CREANDO Familias

THE STERILITY

SOME ANSWERS TO YOUR DOUBTS

Study of the causes | Second part

Reproduction International Group

Editorial

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More and more couples are **finding it difficult** to realise a life choice like **parenthood**.

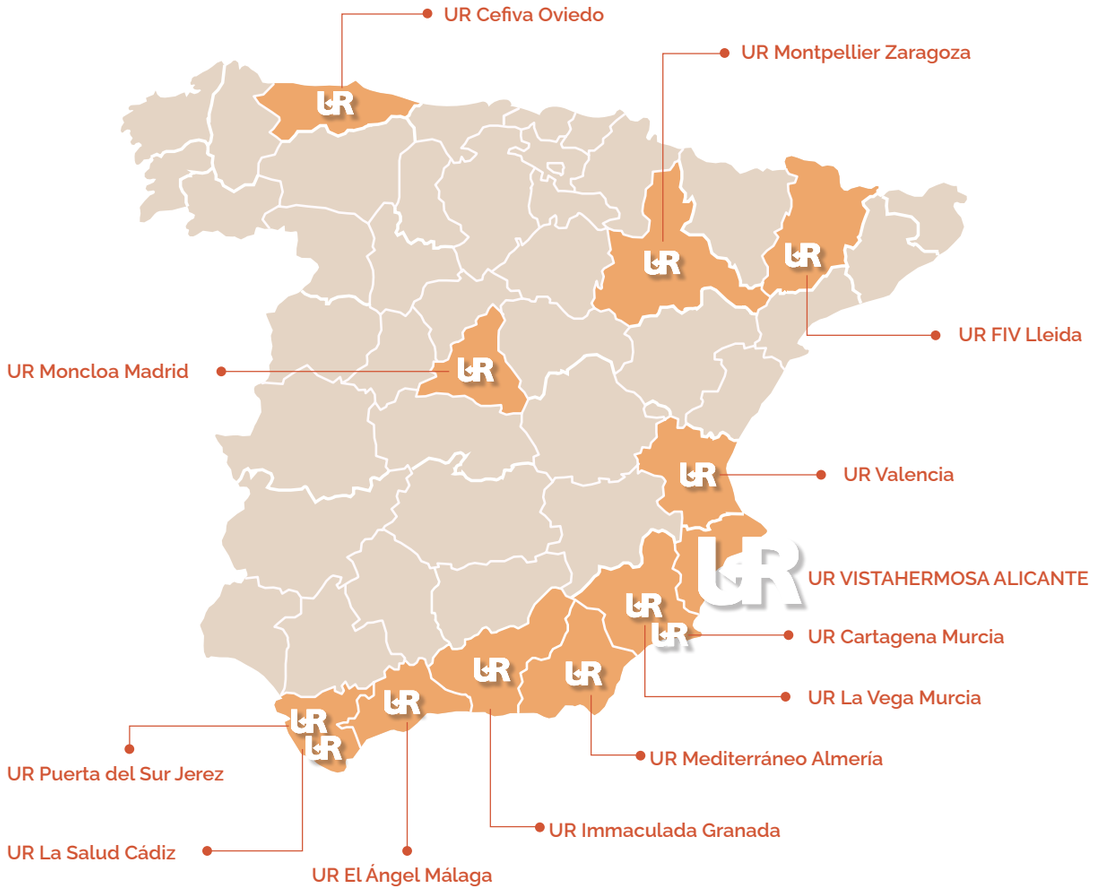
In this number we present the second part of "Study of the causes", which completes the content presented on the previous number of the magazine, both intended to answer all doubts about the origin of the problem, whether from the female, the male or both, without the need to complete the entire reading from beginning to end.

In recent years, diagnostic and treatment techniques for infertility have **advanced enormously** and at the UR Group we have modern advances to be able to offer these couples a solution and help them achieve their dream of **having a healthy child at home.**

However, this process is not always quick and easy, and often creates numerous doubts in the couple which increases the anxiety of an already difficult wait. That is why it is so important to have **clear and concise information** that resolves these doubts and helps to overcome this anxiety. Aware of the importance of supporting patients on their way to parenthood, this new magazine issue has been created with concise answers to **the most frequently asked questions** by couples with fertility problems.

The structure aims to comfortably guide patients through the same steps that will lead them to have their child at home, from the first moment they come to one of our centres, through their **medical history** and the different **diagnostic tests**, to the different **treatments** and the doubts that will arise when they fall pregnant, with a design specially conceived to facilitate access and understanding of its contents.

We hope this guide will fulfil its purpose and help patients who need it face the assisted reproduction process.



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01.

ANALYTICAL

Blood tests and serology

Hormones

Genetic study

What do blood tests tell us?

Blood tests are probably the most used complementary technique in medicine. They allow us to evaluate many aspects of the normal functioning of the body. A part of the analysis is usually called "basic analysis" and it enables us to obtain a general picture of the patient's state of health. This analysis has two main sections: the hemogram and biochemistry.

The **hemogram** is the analysis of blood cells, and in it we analyse the number, size, colour and other characteristics of red blood cells, which are in charge of transporting oxygen to cells, of leukocytes or white blood cells, which defend against infections, and of platelets, which are responsible for cutting haemorrhages. In this way, we can discard the presence of **anaemia**, which is normally caused by a lack of iron, chronic infections, congenital coagulation disorders, which can predispose the patient to haemorrhages and to thrombosis or embolism, as well as some blood cancers.

In **biochemical studies**, glucose is often routinely analysed to evaluate the functioning of the pancreas, urea and creatinine for kidney functioning, bilirubin and transaminase for the liver, and fats (cholesterol and triglycerides) to evaluate cardiovascular risk.

Does the test also tell me if I have infections?

A specific part of the general test that is carried out on all women as part of their basic sterility study is what we call "**serology**". In it we look for a range of infectious diseases that could be related to her sterility or be important if she is pregnant.

Infection via **chlamydias** can go unnoticed in clinical examinations, but this affects the fallopian tubes and obstructs them. **Hepatitis B and C** and **HIV** are illnesses that also go unnoticed and are transmitted to the child during the pregnancy, meaning it is important to determine whether they are present before gestation.

Syphilis is another sexually transmitted disease that can also give rise to malformations in the foetus and it has a simple curative treatment. **Rubeola** is a virus which, if developed during pregnancy, can produce malformations in the foetus. There has been an effective vaccine against the virus for some time.

Toxoplasmosis doesn't have a vaccine to prevent it, but it is a very common infection that hardly produces symptoms outside of pregnancy and leaves lifelong immunity when developed. With the test we can find out if the patient has caught the virus at any time, in which case there is no risk they will suffer it during pregnancy. If this is not the case, a series of hygiene measures, such as avoiding contact with cats and only consuming thoroughly cooked meat, can reduce the risk of catching the virus during pregnancy.

Which hormones are measured at the beginning of the sterility examination?

To find out how well the ovaries are functioning, the following hormones will be studied in the sterility examination: **LH, FSH, oestradiol, AMH** and occasionally **progesterone**. LH, FSH and oestradiol are only detectable in the basal stage of the ovary, that is, between days two and four of menstruation. Progesterone needs to be measured during the second phase of the cycle, that is, from day 14 of menstruation. AMH can be measured at any moment in the cycle.

The **hypophysis**, a gland that is found below the brain, synthesises hormones called gonadotropins in response to instructions from the hypothalamus. These hormones enter the blood in search of the ovaries or testicles. One kind of gonadotropin is called FSH or follicle stimulating hormone, since this is its main function in the ovaries and gives rise to the production and maturation of the ovule inside the follicle and the production of oestradiol. In men, its purpose is to stimulate sperm production. The other hormone is LH or **luteinising hormone**, whose main function is to initiate ovulation when the follicle is mature.

In men, FSH, LH and testosterone levels, just like sperm production, remain practically the same from day to day. In women, however, these levels are incredibly variable throughout their menstrual cycle. Because of this, a measure of any of these is useless if the point of the cycle at which it was taken is unknown. Hormone levels in women help us to identify proper hormonal functioning and the presence of premature menopause, hidden ovary failure, polycystic ovaries or hypogonadotropic hypogonadism.

How is measuring progesterone useful?

When ovulation begins, a small transitory organ called a corpus luteum is formed in the ovary where the ovule was previously. This produces **progesterone**, a hormone that is fundamentally responsible for the maturing of the endometrium inside the uterus, enabling it to accept the fertilised ovule.

If the body detects that fertilisation has taken place, the corpus luteum will maintain the production of progesterone during the first trimester until the placenta is able to produce the hormones necessary to sustain the pregnancy. On the other hand, if after day 14 of ovulation, the body detects that no fecundation or implantation has occurred, the corpus luteum stops producing progesterone. The ceasing of progesterone production makes the **endometrium desquamate** and initiates periodic bleeding or menstruation.

Therefore, determining blood progesterone levels gives us information on two related but different aspects. On one hand, the fact there is progesterone in the blood shows or confirms that ovulation has taken place and has been initiated as a result of the corpus luteum in the ovary. Additionally, it enables us to evaluate whether progesterone levels produced by the corpus luteum, in the case of ovulation, are high enough to allow correct maturation of the endometrium.

What is the Anti-Müllerian hormone?

The Anti-Müllerian hormone or AMH is a hormone present in both men and women, but it has different functions and is found in different areas in each. Its main role is during pregnancy, since it is in charge of the gender of the foetus. It is produced in the testicles in around week **eight or nine of the foetus' development**, with the aim of impeding the **Müllerian ducts** from developing. These are the structures that will give rise to the uterus and the Fallopian tubes. Its absence enables the female reproductive system to form in the foetus.

After birth, AMH levels remain high in males until adolescence, but in adulthood they stay low. In women, however, AMH starts to become important in puberty, since it is produced by the ovarian follicles where ovules are created. The antimüllerian hormone is produced by the ovarian follicles during the entire reproductive life of women – from puberty until the menopause.

Therefore, measuring blood AMH shows approximately how many ovules the women has – her **ovarian reserve**. As this hormone is found in growing follicles (antral and pre-antral), it can be measured in any moment of the ovarian cycle. Very low AMH levels (< 0.3 ng/ml) indicate a low ovarian reserve, while very high levels (>6 ng/ml) can indicate a risk of **ovarian hyperstimulation** or polycystic ovaries.

What is a diminished ovarian reserve?

The ovarian reserve is the amount of ovules a women has at a certain time. This is used to determine the state of her fertility. Women are born with a certain number of ovules (around half a million), and in their fertile life between 400 and 500 are ovulated.

The rest of them degenerate over time. The period of maximum fertility for women is between **ages 16 and 30**. During this time, their ovules are numerous and high-quality. After **ages 35-37** there is a significant decline in the ovarian reserve.

After **age 40**, the ovarian reserve declines until it runs out completely between **ages 45-55**, when the menopause begins. If the ovarian reserve is good, pregnancy is more likely to be achieved. If a diminished ovarian reserve is detected, it may be necessary to resort to in vitro fertilisation (IVF) in order to conceive a child.

Can I find out if I have a diminished ovarian reserve?

A study of the ovarian reserve can be performed in several ways. The most common is a **basal ultrasound scan** and a **hormonal study**.

The eggs (also called oocytes) are found inside structures called follicles, where they mature. In each cycle, several follicles grow in size and begin to develop, but only one of them will be able to reach the final stage and release a mature egg when what is known as ovulation takes place.

Transvaginal ultrasound can be used to count follicles in the antral phase (with a diameter between 2 and 9 mm), which provides valuable information about the follicular reserve of the ovary. For an effective assessment, it is advisable to perform this test during the follicular phase of the woman's ovarian cycle, i.e. between the **3rd and 5th day** of the cycle. For more information, in addition to the basal ultrasound scan, a hormonal study of FSH, LH, oestradiol and AMH is carried out. The latter hormone in particular has been shown to be a predictor of diminished ovarian reserve when found at levels below 0.3 ng/ml.

Can I find out if I'm going to have an early menopause?

The menopause is, by definition, the definitive cessation of menstrual periods due to the depletion of the follicular reserve of the ovary. It therefore means that it will be impossible for a woman to conceive with her own eggs, as these are no longer available, so the only option for achieving pregnancy is to resort to egg donation.

Menopause tends to occur most frequently between the **ages of 44 and 56**, but the point at which it takes place varies greatly from one woman to another, and is considered normal from the **age of 40** on. Statistically, we consider a definitive cessation of menstruation before this date to be abnormal, as it only occurs in **one in a hundred women**; this is what we consider to be early menopause, in the same way that over the age of 60 it would be considered a late menopause.

The most important piece of analytical data is the increase in FSH, but this increase appears much earlier, before the definitive

menopause, meaning that an elevated FSH level can only allow us to be reasonably sure that a late period corresponds to the definitive menopause when the level is above **20 mg/ml**, LH levels are above **30 ng/ml**, and the delay is longer than six months. Similarly, we can only assume that a woman will experience an early menopause when her FSH is already beginning to rise at the age of 27.

The risk of early menopause is therefore difficult to predict, and depends both on the number of follicles a woman is born with, and the rate at which they are used up during her fertile life. The former depends both on **heredity** - the risk is greater if other women in the family have also had an early menopause - and on certain **chromosomal alterations** that can be diagnosed with a **karyotype**. The latter may be related to immunological problems, ovarian infections, previous ovarian surgery or certain cancer treatments.

We also know that **smoking brings the age of menopause** forward by one to two years, and that it is not affected by previous pregnancies, the use of **hormonal contraceptives**, or following assisted reproduction treatments involving **ovulation inducers**, even though logic might suggest otherwise.

Is occult ovarian failure the same as early menopause?

Although the age at which the menopause or last period occur can only be established a posteriori, after waiting at least six months, it is true that in the years prior to the menopause, when the follicular reserve of the ovaries is almost exhausted, the chances of spontaneous pregnancy are much reduced. Under these circumstances, the response of the ovaries to pharmacological induction of ovulation also decreases, and therefore the chances of success for assisted reproductive techniques are reduced. Furthermore, in both cases the number of **eggs with chromosomopathies** rises, which means a high percentage of **early miscarriages** (in addition to the risk of giving birth to a child with one of the chromosomopathies compatible with life, the most frequent of which is trisomy 21 or Down's syndrome).

It would therefore be extremely useful to be able to detect which women are in the period immediately prior to the menopause, even if they are still ovulating and menstruating. Conceptually this situation is what we define as occult ovarian failure, but its diagnosis in practice is complex. This is mainly because the detectable changes begin many years before the definitive decline in fertility, and the onset of the menopause.

Decline in fertility due to an accelerated depletion of the follicular reserve begins thirteen years before the menopause, when there are about 25,000 follicles left in the follicles, so in most women this decline begins between the **ages of 35 and 43**. The first noticeable change is a decrease in AMH. The decrease in AMH due to a shortage of follicles often goes hand in hand with an increase in FSH. Although this window is very wide, these are the basic criteria for diagnosing occult ovarian failure, especially if an ultrasound scan reveals few antral or basal follicles.

At the beginning of this final stage of fertile life, cycles are slightly shortened by a decrease in the length of the follicular phase and earlier ovulation, maintaining normal LH levels and oestradiol levels that are slightly high, although still within the normal range. Years later, the cycles will begin to lengthen and become irregular, with long delays due to failure to ovulate in some months. It is only when the cycles extend beyond **42 days** when LH levels increase and oestradiol values fall, that we can assume the end of a woman's fertility and predict the end of her menstrual periods within two years.

How can polycystic ovary syndrome be detected via blood tests?

The polycystic aspect of the ovaries is simply the physiological consequence of chronic or persistent **anovulation**, whatever the initial cause. Anovulation, which begins with irregular cycles or an occasional late period, leads to weight gain and an increased production of the male hormone testosterone. Both circumstances hamper ovulation, leading to a vicious circle that ends, in extreme cases, in the typical scenario of **amenorrhoea** or a lack of periods due to anovulation, **obesity** and **hirsutism** (excess hair) due to the increase in testosterone that also tends to cause alopecia or hair loss, oily skin and acne.

The most common finding from the analysis is an increase in LH, one that exceeds FSH values, and that in the clearest cases is more than double. This increase in LH is both a cause and a consequence of persistent anovulation, and also plays a role in a decrease in fertility, even when spontaneous ovulation occurs or when assisted reproduction techniques are used, as well as being responsible for a higher rate of miscarriages when pregnancy is indeed achieved.

This characteristic elevation of LH is often accompanied by a rise in free testosterone, and an altered response to oral glucose overload. All these parameters are extremely variable, and are strongly associated with **excess weight**. Hence, the primary treatment for women with chronic anovulation (PCOS) who are overweight is a low-calorie diet to bring their **BMI down to below 27**, not only to achieve pregnancy and avoid subsequent miscarriage, but also to reduce health risks such as diabetes and cardiovascular disease.

How does the thyroid affect fertility?

In a similar way to that of the ovaries and testicles, thyroid function is regulated by the pituitary gland via a hormone, thyroid stimulating hormone or **TSH**, whose production is in turn controlled by the hypothalamus via thyrotropin or TRH. A thyroid malfunction often produces no symptoms at all, as the pituitary gland is able to compensate for the malfunction by increasing or decreasing its production of TSH. This means that it can hyperstimulate a malfunctioning thyroid so that it produces adequate levels of T3 and T4.

These cases are termed **subclinical hypothyroidism** because they do not present any of the clinical symptoms of hypothyroidism, and can only be detected by an elevated level of TSH in the blood. However, although the metabolism is not affected, thanks to thyroid hyperstimulation and normal thyroid hormone levels, hormonal control of the ovaries and fertility may still be affected in these cases.

Subclinical hypothyroidism may be what lies behind **elevated prolactin** levels and **galactorrhoea** or milk secretion in both breasts, as well as infertility with irregular periods or **amenorrhoea**. Furthermore, even if subclinical, hypothyroidism is also associated with a higher rate of early miscarriage.

This is why we routinely include TSH levels in blood tests, since in such cases detection and an appropriate treatment with thyroid hormone supplements quickly and satisfactorily restores at least the regularity and normality of ovulation, and improves the prognosis once pregnancy has been achieved.

What does having high prolactin levels mean?

Prolactin is one of the hormones secreted by the pituitary gland, and its main function is milk production during lactation. Increased prolactin levels interfere with hormonal signals from the hypothalamus to the pituitary gland, disrupting the normal secretion of FSH and LH. The result is the inhibition of ovulation and the disappearance of menstrual periods. This is a process that occurs physiologically during breastfeeding, and is the reason that menstruation does not usually resume during exclusive breastfeeding.

However, it can also occur when a small benign tumour in the pituitary gland called an **adenoma** or **prolactinoma** produces abnormal amounts of prolactin. This hyperprolactinaemia may cause no symptoms, or it may lead to milk secretion in both breasts (galactorrhoea) or alter ovulation, resulting in the suppression of menstrual periods or amenorrhoea. The existence of small adenomas in the pituitary gland is very common. About **10%** of people who are asymptomatic have one, and it causes no problems. They are always benign, and are usually micro adenomas that are very small in size - usually under **100 mm** - with no tendency to grow any bigger. Only larger, **macro adenomas** can affect neighbouring structures by compression, and lead to continuous headaches or visual disturbances. It is only in these instances that the surgical removal of the tumour can be considered, but this may be unnecessary.

Micro adenomas usually only cause problems when they produce an excess of a particular hormone - prolactin being the most common one, seen in half of all cases. Even so, it is only advisable to administer pharmacological treatment to normalise prolactin levels and restart ovulation in cases of breast discomfort due to milk production, or in cases where pregnancy is being sought. Whether treated pharmacologically or not, for the first few years an annual monitoring of prolactin plus a scan should be carried out to ensure that there is no growth of the micro adenoma, which is the norm.

Can tests assess the risk of miscarriage when I become pregnant?

In both spontaneous pregnancies and those achieved by assisted reproduction technology, early miscarriages are very frequent, and most are due to random chromosomopathies. But there are also other factors that may lead to an increased risk of miscarriage that are routinely studied when an infertility study is begun. **Toxic substances** (alcohol, tobacco, coffee, illegal drugs, etc.), **pharmaceutical drugs**, and o**ccupational factors** need to be ruled out or corrected after the interview. Uterine malformations are revealed by ultrasound, hysterosalpingography and/or hysteroscopy.

Infections play a questionable role, but if present, should have been revealed on gynaecological examination and/or serology. Subclinical hypothyroidism, hyperprolactinaemia or polycystic ovarian syndrome can be the cause both of early miscarriage and of infertility, and are therefore routinely investigated in all cases of infertility.

Poorly controlled **diabetes** and certain congenital coagulopathies are also routinely screened for in all studies, because apart from a possible influence on the risk of miscarriage, they may also pose other risks during pregnancy. An increase in eggs with chromosomal abnormalities due to depletion of the ovarian reserve will also have already been diagnosed or ruled out. In view of the above, in the case of a couple whose problem lies not in achieving a pregnancy, but in recurrent pregnancy loss, almost all known causes of greater predisposition to miscarriage have already been studied, or are similar to those carried out on any couple who are trying unsuccessfully to achieve a pregnancy. In view of the specific problem of repeated miscarriages, additional tests are therefore necessary. Special tests are aimed at screening for genetic factors, antiphospholipid syndrome and uterine abnormalities.

Antiphospholipid syndrome is an autoimmune disease in which the body produces antibodies that attack healthy cells, especially those of the vascular system, resulting both in an increased predisposition to thrombosis, and to vascular alterations of the trophoblast and placenta, which are responsible for an increased risk of miscarriage. This condition may either be part of another autoimmune disease, **systemic lupus erythematosus**, or occur in isolation. If everything is normal, a **thrombophilia** study and additional tests such as a genetic study of the sperm or DNA fragmentation are performed to rule out a male contribution.

How can we know if we have a genetic problem?

Although genes are found within chromosomes, it is important to differentiate clearly between the study of genes and the study of chromosomes. Genetic diseases are caused by mutations in one or more genes. When such a mutation is known, it is possible to search for the altered sequence in a patient's genome or DNA strand, using a specific probe for that specific gene and that particular mutation.

A **karyotype** or chromosome study looks for numerical or structural anomalies called **aneuploidies** in the chromosomes. For this reason, infertility of genetic origin is not usually diagnosed until specific genetic tests such as karyotyping, FISH analysis of spermatozoa, pre-implantation genetic diagnosis or prenatal tests are carried out.

What is karyotyping?

The term karyotype refers to the set of chromosomes found inside each cell. In human beings, the karyotype is made up of 22 pairs of **autosomal chromosomes**, and one pair of sex chromosomes that define the sex of the individual: in men, **46 XY** and in women, **46 XX**. Consequently, it is used to study whether the chromosome load is normal, or whether there is some kind of anomaly, such as a numerical or structural alteration of the chromosomes.

The incidence of constitutional chromosomal abnormalities is about **13 times higher** in the pop-

ulation of infertile patients than among the general population, with alterations in the sex chromosomes being more frequent than those in the autosomes. Since this study rules out the most obvious forms of genetic infertility, karyotyping is currently carried out in all basic fertility studies.

Why are blood and urine tests performed on the male partner?

The basic study of male infertility includes a general analysis similar to that carried out in a study of female infertility. Although the presence of any of the diseases we check for in this analysis is less important in the male, it is a good time to do a general health check. With a simple blood test and analysis, the existence of diabetes, anaemia, coagulation problems, **cardiovascular risk** factors such as cholesterol or triglycerides and **liver** or **kidney problems** can be ruled out. Similarly, sexually transmitted **viral infections** such as HIV or hepatitis B and C must also be ruled out, as semen can be a route of infection by these viruses. **Urinalysis** can detect prostate infections that could affect semen quality.

Karyotyping detects chromosomal alterations that could be transmitted to offspring. It is only if serious problems are found in the semen analysis that a determination of FSH and testosterone is added. This is especially useful in cases of azoospermia, in which there are no spermatozoa in the ejaculate. In such cases, normal levels of FSH and testosterone indicate that the testes are functioning well, and that there must be a blockage at some stage in the process of sperm production that is preventing sperm from reaching the ejaculated seminal fluid.

Conversely, high FSH and low testosterone levels indicate general testicular failure, and alongside the assisted reproduction technique required, treatment with **testosterone supplements** may also be beneficial. Although these will not solve the problem of sperm production, they will alleviate some of the symptoms that this testicular malfunction may cause, such as weakness, loss of body hair, sexual appetite or impotence.

In short:

What can be observed from the different analyses?

BLOOD TESTS

HEMOGRAM

BIOCHEMICAL STUDIES

SEROLOGY
Look for a range of infectious diseases that could be related to her sterility or that have significance in pregnancy.

HORMONES TESTS

LH, FSH, OESTRADIOL,

AMH, PROGESTERONE

Proper hormonal functioning, presence of premature menopause, hidden ovary failure, polycystic ovaries or hypogonadotropic hypogonadism.

GENETIC STUDY

STUDY OF GENES
Mutations in one or more genes.

STUDY OF CHROMOSOMES (KARYOTYPE)
Numerical or structural anomalies called in the chromosomes.

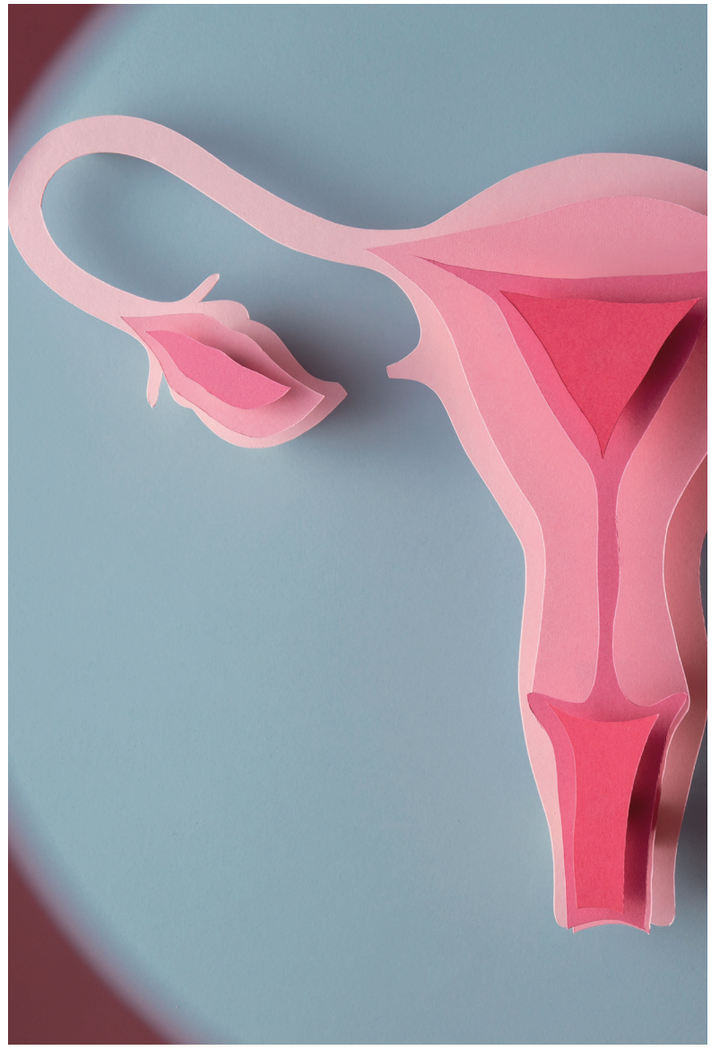
02.

Study of the UTERUS and TUBES

Hysterosalpingography

Hysteroscopy

Laparoscopy



How is a hysterosalpingography performed?

Hysterosalpingography (HSG) is an imaging technique that allows the internal contours of the uterus and the fallopian tubes to be viewed via X-ray.

Hence the long and complicated name:

HYSTERO - SALPINGO - GRAPHY

UTERUS | FALLOPIAN TUBES | IMAGE

Tissues that do not allow radiation to pass through, and so are called **radiopaque**, e.g. bones, can be seen very well on X-rays. Neither the uterus nor the fallopian tubes have bones, so they cannot be seen in a simple abdominal X-ray. In order to visualise them, what we do is to inject a radiopaque liquid into them, as we would in a study of the colon or the stomach for example. This is called **radiological** or **iodinated contrast**. To introduce the contrast in the interior of the uterus, we use the cervical os.

After inserting a flexible probe via this orifice, and inflating the pneumatic balloon at its tip which fully seals the duct, the contrast is slowly and carefully introduced. This liquid completely fills the uterine cavity, and moves through the interior of the fallopian tubes, creating a model of the interior that can be seen on X-rays.

What is hysterosalpingography used for?

Hysterosalpingography explores the anatomical integrity of the interior of two contiguous structures, both essential for reproductive function, that are affected by different alterations. Hysterosalpingography provides information on the configuration of the uterine cavity. The information obtained in this way is extremely varied. The position and the degree of flexion and lateralisation of the uterus can be viewed, as can the size and shape of the cavity, which may be enlarged or deformed due to the existence of large intramural fibroids. All this data is easily assessed by means of an ultrasound scan, and the hysterography provides only minor graphic detail. More important is the assessment of the existence of spaces in the endometrial cavity that are not filled with contrast, and which may correspond to submucosal myomas, endometrial polyps or synechiae, although diagnostic efficacy in the case of these problems is usually lower than with hysteroscopy. Something similar occurs with the assessment of anatomical malformations, such as double or septate uterus.

Thus, the importance of the test lies primarily in **salpingography** or tubal assessment, since the information it provides is only comparable to that gained through laparoscopy, a more invasive technique, and one that needs to be performed in an operating theatre under general anaesthetic. In a simpler way, hysterosalpingography allows us to assess the appearance, location and length of the fallopian tubes, and especially their **permeability**. When the contrast medium is introduced, it passes from the uterus into the fallopian tubes.

We can see if it runs along the entire length, and whether it finally drops through the end into the abdominal cavity, or if on the other hand its passage is blocked at some point, in either one or both tubes. It also allows us to assess whether the lumen is narrow along the entire length, as occurs in healthy fallopian tubes, or if, as well as the obstruction, there is a dilatation of the diameter or **hydrosalpinx**, because in this case the contrast medium would accumulate in the dilatation. Finally, the diffusion of the contrast medium in the pelvic cavity after leaving the fallopian tubes, if these are permeable, also gives us information, as it can be normal or free. Because of all the information it provides, hysterosalpingography is in all centres considered to be an essential test in the basic study of infertility, unless the need for hysteroscopy and laparoscopy is previously indicated for some reason, in which case the information provided by both could make hysterosalpingography unnecessary.

What can cause tubal obstruction?

Tubal obstruction is an extremely common problem, and is found in approximately one third of the women who consult a doctor due to infertility. The main cause of these tubal disorders is an infection inside the fallopian tube also known as **salpingitis** or **pelvic inflammatory disease** (PID). These are usually subacute and chronic processes that have few symptoms, and that may go unnoticed while damaging the tissues over a period of years.

The cause can sometimes be sexually transmitted bacteria such as **neisseria gonorrhoeae**, **chlamydia**, **mycoplasma** or **ureaplasma**, but in other cases it may be caused by germs that are usually found in the body in normal situations. The second most common cause is **endometriosis**. Although it does not usually affect the tubal lumen, the adhesions caused by endometriotic lesions can affect the external surface of the tubes, altering their anatomy or constricting them by closing the tubal lumen.

A third possible cause is previous surgery that has affected these structures. Of course, the most common is **voluntary sterilisation** or **tubal ligation**, the aim of which is precisely to occlude the tubal lumen to prevent the passage of spermatozoa. But it can also occur as a complication following other types of surgery, perhaps gynaecological, such as the removal of fibroids, adhesions or ovarian cysts.

Can the fallopian tubes be permeable, but nevertheless still fail to function properly?

Yes, they can. This may be due to two different types of alterations. On the one hand, the existence of adhesions in the pelvic area, due to endometriosis, infections or previous surgery can distort the shape and position of the tubes, causing the end of the tube to moves away from the position of the ovary. At the time of ovulation, the **fimbriae** or extensions at the end of the tube are located next to the ovary area where the follicle ruptures and the egg is released. If the egg does not find these fimbriae when it leaves the follicle, it will not be able to penetrate the interior of the tubes, and will fall into the abdominal cavity where it will be reabsorbed with no possibility of being fertilised.

On the other hand, the interior of the fallopian tube is not merely passive; the cells that cover the entire surface of its lumen are actively responsible for the nourishment of the egg, both before and after fertilisation, as well as for transporting it from the fimbriae to the uterine cavity. It is transported by the synchronised movement of a multitude of cilia or tiny hairs that cover the entire inner surface of the uterus, rather like velvet. The existence of a chronic infection may not occlude the tube, but it might have damaged this fine cellular envelope and thus prevented it from carrying out its normal function of nourishing and transporting the oocyte and the embryo.

This damage may be responsible both for the impossibility of pregnancy and for the fact that, if pregnancy occurs, the fertilised egg does not reach the endometrium and nests in the tubal mucosa, resulting in an **ectopic** or **extrauterine pregnancy**. Both situations, especially the second one, are difficult to assess with the images provided on a hysterosalpingography.

What if I have one blocked tube and one permeable tube?

The oocyte will reach the uterus and be fertilized along the way in only one of the two tubes, so the other tube's is really irrelevant. But in the event that there is only one healthy tube and the other is functionally damaged, obstructed or non-existent, only the eggs produced in the ovary on the same side as the healthy tube will have a chance of being fertilized and reaching the uterus. Since under normal circumstances only one oocyte is usually produced during each ovulation, there is a **fifty-fifty chance** that this ovulation will take place in the right ovary.

The general understanding that the ovaries alternate month to month during ovulation is not true, whereby several ovulations can occur in a row in the right ovary, but the same can happen in the wrong ovary, the one with a damaged tube. All this means that the chances of pregnancy each month are statistically half what they would be if both tubes were healthy, which means a longer time to become pregnant. But if we give enough time, the chances of pregnancy end up being the same as if the tube were not damaged. What does increase is the risk of ectopic or extrauterine pregnancy in the affected tube if it is not completely blocked and fertilisation occurs without the embryo being able to complete its journey to the uterus.

What is a hysteroscopy?

A hysteroscope is basically an **endoscope** adapted to study the inside of the uterine cavity. An endoscope is simply a tube that has a light source and a camera inside it so that the inside of the cavity where the end of the endoscope is inserted can be viewed on an external monitor.

The hysteroscope is inserted through the cervix, which is the opening that connects the vagina with the uterine cavity and through which sperm cells enter or menstrual blood comes out. Therefore, incisions or stitches are not required. What makes the test uncomfortable is having to dilate that opening to insert the tube, and will depend mainly on the size of the tube. When we only need to look inside the uterus to make a diagnosis or need to insert very small material, a hysteroscope so small that the cervix does not need to be opened any further than it would during menstruation is sufficient. This is what we call **diagnostic hysteroscopy**.

In other cases, however, we need to insert a larger instrument with a handle-shaped electric scalpel, which we call a resectoscope, or we need to remove larger pieces from inside the uterus. For one reason or another, we need a larger tube diameter and, therefore, dilate the neck's opening more. In these cases, which we call **surgical hysteroscopy**, dilating the cervical opening is necessary.

I have a polyp in my uterus, do I need to have a hysteroscopy?

Endometrial polyps are small pedunculated warts that appear on the surface of the endometrium, inside the uterine cavity. They are usually small, but can vary a lot, between **5 and 35 millimetres**, and are usually quite symptomatic. Polyps often cause irregular bleeding, both spotting between periods, usually a few days before menstruation begins or during ovulation, and heavier periods.

They can usually be seen on a vaginal ultrasound. But to be able to see even the smallest ones, it is important to perform the ultrasound at a certain stage of the menstrual cycle. The days immediately prior to ovulation are the best because the endometrium has a dark appearance in the ultrasound and the polyps' light tones stand out very well. However, in the **secretory phase**, between ovulation and menstruation, the endometrium progressively takes on the same light tone as the polyps. Therefore, at this stage even a good-sized polyp may go unnoticed on an ultrasound.

Since they are so small, they do not usually interfere with embryo implantation and do not usually cause infertility or early miscarriages. However, since they tend to show symptoms very frequently and are so easy to remove, the standard practice when a polyp is diagnosed is to remove it without waiting for it to grow larger. Due to their small size and the fact that they detach easily, they are usually very easy to remove and a diagnostic hysteroscopy is usually enough to confirm it and remove it at the same time.

Can fibroids be removed with a hysteroscopy?

Fibroids are benign tumours that develop from the muscular tissue that makes up the uterus. They are usually diagnosed by ultrasound. Both the need for removal and the ease of removal depend on the size of the fibroid, but above all it depends on its location. **Subserosal fibroids** are fibroids that grow outside the uterus, like a wart. It is not usually necessary to remove them, although surgery is not usually that difficult, and can even be done via a laparoscopy. **Intramural fibroids** grow in the muscle layer and only cause problems when they become very large. Neither of these two types can be seen with a hysteroscopy.

In contrast, submucous fibroids, even if small, often cause bleeding problems like endometrial polyps. As they are usually larger than polyps, the percentage of the endometrial cavity's surface area covered by the fibroid is also bigger, and if the embryo, when looking for a place where it can implant and 'take root' in the uterus, falls on the fibroid's surface, the blood supply that will reach it is not the most suitable and it may not implant, thus being lost during menstruation. Therefore, submucosal fibroids are often associated with infertility problems and their removal is usually advised even if they do not cause bleeding problems.

What is a laparoscopy?

Unlike open surgery or laparotomy, where an opening (**tomy**) is made to see inside the abdomen (laparos) from outside, in a laparoscopy a **small camera** is inserted into the abdominal cavity, allowing us to see inside the abdomen on a monitor. To do this, we insert a long stiff tube or laparoscope containing the camera, the light and a hole to insufflate a gas that distends the abdominal cavity. The laparoscope is inserted into a shorter hollow tube through a small incision under **2 cm** just below the navel. Both for mobilising the pelvic and abdominal organs in diagnostic

laparoscopy and for performing multiple therapeutic techniques in surgical laparoscopy, additional incisions are required to insert other types of material into the abdominal cavity. For diagnostic purposes, a second, smaller incision at the side is usually enough to insert a clamp that allows us to move the intestinal loops aside and move the ovaries and tubes so that we can see all anatomical aspects that are of interest to us. Surgery may require up to **four incisions** for inserting forceps, scissors, electric scalpel, aspirator, etc. Normally, a mobiliser is also inserted into the uterus through the cervix so that it can be placed in the correct position externally.

The length of the procedure varies greatly depending on whether it is merely diagnostic, which usually lasts **no more than half an hour**, or whether it involves a surgical procedure which may take several hours. Despite the small incisions, laparoscopy requires general anaesthesia since filling the abdomen with pressurised air to lift the abdominal wall also compresses the diaphragm and if the patient were awake, they would feel an agonising sensation of not being able to breathe. This is why it always needs to be performed in a well-equipped operating theatre, but given laparoscopic techniques are not very aggressive, this procedure tends to be very brief, usually only taking a few hours. Only the most aggressive surgeries usually need longer admissions, up to 48 hours.

It is not a harmless technique like ultrasounds, hysterosalpingographies or hysteroscopies... For this reason, it is usually **not included** in a basic infertility study **as a routine test**, but is indicated only when there is a possible problem that needs to be confirmed or corrected by a laparoscopy.

However, only a laparoscopy can diagnose or definitively rule out a number of infertility-related problems, especially **endometriosis and adhesions**. We can also solve many of the problems that we may encounter, such as ovarian cysts, adhesions, endometriotic foci, hydrosalpinx, etc., in the same surgical procedure.

What is endometriosis?

Endometriosis is a fairly common condition even in fertile, asymptomatic women, and can be found in **3-10%** of these women. Although it is not a hereditary disease, it is more frequent in certain families, because alterations in the **immuno-biological mechanisms** responsible for the fact that retrograde menstruation is not reabsorbed, but forms endometriotic implants, do have a complex inheritance that makes endometriosis up to seven times more likely when a mother or a sister also suffers from it.

But other factors also have an influence, such as obesity or excessive coffee or alcohol consumption being predisposing factors, while regular physical exercise and tobacco use reduce the risk. The age of **first menstruation**, the frequency of menstrual periods and the number of full-term pregnancies are also important factors. Thus, women who have had early periods, have short menstrual cycles and do not have children have a higher risk of developing endometriosis.

As common as endometriosis is, it is not easy to explain and understand what endometriosis is, and even among doctors there are more obscure and unknown aspects than well-known ones. Although many mechanisms have been proposed to explain its aetiology, it is still the '**retrograde menstruation mechanism**', proposed eighty years ago, that best explains its various characteristics. According to this hypothesis, during menstruation, when the blood accumulated inside the uterus exits through the cervix and vagina, some of the blood would go down the tubes and fall into the abdominal cavity. This is normal and occurs in up to 90% of women with permeable tubes.

This blood is reabsorbed in them without major problems; however, in some women, for a reason that is not yet fully understood, some of the endometrial cells present in the bleeding become anchored in the peritoneum or inner surface of the abdominal cavity. The inflammatory reaction itself can also be a direct cause of pelvic pain, especially during menstruation, with progressively increasing pain being characteristic of successive days of bleeding.

Although a correct anamnesis and physical examination may raise suspicion of endometriosis, with the exception of **endometriomas** (cysts formed by the deposit of blood, often called "chocolate cysts") which can be correctly diagnosed with an ultrasound scan, direct visualisation via a laparoscopy is required for diagnosing **endometriotic lesions**. This technique is also the only one that allows for a biopsy of the lesions for pathological examination, the only one that definitively confirms the diagnosis of endometriosis.

How does endometriosis affect fertility?

Infertility is a cause of the development and aggravation of endometriosis and may be the sole cause of endometriosis being found more frequently in infertile patients, with figures as high as **20-40%**. However, today we know beyond doubt that endometriosis also plays an important role in reduced fertility. An obvious reason, never discussed, is the case where adhesions cause **obstruction of both tubes**, preventing eggs from passing into the uterus. But even when the tubes remain permeable, endometriosis is directly related to infertility.

Sometimes, even if they do not obstruct the tubes, adhesions leave the tubes or ovaries fixed in an abnormal anatomical situation that prevents the correct position of the **fimbriae** at the end of the tube on the surface of the ovary at the time of ovulation. When this happens, the egg detached from the ovary falls into the abdominal cavity without being picked up by the fimbriae and inserted inside the tube.

In addition, **immunobiological disorders** responsible for endometriotic implant formation are also responsible for poorer quality of both oocytes and endometrium. This causes fertility to be affected in all cases of endometriosis, even when a laparoscopy reveals no tubal or ovarian adhesions, and is also responsible for poorer outcomes of assisted reproductive treatments in women with endometriosis.

In short:

HYSTEROSALPINGOGRAPHY

X-RAYS Y CONTRAST RADIOPAQUE LIQUID

Information on the configuration of the uterine cavity, position, size and shape of the cavity.

Appearance, location, length and permeability of the fallopian tubes.

HYSTEROSCOPY

ENDOSCOPE

Camera adapted to study the inside of the uterine cavity.

- DIAGNOSTIC HYSTEROSCOPY
- SURGICAL HYSTEROSCOPY

LAPAROSCOPY

A SMALL CAMERA IS INSERTED INTO THE ABDOMINAL CAVITY,

Diagnose or definitively rule out endometriosis and adhesions.

Solve many of the problems such as ovarian cysts, adhesions, endometriotic foci, hydrosalpinx, etc.

03.

The study of **MALES**

Semen analysis

Training

Functional tests

What is a semenogram or spermiogram?

Semenogram and **spermiogram** are synonymous terms and describe the laboratory study of semen characteristics and the spermatozoa it contains. In men, biological participation in reproduction is limited to semen contribution.

Therefore, a thorough study of this allows us a perfect overview of the normality of all the previous physiological steps involved in the production and function of spermatozoa. In addition, the male factor is very common, and is present in two thirds of infertile couples, being the only altered factor found in half of these cases and coexisting with some other female elements in the other half. For this reason, the semenogram is a routine and essential diagnostic test in any infertility study, even when the woman has a known problem affecting her fertility.

The procedure for the test is simple; the man has to take a semen sample by masturbation, and collect it in a sterile container, taking care not to lose part of the sample. One basic criterion is to have been sexually abstinent for **2-5 days** beforehand, as this characteristic can vary the results considerably. If the semen is collected at home, the sample must be kept at body temperature and delivered to the laboratory within **45 minutes** of collection.

In the event that it is not possible to meet this deadline, all fertility clinics have special rooms with 'stimulating' audio-visual material for masturbation and sample collection.

In patients with ejaculation disorders such as **paraplegia**, **prostate electrostimulation** can be used. In exceptional cases where masturbation cannot be used for psychological or moral reasons, semen may be collected through intercourse in special condoms, as regular condoms usually contain spermicidal substances that would alter the results.

Can I find out if I am sterile with a semen analysis?

Diagnosis of the male factor should not normally be based on a single semen analysis, as sperm production can be altered by multiple factors: infections, drugs, heat, smoking, etc. and can last for a few weeks or many years. Even the count may vary from week to week in a normal man. Therefore, at least **two semenograms**, one week to three months apart, are required for a reliable diagnosis.

Furthermore, except in cases of **azoospermia** (absence of spermatozoa in the semen), an irregular semenogram result is not an indication that the man is sterile and cannot conceive, even by natural means, as only one of the several million spermatozoa produced by each ejaculation needs to reach the egg and fertilise it in order for pregnancy to occur. Therefore, although there are specific, international criteria provided by the World Health Organisation that qualify semen as "abnormal" and roughly give an idea of the chances of conceiving, this is not an exact criterion; they can only indicate that a man with certain characteristics in his semen that qualify him as pathological has a lower chance of conceiving in each sexual encounter or 'may' take longer to conceive than a man with semen that meets all the requirements of 'normal' semen.

Furthermore, a semen analysis with all normal parameters does not imply a hidden problem in the spermatozoa that prevents fertilisation or gestation. Therefore, a seminogram cannot be used to determine whether a male is fertile or infertile.

So what is the purpose of semen analysis?

Although the usefulness of a spermiogram on a healthy adult before attempting to become pregnant to assess fertility is scarce, it is very useful when

it comes to discovering clear infertility in some cases, or when seeking the most appropriate treatment for a couple who have been unsuccessfully trying to conceive for a long time. Above all, because, although there are also female factors involved, if we observe abnormal semen, we can infer that the low quality could be a factor in the failure to achieve the desired pregnancy.

We find clear infertility in a seminogram if there are no spermatozoa in the semen (**azoospermia**), or they have hardly any motility (**asthenozoospermia**), the morphology of practically all spermatozoa is abnormal (**teratozoospermia**), or the ratio of live spermatozoa is very low (necrozoospermia). We can also find cases where people have an orgasm, but do not ejaculate (**aspermia**).

When all parameters of the semenogram are normal, but we suspect male infertility, we have to resort to functional tests, or genetic studies, which give us more information about the spermatozoa's behaviour.

What is REM and sperm capacitation?

Recently ejaculated sperm cells do not have fertilising capacity at that time. They are immersed in a secretion formed in the prostate and seminal vesicles that serves as a protective medium against the acidity of the vagina. While these secretions, which constitute the semen itself, remain in the vagina, the spermatozoa, thanks to the active movement of their tails or flagella, enter the cervical mucus through the uterine cervix towards the endometrium and the tubes in search of the egg.

At this stage, once released from the protective secretions of the semen, they begin the sperm capacitation process that allows them to become fertilising spermatozoa.

The process carried out in the laboratory, using various possible techniques, for preparing semen basically consists of washing and '**purification**' of both the seminal fluids and the poorly prepared spermatozoa. By doing this, we obtain a selection of the best spermatozoa, which is what we call **REM** or **Recovery of Motile Spermatozoa**. REM assessment provides a better diagnostic approach to the fertility capacity of semen than fresh semen examination. Below minimum REM values, artificial insemination would be inadvisable due to the low pregnancy rate to be expected.

But, in addition, free of seminal secretions, we leave the spermatozoa in a position to begin the capacitation process, whether they are going to be deposited inside the uterus through artificial insemination or whether they are going to come into contact with the egg during in vitro fertilisation in the laboratory.

What happens if I have no spermatozoa in my semen?

Although rare, sometimes no spermatozoa are found in the ejaculation, which is called azoospermia. There can be many causes and, as with any male pathology, an appointment with an andrologist is necessary.

In these cases, the treatment and prognosis will depend drastically on whether no spermatozoa are produced - secretory azoospermia - or if, after producing spermatozoa, they are unable to join the semen to come out in the ejaculation: **obstructive azoospermia**. This is the case, for example, for men who have had a vasectomy.

Although a detailed interview and an adequate physical and analytical examination can lead us to suspect which of the two causes of azoospermia we are dealing with, only a testicular biopsy and microscopic study of the tissue collected will allow us to make a definitive diagnosis. In addition, a testicular biopsy can be used to collect spermatozoa to be frozen, which can then be used in assisted reproduction treatments (in vitro fertilisation with sperm micro-injection or **ICSI**).

Does temperature affect semen production?

In men, as in other mammals, the testicles descend into the scrotum during foetal life or shortly after birth. In animals with a scrotum, the temperature of the testes is slightly lower than in the rest of the body (approximately **2°C lower in men**).

The reason why a lower temperature is needed for effective spermatozoa formation is not well understood, but it is known that body temperature is detrimental to sperm production and even proper gland development during puberty. Surgical correction of undescended testicles or **cryptorchidism** in boys before the age of seven is therefore important, as delaying it can lead to sterility as adults.

Moreover, temperature affects spermatogenesis not only at the scrotal level. Variations in temperature or ambient light, diet or emotional stress can also affect spermatogenesis through the action of the **hypothalamus**, which is the part of the brainthat, like in women, controls gonadal activity.

What other tests or studies are performed on semen?

When you want to delve deeper into the cause of male infertility, there are a number of other tests that analyse spermatozoa from different properties: Genetic tests such as spermatozoa FISH, DNA fragmentation test, MACS and microfluidic chambers are the most commonly used.

What is FISH?

A genetic study technique that analyses the **chromosomes** of spermatozoa. With the FISH (**Fluorescent In Situ Hybridisation**) technique, we can find out how many copies of a chromosome there are in each spermatozoon.

Thus, it is possible to calculate what percentage of spermatozoa is altered for the chromosomes being studied. The result of this analysis provides the couple with advice on the most appropriate assisted reproduction technique.

A male with a high percentage of chromosomally altered spermatozoa will produce a higher number of chromosomally abnormal embryos after fertilising the oocytes. In most cases these embryos either do not implant or result in miscarriage. In these cases, the recommended assisted reproduction technique is **Preimplantation Genetic Diagnosis**.

FISH is simply performed on a semen sample, which is prepared for the genetic study. However, it should be noted that the spermatozoa analysed cannot be used for assisted reproductive technologies. When resorting to ICSI, the spermatozoa to be used to fertilise the egg must be selected from a sample not studied with FISH and on the basis of the classic morphological parameters, without being able to predict, other than by a probability calculation, whether or not the sperm chosen will carry the alterations described in FISH.

What is the DNA fragmentation test?

The integrity of spermatozoa DNA involved in oocyte fertilisation is a very important parameter for proper embryo development. This is affected when the DNA carried by the spermatozoa is fragmented (the two strands of DNA are separated). In humans, there is a proportion of spermatozoa with fragmented DNA, which is considered common.

A high fraction of this spermatozoa type could lead to problems in collecting quality embryos and possibly in conceiving.

This type of study would be recommended in the following cases:

- **Fertilisation problems, poor quality embryos and/or repeated implantation failure in assisted reproduction techniques.**
- **Repeated miscarriages.**
- **Varicocele.**
- **Genitourinary infections.**
- **Male age > 45 years, smoking, exposure to environmental toxins.**
- **Exposure of the testicle to high temperatures, e.g. after an episode of high fever.**

What are MACS?

All cells, including gametes (oocytes and spermatozoa), undergo a process called **apoptosis** or programmed cell death, which disposes of unnecessary or abnormal cells. With the MACS technique, spermatozoa in apoptosis are separated from healthy spermatozoa. In addition, it can be used when using an assisted reproduction technique, to select the best spermatozoa. This technique is based on the application of magnetic fields, hence its name (**Magnetic Activated Cell Sorting**), and on the use of annexin V, a protein that specifically and with high affinity recognises apoptotic spermatozoa. Thanks to this feature, by attaching annexin V to magnetic microspheres, we can separate spermatozoa that have entered apoptosis using a magnet. This technique is also used in men with a high percentage of fragmented spermatozoa.

What are microfluidic techniques?

Spermatozoa DNA fragmentation can occur on both DNA strands or on a single strand. When the fragmentation is double-stranded, the fertilisation rate decreases even further, and the probability of pregnancy, therefore, decreases as well. There are devices, such as the **Fertile Chip**, that allow the selection of spermatozoa with better motility and less double-stranded DNA fragmentation. This device is therefore capable of separating the best spermatozoa for use in assisted reproduction treatment. The device consists of a lens with two chambers connected through a microfluidic channel. A semen sample is placed in the input chamber and after a period of time the spermatozoa that reached the collection chamber, which will be better quality, are collected.

In short:

What are the main techniques used for semen analysis?

SEMENOGRAM / OR SPERMIOGRAM	*Study of semen characteristics and the spermatozoa it contains.*
FISH	*Technique that analyses the chromosomes of spermatozoa.*
DNA FRAGMENTATION TEST	*Study of the integrity of spermatozoa DNA.*
MACS	*Spermatozoa in apoptosis are separated from healthy spermatozoa.*
MICROFLUIDIC TECHNIQUES	*Selection of spermatozoa with better motility and less fragmentation.*

STERILITY OF UNKNOWN ORIGIN

What is immune-mediated infertility?

Pregnancy represents one of the most fascinating events in human biology. Our immune system has evolved specialised evolutionary mechanisms to tolerate the **"non-self" antigens** of the foetus during gestation.

However, immune system disorders and autoimmune diseases can cause infertility in both men and women. Although such disorders are difficult to diagnose in most cases, approximately **20%** of cases of infertility of unknown origin are due to some type of **immune disorder**. Infertility or sterility of immunological origin can manifest itself by destroying the gametes themselves, thus preventing implantation of the embryo, or even causing repeated miscarriages.

For the diagnosis of these alterations, a complete analytical profile of those immunological factors related to primary infertility, implantation failure after **in vitro fertilisation** (IVF), repeated miscarriages and **pre-eclampsia or eclampsia** in pregnancy is carried out. Depending on the immunological cause, there are different therapeutic protocols to prevent foetal loss and maternal health problems during pregnancy.

The study of sterility of immunological cause is studied in the following cases:

- **Autoimmune Pathologies** (e.g. Systemic Lupus Erythematosus, Antiphospholipid Syndrome, Autoimmune Thyroiditis, Celiac Disease etc).
- **Non-specific autoimmunity** (Positivity for different autoantibodies without clear criteria for autoimmune disease)
- **Immunological humoral alterations** (immunodeficiencies, alterations in the complement system, pro-inflammatory cytokines etc.)
- **Metabolic and coagulation disorders associated with immunological imbalances** (vitamin absorption dysfunction, thyroid dysfunction, insulin tissue dysfunction, thrombophilias etc.).

and the risk of ending up with unproven treatments. Therefore, we must assume that, at least for the time being, we will continue to encounter many couples in whom the cause of infertility is not found, but with whom we have to confront the best therapeutic option to achieve pregnancy.

This group will include, even without knowing the cause, both couples with absolute infertility with total impossibility of achieving a pregnancy naturally and those who would become pregnant within a few months without treatment. This is especially true for young women who have been seeking pregnancy for less than two years, where the chances of a natural pregnancy in the following twelve months are **more than 50%**.

These two parameters, **age** and **duration of infertility**, are the ones that determine to a large extent whether to continue waiting for a prudent period of time or to start the most appropriate treatment now.

What happens if all tests are normal, but we don't get pregnant?

The list of possible diagnostic procedures is enormous, and is growing and changing every year. However, only a few of them have proven their usefulness and a link between the test result and the possibility of pregnancy, either naturally or with the various assisted reproduction techniques.

Many others, older ones, have been discarded because they have demonstrated their lack of usefulness, and many others, newer ones, have not yet demonstrated their usefulness and are therefore of no clinical use except in very specific cases. More tests than indicated are not only more costly, but also more distress

Glossary OF TERMS

A

ALOPECIA: abnormal hair loss.

AMENORRHOEA: lack of menstruation.

AMH: Anti-Müllerian hormone. Measured to determine a woman's ovarian reserve.

ANAMNESIS: information collected by a health professional through a series of questions to learn about the patient's state of health.

ANDROGENS: male sex hormones.

ANEUPLOIDIES: an alteration in the number of chromosomes.

ANTIPHOSPHOLIPID SYNDROME: an autoimmune disease that makes women more prone to blood clots and increases the risk of thrombosis, affecting fertility and the risk of miscarriage.

APOPTOSIS: programmed cell death. A physiological process that occurs naturally in all cells of the body but can sometimes be triggered by external agents such as oxidative stress.

ASTHENOZOOSPERMIA: decreased sperm motility. Progressive sperm motility must be greater than 32%.

AZOOSPERMIA: absence of spermatozoa in the ejaculate.

B

BMI: abbreviation for Body Mass Index, which is calculated by dividing weight in kilograms by height in metres squared.

C

CORPUS LUTEUM: structure that the follicle becomes after ovulation.

D

DNA: abbreviation for Deoxyribonucleic Acid. The material that contains the hereditary information of all living things.

DYSMENORRHOEA: pain during menstruation.

E

ENDOMETRIUM: the layer of cells that lines the inside of the uterus, where implantation of the embryo takes place.

ENDOMETRIOMA: a cyst usually formed in the ovary as a result of endometriosis.

ENDOMETRIOSIS: an often painful condition in which the endometrium grows outside the uterus.

EPISPADIAS: a malformation of the penis in which the urethra ends in an opening in the upper or dorsal side of the penis.

EUMENORRHOEA: normal menstrual function.

F

FIBROID: a benign tumour in the uterus.

FISH: abbreviation for Fluorescent In Situ Hybridisation. A genetic laboratory technique for detecting and locating a specific DNA sequence on a chromosome.

FOLLICLE: structure containing the ovum or oocyte.

FSH: abbreviation for Follicle Stimulating Hormone. It is secreted by the pituitary gland. It stimulates follicular development in women and spermatozoa production in men.

H

HAEMOGRAM: a laboratory test in which the cells contained in the blood are evaluated.

HEMI-UTERUS: a uterus where only one side of the uterus develops, or uterine hemicavity, which is functional.

HYPERPROLACTINAEMIA: higher-than-normal prolactin levels.

HYPOGONADISM: a disorder where the ovaries in females and the testes in males produce little or no sex hormone.

HYPOSPADIAS: a defect in which the opening of the urethra is not at the tip of the penis.

HYPOTHYROIDISM: lower than normal levels of thyroid hormone.

HIRSUTISM: excessive hair growth in women, in areas where it is not usually present.

HYSTEROSALPINGOGRAPHY: radiological test to check the condition of the tubes and uterus.

HYSTEROSCOPY: a diagnostic procedure to view the inside of the uterus by inserting a lens through the cervix.

I

ICSI: abbreviation for Intracytoplasmic Sperm Injection.

INFERTILITY: inability to carry a pregnancy to term after one year of unprotected sex.

IVF: abbreviation for in vitro Fertilisation.

K

KARYOTYPE: laboratory test in which the size, shape and number of an individual's chromosomes are examined.

L

LAPAROSCOPY: surgical technique that allows viewing of the pelvic-abdominal cavity by inserting a tube (laparoscope) with a lens through a small incision in the abdomen.

LH: luteinising hormone, secreted by the pituitary gland, responsible for regulating the menstrual cycle and triggering ovulation when the follicle is mature.

LUTEINISATION: the atrophy process that the corpus luteum undergoes when the egg is not fertilised.

M

MACS: abbreviation for Magnetic Field Cell Separation. This technique is used to separate spermatozoa undergoing apoptosis (programmed cell death) from the rest.

MENARCHE: the beginning of menstruation.

MICROFLUIDICS: devices that allow the separation of spermatozoa according to certain characteristics such as motility, fragmentation index, etc.

N

NECROZOOSPERMIA: when the percentage of non-vital spermatozoa in an ejaculate exceeds 58%.

O

OESTRADIOL: female sex hormone secreted by the ovary.

OLIGOZOOSPERMIA: less than 15 million sperm per ml in the ejaculate, or less than 39 million in total.

P

PITUITARY: an internally secreting gland at the base of the skull, responsible for the secretion of various hormones, e.g. LH and FSH.

POLYCYSTIC OVARY: ovaries where there are more follicles smaller than 10mm than the usual number of follicles in a resting state. It is not the same as polycystic ovary syndrome. This is an endocrine disorder that is linked to obesity, irregular periods, increased androgens, and hirsutism.

POLYMENORRHOEA: a condition with irregular periods, usually menstruation lasting less than 21 days.

PROGESTERONE: a hormone produced by the ovaries and involved in the maintenance of gestation and embryogenesis.

PROLACTIN: a hormone synthesised by the pituitary gland, responsible for the secretion of milk during lactation and the production of progesterone by the corpus luteum.

PROLACTINOMA: a benign tumour in the pituitary gland, which causes increased prolactin secretion.

R

REM: stands for Recovery of Motile Spermatozoids. It is also called sperm capacitation.

S

SEMENOGRAM: a study of the macro- and microscopic characteristics of semen. Also called a spermiogram.

SEROLOGY: a test to check for antibodies in the blood.

SPERM CAPACITATION: the process that spermatozoa undergo from the time they are deposited in the vagina until they reach the egg, to be able to fertilise it. In the laboratory, attempts are made to mimic this process in order to select the best motile spermatozoa.

SPERMIOGRAM: laboratory semen analysis.

STERILITY: inability for a couple to conceive after one year of regular sexual intercourse without contraception.

T

TERATOZOOSPERMIA: when there are less than 4% morphologically normal spermatozoa in the ejaculate.

TESTOSTERONE: male sex hormone (although it is also produced in small amounts in women), responsible for the appearance of secondary sexual characteristics in males.

TUBAL PATHOLOGY: alteration of the functionality of the fallopian tubes.

V

VARICOCELE: enlargement of the veins that carry blood to the testicle.

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