Diagnostic evaluation of the infertile female: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

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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 document of the same name, last published in 2012 (Fertil Steril 2012;98:302–7).
(Fertil Steril® 2015;103:e44–50. ©2015 by American Society for Reproductive Medicine.)
Key Words: Infertility, oocyte, ovarian reserve, unexplained, conception

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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 time interval without medical assistance, evaluation may be indicated for as many as 15% of couples. Earlier evaluation is warranted after 6 months of unsuccessful efforts to conceive in women over age 35 years due to the observed age related decline in fertility as a woman approaches age 40, and also may be justified based on medical history and physical findings, including, but not limited to, the following (2–5):

- History of oligomenorrhea 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 should include 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, developmental delay, early menopause, or reproductive problems
- 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
- Breast characteristics and evaluation for secretions

Received March 13, 2015; accepted March 16, 2015; published online April 30, 2015.
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Fertility and Sterility® Vol. 103, No. 6, June 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.03.019

- 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 (oligomenorrhea/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 (PCOS), 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, generally occurring at intervals of 21–35 days, exhibiting consistent flow characteristics, and accompanied by a consistent pattern of moliminal symptoms (7). 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 6 months and in 75% of those followed for 1 year (8). The expected range of menstrual cycle length also varies according to age with the minimum degree of individual variation occurring at age 36 years (9). Patients with abnormal uterine bleeding, oligomenorrhea, or amenorrhea generally do not require specific diagnostic tests to establish 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 7 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 (10). Grossly short luteal phases (<10 days of temperature elevation) may identify women with more subtle ovulatory dysfunction. The BBT test cannot reliably define the time of ovulation and can become tedious. Consequently, this assessment 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 1 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 (11). Although higher threshold values at the mid-luteal phase have been used commonly as a measure of the quality of luteal function (e.g., greater than 10 ng/mL) (12), 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 (13).

Urinary luteinizing hormone (LH) determinations using various commercial "ovulation predictor kits" can identify the mid-cycle LH surge that precedes ovulation by 1 to 2 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 day (14). 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 (15).

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 (16) 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 (17) and because the test cannot distinguish fertile from infertile women (18). 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 within the corpus luteum, and an increase in cul-de-sac fluid volume (19). Because of the associated cost and logistical demands, this method generally should be reserved for women in whom simpler methods fail to provide the necessary information.

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 3 to 6 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" describes reproductive potential as a function of the number and quality of oocytes (20). Decreased or diminished ovarian reserve (DOR) describes women of reproductive age having regular menses whose response to ovarian stimulation or fecundity is reduced compared with those women of comparable age. Tests utilized to assess 'ovarian reserve' include cycle-day 3 serum FSH and estradiol measurements, the clomiphene citrate challenge test (CCCT), early follicular phase antral follicle count (AFC) (via transvaginal ultrasonography), and serum antimüllerian hormone (AMH) concentrations. These tests may provide prognostic information in women at increased risk of DOR, 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 (21); 5) have demonstrated poor response to gonadotropin stimulation; or 6) are planning treatment with assisted reproductive technology (ART) (21). Measures of ovarian reserve do not establish a diagnosis of DOR, 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 (22). However, poor results with any of the tests do not necessarily imply inability to conceive.

Cycle-Day 3 Serum FSH and E_2

A serum FSH level obtained on cycle-day 2–4 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 (22). Assays standardized against the World Health Organization (WHO) 2nd International Standard demonstrate high specificity of an elevated FSH (83%–100% range) for predicting poor response to stimulation (usually defined as <2–3 follicles or 4 retrieved oocytes) (22). However, sensitivity for identifying women who will respond poorly varies widely (10%–80%) (22). While cycle–to-cycle variation in FSH values has been noted and can be significant, peak FSH values possess the greatest predictive value for in vitro fertilization (IVF) treatment outcome (23). Basal serum estradiol alone should not be used to screen for DOR. The basal serum estradiol test has value only as an aid to interpret a "normal" basal serum FSH value. When the basal serum FSH concentration is "normal" but the serum estradiol level is elevated (>60–80 pg/mL) in the early follicular phase, there is limited evidence for an association with poor response to gonadotropin stimulation, increased IVF cancellation rates, and lower pregnancy rates (24–26).

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 serum FSH levels have a higher sensitivity but lower specificity compared with cycle-day 3 serum FSH concentrations (27). Contemporary use of CCCT has declined as newer tests such as serum AMH and AFC are simpler and highly predictive of ovarian response.

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 in mean diameter in the greatest two-dimensional plane. A low AFC is considered to be 3–6 total antral follicles (mean of 5.2 with SD 2.11) and is associated with poor response to ovarian stimulation during IVF, but does not reliably predict failure to conceive (28). AFC has shown to be significantly lower in infertile compared with fertile women up to age 40 (29). While AFC has good inter-cycle reliability and inter-observer reliability in experienced centers, reproducibility may be limited in less experienced clinics (30–35). In addition, data suggest that AFC is increased in women with PCOS (36) and decreased by exogenous hormones such as oral contraceptives (37).

Serum 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 (38–41). Therefore an AMH level can be obtained on any day of the menstrual cycle. In contrast to original reports, recent evidence suggests that AMH levels may be diminished in the setting of exogenous hormone use (i.e. oral contraceptive pills, gonadotropin-releasing hormone [GnRH] agonist), obesity, and hypogonadotropic hypogonadism (42–45). Conversely, AMH levels are 2–3 fold higher in women with PCOS compared with unaffected women (46, 47). Overall, lower serum AMH levels (<1 ng/mL) have been associated with poor responses to ovarian stimulation, poor embryo quality, and poor pregnancy outcomes in IVF (48–52).

CERVICAL FACTORS

Abnormalities of cervical-mucus production or sperm-mucous 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. At present, the PCT may be considered as an approach to evaluate the presence of sperm in the cervical mucus in couples for whom a formal semen analysis is not accessible or feasible. 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 routine evaluation of the infertile female (53, 54).

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:

Ultrasonography (US) and other imaging modalities such as three-dimensional (3-D) ultrasound and magnetic resonance imaging (MRI) may be used to diagnose uterine pathology, including leiomyomas and congenital malformations as well as ovarian pathology.

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 (55). Because HSG cannot reliably differentiate a septate from a bicornuate uterus, further evaluation with pelvic MRI or 3D ultrasonography may be necessary.

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) (55–57). Both 3D ultrasound and pelvic MRI may also be used to assess the uterus, most often to further characterize findings of an initial study such as a pelvic ultrasound or HSG.

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 (58).

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 (59). 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 (60). 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 (61).

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 with laparoscopy, the CAT has modest sensitivity (40%–50%) and PPV (60%), but high NPV (80%–90%) for detection of distal tubal disease (62, 63).

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 (64).

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 (65, 66), 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 individuals with symptoms or risk factors for

peritoneal disease, or an abnormal HSG or ultrasonography who do not require ART (e.g., severe male factor infertility); its yield in asymptomatic women with normal imaging is low. Laparoscopy is not recommended for the routine evaluation of an infertile woman without pelvic pathology or another specific indication (i.e. severe dysmenorrhea). Given individual circumstances, there may be a place for diagnostic laparoscopy for young women with a long duration (>3 years) of infertility but no recognized abnormalities.

SUMMARY

- A comprehensive medical, reproductive, and family history combined with a thorough physical examination can reveal anatomic and physiologic causes of infertility.
- Infertility can involve both female and male partners.
- Fertility declines as a woman approaches age 40.
- Ovulatory status, structure, and patency of the female reproductive tract, and male semen parameters all affect fertility.
- While measures of ovarian reserve do not establish a diagnosis of diminished ovarian reserve, they may predict ovarian response to stimulation with exogenous gonadotropins.
- HSG has been the standard test for tubal patency. Laparoscopy is useful for the diagnosis of peritoneal factors or tubal patency.
- Postcoital testing and endometrial biopsy are not predictive of reproductive potential.

CONCLUSIONS

- Diagnostic evaluation for infertility should include a comprehensive history and physical exam.
- Diagnostic evaluation of the infertile female should be accompanied by evaluation of the male partner.
- Women under the age of 35 years should seek infertility evaluation if they have not conceived after 1 year of unprotected intercourse. Women over age 35 years should seek infertility evaluation if they have not conceived after 6 months of unprotected intercourse.
- A woman should seek a diagnostic evaluation for infertility immediately if she has a medical history significant for oligomenorrhea, amenorrhea, advanced stage endometriosis, or any other condition that could limit fertility.
- Diagnostic evaluation for infertility should include assessment of ovulatory function, structure, and patency of the female reproductive tract, and semen analysis.
- Ovarian reserve testing should not be performed routinely, but may be used in select women undergoing ovarian stimulation with exogenous gonadotropins.
- Routine laparoscopy should not be performed in the evaluation of the infertile female but may be warranted when there is a strong suspicion of advanced stage endometriosis, tubal occlusive disease, or peritoneal factors.
- Postcoital testing and endometrial biopsy should not be performed as part of the routine diagnostic evaluation of the infertile female.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

The following members of the American Society for Reproductive Medicine Practice Committee participated in the development of this document. All Practice Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document. Samantha Pfeifer, M.D.; Samantha Butts, M.D.; Daniel Dumesic, M.D.; Gregory Fossum, M.D.; Clarisa Gracia, M.D.; Andrew La Barbera, Ph.D.; Randall Odem, M.D.; Margareta Pisarska, M.D.; Robert Rebar, M.D.; Richard Reindollar, M.D.; Mitchell Rosen, M.D.; Jay Sandlow, M.D.; Rebecca Sokol, M.D.; Michael Vernon, Ph.D.; and Eric Widra, M.D.

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