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Evaluation of the Infertile Female

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ABSTRACT

Infertility is defined as failure to conceive after 1 year of regular unprotected intercourse and is estimated to affect 10-15% of couples worldwide. Evaluation of the female partner is started if she fails to achieve pregnancy after 12 months or more of regular unprotected intercourse. This article provides a comprehensive review of the evaluation of a woman with infertility. We discuss the history and physical examination, evaluation of ovulatory function, tubal and peritoneal factors, uterine factors, cervical factors and ovarian reserve testing in detail.

Keywords: Female infertility, ovulatory dysfunction, uterine factors, tubal and peritoneal factors, cervical factors, ovarian reserve test, basal body temperature.

Infertility is defined as failure to conceive after 1 year of regular unprotected intercourse. It affects 10-15% of couples worldwide. Female factor is responsible for infertility in 35-40% of couples. Among females, the major causes of infertility include ovulatory dysfunction (30-40%), tubal and peritoneal pathology (30-40%), cervical factor (3%), uterine factor (rare) and unexplained (10%) (Fig. 1).

Usually, we start evaluation of female partner if she fails to achieve pregnancy after 12 months or more of regular unprotected intercourse. But in certain conditions earlier evaluation is warranted, which include:

- After 6 months of unsuccessful efforts in women over age of 35 years
- History of irregular menstrual cycles
- Known or suspected uterine/tubal or peritoneal disease
- History of pelvic infection
- Endometriosis, particularly Stage III-IV
- Known or suspected male subfertility.

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HISTORY AND EXAMINATION

Both the partners should be made aware of underlying causes of infertility, components of basic evaluation and encouraged for simultaneous testing.

Diagnostic evaluation should begin with thorough history and physical examination. History taking of infertile partner must include the following:

- Duration of infertility and results of any previous evaluation/treatment
- Coital frequency and sexual dysfunction
- Menstrual history (age at menarche, cycle length and characteristics, onset/severity of dysmenorrhea)
- Outcome of previous pregnancy, if any, and use of contraception
- Past or current medical and surgical illness (particularly any history of pelvic infection,

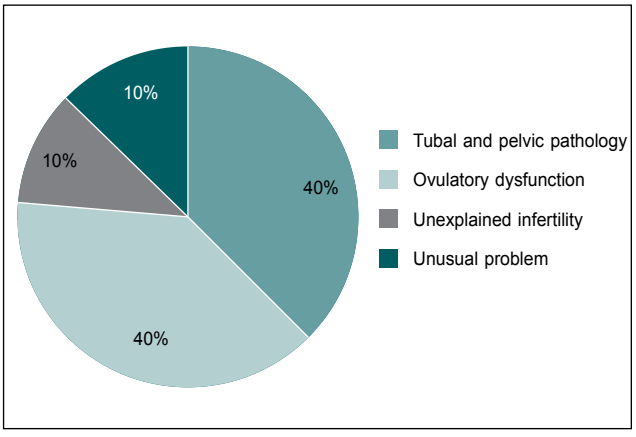

Figure 1. Cause of infertility: Women.

exposure to sexually transmitted infections, septic abortion, ectopic pregnancy, abdominal myomectomy, adnexal surgery)

- Family history of birth defects, mental retardation, early menopause or reproductive failure
- Symptoms of thyroid disease, galactorrhea, hirsutism or acne
- Pelvic or abdominal pain or dyspareunia
- Occupation and addiction history.

Physical examination should document:

- Body mass index (BMI)
- Thyroid nodule or tenderness
- Breast secretions and their character
- Signs of androgen excess
- Abdominal or pelvic mass or tenderness
- Vaginal or cervical abnormality or discharge
- Any mass, tenderness or nodularity in adnexa or cul-de-sac.

Subsequent evaluation should be carried out in a systematic and cost-effective manner to identify underlying cause.

OVULATORY FUNCTION

Ovulatory dysfunction, presenting as menstrual irregularity, is the underlying cause of infertility in approximately 15% of infertile couples and accounts for up to 40% of infertility in women. Diagnosis of ovulatory dysfunction can be made by menstrual history. Further investigations should be aimed to document ovulation and find the pathology of anovulation, if present.

Document Ovulation

A history of regular menstrual cycles occurring at interval of 25-35 days with consistent flow characteristics strongly suggests normal ovulatory function but still objective documentation in infertile women is needed. There are a number of methods to measure normal ovulatory function.

Methods to document ovulation

- Basal body temperature charts
- Urinary luteinizing hormone (LH) Kits
- Mid-luteal serum progesterone level
- Endometrial biopsy

Serial basal body temperature (BBT) measurement is a simple and inexpensive method based on thermogenic properties of progesterone. Ovulatory cycles have typical "biphasic" BBT recording, whereas anovulatory cycles have monophasic pattern. It is not the preferred method for infertile women because there can be few women who menstruate regularly but do not exhibit biphasic BBT.

Urinary LH determination is based on identification of mid-cycle LH surge and provides indirect evidence of ovulation. Since LH has a short half-life and is rapidly cleared of the urine, testing should be done on a daily basis starting 2-3 days before the surge is expected based on the cycle length. It is done using various commercially available "ovulation prediction kits" like i-know, i-can, PregaPlan, etc., which are easy to use but can have false positive and false negative results.

Serum progesterone measurement is simplest, reliable and preferred test of ovulatory function as long as it is appropriately timed. The best time to test is Day 21 of a 28-day cycle or approximately 1 week before the expected onset of next menses. A progesterone concentration of >3 ng/mL provides reliable evidence of recent ovulation, whereas value >10 ng/mL is suggestive of normal "in phase" endometrial histology.

Endometrial biopsy identifies ovulation based on characteristic secretory endometrial changes on histology induced by progesterone. Historically, it was considered "gold standard" for diagnosis of luteal phase deficiency (LPD) but not anymore. Since endometrial biopsy is an invasive test and provides not much added information over other noninvasive methods, it is no longer recommended to evaluate ovulatory or luteal function in infertile women. Its clinical use is limited to identify or exclude endometrial hyperplasia in women with chronic anovulation and to diagnose chronic endometritis. But in our Indian population where tuberculosis is an important cause of infertility, it becomes a part of routine investigations to rule out tubercular endometritis.

Serial transvaginal ultrasonography (TVUS) can be used to monitor number and size of developing follicles. It provides most accurate estimate of ovulation identified by sudden collapse of follicle, loss of clearly defined follicular margins, appearance of internal echoes and increase in cul-de-sac fluid volume. Because of associated cost and logistic demands, it is mainly used to monitor follicle growth in women receiving ovulation induction drugs.

Establish Cause for Anovulation

Patients with irregular or infrequent menses and amenorrhea have ovulatory dysfunction and do

not require any specific test to establish a diagnosis of anovulation. The ovulatory disorders have been classified by World Health Organization (WHO) into three groups (Table 1).

Therefore, in women with irregular cycles, basal (Day 2-4) serum follicle-stimulating hormone (FSH), LH, serum estradiol and prolactin levels should be done to find the cause of anovulation and to treat accordingly. Before that, pregnancy must be excluded by a urine pregnancy test. Serum thyroid-stimulating hormone (TSH) levels should be done if signs and symptoms are suggestive of it.

TUBAL AND PERITONEAL FACTORS

Tubal pathology is the most common cause (30-35%) of infertility among both young as well as older women. Tubal damage should be strongly suspected in women with history of tuberculosis, pelvic inflammatory disease (PID), septic abortion, ectopic pregnancy or tubal surgery. Other important causes of tubal and peritoneal factor infertility include inflammation and adhesions related to endometriosis, inflammatory bowel disease or surgical trauma.

Hysterosalpingography (HSG) is the traditional and standard method for evaluation of tubal patency. It is a procedure which directly visualizes uterotubal anatomy as well as tubal patency with fluoroscopic screen after injecting radio-opaque dye through cervix. It is done as an office procedure in the preovulatory phase of menstrual cycle. It is approximately 65% sensitive, 83% specific with a positive (PPV) and negative predictive value (NPV) of 38% and 94%, respectively. It's low PPV implies that when HSG reveals obstruction, it can be because of mucus plug or cornual spasm and there is high probability (approx. 60%) that tube is open but when it demonstrates patency, there is only 5% chance that tube is actually occluded.

Saline infusion sonography (SIS) involves TVUS after injecting saline into uterine cavity. Apart from delineating intrauterine pathology, it can also be used to determine tubal patency by appearance of fluid in cul-de-sac with saline infusion on TVUS. It does not differentiate between unilateral or bilateral patency.

Laparoscopy and chromotubation is the definitive test for evaluation of tubal factors. It provides both a panoramic view of pelvic reproductive anatomy as well as magnified view of uterine, ovarian, tubal and peritoneal surfaces. Apart from evaluation of tubal patency, it can also identify distal tubal occlusive disease (fimbrial agglutination, phimosis), pelvic or adnexal adhesions and endometriosis that adversely affect fertility but escape detection by HSG. It also provides advantage of treating the pathology at time of diagnosis.

The detection of antibodies to *Chlamydia trachomatis* has also been associated with tubal pathology, including tubal occlusion, hydrosalpinx and pelvic adhesions but its clinical utility has not been proved yet.

UTERINE FACTORS

Anatomic and functional abnormalities of uterus are an uncommon cause but should always be excluded as a part of infertility evaluation. The anatomic abnormalities

Table 1. WHO Classification of Ovulatory Disorders and Serum Concentration of Hormones

Hormone	Normal values	Hypogonadotropic hypogonadal anovulation (WHO Class I) 5-10%	Eugonadotropic eu-estrogenic anovulation (WHO Class II) 75-85%	Hypergonadotropic anovulation (WHO Class III) 10-20%	Hyper-prolactinemia
Day 2/3 FSH	<10 IU/L	Decreased	Normal	Increased	Normal
Day 2/3 LH	<10 IU/L	Decreased	Normal or increased	Increased	Normal
LH:FSH ratio	ABOUT 1:2	Normal	Reversed	Normal	Normal
DAY 2/3 estradiol	<50 pmol/L	Decreased	Normal	Decreased	Decreased
Serum prolactin	15-20 ng/L	Normal	Normal or increased	Normal	Increased
Example		Kallmann's syndrome Excessive exercise Anorexia nervosa	Polycystic ovary syndrome	Premature ovarian failure	Pituitary micro- or macroadenoma

which adversely affect fertility include congenital malformations, leiomyomas, intrauterine adhesions and endometrial polyp. Chronic endometritis is the only functional uterine abnormality. Three basic methods for evaluation of uterine cavity are HSG, pelvic ultrasound or saline sonohysterography and hysteroscopy with each having its own advantage and disadvantages.

- Ultrasound is a noninvasive method which permits visualization of position and size of uterus, fallopian tubes and ovaries. Modern 3-D ultrasonography extends the diagnostic capabilities of ultrasonography and can generate reconstructed images in the coronal plane. It is more useful in diagnosing important uterine pathologies particularly congenital anomalies, to measure endometrial volume, locate fibroids and also defines their relationship to endometrial canal. It has diagnostic accuracy comparable to magnetic resonance imaging.
- SIS can be used for better identification of intrauterine adhesions and endometrial polyps.
- HSG accurately defines size and shape of uterine cavity. It may help in delineating any developmental uterine anomaly (unicornuate, bicornuate, septate, didelphys, etc.) and acquired abnormalities (intrauterine adhesions, endometrial polyps, submucous myomas). It has relatively low sensitivity (50%) and PPV (30%) for diagnosis of endometrial polyp and submucous myomas in asymptomatic infertile women.
- Hysteroscopy is the definitive method for evaluation and treatment of intrauterine pathology. Being more costly and an invasive method, its use is reserved for further evaluation and treatment of abnormalities detected on TVUS, SIS or HSG.

CERVICAL FACTORS

It includes abnormalities of cervical mucus production or sperm/mucus interaction which are rarely the sole cause of infertility. Traditionally, post-coital test (PCT) was considered a basic element of infertility evaluation. It is inconvenient to patient, does not predict inability to conceive and rarely changes clinical management. Therefore, PCT is no longer recommended for evaluation of infertile female.

ROLE OF OVARIAN RESERVE TESTING

Ovarian reserve describes the size and quality of the remaining ovarian follicular pool. This has become a routine element of the diagnostic evaluation of infertility but is best justified for women with any of the following characteristics:

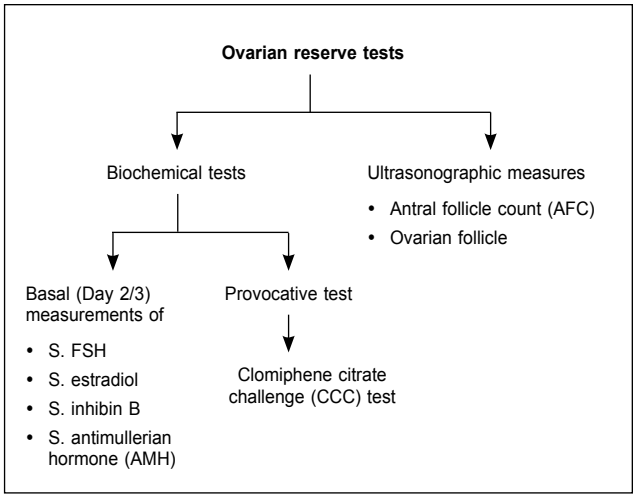

Figure 2. Ovarian reserve tests.

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

It includes a number of biochemical tests and ultrasonographic measures with each test having its own sensitivity and specificity (Fig. 2 and Table 2).

Therefore, ovarian reserve tests should always be interpreted with caution as none of the tests available at present can be recommended as a sole criteria of diminished ovarian reserve (DOR). They should only be used to obtain prognostic information and to choose the best treatment available.

KEY RECOMMENDATIONS: NICE GUIDELINES

- 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.
- A blood test to measure serum progesterone in the mid-luteal phase (Day 21 of a 28-day cycle) is the preferred method to confirm ovulation even if women having regular menstrual cycle.
- Women with irregular menstrual cycle should be offered a blood test to measure serum gonadotropins.

Table 2. Summary of Different Ovarian Reserve Tests

Ovarian reserve test	Cut-off range	Sensitivity (%)	Specificity (%)	Comment
S. FSH (Day2/3)	10-20 IU/L	10-30	83-100	Most widely used; good reliability
S. Inhibin B	40-45 pg/mL	40-80	64-90	High inter- and intracycle variability; not used routinely
S. AMH	0.2-0.7 ng/mL	40-97	78-92	Good reliability
CCC test (Day 10 FSH)	10-22 IU/L	35-98	68-98	Higher sensitivity than basal FSH but needs drug administration
AFC (No)	3-10	40-97	78-92	Good reliability; widespread use
Ovarian volume	>3 mL	11-80	80-90	Limited clinical use

- Serum prolactin should only be offered to women who have an ovulatory disorder, galactorrhea or a pituitary tumor.
- Thyroid function test should not be offered routinely; rather should be estimated only in women with symptoms of thyroid disease.
- The routine use of endometrial biopsy and PCT of cervical mucus is no longer recommended as a part of evaluation of infertile female.
- HSG to screen for tubal patency is a reliable test, less invasive and makes more efficient use of resources than laparoscopy.
- Ovarian reserve testing should be best limited to the women at increased risk of DOR and should be interpreted with caution.

SUGGESTED READING

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WHO Celebrates Big Step Forward in Improving Health Security in the African Region

The World Health Organization (WHO) reached an important milestone globally with the completion of the 100th Joint External Evaluation (JEE)—a voluntary assessment of a country's ability to prevent, detect and respond to public health threats. Forty-two of these 100 countries are in the WHO African region.

"Africa has more than 150 acute public health events a year, including infectious disease outbreaks and humanitarian crises. This is more than in any other region of the world," said Dr Matshidiso Moeti, WHO Regional Director for Africa. "The JEE is critical for identifying priority interventions in developing preparedness capacity and improving health security in the region." (*WHO*)