene in the printing business, ethylene oxide, and mixed solvents have been associated with decreased fecundity. Semen abnormalities have been described in men exposed to radiant heat or heavy metals. Environmental exposure to herbicides or fungicides has been associated with decreased fertility in women,[331] and exposure to pesticides and other chlorinated hydrocarbons with an increased risk of miscarriage.[339]

For couples attempting to conceive, there is fair evidence to support recommendations for smoking cessation and efforts to achieve a BMI between 20 and 25 kg/m^2. Recommendations to limit alcohol consumption to four or fewer drinks per week and to limit caffeine intake to less than 250 mg/d also are reasonable and consistent with available evidence. However, there have been no randomized controlled trials demonstrating that such lifestyle modifications improve fertility.

Normal Reproductive efficiency

As evaluation begins, and again before treatment starts, education on normal human reproductive efficiency can help to provide important perspective for infertile couples. Few realize that, compared to other mammals and even nonhuman primates, humans are not highly fertile. In captive baboons, cycle fecundity ranges as high as 80% when conditions and timing are optimized.[340] ***In normally fertile couples, cycle fecundity averages 20% and does not exceed approximately 35% even when coitus is carefully timed.***[40,341,193] That perspective is particularly helpful when discussing and comparing the efficacy of different treatment options, typically viewed in terms of cycle fecundability. When doing so, it is important for couples to realize that the benchmark for comparison is 20-30%, and not 100%.

Given the average 20% cycle fecundability, the cumulative pregnancy rates observed over time in normal fertile couples are easy to understand. The data in the table below have been a standard since 1956, and have been confirmed by more recent studies.[3,342,343]

Time Required for Conception Among Couples Who Will Attain Pregnancy[342]

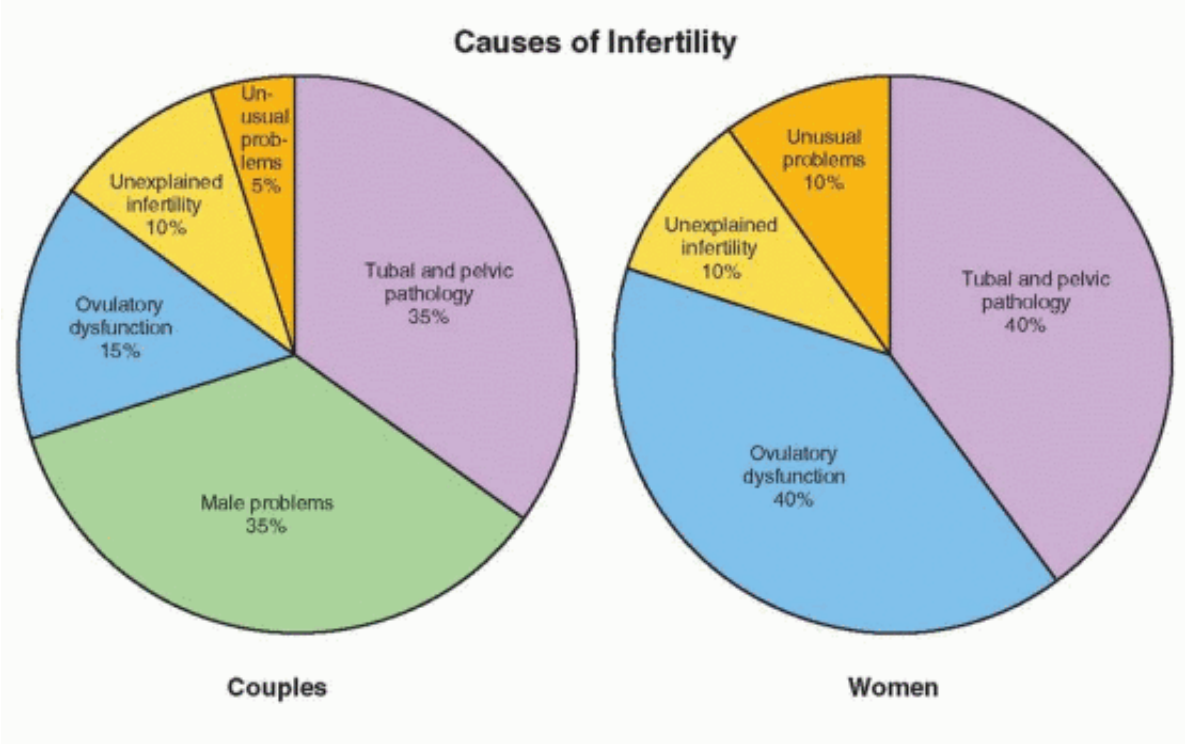
Months of Exposure	*% Pregnant*
3 months	57%
6 months	72%
1 year	85%
2 years	93%

Normal sperm can survive in the female reproductive tract and retain the ability to fertilize an egg for at least 3 and up to 5 days, but an oocyte can be fertilized successfully for only approximately 12-24 hours after ovulation.[344] ***Consequently, virtually all pregnancies result from intercourse occurring sometime within the 6-day interval ending on the day of ovulation.***[193,341,345] Estimates of when fertility peaks vary with the method used to determine the time of ovulation. When ovulation is assumed to occur on the day before the midcycle rise in basal body temperature (BBT), the day of peak fertility falls 2 days prior to ovulation[193]; ovulation generally occurs within 1 day of that predicted.[345] When the time of ovulation is based on daily urine estrogen concentrations, the probability of conception increases steadily as ovulation nears and peaks on the day before and day of ovulation,[341,345] ranging from about 10% at its low to approximately 33% at its peak. When daily urinary LH excretion is monitored to detect the midcycle surge that triggers ovulation, follicular collapse (as determined by serial transvaginal ultrasonography) and, presumably, ovum release generally follows within 14-26 hours, and almost always within 48 hours.[346,347] Regardless of the method used, all studies indicate that fertility plummets almost immediately thereafter, declining to near zero within 24 hours after ovulation.

Timed coitus is frequently recommended to infertile couples as a means to increase the likelihood of pregnancy, even though there are few data to support the recommendation. Although BBT and ovulation predictor kits can help define the time of ovulation, they should be used only when necessary. Scheduled intercourse clearly adds to the already significant stress of infertility. Moreover, much of the interval of peak fertility during the menstrual cycle may be inadvertently excluded while awaiting the appropriate "signal." ***For most couples, the simple recommendation for intercourse approximately twice per week can avoid an unnecessary source of stress while also helping to ensure that coitus occurs during the interval of highest fertility.***[348] ***However, timed coitus may be a reasonable recommendation for couples having infrequent intercourse, by preference or because of circumstance.***

Causes of Infertility

Before any formal investigation begins, the major causes of infertility and the basic components of the infertility evaluation should be outlined for the couple. ***The major causes of infertility include ovulatory dysfunction (20-40%), tubal and peritoneal pathology (30-40%), and male factors (30-40%); uterine pathology is relatively uncommon, and the remainder is largely unexplained.*** To some extent, the prevalence of each cause of infertility varies with age. Ovulatory dysfunction is more common in younger than in older couples, tubal and peritoneal factors have a similar prevalence, and male factors and unexplained infertility are observed somewhat more often in older couples.[349,350] The distribution of causes also varies with the duration of infertility and the level of care.[351,352] and [353]



Most couples seeking evaluation have been trying to conceive for 2 or more years, so few will be normally fertile. Those with longer durations of infertility generally have more severe or multiple problems and tend to congregate in tertiary care centers. The average duration of infertility for couples seen in tertiary care centers (42 months)[353] is twice that for couples seen in the primary care setting (21 months).[351] Predictably, the proportion of couples with easily treatable ovulatory dysfunction decreases from primary to tertiary care, and that with more severe tubal/peritoneal or male factors increases.

The human reproductive process is complex, but for purposes of evaluation, it can be dissected into its most important and basic components.

- Sperm must be deposited at or near the cervix at or near the time of ovulation, ascend into the fallopian tubes, and have the capacity to fertilize the oocyte (male factor).
- Ovulation of a mature oocyte must occur, ideally on a regular and predictable basis (ovarian factor).
- The cervix must capture, filter, nurture, and release sperm into the uterus and fallopian tubes (cervical factor).
- The uterus must be receptive to embryo implantation and capable of supporting subsequent normal growth and development (uterine factor).
- The fallopian tubes must capture ovulated ova and effectively transport sperm and embryos (tubal factor).

The infertility evaluation is designed to isolate and test the integrity of each component, insofar as that is possible, and to identify any abnormalities that might impair or prevent conception. The pace and extent of evaluation should be based on the couple's age, duration of infertility, medical history, physical examination, and preferences.

Some infertility problems once considered insurmountable are now amenable to modern treatments. IVF can effectively bypass irreparable tubal occlusive disease, and intracytoplasmic sperm injection (ICSI) can overcome

even severe abnormalities of semen quality.

Treatments aimed at increasing gamete density—bringing together more than the usual numbers of oocytes and sperm in the right place at the right time—can increase cycle fecundability for couples with age-related or otherwise unexplained infertility, and include ovarian stimulation with intrauterine insemination (IUI) or IVF. In women with premature ovarian failure, women beyond normal reproductive age, and women without ovaries, IVF using donor oocytes is highly successful.

The advent of evidence-based medical practice has had significant impact on the diagnosis and treatment of infertility. Critical analyses of standard diagnostic tests and common therapies have questioned and, in some cases, proven invalid some of the most time-honored methods of evaluation and treatment.[354] ***The scope and sequence of the modern infertility evaluation have shifted focus, from making a specific diagnosis to using the most efficient and cost-effective tests. The focus of treatment for infertility also has shifted, from systematic correction of each identified factor to applying the most efficient and cost-effective therapy, which often is assisted reproductive technology (ART).***

Indications for Evaluation

When should a formal evaluation for infertility begin? After all, most infertile couples are only subfertile, not truly sterile, and many will conceive, eventually, without treatment. Infertility has a significant spontaneous cure rate that varies with female partner age, duration, past conception history, and the cause(s). ***The probability for achieving a live birth without treatment decreases with increasing age and duration of infertility.***[351,352] ***and*** [353,355,356] ***and*** [357] Overall, the likelihood of pregnancy without treatment declines by about 5% for each additional year of female partner age and by 15-25% for each added year of infertility.[353] ***The largest majority of spontaneous pregnancies occur within 3 years; thereafter, the prognosis for success without treatment is relatively poor.*** Couples that have conceived before generally have a better prognosis than those who have never achieved pregnancy. The cause of infertility also affects the prognosis for success without treatment but, of course, cannot be determined without evaluation. Predictably, the diagnoses of anovulation and unexplained infertility have the best prognosis. The likelihood for success without treatment for couples with male factors, tubal disease, and endometriosis varies widely with the severity of disease; the prognosis is reasonably good for mild oligospermia, tubal adhesions, and mild endometriosis, and quite poor for severe male factors, tubal obstruction, and severe endometriosis.

Evaluation should be offered to all couples who have failed to conceive after a year or more of regular unprotected intercourse, but a year of infertility is not a prerequisite for evaluation. Earlier evaluation is justified for women with irregular or infrequent menses, history of pelvic infection or endometriosis, or having a male partner with known or suspected poor semen quality, and also is warranted after 6 months of unsuccessful effort for women over the age of 35 years.[358]

Education should be offered to any couple who seeks it, regardless whether they have made any active effort to conceive. It is always helpful to explain the reproductive process, to inform couples that normal cycle fecundability is approximately 20% (far lower than most realize), and to discuss the relationship between age and fertility, when it is relevant. In concerned couples who have not yet truly tested their fertility and have no obvious problems, some basic preliminary evaluation is reasonable to perform, if requested. Tests to confirm ovulation and semen quality are easy to perform, relatively inexpensive, minimally

invasive, and quickly can identify some of the most common reproductive problems. In women at high risk for diminished ovarian reserve, an ovarian reserve test is also reasonable, because results may help to determine

when and how further evaluation and treatment should be recommended.

Preliminary Evaluation of the Infertile Couple

Any evaluation of infertility must begin with a careful history and physical examination, which often will identify symptoms or signs that suggest a specific cause and help to focus evaluation on the factor(s) most likely responsible. In the female partner, relevant medical history and physical findings include the following[359]:

History

- Gravidity, parity, pregnancy outcomes and associated complications.
- Cycle length and characteristics, and onset and severity of dysmenorrhea.
- Coital frequency and sexual dysfunction.
- Duration of infertility and results of any previous evaluation and treatment.
- Past surgery, its indications and outcome, and past or current medical illnesses, including episodes of pelvic inflammatory disease or exposure to sexually- transmitted infections.
- Previous abnormal pap smears and subsequent treatment.
- Current medications and allergies.
- Occupation and use of tobacco, alcohol, and other drugs.
- Family history of birth defects, mental retardation, early menopause or reproductive failure.
- Symptoms of thyroid disease, pelvic or abdominal pain, galactorrhea, hirsutism, or dyspareunia.

Physical Examination

- Weight and BMI.
- Thyroid enlargement, nodule, or tenderness.
- Breast secretions and their character.
- Signs of androgen excess.
- Pelvic or abdominal tenderness, organ enlargement, or mass.
- Vaginal or cervical abnormality, secretions, or discharge.
- Mass, tenderness, or nodularity in the adnexa or cul-de-sac.

Irregular or infrequent menses indicate ovulatory dysfunction. Previous treatment for cervical intraepithelial neoplasia or observations of a mucopurulent cervicitis or cervical stenosis helps to identify unusual women in whom the cervix may present an obstacle. A history of previous hysteroscopic or reconstructive uterine surgery or recently developing symptoms of menorrhagia suggest an abnormality of the uterine cavity; previous uncomplicated first- and second-trimester pregnancy terminations generally do not adversely affect subsequent fertility.[360,361] Worsening dysmenorrhea, new onset of dyspareunia, or physical findings of focal tenderness or cul-de-sac nodularity suggest endometriosis. A history of pelvic infection, septic abortion, ruptured appendix, ectopic pregnancy, abdominal myomectomy, or adnexal surgery should raise suspicion for tubal or peritoneal disease.

Screening Tests

Pap smear screening is recommended for all sexually-active women of reproductive age who have a cervix. The date and results of the most recent pap smear should be documented and a pap smear performed, if needed. A blood type, Rh factor, and antibody screening (in Rh-negative women) also are recommended, if not already known.

The American College of Obstetricians and Gynecologists and the American College of Medical Genetics recommend that screening for ***cystic fibrosis*** (CF) be offered to individuals with a family history of CF, reproductive partners of individuals with CF, and couples planning a pregnancy or seeking prenatal care wherein one or both partners are Caucasian or of Ashkenazi Jewish descent, and that the test be made available to all patients on request.[362] Sequential screening (testing one partner, and the second only if the first partner is identified as a carrier) is most cost effective. Interestingly, a 2007 study found that only 22/1,006 (2%) infertile non-Hispanic Caucasian couples offered counseling and screening (carrier frequency 1/25, detection rate 88%) chose to be tested, most citing the cost of screening.[363]

All women attempting pregnancy with undocumented previous ***rubella*** infection or vaccination should be tested for immunity, and vaccinated if seronegative. As there has never been a documented case of congenital rubella syndrome attributed to vaccine, the Centers for Disease Control and Prevention (CDC) has determined that women need not avoid pregnancy for more than 1 month after vaccination.[364] The CDC also recommends that all women without history of previous infection or evidence of immunity or vaccination against ***varicella*** (chicken pox) receive two doses of vaccine and avoid pregnancy for 1 month after each dose.[365]

Screening for ***sexually-transmitted infections*** (STI) is recommended for all women at moderate to high risk for infection. Decisions regarding STI screening should consider that current recommendations from the CDC include screening all pregnant women for chlamydia and gonorrhea (nucleic acid-based tests), syphilis (rapid plasma reagin; RPR), hepatitis B (hepatitis B surface antigen; HBSAg), and voluntary screening for human immunodeficiency virus type 1 (HIV-1) at the first prenatal visit.[366] For women receiving inseminations of donor sperm, the American Society for Reproductive Medicine (ASRM) considers HIV-1 screening mandatory, recommends screening for syphilis, hepatitis B and C, cytomegalovirus (CMV), HIV-2, and human T-cell lymphocyte virus (HTLV) types I and II, and suggests screening for chlamydia and gonorrhea at the discretion of the physician.[367] For male partners of women receiving inseminations of donor sperm, the ASRM strongly recommends HIV-1 and recommends other STI screening. For recipients of donor oocytes or embryos and their male partners, the ASRM recommends screening for syphilis, hepatitis B and C, CMV, and HIV-1.[367] Any additional screening laboratory tests should be directed by the medical history and clinical judgment.

Male Factor: Abnormalities of Semen Quality

The evaluation and treatment of male infertility is the focus of Chapter 30, but must be addressed briefly here because male factors explain or contribute significantly to infertility in up to 35% of couples. Semen analysis is therefore always an appropriate and important initial step in the evaluation of the infertile couple. In the absence of any known genital abnormality, trauma, surgery, or sexual dysfunction, physical examination of the male partner can be deferred pending the results of the initial semen analysis.

When semen analysis yields equivocal results, additional analyses are required to better define a suspected abnormality. A frankly abnormal semen analysis is indication for additional evaluation that may be conducted by a

gynecologist having the necessary training and experience, but most often is performed by a urologist or other specialist in male reproduction.[368] Invasive diagnostic procedures in the female partner generally are best deferred until evaluation of the male is completed. The range of effective treatment options for couples with severe male factor infertility is limited, and often will direct or even dictate what additional evaluation may be relevant in the female partner. When semen quality is normal, attention naturally turns to the female partner.

Ovarian Factor: Ovulatory Dysfunction

Overall, disorders of ovulation account for approximately 20% of the problems identified in infertile couples. Ovulatory dysfunction can be severe enough to prevent conception (anovulation), or only a contributing factor (oligoovulation). However, because cycle fecundability averages only approximately 20% even in normally fertile couples, the distinction is moot.

A number of methods can be used to determine if and when ovulation occurs. Directly or indirectly, all are based on one or another of the hormonal events that characterize the normal ovulatory cycle (Chapter 6). Each of the available tests is useful and no one test is necessarily best. Some are simple, noninvasive, and inexpensive, and others are more complicated, invasive, and costly. A few can predict when ovulation is likely, with varying accuracy. However, no test, regardless how sophisticated, can prove that ovulation has actually occurred; the only positive proof of ovulation is pregnancy. The most appropriate test to use varies with the information required. The same tests used to diagnose anovulation can be used to assess the effectiveness of treatment.

Menstrual History

Menstrual history alone often is significaent to establish a diagnosis of anovulation. Menses in normally ovulating women generally are regular, predictable, consistent in volume and duration, and typically accompanied by a recognizable pattern of premenstrual and menstrual symptoms. Conversely, those in anovulatory women generally are irregular, unpredictable or infrequent, vary in flow characteristics, and exhibit no consistent pattern of molimina. Women with regular menses are almost always ovulatory. ***Women with irregular or infrequent menses may ovulate, but not consistently, and do not require specific diagnostic tests to prove what is already obvious.***

Basal Body Temperature (BBT)

Basal body temperature is body temperature under basal conditions, at rest. For practical purposes, BBT is measured each morning, upon awakening and before arising. Traditionally, BBT is measured with an oral glass-mercury thermometer having an expanded scale, typically ranging from 96.0 to 100.0 degrees Fahrenheit and marked in tenths of one degree; modern electronic thermometers are a suitable alternative, but only if they have the necessary accuracy

and precision. As a test of ovulation, daily BBT recordings are based on the thermogenic properties of progesterone; as levels rise after ovulation, BBT also increases. The effects are more qualitative than quantitative, are subtle but nonetheless distinct, and generally easy to detect when daily BBT recordings are plotted on graph paper.[369] ***Synthetic progestins commonly used to induce menses in amenorrheic women (medroxyprogesterone acetate, norethindrone acetate) have similar thermogenic properties and also raise BBT.***

BBT is typically low and fluctuates between 97.0 and 98.0 degrees during the follicular phase of the cycle, modestly but distinctly higher (0.4-0.8 degrees) during the luteal phase, and falls again to baseline levels just before or after the onset of menses. In ovulatory women, a “biphasic” pattern usually is readily evident. ***The ideal***

BBT recording is distinctly biphasic and reveals a cycle between 25 and 35 days in length, with menses beginning 12 days or more after the rise in temperature. When pregnancy occurs in a monitored cycle, onset of menses is delayed and BBT remains elevated, reflecting the sustained production of progesterone by the corpus luteum stimulated by human chorionic gonadotropin (hCG).

BBT recordings provide objective evidence of ovulation and also reveal the approximate time of ovulation. Unfortunately, the temporal relationship between the thermogenic shift in BBT and ovulation frequently is misunderstood. BBT generally falls to its lowest level on the day before or day of ovulation, but the nadir in BBT cannot be reliably identified until after the temperature rises and remains elevated.[370] The shift in BBT occurs when progesterone concentrations rise above approximately 3-5 ng/mL, 1 to 5 days *after* the midcycle LH surge and up to 4 days *after* ovulation.[371] The temperature rise usually is somewhat abrupt, but may be gradual and difficult to define, and once apparent (2 or more days of temperature elevation), the most fertile interval has passed. ***In cycles monitored with BBT, the interval of highest fertility spans the 7-day interval immediately before the midcycle rise in BBT***. Much of the uncertainty in predicting the time of ovulation can be avoided by reviewing a series of recordings, noting the earliest and latest days of the cycle on which the temperature shift occurred. ***Coital timing can be optimized by suggesting intercourse on alternate days beginning 7 days before the earliest observed rise in BBT and ending on the latest day it has been observed***.

The principal advantage that BBT has over other tests of ovulation is low cost. BBT recordings also can reveal an abnormally long follicular phase and grossly short luteal phase that otherwise might go unrecognized, for which treatment is warranted. BBT monitoring is easy and non-invasive, but can become tedious over time. For some it also increases stress, serving as a daily reminder of unsuccessful efforts to conceive, each day beginning with thoughts of a family not yet realized. In the few women who menstruate regularly but do not exhibit a biphasic BBT, an alternative method should be used to document ovulation before assuming that treatment is required. Although there are more reliable methods to evaluate ovulatory function, BBT is still useful and may be the best method for couples who are reluctant or unable to pursue more formal and costly evaluations.

Serum Progesterone Concentration

A serum progesterone measurement is the simplest, most common, objective and reliable test of ovulatory function, as long as it is appropriately timed. Progesterone levels generally remain below 1 ng/mL during the follicular phase, rise slightly on the day of the LH surge (1-2 ng/mL) and steadily thereafter, peak 7-8 days after ovulation, and decline again over the days preceding menses. ***A progesterone concentration less than 3 ng/mL implies anovulation, except when drawn immediately after ovulation or just before the onset of menses, when lower levels naturally might be expected***.[372,373]

When is the best time to measure the serum progesterone concentration to document ovulation? ***Ideally, the serum progesterone level should be drawn approximately one week***

before the expected onset of menses, when the concentration is at or near its peak. Contrary to popular belief and practice, cycle day 21 is not ***always the best time to measure the serum progesterone concentration***. Cycle day 21 is a good choice for women with cycles lasting approximately 28 days, but a poor choice for women with 35 day cycles. The normal ovulatory cycle is 25-35 days long and exhibits a 13-15 day luteal phase. At the extremes of normal, ovulation may occur as early as cycle day 10 (in a 25-day cycle) and as late as day 22 (in a 35-day cycle). If ovulation occurs on cycle day 10, day 21 falls 11 days after ovulation, well after progesterone concentrations peak and when they are again nearing basal levels. If ovulation occurs on cycle day 22, day 21 falls 1 day *before* ovulation, when progesterone levels have not yet started to rise. ***The best time to test will vary with the overall length of the menstrual cycle, aiming for approximately 1 week before the***

expected menses.

Serum progesterone levels also have been used to evaluate the quality of luteal function. Whereas the amount and duration of progesterone production certainly does reflect the functional capacity of the corpus luteum, a truly accurate measure requires daily serum progesterone determinations that are costly, and impractical.[374,375] and [376] Judgments based on limited sampling, regardless how well timed, have numerous pitfalls and cannot define the quality of luteal function reliably.[374,377,378,379,380] and [381] ***There is no consensus minimum serum progesterone concentration that defines normal luteal function***. A midluteal serum progesterone level greater than 10 ng/mL is a popular standard,[382] but the concentrations observed in normal and abnormal cycles and in conception and non-conception cycles in both fertile and infertile women vary widely and overlap greatly.[383] One reason is that progesterone is secreted by the corpus luteum in distinct pulses, temporally linked to pulsatile luteinizing hormone (LH) secretion[384,385]; levels ranging from as low as 4 ng/mL to as high as 40 ng/mL can be observed within brief intervals of time.[385] ***A midluteal serum progesterone concentration cannot define the quality of luteal function and has little value beyond documenting ovulation***.

Urinary LH Excretion

A wide variety of different commercial products allow women to determine not only if they ovulate, but when, in advance of the actual event. Generally known as “ovulation prediction kits” or “LH kits,” the products are all designed to detect the midcycle LH surge in urine. Ovulation predictor kits take advantage of advances in hormone measurement technology, reducing what was once a very labor-intensive process in the hospital laboratory to one or two simple steps requiring only a few minutes time in the home.

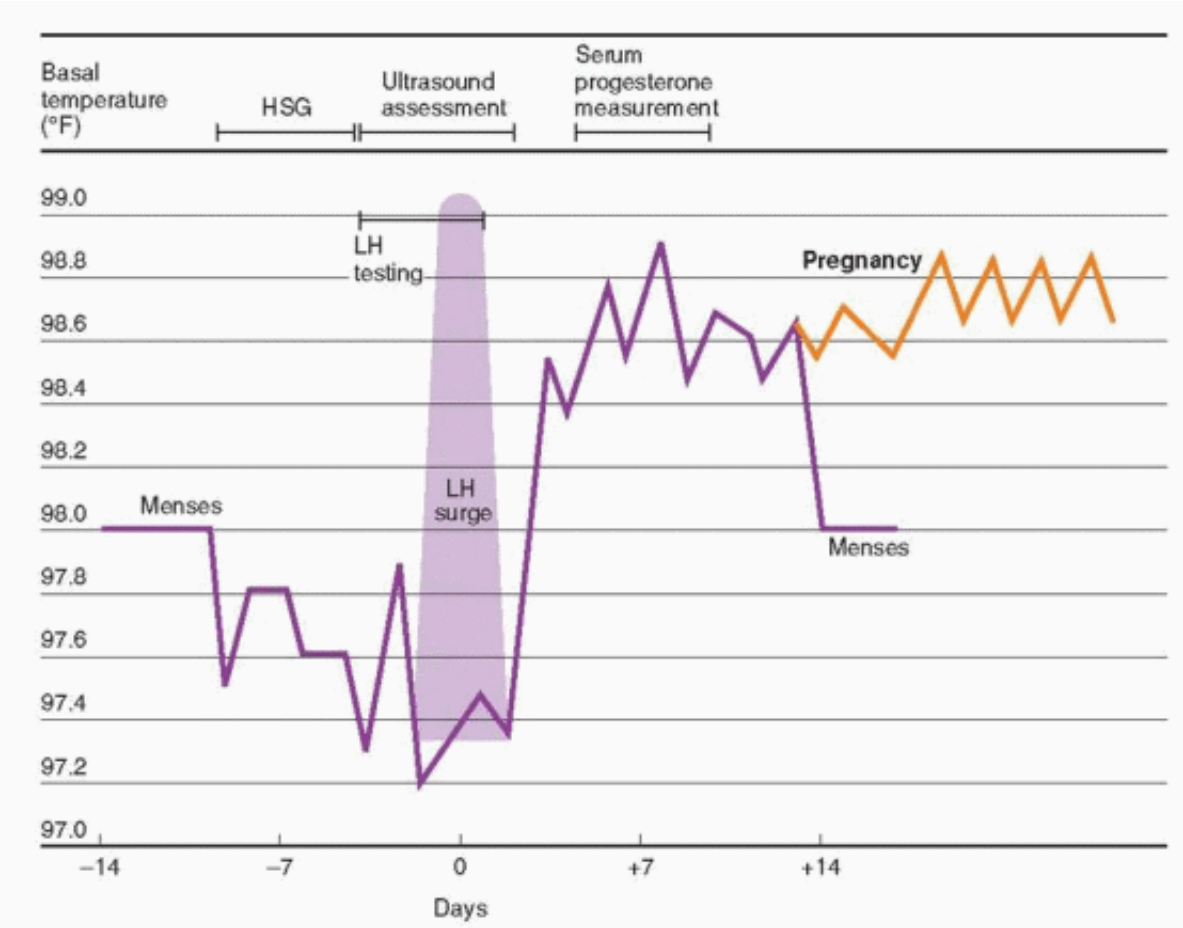
The midcycle LH surge is a relatively brief event, typically lasting between 48 and 50 hours from start to finish. LH has a short half-life and is rapidly cleared via the urine. Ovulation predictor kits turn positive when the urinary LH concentration exceeds a threshold level normally seen only during the LH surge. In most cycles, the test is positive on a single day, occasionally on 2 consecutive days. To detect the LH surge reliably, testing must be done on a daily basis, generally beginning 2 or 3 days before the surge is expected, based on the overall length of the cycle. The first positive test provides all relevant information; there is no value in continued testing.

Test results are sensitive to both the volume of fluid intake and time of day. There is no need to restrict fluid intake, but patients should be advised to avoid drinking large volumes of fluid a short time before they plan to test. Logically, the first morning void would seem an ideal specimen to test because it is usually the most concentrated. However, results correlate best with the serum LH peak when testing is performed in the late afternoon or early evening hours (4:00-10:00 PM),[371] probably because LH surges often begin in the early morning hours and are not detected in urine for several hours. Twice daily testing decreases

the frequency of false-negative results (failure to detect the LH surge in an ovulatory cycle), but generally is unnecessary. When performed daily and properly timed, testing will detect the LH surge in most ovulatory cycles. True false-positive tests (detection of an LH surge in an anovulatory cycle) occur in approximately 7% of cycles;[386] equivocal or “borderline” results also are common and can be both confusing and frustrating.

The accuracy of ovulation predictor kits varies. All are useful and reasonably reliable, but some are better and easier to use than others.[347,387] The best products predict ovulation within the subsequent 24 to 48 hours, with greater than 90% probability.[346,347] ***Ovulation generally occurs 14-26 hours after detection of the LH surge and almost always within 48 hours***.[346] ***Consequently, the interval of greatest fertility includes the day the surge is detected and the following 2 days***. The day *after* the first positive test generally is the one best day for timed

intercourse or insemination.[346,388,389] Ovulation predictor kits are non-invasive, widely available, require relatively little time and effort, and invite women to become actively involved in their care. Their greatest advantage over other methods is their ability to predict when ovulation will occur. Accurate identification of the midcycle LH surge also defines the length of the follicular and luteal phases, which may reveal subtle and otherwise unrecognized cycle abnormalities warranting treatment. Urinary LH monitoring is perhaps best reserved for women who ovulate (based on menstrual history, BBT recordings, or an appropriately timed serum progesterone concentration), but have infrequent intercourse or require insemination.



Endometrial Biopsy and Luteal Phase deficiency

Endometrial biopsy can be used as a test of ovulation, based on the characteristic histologic changes induced by progesterone. During the follicular phase of the cycle, the endometrium exhibits a proliferative pattern, reflecting the growth stimulated by rising levels of estrogen derived primarily from the dominant ovarian follicle. During the luteal phase,

progesterone secreted by the corpus luteum induces the “secretory” transformation of the endometrium. Anovulatory women are always in the follicular phase; their endometrium is always proliferative and even may become hyperplastic with extended exposure to a constant estrogen growth stimulus. ***In the absence of treatment with exogenous progesterone or a synthetic progestin, a secretory endometrium implies recent ovulation.***

Endometrial biopsy is a relatively simple office procedure, usually performed with a disposable plastic aspiration

cannula, and complications are few. Pretreatment with a non-steroidal anti-inflammatory drug (NSAID) helps to reduce pain or cramping associated with the procedure. Sedation or anesthetic (paracervical block) is helpful when the biopsy is technically difficult and in women who are very anxious. When properly timed, in the same way and for the same reasons as a serum progesterone concentration, endometrial biopsy is an effective test of ovulation. However, it is also invasive, uncomfortable, costly, and provides little more information than can be obtained from BBT recordings, a serum progesterone concentration, or monitoring urine LH excretion. Therefore, endometrial biopsy has rather limited and specific indications in the evaluation of infertile women. For women with chronic anovulation of long duration, biopsy can identify or exclude endometrial hyperplasia that requires specific treatment. In those few individuals suspected of harboring a chronic endometritis, biopsy is diagnostic. ***Until recently, endometrial biopsy for diagnosis of luteal phase deficiency was considered a basic element of the infertility evaluation, but no longer***.

Inadequate corpus luteum progesterone production or "luteal phase deficiency" (LPD) was long considered an important cause of both infertility and early pregnancy loss.[390,391] The proposed mechanisms were different but related, representing only different points on a pathophysiologic continuum. In theory, because the human implantation window is relatively narrow (spanning the interval from approximately 6 to 10 days after ovulation)[392,393] and [394] low circulating progesterone levels could be expected to result in delayed endometrial maturation, causing a shift in the implantation window and failed or late implantation. A long delay would threaten embryo viability or prevent implantation. A shorter delay would allow implantation but result in a tardy or low amplitude hCG rescue signal that could not stimulate normal amounts of progesterone from an already regressing corpus luteum, or maintain production for the requisite duration,[395,396] and [397] with either causing a premature luteal-placental shift and pregnancy loss.[398] In this context, endometrial biopsy was viewed as a bioassay of luteal function because it would reflect both the functional capacity of the corpus luteum and the end organ response.

The classic histologic features of secretory endometrial development were described by Noyes, Hertig, and Rock, in the lead article of the inaugural issue of *Fertility and Sterility*.[399] The pattern was considered significaently predictable to allow experienced pathologists to "date" the endometrium, assigning a histologic day that could be compared to the actual day of sampling, estimated by counting backward from onset of the next menstrual period (assuming menses began on the 14th postovulatory day), or defined by the number of days elapsed since detection of the LH surge or observation of follicular collapse by serial ultrasonography.[400] Historically, histologic and sampling dates that agreed, within a 2-day interval, were considered normal, whereas a date more than 2 days "out of phase" was the gold standard criterion for the diagnosis of LPD.[401,402] and [403] Traditionally, diagnosis of LPD required abnormal results in two (preferably consecutive) cycles, reasoning that reproductive failure could only be attributed to LPD if it was consistent or recurring, and acknowledging that LPD also could occur in normal fertile women, at least occasionally.[404,405,406,407,408,409] and [410] Endometrial dating was accepted widely by clinicians and pathologists and the practice endured, despite numerous challenges to its validity.

The first and most fundamental criticism of the traditional histologic dating criteria was that the normal standard was based on analysis of tissue specimens obtained from infertile women;[399] the reference population was abnormal, by definition, and also likely heterogeneous because infertility has many different causes. Second, the sampling date was estimated

retrospectively, after the onset of menses, assuming a uniform 14-day luteal phase, despite numerous studies demonstrating that luteal phase duration varied significantly, even in normal women.[104,109,112,411,412] Moreover, retrospective estimates of the sampling date correlated poorly with the time of ovulation as defined by the LH

surge or observations of follicular collapse,[382,400,413] and ignored any effect that biopsy might have on the onset of menses, or when it was perceived to start.[400,409,414] Third, the traditional histologic dating criteria were inherently subjective, and numerous studies had observed significant intraobserver and inter-observer variations in histologic interpretation that were great enough to affect diagnosis and management in 20-40% of individual women.[403,415,416,417] and [418]

The standard practice of endometrial biopsy and histologic dating for diagnosis of LPD was proven invalid in 2004, for all intents and purposes. A systematic re-analysis of the histologic features used for endometrial dating confirmed the classically described sequence, but revealed the patterns were much less temporally discrete than originally described, and demonstrated that normal variations among individuals, between cycles in individuals, and among different observers were too great to reliably define any specific luteal day or even a narrow interval of days.[419] Soon thereafter, a large multicenter trial demonstrated conclusively that abnormal histologic dating could not discriminate infertile from proven fertile women.[420] The second study invalidated the practice of endometrial dating, and the first explained why the method failed.

Recent evidence challenges even the basic premise on which the concept of LPD is founded: that abnormally low circulating progesterone concentrations result in delayed endometrial maturation. In normal women treated with a fixed physiologic dose of estrogen after downregulation with a GnRH agonist, then randomized to receive physiologic (mean progesterone level 19 ng/mL) or grossly low levels of exogenous progesterone treatment (mean progesterone level 5.5 ng/mL), there was no discernible difference in endometrial histology.[421] These observations suggest the histologic features of secretory endometrium relate more to the duration of progesterone exposure than to the concentration. Studies using a similar design have demonstrated that widely ranging concentrations of estradiol also have no discernible impact on secretory endometrial maturation.[422] Altogether, these data indicate that secretory endometrial development can progress normally despite widely varying concentrations of estradiol and progesterone, challenging the traditional paradigm, and served to further invalidate the use of endometrial histologic dating as a diagnostic tool. ***In sum, endometrial dating cannot guide the clinical management of women with reproductive failure and has no place in the diagnostic evaluation of infertility***.

The lack of any valid method for diagnosis of LPD does not refute its existence or its potential importance in the pathophysiology of reproductive failure. The pathogenic mechanisms outlined above are still viable. Evidence supports the notion of a finite implantation window,[392,393] and [394] that progesterone is essential for embryo implantation,[423] and that delayed implantation might adversely affect corpus luteum function,[395,396] and [397] predisposing to reproductive failure.[398] It is entirely possible, if not likely, that abnormally low levels of progesterone might have important functional consequences with no morphologic correlate. Biochemical or molecular markers of endometrial function provide the means to further explore the possibility. The pattern of endometrial gene expression defines distinct functional phases of the cycle.[424] A number of endometrial proteins exhibit patterns of expression or gene regulation during the putative implantation window, suggesting they might serve as markers of endometrial receptivity, including cytokines (leukemia inhibitory factor, colony-stimulating factor-1, and interleukin-1), cell adhesion molecules (the avb3 integrin), glycodelin, and the polymorphic mucin 1,[425,426] osteopontin,[427,428] and [429] N- acetylglucosamine6-O-sulfotransferase (important in synthesis of L-selectin ligands),[430] and the L-selectin ligand itself.[431] None has yet been validated as a reliable measure of endometrial function or receptivity, but if and when that occurs, a functional marker may become the basis for diagnosis of LPD and endometrial biopsy again may be viewed as offering valuable information beyond that provided by other tests of ovulation.

Transvaginal Ultrasonography

The last and most complicated test of ovulation involves serial transvaginal ultrasonography (TVUS), which permits direct observation of events in the ovary just before and immediately after ovum release. Although still not providing positive proof that ovulation actually occurred, serial TVUS provides detailed information about the size and number of preovulatory follicles and the most accurate estimate of when ovulation occurs.

In its final stages of development, the preovulatory follicle grows at a predictable pace, approximately 2 mm per day (range: 1-3 mm/day). After ovulation, the follicle collapses, margins become less distinct, the density of internal echoes increases, and the volume of culde-sac fluid increases.[432,433] Abnormal patterns of follicle development also can be observed. The follicle may grow at an abnormal pace, collapse when still relatively small, or continue to grow but fail to rupture and persist as a cyst for days after the LH surge—the luteinized unruptured follicle.[434,435] Such subtle forms of ovulatory dysfunction cannot be detected otherwise, but also are rare. ***Because treatment with prostaglandin synthase inhibitors (NSAIDs) can disrupt the ovulatory process and predispose to an luteinized unruptured follicle,[436,437] their use is best limited to the menstrual phase of the cycle in women attempting to conceive***.

Serial TVUS to monitor the size and number of developing follicles is essential to the safety and effectiveness of ovulation induction with exogenous gonadotropins (Chapter 31), but the costs and logistical demands involved are otherwise difficult to justify. Consequently, the method generally should be reserved for the few in whom the safety or effectiveness of treatment truly hinges on the detailed information it offers.

SUMMARY

The evaluation of ovulation is a core component of the evaluation for infertility. All of the different methods are useful and no one method is necessarily best. Whereas some are very simple, noninvasive, and inexpensive, others are more complicated, invasive, and costly. A few provide the means to determine not only if ovulation occurs, but when, with varying accuracy. The best choice among methods varies with the information required. In women with oligomenorrhea or amenorrhea, no formal evaluation is needed to establish a diagnosis of ovulatory dysfunction, but endometrial biopsy to exclude hyperplasia may be prudent, depending on duration. When the only objective is to confirm ovulatory function, as in those with regular monthly menses, a properly timed serum progesterone concentration is the simplest and most reliable method. When circumstances require accurate prediction of ovulation, as in couples having infrequent intercourse or those requiring insemination, urinary LH monitoring generally is the most cost-effective and appropriate choice. In the few who require insemination but consistently fail to detect a midcycle LH surge, serial transvaginal ultrasonography can provide the necessary information. Ultimately, the method chosen should be tailored to the needs of the individual patient.

Infertile women with ovulatory dysfunction are obvious candidates for ovulation induction. In general, only limited additional evaluation is needed to define the initial treatment of choice and most women will respond promptly to one of the simpler treatment strategies (Chapter 31). In the majority of cases, it is reasonable and appropriate to begin treatment immediately, even before other potential causes of infertility have been investigated. If anovulation is the only obstacle to overcome, most couples will conceive promptly without further interventions. Women with amenorrhea or hyperandrogenic anovulation deserve additional preliminary evaluation, applying the principles described in Chapters 11,12, and 13.

Cervical Factor: Abnormalities of Sperm-Mucus Interaction

The cervix participates in the reproductive process in several ways. Cervical mucus accepts or captures sperm from the ejaculate and the vagina, excludes the seminal plasma and morphologically abnormal sperm,[438] nurtures sperm biochemically, and serves as a reservoir, thereby prolonging sperm survival and the fertile interval between intercourse and ovulation. Mucus is a glycoprotein gel with solid and liquid phases and has a mosaic ultrastructure with interstitial channels between mucin strands that expand and contract in response to cyclic changes in the steroid hormone environment across the menstrual cycle to facilitate or inhibit the passage of sperm.[439,440,441,442] and [443] Estrogen stimulates cervical mucus production, and as levels rise during the follicular phase, mucus becomes more abundant and watery, less cellular, and more easily penetrated by sperm.[444] Progesterone inhibits cervical mucus production and renders it opaque, viscid, and impenetrable. The cyclic changes in cervical mucus characteristics help to explain why the cycle day-specific probability of conception rises steadily as ovulation nears and plummets immediately thereafter.

For most of the past century, the postcoital test for diagnosis of cervical factor infertility was considered a basic element of the infertility evaluation. The test involved collection of cervical mucus (by aspiration or with nasal polyp forceps) shortly before the expected time of ovulation (as determined by BBT or urinary LH monitoring in previous cycles) a few to several hours (typically 2-12 hours) after intercourse.[445] The mucus specimen was evaluated for pH, clarity, cellularity, viscosity (the length to which a column of mucus can be stretched in centimeters, known as “spinnbarkeit”), and salinity (evaluated according to the complexity of the network of crystals that forms when mucus is dried on a glass slide, also known as “ferning”), and for the number and motility of surviving sperm. The presence of motile sperm confirmed effective coital technique and sperm survival and the number of sperm (per high power field) was used to predict semen quality (sperm density and motility) and cycle fecundability (inverse correlation with time to conception or cumulative conception rates).[446,447,448,449,450] and [451] Most considered even a single motile sperm in most fields a “positive” or normal test result.[451,452] and [453]

Abnormal or “negative” postcoital test results were common, usually due to improper timing, either too early in the cycle when mucus was relatively scant, or after ovulation when mucus quality was poor.[454] Timing was optimized by performing the test within 2 days before the LH surge or when transvaginal ultrasonography demonstrated a preovulatory follicle.[455] Other explanations for poor quality mucus were cervicitis, previous treatment for cervical intraepithelial neoplasia (e.g., cryotherapy), and treatment with clomiphene citrate. Potential explanations for the absence of motile sperm in good quality mucus included ineffective intercourse, failed ejaculation (frequently resulting from performance anxiety), poor semen quality, and use of spermicidal coital lubricants. Observations of degenerating, immotile, “shaking” or agglutinated sperm were considered reason for antisperm antibody testing.[449] An abnormal result was confirmed by repeat testing to establish the diagnosis of cervical factor infertility,[445,451,456] prompting further evaluation with a nucleic acid test for chlamydia and cultures for ureaplasma and myocoplasma (or empirical treatment with antibiotics),[457,458] and [459] and semen analysis. Normal semen quality and absence of sperm in good quality mucus was regarded as evidence of “hostile” cervical mucus or a sperm function abnormality, differentiated by comparisons of partner and donor sperm survival and motility in bovine cervical mucus *in vitro* and antisperm antibody testing.[460,461] and [462] Strategies for correcting or overcoming cervical factor infertility included treatment with exogenous estrogens (to stimulate mucus production)[463] or mucolytic agents (guanifenesin),[464] precoital douching with a sodium bicarbonate solution,[465] and intrauterine insemination (IUI).[449,466,467] and [468]

Advocates of routine postcoital testing argued that the postcoital test could identify couples who might benefit from a simple treatment and had prognostic value for predicting the probability of pregnancy without treatment.[356,450] Critics reasoned that results achieved even with IUI suggested only a modest benefit at best,[469] that any prognostic value the test might have was limited to young couples with unexplained infertility of short duration because the test surely had no predictive value in women with infertility due to anovulation or tubal occlusive disease, and that male infertility amenable to treatment with IUI could be more accurately defined by the results of semen analysis. The argument for expectant management in couples with unexplained infertility and a normal postcoital test was dismissed as moot, because few couples seeking evaluation and treatment accepted the recommendation.

***The postcoital test for diagnosis of cervical factor is no longer recommended*.[359]** Abnormalities of cervical mucus production or sperm/mucus interaction are rarely, if ever, the sole or principal cause of infertility. Chronic cervicitis or cervical stenosis resulting from conization or other treatment for cervical disease that might impair sperm-mucus interaction can be identified by speculum examination, and in the absence of such findings, the likelihood that cervical mucus represents an important obstacle is remote. Semen analysis identifies couples with significant male factor infertility. The test has no standard methodology or interpretation,[445,453] and has poor reproducibility even among trained observers.[470] The only randomized trial comparing outcomes in women with normal and abnormal postcoital tests found the test invalid because neither test results nor treatment for abnormal tests affected outcome.[471,472] and [473] Office examination after scheduled intercourse is an inconvenient, embarrassing, and unwelcome intrusion for most couples, adding further to their burden of stress. Finally, postcoital test results seldom change clinical management, because contemporary treatments for unexplained infertility include IUI (usually with ovarian stimulation) or IVF, both of which negate any contributing cervical factor.

Uterine Factor: Anatomic and Functional Abnormalities

Abnormalities of the uterus are a relatively uncommon cause of infertility, but should always be considered. If for no other reason, they may adversely affect the outcome of pregnancies achieved by successful treatment of more common male, ovarian, and tubal factors. The anatomic uterine abnormalities that can adversely affect fertility include congenital malformations, leiomyomas, and intrauterine adhesions; endometrial polyps also have been implicated, but their reproductive implications are less clear. The only functional uterine abnormality of specific interest in the evaluation of infertility is chronic endometritis. Whereas abnormalities of endometrial receptivity (including luteal phase deficiency) might be viewed as another, they can have no practical significance until there is conclusive evidence that infertility can result from intrinsic endometrial dysfunction that impairs or prevents implantation and a method for diagnosis has been validated. In the meantime, luteal phase deficiency is best viewed as a subtle form of ovulatory dysfunction, as discussed in an earlier section of this chapter (see Ovarian Factor).

Anatomic and functional uterine abnormalities that can impair fertility also can adversely affect pregnancy outcome. They are discussed here as a cause of infertility, and elsewhere (Chapter 28) as a cause of recurrent pregnancy loss. The embryology or pathogenesis and obstetric consequences of uterine malformations and of leiomyomas are considered at length in Chapter 4. Discussion here is focused on their diagnosis, their impact on fertility, and how they influence evaluation and treatment.

There are three basic methods for evaluation of the uterine cavity: hysterosalpingography, transvaginal ultrasonography or saline sonohysterography, and hysteroscopy. Each has advantages and disadvantages and the choice among them should be tailored to the needs of the individual patient. HSG is the traditional method and

most often still the best initial test because it also evaluates tubal patency. However, in women with no risk factors for tubal disease and those whose tubal status is already known (from earlier surgery for other indications) or is largely irrelevant (as in women who require IVF for severe male factor infertility), ultrasonography offers a simpler and better tolerated alternative that also may reveal unsuspected ovarian pathology (cyst, endometrioma), with no radiation exposure. When symptoms suggest an anatomic lesion of the uterine cavity (menorrhagia, intermenstrual spotting)), sonohysterography is the most sensitive and logical diagnostic test. Hysteroscopy is definitive but has few diagnostic advantages over sonohysterography and generally can be safely reserved for treatment of abnormalities already identified by less invasive and costly methods.

Hysterosalpingography

Hysterosalpingography (HSG) accurately defines the size and shape of the uterine cavity, provides clear images of most uterine developmental anomalies (unicornuate, septate, bicornuate, and didelphys) and, with exceptions, also identifies submucous myomas and intrauterine adhesions that can have important reproductive implications. Although HSG also may reveal endometrial polyps, sonohysterography is a more sensitive method for their detection. A slow injection of contrast medium helps to minimize the risk that a cavitary lesion will be obscured and go undetected.

The normal uterine cavity is symmetrical, roughly triangular in shape, widest at the level of the cornual orifices near the fundus, and relatively smooth in its contours. The various developmental uterine anomalies generally have a fairly characteristic appearance on HSG. A unicornuate uterus is typically somewhat tubular, deviates to the left or right, and has one fallopian tube. Both septate and bicornuate uteri typically exhibit a common lower segment that divides into two distinct horns to yield a Y-shaped configuration with varying distance between the upper arms.[474,475] The two anomalies cannot be differentiated by HSG alone; additional evaluation is required to establish an accurate diagnosis (standard or three-dimensional ultrasonography, sonohysterography, MRI, or laparoscopy).[476] Either anomaly also can be confused with a unicornuate uterus if only one of the two horns is imaged because they divide near or below the tip of the cannula or catheter inserted into the cervix or uterus. To properly study a uterus didelphys or complete septate uterus, the two hemi-uteri must be imaged via their separate cervical openings, often found on opposite sides of a longitudinal vaginal septum of varying length. Myomas and larger polyps generally produce curvilinear filling defects of various size and shape. HSG in women with intrauterine adhesions usually reveals grossly irregular cavity contours and filling defects, and in many with severe disease, no cavity at all.

The accuracy of HSG for detecting intrauterine pathology in infertile women varies with the nature of the abnormality. A large study involving over 300 women comparing HSG to hysteroscopy (the gold standard) observed that HSG had overall 98% sensitivity, 35% specificity, 70% positive predictive value, and 92% negative predictive value, with a 30% false-positive rate and 8% false-negative rate; misdiagnoses almost entirely related to distinguishing submucous myomas from polyps and were, therefore, relatively unimportant.[477] In another study of similar design, HSG had 75% sensitivity for detection of intrauterine adhesions and only 50% sensitivity for detection of endometrial polyps.[478]

specific issues concerning the scheduling and preparation for HSG and details regarding technique and interpretation as they relate to the evaluation of tubal factor infertility are addressed in the following section (see Tubal Factor, below).

Transvaginal Ultrasonography and Saline Sonohysterography

Transvaginal ultrasonography (TVUS) is another method for evaluation of uterine factors in infertile women. Saline sonohysterography, involving TVUS during or after introduction of sterile saline through a catheter designed for the purpose, crisply defines cavity contours and readily demonstrates even small, but potentially important, intrauterine lesions.[479]

In all phases of the cycle, the interface between the endometrium and the myometrium is well defined. The interface between the two layers of the endometrium itself (bordering the uterine cavity) can be difficult to identify very early in the cycle and during the secretory phase, but is visible during the latter half of the proliferative phase. Together, the two layers of the endometrium comprise the "endometrial stripe," which changes in appearance and thickness across the cycle. During the proliferative phase, the endometrium is relatively hypoechoic and grows in thickness to yield a prominent "triple line" or trilamminar pattern. During the secretory phase, the endometrium grows little more, or not at all, and increases in echodensity, possibly because the developing network of coiled basilar vessels presents a great many more reflective surfaces. Cycle-dependent changes in uterine artery blood flow parameters (velocity and pulsatility index) measured using color and pulsed Doppler ultrasonography also have been described,[480,481] but diurnal variations and differences between the two uterine arteries (ipsilateral or contralateral to the dominant ovarian follicle) complicate interpretation. In efforts to define a receptive endometrium, several studies have examined the correlation between endometrial stripe thickness and pattern or uterine artery blood flow parameters with implantation or pregnancy rates in IVF cycles,[482,483,484,485,486] and [487] but results are conflicting. Whereas some have found correlations between one or more parameters and treatment outcomes, others have not. The few studies examining the endometrium in unstimulated cycles in infertile women have not demonstrated any important correlation between endometrial thickness, pattern, or blood flow and the cause of infertility or prognosis.[488,489] and [490] ***In the diagnostic evaluation of infertile women, transvaginal ultrasonography can identify important uterine pathology but provides no useful measure of endometrial function or receptivity***.

For identification of congenital malformations, standard two-dimensional TVUS complements HSG and improves diagnostic accuracy for differentiating septate and bicornuate uteri by revealing the shape of the fundal contour. The septate uterus presents a single unified fundus that often is somewhat broader than normal and sometimes slightly concave; the bicornuate uterus has two entirely separate fundi divided by a distinct midline cleft of varying depth.[474,476] The accuracy of saline sonohysterography exceeds that of HSG, by revealing both the double uterine cavity and the shape of the fundal contour. Modern three-dimensional ultrasonography can generate reconstructed images in the coronal plane and offers diagnostic accuracy comparing favorably with magnetic resonance imaging or combined laparoscopy and hysteroscopy (the gold standard).[475,476,491]

Results of studies evaluating the accuracy of TVUS for detection of submucous myomas and endometrial polyps have varied, but in general, both two-dimensional and three- dimensional TVUS are more sensitive than HSG, and approach the accuracy of hysteroscopy.[492,493,494] and [495] Whereas an overall or focal increase in endometrial thickness or asymmetry between the two layers suggests a polyp or myoma, saline sonohysterography reveals a polypoid projection into the fluidfilled cavity. For diagnosis of intrauterine adhesions, standard TVUS is reasonably specific, but rather insensitive[478,496]; a focally narrowed or discontinuous endometrial stripe suggests the diagnosis. Saline sonohysterography compares with HSG, having relatively high sensitivity (75%) and specificity (over 90%), modest positive predictive value (approximately 50%), and excellent negative predictive value (over 95%) for detection of adhesions.[478,497] Women with mild disease exhibit mobile thin, echogenic bands bridging a normally distensible endometrial cavity. Those with severe disease have more broadly based bands, or no cavity at all.[498]

Hysteroscopy

Hysteroscopy is the gold standard method for both diagnosis and treatment of intrauterine pathology that may adversely affect fertility. Traditionally, hysteroscopy was reserved for treatment of disease identified by other less invasive methods, but modern operative hysteroscopes with an outer diameter measuring 2-3 mm now permit diagnostic and minor operative procedures to be performed safely in the Office setting.[499] Major intrauterine pathology generally requires more traditional operative hysteroscopy using instruments having larger caliber and greater capabilities.

Congenital Uterine Anomalies

Developmental uterine anomalies have long been associated with pregnancy loss and obstetric complications, but affected women generally are not infertile. The prevalence of uterine anomalies in infertile women and fertile women with normal reproductive outcomes is similar, approximately 2-4%.[500,501,502,503,504] and [505] The prevalence is higher among women with poor pregnancy outcomes, such as recurrent miscarriage (10-13%). Consequently, when discovered during an infertility evaluation, anomalies cannot be regarded as the likely cause or even as an important contributing cause of infertility, but only as another obstacle that must be considered when planning treatment after evaluation is completed. For example, treatments associated with substantial risk for multifetal gestation (ovarian stimulation/IUI, IVF) present even greater risks to women with uterine malformations. In most series, septate uterus is the most common anomaly (35%), followed by bicornate (26%), arcuate (18%), didelphys (8%), and agenesis (3%).[505]

Septate uterus is the anomaly most highly associated with reproductive failure and obstetrical complications, including first- and second-trimester miscarriage, preterm delivery, fetal malpresentation, intrauterine growth restriction, and infertility.[476,505] The mechanisms responsible are poorly understood, but poor septal blood supply, resulting in poor implantation efficiency and embryo growth, and cervical incompetence are the usual suspects.[506,507,508] and [509]

Although diagnosis of septate uterus is not an automatic indication for metroplasty, the overall reproductive performance of women with a septum *in situ* (at least those who are recognized), is rather poor, with term delivery rates of approximately 40%. Most losses occur in the first trimester (approximately 65%). ***In the select population of women with a septate uterus and recurrent pregnancy loss, live birth rates are approximately 10% before hysteroscopic septum resection and 75-80% after surgery,[476,505] indicating that hysteroscopic metroplasty restores an almost normal prognosis for term delivery***. A 2010 systematic review of studies relating to outcomes after hysteroscopic septum resection concluded that the procedure results in fewer pregnancies in infertile patients than in those with recurrent miscarriage (RR=0.7, CI=0.5-0.9).[510] In the past, surgical correction of a septate uterus required abdominal metroplasty, risking post-operative adhesions that might impair fertility, and committed all future successful pregnancies to cesarean birth. Surgical treatment was reserved for women in whom the benefits of surgery more clearly outweighed the risks, but modern hysteroscopic surgery has changed the equation. Hysteroscopic septum resection is usually a relatively straightforward and brief outpatient procedure associated with low morbidity, no risk of adnexal adhesions or obligation to cesarean delivery, and a prompt and uneventful recovery; surgical indications now are appropriately more liberal.

Inevitably, systematic infertility evaluations will identify nulligravid women with a uterine septum who present a management dilemma. Given the high probability of successful hysteroscopic surgery and its low morbidity, we believe it is reasonable and appropriate to

consider preemptive surgical correction of a septate uterus, especially in women over age 35, women with infertility of long duration, women with other indications for surgical treatment, and women who require IVF or other treatments associated with increased risk of multifetal gestation and pregnancy loss.[476,505,511] Careful discussion of the relative risks and benefits of surgery is always important, but especially so when the indications for surgery are less clear.

Uterine Myomas

Myomas can be identified in 20-40% of all reproductive aged women and in 5-10% of infertile women[173,512,513]; myomas are the only abnormal finding in 1-2% of women with infertility. Although they are an established cause of abnormal bleeding, pain, and symptoms relating to pressure on adjacent organs, the impact of myomas on fertility has been more difficult to define, with the bulk of evidence coming from studies comparing the prevalence of myomas in fertile and infertile women, or the reproductive performance of women with otherwise unexplained infertility before and after myomectomy.[173,174] Infertility relating to myomas has been attributed to all of the following mechanisms[514]:

- Displacement of the cervix, decreasing exposure to sperm.
- Enlargement or deformity of the uterine cavity, interfering with sperm transport.
- Obstruction of the interstitial segment of the fallopian tubes.
- Distorted adnexal anatomy, inferfering with ovum capture.
- Distortion of the uterine cavity, or increased or abnormal myometrial contractions, inhibiting sperm or embryo transport.
- Impaired uterine blood flow or chronic endometritis, interfering with implantation.

Whereas there is relatively little evidence to support the majority of these mechanisms, a number of observations lend credence to the notion that myomas may impair fertility by interfering with implantation. Glandular atrophy is commonly observed in the endometrium overlying myomas, depending on their proximity, and also can be seen in the opposing endometrium, suggesting it results from mechanical pressure.[515,516] and [517] Recent molecular studies indicate that submucous and intramural myomas also induce a local decrease in *HOX* gene expression, which has been implicated in the cascade of molecular events involved in implantation.[518]

The effects of myomas on fertility are best assessed by studies comparing IVF outcomes in infertile women with and without myomas, because IVF effectively controls for the confounding effects of other fertility factors. Numerous studies have examined the effects of myomas of varying size and location.[519,520] and [521] Altogether, these observations permit some conclusions regarding the effects of myomas on IVF outcomes, and by inference, on overall fertility.

There is a clear consensus that submucous myomas have significant adverse effect on clinical pregnancy rates (OR=0.3, CI=0.1-0.7) and delivery rates (OR=0.3, CI=0.1-0.8).[174,514,522,523,524,525] and [526] Available data also support the conclusion that submucous myomas increase risk for miscarriage by more than 3-fold.[525,526] Results of early studies examining the effect of intramural myomas on IVF outcomes were inconsistent, with some finding adverse effects,[520,521,527,528] and [529] and others not.[519,525,530,531,532,533] and [534] A 2005 systematic review including six studies found that intramural myomas have significant negative impact on implantation rates (OR=0.62, CI=0.48-0.8) and live birth rates (OR=0.69, CI=0.5-0.95), and concluded that myomectomy deserved

consideration, particularly in women with previous failed IVF cycles.[523] A 2007 meta-analysis of data from seven relevant studies also found evidence that intramural myomas adversely affect the clinical pregnancy rate (OR=0.8, CI=0.6-0.9) and delivery rate (OR=0.7, CI=0.5-0.8),[524] and a 2009 systematic review including 23 studies concluded that intramural myomas increase risk for miscarriage (RR=1.7, CI=1.2-2.4).[526]

All of the evidence concerning the effects of subserosal myomas is consistent in finding no evidence of adverse effects on IVF outcomes. ***In sum, the accumulated body of evidence indicates that submucous myomas reduce IVF success rates by approximately 70%, intramural myomas by approximately 30%, and subserosal myomas have no adverse impact on outcomes. Submucous myomas increase risk for miscarriage after successful IVF at least 3-fold, and intramural myomas by more than half.***

Logically, decisions regarding the management of infertile women with myomas should be guided by the evidence concerning their likely importance and the outcomes of surgical intervention. It seems clear that submucous myomas (distorting the uterine cavity) have important adverse effects on fertility and pregnancy outcomes and that myomectomy improves both. A 2009 systematic review of studies examining outcomes after submucous myomectomy concluded that clinical pregnancy rates achieved with IVF were 2-fold higher after surgery than in women with submuous myomas *in situ*, and comparable to those observed in women without myomas.[526] A randomized trial comparing the effects of myomecomy and expectant management on fertility in 181 women with a combination of submucous, intramural, and subserosal myomas observed that myomectomy significantly improved pregnancy rates among women with submucous myomas (43% vs. 27%) and those with both submucous and intramural myomas (26% vs. 15%), without other interventions.[535] Younger women having a single small submucous myoma and otherwise unexplained infertility have the best prognosis. Results are less encouraging for older women and those with multiple or large submucous myomas. Although complications of hysteroscopic myomectomy are relatively few, the risk of postoperative intrauterine adhesions increases with the size, number, and extent of intramural extension of submucous myomas.

Evidence for the benefits of myomectomy in women with intramural myomas (not distorting the uterine cavity) is less compelling, probably because their impact on fertility is not as great. Results of a cohort study suggest that myomectomy can improve cumulative clinical pregnancy and live birth rates after up to three IVF cycles in women having at least one intramural myoma larger than 5 cm in diameter.[536] A randomized trial observed a clinically significant trend toward improved fertility in women with intramural myomas after myomectomy (56% vs. 41%).[535] In contrast, the results of two other studies question the therapeutic value of myomectomy in asymptomatic infertile women with intramural myomas;[537,538] Cumulative conception rates over the first 2 postoperative years related primarily to duration of infertility and the presence or absence of other infertility factors, but *not* to size or site (relationship to the uterine cavity) of the largest myoma removed. Increasing age and posterior myomas (associated with higher risk of postoperative pelvic and adnexal adhesions) were associated with a poorer prognosis, and symptoms (menorrhagia) with a better prognosis.

Decisions regarding the management of infertile women with asymptomatic intramural myomas are among the most difficult clinical judgments. They must consider not only the size, number, and location of myomas and the risks and benefits of the procedure, but also age, duration of infertility, ovarian reserve, other infertility factors, and the treatments they require. In most cases, the benefits of myomectomy are modest or uncertain, and the procedure is not without significant potential risks. Myomectomy commonly results in postoperative pelvic and adnexal adhesions, which can decrease fertility if severe,[538,539] but are less concerning in women who require IVF for other reasons. Myomectomy generally commits the patient to cesarean delivery to avoid the risk of uterine rupture during labor, which has been reported after myomectomy.[540,541,542] and [543]

Whereas excision of large, deep intramural myomas that abut or displace the uterine cavity might reasonably be expected to improve fertility, removal of smaller myomas having no direct anatomical relationship with the cavity probably will not. Whereas excision of anterior and fundal myomas is not likely to result in serious adnexal adhesions, posterior uterine incisions invite the complication. Arguably, excision of any intramural myomas large enough or deep enough to warrant myomectomy also likely warrants recommendation for cesarean delivery. Whereas

myomectomy offers limited, if any, benefits to young women with infertility of short duration and other infertility factors amenable to non-surgical treatments, it is less difficult to justify in older women with unexplained infertility of long duration planning to pursue IVF.

Adherence to basic microsurgical principles—gentle tissue handling, meticulous hemostasis, and minimal exposed suture—help to ensure best surgical results. Adjuvants such as local injection of aqueous pitressin, tourniquets to compress the uterine arteries, and surgical adhesion barriers aim at those goals. Laparoscopic and robotic myomectomy, performed by those having the requisite training and experience, may offer the same benefits as traditional open or minilaparotomy myomectomy for infertile women with intramural myomas, and have the added advantage of lower morbidity (decreased blood loss and shorter recovery time).[544,545,546,547] and [548] A multicenter, randomized trial comparing reproductive outcomes after laparoscopic and minilaparotomy myomectomy in women with unexplained infertility observed no differences in cumulative pregnancy, live-birth and miscarriage rates between the two procedures.[545] ***The careful selection of patients most likely to benefit from myomecomy is far more important than the choice of surgical technique. If the procedure has little or no likely benefit, the choice of technique is irrelevant.***

Intrauterine Adhesions (Asherman's Syndrome)

Intrauterine adhesions develop as a result of trauma.[549,550,551] and [552] Any insult severe enough to remove or destroy endometrium can cause adhesions. The gravid uterus is particularly susceptible to injury, especially between the second and fourth weeks postpartum.[553] inflammation or infection also may predispose to adhesions.[554,555] and [556] In approximately 90% of cases, intrauterine adhesions relate to curettage for pregnancy complications, such as missed or incomplete abortion or retained products of conception.[557] Adhesions also can develop after abdominal or hysteroscopic myomectomy, septum resection, or other uterine surgery. In the developing world, genital tuberculosis is an important cause of intrauterine adhesions; although rare in the U.S., the possibility must be considered in women emigrated from regions where the disease is prevalent.[558]

Intrauterine adhesions can be asymptomatic or cause menstrual disorders (hypomenorrhea, amenorrhea, dysmenorrhea), pain, recurrent miscarriage, or infertility.[551,552] The overall incidence of intrauterine adhesions is uncertain, but may be increasing.[557,559] The risk of intrauterine adhesions associated with elective termination of pregnancy is generally low, but the prevalence and severity of adhesions may increase with the number of procedures.[560] A temporal relationship between symptoms and a predisposing event, the inability to pass a uterine sound, or a negative progestin challenge in amenorrheic women suggest the diagnosis. When suspected, HSG and saline sonohysterography confirm the presence of intrauterine adhesions. Compared to hysteroscopy (the gold standard), HSG has approximately 80% sensitivity and specificity for diagnosis of adhesions.[561] A study comparing HSG and sonohysterography with hysteroscopy concluded the two methods of imaging were equally sensitive for detection of adhesions,[478] but hysteroscopy is required to define the location and extent of disease.

Hysteroscopy can reveal a variety of findings.[549,556,562] Central adhesive bands can appear as columns or bridges

between the opposing walls of the cavity, dividing it into smaller irregular chambers of varying size and shape. Adhesions at the margins of the cavity often appear as half-drawn curtains that may obscure one or both cornual orifices. Depending on their composition (mucosal, fibromuscular, connective tissue), adhesions may or may not have a surface of endometrium; dense connective tissue adhesions typically do not. Whereas mucosal adhesions generally appear similar to surrounding normal tissue and are easy to lyse, fibromuscular and connective tissue adhesions are thicker, typically pale, and must be

mechanically divided or dissected. Numerous classification systems have been proposed, but no system has gained wide acceptance or has prognostic value validated by prospective studies.[551,552] Consequently, outcome studies are difficult to interpret and compare.

Hysteroscopy is the method of choice for treatment of intrauterine adhesions and is both safer and more effective than blind curettage. Often, lysis of adhesions can be accomplished using only the tip of the hysteroscope aided by the pressure provided by continuous infusion of distention media. When needed, an assortment of mechanical, electrosurgical, and laser-based instruments allows adhesions to be lysed or cut under direct vision. In general, best results are achieved when central adhesions are lysed first, moving from the lower uterine segment to the fundus and then to the margins of the cavity, gradually restoring normal cavity architecture. When disease is severe and anatomic landmarks are poorly defined, transabdominal ultrasonography or laparoscopy can help to maintain orientation and to limit the risk of uterine perforation.[563]

Various methods have been used to facilitate hysteroscopic surgery or to improve outcomes. In one randomized clinical trial examining the efficacy of vaginally administered misoprostol (200 μg) for cervical softening before operative hysteroscopy, treatment reduced or eliminated the need for mechanical dilation and the incidence of operative complications.[564] Various physical barriers, including both unmedicated IUDs and balloon catheters, are commonly used as a means to maintain separation between the opposing layers of endometrium during the immediate postoperative interval.[556,557,565] A study comparing outcomes after insertion of an IUD or a balloon catheter observed more frequent return of normal menses (81% vs. 63%) and higher conception rates (34% vs. 23%) in women receiving a catheter.[566] Postoperative treatment with exogenous estrogens to promote rapid re-epithelialization and reduce risks of recurrent adhesions is frequently used, but its efficacy has not been established;[567] a typical regimen involves treatment with 2.5-5 mg conjugated estrogens daily for 4 weeks, adding a progestin (e.g., medroxyprogesterone acetate 10 mg daily) during the last week.

Complications of hysteroscopic adhesiolysis are the same as with any operative hysteroscopic procedure and are relatively uncommon. Acute complications include uterine perforation, fluid overload and electrolyte imbalance, hemorrhage, and infection; late complications include recurrent adhesions and uterine rupture in a subsequent pregnancy.[568]

Surgical results should be evaluated by HSG or saline sonohysterography after menses.[569] A second operation to lyse persistent or recurrent adhesions may be required when disease is severe. Alternatively, pressure lavage with normal saline under guidance of transvaginal ultrasonography can be used to hydro-dissect recurrent adhesions that are not particularly dense or extensive.[570] Lysis using a balloon catheter under fluoroscopic control and local anesthesia or intravenous sedation also has been described.[571] Normal cyclic menses can be restored in from 70% to 90% of women with intrauterine adhesions, depending on severity.[549] Conception and term delivery rates after successful hysteroscopic lysis of intrauterine adhesions have ranged between 25% and 75%[549,556,572,573,574,575,576,577] and [578]; predictably, the prognosis is better for women with mild disease.

Endometrial Polyps

Endometrial polyps are hyperplasic endometrial growths having a vascular center and a sessile or pedunculated shape extending into the uterine cavity. They are generally rare in young women and increase in incidence with age. The overall prevalence of polyps in infertile women ranges between 3% and 10%.[478,579,580,581,582,583] and [584] A number of molecular mechanisms have been implicated in their pathogenesis, including endometrial hyperplasia,[585] overexpresion

of endometrial aromatase,[586,587] and gene mutations.[588] Saline sonohysterography is the most useful method of imaging for detection of endometrial polyps,[494,589,590] although false-positive results due to blood clots, mucus, and shearing of normal endometrium are not uncommon.

Careful, systematic evaluation inevitably will identify polypoid cavitary lesions in some infertile women. Differentiation of small submucous myomas and endometrial polyps can be difficult by any means other than hysteroscopy.[477] Whereas symptomatic women (abnormal bleeding) certainly merit hysteroscopic evaluation and treatment, whether surgery has benefits for asymptomatic infertile women with polyps is less clear. The observation that polyps are resistant to the actions of progesterone suggests they might interfere with implantation[591]; local inflammatory changes or distortion of the uterine cavity also have been implicated.[592]

Evidence from studies examining reproductive performance after hysteroscopic polypectomy is rather weak and conflicting.[175,176,592,593] In a study of infertile women with documented but unresected endometrial polyps (>2 cm), IVF outcomes in treated (preliminary hysteroscopic polypectomy) and untreated women were not different.[176] In two studies examining outcomes in women with polyps (<1.5-2 cm) identified by ultrasonography during ovarian stimulation for IVF, pregnancy rates in women who proceeded to oocyte retrieval and embryo transfer or had hysteroscopic polypectomy after retrieval and later frozen embryo transfer were not different from those in women without polyps having fresh or frozen embryo transfers.[594,595] The only evidence indicating that polyps adversely affect fertility derives from a study comparing outcomes after up to four cycles of IUI in a group of 215 infertile women with polyps who were randomized to receive preliminary polypectomy or no treatment; among 93 total pregnancies, 64 occurred in women having polypectomy and 29 in those who did not (RR=2.1, CI=1.5-2.9).[593] ***Taken together, the available evidence suggests that polypectomy may improve reproductive performance in infertile women. Treatment must be individualized, depending on the size of a polyp, associated symptoms, and on the circumstances leading to its discovery***.[584,596]

Chronic Endometritis

Chronic endometritis has been regarded traditionally as a distinct but uncommon cause of reproductive failure, but its true prevalence in infertile women is unknown.[597] Available evidence suggests that chronic subclinical endometritis is relatively common in women with symptomatic lower genital tract infections, including cervicitis and recurrent bacterial vaginosis[598,599,600] and [601] and may not be altogether rare even in asymptomatic infertile women.[602] Mucopurulent cervicitis is highly associated with chlamydia (*C. trachomatis*) and mycoplasma (*M. genitalium*) infection and both organisms, in turn, are associated with chronic endometritis, which likely plays a role in the pathogenesis of tubal factor infertility.[459,601,603,604] and [605] Although routine serologic testing for past chlamydia exposure, cervical cultures, and endometrial biopsy may be difficult to justify, further evaluation and treatment are appropriate and prudent in infertile women with clinical cervicitis, chronic or recurrent bacterial vaginosis, or other symptoms that suggest pelvic infection.

Tubal Factor: Tubal Occlusion and Adnexal Adhesions

Tubal and peritoneal pathology is among the most common causes of infertility and the primary diagnosis in approximately 30-35% of both younger and older infertile women.[349]

A history of pelvic inflammatory disease (PID), septic abortion, ruptured appendix, tubal surgery, or ectopic pregnancy strongly suggests the possibility of tubal damage. Unquestionably, PID is the major cause of tubal factor infertility and ectopic pregnancies. Classic studies in women with PID diagnosed by laparoscopy revealed that the risk of subsequent tubal infertility increases with the number and severity of pelvic infections; overall, the incidence is approximately 10-12% after one episode, 23-35% after two, and 54-75% after three episodes of acute PID.[606,607,608,609] and [610] The risk of ectopic pregnancy is increased 6- to 7-fold after pelvic infection. Although many women with tubal disease or pelvic adhesions have no known history of previous infection, evidence suggests strongly that "silent" ascending infection is the most likely cause.[601,605] Many such women will have detectable chlamydia antibodies suggesting prior infection (discussed below). Other causes of tubal factor infertility include inflammation related to endometriosis, inflammatory bowel disease, or surgical trauma. Endometriosis is considered at length in Chapter 29; discussion here is focused on intrinsic tubal disease.

The mechanism responsible for tubal factor infertility obviously involves anatomic abnormalities that prevent the union of sperm and ovum. Proximal tubal obstructions prevent sperm from reaching the distal fallopian tube where fertilization normally occurs. Distal tubal occlusions prevent ovum capture from the adjacent ovary. Whereas proximal tubal obstruction is essentially an all-or-none phenomenon, distal tubal occlusive disease exhibits a spectrum ranging from mild (fimbrial agglutination) to moderate (varying degrees of fimbrial phimosis) to severe (complete obstruction). The likelihood or efficiency of ovum capture probably is inversely related to the severity of disease. inflammatory damage to internal tubal mucosal architecture cannot be detected easily but may nonetheless impair sperm or embryo transport functions.

HSG and laparoscopy are the two classic methods for evaluation of tubal patency in infertile women and are complementary rather than mutually exclusive; each provides information the other does not and each has advantages and disadvantages. HSG images the uterine cavity and reveals the internal architecture of the tubal lumen, neither of which can be evaluated by laparoscopy. Laparoscopy provides detailed information about the pelvic anatomy that HSG cannot, including adhesions, endometriosis and ovarian pathology. HSG is performed in an outpatient setting, is far less costly than laparoscopy, and may have some therapeutic value[611]; it also is often uncomfortable or painful, involves some radiation exposure, and has risk of infectious complications that can further impair fertility.[612] Laparoscopy is more invasive, usually requires general anesthesia, provides no information regarding the uterine cavity (unless hysteroscopy is also performed), and involves the usual risks of surgery. Sonohysterosalpingography is similar to HSG, using ultrasonography and sterile saline instead of fluoroscopy and contrast media, and is another, but less common, method for evaluating tubal factor. Chlamydia antibody tests represent a fourth, albeit indirect, method for evaluating tubal factor that is relatively inexpensive and minimally invasive.[613,614,615] and [616] Chlamydia antibody tests have been used primarily for screening infertile women to identify those at high risk for having tubal disease who merit evaluation with laparoscopy.

Hysterosalpingography (HSG)

HSG is best scheduled during the 2-5 day interval immediately following the end of menses, to minimize risk for infection, avoid interference from intrauterine blood and clot, and to prevent any possibility that the procedure might be performed after conception. Even the most sensitive assays for hCG cannot exclude the possibility when HSG is performed during the early luteal phase of the cycle. HSG does not require any specific preparation,

although pretreatment with a NSAID (30-60 minutes before) is helpful to decrease

discomfort associated with the procedure; more potent analgesics and sedatives generally are not required. Infectious complications from HSG are relatively uncommon, even in high risk women (1-3%).[612,617] Nonetheless, routine prophylactic antibiotic treatment can be justified, considering the potential consequences of a post-procedure infection. ***Treatment with antibiotics (doxycycline 100 mg twice daily for 5 days, beginning 1-2 days before HSG) is prudent when tubal disease is highly suspected, and specifically indicated when HSG reveals distal tubal obstruction, because risk for acute salpingitis is increased (approximately 10%) and treatment can prevent clinical infection.***[612,618] To minimize the risk of infection, HSG is best avoided altogether for at least several weeks following any episode of acute PID.

The technique for performing an HSG is quite standard. The study should be performed using image intensification fluoroscopy with a limited number of radiographs. The average HSG requires only 20-30 seconds of fluoroscopic time with minimal radiation exposure and has very low risk. Usually, only three basic films are required (a scout, one film to document the uterine contours and tubal patency, and a post-evaluation film to detect any areas of contrast loculation). Additional oblique films may be needed when the uterus obscures the tubes or the uterine cavity appears abnormal. Otherwise, they provide little or no more useful information and increase radiation exposure unnecessarily.[619] Contrast can be introduced using a common metal “acorn” cannula or via a balloon catheter. In general, the latter technique requires less fluoroscopic time, smaller volumes of contrast, produces less pain, and is easier to perform.[620] Slow injection of contrast (typically 3-10 mL) helps to minimize the discomfort associated with HSG.

Debate regarding the relative advantages and disadvantages of oil-and water-soluble contrast media has raged for years. Advocates of water-soluble contrast media emphasize that oil-soluble media is too viscous to reveal internal tubal architecture (having prognostic significance),[621] disperses poorly in the pelvis (and therefore cannot detect adnexal adhesions), and has significant risks (granulomatous reactions, intravasation, and embolism).[622,623] Those favoring oil-soluble contrast media argue that granulomatous reactions are rare, that intravasation and embolization are uncommon and almost uniformly benign,[624] and cite evidence suggesting that oil-soluble media increases fertility in the months immediately following HSG in women with patent tubes.[611] A 2007 systematic review of 12 studies involving 2,079 patients concluded that tubal perfusion with oil-soluble contrast significantly increased the likelihood of pregnancy, compared to no intervention (OR=3.30, CI=2.0-5.43), but not compared to perfusion with water-soluble contrast (OR=1.21, CI=0.95-1.54). Consequently either choice of media is appropriate.

HSG may reveal bilateral tubal patency (60-75%) or unilateral (15-25%) or bilateral (15-25%) tubal occlusion.[625,626] Both false-negative (obstructions that are not real) and false-positive results (patency that is not real) occur, the former being much more common than the latter. Injection of contrast may cause “cornual spasm” (uterine contractions that transiently close the interstitial segment and prevent distal perfusion) that can be misinterpreted as proximal tubal occlusion. HSG may reveal unilateral tubal patency and contralateral proximal occlusion. Although the observation may represent a true unilateral proximal obstruction, which is rare, catheter placement allowing contrast to take the path of least resistance is the more common cause; most often, the non-visualizing tube is normal. A false-positive HSG may occur when contrast entering a widely dilated hydrosalpinx is diluted to yield a blush that is misinterpreted as evidence of tubal patency. Peritubular adhesions surrounding an otherwise normal and patent tube can sequester contrast as it escapes from the tube, resulting in a focal loculation that can be misinterpreted as distal obstruction.

Compared to laparoscopy (the gold standard method) as a test of tubal patency, HSG has only moderate sensitivity (ability to detect patency when the tubes are open; 65%), but

relatively high specificity (accuracy when patency is detected; 83%) in a typical infertile population.[627,628] ***The clinical implications are that when HSG reveals obstruction there is still a relatively high probability (approximately 60%) that the tube is open, but when HSG demonstrates patency there is little chance the tube is actually occluded (approximately 5%).*** However, interpretation of HSG results can vary significantly among different observers.[629,630] Consequently, when the treating clinician has not performed the HSG, a personal review of the films is prudent before making recommendations for additional evaluation or treatment. The probability of treatment-independent pregnancy is highest when HSG reveals bilateral tubal patency, substantially lower when neither tube is open, and reduced only slightly when one tube is patent.[625,626] These observations help in deciding whether laparoscopy is needed before starting treatment.

Laparoscopy

Laparoscopy is regarded generally as the definitive test for the evaluation of tubal factors. Issues concerning scheduling, the use of antibiotics, and the risks of infectious complications are the same as for HSG. Diagnostic laparoscopy is usually performed under general anesthesia, but may require only deep sedation and local anesthetic; operative laparoscopy for treatment of disease typically requires general anesthesia. With few exceptions, a systematic and thorough inspection of the pelvis will accurately define the location and extent of any disease. Examination should include the uterus, the anterior and posterior cul-de-sacs, the ovarian surfaces and fossae, and the fallopian tubes. Injection of a dilute blue dye through a cannula attached to the cervix or an intrauterine manipulator permits evaluation of tubal patency (“chromotubation”). Indigo carmine is preferred over methylene blue, which rarely may induce acute methemoglobinemia, particularly in individuals with glucose-6-phosphate dehydrogenase deficiency.[631,632] As with HSG, slow injection of fluid helps to reduce the incidence of false-negative results.

Laparoscopy provides both a panoramic view of the pelvic reproductive anatomy and a magnified view of the uterine, ovarian, tubal, and peritoneal surfaces. Consequently, it can identify milder degrees of distal tubal occlusive disease (fimbrial agglutination, phimosis), pelvic or adnexal adhesions, and endometriosis that adversely affect fertility but escape detection by HSG. Most importantly, laparoscopy offers the opportunity to treat disease at the time of diagnosis. Lysis of filmy or focal adhesions and excision or ablation of superficial endometriosis are relatively simple procedures well within the capabilities of most surgeons. Excision of ovarian endometriomas, lysis of dense or extensive adhesions involving the cul-de-sac or bowel, excision or ablation of widely disseminated or deeply invasive endometriosis, and fimbrioplasty or salpingoneostomy procedures require greater technical skill and experience.

Although laparoscopy is a better predictor of future fertility than HSG, it is not a perfect test for diagnosis of tubal pathology. Intraoperative chromotubation is subject to the same pitfalls causing false-negative results with HSG. False-positive results with laparoscopy are uncommon but do occur, particularly in cases where the fallopian tubes are obscured by adhesions. Whereas tubal obstructions detected by HSG are frequently not confirmed at laparoscopy, patency almost always is. Laparoscopy also is a better predictor of future treatment-independent pregnancy than HSG because the information gained is more accurate. Again, the prognosis is best when both fallopian tubes are patent, poor when both are blocked, and intermediate when only one tube is open.[626,633] Because many obstructions detected by HSG are not real and all but a few of those identified by laparoscopy are, the prognoses associated with unilateral and bilateral tubal occlusion diagnosed by laparoscopy are significantly worse than when the same diagnosis is made by HSG.

Sonohysterosalpingography

Sonohysterography is recognized as having greater sensitivity than HSG for detection of intrauterine pathology. A natural extension of that technique, sonohysterosalpingography, has been viewed as a means to evaluate tubal patency at the same time, much like HSG. As originally described, sonohysterosalpingography relied on observations of fluid accumulation in the cul-de-sac as an indication of tubal patency. However, the technique provided no information regarding tubal anatomy and could not determine whether one or both tubes were patent. A new sonographic contrast media consisting of a surfactant that produces microbubbles when stimulated by ultrasound improved sensitivity for detecting tubal patency, but standard two-dimensional imaging in the sagittal and transverse planes was still inadequate to visualize the three-dimensional tubal anatomy.

Technological advances in ultrasonography have expanded the capabilities of sonohysterosalpingography further; three-dimensional transvaginal ultrasonography provides the means to generate coronal images and Doppler techniques have improved visualization of fluid movement through the fallopian tubes. However, even with these improvements, it is unlikely that sonohysterosalpingography will replace traditional HSG anytime soon. Studies directly comparing results of sonohysterosalpingography with those obtained by HSG or laparoscopy have yielded inconsistent results.[634,635,636,637] and [638] The fallopian tube remains difficult to image with ultrasonography, even with three-dimensional equipment, and sonohysterosalpingography has its own unique pitfalls.[639] A 2006 study comparing results with laparoscopy found that three-dimensional sonohysterosalpingography had excellent sensitivity (100%) and moderate specificity (67%) for detecting tubal patency (100%), but 30% of patients judged the procedure unacceptable.[640] Sonohysterosalpingography may yet become a viable alternative to HSG, but currently is not.

Chlamydia Antibody Tests

A number of studies have suggested that chlamydia antibody tests can be as accurate as HSG or even laparoscopy for detection of tubal pathology, including tubal occlusion, hydrosalpinx, and pelvic adhesions.[613,614,641] The performance of the different tests varies widely with the assay method. Commercial assays differ in detection method (immunofluorescence, microimmunofluorescence, ELISA, immunoperoxidase) and in the source of antigen they use (general or genus-specific major outer membrane proteins, an inactivated organism, whole-cell inclusion). Some methods are highly specific for the chlamydia species of interest (*C. trachomatis*) and others do not distinguish antibodies to *C. trachomatis* from those directed against other chlamydia species (*C. pneumoniae*, *C. psittaci*). As expected, tests having the greatest specificity for *C. trachomatis* perform best for detection of tubal pathology.[614,642,643] Practical considerations suggest that a rapid, highly sensitive but less specific assay is the most suitable test for screening, using a more specific test to confirm the antibody specificity of sera selected by the screening assay.

The predictive value of any diagnostic test depends on the prevalence of the disease of interest in the population tested. If the prevalence of disease in the population is very low or very high, diagnostic testing has little or no value because the outcome rarely affects management, and false-positive (when the prevalence is very low) or false-negative test results (when the prevalence is very high) are common. Diagnostic tests tend to have greatest utility when the prevalence of disease is somewhere in between the extremes.[628] Some have suggested that chlalmydia antibody tests might be used to select patients likely to

benefit most from laparoscopy, but the predictive value of even some of the more specific chlamydia antibody tests may not be significaent to justify that approach.[644]

The role for chlamydia antibody tests in the evaluation of infertile women has not been significaently defined. Chlamydia antibody tests could prove useful as a pretest to select women who warrant earlier or more detailed evaluation.[645] If applied as a screening tool early in evaluation, a positive test might alert one to the possibility of tubal factors relating to previous chlamydia infection not otherwise suspected. Although selective laparoscopy based on chlamydia antibody tests may be unjustified for all infertile women,[644] it might be effective if limited to women with unexplained infertility (including a normal HSG), identifying those most likely to have undetected tubal factors best addressed before starting aggressive and costly empirical treatments. The utility of chlamydia antibody tests in these or other clinical contexts is uncertain but warrants further investigation. ***In summary, chlamydia antibody tests can provide useful information, but also have pitfalls that limit their clinical utility.***

Tubal Surgery in the Era of ART

For women with tubal factor infertility, treatment options are reconstructive surgery and IVF. Over the last 2 decades, IVF success rates have increased steadily (from approximately 10% to over 40%) and now frequently exceed those achieved with surgery.[34] Consequently, IVF has become the treatment of choice for much or most tubal factor infertility, particularly for couples with other infertility factors or severe tubal disease. However, surgery remains an appropriate option in select circumstances and for couples with ethical or religious objections or financial restrictions that preclude IVF. The indications, preliminary evaluation, techniques, risks, and outcomes for IVF and other forms of ART are the focus of a separate chapter (Chapter 32); discussion here is limited to surgical treatments for tubal factor infertility and the choice between surgery and IVF.

Sterilization Reversal

Approximately 1 million U.S. women have an elective tubal sterilization procedure each year; up to 7% regret the decision and about 1% later request its reversal.[22,646] The most commonly cited reasons for sterilization reversal requests include new relationships, changes in family planning goals, and death of a child. Regrets are more common in younger women, those who were unaware of the spectrum of contraceptive options, women whose decision for sterilization was influenced by a third-party (partner, other family member, friend, or physician), and those sterilized postpartum or after an abortion.[647,648] Women 30 years old or younger are twice as likely as older women to express regret, 3.5 to 18 times more likely to request information about reversal of the procedure, and approximately eight times more likely to actually have a sterilization reversal or IVF.[649] For women who want to conceive again, tubal anastomosis is a legitimate option. A preoperative HSG can be useful to assess the proximal segments and to confirm the type of sterilization performed. Laparoscopy may occasionally be necessary to assess the feasibility of surgical repair when the type of procedure is unknown and when destruction or removal of large segments of tube or other pelvic pathology is suspected; otherwise fewer than 5% of women will have irreparable tubes.[650]

The prognosis for achieving a live birth after microsurgical sterilization reversal relates to age, the type and location of procedure, and the final length of the repaired fallopian

tubes. Younger women, those whose sterilization was performed using rings and clips, and women having no other infertility factors have the best prognosis; success rates are lower for older women, those who were sterilized by cautery (particularly multiple-burn techniques), and women with other infertility factors.[651,652,653,654,655,656,657] and [658] Cumulative pregnancy rates are similar when one or both tubes are repaired, although the time to conception is longer after unilateral anastomosis.[657] ***In properly selected candidates, overall conception rates***

are generally quite good (45-82%) after microsurgical sterilization reversal. Risk for ectopic pregnancy ranges between 1% and 7% and is higher after isthmic-ampullary than after isthmic-isthmic anastomoses.[659,660] Among all surgical treatments for tubal factor infertility, sterilization reversal has the highest postoperative fecundability. ***Best candidates for the procedure are young women desiring more than one additional pregnancy and having no other infertility factors***. Compared to IVF, the primary advantages of surgery are the opportunity for natural conception and lower risk for multiple gestation; the disadvantages of surgery include the surgical insult itself, a higher risk for ectopic pregnancy, and the need for future contraception. Laparoscopic tubal anastomosis is an option for highly skilled surgeons experienced in the technique, although success rates may be somewhat lower (25-53%).[661,662] Early experience with robotic tubal anastomosis indicates that operating time is modestly greater, but hospital stay and recovery time are shorter, compared to open microsurgical procedures[663,664]; pregnancy rates are comparable, but risk for ectopic pregnancy may be increased.[664]

Distal Tubal Obstruction

Distal tubal occlusive disease exhibits a wide spectrum of severity ranging from adherent fimbrial folds, to varying degrees of phimosis, to complete obstruction with hydrosalpinges. HSG generally will reveal complete distal tubal obstructions but cannot reliably detect or accurately define lesser degrees of disease when the tubes are still patent. Laparoscopy is the definitive method for diagnosis of distal tubal occlusive disease and also provides the means for treatment. Fimbriolysis refers to the separation of adherent fimbria, fimbrioplasty describes the correction of phimotic but patent fimbria, and neosalpingostomy involves the reopening of a completely obstructed tube. Predictably, surgical success inversely relates to the severity of disease. The extent and character of associated tubo-ovarian adhesions, tubal thickness, and the condition of the internal ampullary mucosal architecture are all variables that affect prognosis.[665,666] For the milder forms of distal tubal disease, postoperative live birth rates can exceed 50%.[667,668] and [669] Results achieved with surgery for more severe disease have varied widely but success rates are lower (10-35%) and risk for ectopic pregnancy is higher (5-20%).[666,670,671] and [672] Postoperative tubal patency rates far exceed pregnancy rates; patency is more easily restored than function because mucosal regeneration is slow and often fails altogether.[673,674]

The majority of pregnancies occur within the first 2 years after surgical treatment of distal tubal obstruction. In general, the results achieved by experienced surgeons using traditional microsurgical techniques or laparoscopic methods have been similar. In a case series of 35 women with distal tubal occlusion treated by laparoscopic fimbrioplasty followed for at least 2 years after surgery, the global conception rate was 74%, the intrauterine pregnancy rate was 51%, the live birth rate was 37% and the ectopic pregnancy rate was 23%.[675] ***In younger women with mild distal tubal occlusive disease, laparoscopic surgery may be viewed as an alternative to IVF, but when disease is severe or pregnancy does not occur during the first postoperative year, IVF is the logical choice. For older women with any significant degree of distal tubal disease, IVF is generally the first and best option because cycle fecundability after distal tubal surgery is low (1-2%), time is limited, and IVF is both more efficient and more effective***.[676]

As success rates with IVF have improved steadily, the indications for reconstructive surgery in women with distal tubal occlusive disease have further declined. However, women with severe distal tubal disease still can benefit from surgery (salpingectomy) because a substantial body of evidence indicates that large hydrosalpinges adversely affect IVF outcomes. Several mechanisms have been implicated to explain the observation, including mechanical interference with implantation and toxic effects on the embryo or endometrium.[677,678] and [679] A 2010 systematic review including five randomized controlled trials involving 646 women observed that the odds of achieving an

ongoing pregnancy were twice as great after laparoscopic salpingectomy for hydrosalpinges before IVF (OR=2.14, CI=1.23-3.73).[680] Laparoscopic occlusion of the fallopian tubes increased the odds of clinical pregnancy, compared to no intervention (OR=4.66, CI=2.47-10.01), and neither surgical procedure was superior.[680] ***These data demonstrate clearly that laparoscopic salpingectomy or tubal occlusion improve IVF pregnancy rates in women with hydrosalpinges***. Other treatment strategies, such as ultrasound-guided aspiration of hydrosalpingeal fluid at the time of oocyte retrieval, have been suggested as an alternative treatment,[681] but their effectiveness has not been established and evidence suggests the fluid re-accumulates rapidly.[682]

Proximal Tubal Obstruction

Proximal tubal occlusions represent approximately one-third of all tubal obstructions observed with HSG, many of which are not real (20-40%). ***Efforts to establish a certain diagnosis of true proximal tubal occlusion are justified; otherwise, many women may needlessly undergo major surgery or IVF***. Repeated HSG can decrease the number of false-negative tests of tubal patency; in a case series including 98 infertile women with a diagnosis of proximal tubal occlusion based on an HSG, repeating the procedure revealed bilateral tubal patency in 14 patients (14%), patency of one tube in 12 others (12%), and confirmed bilateral occlusion in 72 patients (74%).[683] In many, if not most, laparoscopy is required to establish an accurate diagnosis, also providing the opportunity to treat coexisting tubo-ovarian disease that may be observed in up to 20% of women.[684,685] and [686] The pathogenesis of proximal tubal occlusive disease is not well understood; most is presumed to result from infection or chronic inflammation. Histologic studies suggest that obliterative luminal fibrosis is most common, followed by salpingitis isthmica nodosa, chronic inflammation, and intratubal endometriosis.[687,688]

Microsurgical segmental tubal resection and anastomosis is a proven treatment for true proximal tubal obstruction. Experienced surgeons can achieve pregnancy rates ranging between 50% and 60%,[688,689,690] and [691] but the number of surgeons having the necessary expertise is fast declining. Outcomes vary with the cause of the obstruction; reocclusion rates are relatively high with causes other than salpingitis isthmica nodosa. Proximal tubal cannulation using hysteroscopic or fluoroscopic methods is a proven alternative to traditional microsurgical repair. In case series, patency rates between 60% and 80% and pregnancy rates between 20% and 60% have been observed,[635,683,684,692,693,694] and [695] with less morbidity and lower cost. The specialized catheter systems involved require some training and experience but allow selective tubal perfusion for accurate diagnosis (true occlusion or not) and provide the means for treatment when needed.

Bipolar tubal disease involves both proximal and distal tubal obstruction. In general, success rates achieved with surgery have been extremely poor and IVF represents the best treatment option.[690,696,697]

SUMMARY

Since only the best surgeons generally publish their results, the best available estimates from surgical series also very likely represent the best possible outcomes. Even so, steady advances in ART have improved IVF outcomes to where they now equal or exceed what can be achieved with tubal reconstructive surgery. Accordingly, surgical treatments for tubal factor infertility are generally in an era of decline; laparoscopic surgery has replaced simple open procedures, and ART has replaced more complicated ones. Tubal surgery remains a legitimate treatment option for women seeking pregnancy after a previous tubal sterilization, for those with mild distal tubal disease (particularly when they are young), and for some women with proximal tubal occlusion. Under virtually all other circumstances, IVF is the best choice.

Laparoscopic salpingectomy or proximal tubal occlusion increases IVF success rates by 2-fold and should be recommended to all women with hydrosalpinges planning IVF.

Unexplained Infertility

Unexplained infertility is a diagnosis of exclusion, after systematic evaluation fails to identify a cause. The incidence of unexplained infertility ranges from 10% to as high as 30% among infertile populations, depending on diagnostic criteria.[698,699] and [700] ***At a minimum, the diagnosis of unexplained infertility implies evidence of normal semen quality, ovulatory function, a normal uterine cavity, and bilateral tubal patency***. In the past, the diagnosis also required a "positive" postcoital test (excluding cervical factor infertility) and "in phase" endometrial dating (excluding luteal phase deficiency), but no longer, because the tests have proven invalid. In the past, the diagnosis also required laparoscopy (excluding pelvic adhesions and endometriosis), but laparoscopy is no longer performed routinely, because evidence indicates it has very limited impact on overall outcomes among women with unexplained infertility. Instead, transvaginal ultrasonography is performed to detect unsuspected ovarian pathology, such as endometriomas. Consequently, much of infertility previously attributed to cervical factors, luteal phase deficiency, and mild endometriosis or adhesions is now "unexplained."

Excluding false-negative results of standard diagnostic tests, which do occur but are uncommon, there are two potential explanations for unexplained infertility: 1) there truly is no abnormality and the couple's natural fertility is at the extreme lower end of the normal range, possibly due to female partner age or advanced reproductive aging; and 2) there is a specific cause, but not one that can be identified with existing diagnostic tests.

Undoubtedly, much of unexplained infertility relates to the natural decline in fertility with increasing age. Unexplained infertility is more common in women over age 35; in a study involving over 7,000 infertile women, those over the age of 35 years were nearly twice as likely to have unexplained infertility (OR=1.8, CI=1.4-2.7).[350] ***Logically, the most likely occult causes of infertility relate to abnormalities in gametes or implantation, for which there is no valid diagnostic test***. Genetic or functional abnormalities in zona pellucida proteins could interfere with sperm penetration and cause fertilization failure.[701] Abnormalities in the centrosome could interfere with normal spindle formation and function, preventing

fertilization or resulting in arrested early embryonic development.[702] Although failed fertilization occurs in less than 5% of IVF cycles and does not always reoccur in subsequent cycles,[703,704] a marked decrease in fertilization efficiency easily could result in unexplained infertility. A higher incidence of fertilization failure has been observed in several, but not all, studies of IVF outcomes in couples with unexplained infertility.[705,706,707] and [708] Evidence that up to 75% of human pregnancies fail soon after conception implicates early embryopathy and implantation failure as likely causes of unexplained infertility.[39,709,710] Although aneuploidy is common in early human embryos,[711,712] a recurring nonrandom genetic defect in the embryo or trophectoderm could cause early loss. Intrinsic genetic abnormalities in endometrial function and receptivity could interfere with apposition, adhesion, attachment, or invasion of the embryo, causing implantation failure.[713,714] and [715] ***It is important to emphasize that all of the potential causes of unexplained infertility could co-exist with known causes for infertility, helping to explain why many couples with identified ovarian, male, uterine, or tubal infertility factors fail to achieve a successful pregnancy despite receiving proven effective treatments***.[716]

Unexplained infertility likely represents either the lower extreme of the normal distribution of reproductive efficiency or abnormalities of sperm or oocyte function, fertilization, implantation, or embryo development that cannot be detected reliably by standard methods of evaluation. Although many couples with unexplained infertility

may be expected to conceive without treatment, their already low and steadily declining cycle fecundity provides ample justification for offering treatment to those concerned enough to seek evaluation. The goal of treatment is to increase monthly fecundability to a level more closely approximating that observed in normally fertile couples.

The prognosis for untreated couples with unexplained infertility is similar to that for couples with minor infertility factors, such as mild oligospermia or endometriosis; age of the female partner and duration of infertility are the primary variables that affect pregnancy rates.[353,717,718] ***In studies evaluating treatments for unexplained infertility, untreated patients have a cycle fecundability ranging typically between 2% and 4%,[719] or about 80-90% lower than in normal fertile couples (20-25%) The likelihood of pregnancy without treatment decreases progressively with increasing age of the female partner and increasing duration of infertility.[353,720]*** After 3 years of infertility, the likelihood of pregnancy without treatment falls to approximately 40%, and after 5 years to about 20%, of what it was when efforts to conceive first began.[343] Only approximately 14% of couples with unexplained infertility managed expectantly for up to 7 years achieve a pregnancy resulting in a live birth within a year; the prognosis is better when the female partner is under age 30.[353,718] ***The effect of duration of infertility is important to understand. Because spontaneous pregnancy rates are highest among couples with a relatively short duration of infertility and success rates achieved with all forms of treatment for unexplained infertility other than IVF are similar, treatments can appear more effective in couples with a longer duration of infertility having a lower probability for conceiving without treatment.***

By definition, the cause of unexplained infertility is unknown. Consequently, all treatments for unexplained infertility are empiric. Although methods differ, the basic strategy is the same for all—to bring together more than the usual numbers of oocytes and sperm in the right place at the right time. To this end, the most common treatments include intrauterine insemination (IUI), ovarian stimulation with clomiphene or gonadotropins and IUI, and IVF. It is important to realize that none of the current treatments for unexplained infertility targets the most likely causes, which all involve events occurring during or after fertilization. Empiric treatments for unknown disorders cannot be expected to achieve dramatic results. In small studies, modest effects can be difficult to demonstrate, and large effects can occur by chance.

Intrauterine Insemination (IUI)

Although several studies have examined the effectiveness of intrauterine insemination (IUI) as treatment for unexplained infertility in natural cycles,[449,467,719,721,722] a 2006 metaanalysis concluded that none provided reliable data because of problems with design, such as cross-over trials that do not include data from the first phase of the study or populations not limited to couples with unexplained infertility.[723] The two most informative studies were published more recently and included only couples with unexplained infertility or an abnormal postcoital test, with expectant management as the control treatment.[724,725] In the first trial (average age 32 years, average duration of infertility 2.5 years), 43 live births were observed among 191 couples receiving IUI (23%) over 6 months, compared to 32 in 193 couples (17%) managed expectantly.[724] Although the effect difference (6% over 6 months) was not significant (OR=1.46, CI=0.88-2.43), more women randomized to IUI judged their treatment acceptable. In the second trial (average age 30 years, average duration of infertility 1.7 years), 11 ongoing pregnancies were observed among 51 couples receiving IUI (22%), compared to 9 in 48 couples (19%) managed expectantly.[725] ***The best available evidence suggests that treatment with IUI in natural cycles has no clinically important effects.***

Clomiphene Citrate and IUI

Numerous studies have examined the effectiveness of clomiphene therapy without IUI as treatment for unexplained infertility.[726,727,728] and [729] However, only two are truly informative trials, including only patients with unexplained infertility, using placebo or expectant management as the control treatment.[724,730] In one trial (average age 30 years, average duration of infertility 4.3 years), 10 pregnancies were observed among 76 couples (13%) receiving clomiphene treatment over 290 cycles (3%/cycle), compared to 4 in 72 couples (6%) receiving placebo over 274 cycles (1%/cycle).[730] In the other (average age 32 years, average duration of infertility 2.5 years), 26 pregnancies were observed among 192 couples receiving clomiphene (14%), compared to 32 in 193 couples (17%) managed expectantly.[724] The differences between treatment and control pregnancy rates (per couple or per cycle) were not significant in either trial. ***Although clomiphene is commonly used as a treatment for unexplained infertility, the best available evidence indicates it has no significant benefit.***

Combined treatment with clomiphene and IUI is commonly recommended for couples with unexplained infertility, but evidence for its effectiveness is quite limited. In a review of eight studies involving 932 treatment cycles, the estimated cycle fecundity was 5.6% with clomiphene and 8.3% with clomiphene and IUI.[719] The one trial (average age 33 years, average duration of infertility 3.5 years) including an untreated control group (timed intercourse), included patients with unexplained infertility or treated endometriosis.[731] Limiting analysis to cycles observed before cross-over, eight pregnancies were observed in 23 couples (35%) receiving clomiphene and IUI over 73 treatment cycles (11%/cycle), compared to 4 in 28 couples (14%) over 103 cycles (4%/cycle). The 7.1% absolute difference (CI=-1.0-15.2) in cycle fecundability was not significant, and even if it were, the treatment effect was quite modest; the calculated number needed to treat was 15, implying that one additional pregnancy might be expected for every 15 treatment cycles.

Results of three other cross-over trials involving control groups receiving an active treatment (instead of placebo or no treatment) are difficult to interpret confidently, because no data were provided for the first phase of the study.[732,733] and [734] A fourth management trial (the fast track and standard treatment "FASTT" trial) compared outcomes in two groups, one

randomly assigned to receive three cycles of treatment with clomiphene and IUI followed by up to six cycles of IVF, and the other assigned to receive three cycles of clomiphene and IUI, followed by three cycles of treatment with gonadotropins and IUI, followed by up to six cycles of IVF.[735] Notably, 55 pregnancies were observed among 233 couples over 646 treatment cycles (8.5%/cycle) in the first group and 68 in 242 couples over 648 treatment cycles (10.5%/cycle) in the second; overall, 123 pregnancies were observed in 475 couples (26%) over 1,294 cycles (9.5%/cycle). The overall pregnancy rate compares favorably with the expected 2-4% cycle fecundability among couples with unexplained infertility, which supports the use of clomiphene and IUI in the treatment of unexplained infertility. In two large retrospective studies involving a total of more than 8,000 cycles of treatment with clomiphene and IUI, cycle fecundability ranged between 5% and 10% per cycle after four to six cycles for women age 40 years and younger, and were under 5% for those over age 40.[736,737]

In sum, evidence for the effectiveness of combined treatment with clomiphene and IUI is not compelling. However, considering its relatively modest cost and complexity (compared to the alternatives, discussed below), treatment with clomiphene and IUI seems justified because the cycle fecundability observed in large prospective and retrospective studies is significantly higher than can be expected in couples with unexplained infertility receiving no treatment.

Gonadotropins and IUI

Gonadotropin therapy without IUI for treatment of unexplained infertility has been evaluated in only a few clinical

trials. In the largest, pregnancy rates resulting from treatment with gonadotropins and intracervical insemination were higher than was achieved with insemination alone, but the difference was small (3.6%).[738] ***Although treatment with gonadotropins alone can increase cycle fecundability, compared with no treatment, the effect is quite modest and no better than can be achieved by treatment with clomiphene and IUI.***

More commonly, gonadotropin treatment is combined with IUI for the treatment of unexplained infertility. Among four trials comparing gonadotropins and IUI with no treatment, two were cross-over trials providing no results for the first phase of treatment.[739] In a U.S. trial (average age 32 years, average duration of infertility 3.6 years), 77 pregnancies were observed among 231 couples (33%) receiving treatment with gonadotropins and IUI over 618 cycles (12%/cycle), compared to 23 pregnancies in 233 couples (10%) receiving intracervical insemination over 706 cycles (3%/cycle); pregnancy rates per couple were 18% for treatment with insemination alone and 19% for gonadotropins and IUI.[738] A Dutch trial (average age 33 years, average duration of infertility 2 years) observed 29 pregnancies among 127 couples (23%) receiving gonadotropins and IUI over 676 cycles (4%/cycle), compared to 34 in 126 couples (27%) managed expectantly over 737 cycles (5%/cycle).[740]

The differing results of the two trials emphasize again the influence of the duration of infertility on outcomes achieved with treatment for unexplained infertility. In the U.S. trial, involving couples infertile for an average of 3.6 years, fecundability in those receiving treatment with gonadotropins and IUI (12%/cycle) was 9% higher than in couples receiving intracervical insemination (3%/cycle), and only 10% of couples in the latter group conceived. In the Dutch trial, involving couples with an average of 2 years of infertility and a better prognosis for achieving pregnancy without treatment,[718] fecundability of those receiving gonadotropins and IUI (4%/cycle) was no better than in couples managed expectantly (5%/cycle), and 27% of couples receiving no treatment conceived. Together, the results of the two trials indicate that treatment with gonadotropins and IUI has little benefit when the prognosis is reasonably good, and modest benefit when the prognosis is poor (one additional pregnancy for every 11 treatment cycles).

The results of treatment with gonadotropins and IUI for unexplained infertility raise two clinically relevant questions. The first concerns what benefits treatment with gonadotropins and IUI might have in couples first treated with clomiphene and IUI and failing to conceive. The only data addressing the question directly comes from the “FASTT” trial described above, in which 50 pregnancies were observed among 169 couples (30%) receiving treatment with gonadotropins and IUI over 439 cycles (11%/cycle) after failing to conceive over three cycles of treatment with clomiphene and IUI.[735] Although cycle fecundability (11%/cycle) was slightly higher than was achieved with clomiphene and IUI in the same population (9.5%/cycle), the difference is not clinically important, especially when considering the greater costs, complexity, and risks associated with use of gonadotropins. Consistent with that view, a 2002 systematic review of trials comparing outcomes of treatment with clomiphene/IUI and gonadotropins/IUI concluded that evidence is insignificaent to suggest that either treatment is superior.[741] The second question relates to whether success with clomiphene and IUI depends on multifollicular development, and there are no reliable data that address the question directly.

A number of studies have examined the efficacy of various adjuvant treatments in couples receiving treatment with gonadotropins and IUI for unexplained infertility. The available evidence indicates that whereas pre-treatment with a GnRH agonist does not improve outcomes,[742] adding a GnRH antagonist to the treatment regimen can (OR=1.6, CI=1.1-2.3).[743]

In summary, treatment with gonadotropins and IUI is modestly effective treatment for couples with longer durations of unexplained infertility (>3years). Treatment with gonadotropins and IUI is reasonable to

consider for couples who fail to conceive during treatment with clomiphene and IUI and when clomiphene treatment fails to stimulate multiple follicular development, especially when IVF is not a viable option.

Assisted Reproductive Technology

Observations in ART cycles frequently provide insight into the possible causes of a couple's unexplained infertility because the procedures involved address or eliminate many of the unknown variables. Sperm and oocytes will be combined effectively. Fertilization and early embryonic development can be observed directly, and embryo transfer ensures that embryos will reach the endometrial cavity. Although the chromosomal composition of embryos and endometrial receptivity may seem like the only factors remaining, the list of unknowns is, in truth, much longer.

Although hundreds of studies of ART outcomes have been published, the large majority involve comparisons between two different treatment protocols; few have compared ART with no treatment or a different treatment such as gonadotropins and IUI,[744,745] and none has been limited to couples with unexplained infertility. Excluding trials comparing IVF with GIFT,[746] which are no longer relevant, and one comparing immediate IVF to IVF after various other treatments, leaves only a single multicenter trial, in which 139 couples were randomly assigned to receive immediate IVF (within 6 weeks) or 3 months of expectant management.[747] In that trial, the average patient age was 33 years and the average duration of infertility was 4.8 years. Among the 51 couples with unexplained infertility (37%), clinical pregnancies were observed in 12/24 (50%) couples receiving immediate IVF and in 3/27 (11%) receiving expectant management, yielding a large difference of 39% per couple or 46% per cycle.[747] In the 2007 U.S. national summary of ART outcomes, the overall live birth rate per cycle start for couples with unexplained infertility (all ages) was 31.8%.[34] Evidence from three relevant trials suggest that intracytoplasmic sperm injection (ICSI) does not significantly improve IVF outcomes, compared to conventional fertilization, although the studies were not limited to couples with unexplained infertility.[748,749] and [750]

In summary, IVF is clearly the most effective treatment for couples with unexplained infertility, regardless whether it is the first or the last treatment.

efficacy of Treatments for Unexplained Infertility

Treatment	*Approximate Cycle Fecundability*
No treatment	2-4%
IUI	2-4%
Clomiphene	2-4%
Gonadotropins	5-7%

Clomiphene/IUI	5-10%
Gonadotropins/IUI	7-10%
IVF	25-45%

SUMMARY

Overall, the treatment effects of treatments for unexplained infertility other than IVF are relatively small. In many cases, treatment may only hasten pregnancy for couples who would ultimately conceive on their own, given time. Careful counseling is essential and must take into account the couple's age, the duration of infertility, and the outcome of any previous pregnancies; before treatment is recommended, an ovarian reserve test also is prudent.[141] Couples who choose treatment should be informed thoroughly about the relative costs, risks, prognoses, and logistical challenges associated with different treatments so that they may select the one that best meets their needs and preferences. Partners can have differing levels of concern about their infertility and tolerance for risk and uncertainty.[751] Together, the medical evidence and shared decision-making determine the choice of management.[752]

Adoption

With proper evaluation and treatment, the majority of couples evaluated for infertility will achieve pregnancy. For those who fail simpler specific treatments, ART and adoption are both realistic options. Couples considering adoption have a wide range of choices including social agency adoptions, private adoptions, and international adoptions. In some states, private adoption is not legal, but where it is, private adoption can be an effective, more rapid alternative to adoption through a social agency. In most cases, the biologic mother has the opportunity to know the adopting parents and may reconsider her decision and reclaim her child for a time before the adoption is finalized. Those who prefer anonymity or who wish to avoid such potentially devastating disappointments likely will make a different choice. Couples interested in adoption should be referred to those knowledgeable about adoption laws in individual states and all of the available options.

All references are available online at: http://www.clinicalgynendoandinfertility.com

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