

# Diagnosis and management of couple infertility

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## ABSTRACT

It is estimated that about 10-15% of couples of fertile ages suffer from infertility worldwide, in over a third cases of infertility are caused by female infertility, but most often the gynaecologist is the first provider of medical services that the couple reaches. The studies in this field are multiple and with a very accelerated rhythm, this study aimed to make a review of the most relevant new studies in the field of infertility.

**Keywords:** infertility, infertility diagnosis, infertility conduct

## INTRODUCTION

Infertility is defined as failure to achieve pregnancy after 12 months or more of unprotected sex for women under 35 and after 6 months in women over 35 according to the American College of Obstetricians and Gynaecologists. Couples who fall into the definition of infertility should be offered a clinical evaluation and specialized investigations. The initial assessment of the couple will also include a thorough investigation of lifestyle and sex life and will be useful in quickly identifying those couples who have a low chance of conceiving unassisted.

For the examination of infertile women, the tests mainly focus on ovarian reserve, ovarian function and structural abnormalities, the evaluation includes imaging tests that can highlight pelvic pathologies, tubal permeability and laboratory tests to assess ovarian function. For the examination of the infertile man, semen analysis and a whole pathological history are the first things to evaluate.

## PATIENT HISTORY

A complete medical history must be obtained from infertile couples, information that can be targeted to indicate possible causes of infertility, duration of infertility and possible treatments performed, data related to menstrual history, data

related to obstetrical history, possible contraceptive methods used, sexual dysfunctions, surgical and gynaecological history, thyroid pathology, family history of reproductive problems, premature menopause or genetic defects in the family, data on occupation and risk of exposure and consumption of toxic or tobacco.

## CLINICAL EXAMINATION

Among the pathology and risk factors that can be discovered on a general clinical examination, there are more factors to discuss in the clinical examination.

Patient's weight plays an important factor in infertility, obese and overweight patients have a high risk of menstrual disorders, anovulatory cycles and infertility (1,2), and also obesity has a negative impact on all ART (Assisted reproductive technology) and obstetric results (3), Underweight patients also have a risk of infertility, losing 5% to 10% of weight has beneficial results on endocrine parameters and improved ovulation and fertility rate (4).

Thyroid pathologists are strongly involved in infertility, any abnormality in the examination of the thyroid should be further evaluated, the assessment of thyroid function is indicated in patients with low fertility and those with repeated abortions. Studies in this pathology show that in patients with antithy-

roid antibodies present it is recommended to keep the TSH value between 2.5 and 4 mIU/l for favourable results on fertility (5). Also, new studies seem to show a correlation between thyroid pathology in men and a negative impact on sperm quality (6).

Presence of breast secretions and their character: One cause of infertility may be hypersecretion of prolactin, which may be idiopathic or caused by a tumour, studies show that dopaminergic treatment significantly improves fertility outcomes in patients with hyperprolactinemia as a cause of infertility (7,8), there also appears to be a strong correlation between male infertility and elevated prolactin levels in men (9).

Signs of excess androgens (hirsutism, acne, oily skin, alopecia, *Acanthosis nigricans*, menstrual irregularities, clitoral enlargement and thick voice) which may indicate a hormonal disorder such as PCOS (polycystic ovary syndrome).

Vaginal or cervical abnormalities (STDs, Pap-T): Vaginal infections can be a cause of infertility due to changes in the vaginal flora (10), the effects of vaginal infections on infertility are further studied (11), but sexually transmitted infections are known to be the main cause of pelvic inflammatory disease and tubal blockage (12).

Smoking patients have a lower success rate for fertility treatment than former smoking patients (13). There is also a negative impact on sperm quality and smoking (14).

## TESTS TO ASSESS THE CAUSES OF INFERTILITY

Tests performed to assess certain causes of infertility include laboratory and imaging tests, for the evaluation of women the tests focus on assessing the ovarian reserve, ovulation function, possible structural abnormalities.

The investigation of the infertile woman begins with the general evaluation of good liver and kidney function, complete blood count and imaging investigation by general and pelvic ultrasound, the investigation of the infertile man also begins with blood tests of liver, kidney, complete blood count and semen analysis.

The postcoital test: It is performed from the vaginal mucus after 12-24 hours after sexual intercourse on the day of ovulation, sperm must be activated and begin their mobility to the uterine cavity, the presence of a thinner mucus can affect their mobility, but the prediction of fertility with this test is quite weak, in many parts this test is abandoned (15), NICE Clinical Guide for Infertility 2017 does not recommend performing the postcoital test to assess infertility.

Immunological testing in certain specific pathologies (anti-beta2 glycoprotein 1, anti-cardiolipin an-

tibodies, anti-DNA/histone antibodies, anti-mitochondrial antibody, antinuclear antibody, anti-ovarian antibodies, anti-phospholipid antibodies (apa), anti-sperm antibody (male), anti-sperm antibody (female), anti-thyroglobulin antibody, embryo toxic factor, human lymphocyte antigen, leukocyte antibody detection, natural killer cells, reproductive immunophenotyping) has a very specific indications, not to be tested in the first steps, most of them are used to increase the chance fertility outcome in IVF (In vitro fertilization) procedures.

Anti-sperm antibodies have been found not only in cases of infertile couples but also in fertile women and men, with no recommendation to perform anti-sperm antibodies except in cases of in vitro fertilization (16). In cases with anti-sperm antibodies present, intra cytoplasmic injection of sperm appears to be the solution, completely avoiding the risk of failure due to antibodies (17), new studies show that there is more than one type of anti-sperm antibodies, further studies are needed to determine the link between the presence of antibodies and the problem of infertility (18).

Endometrial microbial evaluation is a new era in infertility assessment (19), many studies show that changes in endometrial microbiome affect implantation in cases of in vitro fertilization (20,21,22), Changes in endometrial microbiome appear to be closely related to vaginal infections (23).

The presence of fragmented DNA in the nucleus of spermatozoa negatively influences reproductive outcomes. Sperm DNA fragmentation test uses flow cytometry to measure the stability of sperm chromatin and provide an estimate of the percentage of spermatozoa with fragmented DNA.

## OVARIAN RESERVE

The ovarian reserve, the term used to describe the reproductive potential of the ovaries, is represented by the number of primordial follicles available for development and fertilization at some point in life. A woman is born with about 2 million primary follicles, but at the beginning of menarche only about 400,000 follicles remain due to natural follicular atresia. When a woman reaches the age of 30, the rate of oocyte depletion begins to increase, and when she reaches the age of 30, the number of follicles decreases to about 25,000, while a significant increase in the rate of miscarriages.

The first test that was introduced to assess ovarian reserve was follicle-stimulating hormone (FSH) on day 3 (1988), followed by the clomiphene citrate challenge test (CCCT, 1989), a gonadotropin-releasing hormone agonist (GnRH, 1989), inhibin B (1997), antral follicular number (AFC, 1997) and anti-müllerian hormone (AMH, 2002). Most of these measures,

however, have poor predictive value, often because they are indirect measures of ovarian reserve (e.g., FSH, CCCT, GnRH agonists) or have substantial inter-cyclic or inter-cyclic variability (e.g., FSH) (24).

Basal follicle stimulating hormone (FSH) levels measured on the 3rd day of the menstrual cycle is the most widely used method to assess the ovarian response to stimulation for over two decades. An increase in FSH levels occurs due to follicle depletion. FSH measurement is easy and inexpensive (25).

Serum AMH is produced by granular cells of the antral follicles and is therefore another serum marker of the ovarian reserve. The values of serum AMH results remain stable during the menstrual cycle, which is why there are no recommendations for harvesting the analysis on a certain day of the menstrual cycle (26,27).

Test values for ovarian reserve should be interpreted in the context of age, are good predictors of ovarian response to stimulation and poor predictors of gestational capacity (28,29,30). the following parameters may indicate a low ovarian reserve: anti-müllerian hormone (AMH) with a value of less than: 1 ng/ml and number of antral follicles less than 5-7 and follicle stimulating hormone (FSH) greater than 10 IU/L.

## OVULATION DYSFUNCTION

Ovulation dysfunction defined as a history of oligomenorrhea or amenorrhea or recurrent luteal progesterone levels less than 3 ng/ml or both is a significant diagnosis of female infertility. For many women, a menstrual history may be enough to assess ovulation function. However, up to a third of women with normal menstrual cycles are anovulatory, so confirmation of ovulation should be considered. Objective quantification of ovulation can also be obtained with a measurement of mean luteal progesterone, positive tests of luteinizing hormone. A progesterone value greater than 3 ng/ml is evidence of ovulation, anovulation may be related to obesity, hypothalamic and pituitary dysfunction, PCOS (polycystic ovary syndrome) and other causes. Polycystic ovary syndrome is the most common cause of infertility due to ovulation dysfunction (31). There is no universally accepted definition of PCOS; however, it can be diagnosed on the basis of the criteria of the National Institutes of Health, Rotterdam or excess androgens and PCOS Society (32,33,34), the first presence of at least two of the following: irregular periods, excess androgens, polycystic ovaries.

Thyroid disease and hyperprolactinemia can cause ovulation dysfunction, ranging from an inadequate luteal phase to oligo-ovulation to amenorrhea. Serum thyrotropin should be measured in

women with ovulation dysfunction, infertile women or those with signs of thyroid disease. Serum prolactin should be measured in infertile women with irregular menstruation or other signs and symptoms of hyperprolactinemia.

## THE TUBAL FACTOR

Tubal infertility due to peritoneal adhesions is the most common cause of female infertility, diagnosed in about 30% to 35% of infertile couples. *Neisseria gonorrhoea* and *Chlamydia trachomatis* are the main causes of pelvic inflammatory disease (35). Tubal permeability testing should be performed before initiating ovulation induction treatment and not before completing the full list of possible causes of couple infertility, male infertility and the causes organic. For tubal permeability testing, the gold standard is laparoscopy (36,37), but tubal permeability imaging techniques appear to be of significant accuracy especially in the case of permeable fallopian tubes, hysterosalpingography (HSG) is a screening method with fairly good results. accepted and much less invasive (38,39). For hysterosalpingography there are many techniques, with different costs and the difference in accuracy of the results. In a meta-analysis that included 24 studies and 1,340 patients, HSG with radiographic imaging had a sensitivity of 89% (95% confidence interval [CI], 87-91%), and 93% specificity (95% CI, 91-94%) (40). HSG with nuclear magnetic resonance imaging has a sensitivity of 100% (95% CI, 98% -100%), and a specificity of 82% (95% CI, 74-89%) (40). Another meta-analysis studied the accuracy of sonohysterography (HyFoSy) with ultrasound imaging and included a number of 622 patients with a result that estimated sensitivity and specificity at 99% (95% CI, 0.89-0.99) and 91% (95% CI, 0.53-0.98) (41).

a meta-analysis that included 3,852 patients to study the effects of tubular instillations with oily substances after hysterosalpingography shows favourable results for patients who had instillations with odds ratio (OR) 1.67 (95% CI, 1.38-2.03) (42).

In recent years, a correlation has been attempted between anti-chlamydia IgG antibodies and the result of tubal permeability tests, but recent studies show a weak correlation between these two indicators (43,44).

In the case of blocked fallopian tubes, surgery may be a curative treatment for certain cases, the success rate of surgery is estimated to be between 9% for severe damage and 69% for moderate and mild damage (45), a meta-analysis that included 27 Observational studies and 1720 patients show that the pregnancy rate obtained after surgical treatment of clogged fallopian tubes is about 27% (95% CI 25-30%) (46).

## THE UTERINE FACTOR

Uterine infertility is estimated to affect 1 in 500 women of childbearing potential (47,48). Uterine factors associated with infertility can be classified into congenital factors and gained factors, gained factors include endometrial polyps, synechiae and leiomyomas, congenital factors are Müllerian abnormalities.

For the examination of the female genitals, transvaginal ultrasound is recommended, and in case of the suspicion of the presence of certain pathologies, other more invasive techniques can be used. Transvaginal ultrasound is sensitive in proportion of approximately 90% to 99% for the detection of uterine fibroids (49). HyFoSy or hysteroscopy improves sensitivity for the detection of submucosal fibroids (50,51). Hysterosalpingography is limited in its ability to identify masses or adhesions of the uterine cavity because these structures are not radiopaque.

Direct visualization of the uterine cavity by hysteroscopy provides the most definitive method of diagnosing endometrial polyps, uterine synechiae and submucosal fibroids (52). Hysteroscopy is indicated for the confirmation and treatment of intra cavity lesions detected by other imaging methods (53).

Fibroma is present in up to 27% of patients seeking reproductive assistance. There is a clear consensus that submucosal fibroids, which distort the uterine cavity, have detrimental effects on fertility with decreasing clinical pregnancy rates and birth rates. Studies show that fertility outcomes are low in women with submucosal fibroids, and removal seems to be beneficial. Subserous fibroids do not affect fertility outcomes, and removal does not provide benefits. Intramural fibroids appear to decrease fertility, but the results of therapy are unclear (54).

There are several options available for patients with uterine fibroids, ranging from expectant management, medical therapies that have been shown to decrease fibroid size, and therefore symptomatology, to uterine artery embolization leading to necrosis and myomectomy surgery. Because current medical therapy for fibroids is associated with suppression of ovulation, reduced estrogen production, or disruption of estrogen or progesterone target action at the receptor and has the potential to interfere with endometrial development and implantation, medical therapy has no role as a stand-alone treatment for fibroids in the infertile population (55). Uterine artery embolization appears to have negative effects on fertility in the near future, which is why this treatment is not recommended for patients suffering from infertility (56).

## UNEXPLAINED INFERTILITY

Unexplained infertility occurs when the definition of infertility is met, the basic assessment of infertility is performed and all test results are normal, and it can be diagnosed in up to 30% of infertile couples (57).

## CONCLUSIONS

Infertility is a serious problem that affects up to 15% of couples. Evaluation of the infertile couple focuses on the cause of infertility. Studies in the field are emerging very quickly, some of which with an important impact on the outcome, the fact that there is no updated guideline to evaluate and to treat infertility make it easy to overvaluation and to wrongly treat couples that suffer from infertility.

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