

Diagnostic evaluation of the infertile female: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Diagnostic evaluation for infertility in women should be conducted in a systematic, expeditious, and cost-effective manner to identify all relevant factors with initial emphasis on the least invasive methods for detection of the most common causes of infertility. The purpose of this Committee Opinion is to provide a critical review of the current methods and procedures for the evaluation of the infertile female, and it replaces the 2006 ASRM Practice Committee document titled "Optimal evaluation of the infertile female." (Fertil Steril® 2012;98:302-7. ©2012 by American Society for Reproductive Medicine.)

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A diagnostic evaluation for infertility is indicated for women who fail to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse (1). Since approximately 85% of couples may be expected to achieve pregnancy within that interval without medical assistance, evaluation may be indicated for as many as 15% of couples. Earlier evaluation is warranted after six months of unsuccessful efforts to conceive in women over age 35 years and also may be justified based on medical history and physical findings, including, but not limited to, the following (2-4):

- History of oligo- or amenorrhea
- Known or suspected uterine/tubal/peritoneal disease or stage III-IV endometriosis
- Known or suspected male subfertility

Where applicable, evaluation of both partners should begin at the same time. Methods for the evaluation of the male partner are described in a separate

document (5). Women who are planning to attempt pregnancy via insemination with sperm from a known or anonymous donor may also merit evaluation before such treatment begins.

HISTORY AND PHYSICAL EXAMINATION

Ideally, the initial consultation should be scheduled to allow sufficient time to obtain a comprehensive medical, reproductive, and family history and to perform a thorough physical examination. This is also an opportune time to counsel patients regarding preconception care and screening for relevant genetic conditions.

Relevant history includes the following:

- Duration of infertility and results of any previous evaluation and treatment
- Menstrual history (age at menarche, cycle length and characteristics,

presence of molimina, and onset/severity of dysmenorrhea)

- Pregnancy history (gravidity, parity, pregnancy outcome, and associated complications)
- Previous methods of contraception
- Coital frequency and sexual dysfunction
- Past surgery (procedures, indications, and outcomes), previous hospitalizations, serious illnesses or injuries, pelvic inflammatory disease, or exposure to sexually transmitted infections
- Thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, and dyspareunia
- Previous abnormal pap smears and any subsequent treatment
- Current medications and allergies
- Family history of birth defects, mental retardation, early menopause, or reproductive failure or compromise
- Occupation and exposure to known environmental hazards
- Use of tobacco, alcohol, and recreational or illicit drugs

Physical examination should document the following:

- Weight, body mass index (BMI), blood pressure, and pulse
- Thyroid enlargement and presence of any nodules or tenderness

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- Breast secretions and their character
- Signs of androgen excess
- Vaginal or cervical abnormality, secretions, or discharge
- Pelvic or abdominal tenderness, organ enlargement, or masses
- Uterine size, shape, position, and mobility
- Adnexal masses or tenderness
- Cul-de-sac masses, tenderness, or nodularity

DIAGNOSTIC EVALUATION

Subsequent evaluation should be conducted in a systematic, expeditious, and cost-effective manner so as to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility. The pace and extent of evaluation should take into account the couple's preferences, patient age, the duration of infertility, and unique features of the medical history and physical examination.

OVULATORY FUNCTION

Ovulatory dysfunction will be identified in approximately 15% of all infertile couples and accounts for up to 40% of infertility in women (6). It commonly results in obvious menstrual disturbances (oligo/amenorrhea), but can be more subtle. The underlying cause should be sought because specific treatment may be indicated and some conditions may have other health implications and consequences. The most common causes of ovulatory dysfunction include polycystic ovary syndrome, obesity, weight gain or loss, strenuous exercise, thyroid dysfunction, and hyperprolactinemia. However, the specific cause of ovulatory dysfunction often remains obscure. Methods for evaluating ovulatory function may include any of the following:

Menstrual history may be all that is required. In most ovulatory women, menstrual cycles are regular and predictable, occurring at intervals of 25–35 days, exhibiting consistent flow characteristics, and accompanied by a consistent pattern of minimal symptoms. Some degree of variation is entirely normal; in a study of more than 1,000 cycles, variations in inter-menstrual interval exceeding 5 days were observed in 56% of patients within six months and in 75% of those followed for one year (7). Although a history of regular and consistent menses strongly suggests normal ovulatory function, an objective measure is warranted in infertile women. Patients with abnormal uterine bleeding, oligomenorrhea, or amenorrhea generally do not require specific diagnostic tests to establish a diagnosis of anovulation.

Serial basal body temperature (BBT) measurements provide a simple and inexpensive method for evaluating ovulatory function. In cycles monitored with BBT, the period of highest fertility spans the seven days prior to the mid-cycle rise in BBT. Whereas ovulatory cycles generally are associated with clearly biphasic BBT recordings and anovulatory cycles typically result in monophasic patterns, some ovulatory women cannot document clearly biphasic BBT patterns (8). Grossly short luteal phases (<10 days of temperature elevation) may identify women with more subtle ovulatory dysfunction. The test cannot reliably define the time of

ovulation and can become tedious. Consequently, BBT is no longer considered the best or preferred method for evaluating ovulatory function for most infertile women.

Serum progesterone determinations provide a reliable and objective measure of ovulatory function as long as they are obtained at the appropriate time in the cycle. Given the range of normal variation in ovulatory cycles, a serum progesterone measurement generally should be obtained approximately one week before the expected onset of the next menses, rather than on any one specific cycle day (e.g., cycle day 21). A progesterone concentration greater than 3 ng/mL provides presumptive but reliable evidence of recent ovulation (9). Although higher threshold values have been used commonly as a measure of the quality of luteal function (e.g., ≥ 10 ng/mL) (10), the criterion is not reliable because corpus luteum progesterone secretion is pulsatile and serum concentrations may vary up to 7-fold within an interval of a few hours (11).

Urinary luteinizing hormone (LH) determinations using various commercial "ovulation predictor kits" can identify the midcycle LH surge that precedes ovulation by one to two days. Urinary LH detection provides indirect evidence of ovulation and helps to define the interval of greatest fertility: the day of the LH surge and the following two days (12). Results generally correlate well with the peak in serum LH, particularly when the test is performed on midday or evening urine specimens (8). However, accuracy, ease of use, and reliability vary among products, and testing may yield false positive and false negative results (13).

Endometrial biopsy (EBM) and histology can demonstrate secretory endometrial development, which results from the action of progesterone and thus implies ovulation. "Dating" the endometrium using traditional histologic criteria (14) was long considered the "gold standard" among methods for evaluating the quality of luteal function and for diagnosis of luteal phase deficiency (LPD). However, careful studies have since demonstrated clearly that histologic endometrial dating is not a valid diagnostic method because it lacks both accuracy and precision (15) and because the test cannot distinguish fertile from infertile women (16). Therefore, endometrial biopsy is no longer recommended for the evaluation of ovulatory or luteal function in infertile women and should be limited to those in whom specific endometrial pathology (e.g., neoplasia, chronic endometritis) is strongly suspected.

Transvaginal ultrasonography can reveal the size and number of developing follicles and also provide presumptive evidence of ovulation and luteinization by demonstrating progressive follicular growth, sudden collapse of the preovulatory follicle, a loss of clearly defined follicular margins, the appearance of internal echoes, and an increase in cul-de-sac fluid volume (17). Because of the associated cost and logistical demands, the method generally should be reserved for women in whom simpler methods fail to provide the necessary information and those receiving ovarian stimulation for purposes of ovulation induction.

Other evaluations aimed at defining the best choice of treatment may be indicated for anovulatory infertile women. Serum thyroid-stimulating hormone (TSH) and prolactin

determinations can identify thyroid disorders and/or hyperprolactinemia, which may require specific treatment. In women with amenorrhea, serum follicle-stimulating hormone (FSH) and estradiol measurements can distinguish women with ovarian failure (high FSH, low estradiol), who may be candidates for oocyte donation, from those with hypothalamic amenorrhea (low or normal FSH, low estradiol), who will require exogenous gonadotropin stimulation for ovulation induction.

In anovulatory infertile women, failure to achieve pregnancy after three to six cycles of successful ovulation induction should be viewed as an indication to perform additional diagnostic evaluation or, if evaluation is complete, to consider alternative treatments.

OVARIAN RESERVE

The concept of “ovarian reserve” views reproductive potential as a function of the number and quality of remaining oocytes. Decreased or diminished ovarian reserve (DOR) describes women of reproductive age having regular menses whose response to ovarian stimulation or fecundity is reduced compared to those women of comparable age. Tests utilized to assess “ovarian reserve” include cycle day 3 FSH and estradiol measurements, a clomiphene citrate challenge test, an early follicular phase antral follicle count (via transvaginal ultrasonography), or a serum antimüllerian hormone (AMH) level. These tests may provide prognostic information in women at increased risk of diminished ovarian reserve, such as women who: 1) are over age 35 years; 2) have a family history of early menopause; 3) have a single ovary or history of previous ovarian surgery, chemotherapy, or pelvic radiation therapy; 4) have unexplained infertility (18); 5) have demonstrated poor response to gonadotropin stimulation; or 6) are planning treatment with assisted reproductive technology (ART) (18). Measures of ovarian reserve do not establish a diagnosis of diminished ovarian reserve, but instead help to predict response to ovarian stimulation with exogenous gonadotropins and, to a lesser extent, the likelihood for achieving a successful pregnancy with ART (19). However, poor results with any of the tests do not necessarily imply inability to conceive.

Cycle Day 3 FSH and Estradiol

FSH obtained on cycle day 2–5 is commonly used as a measure of ovarian reserve. High values (10–20 IU/L) have been associated with both poor ovarian stimulation and the failure to conceive (19). Assays standardized against the World Health Organization (WHO) 2nd International Standard demonstrate high specificity (83%–100% range) for predicting poor response to stimulation (usually defined as <2–3 follicles or ≤4 retrieved oocytes) (19). However, sensitivity for identifying women who will respond poorly varies widely (10%–80%) (19). Basal estradiol alone should not be used to screen for DOR. The test has value only as an aid to correct interpretation of a “normal” basal serum FSH value. When the basal FSH concentration is “normal” but the estradiol level is elevated (>60–80 pg/mL) in the early follicular phase, there is limited evidence for an association with poor response, increased cancellation rates, and lower pregnancy rates (20–22).

Clomiphene Citrate Challenge Test

The CCCT involves measurements of serum FSH before and after treatment with clomiphene citrate (100 mg daily, cycle days 5–9), typically on cycle day 3 and cycle day 10. An elevated FSH concentration after clomiphene stimulation therefore suggests DOR. Cycle day 10 FSH levels have a higher sensitivity but lower specificity compared to cycle day 3 FSH concentrations (23).

Antral Follicle Count

Antral follicle count (AFC) is the sum of antral follicles in both ovaries, as observed with transvaginal ultrasonography during the early follicular phase. Antral follicles have been defined as measuring 2–10 mm or 3–8 mm in mean diameter in the greatest 2-dimensional plane. A low AFC (range 3–10 total antral follicles) has been associated with poor response to ovarian stimulation and with the failure to achieve pregnancy (24).

Serum Antimüllerian Hormone (AMH) Level

Serum concentrations of AMH, produced by granulosa cells of early follicles, are gonadotropin-independent and therefore remain relatively consistent within and between menstrual cycles in both normal young ovulating women and in women with infertility (25–28). Therefore an AMH level can be obtained on any day of the menstrual cycle. Overall, lower AMH levels (<1 ng/mL) have been associated with poor responses to ovarian stimulation, poor embryo quality, and poor pregnancy outcomes in IVF (29–33).

CERVICAL FACTORS

Abnormalities of cervical mucus production or sperm/mucus interaction rarely are the sole or principal cause of infertility. Examination of cervical mucus may reveal gross evidence of chronic cervicitis that warrants treatment. The postcoital test (PCT), in which a specimen of cervical mucus obtained shortly before expected ovulation is examined microscopically for the presence of motile sperm within hours after intercourse, was the traditional method for diagnosis of cervical factor infertility. However, because the test is subjective, has poor reproducibility, is inconvenient to the patient, rarely changes clinical management, and does not predict inability to conceive, the PCT is no longer recommended for the evaluation of the infertile female (34, 35).

UTERINE ABNORMALITIES

Abnormalities of uterine anatomy or function are relatively uncommon causes of infertility in women, but should be excluded. Methods for evaluation of the uterus include the following:

Hysterosalpingography (HSG) defines the size and shape of the uterine cavity and can reveal developmental anomalies (unicornuate, septate, bicornuate uteri) or other acquired abnormalities (endometrial polyps, submucous myomas, synechiae) having potential reproductive consequences. However, HSG has relatively low sensitivity (50%) and

positive predictive value (PPV; 30%) for diagnosis of endometrial polyps and submucous myomas in asymptomatic infertile women (36).

Ultrasonography (US) can be used to diagnose uterine pathology, including myomas (37).

Sonohysterography, involving transvaginal ultrasonography after introduction of saline into the uterine cavity, better defines the size and shape of the uterine cavity and has high PPV (>90%) and negative predictive value (NPV) for detection of intrauterine pathology (endometrial polyps, submucous myomas, synechiae) (36, 38, 39).

Hysteroscopy is the definitive method for the diagnosis and treatment of intrauterine pathology. As it is also the most costly and invasive method for evaluating the uterus, it generally can be reserved for further evaluation and treatment of abnormalities defined by less invasive methods such as HSG and sonohysterography (40).

TUBAL PATENCY

Tubal disease is an important cause of infertility and should be specifically excluded. The methods for evaluating tubal patency are complementary and not mutually exclusive (41). Accurate diagnosis and effective treatment of tubal obstruction often requires more than one of the following techniques:

Hysterosalpingography (HSG), using either a water- or lipid-soluble contrast media, is the traditional and standard method for evaluating tubal patency and may offer some therapeutic benefit. HSG can document proximal and distal tubal occlusion, demonstrate salpingitis isthmica nodosa, reveal tubal architectural detail of potential prognostic value, and may suggest the presence of fimbrial phimosis or peritubal adhesions when escape of contrast is delayed or becomes loculated, respectively. The PPV and NPV of HSG are 38% and 94%, respectively (42). Findings suggesting proximal tubal obstruction require further evaluation to exclude artifacts resulting from transient tubal/myometrial contractions or relating to catheter position.

Saline infusion sonography (SIS) is a test to determine tubal patency using fluid and ultrasound. Although tubal patency can be observed by the appearance of fluid in the cul de sac with the saline infusion, the test does not differentiate between unilateral or bilateral patency.

Laparoscopy and chromotubation with a dilute solution of methylene blue or indigo carmine (preferred) introduced via the cervix can demonstrate tubal patency or document proximal or distal tubal obstruction. The procedure also can identify and correct tubal factors such as fimbrial phimosis or peritubal adhesions, which may not be identified with less invasive methods such as HSG.

Fluoroscopic/hysteroscopic selective tubal cannulation will confirm or exclude any proximal tubal occlusion suggested by HSG or laparoscopy with chromotubation and provides the means for possible correction via recanalization using specialized catheter systems (43).

Chlamydia Antibody Test (CAT)

The detection of antibodies to *Chlamydia trachomatis* has been associated with tubal pathology; however, this test has

limited clinical utility. Compared to laparoscopy, the CAT has modest sensitivity (40%–50%) and PPV (60%), but high NPV (80–90%) for detection of distal tubal disease (44, 45).

PERITONEAL FACTORS

Peritoneal factors such as endometriosis and pelvic or adnexal adhesions may cause or contribute to infertility. History and/or physical examination findings may raise suspicion but rarely are sufficient for diagnosis. Peritoneal factors also should be considered in women with otherwise unexplained infertility.

Transvaginal ultrasonography can reveal otherwise unrecognized pelvic pathology that may have reproductive implications, such as an endometrioma (46).

Laparoscopy with direct visual examination of the pelvic reproductive anatomy is the only method available for specific diagnosis of peritoneal factors that may impair fertility. However, the impact of minimal and mild endometriosis on fertility is relatively small (47, 48), and most women with significant adnexal adhesions have historical risk factors (pelvic pain, moderate or severe endometriosis, previous pelvic infection or surgery) or an abnormal HSG. Consequently, laparoscopy is most clearly indicated for those with symptoms or risk factors or an abnormal HSG or ultrasonography who have no other clear indications for ART (e.g., severe male factor infertility); its yield in asymptomatic women with normal imaging is low. Given individual circumstances, there may be a place for diagnostic laparoscopy for young women with a long period (>3 years) of infertility but no recognized abnormalities.

SUMMARY

- Evaluation of ovulatory function should be an initial diagnostic step in the evaluation of all infertile women. When the menstrual history is grossly abnormal, no additional evaluation is required to establish a diagnosis of anovulation. Otherwise, an objective measure of ovulatory function is warranted. If appropriately timed, a serum progesterone concentration greater than 3 ng/mL provides reliable objective evidence for recent ovulation.
- In anovulatory infertile women, failure to achieve pregnancy after three to six cycles of successful ovulation induction should be viewed as an indication to perform additional diagnostic evaluation or, if evaluation is complete, to consider alternative treatments.
- Ovarian reserve should be assessed in select women at increased risk of diminished ovarian reserve. Options include cycle day 3 FSH and estradiol, clomiphene citrate challenge test, US to assess antral follicle count, or serum AMH.
- Histologic endometrial dating is not a valid method for evaluation of luteal function or for diagnosis of luteal phase deficiency. Endometrial biopsy should be limited to those in whom specific endometrial pathology (e.g., hyperplasia/neoplasia, chronic endometritis) is strongly suspected.
- The postcoital test is not a valid method for evaluation of cervical factors and should not be included in the evaluation of the infertile female.

- Routine use of PCT and EMB has not been shown to be beneficial and are no longer recommended as part of the standard evaluation of the infertile female.
- Examination of the uterine cavity is an important part of the evaluation of infertile women and can be accomplished using hysterosalpingography, sonohysterography, or hysteroscopy.
- Evaluation of tubal patency is a key component of the diagnostic evaluation of infertile women. All methods for the evaluation of tubal patency have technical limitations that must be considered when interpreting test results. A second and different test should be considered when the diagnosis remains in doubt.
- Laparoscopy may be indicated when there is evidence or strong suspicion of advanced stages of endometriosis, tubal occlusive disease, or significant adnexal adhesions.

CONCLUSIONS

- A careful history and physical examination can identify a specific cause of infertility and help to focus the diagnostic evaluation on the most likely cause(s).

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