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Evaluation and Interpretation of Female Infertility

Kadın İnfertilitesinin Değerlendirilmesi ve Yorumlanması

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ABSTRACT

Infertility is a problem that affects one out of seven couples and is defined as the inability to achieve pregnancy despite unprotected intercourse for 1 year. One of the most important enemies of infertile patients is time. In order to reveal the possible causes of infertility, importance should be given to the systematic, rapid, and cost-effective evaluation, and the evaluation should be started with the least invasive examinations. In the evaluation of an infertile woman, a detailed medical history, reproductive history, family history, and physical examination are required to reveal the anatomical and physiological causes of infertility. This evaluation process is also the most suitable period for giving pre-pregnancy counseling, providing necessary counseling for preventive medicine practices, and conducting genetic research and consultations if necessary. In the evaluation of infertility, the presence of ovulation, the structure and function of the female genital system, and semen analysis in the male partner should also be evaluated. During all these evaluation processes, the psychological morbidity caused by the inability to have children should also be taken into consideration and the couples should also be supported in this respect. In this review, it was aimed to present the steps to be followed in the evaluation of an infertile woman in the light of current literature.
Keywords: Biochemical tests; genital system; imaging; infertility; ovulation.

ÖZ

İnfertilite, her yedi çiftten birisini etkileyen bir sorun olup 1 yıl boyunca korunmasız cinsel ilişkiye rağmen gebelik elde edilememesi olarak tanımlanır. İnfertil hastaların en önemli düşmanlarından birisi zamandır. İnfertilitenin olası nedenlerini ortaya çıkarmak için yapılacak değerlendirmenin sistematik, hızlı ve maliyet-etkin olmasına önem gösterilmeli ve değerlendirmeye en az invaziv olan tetkiklerle başlanmalıdır. İnfertil bir kadının değerlendirilmesinde, infertilitenin anatomik ve fizyolojik nedenlerini ortaya çıkarmak için ayrıntılı bir tıbbi öykü, üreme öyküsü, aile öyküsü ve fizik muayene gereklidir. Bu değerlendirme süreci aynı zamanda gebelik öncesi danışmanlık verilmesi, koruyucu hekimlik uygulamaları için gerekli danışmanlığın verilmesi, gerektiğinde genetik araştırma ve konsültasyonların yapılması için de en uygun dönemdir. İnfertilitenin değerlendirilmesinde ovülasyonun varlığı, kadın genital sisteminin yapısı ve işlevi ve aynı zamanda erkek partnerde semen analizi de değerlendirilmelidir. Tüm bu değerlendirme süreçleri boyunca çiftlerde çocuk sahibi olamamanın neden olduğu psikolojik morbidite de göz önüne alınmalı ve aynı zamanda çiftler bu açıdan da desteklenmelidir. Bu derlemede, infertil bir kadının değerlendirilmesinde izlenecek olan adımların güncel literatür bilgileri ışığında sunulması amaçlanmıştır.
Anahtar kelimeler: Biyokimyasal testler; genital sistem; görüntüleme; infertilite; ovulasyon.

INTRODUCTION

If pregnancy cannot be achieved despite regular sexual intercourse for 1 year in women younger than 35 years of age, and for 6 months in women over 35 years of age, infertility evaluations should be started. This period can be kept shorter than 6 months in women aged 40 and over, women with menstrual irregularities, or women with known risk factors for infertility, for example, those with endometriosis, those with genital system anomalies, those with a history of chemotherapy or radiotherapy, and those with a known male factor in their partner (1,2).

In the evaluation of an infertile woman, a detailed medical, reproductive history, family history, and physical examination are required to reveal the anatomical and physiological causes of infertility. This evaluation process is also the most suitable period for giving pre-pregnancy counseling, providing necessary counseling for preventive medicine practices, and conducting genetic research and consultations if necessary.

Inability to have children causes significant psychological morbidity for couples. The process, which includes making the diagnosis of infertility, and making the necessary evaluations and treatments, is also a very stressful process for infertile couples from a psychological point of view. When evaluating an infertile couple, clinicians should also consider the possibility that they may have mood states such as depression, anger, anxiety, and marital conflicts (2).

As with all diseases, the evaluation of an infertile woman begins as soon as the patient enters the examination room. The physician can obtain many clues from the patient's external appearance (short stature, extreme thinness, obesity, male pattern baldness, presence of acne, moon face, etc.), even from her speech (voice thickening due to virilization). Afterward, the evaluation continues with taking a detailed anamnesis of the patient and her family, performing a physical examination, and performing the necessary laboratory tests and imaging.

Anamnesis

As with all patients, a detailed anamnesis is one of the most basic parts of the examination in the evaluation of an infertile woman. The patient's age, how long the pregnancy is desired, the frequency of coitus, the drugs used (including those taken without a prescription), alcohol, smoking, history of illegal substance use, occupation, presence of stress, weight/diet changes, previous pregnancies, if any, should be questioned in detail. Low body weight, heavy exercise, presence of psychological stress may cause hypothalamic amenorrhea (3).

Menarche age, number of menstruation in a year, average menstrual cycle length, and whether menstrual cycles are painful should be questioned in the menstrual history of the patients. Regular cycles occurring at intervals of 21-35 days accompanied by moliminal symptoms (breast tenderness, ovulatory pain, a feeling of bloating in the body, etc.) show that the woman is ovulatory with a probability of 99.5% (4). The probability of sporadic anovulatory cycles in a regularly menstruating woman is very low (1-14%). Even in an ovulatory woman, slight shifts in cycle duration are normal (5). In a study involving more than 1000 cycles, 56% of women had a shift in menstrual cycle duration of >5 days over a 6-month period and 75% of women at 1-year follow-up (6).

A history of oligomenorrhea or amenorrhea is sufficient to clinically diagnose anovulation. The etiology of anovulation should be investigated in these patients, but tests to confirm ovulation are not required. In a meta-analysis of more than 12000 women, normal (28-31 days) or long (32-35 days) and short (21-27 days) menstrual cycle duration was shown to be associated with reduced ovarian reserve (7).

The presence of intermittent bleeding suggests problems such as polyps and chronic endometritis. Cervicitis, cervical polyps, and cervical dysplasias should be considered in postcoital bleeding. In heavy and/or prolonged menstrual bleeding, myomas, bleeding diathesis (Von Willebrand's disease, etc.), and adenomyosis are among the probable diagnoses. In the gynecological history, sexually transmitted infections, previous surgeries, history of pelvic inflammatory disease (PID), presence of abnormal pap smear, dyspareunia (pain during sexual intercourse), and pelvic/abdominal pain should be questioned. In the presence of severe dysmenorrhea, dyspareunia, and pelvic pain, endometriosis should be kept in mind. Ovarian reserve usually does not decrease in young women who have undergone a unilateral oophorectomy because there are many primordial follicles in the other ovary. However, unilateral oophorectomy in older women may cause a decrease in ovarian reserve (8).

The contraceptive methods they used before should be questioned in detail. For example, patients should be told that there may be a fertility delay of up to 18 months in the use of intramuscular depo medroxyprogesterone (9). It should be kept in mind that in infertile women with a history of using an intrauterine device (IUD) as a contraceptive method, IUD fragments may remain in the uterine cavity or that the patient may be misremembering that the IUD was removed although it had not been removed (10).

Symptoms of hyperandrogenism (hirsutism, male pattern hair loss, acne, virilization) should be questioned. These symptoms suggest polycystic ovary syndrome (PCOS). Weight gain and the presence of PCOS in the family should also be evaluated in favor of PCOS (11). It should be questioned how long hirsutism has existed. In the presence of severe hirsutism of sudden onset, androgen-producing tumors should be investigated. Congenital adrenal hyperplasia (CAH) may be partial and diagnosis may be delayed in patients with hyperandrogenism since CAH is not considered among the preliminary diagnoses (11).

Symptoms of thyroid diseases (weight gain, constipation, palpitations, heat/cold intolerance, etc.), the existence of galactorrhea, sexual dysfunctions, frequency, and timing of coitus should be questioned.

Family history should be questioned in detail, including individuals with infertility, birth defects, genetic mutations, and intellectual limitations. Premature ovarian insufficiency (POI) may develop in women with fragile X premutation, while male relatives of these women may have learning problems, developmental delay, or autism. Menarche history of family members and whether they have menstrual disorders should be questioned (3).

Physical Examination

Secondary sex characteristics of both partners should be evaluated. Insufficient development or absence of secondary sexual characteristics in women with primary

amenorrhoea suggests hypogonadotropic or hypergonadotropic hypogonadism. In patients with primary amenorrhea, physical examination findings such as short stature, square-shaped rib cage, and low hairline suggest Turner syndrome (3).

Visual field examination should be performed in cases with symptoms suggestive of headache, galactorrhea, or pituitary dysfunction. In the presence of hirsutism, modified Ferriman-Gallwey scoring should be done (3).

In the gynecological examination, adnexal tenderness, presence of mass, uterine mobility, shape, and size should be evaluated. Tenderness in the adnexal region or pouch of Douglas should suggest the presence of endometriosis or PID. The presence of fibroids can cause an increase in the size of the uterus and irregularity in its contours. The absence of uterine mobility should suggest the presence of pelvic adhesions (1).

The presence of vaginal and/or cervical anomalies in gynecological examination suggests Müllerian anomalies. Abnormal vaginal/cervical discharge may indicate infection. Chlamydia trochomatis and gonorrhea infections are among the common causes of tubal subfertility. Each acute episode of PID causes subfertility in 10-15% of cases (12).

The body mass index (BMI) of the patients should be calculated. Abnormalities in BMI may accompany problems such as hypothalamic amenorrhea, and PCOS hypogonadism. Obesity causes insulin resistance, a decrease in serum sex hormone binding globulin (SHBG) levels, and thus an increase in free androgen levels.

Ovulation

15% of all infertility causes and 40% of female infertility are due to ovulatory disorders. Although ovulation disorders mostly cause menstrual disorders such as oligomenorrhea/amenorrhea, they may rarely be present in women with regular menstruation. The underlying cause of the ovulation disorder should be investigated and treated if a specific cause is found. The most common causes of ovulation disorder include PCOS, obesity, perimenopause, weight changes, excessive exercise, thyroid dysfunction, and hyperprolactinemia (1).

Almost all women with regular cycles are ovulatory. About 60% of women with hyperandrogenism and regular cycles are ovulatory. The midluteal (1 week after ovulation or 7 days before the expected menstruation) serum progesterone value can be measured to indicate ovulation. Although a single serum progesterone measurement >30 nmol/L (>3 ng/ml) is generally used as an ovulation finding, ovulation may occur at lower values. A value of ≥15.9 nmol/L for serum progesterone has been shown to have 89.6% sensitivity and 98.8% specificity in detecting ovulation (13). Since serum progesterone levels fluctuate up to 7 times within hours, a single progesterone measurement should not be used to indicate the quality of the luteal phase, although it is used to indicate ovulation (14).

There are urinary luteinizing hormone (LH) detection kits produced to detect the mid-cycle LH peak (surge) occurring 1-2 days before ovulation and thus to indicate ovulation. Detection of urinary LH is an indirect indicator of ovulation (15). Urinary kit results show a good correlation with serum LH peak, especially when performed in the middle of the day or in the evening. In PCOS cases, the basal LH level is tonically high, which may cause false positive results in urinary kits. Ease of use, reliability, and the rate of false positive and false negative results may vary according to the kit brand used (16). The rate of false positivity and negativity in urinary kits is around 5-10% on average (1). In cases where no ovulation can be detected using a urinary kit at home, it may be useful to measure serum LH levels.

There is usually a biphasic body temperature pattern in ovulatory cycles and a monophasic temperature pattern in anovulatory cycles. Because the thermogenic effect of progesterone released from the corpus luteum with ovulation on the hypothalamus causes an increase in body temperature. Therefore, if the body temperature is regularly measured sublingually every morning from the first days of the menstrual cycle (while the body is in a basal state, not getting out of bed yet, not eating or drinking anything), an approximate increase in body temperature is detected during the luteal period (17). In a normal cycle, body temperature increases 1-2 days after the LH surge and this increase continues to be detected for at least 10 days. The 7 days before this increase is detected is the period when fertility is highest. However, since the increase in body temperature shows ovulation retrospectively, it is useless to determine the coitus time in women who want to become pregnant. In addition, sometimes the biphasic temperature pattern may not be detected in ovulatory cycles. The body temperature monitoring test is not a routinely recommended test for detecting ovulation (1).

Daily ultrasonographic follow-up (showing the disappearance of the growing follicle) or endometrial biopsy (demonstrating the secretory endometrium) to detect ovulation is not part of the routine evaluation because they are too expensive or invasive (18). In addition to detecting ovulation, endometrial biopsy has also been used in the past to demonstrate a luteal phase defect. However, it is no longer used for this purpose as it is an expensive, invasive procedure and is useless in evaluating endometrial receptivity (19).

Biochemical Tests

In all women with amenorrhea, pregnancy should be excluded by the serum beta human chorionic gonadotropin (beta-hCG) analysis. PCOS is usually associated with increased gonadotrophin releasing hormone (GnRH) pulsatility (increased serum LH level), while hypothalamic amenorrhea or hyperprolactinemia is associated with decreased GnRH pulsatility (decreased serum LH level) (11). While serum estradiol level is usually normal in PCOS cases, it may be decreased in hypothalamic amenorrhea, POI, and hyperprolactinemia cases. High serum androgen levels can be detected in association with PCOS or CAH (3).

If the total testosterone level is >200 ng/ml, computed tomography imaging of the ovaries and adrenal glands is recommended to exclude androgen-producing tumors (1).

In cases with hyperandrogenism, the level of 17-hydroxy progesterone should be measured in the early follicular phase of the menstrual cycle, and if it is found to be high (>200 ng/dl), the patient should be consulted with endocrinology for stimulation tests to exclude the diagnosis of non-classical 21 hydroxylase deficiency (3).

Serum prolactin level measurement is not routinely recommended in infertile patients. Serum prolactin level

should be measured in those with galactorrhea, amenorrhea, or oligomenorrhea. Serum prolactin level shows diurnal variation and reaches its highest level at night during sleep. Prolactin level can be measured at any time during the day. Slightly elevated prolactin levels (500-1000 mIU/L) may be due to reasons such as exercise, nipple stimulation, coitus, and stress related to venipuncture. Dopamine antagonist drugs (antiemetics, antipsychotics), dysfunctional pituitary adenomas causing disconnection hyperprolactinemia, and pituitary adenomas producing prolactin cause high prolactin levels. If the prolactin level is >1000 mIU/L in repeated measurements and if there are complaints of accompanying amenorrhea, galactorrhea, visual field disorders, and headache, patients should be consulted with endocrinology (20).

In cases with hyperprolactinemia, the elevation of macroprolactin (large aggregates of prolactin molecules in complex with antibodies), a type of prolactin with low bioactivity, should also be considered.

Measuring follicle stimulating hormone (FSH) and estradiol levels in women presenting with amenorrhea is useful in the differential diagnosis of women with ovarian failure (high FSH, low estradiol) from women with hypothalamic amenorrhea. Women mostly go through menopause between the ages of 45-55 (21). However, 1% of women enter menopause before the age of 40, and this is defined by the term 'POI'. POI is diagnosed in a woman younger than 40 years of age who presents with amenorrhoea, if the FSH level measured twice, at least 4 weeks apart, is >25 IU/L. The clinical course may be variable in POI cases according to natural menopause, and spontaneous pregnancies may occur in approximately 20% of cases. Therefore, it is more appropriate to use the term POI instead of early menopause when describing these cases. It is important to investigate the etiology in POI cases, including possible causes such as autoimmune causes, chromosomal abnormalities, and fragile x syndrome premutation. Oocyte donation can be offered as an option to women diagnosed with POI and wanting a child (22).

Cushing's syndrome may cause menstrual irregularities accompanied by weight gain, and hyperandrogenism. Therefore, if there are clinical signs suggesting Cushing's syndrome (red-purple striae, plethora, proximal muscle weakness, ecchymosis without trauma, unexplained osteoporosis, etc.) in patients presenting with menstrual cycle disorders, patients should be referred to endocrinology for further evaluation.

Overt thyroid dysfunctions can cause menstrual and ovulatory disorders and thus subfertility. However, The National Institute for Health and Care Excellence (NICE) recommends that thyroid function tests be performed only in women with symptoms of thyroid disease and not in all menstrual irregularities (23).

Ovarian Reserve Tests

A woman's age is one of the factors that most affect the risk of subfertility and the response to fertility treatments. Ovarian reserve reflects the number of oocytes in the ovary and is an indicator of a woman's fertility potential. Decreased ovarian reserve indicates that a woman who is in the reproductive period and who has regular menstruation will have a lower response to ovarian stimulation compared to her peers. However, female age is the single most important determinant of fecundity and is more valuable than ovarian reserve markers in predicting fertility-related clinical outcomes such as 'time to conception' and 'at what age to enter menopause'. Therefore, ovarian reserve markers should not be used to determine a patient's likelihood of spontaneous conception (24).

If a decreased ovarian reserve is detected in the evaluations, this does not mean that the woman cannot conceive or is subfertile. Ovarian reserve markers are useful in estimating the number of follicles that will respond to gonadotropin stimulation and the number of oocytes to be collected in in vitro fertilization (IVF) treatments. For this reason, evaluation of ovarian reserve markers before IVF treatments may be useful in adjusting the gonadotropin dose in patients who are predicted to have an excessive or low response, and in counseling patients to have realistic expectations from treatment (25). While interpreting the results of all ovarian reserve tests, the patient's age, risk factors, previous treatments, and the patient's response to reproductive treatments should also be considered. Ovarian reserve tests are not helpful in fertile women and should not be used for the purpose of routine screening.

Ovarian reserve tests include both biochemical analyzes and ultrasonographic imaging of the ovary. Total antral follicle count (AFC), 2-10 mm in size, in the ovaries in ultrasonography (USG) should be done in the follicular phase. Although it is not a definitive criterion accepted all over the world, AFC <4 may be useful in predicting low response and AFC >16 in predicting excessive response.

Anti-mullerian hormone (AMH) is a glycoprotein that is a member of the TGF-beta family and is secreted by small antral (<8 mm) and preantral follicles. During the menstrual cycle, there is minimal fluctuation in serum AMH level. Therefore, serum AMH level can be measured on any day of the menstrual cycle (24). When different kits are used in AMH measurements, different results can be obtained (26). Thanks to the developments in the kits used for measurement over the years, serum AMH level measurements have become more reliable.

In IVF treatments, AMH level correlates with the number of eggs to be collected and is the biomarker that best predicts poor or excessive response. However, because of its low diagnostic sensitivity in predicting live birth, low AMH values should not be used as a criterion for not accepting patients for IVF treatment (27). Although there is no definitively accepted international threshold value, NICE states that <5.4 pmol/L (Beckman Coulter generation II assay) can predict low ovarian response, and a value >25 pmol/L can predict excessive response (23).

In some patient groups, such as infertile patients, cancer patients, and patients with significant ovarian damage due to radiotherapy or surgery, serum AMH levels may be useful to detect a decrease in the ovarian follicle pool (28). However, in women without infertility problems, serum AMH levels are not useful in predicting future fertility potential, time to conception, or age at menopause (29).

The serum AMH level is increased in PCOS cases and has the potential to be used as a diagnostic criterion for PCOS in the future, although not yet (30).

Although measurement errors may occur for technical reasons in both serum AMH level and total AFC measurement, these two indicators correlate well with each

other and can be used separately or in combination for ovarian reserve (24).

In the guideline of the American Society for Reproductive Medicine (ASRM), AMH, AFC, basal FSH, and estradiol measurements are recommended as ovarian reserve markers. Increased serum FSH (>8.9 IU/L) level in the early follicular phase indicates decreased ovarian reserve (1). NICE guidelines do not recommend using markers such as ovarian volume, ovarian blood flow, serum estradiol level, serum inhibin B level, or clomiphene citrate challenge test to predict fertility treatment outcomes (23).

Imaging

USG is useful in the evaluation of uterine/ovarian anatomy and morphology and AFC. Uterine abnormalities can be detected in 16.2% (13% polyps, 2.8% submucous fibroids, 0.3% adhesions) of patients who applied for infertility evaluation (31). The incidence of these uterine abnormalities increases to 39.6% in those with abnormal uterine bleeding. Therefore, it is important to evaluate infertile cases with USG. Transvaginal USG (TVUSG) is valuable in the diagnosis of pathologies such as fibroids, polyps, and adenomyosis that play a role in infertility. Since intramural fibroids cannot be seen in hysteroscopy (HS) or hysterosalpingography (HSG), USG is used for diagnosis.

HSG or hystero contrast sonography (HyCoSy), sonohysterography (SHG), and laparoscopic chromopertubation (gold standard) can be used to evaluate tubal patency.

HSG is valuable in terms of showing whether the occlusion in the tuba is proximal or distal, giving an idea not only about the patency of the tuba but also its structure. When performing HSG, the delayed transmission of contrast medium suggests fimbrial phimosis or loculation of contrast medium at the tip of the tubal suggests peritubal adhesions (1). HSG has a sensitivity and specificity of 65% and 83%, respectively, in demonstrating tubal patency. HSG is more successful in demonstrating distal tubal occlusion than proximal occlusion (32). If a proximal occlusion is seen in both tubes, the possibility of transient tubal/myometrial contraction or displacements in catheter position should be considered rather than a true occlusion, and additional tests (eg, repeat HSG withdrawal, fluoroscopic/hysteroscopic selective tubal perfusion, laparoscopic chromopertubation) should be considered to see if there is a true occlusion (1).

HSG may also be useful in the diagnosis of congenital uterine anomalies as it shows the size and shape of the uterine cavity. However, HSG is not sufficient in the differential diagnosis of the septate uterus and bicornuate uterus. Magnetic resonance imaging or three-dimensional USG can be used for this distinction. Although HSG is useful in the evaluation of polyps and submucous fibroids extending into the cavity, it has low sensitivity (50%) and a low (30%) positive predictive value (33). The fact that the patient is given X-rays is among the disadvantages of HSG.

Diagnostic HSG also has a therapeutic effect. In a systematic review including 12 randomized studies, it was shown that the pregnancy rate in subfertile cases who underwent HSG with oil-based media was 3.3 times higher than in those who did not have HSG. That increase in pregnancy rates was found to be similar if the medium used was water-based or oil-based (odds ratio, OR: 1.21, 95% confidence interval, CI: 0.95-1.54) (34).

HyCoSy is based on the principle of imaging the contrast agent (often a contrast agent containing air bubbles) introduced into the uterine cavity with a transcervical catheter, accompanied by USG. Compared to the standard HSG, the experience of the person performing the HyCoSy is more important. HyCoSy has a sensitivity of 76-96% and a specificity of 67-100% in demonstrating tubal patency and has >%90 accuracy for evaluation of uterine cavity when compared with HS. (35). In a systematic review published in 2014, HSG and HyCoSy were shown to have similar diagnostic values in demonstrating tubal occlusion in subfertile women (35).

Demonstrating tubal patency with HS is a newly used method. In a meta-analysis including 6 studies, the sensitivity and specificity of HS in evaluating tubal patency were reported as 88% and 85%, respectively (1).

In SHG, saline is administered into the uterine cavity with the help of a catheter. SHG is useful in demonstrating the shape and size of the uterine cavity and shows that at least one tuba is open (not which tuba is open) by monitoring fluid collected in the Douglas pouch. SHG has a high (>90%) positive and negative predictive value in the detection of intrauterine pathologies, synechia, polyps, and submucous myomas (33).

Although laparoscopy is the gold standard for the evaluation of tubal patency, it is not a routinely used method in infertility evaluation. However, if laparoscopy is to be performed for another indication, the patency of the tuba can be shown by chromopertubation performed by giving diluted methylene blue or indigo carmine dye from the cervical canal, or if there is tubal obstruction, the location of this obstruction (proximal or distal segment) can be determined. Laparoscopy also allows the diagnosis and treatment of fimbrial phimosis or peritubal adhesions because these problems may not be detected by methods such as HSG or SHG. If HSG or laparoscopy findings suggest proximal tubal occlusion, fluoroscopic/hysteroscopic elective tubal cannulation is performed to confirm the diagnosis and provide tubal recanalization (1).

Some clinics request a chlamydia antibody test (CAT) in the first step when evaluating tubal patency. If the antibody is positive, it suggests a tubal pathology but does not provide a prediction of whether the tuba is open or not. For the diagnosis of distal tubal disease, CAT has an average sensitivity (40-50%) and positive predictive value (60%), while its negative predictive value is quite high. Therefore, a positive CAT requires additional evaluation for tubal evaluation, while a negative CAT suggests no tubal damage (1).

HS is the gold standard method for the diagnosis and treatment of intrauterine pathologies. However, when performed alone, HS does not provide any information about the myometrium, fallopian tubes, and adnexal structures. Operative HS is a more expensive and invasive method than HSG or SHG. The use of office HS, which has a smaller diameter compared to operative HS, is more comfortable for the patient, has a lower cost, and allows the treatment of some intrauterine pathologies. If imaging of the tuba is not required, SHG or office HS will be sufficient for imaging the cavity only (1).

Evaluation of Cervical Factor

Evaluation of the cervical canal in a gynecological examination is important in detecting pathologies such as cervical stenosis and chronic cervicitis. Infectious cervicitis should be treated. It is very unlikely that abnormalities in cervical mucus production alone are a cause of infertility. A sperm mucus penetration test or postcoital test is not recommended for infertility evaluation. The postcoital test is a historical test used in the diagnosis of cervical-factor infertility, based on the principle of microscopic examination of the cervical mucus sample and detection of motile sperm in the first hours after coitus that occurs before the expected ovulation. Postcoital testing is no longer recommended in the evaluation of an infertile woman since the postcoital test is subjective, has low reproducibility, low patient compliance, does not change our clinical management, and does not predict the potential for conception (36).

Evaluation of Peritoneal Factors

Peritoneal factors due to endometriosis, and pelvic/adnexal adhesions may cause or contribute to infertility. The patient's history and/or physical examination findings may give an idea of peritoneal factors, but they are not sufficient for diagnosis. If no reason was found to explain infertility in the evaluation of women, peritoneal factors should be considered. The definitive diagnosis of peritoneal factors can be made by laparoscopy. Mild or minimal endometriosis has little effect on fertility. Most women with severe adnexal adhesions have data suggesting the presence of these adhesions either in the history (pelvic pain, presence of endometrioma on ultrasound, dyspareunia, previous pelvic surgery or infection), or in HSG findings.

As a result, laparoscopy is not routinely recommended in infertile women unless there are findings suggestive of pelvic pathology (37).

Karyotyping

Karyotyping should be requested in women with primary amenorrhea due to hypergonadotropic hypogonorrhea and/or with the phenotypic features of Turner syndrome, in women with ambiguous external genitalia, and in women with a presumptive diagnosis of androgen insensitivity syndrome. Karyotyping and fragile X premutation tests should be requested in women with a personal or family history of early (<40 years) ovarian failure.

If the male partner has severe oligospermia or azoospermia, karyotyping and additional Y chromosome microdeletion tests should be recommended.

If there is a history of recurrent pregnancy loss, karyotyping of both partners should be performed (3).

Antibody Tests

Antiphospholipid, antisperm, antinuclear, and antithyroid antibodies are not required in routine infertility evaluation. It is recommended to evaluate women with recurrent pregnancy loss in terms of antiphospholipid syndrome (38).

Mycoplasma Culture

Routine culture of ureaplasma urealiticum and mycoplasma hominis is not recommended in the evaluation of infertile women because these organisms have not been shown to have a significant role in female infertility (39).

CONCLUSION

Female fertility declines with advancing age, and the single most important predictor of fecundity is age. A detailed medical, reproductive anamnesis, family history, and physical examination are necessary to reveal the anatomical and physiological causes of infertility. Infertility evaluations should be started after 12 months in women <35 years old, after 6 months in women aged ≥35 years, and immediately in women aged >40 years. In the evaluation of infertility, the presence of ovulation, the structure and function of the female genital system, and semen analysis in the male partner should be evaluated. HSG or SHG may be preferred for the evaluation of tubal patency. In cases without hirsutism, the presence of regular menstrual cycles at intervals of 21-35 days is sufficient to indicate ovulation. Ovarian reserve tests should not be used for screening in non-infertile women. Laparoscopy, advanced sperm function testing, postcoital testing, thrombophilia testing, immunologic testing, karyotype, endometrial biopsy, and serum prolactin have no place in the routine evaluation of infertile women.

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