Female Fertility Assessment

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Abstract A fastidious fertility evaluation designed to discern all factors contributing to a couple's inability to conceive is the quintessential approach to a well-justified, cost-effective treatment plan. The purpose of this review is to outline the steps of female infertility evaluation as well as all evidence-based methods in a reproductive endocrinologist's armamentarium to perform it. Evaluation should always start with the least invasive approaches for detection of the most common causes of infertility. The most common identifiable causes of female infertility include ovulatory disorders, tubal blockade or other reproductive tract pathology (irregular cervical mucus production, endometriosis, pelvic adhesions), and/or other medical condition interacting with the above (hyperprolactinemia, thyroid disorder). Incessant advancement of Assisted Reproductive Technology techniques renders more and more infertility causes amenable to treatment; a rational use of available approaches in terms of both personalized feasibility and cost-effectiveness should be applied.

Keywords Female infertility · Assisted reproductive technology · Evaluation of ovulatory function · Evaluation of female reproductive tract · Tubal patency · Hysterosalpingo-contrast sonography (HyCoSy) · Evaluation of ovarian reserve · Serum anti-müllerian hormone (AMH)

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Introduction

According to the *Practice Committee of the American Society for Reproductive Medicine* definition of infertility, a diagnostic workup for infertility is evidenced for females who fail to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment is warranted after 6 months of fruitless attempts to conceive for women older than age 35 years and may be justified based on medical history and physical findings [1], including but not limited to history of oligo- or amenorrhea, known or suspected uterine/tubal/peritoneal disease or stage III–IV endometriosis, and known or suspected male subfertility [2–4]. This definition has been censured as vague due to the fact that treatment-independent pregnancy rates after 12 months of trying have been shown to be as high as 61 % among couples defined as “infertile” [5, 6]. Instead, the term subfertility often is used to describe the failure to conceive unless the couple has been proven to be sterile. Fecundability, the probability of achieving a pregnancy in a given menstrual cycle, also is utilized as a more accurate descriptor because it recognizes varying degrees of infertility. A system of prognostic grading in conjunction with statements regarding the couple's fertility history and diagnosis has been proposed to diminish confusing terminology, yet has not been widely accepted [7].

Because approximately 85 % of couples will conceive within 12 months of attempting pregnancy—with fecundability progressively decreasing over time—evaluation may be indicated for as many as 15 %. Diagnostic assessment for female infertility should be performed in a systematic, expeditious, and cost-effective mode to determine all relevant factors, starting with the least invasive approaches for detection of the most common causes of infertility. Evaluation of both partners should be performed concurrently [8•].

Recognition, evaluation, and treatment of infertility can be a stressful and emotionally taxing process for the woman [9]. Involved health care professionals have to bear in mind that under no circumstances should the medicalization of infertility bring about disregard for the woman's emotional

state, because psychological interventions have been found to improve some patients' chances of becoming pregnant [10].

History and Physical Examination

Findings on history and physical examination may imply the cause of infertility, narrowing the focus of the diagnostic evaluation. This is why primary counseling should include a comprehensive medical, reproductive, and family history and performance of a meticulous physical examination.

Appropriate history includes several points starting with duration of infertility—defined as the period of time during which unprotected intercourse has taken place—as well as the results of any previous evaluation and therapy. Menstrual history, including age of menarche, cycle length and characteristics, presence of molimina, and presence/severity of dysmenorrhea, should be queried. Complete obstetrical history outlining gravidity, parity, pregnancy outcomes, and related complications along with medical and surgical history has to be requested. In addition, gynecological history, including pelvic inflammatory disease, sexually transmitted infections, and treatment of any previous abnormal Pap smears, as well as sexual history pertaining to coital frequency and sexual dysfunction, should be obtained. Presence of thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, and dyspareunia has to be determined. Past use of contraceptive methods together with current medications and allergies should be disclosed as well as any exposure to known environmental/occupation-associated toxin, tobacco, alcohol or illicit/recreational drug, or chemotherapeutic agents. Determining any family history of birth defects, mental retardation, early menopause, and reproductive failure/compromise is of equal importance [8••].

Physical examination should evaluate for signs indicative of potential infertility causes. Because association between extreme values of body mass index (BMI) and ovulatory infertility has been documented [11, 12], patient's weight and BMI should be noted, as well as blood pressure and pulse. A thorough physical examination should identify thyroid enlargement, nodules, or tenderness suggestive of thyroid dysfunction, breast secretions due to hyperprolactinemia, and virilizing effects of androgen excess (hirsutism, acne, hair thinning, male pattern baldness), due to adrenal disorder or polycystic ovary syndrome. Pelvic examination to assess vaginal/cervical anatomical abnormalities or discharge, as well as masses or tenderness in the adnexa or pouch of Douglas should evaluate for the presence of müllerian anomalies, infection, and pelvic inflammatory disease or endometriosis. Size, shape position, and mobility of uterus has to be documented to exclude leiomyomas, endometriosis, or uterine adhesive disease [8••].

Evaluation of Ovulatory Function

Ovulatory disorders can be identified in 15–25 % of couples presenting with infertility and makes up approximately 40 % of female infertility [13, 14].

Irregular or absent menstruation and molimina are commonly, but not always, revealing of the dysfunction. Potential causes of ovulatory dysfunction include most commonly polycystic ovary syndrome and thyroid disorders, or accompany primary hypothalamic-pituitary dysfunction (intense exercise, eating disorders, hyperprolactinemia, pituitary adenoma, Kallmann's syndrome). Often anovulatory dysfunction may be related to decreased ovarian reserve (as will be discussed later) or congenital adrenal hyperplasia.

When oligomenorrhea or amenorrhea is reported in patient's menstrual history, diagnosis of anovulation is very likely. A basic hormonal evaluation, including follicle-stimulating hormone (FSH), estradiol, thyroid-stimulating hormone (TSH), and prolactin, as well as a serum HCG, is a cost-efficient approach to establish the underlying etiology in the majority of the cases. However, ovulatory function assessment in infertile women with normal menses (monthly episodes of bleeding) necessitates an objective marker.

Basal body temperature (BBT) recording throughout the cycle can be an undemanding ovulation index. Ovulatory cycles are principally inferred by a biphasic BBT pattern and anovulatory by a monophasic one; however, several cases of ovulatory women failing to document a biphasic BBT charting have been reported [15]. Because the BBT nadir is thought to precede ovulation, it has been proposed that the low temperature could be a useful predictor of ovulation. BBT nadir timing has been shown to be scattered from day -4 to day +6 of actual ovulation, proving itself as an unreliable ovulation marker [16]. Some providers suggest that the shift in BBT during a menstrual cycle is more reliable as a confirmatory marker of ovulation than the BBT nadir as a predictor of ovulation. The BBT test cannot accurately define ovulation and is no more deemed a preferable method for assessing ovulatory function for most infertile women [8••].

Ovulation can simply be confirmed by a mid-luteal progesterone level measurement. In the light of the normal range in cycle length, serum progesterone levels should be obtained approximately 1 week before the expected onset of the upcoming menstrual period [8••]. For a typical 28-day cycle, this coincides with day cycle day 21. A progesterone level >3 ng/ml is a putative but credible marker of ovulation occurrence [17]. However, failure of ovulation in which, despite the absence of follicular rupture and release of the oocyte, the unruptured follicle undergoes luteinization under the action of luteinizing hormone (LH) and normal production of progesterone and duration of the

luteal phase of the cycle are evidenced, has been widely reported and is defined as luteinized unruptured follicle syndrome [18–20]. Urinary over-the-counter ovulation prediction kits, by determining LH can detect effectively the LH surge, which is the prelude to ovulation. Thus, urinary LH surge determination provides indirect evidence of imminent ovulation and denotes the 3-day interval (the day of LH surge and the following two [21]) during the course of which conception rates are optimal, serving to maximize the user's knowledge of the fertile window and thus time intercourse or insemination. However, additional confirmatory testing occasionally may be necessary, because a 7 % false-positive rate has been reported [22].

Endometrial biopsy (EMB) and subsequent histological evaluation can confirm the secretory uterine lining, which is entailed and maintained by progesterone, implying ovulation. Histological dating of timed endometrial biopsy tissue according to the criteria of Noyes et al. [23], has long been established as the “gold standard” for assessing the functional integrity of the corpus luteum and diagnosing luteal phase deficiency (LPD) [8•]. However, results from a large, prospective, multicenter study demonstrated that histological dating of the endometrium fails to discriminate between women of fertile and infertile couples [24]; this along with proven lack of both accuracy and precision [25] renders the test an unsound, expensive, painful method to guide the clinical management of women with reproductive failure [26]. In view of these, endometrial biopsy is no longer recommended as a diagnostic tool for ovulatory or luteal function evaluation in infertile women and should only be applicable for women in whom specific endometrial pathology (e.g., neoplasia, chronic endometritis) is highly suspected [8•, 27].

Serial sonographic examinations can track the sizes of ovarian follicles throughout the preovulatory phase of the menstrual cycle, detect the collapse of the dominant follicle at ovulation, and identify that the collapsed cyst has reaccumulated with fluid to become the progesterone producing corpus luteum cyst (following ovulation) [28]. This can be burdensome for the patient, and given the relevant cost, this method is only recommended for women in whom other methods proved inefficient to elucidate any ovulation-associated disorder and those undergoing drug-induced ovarian stimulation [8•].

Thyroid-stimulating hormone and prolactin levels also should be measured in anovulatory women to identify thyroid dysfunction and/or hyperprolactinemia. In women presenting with amenorrhea, serum FSH and estradiol levels have to be determined so that differentiation between ovarian failure (high FSH, low estradiol) and hypothalamic amenorrhea (low FSH, low estradiol) is feasible and appropriate management approach/counseling is applied.

Having confirmed tubal patency and normality of semen analysis (discussed below), if infertile, anovulatory women, who have successfully undergone three to six cycles of ovulation induction, still fail to conceive, additional diagnostic evaluation should be performed or, if evaluation is over, other treatment options should be considered [8•].

Semen Analysis

Appropriate semen laboratory testing is an integral component of the proper evaluation of the couple presenting with infertility. The assessment of male fertility is based on examination of a freshly produced ejaculate submitted to the laboratory within 1 hour of collection, which takes place after 2 to 7 days of abstinence have elapsed [29]. A semen volume of 1.5 ml and a sperm count (or sperm concentration) of more than 15 million sperm per milliliter is considered normal, according to the World Health Organization. According to WHO, lower reference limit for total sperm count (or total sperm number) defined as the total number of spermatozoa in the entire ejaculate is 39 million per ejaculate. With regard to total spermatozoa motility and vitality, WHO sets a value of 40 % and 58 % live, respectively. A percentage of morphologically normal forms as high as 4 % renders the sample normal [30].

Evaluation of Female Reproductive Tract

Cervical Factors

Irregular cervical mucus production or sperm-mucous interaction are hardly ever demonstrated as the leading cause of infertility [8•]. The postcoital test (PCT) is scheduled close to ovulation and involves examination of active sperm presence in cervical mucus obtained from the female partner within hours after sexual intercourse. Despite its longstanding use in the female infertility evaluation, PCT has been proved to lack validity as a diagnostic tool for infertility [31, 32]. Due to its poor to fair reproducibility among trained observers [33], burden presented to patients and its insufficiency to predict conception achievement [34], it rarely affects clinical management and its incorporation in the routine workup for infertility evaluation is no longer recommended [8•].

Uterine Cavity

Uterine anatomy is a fairly unusual infertility cause that has to be ruled out [8•]. Hysterosalpingography (HSG) is regarded as an effective screening assessment of the internal uterine cavity architecture and tubal patency but provides no information regarding ovarian morphology.

HSG entails the injection of a radio-opaque material into the cervical canal, usually under fluoroscopy; it is used to investigate shape and size of the uterine cavity and determine the presence of any uterine filling defects (endometrial polyps, adhesions, submucous myomas) or congenital müllerian anomalies (unicornuate, septate, bicornuate uterus), which can adversely affect fertility.

HSG is reported to have a sensitivity as low as 50 % and a positive predictive value of 28.6 % for polypoid lesions [35]. Although the HSG is regarded to be safe, the procedure exposes patients to ionizing radiation and potentially allergenic contrast media [36•].

Transvaginal sonography (TVS) is considered a simple and innocuous examination with quite good accuracy for the evaluation of the uterine cavity [37–39]. When conventional TVS is not able to ensure uterine cavity normality or detects an abnormality but is proved insufficient to define its nature, saline infusion sonohysterography (SIS) can be utilized [40, 41].

Sonohysterography uses infusion of sterile saline through a soft plastic catheter placed in the cervix in conjunction with transvaginal ultrasound. Sonohysterography has been shown to have a diagnostic accuracy of 100 % compared with hysteroscopy, defined as the “gold standard,” for polypoid lesions (polyps or myomas) and 100 % specificity for uterine malformations. In diagnosis of intrauterine adhesions, SHG has limited accuracy, similar to that obtained by HSG, with a high false-positive diagnosis rate [35].

Hysterosalpingo-contrast sonography (HyCoSy) is an ultrasound procedure used to assess abnormalities of the uterine cavity, myometrium, and adnexal architecture, as well as patency of the fallopian tubes before and after transcervical injection of a noniodine contrast agent. This method has proven to be a time-efficient, safe, and well-tolerated alternative to HSG with comparable accuracy in the assessment of the uterine cavity and tubal patency [36•, 42•].

Hysteroscopy is the authoritative method for the diagnosis and treatment of intrauterine abnormalities. However, due to its high cost and invasiveness, it is advised to be reserved for supplemental evaluation and treatment of pathology already determined by the other, less invasive methods [8••].

Tubal Patency

Tubal pathology accounts for 25–35 % of female factor infertility, with more than half of the cases due to pelvic inflammatory disease (PID) [43]. A history of ectopic pregnancy, pelvic PID, endometriosis, or prior pelvic surgery can be considered as risk factors for tubal factor fertility [44].

Hysterosalpingography (HSG) is the standard first-line test to evaluate tubal patency and also may be of therapeutic benefit with higher fecundity rates reported several months after the procedure [8••, 45]. If HSG indicates patent tubes,

tubal blockage is very unlikely [46]. However, almost 60 % of patients in whom HSG showed proximal tubal blockage had been proved to have patent tubes by a second HSG performed 1 month later or on subsequent laparoscopy [46, 47]. Thus, revelations indicative of proximal tubal blockade have to be further assessed to rule out testing artifacts due to transient tubal spasm or poor catheter positioning [8••]. Saline infusion sonography (SIS) also can be used for evaluation of tubal patency. However, the test cannot define unilaterality or bilaterality of patency [8••].

As discussed above, hysterosalpingo-contrast sonography (HyCoSy) has clinical applicability to tubal patency assessment. A comprehensive meta-analysis involving 1,007 women who underwent diagnostic imaging for tubal-related subfertility has revealed a concordance of 83 % between HyCoSy and HSG when detecting tubal pathology. However, a 10.3 % false occlusion rate and 6.7 % false patency rate were determined when HyCoSy was compared with laparoscopy [48]. Overall, increasing evidence supports HyCoSy as an acceptable screening method for the subfertile patient, combining comprehensive evaluation with methodological simplicity, cost-effectiveness, and time efficiency [36•].

Laparoscopy with chromotubation can determine tubal patency, detect proximal or distal tubal occlusion, and identify and rectify tubal-associated pathology, such as fimbrial phimosis and peritubal adhesions, which can easily slip when less invasive methods, such as HSG, are used [8••]. However, randomized trials evaluating cost-effectiveness and timing of diagnostic laparoscopy before ovarian stimulation in females with unexplained infertility are yet to be conducted. Fluoroscopic/hysteroscopic selective tubal cannulation while verifying diagnosis based on HSG or laparoscopy with chromotubation can be used as the initial method to attempt treatment of tubal obstruction [49].

Some evidence has been reported in support of chlamydia antibody testing (CAT) as a method to evaluate tubal pathology presence. Some studies have suggested that chlamydia trachomatis IgG antibodies determination is a method of equal or superior predictive value compared with HSG for prediction of tubal factor infertility [50–52]. False-positive results can ensue due to cross-reactivity with *C. pneumoniae*, whereas a positive CAT is indicative of a previous infection but not of a persistent one and cannot clearly define causality between the infection and any tubal damage [53]. ASRM practice committee classifies CAT as a method of limited clinical utility [8••].

Peritoneal Factors

Endometriosis and pelvic or adnexal adhesions often may interfere with fertility. Several revelations on history/physical examination, such as dysmenorrhea, pelvic pain or cramping, dyspareunia, prior pelvic surgery or infection, or ectopic

pregnancy, can infer peritoneal pathology but cannot adequately justify diagnosis [8••].

Transvaginal ultrasound can be utilized as a display of pelvic pathology; however, laparoscopy with direct visualization of the pelvis is the “gold standard” for accurate and specific detection of peritoneal pathology. Per ASRM Practice Committee report, laparoscopy is indicated for women with symptoms or risk factors suggestive of pelvic pathology or women with an abnormal HSG/ultrasound having no other indication for undergoing ART [8••, 54, 55]. Diagnostic laparoscopy occasionally can be applicable for young women who have more than a 3-year period of infertility but no other pathology has been determined [8••].

Evaluation of Ovarian Reserve

Ovarian reserve alludes to the residual repertory of follicles left in the ovary at any given time, with respect to number and quality, providing evidence of pacing along the continuum of reproductive senescence.

Testing for diminished ovarian reserve (DOR) has become an integral part of evaluation of women at increased risk, such as those who 1) are older than 35 years, 2) have family history of early menopause, 3) have a solitary ovary or have undergone ovarian surgery, chemotherapy, or pelvic radiation therapy, 4) have unexplained infertility, 5) are poor responders to gonadotropin stimulation, or 6) intend to undergo treatment with any assisted reproductive technology technique [8••].

Because no benchmark for ovarian reserve status, in terms of quantity and quality, is applicable and proxy variables of true ovarian reserve (poor ovarian response to maximal stimulation and nonpregnancy after IVF) are used for evaluation of available tests, it should become clear that ovarian reserve tests are better considered as screening tests and not diagnostic ones; they do not establish diagnosis but only provide an accurate estimate of ovarian response to stimulation with exogenous gonadotropins and, to a much lesser extent, of the likelihood of pregnancy occurrence with ART [56]. Tests utilized for ovarian reserve assessment are briefly discussed below.

Day 3 FSH and Estradiol

Substantiation of day 3 FSH as a useful test for ovarian reserve lies upon the principle that women with good ovarian reserve can produce adequate amounts of Inhibin B early in the menstrual cycle to maintain a low FSH level, contrary to women with DOR who fail to provide normal feedback inhibition of pituitary secretion of FSH and demonstrate high FSH levels early in the cycle [57, 58]. Values less than 10–15 mIU/ml suggest adequate

ovarian reserve. Exact cutoff depends on the particular laboratory reference standards [59].

Basal estradiol levels alone should not be considered as a screening method for DOR, but should only be used as an adjunct to correctly interpret a “normal” basal serum FSH value [8••], because abnormally high estradiol levels due to advanced premature follicle recruitment in women with DOR can inhibit FSH secretion and thus mask this sign of DOR. When basal FSH is “normal” but estradiol is high (>60–80 pg/ml) in the early follicular phase, some evidence of associated poor ovarian response, higher cycle cancellation rates, and lower pregnancy rates has been reported [60–62].

Clomiphene Citrate Challenge Test

Clomiphene citrate challenge test (CCCT) involves FSH measurement before clomiphene citrate administration (50-mg tablets, 2 daily) on cycle days 5 through 9 and subsequent FSH levels determination on day 10. Administration of clomiphene citrate stimulates follicular development and thus estradiol and inhibin B production, which in turn suppresses pituitary FSH production. By day 10 of the CCCT, the FSH levels should be suppressed down to the normal range (<10 mIU/ml). Elevated FSH concentration after CCCT is therefore indicative of DOR. Cycle day 10 FSH determination seems to be more sensitive but less specific compared with cycle day 3 FSH measurement [63]. It must be stressed that a normal Clomid challenge test is not evidential of fertility and it does not prove that ovaries have normal functioning; it simply fails to prove otherwise [64]. Studies comparing basal FSH and CCCT showed that the CCCT has hardly any additional value [63, 64].

Antral Follicle Count

Antral follicle count (AFC) is the number of antral follicles in both ovaries during the early follicular phase (cycle days 2 to 4 of a regular menstrual cycle) determined with transvaginal ultrasound. Antral follicles are defined as follicles 2–10 mm or 3–8 mm in mean diameter in the greatest two-dimensional plane [8••, 65]. An AFC of 4–10 is suggestive of an acceptable ovarian reserve, whereas a low AFC (3–10 antral follicles) indicates poor ovarian reserve and serves as a good predictor of poor response to ovarian stimulation and, to a much lesser extent, of poor oocyte quality and nonpregnancy [66, 67].

Serum Antimüllerian Hormone

Antimüllerian hormone (AMH) has been acknowledged as an ovarian reserve marker of emerging clinical significance. AMH is a member of the large transforming growth factor β (TGF β) family of growth and differentiation factors and is

highly expressed in granulosa cells of preantral and small antral follicles until they become sensitive to FSH [68]. Being independent of gonadotropin effect, along with being the earliest marker to change with age and the least to vary within menstrual cycle, AMH is acclaimed as a useful and sensitive marker of ovarian follicular primordial pool and thus ovarian reserve [69, 70–74]. On the whole, AMH levels <1 ng/ml have been correlated with poor oocyte number and quality as well as poor response to IVF in terms of embryo quality and pregnancy outcomes [8, 56, 75–78].

Conclusions

A rational, cost-effective evaluation of the female partner in an infertile couple should include a thorough history and physical examination combined with the selective use of specific tests. These include a basic hormonal evaluation in the follicular phase of the cycle (FSH, estradiol, TSH, and prolactin) combined with information obtained from the HSG on the anatomy of the reproductive organs. This initial evaluation together with a semen analysis may identify the majority of the reasons for infertility. Additional tests may be required on an individual basis.

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References

- Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril*. 2008; 90(5 Suppl):S60. doi:10.1016/j.fertnstert.2008.08.065.
- Guttmacher AF. Factors affecting normal expectancy of conception. *J Am Med Assoc*. 1956;161(9):855–60.
- Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med*. 1995;333(23):1517–21. doi:10.1056/nejm199512073332301.
- Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. *Fertil Steril*. 1996;65(3):503–9.
- Collins JA, Wrixon W, Janes LB, Wilson EH. Treatment-independent pregnancy among infertile couples. *N Engl J Med*. 1983;309(20):1201–6. doi:10.1056/nejm198311173092001.
- Zhao Y, Kolp L, Yates M, Zacur H. Clinical evaluation of female factor infertility. Reproductive endocrinology and infertility: integrating modern clinical and laboratory practice. New York: Springer; 2010.
- Habbema JD, Collins J, Leridon H, Evers JL, Lunenfeld B, te Velde ER. Towards less confusing terminology in reproductive medicine: a proposal. *Fertil Steril*. 2004;82(1):36–40. doi:10.1016/j.fertnstert.2004.04.024.
- Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril*. 2012. doi:10.1016/j.fertnstert.2012.05.032. A very recently released report on appropriate female infertility evaluation developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM); this can roughly be a useful guide for the practicing clinician.
- Cousineau TM, Domar AD. Psychological impact of infertility. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(2):293–308. doi:10.1016/j.bpobgyn.2006.12.003.
- Hammerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279–95. doi:10.1093/humupd/dmp002.
- Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. *Epidemiology*. 1994;5(2):247–50.
- Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, et al. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol*. 1994;171(1):171–7.
- WHO Technical Report Series. Recent advances in medically assisted conception number 820, 1992, pp 1–111.
- Mosher WD, Pratt WF. Fecundity and infertility in the United States: incidence and trends. *Fertil Steril*. 1991;56(2):192–3.
- Luciano AA, Peluso J, Koch EI, Maier D, Kuslis S, Davison E. Temporal relationship and reliability of the clinical, hormonal, and ultrasonographic indices of ovulation in infertile women. *Obstet Gynecol*. 1990;75(3 Pt 1):412–6.
- Guermandi E, Vegetti W, Bianchi MM, Uglietti A, Ragni G, Crosignani P. Reliability of ovulation tests in infertile women. *Obstet Gynecol*. 2001;97(1):92–6.
- Wathen NC, Perry L, Lilford RJ, Chard T. Interpretation of single progesterone measurement in diagnosis of anovulation and defective luteal phase: observations on analysis of the normal range. *Br Med J (Clin Res Ed)*. 1984;288(6410):7–9.
- Marik J, Hulka J. Luteinized unruptured follicle syndrome: a subtle cause of infertility. *Fertil Steril*. 1978;29(3):270–4.
- Kerin JF, Kirby C, Morris D, McEvoy M, Ward B, Cox LW. Incidence of the luteinized unruptured follicle phenomenon in cycling women. *Fertil Steril*. 1983;40(5):620–6.
- LeMaire GS. The luteinized unruptured follicle syndrome: anovulation in disguise. *J Obstet Gynecol Neonatal Nurs*. 1987;16(2):116–20.
- Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility. *Fertil Steril*. 2008;90(5 Suppl):S1–6. doi:10.1016/j.fertnstert.2008.08.122.
- McGovern PG, Myers ER, Silva S, Coutifaris C, Carson SA, Legro RS, et al. Absence of secretory endometrium after false-positive home urine luteinizing hormone testing. *Fertil Steril*. 2004;82(5):1273–7. doi:10.1016/j.fertnstert.2004.03.070.
- Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. *Am J Obstet Gynecol*. 1975;122(2):262–3.
- Coutifaris C, Myers ER, Guzik DS, Diamond MP, Carson SA, Legro RS, et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. *Fertil Steril*. 2004;82(5):1264–72. doi:10.1016/j.fertnstert.2004.03.069.
- Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. *Fertil Steril*. 2004;81(5):1333–43. doi:10.1016/j.fertnstert.2003.11.030.

26. Haney AF. Endometrial biopsy: a test whose time has come and gone. *Fertil Steril*. 2004;82(5):1295–6. doi:10.1016/j.fertnstert.2004.06.037. discussion 301–2.
27. Kazer RR. Endometrial biopsy should be abandoned as a routine component of the infertility evaluation. *Fertil Steril*. 2004;82(5):1297–8. doi:10.1016/j.fertnstert.2004.05.080. discussion 300–2.
28. de Crespigny LC, O'Herlihy C, Robinson HP. Ultrasonic observation of the mechanism of human ovulation. *Am J Obstet Gynecol*. 1981;139(6):636–9.
29. World Health Organization. WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th ed. Cambridge: Cambridge University Press; 1999.
30. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010;16(3):231–45. doi:10.1093/humupd/dmp048.
31. Griffith CS, Grimes DA. The validity of the postcoital test. *Am J Obstet Gynecol*. 1990;162(3):615–20.
32. Collins JA, So Y, Wilson EH, Wrixon W, Casper RF. The postcoital test as a predictor of pregnancy among 355 infertile couples. *Fertil Steril*. 1984;41(5):703–8.
33. Glatstein IZ, Best CL, Palumbo A, Sleeper LA, Friedman AJ, Hornstein MD. The reproducibility of the postcoital test: a prospective study. *Obstet Gynecol*. 1995;85(3):396–400. doi:10.1016/0029-7844(94)00390-y.
34. Oei SG, Helmerhorst FM, Bloemenkamp KW, Hollants FA, Meerpoel DE, Keirse MJ. Effectiveness of the postcoital test: randomised controlled trial. *BMJ*. 1998;317(7157):502–5.
35. Soares SR, Barbosa dos Reis MM, Camargos AF. Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography in patients with uterine cavity diseases. *Fertil Steril*. 2000;73(2):406–11.
36. • Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. *Fertil Steril*. 2011;95(7):2171–9. doi:10.1016/j.fertnstert.2011.02.054. *A comprehensive, critical review of the existing literature on current methods of uterine cavity and tubal patency assessment as compared with the gold standard – laparoscopy-. Special reference is made on the increasing evidence in support of hysterosalpingo-contrast sonography (HyCoSy) as a useful, screening method for the subfertile patient.*
37. Emanuel MH, Verdel MJ, Wamsteker K, Lammes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: clinical implications. *Am J Obstet Gynecol*. 1995;172(2 Pt 1):547–52.
38. Fedele L, Bianchi S, Dorta M, Vignali M. Intrauterine adhesions: detection with transvaginal US. *Radiology*. 1996;199(3):757–9.
39. Glatstein IZ, Harlow BL, Hornstein MD. Practice patterns among reproductive endocrinologists: further aspects of the infertility evaluation. *Fertil Steril*. 1998;70(2):263–9.
40. Cullinan JA, Fleischer AC, Kepple DM, Arnold AL. Sonohysterography: a technique for endometrial evaluation. *Radiographics*. 1995;15(3):501–14. discussion 15–6.
41. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. *J Obstet Gynaecol*. 2011;31(1):54–8. doi:10.3109/01443615.2010.532246.
42. • Luciano DE, Exacoustos C, Johns DA, Luciano AA. Can hysterosalpingo-contrast sonography replace hysterosalpingography in confirming tubal blockage after hysteroscopic sterilization and in the evaluation of the uterus and tubes in infertile patients? *Am J Obstet Gynecol*. 2011;204(1):79 e1–5. doi:10.1016/j.ajog.2010.08.065. *This study provides evidence that hysterosalpingo-contrast sonography (HyCoSy) is a time-efficient, safe and well-tolerated alternative to HSG with comparable accuracy in the assessment of the uterine cavity and tubal patency.*
43. Honore GM, Holden AE, Schenken RS. Pathophysiology and management of proximal tubal blockage. *Fertil Steril*. 1999;71(5):785–95.
44. Practice Committee of the American Society for Reproductive Medicine. Committee opinion: role of tubal surgery in the era of assisted reproductive technology. *Fertil Steril*. 2012;97(3):539–45. doi:10.1016/j.fertnstert.2011.12.031.
45. Johnson N, Vandekerckhove P, Watson A, Lilford R, Harada T, Hughes E. Tubal flushing for subfertility. *Cochrane Database Syst Rev*. 2005;18(2):CD003718. doi:10.1002/14651858.CD003718.pub2.
46. Evers JL, Land JA, Mol BW. Evidence-based medicine for diagnostic questions. *Semin Reprod Med*. 2003;21(1):9–15. doi:10.1055/s-2003-39990.
47. Dessole S, Meloni GB, Capobianco G, Manzoni MA, Ambrosini G, Canalis GC. A second hysterosalpingography reduces the use of selective technique for treatment of a proximal tubal obstruction. *Fertil Steril*. 2000;73(5):1037–9.
48. Holz K, Becker R, Schurmann R. Ultrasound in the investigation of tubal patency. A meta-analysis of three comparative studies of Echovist-200 including 1007 women. *Zentralbl Gynakol*. 1997;119(8):366–73.
49. Valle RF. Tubal cannulation. *Obstet Gynecol Clin North Am*. 1995;22(3):519–40.
50. 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(5):833–7.
51. Veenemans LM, van der Linden PJ. The value of Chlamydia trachomatis antibody testing in predicting tubal factor infertility. *Hum Reprod*. 2002;17(3):695–8.
52. Rodgers AK, Budrys NM, Gong S, Wang J, Holden A, Schenken RS, et al. Genome-wide identification of Chlamydia trachomatis antigens associated with tubal factor infertility. *Fertil Steril*. 2011;96(3):715–21. doi:10.1016/j.fertnstert.2011.06.021.
53. den Hartog JE, Morre SA, Land JA. Chlamydia trachomatis-associated tubal factor subfertility: Immunogenetic aspects and serological screening. *Hum Reprod Update*. 2006;12(6):719–30. doi:10.1093/humupd/dml030.
54. Smith S, Pfeifer SM, Collins JA. Diagnosis and management of female infertility. *JAMA*. 2003;290(13):1767–70. doi:10.1001/jama.290.13.1767.
55. Luttjeboer FY, Verhoeve HR, van Dessel HJ, van der Veen F, Mol BW, Coppus SF. The value of medical history taking as risk indicator for tuboperitoneal pathology: a systematic review. *BJOG*. 2009;116(5):612–25. doi:10.1111/j.1471-0528.2008.02070.x.
56. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update*. 2006;12(6):685–718. doi:10.1093/humupd/dml034.
57. Abdalla H, Thum MY. An elevated basal FSH reflects a quantitative rather than qualitative decline of the ovarian reserve. *Hum Reprod*. 2004;19(4):893–8. doi:10.1093/humrep/deh141.
58. Klein NA, Illingworth PJ, Groome NP, McNeilly AS, Battaglia DE, Soules MR. Decreased inhibin B secretion is associated with the monotropic FSH rise in older, ovulatory women: a study of serum and follicular fluid levels of dimeric inhibin A and B in spontaneous menstrual cycles. *J Clin Endocrinol Metab*. 1996;81(7):2742–5.
59. Hurt KJ, Guile MW, Bienstock JL, Fox HE, Wallach EE. The Johns Hopkins manual of gynecology and obstetrics. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
60. Evers JL, Slaats P, Land JA, Dumoulin JC, Dunselman GA. Elevated levels of basal estradiol-17beta predict poor response in patients with normal basal levels of follicle-stimulating hormone undergoing in vitro fertilization. *Fertil Steril*. 1998;69(6):1010–4.
61. Licciardi FL, Liu HC, Rosenwaks S. Day 3 estradiol serum concentrations as prognosticators of ovarian stimulation response and pregnancy outcome in patients undergoing in vitro fertilization. *Fertil Steril*. 1995;64(5):991–4.

62. Smotrich DB, Widra EA, Gindoff PR, Levy MJ, Hall JL, Stillman RJ. Prognostic value of day 3 estradiol on in vitro fertilization outcome. *Fertil Steril*. 1995;64(6):1136–40.
63. Hendriks DJ, Mol BW, Bancsi LF, te Velde ER, Broekmans FJ. The clomiphene citrate challenge test for the prediction of poor ovarian response and nonpregnancy in patients undergoing in vitro fertilization: a systematic review. *Fertil Steril*. 2006;86(4):807–18. doi:10.1016/j.fertnstert.2006.03.033.
64. 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(1):180–5. doi:10.1016/j.fertnstert.2003.11.045.
65. Broekmans FJ, de Ziegler D, Howles CM, Gougeon A, Trew G, Olivennes F. The antral follicle count: practical recommendations for better standardization. *Fertil Steril*. 2010;94(3):1044–51. doi:10.1016/j.fertnstert.2009.04.040.
66. Hendriks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. *Fertil Steril*. 2005;83(2):291–301. doi:10.1016/j.fertnstert.2004.10.011.
67. Hsu A, Amy M, Knee AB, Bell C, Cook E, Novak AL, et al. Antral follicle count in clinical practice: analyzing clinical relevance. *Fertil Steril*. 2011;95(2):474–9. doi:10.1016/j.fertnstert.2010.03.023.
68. Visser JA, de Jong FH, Laven JS, Themmen AP. Anti-Mullerian hormone: a new marker for ovarian function. *Reproduction*. 2006;131(1):1–9. doi:10.1530/rep. 1.00529.
69. • Seifer DB, Baker VL, Leader B. Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. *Fertil Steril*. 2011;95(2):747–50. doi:10.1016/j.fertnstert.2010.10.011. *A retrospective study of 17,120 women of reproductive age ranging from 24 to 50 years old, reiterating the decreasing trend of AMH levels as age increases thus, reinforcing the value of AMH as an ovarian reserve marker.*
70. de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Antimullerian hormone serum levels: a putative marker for ovarian aging. *Fertil Steril*. 2002;77(2):357–62.
71. van Rooij IA, Tonkelaar I, Broekmans FJ, Looman CW, Scheffer GJ, de Jong FH, et al. Anti-mullerian hormone is a promising predictor for the occurrence of the menopausal transition. *Meno-pause*. 2004;11(6 Pt 1):601–6.
72. Seifer DB, Maclaughlin DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. *Fertil Steril*. 2007;88(3):539–46. doi:10.1016/j.fertnstert.2007.02.014.
73. Fanchin R, Schonauer LM, Righini C, Guibourdenche J, Frydman R, Taieb J. Serum anti-Mullerian hormone is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3. *Hum Reprod*. 2003;18(2):323–7.
74. Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy C, Englert Y. Stable serum levels of anti-Mullerian hormone during the menstrual cycle: a prospective study in normo-ovulatory women. *Hum Reprod*. 2007;22(7):1837–40. doi:10.1093/humrep/dem101.
75. Gnath C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. *Hum Reprod*. 2008;23(6):1359–65. doi:10.1093/humrep/den108.
76. Muttukrishna S, McGarrigle H, Wakim R, Khadum I, Ranieri DM, Serhal P. Antral follicle count, anti-mullerian hormone and inhibin B: predictors of ovarian response in assisted reproductive technology? *BJOG*. 2005;112(10):1384–90. doi:10.1111/j.1471-0528.2005.00670.x.
77. van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, et al. Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod*. 2002;17(12):3065–71.
78. Ebner T, Sommergruber M, Moser M, Shebl O, Schreier-Lechner E, Tews G. Basal level of anti-Mullerian hormone is associated with oocyte quality in stimulated cycles. *Hum Reprod*. 2006;21(8):2022–6. doi:10.1093/humrep/del127.