

Evaluation of Female Infertility

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Introduction:

Infertility is defined as the inability of a couple to conceive within 1 year¹. Existing definitions of infertility lack uniformity. A couple that has tried unsuccessfully to have a child after a certain period of time (often a short period) is said to be subfertile, meaning less fertile than a typical couple. Both infertility and subfertility are defined as the inability to conceive after a certain period of time (the length of which vary).

The term subfertility may be preferable to infertility as many of the bars to conception are relative rather than absolute and in about 30% of cases no cause is found. However, some degree of difficulty conceiving is normal. Even with regular intercourse, 6% of women aged 35 years and 23% of those aged 38 years will not conceive after three years.²

About 84% of all couples (in normal reproductive age range) will conceive within one year and 92% within two years, if they have regular unprotected sexual intercourse.³

WHO defines infertility as :

Infertility is the inability to conceive a child. A couple may be considered infertile if, after two years of regular sexual intercourse, without contraception, the women have not become pregnant (and there is no other reason, such as breast feeding or postpartum amenorrhoea).

In United States infertility is-

- a women under 35 has not conceived after 12 months of contraceptive free intercourse. Twelve months is the lower limit for *time to pregnancy* (TTP) by the World Health Organization.⁴
- a women over 35 has not conceived after 6 months of contraceptive free sexual intercourse.

In United Kingdom-

The NICE guideline defines infertility as failure to conceive after regular unprotected sexual intercourse for two years in the absence of known reproductive pathology⁵.

Prevalence

Prevalence of infertility varies depending on the definition, i.e. on the time span involved in the failure to conceive.

The prevalence of women diagnosed with infertility is approximately 13%, with the range from 7-28% depending on the age of the women.¹

The prevalence has increased in the last decade or so, in large part because of an increase in sexually transmitted disease resulting in pelvic inflammatory disease and because of an increasing tendency to delay childbearing.^{6, 7}

Etiology :

Infertility can be either partner or both. Many things may affect fertility: the patient's age, duration of infertility, frequency of coitus, certain drugs, and medications, nutritional and emotional factors. According to the American Society for Reproductive Medicine (ASRM), Smoking, Sexually Transmitted Infections, and Being Overweight or Underweight can all affect fertility.^{8, 9}

Basic factors those are responsible for majority of the cases of infertility are-1) male factor, 2) cervical factor, 3) endometrial-uterine factor, 4) tubal factor, 5) peritoneal factor, and 6) ovulatory factor. (Review Article: Infertility in women: Diagnostic evaluation with Hysterosalpingography..) Primary diagnosis of male factor is made in approximately 25% of cases. Ovulatory dysfunction and tubal/ peritoneal factors comprise the majority of female factor infertility. In 15-20% of infertile couples, the etiology cannot be found and a diagnosis of unexplained infertility is made.¹⁰

Causes of female infertility:

Age

A woman's fertility is affected by her age. A woman's fertility peaks in the early and mid twenties, after which it starts to decline, with this decline being accelerated after age 35.

However, the exact estimates of the chances of a woman to conceive after a certain age are not clear, with research giving differing results. The chances of a couple to successfully conceive at an advanced age depend on many factors, such as the general health of a woman, but also the fertility of the male partner.

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According to the National Institute for Health and Clinical Excellence, for women aged 35, about 94 out of every 100 who have regular unprotected sexual intercourse will get pregnant within 3 years of trying. For women aged 38, however, only 77 out of every 100 will do so.³

Tobacco Smoking

Tobacco smoking is harmful to the ovaries, and the degree of damage is dependent upon the amount and length of time a woman smokes or is exposed to a smoke-filled environment. Nicotine and other harmful chemicals in cigarettes interfere with the body's ability to create estrogen, a hormone that regulates folliculogenesis and ovulation. Also, cigarette smoking interferes with folliculogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and the uterine myometrium.¹⁰

Some damage is irreversible, but stopping smoking can prevent further damage.^{11, 12}

Smokers are 60% more likely to be infertile than non-smokers.¹³

Also, female smokers have an earlier onset of menopause by approximately 1–4 years.¹⁴

Sexually transmitted disease may cause infertility, largely through associated PID

- Chlamydia and gonorrhoea are the most important.¹¹

Body weight and eating disorders

Twelve percent of all infertility cases are a result of a woman either being underweight or overweight. Fat cells produce estrogen¹⁵, in addition to the primary sex organs. Too much body fat causes production of too much estrogen and the body begins to react as if it is on birth control, limiting the odds of getting pregnant. Too little body fat causes insufficient production of estrogen and disruption of the menstrual cycle. Both under and overweight women have irregular cycles in which ovulation does not occur or is inadequate.¹¹ Proper nutrition in early life is also a major factor for later fertility.¹⁶

A study in the US indicated that approximately 20% of infertile women had a past or current eating disorder, which is five times higher than the general lifetime prevalence rate¹⁷.

A review from 2010 concluded that overweight and obese subfertile women have a reduced probability of successful fertility treatment and their pregnancies are associated with more complications and higher costs.¹⁸

Chemotherapy

Chemotherapy poses a high risk of infertility. Antral follicle count decreases after three series of chemotherapy, whereas follicle stimulating hormone (FSH) reaches menopausal levels

after four series¹⁹. Chemotherapies with high risk of infertility include procarbazine and other alkylating drugs such as cyclophosphamide, ifosfamide, busulfan, melphalan, chlorambucil and chlormethine. Drugs with medium risk include doxorubicin and platinum analogs such as cisplatin and carboplatin. On the other hand, therapies with low risk of gonadotoxicity include plant derivatives such as vincristine and vinblastine, antibiotics such as bleomycin and dactinomycin and antimetabolites such as methotrexate, mercaptopurine and 5-fluorouracil.²⁰

Patients may choose between several methods of fertility preservation prior to chemotherapy, including cryopreservation of ovarian tissue, oocytes or embryos.²¹

Hypothalamic-pituitary factors

- Hypothalamic dysfunction
- Hyperprolactinemia.

Ovarian factors

- Polycystic ovary syndrome,
- Anovulation. Female infertility caused by anovulation is called “anovulatory infertility”, as opposed to “ovulatory infertility” in which ovulation is present²². Diminished ovarian reserve, also see Poor Ovarian Reserve
- Premature menopause
- Menopause
- Luteal dysfunction
- Gonadal dysgenesis (Turner syndrome)
- Ovarian cancer

Tubal (ectopic)/peritoneal factors

Endometriosis: Endometriosis can lead to anatomical distortions and adhesions (the fibrous bands that form between tissues and organs following recovery from an injury). However, the link between infertility and endometriosis remains enigmatic when the extent of endometriosis is limited. It has been suggested that endometriotic lesions release factors which are detrimental to gametes or embryos, or, alternatively, endometriosis may more likely develop in women who fail to conceive for other reasons and thus be a secondary phenomenon; for this reason it is preferable to speak of endometriosis-associated infertility in such cases.²³

- Pelvic adhesions
- Pelvic inflammatory disease (PID, usually due to chlamydia).²⁴
- Tubal occlusion.²⁵
- Tubal dysfunction

Uterine factors

- Uterine malformations
- Uterine fibroids (leiomyoma) Significant distortion of the uterine cavity by fibroids can prevent implantation and hence fertility, although the impact on fertility remains a subject for debate.²⁶
- Asherman's Syndrome

Cervical factors

- Cervical stenosis
- Antisperm antibodies
- Non-receptive cervical mucus

Vaginal factors :

- Vaginismus
- Vaginal obstruction

Evaluation :

An infertility evaluation is usually initiated after one year of regular unprotected intercourse in women under age 35 and after six months of unprotected intercourse in women age 35 and older. However, the evaluation may be initiated sooner in women with irregular menstrual cycles or known risk factors for infertility, such as endometriosis, a history of pelvic inflammatory disease, or reproductive tract malformations.

Both partners of an infertile couple should be evaluated for factors that could be impairing fertility.

It is important to remember that the couple may have multiple factors contributing to their infertility; therefore, a complete initial diagnostic evaluation should be performed to detect the most common causes of infertility, if present. Evaluation of both partners is performed concurrently.²⁷

The recognition, evaluation, and treatment of infertility are stressful for most couples.²⁸

The clinician should not ignore the couple's emotional state, which may include depression, anger, anxiety, and marital discord.

History

- Coitus must be satisfactory and occurring on a frequent basis, preferably at least three times a week:
 - o Perhaps her partner is away much of the time of there may be physical or emotional problems.
 - o Is penetration adequate?
- Anatomical considerations:
 - o Congenital abnormalities of the vagina will cause problems, as may dyspareunia from whatever cause.

- o In certain parts of the world, mainly the Horn of Africa, female genital mutilation is still performed and this can impair coitus and fertility.

- There may be psychosexual dysfunction presenting as infertility.
- Systemic disease may well impair fertility, probably by interference with the hypothalamic-pituitary axis:
 - o This may include autoimmune disease such as rheumatoid disease or systemic lupus erythematosus (SLE), although the latter, like antiphospholipid syndrome, may be associated with recurrent abortion. Antiphospholipid antibodies should not be part of routine testing for infertility.³
 - o Chronic renal failure will impair fertility.
 - o Poorly controlled diabetes mellitus needs correction, not just to improve fertility but to take account of the demands of diabetes in pregnancy, which dictate that control should be immaculate from the outset.
- Coeliac disease is often undiagnosed and may be associated with subfertility.²⁹
- Medication history

A thorough review of all medication is required with a view to both fertility and possible adverse effects on pregnancy, including teratogenicity.

- Legal drugs taken for legitimate purposes may also cause problems:
 - o Phenothiazines and the older typical antipsychotics as well as metoclopramide increase levels of prolactin (PRL).
- Non-steroidal anti-inflammatory drug (NSAID) use is associated with luteinised unruptured follicles.³⁰
- The patient may be taking drugs like immunosuppressants for autoimmune disease or after transplantation.

Past medical history

Previous treatment for malignancy (chemotherapeutic agents, such as those used in childhood leukaemia) may result in subsequent sterility. Surgery and radiotherapy may be relevant if they involved the pelvic region.

General health

Even in the absence of systemic illness, poor general health will impair fertility.

- Being overzealous about fitness with an obsession to run many miles a week may also be counterproductive but this is probably quite rare:
 - o Athletic amenorrhoea, related to excessive training and not being underweight is uncommon.

- o The most common reason for failing to start the London Marathon, is pregnancy.
- Aim for an ideal body mass index (BMI):
 - o A BMI below 19 is often associated with amenorrhoea, as occurs with anorexia nervosa.
- At the other end of the scale, a BMI below 25 should be the aim, but the National Institute for Health and Clinical Excellence (NICE) gives a BMI above 29 as cause for concern.^{3, 31}
- It may be associated with polycystic ovarian disease.
- Smoking cigarettes impairs fertility and smoking in pregnancy increases the risk of miscarriage, obstetric complications, intrauterine growth restriction and even delayed reading ability (at least to the age of 7).³²
- Excessive alcohol consumption also impairs fertility as well as risking fetal alcohol syndrome and fetal alcohol effects that occur at lower levels of consumption.³
- There is currently insufficient evidence for a strong association between excessive caffeine consumption and poor pregnancy outcomes, including subfertility.³³
- Illicit drugs should be avoided³. Some have adverse effects on fertility or the fetus or both and, for most; the question of teratogenicity has not been adequately addressed. Cannabis can impair ovulation and cocaine can cause tubal infertility. There is also reason to be concerned about the effect these drugs may have in pregnancy.

Examination

- Look for signs of hirsutism:
 - o Facial hair may be more profuse than normal, although this should be interpreted in the light of racial norms.
 - o Acne may also indicate high androgen levels.
 - o There may be a hint of male pattern alopecia with slight bitemporal recession.
 - o The pubic hairline may extend up towards the umbilicus in a typical male pattern.
- Examination of the cardiovascular or respiratory system is unlikely to be rewarding, as is examining the breasts for galactorrhoea, unless indicated by history.
- Abdominal examination should be performed and it must precede bimanual pelvic examination or it is very easy to miss a large mass like a big ovarian cyst.
- Gynaecological examination, especially vaginal examination, may indicate undisclosed sexual difficulties:

- o For example, her response may suggest vaginismus and you may even find an intact hymen.
- An unusually large clitoris would suggest excessive androgen activity, but this is more likely to be a long-standing condition such as congenital adrenal hyperplasia. This will probably be in a mild form, as it is presenting so late.
- Bimanual examination:
 - o May find an adnexal mass from an ovary of tubo-ovarian mass or tenderness suggesting pelvic inflammatory disease (PID) or endometriosis.
 - o Uterine fibroids can distort the uterus and interfere with implantation.

Investigation

Diagnostic tests — In addition to the history and physical examination, the initial diagnostic evaluation consists of:

- **Semen analysis** to detect male factor infertility.
- **Documentation of normal ovulatory function.** Women with regular menses approximately every four weeks with minimal symptoms are almost always ovulatory.
- **A test to rule out tubal occlusion.** We usually perform a hysterosalpingogram (HSG), but laparoscopy with chromotubation may be more appropriate in women suspected of having endometriosis.

Risk factors noted from the couple's history may indicate the need for additional testing after the initial infertility evaluation.

Semen analysis - The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple. The semen sample should be collected after two to seven days of abstinence and should be submitted to the laboratory within one hour of collection.³⁴

Assessment of ovulatory function — Assessment of ovulatory function is a key component of the evaluation of the female partner since ovulatory dysfunction is a common cause of infertility.

In contemporary practice, the laboratory assessment of ovulation is most easily monitored by a mid-luteal phase serum progesterone level, which should be obtained approximately one week before the expected menses. For a typical 28-day cycle, the test would be obtained on day 21. A progesterone level >3 ng/mL is evidence of ovulation.³⁵

An alternative is to have the patient use an over-the-counter urinary ovulation prediction kit. These kits detect luteinizing hormone (LH) and are highly effective for predicting the

timing of the LH surge that reliably indicates ovulation. Home kits have a 5 to 10 percent false positive and false negative rate. Therefore, serum confirmation can be useful in patients who are unable to detect a urinary LH surge.

Other methods of determining ovulation, such as serial ultrasounds to follow the development and ultimately the disappearance of a follicle and endometrial biopsy to document secretory changes in the endometrium are too expensive or invasive for routine diagnostic assessment of ovulation.

If the progesterone concentration is <3 ng/mL, the patient is evaluated for causes of anovulation. The minimal work-up includes serum prolactin, thyrotropin (TSH), follicle-stimulating hormone (FSH), and assessment for polycystic ovary syndrome (PCOS).

Assessment of ovarian reserve

The identification of diminished ovarian reserve is an increasingly important part of the initial infertility evaluation. Accurate estimate of ovarian function has become a core part of the fertility work-up as patients present for diagnostic evaluation later in their reproductive lifespan. An inverse relationship exist between fecundity and the age of the women.(current). Ovarian reserve should be evaluated in women older than 35 years and younger women with risk factors for premature ovarian failure. (Update). The decline in fecundity is a result of progressive follicular atresia through apoptosis, which accelerates in the early thirties and progresses rapidly in the late thirties and early forties. Concomitantly, there is a decrease in follicular quality as a result of an increase in oocyte with chromosomal anomalies and progressive deletions in mitochondrial DNA. The concept of ovarian reserve represents the remaining follicular pool of the ovaries. As ovarian reserve decrease, the ovaries responsiveness to gonadotropins decreases necessitating higher amounts of FSH to achieve follicular growth and maturation.

However, there is no ideal test for assessing ovarian reserve. A number of screening tests are utilized, but no test is highly reliable in predicting fertility potential.

There are several test for evaluation of ovarian reserve like-day 3 FSH level, CCCT, antral follicle count and anti- müllerian hormone (AMH) level.

For women over 35 years of age and younger women with risk factors for premature ovarian failure, we suggest testing ovarian reserve with a day 3 FSH level. Other tests such as the clomiphene citrate challenge test (CCCT), antral follicle count, and anti-müllerian hormone (AMH) level are utilized by specialists and in special circumstances.

Day 3 FSH and CCCT — Both the day 3 FSH level and the CCCT, which is a provocative test for measurement of FSH, are widely used for screening ovarian reserve. The CCCT involves oral administration of 100 mg clomiphene citrate on cycle days 5 through 9 with measurement of day 3 and day 10 FSH levels and day 3 estradiol levels.

The basis of these tests is that women with good ovarian reserve have sufficient production of ovarian hormones from small follicles early in the menstrual cycle to maintain FSH at a low level. In contrast, women with a reduced pool of follicles and oocytes have insufficient production of ovarian hormones to provide normal inhibition of pituitary secretion of FSH, so FSH rises early in the cycle.³⁶

Meta-analyses of nonrandomized studies concluded that basal cycle day 3 FSH and the CCCT testing perform similarly for predicting ability to achieve a clinical pregnancy in women undergoing infertility treatment³⁷. With either test, a normal result is not useful in predicting fertility, but a highly abnormal result (we use FSH >20 mIU/mL) suggests that pregnancy will not occur with treatment involving the woman's own oocytes.

It is also suggested for day 3 estradiol level, although there are conflicting data as to whether it is predictive of ovarian reserve and the response to ovarian stimulation (as in IVF)-^{38,39}

Day 3 estradiol value <80 pg/mL suggestive of adequate ovarian reserve, but other cut-offs are also utilized. In one prospective study of women undergoing IVF, day 3 estradiol levels >80 pg/mL resulted in higher cycle cancellation rates and lower pregnancy rates, and estradiol levels >100 pg/mL were associated with a 0 percent pregnancy rate.⁴⁰

Elevated basal estradiol levels are due to advanced premature follicle recruitment that occurs in women with poor ovarian reserve. High estradiol levels can inhibit pituitary FSH production and thus mask one of the signs of decreased ovarian reserve in perimenopausal women. Thus, measurement of both FSH and estradiol levels helps to avoid false-negative FSH testing.

If CCCT is performed, we consider FSH less than 15 mIU/mL on both day 3 and day 10 suggestive of adequate ovarian reserve; an elevated FSH level on either day 3 or day 10 suggests decreased ovarian reserve. Estradiol can be measured on day 3, but a cycle day 10 estradiol is not part of the standard CCCT as it reflects the magnitude of the ovarian follicular response to clomiphene 100 mg daily for five days, not ovarian reserve.

Investigations

The search for the cause of infertility or subfertility should be systematic and led by clinical features, not a blind screening process for everything.

- Mid-luteal progesterone level to assess ovulation:
 - If low, it may need repeating, as ovulation does not occur every month.
 - The blood test is taken seven days before the anticipated period, that is on day 21 of a 28-day cycle but this day will need to be adjusted for different lengths of cycle.
- Basal body temperature charts are not recommended as they are unreliable.
- FSH and LH should be measured, especially if there is menstrual irregularity:
 - High levels may suggest poor ovarian function.
 - A comparatively high LH level relative to FSH level is typical of polycystic ovarian disease.
- Prodigy and NICE advice that TFTs should only be undertaken if there are grounds for suspicion, as infertile women are no more likely to have thyroid disease than the rest of the population.^{2, 3}
- Similarly, prolactin (PRL) should only be measured where there is clinical suspicion.
- Screening for chlamydia is recommended:
 - Not only may it be a cause of infertility but instrumentation of the genital tract in subsequent investigations may produce pelvic inflammatory disease (PID).

Secondary care investigations

Each clinic may well have its own protocol for the investigation of couples in whom no problem has been identified, and even after extensive investigation no problem is found in 30%.

Tubal patency

Tubal damage is estimated to account for 14% of infertility in women².

Assessment of fallopian tube patency — American Society for Reproductive Medicine recommend that the HSG should be the first-line test for evaluation of tubal patency⁴¹. HSG provides higher sensitivity and specificity for diagnosis of tubal disease than chlamydia antibody testing or hysterosalpingo-contrast sonography (HyCoSy). Hysterosalpingogram (HSG) is recommended by NICE for

women who are not known to have had pelvic inflammatory disease (PID), ectopic pregnancy or endometriosis³. The test is reliable and less invasive than laparoscopy. A meta-analysis of 20 studies involving 41 79 patients compared HSG and laparoscopy with chromotubation (the gold standard); the calculated sensitivity and specificity for diagnosis of tubal patency were only 65 and 83 percent, respectively.⁴²

However, when subgroups of women undergoing HSG were analyzed, HSG appeared to have very high specificity and sensitivity for diagnosing distal tubal occlusion or major distal tubal adhesions, but much lower specificity for diagnosing proximal tubal occlusion.

Proximal tubal occlusion on HSG often represents testing artifact due to tubal spasm or poor catheter positioning leading to unilateral tubal perfusion. Given these deficiencies, findings of proximal tubal occlusion on HSG could be confirmed by a secondary test such as a repeat HSG, fluoroscopic or hysteroscopic selective tubal perfusion, or laparoscopic chromotubation if definitive diagnosis will influence further management.

A substantial number of pregnancies occur follow an HSG, suggesting the test has therapeutic, as well as diagnostic, and benefits. Diagnostic HSG also appears to have therapeutic effects. A systematic review of 12 randomized trials found that pregnancy rates were significantly higher in subfertile women who underwent tubal flushing with oil soluble media than in those who did not undergo HSG (OR 3.30, 95% CI 2.00-5.43), and that pregnancy rates were similar whether oil or water soluble media were used (OR 1.21, 95%CI 0.95-1.54).⁴³

The investigation of female tubal subfertility can also be undertaken using an alternative approach involving chlamydia antibody testing and/or HyCoSy.⁴⁴

Some author suggest HSG to look for tubal occlusion in all patients, unless laparoscopy is planned^{45, 46}.

HSG also provides information about the uterine cavity. However it is not useful for detecting peritubal adhesions or endometriosis.⁴⁵

NICE recommended Laparoscopy if there are known problems such as PID, endometriosis or previous ectopic pregnancy.³

Chlamydia antibodies — Chlamydia trachomatis IgG antibody testing is a simple, inexpensive, noninvasive test with some evidence supporting its use as a method for predicting the presence of tubal disease. Studies suggest that antibodies to chlamydia are more predictive of infertility than an abnormal HSG.^{47, 48}

A cost-effective approach might be to screen women at low risk of tubal disease with chlamydia antibodies. A negative test is associated with <15 percent likelihood of tubal pathology and thus does not require further assessment.⁴⁹

False positives are due to cross reactivity with *C. pneumoniae*, do not distinguish between remote and persistent infection, and do not indicate whether infection resulted in tubal damage,⁴⁹ therefore, an HSG is performed if the test results are positive.⁵⁰ Women at high risk of tubal disease would be screened by HSG primarily.

Assessment of the uterine cavity

Assessment of the uterine cavity: In addition to assessment of tubal patency, HSG may identify developmental or acquired abnormalities of the uterine cavity with potential effects on fertility, such as submucous fibroids, a T-shaped cavity (associated with DES exposure), polyps, synechiae, and congenital müllerian anomalies (although HSG alone cannot reliably distinguish between a uterine septum or bicornuate uterus). Abnormalities found on HSG generally require further evaluation by other imaging modalities (ultrasonography or magnetic resonance imaging), hysteroscopy, or laparoscopy and referral to a reproductive endocrinologist.

Ultrasonography is a useful test for evaluation of suspected leiomyomata, while saline infusion sonohysterography is the best imaging modality for detection of submucosal leiomyomas and is much better than routine ultrasonography for diagnosis of intrauterine adhesions, polyps, and congenital uterine anomalies.⁵¹

As discussed above, HyCoSy is a simple, time-efficient, and effective method for evaluation of tubal patency, the uterine cavity, and the myometrium.⁵²

Hysteroscopy is the definitive method for evaluation of abnormalities of the endometrial cavity, and also offers the opportunity for treatment at time of diagnosis. In patients undergoing laparoscopy, performing hysteroscopy at the same time and omitting HSG is efficient.²⁷

Role Of Laparoscopy

The role of laparoscopy in the evaluation of infertility is controversial. Laparoscopy is invasive and expensive.

Laparoscopy is indicated in women with a suspicion of endometriosis (dysmenorrhea, pelvic pain, deep dyspareunia) or pelvic adhesions/tubal disease (history of pelvic pain, complicated appendicitis, pelvic infection, pelvic surgery, or ectopic pregnancy) based on history, physical examination, or HSG.^{53, 54}

When we perform laparoscopy, we also perform chromotubation to assess tubal patency and hysteroscopy to evaluate the uterine cavity. For this reason, if laparoscopy is planned, then HSG can be omitted.

The advantage of performing laparoscopy early in the evaluation of women suspected of having endometriosis or pelvic adhesions is that surgical therapy can be initiated, while avoiding potentially ineffective or unnecessary empiric medical treatment for ovulation induction. Endometriosis, if identified, can be excised/ ablated at the time of the diagnostic procedure and pelvic adhesions can be lysed.⁵⁵

Tests Of Limited Clinical Utility

Postcoital test - the postcoital test is not recommended. The test has been widely used in infertility investigations since 1866, but has limited diagnostic potential and poor predictive value.⁵⁶

Endometrial biopsy - Endometrial biopsy has been performed for two reasons: (1) to document a secretory endometrium, which is indirect evidence that ovulation has occurred, and (2) to evaluate whether the maturity of the secretory endometrium is in phase (ie, consistent with menstrual cycle date) or out of phase (ie, luteal phase defect). It is not a good test for either indication because it is invasive, expensive, uncomfortable, unnecessary for evaluation of ovulation, and ineffective for assessment of endometrial receptivity (ie, the ability of the endometrium to allow the blastocyst to attach, invade, and implant).

As discussed above, ovulation is optimally assessed using serum progesterone level >3 ng/mL obtained in the late luteal phase.⁵⁷

Basal body temperature records - Basal body temperature charts are the least expensive method for detecting ovulation, but interpretation of the charts can be difficult and subject to wide interobserver variation.⁵⁸

Testing for antibodies - routine testing for antiphospholipid, antisperm, antinuclear, and antithyroid antibodies is not supported by existing data. Although an association between antiphospholipid antibodies and recurrent pregnancy loss has been established, the other autoimmune factors remain under investigation as markers of fertility treatment failure.⁵⁹

Karyotype - There is a general consensus to counsel and offer to karyotype the male partner if there is severe oligospermia, as these men are at higher risk of karyotypic abnormalities. Separate testing for Y chromosome microdeletions may also be offered. We suggest karyotyping women with very early premature menopause (prior to age

40) and both partners if there have been recurrent pregnancy losses. In most other circumstances, karyotyping is not indicated as part of the initial evaluation because of the low incidence of abnormalities in women with unexplained infertility, endometriosis, or tubal factor infertility.⁶⁰

Karyotype may be useful in patients with these conditions who have failed initial treatment approaches and plan to undergo IVF, although the cost-effectiveness of universal karyotype screening prior to IVF has not been established.⁶¹

Summary and Recommendations:

- Infertility evaluation is to be offered to couples who have not been able to conceive after 12 months of unprotected and frequent intercourse. Earlier evaluation (eg, after six months) is indicated in some couples, such as those in whom the female partner is over 35 years of age or has a history of oligo/amenorrhea, known or suspected tubal disease or endometriosis, a history of chemotherapy or radiation therapy, and those in whom the male partner is known to be subfertile.
- The history and physical examination are directed at identifying signs and symptoms suggestive of the etiology of the infertility.

The basic infertility evaluation of all couples consists of:

- Semen analysis.
- Assessment of ovulatory status by history or laboratory testing.
- Determination of tubal patency and presence or absence of abnormalities of the uterine cavity, usually by hysterosalpingogram.
- Ovarian reserve is assessed with a day 3 follicle-stimulating hormone (FSH) level in women over 35 years of age and younger women with risk factors for premature ovarian failure. Other tests such as the clomiphene citrate challenge test (CCCT), antral follicle count, and anti-müllerian hormone (AMH) level are utilized in special circumstances.
- Diagnostic laparoscopy is indicated for women with suspected endometriosis or pelvic adhesions. When we perform laparoscopy, we also perform chromotubation to assess tubal patency and hysteroscopy to evaluate the uterine cavity.

Conflict of Interest : None

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