

# CREANDO

## Familias

WHAT IS THE  
OVARIAN RESERVE?

EMBRYO QUALITY  
AND CLASSIFICATION

FERTILITY AND  
SPORT IN MEN



# Editorial

Dr. José Jesús López Gálvez  
CEO of the UR Group



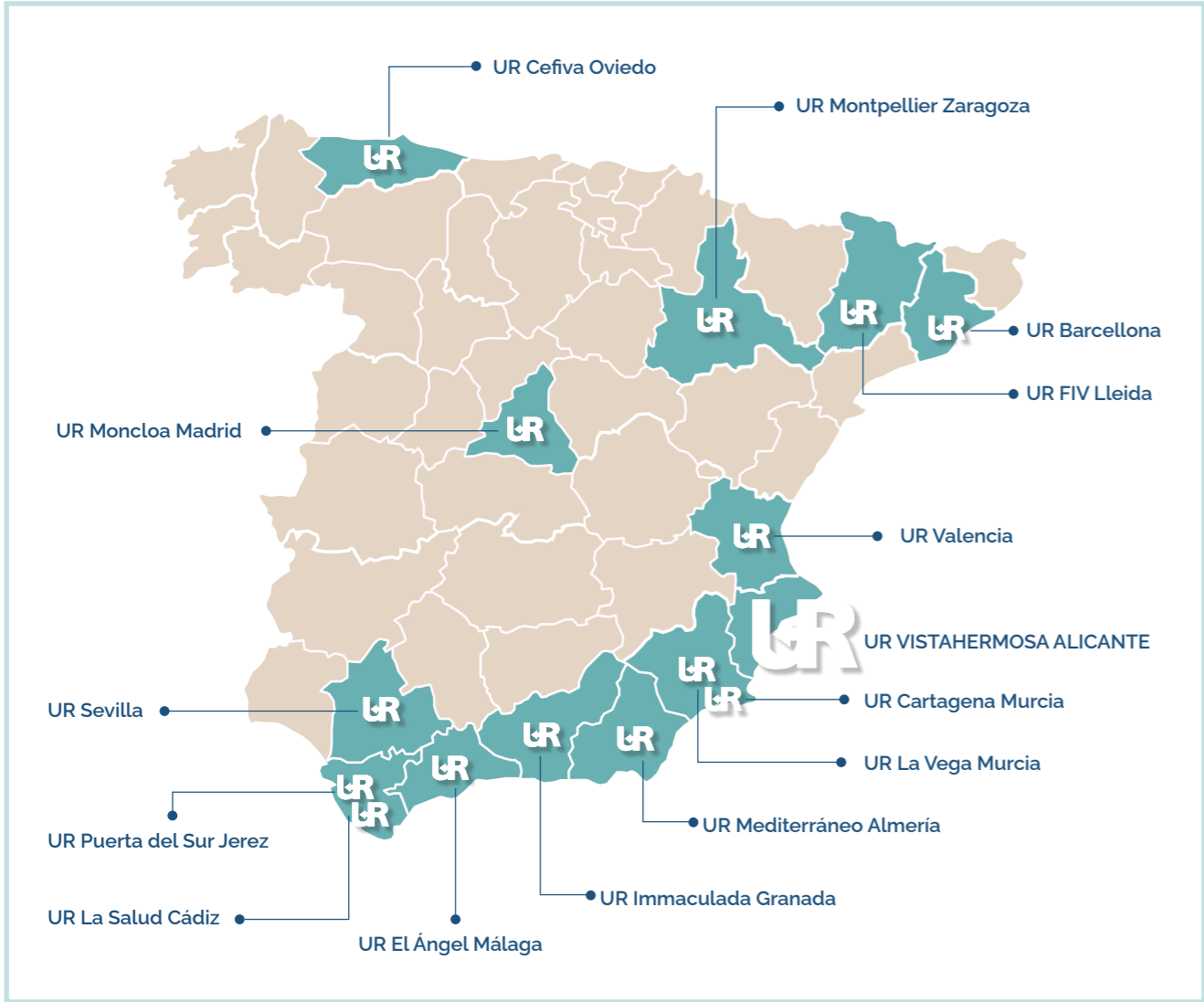
**T**his new edition of Creando Familias magazine is an important one, as it is the **last issue of 2022**.

I would firstly like to send my greetings and an enormous thank you to everyone in the Reproduction Units, patients, partners, and friends for sticking by our side and for being part of the UR International Group family. As 2022 comes to a close, I would like to send you a message of peace and confidence in these turbulent times that we are experiencing all around the world due to various circumstances. It is the end of a complicated year in which we have seen that the current situation will have a negative impact on our work in assisted reproduction. This is due, in particular, to the unfavourable economic conditions, both in terms of the difficulties people have in paying for reproductive treatments and the fact that it is **a tough time to plan having children**.

This is evidenced in the **declining birth rate**, both naturally and those through fertility treatments. But it is from these circumstances that our Group emerges even stronger. In all our units, we continue help our patients to fulfil their dream of having a baby. We do this through the work, care and commitment of our team but, in particular, through financing programmes and cost stabilisation programmes. And we do all of this with our patients at the forefront of our minds.

Furthermore, this year we have worked to make contributions of the highest level both on the **national and international stage**, showcasing all our services and treatments that can make our processes safer and promote our units in the best way to patients in Spain and around the world. We have recently incorporated new procedures such as UR sensor, PRP, radiofrequency... **cutting-edge techniques** that offer the best response to current demands.

We are also committed to people, quality and growth with new Reproductive Units. A new unit will open soon in **Seville** and another in **Barcelona**. With these new units we will be able to strengthen the Group and improve the close relationship with our clients. This is yet another motive for taking on new and important challenges in the near future, and that demonstrates the commitment of our group, and each person that forms part of it, to continue advancing and becoming a leader in assisted reproduction. Our goal will always be to offer the very best service to our patients. **I would like to end this message by wishing you a good end to the year 2022, happy holidays and all the best for 2023.**



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# 01.

## What is the OVARIAN RESERVE?

Dr. Iván Giménez  
Gynaecologist - UR HLA Mediterráneo



What can  
affect ovarian  
reserve?

How is the  
most appropriate  
treatment  
determined  
for the outcome  
of the trial?

If you're currently researching topics related to fertility, one aspect you're bound to hear more and more about is the ovarian reserve. We are receiving more and more queries related to the ovarian reserve, a topic which can cause confusion at times and represents a fundamental concept in the field of human reproduction.

At birth, women have some two million eggs, of which just **200,000 or 300,000** will survive to adolescence, when the female fertile period begins. Of these, one is used in the ovulation process approximately each month (except in cases of multiple ovulation or anovulation – in other words, when ovulation does not occur), and around a thousand are lost each month. The eggs that remain throughout women's fertile lives are susceptible to fertilisation, leading to gestation or pregnancy.

As such, at approximately 50 or 51 years of age, these eggs will have run out – causing the menopause, which is considered normal at between 45 and 55. Occasionally, however, the menopause may appear before the age of 45, which we refer to as early menopause. On the other hand, when the ovaries become inactive **before age 40**, we speak of **premature ovarian failure**.

In general, women's fertility becomes impaired from the age of 37 or 38, and although potentially fertile eggs remain, their quality may be degraded as a result of age.

Female fertility is a **highly individual factor**, and while some women aged 40 and older will have no problem getting pregnant, others may find it more difficult after the age of 35 or even younger. Apart from other potentially influential aspects, and with the exception of other pathological factors, this depends to a large extent on the ovarian reserve. As such, we can define this reserve as a woman's capacity to generate fertile eggs, which depends both on their age and on individual factors.

When it comes to planning an assisted-reproduction treatment, it is important to determine and consider the ovarian reserve whenever the ovaries will be involved –



in other words, when the woman's own eggs are to be used. The ovarian reserve helps to predict the response to fertility treatment, but this factor is not just important for planning a treatment – it can also be useful in those cases in which patients wish to defer childbearing and resort to fertility preservation via egg freezing, preparing for a future when the ovaries may not respond adequately.

Certain elements may point to a low ovarian reserve, such as a family history of early menopause or a short menstrual cycle of less than 28 days. However, this condition is best determined through hormonal tests such as a simple **Anti-Müllerian hormone** analysis or an **ultrasound count of follicles** in the ovaries.

As such, the study of the ovarian response helps to decide not only which will be the most optimal treatment for a good response from the ovaries, but also which **treatment will be the most appropriate**, thereby determining whether or not it will be possible to obtain the necessary number of eggs for the process' success, or if we may need to make use of donor eggs.



# AGE

## The most frequent cause of poor oocyte quality

**Carolina Orjuela Gasca**  
Embryologist - UR HLA La Vega

In many areas of life, we are told that quantity is not the same as quality and, of course, this also applies to our eggs or oocytes. To understand this affirmation, we must start with the fact that women are born with a **limited number of oocytes**. Throughout our lives, this quantity of oocytes, known as the ovarian reserve, decreases until we reach the menopause and, with it, the end of the **fertile stage**.

The ovarian reserve is a parameter that may be assessed through various different tests, such as an ultrasound antral follicle count, and analysis of the **Anti-Müllerian hormone (AMH)**, **follicular-stimulant hormone (FSH)** and oestradiol



levels. As such, it is relatively easy to calculate our ovarian reserve.

However,

**Does a good reserve mean good-quality eggs?**

**Unfortunately not.** It is impossible to determine oocyte quality before carrying out an assisted-reproduction technique, as no tests currently exist to indicate their condition. In the laboratory, when it comes to performing the indicated technique, we as embryologists assess the quality of each oocyte through its morphology; though genetic alterations may also exist that cannot be seen under the microscope.

**How can we tell if this is the cause of infertility?**

Certain factors cause poor oocyte quality and can help us to predict whether or not we are likely to encounter this problem. The poor quality of eggs may be caused by habits such as **smoking** or **alcoholism**, and even by **obesity**, due to its effect on oestrogen metabolism. On the other hand, it may be caused by illnesses, such as **endometriosis**, or disorders like **polycystic ovarian syndrome (POS)**.

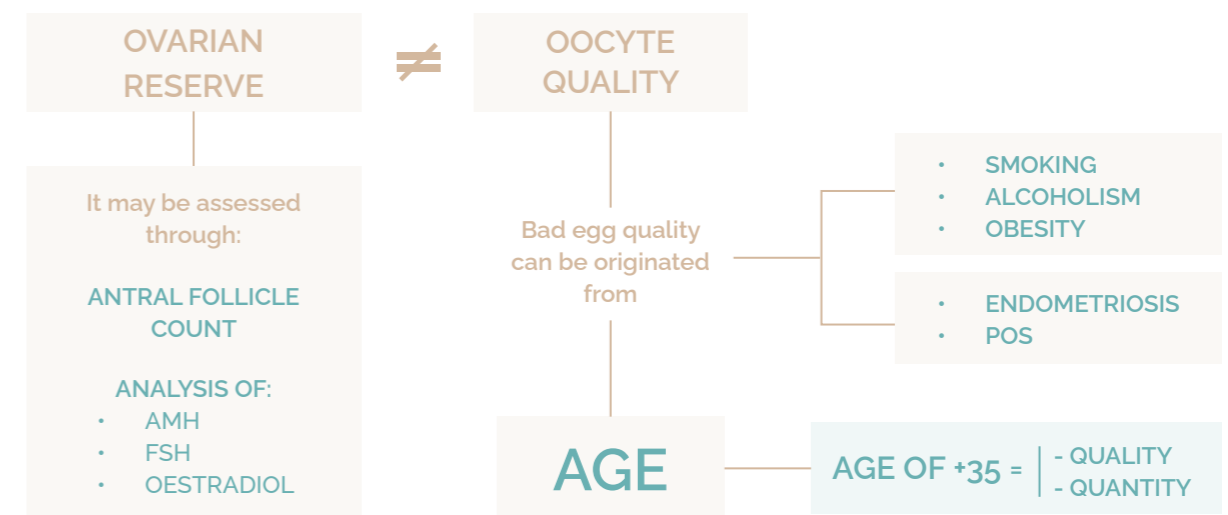
These circumstances can be improved in order to optimise the success of the indicated assisted-reproduction technique. How-

ever, the most common cause of poor oocyte quality is the **age of the woman**.

Just as the number of eggs decreases with the passage of time, particularly after the age of 35, so too does their quality. Oocytes present an inevitable ageing which results in more genetic alterations and their consequent effects on the couple's fertility.

As such, we can conclude that, though age affects both factors, the quality and quantity of oocytes are completely different aspects and that the cause of a couple's infertility must be studied individually in order to tackle the problem in the most appropriate and successful way possible.

### In short:



# 02.

## Embryo QUALITY and CLASSIFICATION

**Candela Martos García**  
Embryologist - UR HLA Sevilla



What are the stages of development of the embryo?

How are embryos classified?

The embryos obtained during in-vitro fertilisation (IVF) are cultivated in a laboratory under controlled conditions for several days. Once developed, the best-quality embryo or embryos are selected and transferred to the mother's uterus, or vitrified for future cycles.

The success rate of an IVF assisted-reproduction process depends largely on the **quality of the embryo transferred**. The best-quality embryos are likely to implant better within the uterus and result in a pregnancy.

As such, embryos are classified according to **morphological characteristics** such as number of cells, size, symmetry, shape, fragmentation, vacuolation, etc., and kinetic characteristics such as division times and cell reversal movements during division, which can only be observed through time-lapse incubator culture.

To get started, we're going to explain how the embryo develops during the days spent in the incubator:

- The day on which the oocytes are inseminated with the semen sample is considered **day 0 of culture**.
- **17/18 hours** after insemination, we can observe fertilisation, on **day 1 of culture**. This is a cell which has not yet started to divide, with two nuclei – one maternal and one paternal – known as a **zygote**.
- On **day 2 of culture**, we can see the first cellular divisions, obtaining an embryo of **2 to 4 cells or blastomeres**.
- On the **third day**, the embryo should continue dividing itself into **eight cells**.

- On **day 4**, the embryos start their transition from a multicellular embryo to a more advanced stage of development – with around **16 cells or blastomeres**, which should start to compact and form the so-called "**morula**" (Latin for mulberry, due to its similarity to the fruit).
- On **day 5 of culture**, a cavity starts to form within the embryos, becoming "**blastocysts**". These are composed of two different types of cells: a group of cells known as the inner cell mass, which will become the foetal tissue, embedded in the **blastocoel** (a liquid-filled cavity), surrounded by the **trophectoderm**, a group of flattened cells that envelop the blastocysts and will become the placenta.



In the laboratory, the embryologist must pay close attention to the cellular divisions of the embryos, as well as other **morpho-kinetic aspects** that will help us to decide which embryo is the most suitable for transfer – in other words, which of the available embryos will have the greatest chance of implantation. For this, we observe certain criteria or factors that allow us to positively or negatively catalogue the embryo according to its quality.

The factors that positively affect good embryo quality are: synchrony of cell division, similarity of size between blastomeres, the number and shape of blastomeres, and the absence of fragmentation.

The factors that negatively affect embryo quality are: asynchronous blastomere division, irregular and asymmetric shape, number of blastomeres below that considered optimal on the day of culture, or the presence of cellular fragments, as well as vacuoles or blastomere multinucleation.

In embryology laboratories, it is vitally important that an exhaustive selection process is carried out for the embryos to be transferred, making it essential that we **classify them according to a single criterion**, in order to take the most objective decision possible.

In the laboratories of the UR International Reproduction Group, we carry out embryonic classification according to the **ASEBIR** criteria (Spanish Association for the Study of Reproductive Biology), which differentiates embryos into **four categories** according to implantation capacity:

- **CATEGORY A:** Optimal-quality embryo, with maximum capacity for implantation.
- **CATEGORY B:** Good quality embryo, with high capacity for implantation.
- **CATEGORY C:** Regular embryo, with low capacity for implantation.
- **CATEGORY D:** Poor-quality embryo, with very little chance of implantation.

It is important to note that neither a category A embryo guarantees success, nor does a category D ensure failure. Embryo quality, determined according to morphological criteria, significantly affects the chances of implantation, but other factors are also at play: such as the **state of the endometrium** at the time of transfer, **the age** of the mother, the **cause of infertility** or the **embryo's genetics**.

### In short:

**1.** THE OOCYTES ARE INSEMINATED WITH THE SEMEN SAMPLE.

**2.** EMBRYO DEVELOPS IN THE INCUBATOR.

**3.** EMBRYO ANALYSIS

Which of the available embryos will have the greatest chance of implantation.



# EMBRYO TRANSFER

## An essential intervention in achieving pregnancy

**Dr. Nuria Castelló**

Gynaecologist - UR HLA La Vega

Embryo transfer is a **key procedure** in achieving pregnancy, as it is in this technique that all the work, effort and dedication ensured by the professional team will be reflected.

In this technique, gynaecologists deposit embryos in the mother's uterus. This is the moment when the embryo or embryos come into contact with the uterine cavity. It represents a **crucial step in assisted-reproduction treatments** – in-vitro fertilisation (IVF), egg donation or embryo donation – following fertilisation and the development of embryos in the laboratory.

Three factors can be influenced during the act of transfer: **the embryo, the endometrium and the technique used**.

Though this is a relatively uncomplicated process, at the UR Group, we believe that the biological potential of the embryo and endometrial receptivity are as important as the proper performance of the transfer.



Endometrial preparation may be carried out both in a natural or modified cycle. The first consists in taking advantage of the hormones produced by the woman's body itself for said preparation, while in the second, said hormones – oestrogen and progesterone – are administered exogenously. Today, **ultrasound** remains the most useful and non-invasive method available to us for endometrial assessment. To establish whether or not the endometrium is ready for implantation, we consider both its thickness and appearance. This study can be complemented by analysing the blood hormone levels of these two hormones in the hours prior to the transfer. On the other hand, tests have been

developed that analyse the genetic expression of the endometrium, though more evidence is required to prove their indications.

Embryologists play a key role in terms of the variables that may affect the embryo. The main variables at play here are the degree of embryo development, their quality and the number of embryos to be transferred. These may be “fresh” or previously **vitrified embryos**. Vitrification is a technique which allows embryos to be preserved in optimal conditions for subsequent use.

The technique used to carry out the transfer must be adapted to each patient, bearing in mind

factors such as the transfer test or any previous transfers, if applicable. The transfer test uses the same cannula that will later be used to insert the embryos into the uterus. This is carried out in a previous cycle, so that if any problems arise that hinder the passage of the transfer cannula, the necessary treatment or action will be taken to remove said difficulty.

**Coordination within the team**, and more specifically between embryologists and gynaecologists, is essential in order to agree on the optimal embryo-transfer conditions, aiming to guarantee a procedure that has been personalised to best adapt to the reproductive situation of each case. At UR Group, we ensure the utmost care in each step of the procedure.

Once patients leave our reproduction unit, the “**beta waiting**” period begins, in which they will experience a wide range of emotions and feelings that will remain with them until the decisive moment: **the pregnancy test**. During this period, it is essential that the gynaecologist's instructions are followed: in particular, progesterone levels must be maintained.

Though no studies have proven that our attitudes can influence results, we believe that a positive and relaxed state of mind causes a chain reaction of thoughts, events and optimal results.

# EMPTY FOLLICLES

## An abnormal and difficult-to-diagnose syndrome

**Lourdes del Águila Ramos**  
*Embryologist - UR HLA Mediterráneo*

**Empty follicle syndrome (EFS)** is an uncommon and highly frustrating condition, the origin of which is not yet known, in which no oocytes are recovered from the ovarian follicles after ovarian puncture, even if normal follicle growth with suitable levels of oestradiol has been developed in the days prior.

Two typologies can be observed: **false empty follicle syndrome (FEFS)**, when the level of human chorionic gonadotrophins (HCGs) is low on the day of oocyte collection; and **genuine empty follicle syndrome (GEFS)**, when their level is optimal.

FEFS is normally caused by errors in the administration of medications or the drugs themselves, while GEFS may be defined as the incapacity to retrieve oocytes after induction, optimal follicular development and suitable levels of HCG on the day of puncture. These patients do not appear to respond well to the

dose of HCG and oocytes are not normally recovered in subsequent cycles. This syndrome occurs in **0.5-7% of patients** subject to assisted-reproduction cycles and, according to some scientific articles, the prevalence of genuine cases was as low as 0.016% in a large cohort of over 12 thousand IVF patients.

The mechanism responsible for EFS is not known. However, some authors have pointed to early **follicular atresia** or **abnormal folliculogenesis** as possible causes for this syndrome. Another potential cause may be the ovarian reserve, the woman's advanced age or the presence of a hereditary genetic factor.

For patients, the failure to retrieve oocytes carries a heavy emotional and financial burden, and as such it is vitally important that we are able to detect these cases when they arise, in order to carry out better diagnosis and offer the best recommendations to the couple.



# 03.

## ASHERMAN'S SYNDROME and its influence on sterility

**Dr. Francisco Anaya**  
Gynaecologist - UR HLA Vistahermosa



What are the causes and symptoms?

Is there a treatment?

This disease takes its name from the Israeli gynaecologist **Josef Asherman**, who first discovered it in **1948**. Women affected by this medical condition present with **adherences or synechiae** inside their uterine/endometrial cavity. These adherences cause the total or partial obliteration of the cavity, narrowing or deforming it – and, in extreme cases, occluding it entirely.

According to the degree of **impact to the endometrium**, we may find mild, moderate or severe cases of this syndrome. These severe cases, as we might imagine, are those with the worst reproductive prognosis, as in this case the uterine walls present fully adhered.

## Causes of Asherman's Syndrome

Though a **vast number of causes** have been described that may cause this illness, such as endometrial infections, surgery or embolisation of uterine fibroids, etc., in more than **90%** of cases, the origin of this condition lies in **uterine curettage**, whether after an abortion or birth (puerperal).

The latter cases represent the greatest risk as these are difficult interventions, often associated with haemorrhaging and infections.

### What symptoms do affected patients present?

The most common symptoms of this disease are:

- **Menstrual alterations:**  
Hypo- or amenorrhea (decrease or total absence of period) fundamentally due to the reduction in functional endometrial tissue and by the obstruction of the cervix due to the aforementioned adherences.
- **Pelvic or abdominal pain:**  
Caused by the retention of menstrual blood.
- **Endometriosis:**  
Menstrual retention can retrograde into the abdominal cavity, leading to the appearance of endometriotic foci.



■ **Infertility:**

Adherences and endometrial damage prevent the proper growth of the uterine mucosa, leading to a failure in embryo implantation or, in the case of pregnancy, increasing the chances of spontaneous abortion.

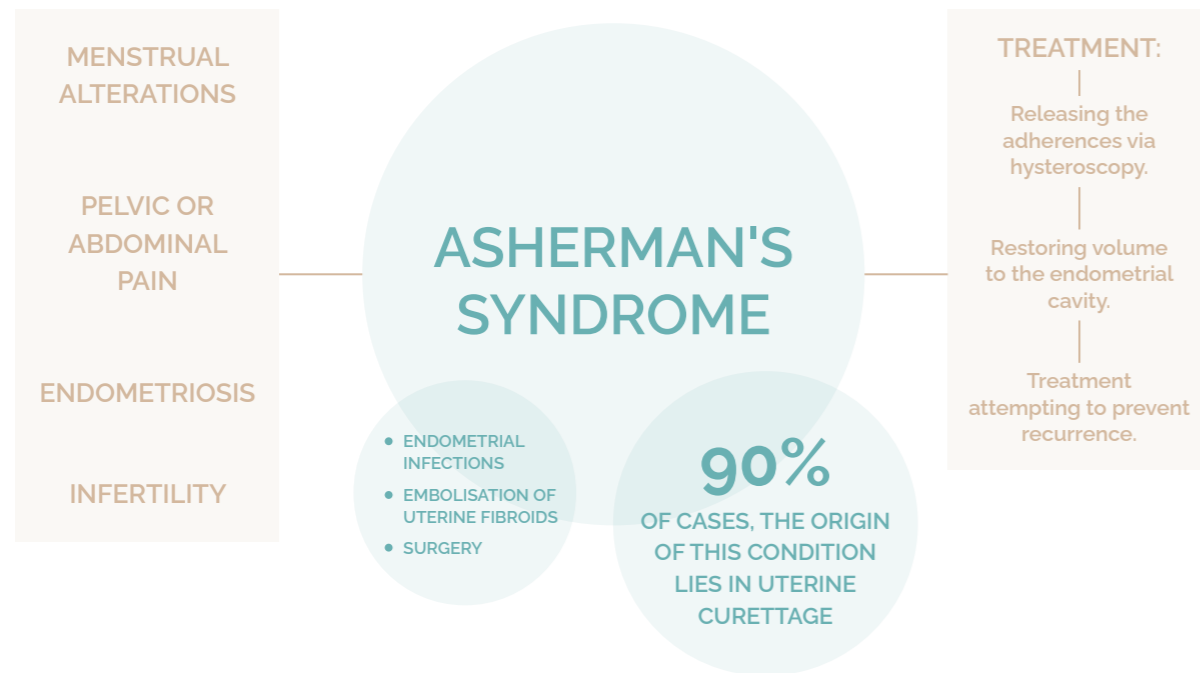
This condition is diagnosed clinically and should be suspected in patients presenting an absence or decrease in menstrual blood, whether or not this is associated with any of the other aforementioned symptoms. The study should be completed with an **imaging technology** such as transvaginal ultrasound, hysterosalpingography or pelvic MRI, and confirmed by **hysteroscopy**.

The treatment for this condition consists in releasing the adherences via hysteroscopy, restoring volume to the endometrial cavity, followed by medical treatment attempting to prevent recurrence.

Today, studies have been carried out with alternative therapies such as **endometrial PRP** (platelet-rich plasma) or **stem-cell infusions** that may help regenerate the damaged endometrium.

In our patients with fertility problems, the aim is to improve expectations of achieving a viable pregnancy.

*In short:*



# 04.

## FERTILITY and SPORT in men

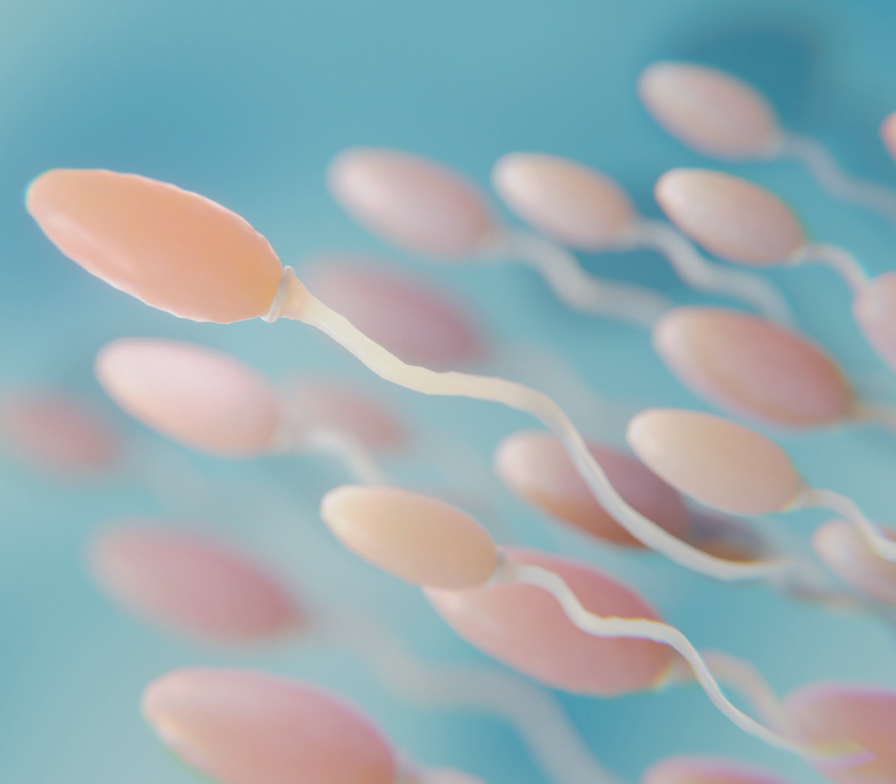
**Bernardo Fernández Martos**  
Nurse - UR HLA Vistahermosa



How does sport affect male fertility?

What sports can alter seminal quality or increase the incidence of erectile dysfunction?





that it is subject to significant **inter-individual** and **intra-individual** variability. Its parameters undergo periodic variations, and periods of sexual abstinence will affect the results obtained. Nevertheless, it represents a basic study technique in providing an initial prognostic estimate of the male athlete's reproductive potential.

On the other hand, there has been an **increase in the incidence of erectile dysfunction**. In this regard, cycling has been the most analysed sporting discipline when studying the relationship between physical exercise and impotence, with results that suggest the possible presence of **nervous and/or vascular lesions** after long races or prolonged training sessions. However, the incidence of this alteration's occurrence is low and generally transitory, though total recovery will normally take around **six months**. As such, the bicycle industry has adopted measures such as the incorporation of structural improvements to saddle design, intended to reduce the incidence of these problems.

Certain physiological mechanisms have been proposed and researched which may link clinical disorders with the practice of physical exercise. These include **hormonal alterations, oxidative stress, increased scrotal temperature, trauma, and even situations of hypoxia** related with high-altitude sports.

The growing trend of doing sport in our modern society has resulted in an increasing number of couples in which both partners do sport, while attempting to become pregnant. As in women, reproductive disorders can also be seen in male athletes. However, research in this regard is much more limited and the indirect means of obtaining data has meant that less information is available on the subject. Nonetheless, studies have been carried out which offer clues as to the direction future research should take in order to focus on diagnosis and treatment.

The clinical disorders related sports-induced infertility in males have also been **catalogued and researched**. The results obtained show two critical areas of study.

On the one hand, alterations may be observed in **semen analysis**. The semen quality of resistance athletes has been the subject of numerous studies. The majority show that intense physical activity has a significant effect on athletes' semen quality. In runners, alterations may be observed in all parameters, and the volume of training undertaken appears to be directly proportional to the degree of the negative effect reported. Resistance training among cyclists has been proven to cause **morphological alterations to semen**.

It is important to emphasise that semen analysis is a technique of little diagnostic value in determining decreased reproductive capacity in male athletes, given

Both the **volume and the intensity of exercise** have been raised in numerous studies as determining factors in the alteration of fertility markers among male athletes, such as hormonal levels and the results of semen analysis. Due to variations in the conditions and characteristics of the **bodily stress** produced by different sports, it is expected that the type of activity carried out will also represent another important variable.

The results of the studies that have attempted to compare the effects of different sporting disciplines show a direct relationship between **training load and seminal alterations**, with morphology being the most affected parameter.

These results suggest that those who opt for a discipline with longer and more intense training are more likely to present alterations in their reproductive capacity.

Despite this, before clinical advice can be given stating that "less physical activity will be beneficial for the male factor in an infertile couple", a cause-and-effect relationship must be established between intense physical exercise and male reproductive disorders.

This **cause-and-effect relationship** can only be established through well-designed, properly controlled studies using relevant and appropriate assessment criteria, with no such studies having been carried out to date.

Although it seems that a high degree of physical activity may have a negative effect on the fertility of some athletes, it is not yet clear which population groups may be affected and to what degree.

As such, the clinical attitude today should only be one of warning or advice: if a male factor is diagnosed or suspected in a couple with fertility problems, a **decrease in exercise among extremely** active men may be one way to begin treatment. However, it should always be considered that, to date, this recommendation has **no solid scientific basis**, and that this may impact other aspects of the patient's quality of life.

## In short:

### THE CLINICAL DISORDERS RELATED SPORTS-INDUCED INFERTILITY IN MALES



### BEFORE CLINICAL ADVICE:

**ESTABLISH A CAUSE-AND-EFFECT RELATIONSHIP**

# “What I like best is seeing and hearing embryos’ heartbeats”

Doctor Carmen Segura, Medical Director of the Reproduction Unit at the HLA Moncloa Hospital, highlights her time as a resident at the **Madrid 12 de Octubre Hospital Gynaecology and Obstetrics department** as an important stage in her career, where she gained in-depth knowledge of in-vitro techniques, at “a pioneering centre in the field of human reproduction in the 1990s, offering incredibly comprehensive training in reproductive medicine”.



**Dr. Carmen Segura**  
Medical Director of the Moncloa  
Reproduction Unit

Developing her professional career in public hospitals in Madrid was also fundamental – such as her time at the Gregorio Marañón hospital, where, given the pathology and number of patients treated, she acquired significant professional experience and an “infinite” diversity of clinical cases. Today, she works with the UR Group, to

which the fertility clinic she directs belongs, “where we have patients from both the public and private sphere, and where we can develop all our professional strategies with no restraints”.

Today, Doctor Carmen Segura is happy to work with both autonomy and professionalism, following

her own opinion and offering her patients the knowledge acquired throughout her career, with state-of-the-art technological resources at the disposal of both her and her team. She defines herself as a person passionate about her work and confesses that “what I like best is **seeing and hearing embryos’ heartbeats and patients’ faces**

when they succeed in becoming pregnant. It’s an indescribable feeling which, even if you’ve experienced it many times, is always absolutely magical”. In these cases, she says she feels like a kind of fairy godmother with a huge responsibility, centred around that moment in which you are working to contribute to achieving this goal of infinite importance for two would-be parents, unable to conceive, and who need specialist help to see their reproductive wish fulfilled.

Delaying childbearing is often responsible for making natural conception difficult: “At more advanced ages, the possibility of female fertility reduces and this represents a handicap when it comes to conceiving a child. Fortunately, thanks to science and research, we have been able to develop techniques in the field of human reproduction that allow us to overcome this difficulty and become increasingly effective to obtain better results”.

Doctor Carmen Segura believes that **synchronised teamwork** is fundamental for the success of these processes, ensuring a consistent level of dedication with a clear understanding that they are working with people, “making it essential that we develop a degree of empathy which allows us to put ourselves in our patients’ shoes”.

The specialist notes that the cornerstones of the UR International



Group’s success are the precision acquired through experience and the ability to work with the greatest resources, in a highly professional way – in other words, with a team of top-rate doctors and embryologists, all passionate about their work.

*“We have the best pregnancy rates and results compared to our competitor clinics. We maintain a relationship of absolute trust and empathy with our patients, with informative transparency and a great deal of honesty on our part, and this offers significant added value”.*

As the doctor notes, one of the main factors that distinguishes the reproduction units of the UR International Group from other fertility clinics is the pursuit of results with minimal impact for the patient,

both in **clinical aspects, and in emotional and financial terms**. “It’s important that our patients know that when they visit a UR Group unit, they will be seen by a specialist doctor, not a medical-service company. It is important to bear in mind that there are fertility clinics where, from the outset, you won’t be seen by a doctor, but an assistant or even a salesperson, and this greatly detracts from the final result.

Another distinguishing factor noted by Doctor Carmen Segura is that, as an international reproduction group, their units welcome many foreign patients, attracted by the high level of assistance offered in fertility treatments.

*“We are at the cutting edge of reproductive medicine, and having fertility clinics in other countries allows us to export our experience, working model, technology and knowledge”.*



# Acknowledgements

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Embryologist



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**Lourdes del Águila Ramos**  
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