Etiology and evaluation of female infertility

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INTRODUCTION — Infertility is a complex disorder with significant medical, psychosocial, and economic aspects. Both the prevalence of infertility and the number of patients seeking treatment of this disorder are increasing [1]. While great strides have been achieved in infertility therapy, evidence-based studies have questioned the validity of historically accepted tests for its diagnosis.

An overview of the infertility evaluation in females will be reviewed here. Infertility related to recurrent pregnancy loss and male factors are discussed separately. (See "Evaluation and management of couples with recurrent pregnancy loss" and see "Evaluation of male infertility").

DEFINITIONS — Infertility is a unique medical condition because it involves a couple, rather than a single individual. It is classically defined as the failure of a couple to conceive after 12 months of frequent intercourse without contraception. Fecundability, the probability of achieving a pregnancy in one menstrual cycle, is a more accurate descriptor because it recognizes varying degrees of infertility.

NORMAL FERTILITY — The concept of fecundability has proven useful for establishing normal fertility parameters in studies of fertility potential:

- A study of 5574 normal women who had unprotected intercourse and who became pregnant between 1946 and 1956 examined the number of months to conception [2]. Eighty-five percent of the women had conceived by 12 months. Fecundability was 0.25 in the first three months of observation, and then decreased to 0.15 during the next nine months of observation.

- Another study of 200 healthy couples who desired pregnancy also found that fecundability declined from 0.25 in the first three months to 0.11 in the next nine months of observation (show table 1) [3]. 82 percent of the couples followed for the entire study period conceived.

While these studies demonstrate that the large majority of normal couples will conceive within a one-year period, they also show that the fecundability of the cohort decreases over long-term follow-up. The remaining patients who have not achieved pregnancy after 12 months have even lower fecundability; hence the use of one year as a time interval for attempting conception before assigning a diagnosis of infertility.

Subsequent prospective population-based studies have confirmed these observations and also demonstrated that between 80 to 90 percent of women will conceive during the first six months of attempting pregnancy.:

- A study conducted in China reported that 518 newly married textile workers aged 20 to 34

years who intended to conceive did so at a rate of about 50 percent within two cycles and 88 percent within six months [4]. Monthly fecundity ranged from 30 to 35 percent.

- A large prospective European study investigated 346 users of natural family planning methods trying to achieve conception [5]. The estimated cumulative probabilities of conception for the total group at 1, 3, 6, and 12 months were 38, 68, 81, and 92 percent, respectively. The authors postulated that after six months, 50 percent of the remaining couples were subfertile or infertile.

These studies suggest that the diagnosis of infertility may be suspected after only six months of unprotected intercourse without conception.

Several authorities have proposed a system of prognostic grading in conjunction with statements describing the couple's fertility history and diagnosis in order to reduce confusing terminology and to facilitate an appropriate treatment plan [6]. This system has not yet been widely accepted.

INCIDENCE — Data from the 1995 National Survey of Family Growth, which interviewed 10,847 women aged 15 to 44, revealed that the proportion of United States women who reported some form of fecundity impairment rose from 8 percent in 1982 and 1988 to 10 percent in 1995, with an increase in absolute numbers from 4.6 million to 6.2 million women [1]. Although the proportion of infertile women who had ever sought medical help did not change between 1988 and 1995 (44 percent), the absolute numbers of such women grew by nearly 30 percent, from 2.1 million to 2.7 million. This increase in the observed percentage of infertile women in 1995 resulted in a substantial upward revision in the projected number of infertile women in 2025, to approximately 6.5 million [7]. The authors of this study attributed the rise in infertility rates seen across all age groups to three factors:

(1) A lower proportion of women surgically sterilized for noncontraceptive reasons (eg, hysterectomy for endometriosis)

(2) A greater public awareness of infertility resulting in higher self-reporting

(3) A larger percentage of patients with subclinical pelvic inflammatory disease among women with gonorrhea or chlamydial infection

ETIOLOGY — The World Health Organization (WHO) task force on Diagnosis and Treatment of Infertility performed a study of 8500 infertile couples and utilized standard diagnostic criteria to determine the medical conditions contributing to infertility [8]. In developed countries, female factor infertility was reported in 37 percent of couples, male factor infertility in 8 percent of couples, and both male and female factor infertility in 35 percent of couples. Five percent of couples had unexplained infertility and 15 percent of couples became pregnant during the study. The most common identifiable female factors, which accounted for 81 percent of female infertility, included:

- Ovulatory disorders (25 percent)
- Endometriosis (15 percent)
- Pelvic adhesions (12 percent)
- Tubal blockage (11 percent)
- Other tubal abnormalities (11 percent)
- Hyperprolactinemia (7 percent)

Another study of 2198 infertile couples in Canada found the chief infertility diagnoses were

unexplained infertility (26 percent), male factor infertility (24 percent), tubal disease (23 percent), ovulation disorders (18 percent), endometriosis (7 percent), and other (luteal phase, cervical or uterine defects, 2 percent) [9].

These studies show that it is important to evaluate both partners of the infertile couple, focusing on the major processes which affect fertility.

Anovulation/oligoovulation — Anovulation/oligoovulation decreases the number of oocytes available for fertilization. Women who report monthly menses and moliminal symptoms (breast tenderness, dysmenorrhea, bloating) are typically ovulatory. If menses and molimina are irregular or absent, pregnancy or another condition associated with anovulation/oligoovulation is possible. Potential causes of anovulation/oligoovulation are listed in Table 2 (show table 2). (See "Etiology, diagnosis, and treatment of secondary amenorrhea").

Oocyte aging — The germ cell complement of the ovary reaches its apex of 6 to 7 million in the midgestation female fetus, followed by a steady attrition from 1 to 2 million follicles at birth to 300,000 follicles at the onset of puberty [10]. The rate of follicle loss accelerates after the midthirties [11,12]. (See "Effect of advanced age on fertility and pregnancy in women").

Women with a depleted ovarian follicle pool may continue to ovulate regularly, but have infertility due to the poor quality of oocytes remaining in the terminal follicular pool. Thus, the decrease in fecundability with aging is likely due to a decline in both the quantity and quality of the oocytes. Other insults to the ovary such as cigarette smoking [13-15], radiation, chemotherapy, and autoimmune disease also accelerate follicular loss. (See "Ovarian failure due to anticancer drugs and radiation" and see "Pathogenesis and causes of spontaneous premature ovarian failure").

Fallopian tube abnormalities/pelvic adhesions — The primary cause of tubal factor infertility is pelvic inflammatory disease caused by pathogens such as chlamydial or N. gonorrhea. Other conditions that may interfere with tubal transport include severe endometriosis, adhesions from previous surgery or nontubal infection, and pelvic tuberculosis. (See "Treatment and sequelae of pelvic inflammatory disease in adults" and see "Treatment of infertility in women with endometriosis").

Patients with distal tubal obstruction may develop hydrosalpinges, which decrease the success rate of in vitro fertilization (IVF), presumably due to embryotoxic factors contained in the hydrosalpinx fluid [16]. The removal of a hydrosalpinx visible on ultrasound prior to IVF treatment can increase pregnancy and birth rates. In one study, for example, 204 women were randomly assigned to undergo salpingectomy prior to IVF or to proceed to IVF without prior salpingectomy [17]. The live birth rate was significantly higher in women who had salpingectomy prior to IVF (29 percent versus 16 percent in women who underwent only IVF). This indicates that tubal blockage may reduce fertility, both by causing blockage in the fallopian tube and by creating a hostile environment to implantation of an embryo in the uterus.

Uterine leiomyomata — Uterine leiomyomata are benign smooth muscle monoclonal tumors. They are the most common pelvic tumors of women. A meta-analysis of studies comparing women with infertility and leiomyomata versus infertile controls showed that only leiomyomata with a submucosal or intracavitary component were associated with lower pregnancy and implantation rates [18]. When women with submucous myomas underwent myomectomy, pregnancy rates increased significantly compared with infertile controls. Thus, it appears that only those fibroids with a submucosal or an intracavitary component are associated with decreased fecundability as they may impede normal implantation. (See "Epidemiology; pathogenesis; diagnosis; and natural history of uterine leiomyomas" section on Effects on reproduction).

Uterine anomalies — Müllerian anomalies are a significant cause of recurrent pregnancy loss (RPL), with the septate uterus associated with the poorest reproductive outcome [19]. Other structural abnormalities include those associated with in utero exposure to diethylstilbestrol (T-

shaped or hypoplastic uteri), polyps, and synechiae from prior pregnancy-related curettage. Data on these uterine abnormalities establishing a causal link to infertility are lacking. (See "Congenital anomalies of the uterus", see "Outcome of diethylstilbestrol exposed individuals", and see "Incidence and etiology of recurrent pregnancy loss").

Endometriosis — Endometriosis, the growth of endometrial tissue outside of the uterine cavity, is associated with an increased risk of infertility. Mechanisms which decrease fertility include anatomic distortion from pelvic adhesions, damage to ovarian tissue by endometrioma formation and removal, and the production of substances such as cytokines and growth factors which impair the normal processes of ovulation, fertilization, and implantation. (See "Treatment of infertility in women with endometriosis").

The prevalence of endometriosis is higher among infertile than fertile women. In a prospective study, 1542 premenopausal Caucasian women either underwent laparoscopy for infertility, laparoscopic tubal sterilization, laparoscopy for chronic pelvic pain, or abdominal hysterectomy for dysfunctional uterine bleeding [20]. Endometriosis was seen more frequently among infertile women than fertile women undergoing sterilization (21 versus 6 percent). For those experiencing chronic pelvic pain, the incidence of endometriosis was 15 percent, while among those undergoing abdominal hysterectomy it was 25 percent.

Cervical factors — In the normal cervix, secreted cervical mucus facilitates the transport of sperm. Congenital malformations of and trauma to the cervix (including surgery) may result in stenosis or impair the ability of the cervix to produce normal mucus, thereby impairing fertility. Cervical infection may also impede normal sperm migration.

Luteal phase defect — An endometrial biopsy for histologic dating may be done in the late luteal phase (ie, 10 to 12 days after an LH surge or 4 to 5 days before anticipated menses). The theoretical menstrual date is calculated by subtracting the number of days between the endometrial biopsy and subsequent menses from 28, the average length of a normal menstrual cycle (eg, 28 - 2 = histologic menstrual day 26 endometrium).

Diagnosis of a luteal phase defect is made by two consecutive endometrial biopsy specimens showing histology more than two days out-of-phase with the actual biopsy date [21]. The delayed endometrial maturation may be caused by a deficiency of corpus luteum progesterone production, either in amount or duration [22]. However, up to 50 percent of normal women may have a two-day lag in endometrial maturation on a single biopsy [23].

The proportion of out-of-phase biopsies depends upon the method used to date ovulation, with sonography and measurement of the LH surge yielding the fewest biopsies with delayed maturation [24]. Controversy exists over the relevance of luteal phase defect as a cause of infertility and the accuracy of the endometrial biopsy in assessing the delay [25,26].

Immunologic and thrombophilic factors — A hypercoagulable state due to inherited or acquired thrombophilia and abnormalities of the immune system (eg, systemic lupus erythematosus, antiphospholipid antibody syndrome) that lead to immunological rejection of the early pregnancy or placental damage are active areas of investigation. (See "Incidence and etiology of recurrent pregnancy loss").

Genetic causes — Infertile couples have been shown to have a higher prevalence of karyotype abnormalities (trisomies, mosaics, translocations, etc) than the general population [27]. The frequency varies according to the cause of infertility and clinical history. The most common aneuploidies associated with infertility are 45, X (Turner syndrome) in women and 47, XXY (Klinefelter syndrome) in men. (See "Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis)" and see "Causes of primary hypogonadism in males" section on Klinefelter's syndrome).

Individual genes that affect fecundity have been identified, including KAL1 (Kallman's syndrome) [28], GnRH receptor [29,30], FSH receptor [31], beta subunit of FSH [32], LH

receptor [33], FMR1 (fragile X syndrome) [34], SF1, DAX1 [35], LEP (leptin) [36], LEP receptor [37], GPR54 [38,39], and FGFR1 [40].

Unexplained — Unexplained infertility is the diagnosis given to couples after a thorough evaluation has not revealed a cause. Many cases of unexplained infertility may be due to small contributions from multiple factors (borderline semen analysis, subtle changes in follicle dynamics, etc). In an analysis of IVF outcomes by diagnosis, fertilization and cleavage rates were significantly reduced in couples with unexplained infertility compared to couples with tubal factor infertility, and an increased proportion of couples with unexplained infertility experienced complete fertilization failure [41] (See "Treatment of unexplained infertility").

EVALUATION — In geographic areas where an adequate number of specialists are available, most infertility evaluation and treatment should be directed by fertility specialists.

Timing — The timing of initial evaluation of infertility depends upon the couple's historical risk factors (show table 3), especially the age of the female partner. As a general rule, infertility evaluation should be undertaken for couples who have not been able to conceive after 12 months of unprotected and frequent intercourse. However, women experience a decline in fecundity due to ovarian aging, which correlates with increased chronological age [42]. Thus, delaying evaluation and treatment in a woman in her midthirties may condemn her to lower success rates once therapy is initiated (show figure 1). In addition, prospective cohort studies of fecundity () [4,5], have led some authorities to propose initiating infertility workup after six months of fertility-oriented intercourse without conception [43].

In light of these data, we recommend initiating evaluation after six months of unprotected intercourse without conception in women between 35 and 40 years of age, and we consider immediate evaluation in women over 40 years of age. Evaluation may also be initiated sooner if the female partner has a history of oligomenorrhea, pelvic infection or surgery, chemotherapy and/or radiation, or endometriosis. Early evaluation of the male partner may be warranted if there is a history of testicular trauma requiring treatment, adult mumps, impotence or other sexual dysfunction, or chemotherapy and/or radiation.

For a young couple (where the female partner is less than 30 years of age), it may be appropriate to limit the initial intervention to teaching timed intercourse with the aid of a urinary ovulation predictor kit, and to advise at least 12 months of attempts at conception before initiating the infertility evaluation.

Recommended tests — Basic testing that should be initiated at the time of referral include the following:

- Semen analysis to detect male factor infertility
- Documentation of normal ovulation by history and midluteal serum progesterone level
- Day 3 serum follicle-stimulating hormone (FSH) level to assess ovarian reserve (especially in women over 35 years of age)
- Hysterosalpingogram (HSG) to rule out tubal obstruction

Risk factors noted from the couple's history may mandate additional testing after the initial fertility consultation. Preconceptional laboratory assessment may also be undertaken at this time so these results can be considered in diagnostic and therapeutic counseling. (See "Preconceptional evaluation and counseling").

Semen analysis — The semen sample should be collected after two to seven days of abstinence. If the specimen cannot be given at the laboratory or doctor's office, then the sample should be delivered to the laboratory within an hour of collection.

By WHO guidelines, the reference range of the prewash semen analysis is volume of 2 to 5 mL, sperm count of greater than 20 million sperm/mL, greater than 20 percent normal morphology and sperm motility of over 50 percent with good forward progression [44]. It is difficult to predict pregnancy based on the semen analysis alone as there is extensive overlap between the semen parameters of fertile and infertile men. Sperm morphology best discriminates between fertile and infertile men, but there is no parameter diagnostic of infertility [45]. The lower limit of normal sperm morphology was established as 14 to 15 percent normal forms using Kruger morphology criteria and corresponding IVF fertilization and pregnancy rates [46,47].

If the semen analysis is abnormal, the clinician should review the details of specimen collection and transport, the timing of the previous ejaculation, and any history of diabetes, urologic surgery, and medication or substance use with the patient. The test should also be repeated due to the marked inherent variability of semen analyses.

Lack of sperm in the ejaculate does not indicate the absence of testicular sperm production; the clinician should refer such patients to a urologist to rule out retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia. (See "Evaluation of male infertility").

Documentation of ovulation — If the woman's menstrual cycles are not regular (ie, every 25 to 35 days), the clinician should test for ovulation by having the patient use an over-the-counter urinary luteinizing hormone (LH) kit or by obtaining a midluteal serum progesterone level. We obtain a midluteal serum progesterone level 18 to 24 days after the onset of menses; a value greater than 3 ng/mL is diagnostic of ovulation. The serum test is not subject to observer misinterpretation as with home urine tests. (See "Evaluation of the menstrual cycle and timing of ovulation" section on Measurement of LH surge).

In amenorrheic patients (after pregnancy has been excluded), a progestin challenge test may be utilized to verify ovarian estradiol production and the presence of a normal outflow tract. A progestin (eg, medroxyprogesterone acetate 10 mg/day orally for 5 days or progesterone 100 mg IM in oil) is administered; bleeding in the week after the challenge indicates that significant estrogen is present and able to impact the endometrium and that a patent outflow tract exists.

Prolactin and thyroid-stimulating hormone (TSH) levels may be assessed to rule out other causes of irregular menses, especially if galactorrhea is also present. (See "Etiology, diagnosis, and treatment of secondary amenorrhea").

Ovarian reserve — Identification of a depleted ovarian reserve is the goal of a number of tests, including:

- Day 3 FSH concentration

- Clomiphene citrate challenge test (CCCT) (oral administration of 100 mg clomiphene citrate on cycle days 5 through 9 with measurement of day 3 and day 10 FSH levels)

- Day 3 inhibin-B

- Ultrasound imaging of the ovary to determine either ovarian volume and/or antral follicle counts.

In large groups of women these markers predict the quality and number of oocytes in the ovary and hence the pregnancy rate, spontaneously or with assisted reproductive technologies (ART). However, for any given woman, they are not precisely accurate, raising the ethical problem of whether women should be denied infertility treatment if one of these tests of ovarian function is abnormal.

Inhibin-B levels rise in women with decreased ovarian reserve prior to the elevation in FSH levels [48], prompting investigations into the potential of inhibin-B as a marker of ovarian

reserve. One study demonstrated that women with low day 3 serum inhibin-B concentrations had a poorer response to ovulation induction and were less likely to conceive through ART relative to women with a high day 3 inhibin-B [49]. Other studies, however, have failed to show inhibin-B to be predictive of pregnancy in women undergoing infertility or ART therapies [50,51]. Moreover, there is no accepted international standard for the inhibin-B assay, making correlation between laboratories difficult.

A comparison of the ability of ovarian reserve tests to predict ovarian response and pregnancy found that ovarian volume and an abnormal CCCT were better than other hormonal and sonographic tests in predicting the response to ovarian stimulation in IVF cycles [52]. In this study, however, age was the only independent predictor of pregnancy in IVF as compared to hormonal and ultrasound indices of ovarian reserve. Two other studies demonstrated that low antral follicle counts were predictive of poor ovarian response in IVF but did not predict pregnancy, even in combination with other ovarian reserve factors. [53,54].

At present, the most widely used tests for assessment for ovarian reserve are day 3 FSH levels and the CCCT. A meta-analysis of 19 published studies evaluated either basal FSH level or the CCCT for predicting treatment outcome in an infertility clinic population [55]. Both tests were similar in predicting achievement of pregnancy in women undergoing infertility treatment: while a normal result was not useful (many infertile women had normal tests), an abnormal result with either test virtually confirmed that pregnancy would not occur with treatment. Unfortunately, few infertile women had FSH levels high enough to be considered abnormal. Combining a basal estradiol level with FSH measurement on day 3 improved the sensitivity (elevated basal estradiol levels are due to rapid premature follicle recruitment which occurs in women with poor ovarian reserve) [56]. Another meta-analysis of FSH and CCCT testing, which used failure to become pregnant after IVF as the outcome measure, came to a similar conclusion [57].

We obtain a cycle day 3 FSH concentration and consider a value less than 15 mIU/mL suggestive of adequate ovarian reserve. However, the upper threshold for a normal FSH concentration is laboratory dependent; cutoff values of 10 to 25 mIU/mL have been reported because of use of different FSH assay reference standards.

Assessment of tubal status — A meta-analysis of 20 studies involving 4179 patients comparing HSG and laparoscopy with chromopertubation (the gold standard) revealed that the high specificity of the HSG (83 percent) makes it useful for confirming tubal patency [58]. However, the HSG is less sensitive (65 percent) for diagnosing tubal occlusion due to a high false positive rate and is not reliable in the evaluation of peritubal adhesions or endometriosis.

HSG may also identify abnormalities of the uterine cavity, such as submucous fibroids, a T-shaped cavity (associated with DES exposure), polyps, synechiae, and congenital müllerian anomalies, although HSG alone cannot reliably distinguish between a uterine septum or bicornuate uterus.

Thus, HSG is a reasonable initial screening test of tubal and uterine cavity status [58,59]. Abnormalities found on HSG may require follow-up evaluation by laparoscopy and/or hysteroscopy or other imaging modalities (three dimensional ultrasound or magnetic resonance imaging) (see "Diagnostic laparoscopy" below). (See "Congenital anomalies of the uterus").

Diagnostic HSG was originally performed with oil soluble contrast media, which was gradually replaced by water soluble contrast media for the following reasons: lower cost; better imaging of the tubal mucosa; more prompt demonstration of tubal patency; less likelihood of persistence of contrast medium within the pelvic cavity; reduction of complications such as intravasation resulting in allergic reactions; and reduction in long-term lipogranuloma formation [60]. There were several reports of deaths after the use of oily media for imaging studies before the use of fluoroscopy screening, but none have been reported since use of fluoroscopy; therefore, the use of oil soluble contrast media for HSG is not unreasonable [61].

Diagnostic HSG may also have therapeutic effects. (See "Treatment of unexplained infertility").

Several studies support Chlamydia trachomatis antibody testing as a simple, inexpensive, and noninvasive method of testing for tubal disease with a higher positive predictive value than HSG [62,63]. In one study, the presence of antibodies to chlamydia were associated with infertility, while previous copper IUD use was not [64]. Testing for C. trachomatis antibody has not yet come into widespread use. Multiple tests are available [65].

Diagnostic laparoscopy — The role of laparoscopy in the evaluation of infertility is controversial. Laparoscopy is invasive and expensive and does not usually alter the treatment of the infertile couple, particularly in couples where the HSG is normal. This is especially true if the clinician plans to recommend IVF relatively early in the couple's treatment plan, such as in cases of severe male factor or complete bilateral proximal tubal obstruction.

Generally, laparoscopy is indicated in women with otherwise unexplained infertility and a suspicion of endometriosis or pelvic adhesions due to a history of pelvic pain and/or previous surgery or infection [66,67]. The use of laparoscopy to obtain a diagnosis in cases of unexplained infertility also affords the opportunity to treat any existing pathology.

One randomized controlled trial reported that laparoscopic ablation of minimal to mild endometriosis improved the fecundity of infertile women for at least nine months following the surgery [68]. A subsequent smaller randomized study of laparoscopic treatment of endometriosis could neither confirm nor refute this observation, possibly due to inadequate power [69].

There are currently no randomized studies assessing the cost effectiveness and timing of diagnostic laparoscopy prior to ovulation induction. As there is a relatively high likelihood (above 20 percent) of finding a significant abnormality at laparoscopy in a woman with normal testing [20,70], we offer laparoscopic evaluation to couples with unexplained infertility, usually prior to initiating gonadotropin therapy. The use of laparoscopy to treat infertility is covered in more detail separately. (See "Laparoscopic surgery for treatment of infertility in women").

Tests of limited clinical utility

Postcoital test — The postcoital test is most frequently utilized to assess the adequacy of the cervical mucus and its interactions with sperm. After intercourse in the late follicular phase, the female partner is examined and a small amount of cervical mucus is obtained for assessment of spinnbarkeit (stretchability) and microscopic examination of fern and sperm motility (at least 5 motile sperm per high power field is considered normal).

The postcoital test has been widely used in infertility investigations since 1866, but has limited diagnostic potential and poor predictive value [71,72]. There is no consensus on the normal range of sperm per high-power field and there is low inter- and intraobserver reproducibility [73]. The marked heterogeneity of results and the limitations of study design raise serious doubts about the utility of the postcoital test [74]. In addition, various treatments for abnormal test results have not been shown to be effective, and widely used infertility therapies (eg, intrauterine insemination, IVF) bypass the cervix. A randomized controlled trial comparing infertility investigations with and without the postcoital test showed no difference in pregnancy rates at 24 months [75]. Thus, incorporation of the postcoital test in standard infertility evaluations increases the number of tests and treatments but has no effect on the pregnancy rate. Therefore, we do not recommend it.

Endometrial biopsy — An endometrial biopsy is unnecessary for ovulation evaluation. Although endometrial receptivity during the implantation window is crucial for achieving pregnancy, no histological or biochemical assessment of endometrial responses has been reliably associated with conception [25,76-79]. This was illustrated in the following representative examples:

• A study of repeated endometrial biopsies in normal fertile women showed that 51 percent have a single out-of-phase biopsy (using 2-day or greater lag criteria) and 27 percent have sequential out-of-phase biopsies [23].

• A study of 619 women with regular menstrual cycles compared the frequency of out-of-phase endometrium in fertile (n = 332) and infertile couples (n = 237) [26]. Daily LH testing was performed until an LH surge was detected and then the women were randomly assigned to endometrial biopsy on day 21-22 or day 26-27. An out-of-phase biopsy of greater than two days was actually more common in fertile women (49 versus 43 percent at D21-22, 35 versus 23 percent at D26-27).

Thus, it appears that luteal phase defect is often present in fertile women and histological dating does not discriminate fertile from infertile couples [23,26]. As the treatment of luteal phase defect does not improve pregnancy outcome in infertile women, luteal phase evaluation by histological dating of the endometrium is not worthwhile.

Basal body temperature records — Basal body temperature charts are the least expensive method for detecting ovulation, but interpretation of the charts may be difficult and subject to wide interobserver variation [80,81]. (See "Evaluation and management of abnormal uterine bleeding in premenopausal women" section on Basal body temperature monitoring).

Zona-free hamster oocyte penetration test — Also known as the sperm penetration assay, this test should be reserved for patients in whom results will influence treatment strategy. Conflicting literature exists on whether the hamster oocyte test predicts human oocyte fertilization [82,83]. The utility of test results depends, in part, on the experience of the laboratory performing the assay. (See "Evaluation of male infertility" section on Zona-free hamster oocyte penetration test).

Routine mycoplasma cultures — Routine Ureaplasma urealyticum and Mycoplasma hominis cultures should not be performed as there is minimal evidence for a role in female infertility. Mycoplasma and Ureaplasma may reside in normal flora and can recur after treatment [84].

Immune testing — Routine testing for antiphospholipid, antisperm, antinuclear, and antithyroid antibodies is not supported by existing data [85]. An association between antiphospholipid antibodies and RPL has been established, but other autoimmune factors are under investigation as markers of fertility treatment failure. (See "Clinical manifestations and diagnosis of the antiphospholipid antibody syndrome in pregnancy").

Karyotype — At this time, the general practice is to karyotype the male partner if there is severe oligospermia as these men are at high risk of microdeletion or other karyotypic abnormalities. Women with very early premature menopause may also be karyotyped. Both partners are karyotyped if there have been recurrent pregnancy losses. In most other circumstances (eg, unexplained infertility, endometriosis, tubal factor infertility), karyotyping is not indicated.

REFERENCES

1. Chandra, A, Stephen, ß. Impaired fecundity in the United States: 1982-1995. Fam Plann Perspect 1998; 30:34.

2. Guttmacher, AF. Factors affecting normal expectancy of conception. J Am Med Assoc 1956; 161:855.

3. Zinaman, MJ, Clegg, ED, Brown, CC, et al. Estimates of human fertility and pregnancy loss. Fertil Steril 1996; 65:503.

4. Wang, X, Chen, C, Wang, L, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril 2003; 79:577.

5. Gnoth, C, Godehardt, D, Godehardt, E, et al. Time to pregnancy: results of the German prospective study and impact on the management of infertility. Hum Reprod 2003; 18:1959.

6. Habbema, JD, Collins, J, Leridon, H, et al. Towards less confusing terminology in reproductive medicine: a proposal. Fertil Steril 2004; 82:36.

7. Stephen, EH, Chandra, A. Updated projections of infertility in the United States: 1995-2025. Fertil Steril 1998; 70:30.

8. WHO Technical Report Series. Recent Advances in Medically Assisted Conception Number 820, 1992, pp 1-111.

9. Collins J, Burrows E, Willan A. Infertile couples and their treatment in Candaian Academic Infertilty Clinics. In: Royal Commission on New Reproductive Technologies. Treatment of infertility: current practices and psychosocial implications. Vol 10. Ottawa, Ontario, Minister of Supply and Services, 1993 p. 233.

10. Baker, TG. Radiosensitivity of mammalian oocytes with particular reference to the human female. Am J Obstet Gynecol 1971; 110:746.

11. Richardson, SJ, Senikas, V, Nelson, JF. Follicular depletion during the menopausal transition: evidence for accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab 1987; 65:1231.

12. Faddy, MJ, Gosden, RG. A mathematical model of follicle dynamics in the human ovary. Hum Reprod 1995; 10:770.

13. Jick, H, Porter, J. Relation between smoking and age of natural menopause. Report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. Lancet 1977; 1:1354.

14. Cramer, DW, Barbieri, RL, Xu, H, Reichardt, JK. Determinants of basal follicle-stimulating hormone levels in premenopausal women. J Clin Endocrinol Metab 1994; 79:1105.

15. Westhoff, C, Murphy, P, Heller, D. Predictors of ovarian follicle number. Fertil Steril 2000; 74:624.

16. Mukherjee, T, Copperman, AB, McCaffrey, C, et al. Hydrosalpinx fluid has embryotoxic effects on murine embryogenesis: a case for prophylactic salpingectomy. Fertil Steril 1996; 66:851.

17. Strandell, A, Lindhard, A, Waldenstrom, U, et al. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. Hum Reprod 1999; 14:2762.

18. Pritts, EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv 2001; 56:483.

19. Homer, HA, Li, TC, Cooke, LD. The septate uterus: A review of management and reproductive outcome. Fertil Steril 2000; 73:1.

20. Mahmood, TA, Templeton, A. Prevalence and genesis of endometriosis. Hum Reprod 1991; 6:544.

21. Peters, AJ, Lloyd, RP, Coulam, CB. Prevalence of out-of-phase endometrial biopsy speciments. Am J Obstet Gynecol 1992; 166:1738.

22. Soules, MR, McLachlan, RI, Ek, M, et al. Luteal phase deficiency: characterization of reproductive hormones over the menstrual cycle. J Clin Endocrinol Metab 1989; 69:804.

23. Davis, OK, Berkeley, AS, Naus, GJ, et al. The incidence of luteal phase defect in normal, fertile women, determined by serial endometrial biopsies. Fertil Steril 1989; 51:582.

24. Shoupe, D, Mishell, DR Jr, Lacarra, M, et al. Correlation of endometrial maturation with four methods of estimating day of ovulation. Obstet Gynecol 1989; 73:88.

25. Balasch, J, Fábregues, F, Creus, M. et al. The usefulness of endometrial biopsy for luteal phase evaluation in infertility. Hum Reprod 1992; 7:973.

26. Coutifaris, C, Myers, ER, Guzick, DS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertil Steril 2004; 82:1264.

27. Clementini, E, Palka, C, Iezzi, I, et al. Prevalence of chromosomal abnormalities in 2078 infertile couples referred for assisted reproductive techniques. Hum Reprod 2005; 20:437.

28. Christensen, RB, Matsumoto, AM, Bremmer, WJ. Idiopathic hypogonadotropic hypogonadism with anosmia (Kallmann syndrome). Endocrinologist 1992; 2:332.

29. de Roux, N, Young, J, Misrahi, M, et al. A family with hypogonadotropic hypogonadism and mutations in the gonadotropin-releasing hormone receptor. N Engl J Med 1997; 337:1597.

30. Layman, LC, Cohen, DP, Jin, M, et al. Mutations in gonadotropin-releasing hormone receptor gene cause hypogonadotropic hypogonadism. Nat Genet 1998; 18:14.

31. Aittomaki, K, Lucena, JL, Pakarinen, P, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell 1995; 82:959.

32. Phillip, M, Arbelle, JE, Segev, Y, Parvari, R. Male hypogonadism due to a mutation in the gene for the beta-subunit of follicle-stimulating hormone. N Engl J Med 1998; 338:1729.

33. Toledo, SP, Brunner, HG, Kraaij, R, et al. An inactivating mutation of the luteinizing hormone receptor causes amenorrhea in a 46,XX female. J Clin Endocrinol Metab 1996; 81:3850.

34. Schwartz, CE, Dean, J, Howard-Peebles, PN, et al. Obstetrical and gynecological complications in fragile X carriers: a multicenter study. Am J Med Genet 1994; 51:400.

35. Achermann, JC, Meeks, JJ, Jameson, JL. Phenotypic spectrum of mutations in DAX-1 and SF-1. Mol Cell Endocrinol 2001; 185:17.

36. Montague, CT, Farooqi, IS, Whitehead, JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997; 387:903.

37. Clement, K, Vaisse, C, Lahlou, N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998; 392:398.

38. de Roux, N, Genin, E, Carel, JC, et al. Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide receptor GPR54. Proc Natl Acad Sci U S A 2003; 100:10972.

39. Seminara, SB, Messager, S, Chatzidaki, EE, et al. The GPR54 gene as a regulator of puberty. N Engl J Med 2003; 349:1614.

40. Dode, C, Levilliers, J, Dupont, JM, et al. Loss-of-function mutations in FGFR1 cause autosomal dominant Kallmann syndrome. Nat Genet 2003; 33:463.

41. Hull, MG, Williams, JA, Ray, B, et al. The contribution of subtle oocyte or sperm dysfunction affecting fertilization in endometriosis-associated or unexplained infertility: a controlled comparison with tubal infertility and use of donor spermatozoa. Hum Reprod 1998; 13:1825.

42. Schwartz, D, Mayaux, MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS. N Engl J Med 1982; 306:404.

43. Brosens, I, Gordts, S, Valkenburg, M, et al. Investigation of the infertile couple: when is the appropriate time to explore female infertility?. Hum Reprod 2004; 19:1689.

44. World Health Organization. WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction, 4th ed, Cambridge, England, Cambridge University Press, 1999.

45. Guzick, DS, Overstreet, JW, Factor-Litvak, P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001; 345:1388.

46. Kruger, TF, Menkveld, R, Stander, FS, et al. Sperm morphologic features as a prognostic factor in in vitro fertilization. Fertil Steril 1986; 46:1118.

47. Kruger, TF, Acosta, AA, Simmons, KF, et al. Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril 1988; 49:112.

48. Danforth, DR, Arbogast, LK, Mroueh, J, et al. Dimeric inhibin: a direct marker of ovarian aging. Fertil Steril 1998; 70:119.

49. Seifer, DB, Lambert-Messerlian, G, Hogan, JW, et al. Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. Fertil Steril 1997; 67:110.

50. Corson, SL, Gutmann, J, Batzer, FR, et al. Inhibin-B as a test of ovarian reserve for infertile women. Hum Reprod 1999; 14:2818.

51. Hall, JE, Welt, CK, Cramer, DW. Inhibin A and inhibin B reflect ovarian function in assisted reproduction but are less useful at predicting outcome. Hum Reprod 1999; 14:409.

52. Erdem, M, Erdem, A, Gursoy, R, Biberoglu, K. Comparison of basal and clomiphene citrate induced FSH and inhibin B, ovarian volume and antral follicle counts as ovarian reserve tests

and predictors of poor ovarian response in IVF. J Assist Reprod Genet 2004; 21:37.

53. Chang, MY, Chiang, CH, Hsieh, TT, et al. Use of the antral follicle count to predict the outcome of assisted reproductive technologies. Fertil Steril 1998; 69:505.

54. Tomas, C, Nuojua-Huttunen, S, Martikainen, H. Pretreatment transvaginal ultrasound examination predicts ovarian responsiveness to gonadotrophins in in-vitro fertilization. Hum Reprod 1997; 12:220.

55. Jain, T, Soules, MR, Collins, JA. Comparison of basal follicle-stimulating hormone versus the clomiphene citrate challenge test for ovarian reserve screening. Fertil Steril 2004; 82:180.

56. Licciardi, FL, Liu, HC, Rosenwaks, Z. Day 3 estradiol serum concentrations as prognosticators of ovarian stimulation response and pregnancy outcome in patients undergoing in vitro fertilization. Fertil Steril 1995; 64:991.

57. Bancsi, LF, Broekmans, FJ, Mol, BW, et al. Performance of basal follicle-stimulating hormone in the prediction of poor ovarian response and failure to become pregnant after in vitro fertilization: a meta-analysis. Fertil Steril 2003; 79:1091.

58. Swart, P, Mol, BW, van der, Veen F, et al. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril 1995; 64:486.

59. Papaioannou, S, Bourdrez, P, Varma, R, et al. Tubal evaluation in the investigation of subfertility: a structured comparison of tests. BJOG 2004; 111:1313.

60. Johnson, NP, Farquhar, CM, Hadden, WE, et al. The FLUSH trial--flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. Hum Reprod 2004; 19:2043.

61. Lindequist, S, Justesen, P, Larsen, C, Rasmussen, F. Diagnostic quality and complications of hysterosalpingography: oil- versus water-soluble contrast media--a randomized prospective study. Radiology 1991; 179:69.

62. Thomas, K, Coughlin, L, Mannion, PT, Haddad, NG. The value of Chlamydia trachomatis antibody testing as part of routine infertility investigations. Hum Reprod 2000; 15:1079.

63. Dabekausen, YA, Evers, JL, Land, JA, Stals, FS. Chlamydia trachomatis antibody testing is more accurate than hysterosalpingography in predicting tubal factor infertility. Fertil Steril 1994; 61:833.

64. Hubacher, D, Lara-Ricalde, R, Taylor, DJ, Guerra-Infante, F, Guzman-Rodriguez, R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. N Engl J Med 2001; 345:561.

65. Fiddelers, AA, Land, JA, Voss, G, et al. Cost-effectiveness of Chlamydia antibody tests in subfertile women. Hum Reprod 2005; 20:425.

66. Balasch, J. Investigation of the infertile couple: investigation of the infertile couple in the era of assisted reproductive technology: a time for reappraisal. Hum Reprod 2000; 15:2251.

67. Smith, S, Pfeifer, SM, Collins, JA. Diagnosis and management of female infertility. JAMA 2003; 290:1767.

68. Marcoux, S, Maheux, R, Berube, S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 1997; 337:217.

69. Parazzini, F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Hum Reprod 1999; 14:1332.

70. Tanahatoe, SJ, Hompes, PG, Lambalk, CB. Investigation of the infertile couple: should diagnostic laparoscopy be performed in the infertility work up programme in patients undergoing intrauterine insemination?. Hum Reprod 2003; 18:8.

71. Griffith, CS, Grimes, DA. The validity of the postcoital test. Am J Obstet Gynecol 1990; 162:615.

72. Collins, JA, So, Y, Wilson, EH, et al. The postcoital test as a predictor of pregnancy among 355 infertile couples. Fertil Steril 1984; 41:703.

73. Glatstein, IZ, Best, CL, Palumbo, A, et al. The reproducibility of the postcoital test: a prospective study. Obstet Gynecol 1995; 85:396.

74. Oei, SG, Helmerhorst, FM, Keirse, MJ. When is the post-coital test normal? A critical

appraisal. Hum Reprod 1995; 10:1711.

75. Oei, SG, Helmerhorst, FM, Bloemenkamp, KW, et al. Effectiveness of the postcoital test: randomised controlled trial. BMJ 1998; 317:502.

76. Edwards, RG. Physiological and molecular aspects of human implantation. Hum Reprod 1995; 10 Suppl 2:1.

77. Creus, M, Balasch, J, Ordi, J, et al. Integrin expression in normal and out-of-phase endometria. Hum Reprod 1998; 13:3460.

78. Giudice, LC. Potential biochemical markers of uterine receptivity. Hum Reprod 1999; 14 Suppl 2:3.

79. Murray, MJ, Meyer, WR, Zaino, RJ, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril 2004; 81:1333.

80. Bauman, JE. Basal body temperature: unreliable method of ovulation detection. Fertil Steril 1981; 36:729.

81. Kambic, R, Gray, RH. Interobserver variation in estimation of day of conception intercourse using selected natural family planning charts. Fertil Steril 1989; 51:430.

82. Shibahara, H, Mitsuo, M, Inoue, M, et al. Relationship between human in-vitro fertilization and intracytoplasmic sperm injection and the zona-free hamster egg penetration test. Hum Reprod 1998; 13:1928.

83. Zainul Rashid, MR, Fishel, SB, Thornton, S, et al. The predictive value of the zona-free hamster egg penetration test in relation to in-vitro fertilization at various insemination concentrations. Hum Reprod 1998; 13:624.

84. Gump, DW, Gibson, M, Ashikaga, T. Lack of association between genital mycoplasmas and infertility. N Engl J Med 1984; 310:937.

85. Kallen, CB, Arici, A. Immune testing in fertility practice: truth or deception?. Curr Opin Obstet Gynecol 2003; 15:225.

GRAPHICS

The Fecundability in a Cohort of Healthy Couples Attempting to Conceive†

Cycle	Number of women (or couples) trying to conceive at start of each cycle	Number of pregnancies in study cycle	Per cycle pregnancy rate
1	200	59	0.30
2	137	41	0.30
3	95	16	0.17
4	78	12	0.15
5	66	14	0.21
6	52	4	0.08
7	48	5	0.10
8	43	3	0.07
9	40	2	0.05
10	38	1	0.03
11	37	2	0.05
12	35	1	0.03

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Causes of Anovulation and Oligoovulation

Age-related
Immature hypothalamic-pituitary-ovarian axis at the onset of menarche
Decline in ovarian function during menopause

Systemic illness and neoplasms
Hypothyroidism and hyperthyroidism
Chronic liver and renal disease
Cushing's disease
Polycystic ovary syndrome
Prolactinoma
Empty sella syndrome
Sheehan's syndrome
Adrenal and ovarian tumors
Tumors infiltrating the hypothalamus

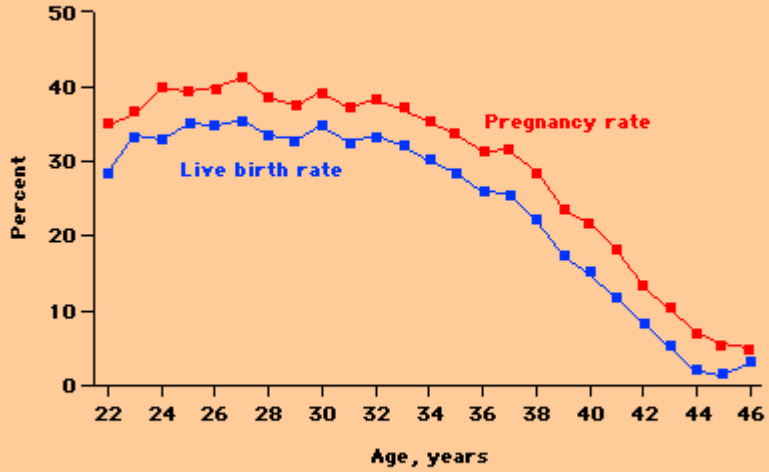
Medications
Oral contraceptives
Progestins
Antipsychotic drugs
Corticosteroids
Chemotherapeutic agents

Other
Sudden weight loss
Stress
Intense exercise

History Taking in Infertile Couples

Male	Female
Duration of infertility	Duration of infertility
Fertility in other relationships	Prior pregnancies, fertility in other relationships
Medical and surgical history, including testicular surgery and history of mumps	Gynecologic history, including history of pelvic inflammatory disease, fibroids, endometriosis, cervical dysplasia, surgery of the cervix, pelvis, or abdomen, intrauterine device use, other prior contraceptive use, diethylstilbestrol exposure in utero
	Menstrual history (age at menarche, cycle length, and regularity) and presence of vasomotor symptoms (hot flashes)
	Changes in hair growth, body weight, or breast discharge
	Other medical and surgical history
History of chemotherapy or radiation	History of chemotherapy or radiation
Cigarette smoking, alcohol, marijuana and other drug use; environmental and occupational exposures	Cigarette smoking, alcohol, marijuana and other drug use; environmental and occupational exposures
Sexual dysfunction or impotence	Exercise and dietary history
Frequency of intercourse, use of lubricants	Frequency of intercourse, use of lubricants
Previous infertility testing and therapies	Previous infertility testing and therapies

Pregnancy and Live Birth Rates for Assisted Reproductive Technology (ART) Cycles Using Fresh, Non-Donor Eggs or Embryos, by Age Of Woman, 2000†



† Data from: 2000 ART Success Rates, at http://www.cdc.gov/reproductivehealth/ART00/sect2_fig3-13.htm#Figure%2010