creando familias

RADIOFREQUENCY
A CUTTING-EDGE INNOVATION TO TREAT UTERINE FIBROIDS

PREIMPLANTATION GENETIC TESTING
A PATH TO HEALTHIER PREGNANCIES

YOUR PREGNANCY IS OUR GUARANTEE
MONEY-BACK GUARANTEE PROGRAMMES

N° 16 DECEMBER 2025

Reproduction International Group

OVER 40 YEARS CREATING FAMILIES

IN RECENT DECADES, THE TRADITIONAL CONCEPT OF FAMILY HAS UNDERGONE A PROFOUND TRANSFORMATION.

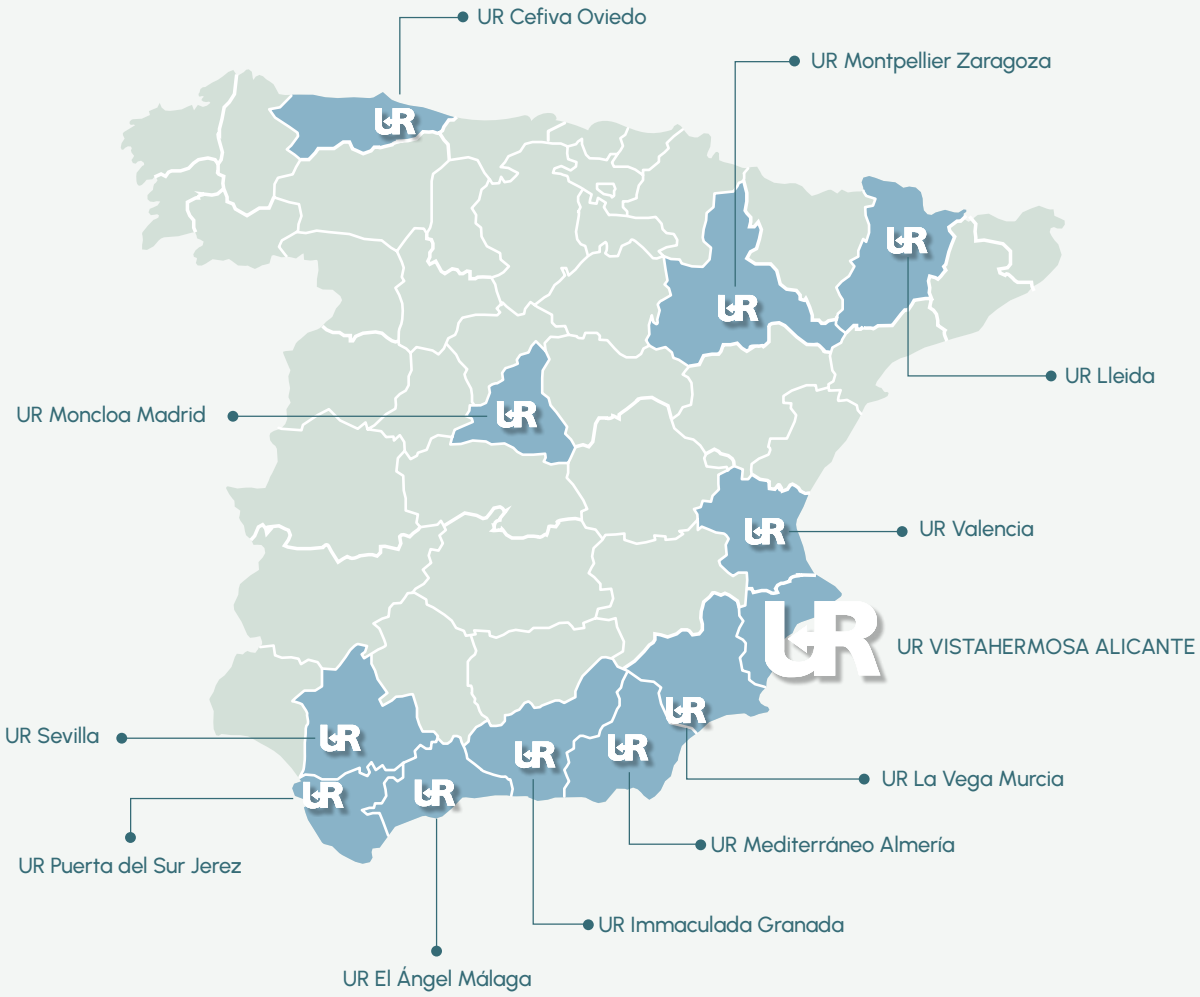
Today, the decision to become a mother **is shaped by multiple factors** that didn't carry the same weight in the past, such as financial stability, work pressures, relationships and alternative family models.

One of the most significant changes has been the gradual **fading of the traditional family model.** In many countries, birth rates have dropped dramatically, and more and more women are choosing to postpone or forgo motherhood in order to prioritise their careers. According to recent studies, the average age for having a first child has risen in nearly all industrialised societies, while the proportion of women without children has also increased. There are many reasons behind these decisions, but a shared factor is the economic and employment uncertainty that many women face.

Infertility, a challenge affecting millions of people worldwide, **is no longer an insurmountable barrier thanks to remarkable advances in reproductive medicine.** What was once an almost impossible challenge for many women and couples wishing to have children has now opened up a world of possibilities. From in vitro fertilisation (IVF) to advanced genetic treatments, medical innovations have transformed our understanding of reproduction, offering hope to those struggling to conceive.

The **UR Reproduction Units Group**, headquartered at the Vistahermosa Reproduction Unit, boasts a successful track record of over 40 years, reflecting an approach to medicine that is truly patient-centred. The **multidisciplinary approach, integrated within a hospital infrastructure, is a key factor in improving both the quality and outcome of treatments. A strong professional commitment** to patients, along with a constant pursuit of **greater efficiency**, is the driving force that inspires the specialist teams within the UR Group.

With over four decades of continuous advancement, focused on research and ongoing training in reproductive medicine, the UR Group **looks to the future with determination, innovation and unwavering dedication** to giving couples and women the opportunity to fulfil their dream of starting a family.



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Dr. Francisco Anaya Blanes | *Medical Director* - *Vistahermosa Reproduction Unit, Alicante*

RADIOFREQUENCY

A CUTTING-EDGE INNOVATION TO TREAT UTERINE FIBROIDS

THANKS TO RADIOFREQUENCY TECHNOLOGY, MANY WOMEN CAN NOW HAVE THESE BENIGN TUMOURS TREATED EFFICIENTLY AND SAFELY, WITHOUT THE NEED FOR HOSPITALISATION OR RECOVERY TIME.

Uterine fibroids, or myomas, are the most common benign tumours among women of reproductive age, affecting approximately **50% to 70%** during their lifetime. These muscular growths can form in different parts of the uterus, leading to symptoms such as discomfort and, in some cases, affecting fertility or assisted reproduction treatments. Until quite recently, the only effective treatment options were surgical procedures such as myomectomy or, in more advanced cases, hysterectomy. Both procedures required anaesthesia, hospitalisation, and an extended recovery period. However, the advent of **radiofrequency** technology has shaken this up.

This is a minimally invasive technique and does not damage the endometrium. The treatment works by **applying heat directly inside the fibroid**, disrupting its blood supply and inducing necrosis. The necrotic tissue is gradually reabsorbed, leading to a reduction in fibroid size and associated symptoms. The procedure is carried out under ultrasound guidance via the vagina, using a very fine needle. Just one single procedure can treat multiple fibroids, which are subsequently reabsorbed by the body over the course of several months.

A major benefit of this technique is that it can be performed on an **outpatient basis**, without the need for general anaesthesia, hospitalisation, or an extended recovery period. This breakthrough represents a significant advancement for women seeking to preserve their fertility while avoiding the drawbacks of traditional surgery.

Indications

In reproductive medicine, radiofrequency therapy is recommended to treat uterine fibroids in the following situations:

FIBROIDS AFFECTING THE UTERINE CAVITY

Submucosal or intramural fibroids that distort the endometrium can interfere with embryo implantation and increase the risk of miscarriage.

PATIENTS WHO HAVE HAD UNSUCCESSFUL IVF CYCLES

In cases of repeated unexplained IVF cycle failure, fibroids should be considered as a potential contributing factor.

REPRODUCTIVE MEDICINE HAS TAKEN A GIANT LEAP FORWARD WITH THE GROUNDBREAKING, NON-SURGICAL OPTION TO TREAT UTERINE FIBROIDS.

WOMEN WITH MILD OR MODERATE SYMPTOMS

Radiofrequency is particularly suitable for patients experiencing heavy bleeding, pain, or pelvic pressure who wish to avoid major surgical intervention.

CASES IN WHICH RAPID RECOVERY IS SOUGHT

For patients looking to undergo fertility treatments as soon as possible, this technique offers shorter recovery times compared to conventional surgery.

ADVANTAGES OF RADIOFREQUENCY IN ASSISTED REPRODUCTION:

Radiofrequency is a technique endorsed by the Spanish Society of Gynaecology and Obstetrics and offers no shortage of benefits:

PRESERVES FERTILITY: By preserving healthy uterine tissue, this technique supports the possibility of future pregnancies.

MINIMALLY INVASIVE: The procedure avoids open surgery and hospitalisation, thereby minimising risks and speeding up recovery.

WITHOUT GENERAL ANAESTHETICL: It is performed under local anaesthesia or mild sedation, avoiding the potential side effects associated with general anaesthesia.

FASTER RECOVERY TIME: Patients can go about their usual activities almost immediately and can start undergoing reproductive treatments within a few weeks.

HIGHLY EFFECTIVE: The procedure significantly reduces fibroid size and improves the success rates of fertility treatments.

It should be noted that this treatment is not appropriate for all fibroid types or sizes. Not all patients are suitable candidates for this procedure, and eligibility should be determined following a thorough evaluation by a gynaecology specialist. **Each patient is different, therefore treatment decisions should be made with a qualified healthcare professional.**

Antonio Urbano | *Genetics Unit Director* - *Grupo UR*

PREIMPLANTATION GENETIC TESTING

A PATH TO HEALTHIER PREGNANCIES

IN RECENT YEARS, REPRODUCTIVE MEDICINE HAS UNDERGONE NO SHORTAGE OF ADVANCES, WITH EMERGING STRATEGIES AIMED AT A SHARED GOAL: **THE BIRTH OF A HEALTHY CHILD.**

Among the emerging techniques in reproductive medicine is non-invasive **Preimplantation Genetic Testing (PGT)**, that strives to obtain genetic information from the embryo in the least harmful way possible prior to transferring it to the uterus.

The first step involves performing **in vitro fertilisation (IVF)**, where eggs and sperm are combined in a laboratory to create an embryo. This treatment is indicated in a number of different situations, including advanced maternal age, low sperm count, ovulatory disorders, or when simpler assisted reproduction methods have been proven unsuccessful.

If fertilisation is successful, the fertilised egg will begin cell division and develop into an embryo. Embryos are cultured in specialised **incubators** within the embryology laboratory, where embryologists monitor their development and select the highest-quality embryos to be transferred to the maternal uterus or they undergo cryopreservation with a view to being used at a later date. Until only a few years ago, embryos were selected exclusively based on morphology, taking into account parameters such as cell count, cell size, and fragmentation rate. However, morphology is not necessarily indicative of the embryo's chromosome complement.

Human cells contain **46 chromosomes**, which are structures that house our genetic material, DNA. Half of them are inherited from our father and half from our mother. An embryo is considered euploid when all its cells contain 46 chromosomes, whereas an aneuploid embryo has extra or missing chromosomes.

It is now well established that aneuploid embryos are relatively common, with maternal age being one of the contributing factors. For instance, approximately **25%** of embryos from women **aged 30** are aneuploid, rising to **50%** by **age 40** (Franasiak JM et al., Fertil Steril, 2014).

Aneuploid embryos are not viable and most result in miscarriage or fail to implant. During in vitro fertilisation, the best embryo can be selected based on morphology, but they may still be aneuploid, increasing the risk of implantation failure, miscarriage, or the birth of a child with significant abnormalities.

GENETIC TESTING OF THE EMBRYO

The only current method we have to reduce the risk of transferring aneuploid embryos is to perform a genetic test to determine the number of chromosomes in the embryo during the pre-implantation phase; in other words, before the embryo is transferred to the maternal uterus.

This is called **PGT-A** (Preimplantation Genetic Testing for Aneuploidy) and is used in particular in cases of advanced maternal age, recurrent miscarriages, recurrent implantation failures, among others. This genetic test is performed **3 to 5 days post-fertilisation** and begins with an embryo biopsy, in which one or more cells are extracted from each embryo. The sample is then analysed in the laboratory to identify embryos with a normal chromosome complement, which are more likely to lead to a successful pregnancy.

EMBRYO BIOPSY

The embryo biopsy is a crucial step during PGT. The procedure can be performed on day three post-fertilisation, when the embryo has reached the **six- to eight-cell** stage. In this case, a tiny hole is made in the **zona pellucida** (membrane encasing the embryo) and a cell is extracted for genetic testing.

Embryo biopsy is currently most often performed on day 5 or 6 post-fertilisation, at the blastocyst stage, when the embryo has more than 100 cells. In this case, a small cluster of cells is removed from the trophectoderm, the outer layer of the blastocyst that will develop into the placenta. The biopsy at the blastocyst stage provides significant advantages over day 3 biopsy; on the one hand, it allows for more genetic material to be collected due to the larger number of cells extracted, and it is less detrimental to the embryo because it contains more cells. Furthermore, it allows for the detection of **embryonic mosaicism** (embryos that contain a mix of cells with normal chromosome numbers and cells with abnormal numbers).

ADVANTAGES AND LIMITATIONS

Like all techniques, PGT-A has some advantages and limitations. Among the benefits, compared to IVF cycles in which PGT has not been performed, we find that it:

- Improves implantation rates
- Reduces miscarriage rates
- Improves pregnancy rates per embryo transfer
- Reduces the risk of a baby being born with a chromosome abnormality

ON THE OTHER HAND,
SOME OF ITS LIMITATIONS ARE:

- This is an invasive procedure in which most embryos survive the biopsy, although there is a slight risk that the embryo may fail to continue developing.
- It is a complex procedure that calls for specialised equipment and highly experienced professionals.
- There is a risk of misdiagnosis due to embryonic mosaicism, since only one cell line of the embryo is analysed.

NON-INVASIVE PGT

In 2016, the presence of free DNA in blastocyst culture medium was published and suggested as a method for non-invasive screening of the embryo's chromosome complement.

This DNA is released by the embryo into the culture medium during in vitro development through mechanisms that are not yet fully understood. Recent studies have shown that DNA can be detected, extracted and amplified from the embryonic culture medium, particularly at the blastocyst stage, and have looked into its potential clinical use for non-invasive PGT. At present, the **clinical utility of non-invasive PGT is still a topic of debat**e. Recent studies suggest that, once contamination from maternal DNA is eliminated and laboratory protocols are optimised, the DNA released by the embryo into the culture medium provides an **accurate indication of its chromosome complement** (Huang et al., Proc Natl Acad Sci USA, 2019; Chen et al., Front Cell Dev Biol, 2021).

HOW IS NON-INVASIVE PGT PERFORMED?

The protocol is much less complex than conventional PGT, as it eliminates the need for an embryo biopsy. The basic steps are as follows:

1. On days 3-4 post-fertilisation, each embryo is washed and placed in fresh culture medium, where it is incubated until days 5-6.
2. During this period, the embryo releases free DNA into the environment.
3. On day 6, embryos are vitrified (they undergo ultra-fast freezing), and the culture medium is collected and analysed to detect cell-free DNA and identify potential aneuploidy.

NON-INVASIVE PGT HAS SEVERAL ADVANTAGES OVER TRADITIONAL PGT:

The risk of potential damage to the embryo post-biopsy is eliminated.

The protocol is much more straightforward.

Expenses for specific equipment are reducedo.

However, it has some limitations:

> The origin of free DNA in cells remains unclear. There is still some debate over whether the cell-free DNA in the culture medium accurately reflects the chromosomal composition of the entire embryo.

> Reducing the risk of maternal DNA contamination is of utmost importance to prevent potential misdiagnosis.

> It must be validated in each laboratory, optimising and standardising culture conditions and medium collection protocols to ensure sufficient free DNA and prevent maternal DNA contamination.

Despite the technique's limitations, non-invasive PGT can currently be used as a system to prioritise the identification of embryos with the highest likelihood of being euploid, thereby improving the chances of a successful pregnancy.

Non-invasive PGT is a promising technique with certain limitations that are expected to be addressed in the near future.

Salomé López Garrido | *Operations Manager - Grupo UR*

YOUR PREGNANCY IS OUR GUARANTEE

MONEY-BACK GUARANTEE PROGRAMMES

In contemporary industrialised societies, women are having their first child at increasingly older ages, and the number of childless women continues to grow.

Today, motherhood is shaped by factors rarely considered in the past, including financial security, job-related pressures, interpersonal relationships, and new family models. The shift is clear: traditional family models have evolved, and an increasing number of women are choosing to delay or forgo motherhood to focus on professional or personal development.

Age, however, is a determining factor in female fertility. As women age, the number and quality of a woman's eggs decline, potentially making natural conception more challenging. Confronted with these challenges, reproductive medicine offers strategies that make it possible to have a baby, even in the most complex of cases, such as **programs with guaranteed pregnancy outcomes or reimbursement policies.**

Our objective is clear: **to break down the barrier of infertility to help patients get pregnant.** While most cases are successful within one or two cycles; others call for perseverance and optimism that can go on for three or four IVF cycles.

With a view to instilling peace of mind, we have implemented a trailblazing programme that **ensures pregnancy or a 100% money-back guarantee** in the event of unsuccessful outcomes.

These **money-back guarantee programmes** are fully personalised and tailored to each patient's circumstances. These programmes cover highly complex cases, including implantation failure, recurrent miscarriage, poor ovarian reserve, endometriosis and fertility challenges related to being overweight, to name but a few. While no treatment can guarantee pregnancy with absolute certainty, we can **guarantee our full commitment:**

BEING A MOTHER IS ONE OF THE MOST SIGNIFICANT AND WONDERFUL EXPERIENCES A WOMAN CAN HAVE. DESPITE ITS CHALLENGES, IT IS INCREDIBLY REWARDING. HOWEVER, TODAY, DECIDING WHETHER TO BECOME A MOTHER OR NOT COMES WITH MIXED EMOTIONS AND SOCIAL RESTRAINTS.

if the goal is not reached, up to 100% of the investment will be paid back. This approach provides couples and women undergoing treatment with **emotional and financial reassurance** alike, knowing they are not alone and that the medical team also shares their goal.

Choosing us means choosing excellence Our commitment can be seen in **high quality processes, personalised medical care and outcomes that go above and beyond the success rates reported by the Spanish Fertility Society (SEF).**

To support you on your journey towards motherhood, we provide **100% financing for treatment**, interest-free and with no setup fees, for up to 24 months. We also **take care of all the paperwork** so your treatment can start as soon as possible, without any administrative hurdles getting in the way.

A track record dating back over 40 years

With over forty years' experience in **reproductive medicine**, Grupo UR's Reproduction Units, based at the Vistahermosa Reproduction Unit in Alicante, are renowned for their state-of-the-art technology and highly specialised team of professionals. Our **time-lapse incubators** enable selecting embryos with the highest implantation potential, while our **in-house Reproductive Genetics department** conducts advanced analyses to maximise the likelihood of success.

OUR EXPERTISE, INNOVATIVE APPROACH AND COMMITMENT ALLOW US TO ENSURE THAT **OUR PATIENTS GET PREGNANT AS QUICKLY AS POSSIBLE**, GUIDING THEM THROUGH ONE OF LIFE'S MOST SIGNIFICANT JOURNEYS: THE PATH TOWARDS MOTHERHOOD.

Marta Masip | *Embryologist - UR IMED Valencia Reproduction Unit*

Beyond the MICROSCOPE

WHEN SCIENCE MEETS EMOTION

When we think about assisted reproduction laboratories, we often picture cutting-edge facilities, high-tech incubators and meticulously controlled procedures.

Yet, the human side in these laboratories goes largely unnoticed. And I'm not just talking about the patients: behind every embryo cultivated, every transfer scheduled and every call sharing the news of a positive or negative result; we, the embryologists, are there. **Technically invisible, but profoundly emotionally present.**

Yes, we work with cells; but above all we **work with people's hope** in mind. Over time, these hopes become names, stories, and quite often familiar faces.

One of the most profound moments in my career was when we performed an IVF cycle on a colleague from our own clinic. She was part of the team, but above all she was a friend. Her treatment was successful: she got pregnant on the first attempt, becoming a mother thanks to one of the embryos we cultivated as meticulously as we do with all our embryos, although my hands were shaking in a way I hadn't even

experienced during my very first embryo thawing. Since then, she has developed an even deeper empathy for patients, because she truly understands what they are going through. She often said that, after becoming a mother, she saw us as gods. And while she was exaggerating, her admiration had some truth to it: she understood, like few others, what goes into every attempt.

However, not every journey is as plain sailing or successful. Sometimes life, or biological factors, make things rather challenging.Years later it was time to accompany one of my best friends. Her case was more complex from the outset. The first cycle resulted in a single embryo... and, although she got pregnant, unfortunately, she had a miscarriage. Miscarriage is still often treated as a taboo, even though it happens far more often than we realise. And when it happens, the p**ain is as real as it is invisible.**

I recall experiencing that miscarriage as profoundly, if not more so, than when I had one. I felt responsible, as if I had let her down not only as a professional, but also as a friend. Still, she, strong like few others, chose to continue with a new round of treatment. With every new stimulation and transfer, I had a lump in my throat: **why wasn't she getting pregnant? What were we overlooking? What could we do differently?**

By that point, the whole team had been sharing the burden of the pressure. We had all become emotionally involved. Because, although we try to remain objective, we are not made of stone. Sometimes we cannot help being deeply moved by patients, especially when they are part of our personal life. And so came the attempt that we all knew would be the last. We were over the moon when we found out that she was pregnant. It is difficult to describe just how fast our hearts were beating while waiting for the result, how we looked at each other without daring to say a word. Because at that moment, that positive result was a victory, not just for science, but for shared hope too.

Throughout this entire process, friends were announcing their pregnancies, they were having baby showers and their children were being born. The pressure was growing for her... and for me too. At this point in life, when it's "time" to become parents, all you see around you are baby bumps and advertisements, and you keep getting asked: **"What about you? Do you not want to have children?"** A seemingly innocent question that can sting. Because no one sees what's going on behind closed doors, the negative tests, the miscarriages, the physical and emotional exhaustion, and the sense of failure that so many couples feel.

In assisted reproduction, we work with much more than just eggs and sperm. We work with hopes, grief, fears, and the weight of the social pressure that so often overwhelms our patients. Being an embryologist isn't just about spending hours at the microscope; **it's also about carrying,** as best we can, the emotional weight of those who place their trust in us. And believe me, we often carry a bit of that weight home with us.

Not all stories have a happy ending, but when they do the joy is beyond words. Not because we see ourselves as gods, as a colleague once joked, but because we understand just how difficult this journey can be. **And how profoundly human it is to be a part of this journey.**

Dr. Rocio Nuñez Calonge | *Scientific Coordinator - Grupo UR*

HPV IMPACT

HIGH- *and* LOW-RISK TYPES IN THE MALE GENITAL TRACT

HPV (human papillomavirus) is the most common sexually transmitted infection and accounts for **95%** of cases of cervical cancer, the fourth most common cancer among women.

> THIS CANCER CLAIMS AROUND 350,000 LIVES EACH YEAR, PREDOMINANTLY IN LOW- AND MIDDLE-INCOME COUNTRIES.

PUBLIC HEALTH AUTHORITIES IN 37 COUNTRIES NOW VACCINATE GIRLS AGED NINE TO 14, BEFORE THEY BECOME SEXUALLY ACTIVE.

HPV has also been linked to a higher risk of genital warts and **cancers of the penis, anus, mouth**, and throat in men, which is why both the WHO and the US Centers for Disease Control and Prevention (CDC) recommend routine vaccination for boys as well. HPV infection has been detected in the semen of about **10% of men** in the general population and around **16% of men with unexplained infertility**, although clinical experience suggests these figures are likely significantly underestimated. Specifically, HPV infection in semen seems to be more closely associated with asthenozoospermia (reduced sperm motility) and the presence of antisperm antibodies (ASA) (Garolla et al.).

HPV includes both high-risk viruses (HPV-HR) and low-risk viruses (HPV-LR). The high-risk types are more likely to cause malignant tumours, whereas the low-risk types primarily lead to benign warts. Although awareness of HPV's impact on male health is on the rise, the effects of high- and low-risk urogenital HPV infections on male fertility potential are still not fully understood.

Rivera et al. published an insightful study investigating whether male urogenital infections with high- and low-risk HPV are linked to reduced sperm quality, oxidative stress and inflammation. To analyse this, they examined the effects of the virus in a representative sample of the male population in Argentina: A total of 205 adult male volunteers who visited a single urology and andrology clinic for an initial evaluation of fertility or urinary tract issues between 2018 and 2021. None of them had been vaccinated against HPV. The volunteers provided semen samples, which were analysed using PCR to detect the presence of HPV and other sexually transmitted infections.

Of the 205 individuals analysed, **19% tested positive for HPV.** Specifically, 20 men tested positive for high-risk HPV, while 7 were identified as carrying low-risk HPV. These HPV-positive men were compared with 43 men who showed no detectable infections. An additional 12 men tested positive for HPV, but their genotypes could not be determined due to low viral loads. First, the researchers analysed the semen samples in accordance with the World Health Organization (WHO) criteria. Following these criteria, they found no significant differences in semen quality among the three groups.However, when Rivera et al. analysed the samples with more precise, high-resolution techniques, they discovered that men who had tested positive for high-risk HPV had significantly lower counts of CD45+ white blood cells (leukocytes) in their semen.

They also observed that sperm appear to undergo frequent oxidative damage, as shown by their elevated production of reactive oxygen species (ROS). While low levels of ROS are a normal part of sperm function, elevated levels can lead to cell membrane damage, DNA fragmentation and non-programmed cell death. In fact, the researchers showed that men who had tested positive for high-risk HPV had a **higher percentage of dead sperm cells** caused by oxidative stress, potentially contributing to reduced fertility.

Rivera et al. attributed the lower immune cell counts observed in the semen of men with high-risk HPV to the virus's well-known ability to evade or subvert the immune response. This likely results in fewer leukocytes reaching the site of HPV infection and a diminished capacity to clear the virus.

Although most studies published on HPV's impact on male fertility indicate that

THE INFECTION **CAN AFFECT SEMEN QUALITY**, THE VIRUS'S EXACT MECHANISM OF ACTION REMAINS UNCLEAR.

The importance of Rivera's work lies in distinguishing between high-risk and low-risk HPV strains. In the former case, **semen quality declines** and, more importantly, the likelihood of serious pathologies increases. This failure to distinguish between HPV types may explain the contradictory results reported in other studies. This difference between HPV types is even more important than the observed increases in oxidative stress, impaired immune response and cell death, as these effects are direct consequences of the infection itself.

From a fertility perspective, it is important to consider not only how the virus affects sperm, but also how sperm **can transport it to the female reproductive tract** during intercourse, potentially leading to female pathologies and infertility.

Therefore, while highlighting the importance of **vaccinating** girls and boys alike, the study opens a new avenue of research focused on identifying whether infected individuals carry **high- or low-risk** HPV strains.

Although Rivera's work offers promising insights into the biological mechanisms of human papillomavirus, it has limitations, including the relatively small sample size. Furthermore, comparing the infected group with the healthy control group assumes that the **reduced semen quality in the infected men is caused by the virus, without knowing their baseline semen quality prior to infection.**

Dr. Germán Fernández | *Medical Director* - *UR Managua Reproduction Unit*

THE GLOBAL IMPACT OF OVARIAN RESERVE

CLINICAL BIOLOGY AND PUBLIC HEALTH

OVARIAN RESERVE, THE NUMBER OF EGGS A WOMAN HAS REMAINING AND HER FERTILITY POTENTIAL, HAS BECOME THE KEY TO UNDERSTANDING FERTILITY FROM A BIOLOGICAL PERSPECTIVE, GUIDING CLINICAL DECISIONS WHILE FORESEEING IMPLICATIONS FOR PUBLIC HEALTH AND THE ECONOMY ALIKE.

WITHIN THE CONTEXT OF DELAYED MOTHERHOOD, HIGHER CANCER SURVIVAL RATES AND GREATER ACCESS TO ASSISTED REPRODUCTIVE TECHNOLOGIES (ART), OVARIAN RESERVE ACTS AS A BRIDGE BETWEEN SCIENCE AND POLICY, OFFERING INSIGHTS ON REPRODUCTIVE TIMING, STIMULATION PROTOCOLS, FERTILITY PRESERVATION AND THE EFFICIENT ALLOCATION OF HEALTHCARE RESOURCES.

WHY ALL THE TALK OF OVARIAN RESERVE NOW?

Societies are seeing a steady rise in the age at which women are having their first child The natural decline of ovarian reserve impacts the likelihood of spontaneous conception, the response to gonadotropins and embryonic euploidy.

AT THE POPULATION LEVEL, this leads to increased demand for fertility services, direct costs (diagnosis and treatment), indirect costs (productivity and mental health) and inequalities stemming from geography, coverage, and health literacy.

AT THE INDIVIDUAL LEVEL, there is an increasing need to interpret biomarkers (AMH, AFC, basal FSH) as tools for informed decision-making rather than as deterministic labels.

UNDERSTANDING OVARIAN RESERVE:

QUANTITY, QUALITY, AND PROGNOSIS

Ovarian reserve is not a single "number"; it is dynamic: it declines in quantity and oocyte quality diminishes with age. This forces us to reframe the key clinical question: it's not "How many eggs can I retrieve?' but rather "How many high-quality eggs are needed to produce at least one healthy embryo and

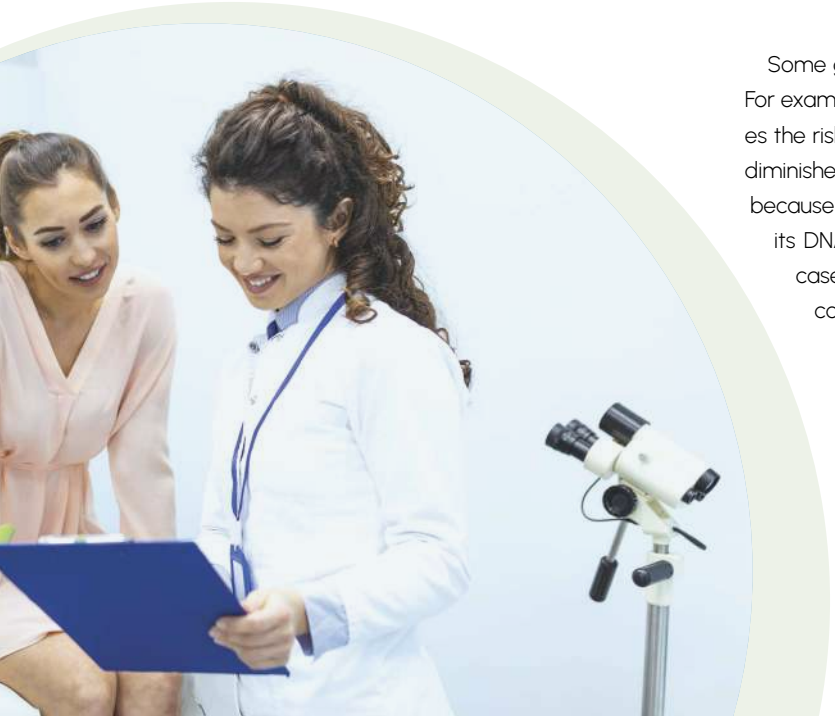
result in a successful pregnancy?". With age, the number of eggs needed rises, since embryos are more likely to have genetic abnormalities (aneuploidy) Therefore, having more eggs does not necessarily result in a higher likelihood of success.

This perspective on fertility underpins the **POSEIDON** approach, a system that moves away from the traditional label of "poor responder" and instead refers to "women with a poor prognosis". This approach takes into account factors such as age, hormone levels and previous treatment responses to tailor medical decisions.

POSEIDON strives to acknowledge that not all women with a poor ovarian response are the same and that treatments should be tailored to each individual. This enables adjustments to protocols, medication doses, and strategies, such as accumulating eggs over multiple cycles, using double stimulation, or synchronising follicular growth, striving to obtain real results rather than merely higher numbers on reports.

FACTORS THAT ACCELERATE OVARIAN AGEING

Ovarian ageing, the gradual decline in egg quantity and quality, is affected by **more than just the passage of time**. Various genetic, immunological, medical and even surgical factors can accelerate this process. Being aware of these factors enables more informed decisions to be made regarding fertility and fertility preservation.



1. Genetic, hormonal, and immunological factors

Some genetic alterations can influence ovarian reserve. For example, women with the **BRCA1** mutation, which raises the risk of breast and ovarian cancer, may also lead to diminished ovarian reserve at an earlier age. This occurs because the mutation impairs the cells' ability to repair its DNA, leading to diminished ovarian reserve. In such cases, the option of fertility preservation should be considered first.

Certain autoimmune conditions, such as **autoimmune thyroiditis**, have also been potentially linked to reduced ovarian function in some women. Therefore, assessing hormonal and immune system balance is of utmost importance when addressing fertility concerns.

Furthermore, certain genetic variants in the **progesterone receptor**, a key reproductive hormone, may affect both recurrent miscarriages and diminished ovarian reserve.The practical takeaway is not to "treat just in case", but to understand each case holistically, taking into account age, hormone analyses, family history and potential immunological factors before making decisions.

2. Medical or iatrogenic factors

Certain medical procedures can accelerate egg loss if not carried out carefully. One example is **endometriosis surgery** (ovarian cysts caused by endometriosis). This type of procedure can damage healthy ovarian tissue, particularly if electrical energy is used to control bleeding rather than precise suturing. If both ovaries are affected, the impact is even more significant.

This doesn't mean surgery should be avoided when necessary, but the recommendation would be for more conservative techniques, to consider **fertility preservation before opting for surgery**, and to strike a balance between treating the condition and protecting fertility.

Chemotherapy and **radiotherapy** can also damage the ovaries. Therefore, providing guidance and **fertility preservation options before treatment**, such as egg or embryo freezing, or even ovarian tissue preservation at specialised clinics is recommended. Once seen as "optional", these measures are now considered an **ethical standard of best medical practice.**

Moreover, advances in ovarian stimulation techniques allow preservation treatments to be started without having to wait for a specific phase of the menstrual cycle ("random-start protocols"), thereby cutting down on waiting times without compromising effectiveness. In certain cases, **in vitro maturation of eggs** provides an alternative option when there isn't enough time or resources for full ovarian stimulation.

All of this calls for a healthcare system that acknowledges fertility as part of women's overall well-being and ensures access to these resources.

3. Supplements and micronutrients: use with discretion

- **DHEA:** a hormone that may enhance ovarian follicle development in women with a poor response, although results can vary. Use thereof should be overseen by a specialist.
- **ANTIOXIDANTS:** are studied for their potential to reduce age-related oxidative damage to eggs, although scientific findings remain inconclusive.
- **OTHER MICRONUTRIENTS, such as vitamin D, coenzyme Q10, myoinositol** (for polycystic ovary syndrome), **or polyphenols**, may offer benefits depending on a woman's individual profile, but always as part of a tailored, evidence-based treatment plan.

Ovarian ageing is influenced by a variety of factor, some of which are unavoidable, while others can be managed or prevented.
UNDERSTANDING THESE FACTORS ENABLES MORE INFORMED DECISIONS ABOUT WHEN AND HOW TO PRESERVE FERTILITY, FOSTERING A MORE TAILORED AND COMPASSIONATE APPROACH TO MEDICAL CARE.

HEALTHY BEHAVIOURS AND MODIFIABLE FACTORS

Avoiding smoking, maintaining a healthy BMI, engaging in regular physical activity, getting adequate sleep, and managing stress are reasonable lifestyle behaviours that can indirectly support reproductive health. Strictly speaking they do not "improve the reserve", but they contribute to oocyte quality and response.

Under the concept of "ovarian rejuvenation", various approaches converge, including intraovarian PRP, in vitro activation (IVA) of dormant follicles and mitochondrial support. The logic behind it, enhancing the microenvironment; signalling pathways and bioenergetics, is compelling, yet definitive clinical evidence is still emerging. Ethically and scientifically, the priority should be on **transparency**, managing expectations responsibly and emphasising the need for well-controlled clinical trials.

360° ASSESSMENT OF OVARIAN RESERVE

Evaluating **ovarian reserve** calls for a comprehensive approach rather than relying on a single number. **Anti-Müllerian hormone (AMH)** testing offers a reliable estimate of the number of available follicles (the "precursors" to eggs) and tends to remain stable over short periods. **Antral follicle count (AFC)** ultrasound enables direct visualisation of the follicles and offers detailed insight into the condition of the ovary, provided the procedure is performed using a well-standardised technique.

FSH and estradiol (E2) levels measured in the first few days of the menstrual cycle remain valuable indicators, despite their potential month-to-month fluctuations. Above all, **age** continues to be the most reliable predictor of egg quality.

However, the aim is not to "diagnose infertility" based on a single number, but to **use the information to make personalised decisions**: when to continue trying naturally, when to turn to assisted reproductive technologies, when to consider egg preservation, and how to customise treatments according to each individual's goals and values.

BEYOND THE NUMBERS

Interpreting these results in isolation can be misleading. An isolated number can cause **anxiety or a false sense of security**. Which is why professionals should provide clear explanations, **conveying uncertainty in an accessible way**: such as using graphs to illustrate age-related probabilities or the natural variability of hormone levels.

It is equally important to provide **emotional and psychological support**, through counselling or support groups, because fertility is more than just a biological matter; it is also an integral part of a woman's overall health and life journey.

ARE WE FALLING BEHIND IN THE RACE AGAINST TIME?

The question often raises concern, yet it carries important nuances. At a societal level, lack of fertility awareness and the tendency to delay motherhood are slowly but surely reducing reproductive opportunities. However, on a case by case basis, the situation depends on a range of factors: age, health, lifestyle, medical history and access to treatment options. The good news is that early awareness, proactive planning, and timely access to fertility preservation **can broaden options and help avoid decisions made under pressure.**

For medical teams, the challenge is to remain abreast, apply evidence cautiously and communicate with empathy, avoiding deterministic or scaremongering messages. In short, ovarian reserve is not the be all and end all of a woman's reproductive future, but a clear understanding of it **empowers her to make informed decisions aligned with her life goals.**

Lourdes del Águila | *Embryologist* - *UR Mediterráneo Almería Reproduction Unit*

ASSISTED REPRODUCTION

ANSWERING YOUR QUESTIONS AND DOUBTS

Thanks to the medical and technological advances, today there are innovative processes that offer hope and solutions adapted to each individual situation. Nonetheless, this process may give rise to **doubts, complex emotions and legal or ethical questions.**

> THIS ARTICLE ANSWERS 10 FREQUENTLY ASKED QUESTIONS ABOUT ASSISTED REPRODUCTION WITH THE AIM OF ADDRESSING CONCERNS AND PROVIDING VALUABLE INFORMATION TO THOSE WHO ARE CONSIDERING OR ALREADY UNDERGOING FERTILITY TREATMENT.

FTER TRYING TO CONCEIVE FOR QUITE SOME TIME, WE DECIDED TO MAKE AN APPOINTMENT AT THE FERTILITY CLINIC. IN THIS FIRST APPOINTMENT:

1. WHAT SHOULD I EXPECT? WHAT DO I NEED TO BRING WITH ME?

At this initial consultation, a medical record will be created for the patient and the couple's preliminary evaluation will get underway. During this process, a comprehensive medical history will be obtained for both partners: family history, past and current medical conditions and lifestyle habits, followed by a transvaginal ultrasound examination.

On the same day, the medical team can offer **initial guidance**; however, a number of tests will typically be requested if they have not already been performed. The most common tests include general laboratory analysis, hormone and serological testing, karyotyping and a basic male factor evaluation (semen analysis and REM). Further tests may be recommended based on the results and the information gathered from the medical history.

Regarding the required documentation, it is important to bring or send in advance (according to the reproductive unit's protocol) **all available previous test results and reports**, including those from any prior treatment cycles. This will give the medical team the necessary information to make an accurate diagnosis and decide which type of cycle should be performed.

2. WHAT IS THE ROPA METHOD? DO WE NEED TO BE MARRIED?

The **ROPA** method is a reproductive technique that enables two women to share the experience of motherhood. One partner is the donor, providing the **genetic material** (the genetic mother), while the other **receives the embryo** and carries the pregnancy (the gestational mother).

In accordance with Law 14/2006 on assisted human reproduction techniques, all women of legal age are eligible for treatment, regardless of their marital status or sexual orientation and, in the case of the ROPA method, **both women must be registered as a couple** in the treatment, as it involves sharing genetic material and the filiation of the child.

In clinical practice, most centres require the couple to be married or legally registered as civil partners, as this ensures the legal recognition of

both partners' maternity at the time the child is born. If you are not married or registered as civil partners, you can still undergo treatment; however, additional legal procedures will be necessary afterward to recognise the second mother (such as adopting your partner's child).

3. CAN A TRANSGENDER WOMAN USE HER OWN GENETIC MATERIAL IN ASSISTED REPRODUCTION TREATMENT ALONGSIDE HER PARTNER?

A transgender woman's sperm can be used to conceive, ideally preserved before undergoing hormone therapy. However, hormone treatment would need to be temporarily put on hold, and even then, the likelihood of success may be limited.

For transgender women who wish to have biological children, it is important to bear in mind that both antiandrogens and oestrogen therapy can negatively impact the function and structure of the testes. This affects sperm production, maturation and motility. While these effects may be partially reversible after stopping hormone therapy, making a full recovery is not always guaranteed.

4. COULD A TRANSGENDER MAN BECOME PREGNANT?

Ideally, fertility preservation should be considered before undergoing hormone therapy to allow for the possibility of having children further down the line. Although a transgender man who retains his uterus and ovaries and is on testosterone therapy can technically ovulate and become pregnant, this is not the most recommended way to conceive. When a transgender male wishes to become a parent and carry a pregnancy, **testosterone treatment must be put on hold**, resulting in various physical and hormonal changes. When hormone therapy is stopped, ovarian function may resume and the menstrual cycle may come back, opening up the possibility of attempting to try for a baby.

5. CAN A TRANSGENDER MAN BE REGISTERED AS THE CHILD'S FATHER?

In accordance with Law 4/2023 of 28 February, "The purpose of this law is to protect and guarantee the rights of lesbian, gay, bisexual, transgender, and intersex (LGBTI+) individuals by eliminating discrimination, ensuring that in Spain, sexual orientation, gender identity, gender

expression, sexual characteristics, and family diversity are respected in total freedom." This issue should no longer arise, as an indirect amendment is being made to the laws governing the Civil Registry. These regulations set forth the requirements and conditions for birth registration and, in this context, recognise the biological parent without making gender-based distinctions.

Therefore, a transgender man who retains his uterus and is able to get pregnant and give birth **can register his child's birth** in the Civil Registry and obtain the corresponding birth certificate.

6. HOW MANY EMBRYOS DO I NEED TO BE ABLE TO CONCEIVE?

There is no definitive answer to this question, as each patient's situation is unique and there are a wide range of treatments available. However, Spanish Fertility Society (SEF) data indicate that pregnancy rates per embryo transfer decline as maternal age increases. This means that **more embryos are needed if one wishes to get pregnant**. The biggest issue is that, as age increases, both ovarian reserve and egg quality tend to decline, leading to fewer embryos being obtained per cycle. According to 2021 SEF data, the average number of embryos transferred per birth is **5.4, in fresh IVF/ICSI cycles.**

7. URINE TEST OR WAIT FOR THE BLOOD TEST?

We always recommend waiting until the date specified by the medical unit to perform the **β-HCG (beta subunit of human chorionic gonadotropin)** blood test. However, we understand that the wait until the "pregnancy test" test can be very challenging. If you cannot wait, we recommend taking the test first thing in the morning and as close as possible to the date scheduled for the blood test, since testing earlier may result in false positives or false negatives. It is important to note that the hormone first rises in the blood after embryo implantation and is not detectable in the urine until several days later. Therefore, a urine test taken too early, whether positive or negative, cannot be considered conclusive.

8. CAN EMBRYOS TO FAIL TO SURVIVE AFTER THAWING?

Flash-freezing and thawing techniques are currently highly effective. However, there is a small risk that some embryos may not survive the thawing process. Although **the survival rate is very high**, this risk cannot be eliminated entirely. According to the 2021 Registry of the Spanish Fertility Society (SEF), **89%** of thawed embryos are successfully transferred, highlighting the high effectiveness of these techniques.

9. DO FROZEN EGGS HAVE THE SAME SURVIVAL RATE AFTER THAWING?

Vitrified oocytes also show a good survival rate after thawing, although it is typically slightly lower than that of embryos. This rate is directly influenced by the quality of the egg at the time of flash-freezing.

10. CAN A SINGLE TRANSFERRED EMBRYO TO SPLIT?

Yes, a single embryo can split post-transfer. Embryos can split during the first 14 days of development, a process that may lead to monozygotic (identical) twin pregnancies. Even if the transfer is performed on **day 5** (D+5), the embryo can still split afterward, resulting in two genetically identical embryos with the same genetic makeup. This means that even when only one embryo is transferred, **a twin pregnancy is still a possibility**. These type of twins differ from dizygotic twins, which in IVF can occur from the transfer of two embryos.

Dr. Patricia Barbero | *Gynaecologist - Unidad de Reproducción Sevilla*

GLOSSARY OF THE MOST FREQUENTLY

USED TERMS IN THE ASSISTED REPRODUCTION CONSULTATION

> PATIENTS OFTEN COME TO SEEK INFORMATION IN OUR DAY-TO-DAY CONSULTATIONS.

During the initial consultation, there is so much information that we want to provide that we often end up overwhelming patients so they do not grasp what we are trying to convey, precisely down to a lack of knowledge of basic terms, which often leads to misunderstandings and doubts seeping in.

WITH THIS IN MIND, I THOUGHT IT WOULD BE A GOOD IDEA TO COMPILE THE TERMS THAT MOST FREQUENTLY COME UP IN CONSULTATIONS WITH A VIEW TO HELPING TO CLARIFY THE PROCESS AND MAKE THE ENTIRE ASSISTED REPRODUCTION JOURNEY EASIER TO UNDERSTAND.

ARTIFICIAL INSEMINATION (AI):

A procedure in which sperm are directly placed into the uterus on the day of ovulation to increase the chances of fertilisation. These sperm can be the partner's or come from a donor.

ASSISTED REPRODUCTION:

Techniques that involve handling eggs, sperm or embryos outside the body to help a person conceive. It includes procedures such as in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), gamete donation and embryo transfer, to name but a few.

CERVIX (UTERINE NECK):

It is the lower, narrow part of the uterus that connects to the vagina. The cervix can affect the passage of sperm and acts as the channel for procedures such as intrauterine insemination or embryo transfer.

EGG:

This is the term used for the oocyte once it has fully matured and is released from the follicle during ovulation. The egg is the cell ready to be fertilised by a sperm cell.

EGG/SPERM DONATION:

The use of donor gametes to achieve pregnancy when the patient's own gametes are not viable.

EMBRYO TRANSFER:

The placement of one or more embryos into the uterus with the goal of achieving pregnancy.

ENDOMETRIUM:

It is the inner lining of the uterus. It changes throughout the menstrual cycle, becoming thicker and more receptive to support embryo implantation. The condition thereof is evaluated prior to embryo transfer.

FALLOPIAN TUBES:

They are two tubes that connect the ovaries to the uterus. In a natural cycle, the egg moves through the fallopian tube, where it may encounter sperm and become fertilised. In certain treatments, such as in vitro fertilisation, this process takes place outside the body.

FERTILITY PRESERVATION:

Techniques for preserving eggs, sperm or embryos for future use, such as before medical treatments that may impact fertility.

FIBROID (MYOMA):

a benign tumour that forms in the muscle of the uterus. Fibroids can vary greatly in size and location. Although

most are asymptomatic, some can lead to heavy bleeding, pelvic pain or complications during pregnancy. It is not always necessary to remove them although they can be removed through a type of surgery known as a myomectomy via hysteroscopy, laparoscopy or laparotomy, depending on their size and location.

FOLLICLE:

It is a small, fluid-filled structure within the ovary that contains a developing egg. The follicles grow and mature throughout the menstrual cycle (it is the image used to monitor their development in the ovary during stimulation cycles). In natural cycles, typically only one follicle becomes dominant and releases its egg during ovulation whereas for in vitro fertilisation cycles, the goal is to stimulate and select multiple follicles.

GAMETES:

the female (egg) and male (sperm) reproductive cells that, when combined, form an embryo. Gametes can come from the patient or partner, or from a donor (from an egg or sperm donor).

IN VITRO FERTILISATION (IVF):

A procedure in which eggs are retrieved from the ovary and fertilised with sperm in a laboratory setting. The resulting embryos are transferred to the uterus.

INFERTILITY:

Inability to carry a pregnancy to term and have a healthy newborn. This is the case with recurrent miscarriages.

OOCYTE:

It is the immature female reproductive cell found inside the follicle. As the follicle grows, the oocyte matures. When the oocyte reaches full maturity, it can be released during ovulation and is referred to as an egg.

OVULATION:

The release of a mature egg from the ovary, typically occurring mid-cycle (around day 14 of a 28-day menstrual cycle).

OVARIAN RESERVE:

Number of eggs remaining in the ovaries. It is assessed using hormone tests and transvaginal ultrasound. It is not an indicator of a person's ability to get pregnant naturally or through assisted reproductive techniques.

OVARIAN STIMULATION:

Using medication to stimulate the ovaries to produce more eggs than usual, increasing the chances of success in fertility treatments.

OVARIES:

They are two small organs located on either side of the uterus. They produce eggs and female hormones (oestrogen and progesterone). During assisted reproduction treatments, the ovaries are stimulated to produce multiple follicles and eggs.

POLYP:

A benign tumour that forms in the uterine cavity (endometrium). Polyps are typically small and soft, and they can cause irregular bleeding or interfere with embryo implantation. The polyp is removed surgically via a hysteroscopy.

SEMEN:

A fluid produced by the male reproductive system that contains sperm.

STERILITY:

The inability to conceive after 12 months of regular, unprotected intercourse. It can be due to female factors, male factors, or a combination of both. When there is a known medical condition or the woman is over 35, beginning basic infertility testing after six months of actively trying to conceive is recommended.

UTERUS:

It is the organ where the pregnancy develops. It has an internal lining called the endometrium, which prepares itself each month to receive an embryo. In assisted reproduction treatments, embryos are placed in the uterus with the goal of achieving implantation and conceiving.

If you cannot find the definition of a term that came up during your consultation, we recommend speaking to your gynaecologist. **We are always happy to explain any term to help you grasp the process you are about to undergo.**

Acknowledgements

special thanks to:

Dr. Francisco Anaya Blanes
Medical Director

Dr. Rocio Nuñez Calonge
Scientific Coordinator

Antonio Urbano
Genetics Unit Director

Dr. Germán Fernández
Medical Director

Salomé López Garrido
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