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The genetics of
PRIMARY OVARIAN INSUFFICIENCY

Advanced paternal age,
HOW DOES IT INFLUENCE FERTILITY?

WHY DON'T I GET PREGNANT IF EVERYTHING IS FINE?

REPRODUCTION

Our role in society

Dr. José Jesús López Gálvez
CEO of the UR Group

Perhaps what the COVID pandemic is leaving us with is one of the most important challenges in reproduction in recent decades.

If we look at the statistics, we see that there has been an **increase of some 17% in deaths** in Spain last year compared to the previous year. At the same time, there has been a **decrease in the number of births** in Spain once again, specifically of about **6%**.

This has been happening continuously since 2010, reaching a total of 30% over the past few years. This means that Spanish women are having an average of 1.8 children, continuing with the decrease that would now be some six one-hundredths more than the previous year. All this has led to a vegetative growth of the population with a negative balance, making the problem that it creates for our future extremely important in all aspects and levels. Because of this, those of us who work in assisted reproduction must help to propose a solution for this situation. We must alert our society of this problem, and reach out to it, explaining and clarifying the danger it entails. We should also show and detail the continuing advances that appear in the techniques applied in reproduction, but not with the intention that our population should trust and delay their reproduction project, but so that it trusts them and start to use them as soon as possible, because **age is the greatest enemy**.

Furthermore, we must be increasingly technologically effective in order to help solve this great generational problem.

All our Units, the facilities that make up UR Group, are fully integrated in this line. The publication of this magazine is one example. We publish it to share knowledge, along with our commitment to training, the expansion of knowledge and the continuous updating of the reproductive procedures we use.

This makes us fully aware of our role in this social problem. **And we are acting accordingly**.

HLA Grupo Hospitalario
Reproduction International Group

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Criteria for

Embryo Classification

Categories of embryo quality

Mireia Poveda
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In vitro fertilisation treatments generate a number of embryos that are left cultured in the laboratory where there is an attempt to **imitate in vivo conditions** using the necessary tools, such as specific incubation systems and certain culture media, depending on the embryo's needs during the days it is cultured.

This way, the embryos that are of better quality - i.d. those that have grown properly and are in the best conditions - are the ones that will be selected for transfer and/or cryopreservation.

We could define **embryo quality** as the probability of an embryo being implanted in the uterus and leading to a full-term pregnancy with a healthy baby. Therefore, a good quality embryo will have a greater chance of achieving pregnancy than a lower quality embryo.

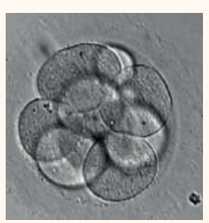
Over the years, attempts have been made to standardise embryo scoring criteria. The criteria used in Spanish assisted reproduction centres are those of **ASEBIR** (Association for the Study of Reproductive Biology).

In line with this system, we classify the embryos according to the **number** of cells, cell **symmetry**, **degree of fragmentation, presence of vacuoles**, etc., taking into account the embryo's day of development.

ASEBIR

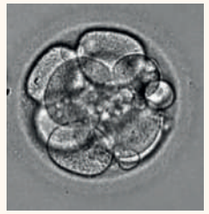
Association for the Study of Reproductive Biology

ASEBIR's classification establishes four categories of embryo quality.



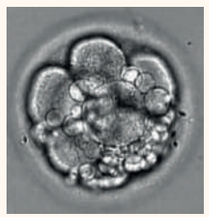
A.

An optimum quality embryo which has the best chance of implanting.



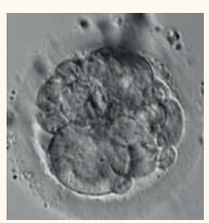
B.

A good quality embryo which is very likely to implant.



C.

An embryo that is not great quality and which is unlikely to implant.



D.

A poor quality embryo which is very unlikely to implant.

Classification in each of these **4 categories** is done on the day of transfer. However, during their previous development, the embryos are rated daily. Different morphological aspects are analysed and will be taken into account when classification occurs.

It is important to clarify that **all embryos that are transferred have the possibility of leading to pregnancy**. We know that, statistically, Category A embryos are more likely than the others and that, as the categories progress, this probability decreases. Still, an assisted reproduction cycle is not always a statistic, and therefore all categories of embryo represent a probability of pregnancy.

Likewise, embryo implantation is a very complex process influenced by many factors in addition to embro quality, such as **endometrial receptivity, maternal age or immune factors.**

Embryo Freezing

A revolutionary advance

Carolina Orjuela Gasca
Embryologist
UR HLA La Vega

After an assisted reproduction technique is carried out, embryos that have not been transferred at this time may be preserved thanks to cryopreservation. This has resulted in great progress over the years because, on the one hand, it is possible to not waste the remaining embryos from a treatment and, on the other hand, to schedule frozen embryo transfers in the cases of women who, for medical reasons, cannot undergo a fresh embryo transfer.

In what cases can a fresh transfer not be done?

Usually, at the end of the assisted reproduction cycle, embryo transfer is carried out to complete the process. However, in some cases, the woman's uterus may be affected by the risk of ovarian hyperstimulation syndrome or the endometrium may not have thickened enough and is not receptive. Thus, it is advisable to wait for it to be properly prepared before carrying out the embryo transfer and ensuring the possibility of pregnancy.

What does the technique used to freeze the embryos consist of?

The technique that has been consolidated and that is used across the board in all centres is vitrification. Vitrification consists of an **ultra-rapid freezing** of the embryos after the use of various cryoprotrectors, i.e. substances responsible for protecting the cells from the high speed of freezing. Without them, it would cause the formation of crystals and cell damage. The **devitrification**, done before the embryo transfer, consists of the reverse process, i.e. a sudden change in temperature from the -196 °C of liquid nitrogent to the 37 °C required for the embryo to survive and the gradual elimination of the cryoprotectors used during freezing.

How long can an embryo remain frozen? Does freezing influence its characteristics?

Once the embryos are frozen, they may be preserved for an indefinite time in liquid nitrogen banks that are kept and a very low (-196 °C) temperature and are continually maintained. Thus, the transfer of frozen embryos may be carried out after months, and even years, without losing the quality and characteristics they had when they were frozen.

In fact, recently - February 2020 - a healthy girl from an embryo frozen for 27 years was born; this is the maximum time observed to date.

What are the survival and transfer success rates of frozen embryos?

As in any assisted reproduction cycle, the likelihood of pregnancy in a cycle with frozen embryos depends greatly on the quality of the embryos and the preparation of the uterus, as well as on various factors involved in the implantation of the embryo. In any case, the process of embryo thawing or devitrification has a survival rate that currently exceeds 95%, and the pregnancy rate using the transfer of frozen embryos does not vary greatly from those using fresh embryos.

This procedure has become a basic tool for human assisted reproduction and, thanks to the high survival rates observed, it has been possible to improve the techniques for achieving pregnancies with a lower number of hormonal stimulations, thus reducing the impact on patients as well.

Endometrial microbiota

Susana Malkhasian
Gynaecologist
UR HLA La Vega

The importance of its study in assisted reproduction

For many years it was thought that the endometrium (the inner layer of the uterus, where the implantation of the embryo occurs) was a sterile organ. However, several studies showed that different groups of microorganisms (mainly bacteria and fungi) live in the endometrium.

Together, this is known as the **endometrial microbiota**. The presence of these microorganisms is closely linked to our health. Thus, when there is an imbalance in these colonies, various diseases usually appear.

It has been observed that the microbiota may have an effect on the course of the pregnancy during its various stages:

- **During the implantation of the embryo into the endometrium.** It may alter the receptivity of the endometrium and condition its preparation so that the embryo will adhere.
- **During pregnancy.** Its alteration may be one of the causes of premature births and miscarriages.

This is why the subject of the microbiota has become more relevant in the field of gynaecology and assisted reproduction. Knowledge of its implications for fertility may help improve the outcome of our treatments, including in patients for whom the cause of sterility or infertility is currently unknown.If we delve into the study of the **urogenital microbiota**, we see that what is normal and desirable in healthy women is that most of the bacteria in the reproductive tract belong to the Lactobacillus genus, although other genuses - such as Gardnerella, Atopobium, Prevotella and Acidobacteria may also be found.

Another important fact is that approximately 20% to 30% of women of reproductive age have altered vaginal flora. That is, it is not dominated by lactobacilli, but rather has another type of flora that we may consider pathogenic or dysbiotic. For women involved in assisted reproduction processes due to a fertility problem, this prevalence rises to 40%.

How does the endometrial microbiota influence fertility?

Direct cause

Some pathogenic bacteria are a direct cause of infertility. For example: bacteria that cause gonorrhea or trachomatis; some species of Mycoplasma or Mycobacterium tuberculosis, which cause genital tuberculosis.

Gametogenesis

Sperm quality may be altered, depending on which bacteria predominate in the semen sample. It has also been discovered that areas that were believed to be sterile, such as the ovarian follicles, have a very active microbiota.

Endometrial receptivity and pregnancy

The endometrial microbiota may influence its ability to allow an embryo to be implanted and condition success when attempting to become pregnant. It may also influence more advanced stages of pregnancy. For example, a premature birth, where the premature rupture of the membrane occurs or even when it ends in a miscarriage.

Recent studies show that women **with 90% of the flora dominated** by lactobacilli in the uterine cavity have better rates of implantation, gestation and live birth compared to the group of women with a receptive endometrium with a lactobacilli population of less than 90%.

Thus, the low presence of lactobacilli in the uterus is related to a worse reproductive prognosis, and may be the of some implantation failures and miscarriages.

Strategies to improve the microbiota and increase pregnancy rates

We have different techniques for studying the type of microorganisms that colonise our genital tract. For example, vaginal and endometrial cultures to detect asymptomatic infections or chronic endometritis.

Currently, research is being undertaken on the benefit of modulating the microbiota to improve the results in assisted reproduction techniques by administering **biotherapeutic products** containing one or more specific bacterial strains (lactobacilli) that are administered to colonise the relevant niche, while simultaneously displacing the dysbiotic bacteria.

This is why orally administered **probiotics** have been added as adjuvants to the assisted reproduction treatment. This treatment is well tolerated and makes it possible to effective colonise both the vaginal mucosa and the endometrium. Studies indicate that the administration of lactobacilli should be initiated from at least the beginning of ovarian stimulation with preparations containing, among other subtypes, the Lactobacillus rhamnosus. Given that **probiotics beneficial effect on the prevention of premature abortions** and births is known, treatment may be prolonged during pregnancy.

Conclusion

The microbiota is another key part of the complex mechanism of human reproduction. New knowledge highlights the need to act on it in couples who come in with reproductive problems, especially with a history of implantation failures. Since there is a correlation between the vaginal and the endometrial microbiotas, the therapeutic strategies we have seem to be useful in improving the reproductive prognosis of these couples.

The genetics of Primary Ovarian Insufficiency

Isabel Ochando
Geneticist
UR HLA Vistahermosa

THE OVARIES ARE THE ORGANS RESPONSIBLE FOR PRODUCING THE FEMALE GAMETES (OOCYTES) AND THE SEX HORMONES CONTROL THE REPRODUCTIVE SYSTEM ORGANS AND INFLUENCE OTHER ORGANS IN THE BODY.

During a woman's reproductive stage, a certain number of follicles (the combination of the oocyte and the cells containing it) is produced. One of these will be ovulated while the others will disappear as the result of cell death by atresia. Consequently, **only some 400 to 500 oocytes of the 2,000,000 a woman has will reach ovulation** during her lifetime.

> The total number of follicles that a woman has at a given time is her ovarian reserve and determines the status of her fertility.

This depends mainly on how old the woman is, with the most fertile period being between the ages of **17 and 30**. From the **age of 35**, there is a significant decrease in the ovarian reserve and, from **the age of 40**, the ovarian reserve is gradually compromised until it is completely exhausted, sometime between **45 and 55 years** of age, when menopause usually begins.

In some cases, the decrease in the ovarian reserve occurs before it is expected. This is know as **primary ovarian insufficiency (POI)**, which is characterised by the loss of ovarian function before the age of 40 or by a primary ovarian defect (primary amenorrhea). It is currently one of the main causes of female infertility. The fact that most women are currently planning their first pregnancy after the age of 30 is increasing the relevance of POI, whose prevalence is 1% before the age of 40 and 0.1% before the age of 30.

Since fertility begins to decrease about 20 years before menopause, and because when ovarian insufficiency becomes clinical and biochemically identifiable, the ovarian reserve is already severely reduced, there is justification for considering studies that allow us to predict a woman's risk of premature menopause in order to consider bringing forward the age at which she gets pregnant or preserve the oocytes by freezing them.

The age at which a woman begins menopause is **inheritable**, and POI has a strong genetic component, in addition to other possible aetiologies such as autoimmune, metabolic, infectious or iatrogenic factors but, in most cases, it is classified as idiopathic. Epidemiological studies suggest an incidence of familial POI **of 13% to 30%**, showing that one-third of idiopathic POI is actually inherited A proper family history will make it possible to identify familial POI. This is of great importance since the risk of early menopause in direct female members who are female must be considered initially high in familial cases.

Some of the genetic causes of **Primary Ovarian Insufficiency** are:

1. Chromosomal anomalies:

The X chromosome has an essential role in maintaining ovarian function. Women with X monosomy - or **Turner syndrome** - have ovarian dysgenesis due to accelerated follicular atresia which typically results in primary amenorrhea. *Turner syndrome* has a prevalence of **1 in 2,500 girls born**. In addition to X monosomy (50% of the patients with Turner syndrome), it may be produced by mosaicism (40% to 45%) and/or an anomalous chromosome. When the X monosomy is present with mosaicism, patients tends to have a less severe phenotype. Some **12% to 40%** of 45X/46XX and 45X/47XXX mosaicisms have menstruations for several years until ovarian failure occurs.

X trisomy is also associated with ovarian dysfunction. This is the most common chromosomal anomaly in women, affecting **1 in 1,000 girls born**. However, since most patients have mild or asymptomatic involvement, it is estimated that only 10% of cases with X trisomy are diagnosed.

Some X chromosome deletions and balanced translocations between an X chromosome and an autosome also cause POI. All these alterations are diagnosed by the peripheral blood karyotype study.. This should be requested for all women with POI.

2. Decreased ovarian reserve and primary ovarian insufficiency associated with X-fragile:

The **FMR1** (Fragile X Mental Retardation type 1) gene is located on the X chromosome and contains a sequence of three nucleotides (CGG) that repeats from 6 to 44 times. When this number of repeats increases to 55 to 200 repeats, it's called premutation and becomes unstable when transmitted to the offspring; it may increased to more than 200 repeats. The result of the complete mutation (>200 repeats) the complete silencing of the gene that

causes Fragile X syndrome, the most frequent form of inherited intellectual disability in men. Of every **150 to 300 women**, one is a carrier of a premutation in the FMR1 gene. Women who are carriers of a premutation may develop primary ovarian insufficiency or a decrease in the ovarian reserve.

Approximately **20% of women with a premutation** will develop POI. Of women with spontaneous idiopathic POI, **2% to 6%** will have a premutation on FMR1, while 14% of women with familial POI will have one. Therefore, the premutation on the FMR1 gene is the main known inheritable cause of both sporadic* and familial POI. Approximately **3%** percent of women carrying the premutation will have **irregular menstrual cycles** during adolescence and altered hormonal profiles. Women carrying a premutation have a **5% to 10%** risk of having a child with Fragile X syndrome. Consequently, the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists* recommend carrying out a study of the FMR1 gene premutation to all women with POI or with a family history of it.

3. Genetic variants associated with POI:

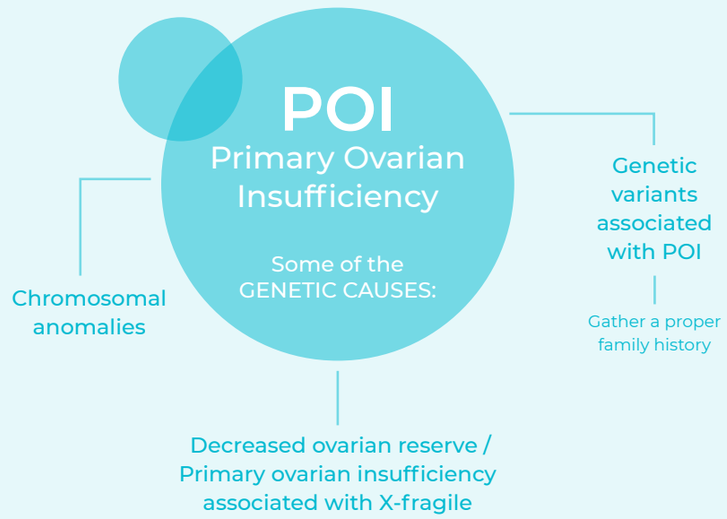
Most often, POI has a highly variable expression in members of the same family, suggesting that it should be considered a multifactorial disease, which makes it extremely difficult to study. Although a large number of genes associated with POI have been published, it has not been possible to demonstrate causality in all cases and they are not accepted as diagnostic markers.

Therefore, it is important to gather a proper **family history** for each patient in order to pre-empt an irreversible situation of ovarian insufficiency and allow her to plan her pregnancy. A karyotype study should be requested for all patients with POI and a Fragile-X study for patients with POI and a normal karyotype, and all patients with a family history of POI.

In short...

Fertility:
Depends on the woman age

- ***17-30 years:*** the most fertile period
- ***35 years:*** significant decrease in the ovarian reserve
- ***40 years:*** ovarian reserve is gradually compromised
- ***45-55 years:*** menopause



AGE
The best measure of fertility

Bárbara Romero
Gynaecologist
UR HLA Inmaculada

Will I be able to have children when I want?

Is there any way to measure my fertility?

If my ovarian reservation is good, can I wait with peace of mind?

Today's society increasingly delays motherhood, sometimes by our own decision, but often because we do not have the time, or a stable partner, or job stability. Be that as it may, these and many other questions pass through our heads at some point in our life.

Most couples under the age of 35 get pregnant after six months of trying, and more than **90% after two to three years of unprotected sexual intercourse**. Getting pregnancy takes time, and this time increases with age. The first thing we must know is that age is the best measure of our fertility, so that, after the age of 35, fertility begins to decrease, and even more after the age of **38-40**. This does not mean that a woman cannot become pregnant at the age of 35, but that it may be more difficult. Therefore, the first recommendation would be to try to get pregnant before this age or get advice from specialists to find out what options there are to protect fertility.

Women are born with a limited amount of eggs; this is called the ovarian reserve. These oocytes do not regenerate and are gradually lost over the years, so that as we age, we have fewer and fewer eggs, and they are of worse quality.

There are studies that can assess the ovarian reserve, but there is no evidence as such that can tell us whether we are fertile or not, since fertility not only depends on the eggs, but also "takes two to tango". A consultation with a gynaecologist who is an expert in human reproduction can diagnose the **level of the ovarian reserve**, and let you know what options exist if you want to delay motherhood.

A good ovarian reserve, measured by age, by ultrasound with an ovarian follicle count and by an **anti-mullerian hormone** test, brings more peace of mind when it comes to fertility if you are young. On the other hand, if the ovarian reserve is compromised or altered, or you are over 35, this would mean that the decision to be a mother should not be delayed.

If a woman wishes to delay reproduction, she can choose the possibility of preserving fertility with the vitrification of oocytes, which is increasingly frequent and necessary in our society and basically consists of storing young and fertile eggs so she can be a mother in the future with her own eggs. The vitrification of eggs allows us to preserve a woman's mature eggs. The method we use is **ultra-rapid freezing**, which keeps these cells unchanged for an indefinite time until they are used.

Advanced paternal age

How does it influence fertility?

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The impact of a woman's age on her fertility is of great importance, since there is a natural limit to being able to conceive a child. However, **what about the impact of the man's age on fertility?** Although men are apparently not affected by the biological clock, the probability of having reproductive problems increases with age.

Furthermore, due to socio-cultural and economic factors, the number of men over the age of 35 with the desire to produce has increased significantly in recent years.

Paternal age has been linked to the semen quality, decreased fertility and spontaneous abortions. Some age-related effects related to sperm quality are:

Effect on the volume

It has been observed that the increase in age is associated with a **decrease in semen volume** secondary to a decrease in the accessory glands. It is believed that each year of age is associated with a volume decrease of between 0.03 and 0.22 mL. This decrease begins at the **age of 35**, but the sharp decline begins at the age of 50.

Sperm count

Although there is controversy about the effect of the concentration, several studies have found an inverse relationship between paternal age and sperm count. This suggests a significant decrease beginning at the **age of 41**. This appears to not affect the sperm recovery rate obtained by testicular biopsy.

Effect on motility, morphology and vitality

There is a **reduction in sperm motility** with respect to age; some research reports a decrease of approximately 1.2% for every 5 years of delay in the age of paternity. On the other hand, no age-related changes in morphology have been observed. By comparison, sperm vitality does constantly decrease with age (approximately 10% in men over 40).

Sperm cryopreservation

In theory, the increase in the number of cell divisions due to age during spermatogenesis (the mechanism through which sperm is formed) would be an argument supporting the risk of mutations in the gametes of older men. It has been shown that the increase in DNA damage in men between 36 and 57 years of age **is three times greater** than in men under 35. Nevertheless, it has not been possible to demonstrate that advancedpaternal age is a risk factor for having children affected by chromosomal anomalies -- whether numerical or structural - except for trisomy 21, 22, X/Y, in which a certain association has been reported. However, **less than 10% of cases of trisomy 21 are associated with advanced paternal age**, which may increase if it is combined with a maternal age of over 35.

One option to prevent the adverse effects of advanced paternal age on the result of pregnancy would be **sperm cryopreservation** at an early age. Nonetheless, cryopreservation may reduce sperm quality, including **motility, viability and the increase in the DNA fragmentation index**, although there is insufficient data to know whether the benefits exceed the risks at this time. What can be done are complementary assisted reproduction techniques such as the evaluation of DNA fragmentation for patients over 40.

Consideration should also be given to **preimplantation genetic testing** (PGT) to detect **aneuploidies** in embryos created with sperm from older fathers. It has been discovered that the use of antioxidants, diet changes and some dietary supplements may help improve sperm quality, which will probably be reflected in an improvement in the results of assisted reproduction treatments in older fathers. However, it is always better for the fertility specialist to provide these recommendations and evaluations.

Polycystic ovary syndrome (PCOS)

A difficult-to-diagnose pathology

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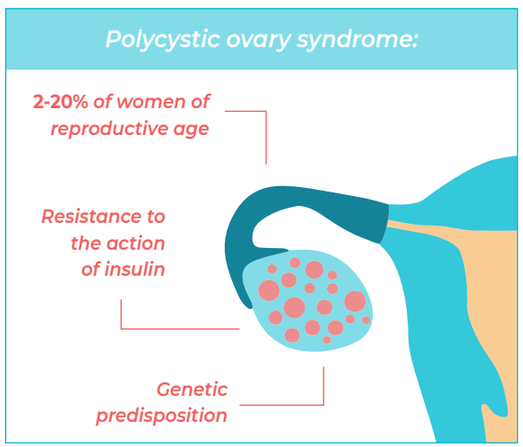
Polycystic ovary syndrome is the most frequent **endocrine alteration in women of fertile age**. This is a complex and sometimes difficult-to-diagnose condition that may affect a woman reproductively, metabolically and psychologically. Although the incidence may vary depending on race and diagnostic criteria, it is estimated that **2% to 20% of women of reproductive age** may have it.

Despite the cause of its origin being unknown, it seems evident that there is a **genetic predisposition** to developing this syndrome that may presumably cause several members of the family to have it. Thus, it is not uncommon to find mothers and daughters or sisters affected within the same household. Furthermore, exposure to various environmental factors, including from foetal development during pregnancy, as well as lifestyle, seemingly contributes to the appearance of the syndrome in susceptible individuals.

Polycystic ovary syndrome is a metabolic disorder characterised by a **resistance to the action of insulin** (the hormone responsible for metabolising sugars within cells) and an increase in its concentration (hyperinsulinemia). This causes elevated blood sugar levels and makes women more likely to have an intolerance to sugar, diabetes mellitus or diabetes during pregnancy.



On the other hand, the association between polycystic ovary syndrome and obesity is frequent and may occur in up to **90% of patients**. It is important to remember that obesity is an isolated risk factor for infertility and that it reduces the effectiveness of assisted reproduction treatments.

Although it is sometimes difficult to identify, several criteria must be met in order to establish the diagnosis of PCOS:

- Elevation of **male hormone** levels (hyperandrogenism). In 60% of women, this may produce an increase in body hair (hirsutis), alopecia or acne. Although in most cases the diagnosis is made by evaluating these signs, a specific test may sometimes be carried out to determine the level of male hormones. These signs, along with excess weight, obesity, or difficulties in becoming pregnant, means that the emotional impact on women suffering from polycystic ovary syndrome may be significant.

- **Menstrual irregularities** such as a **lengthening of the cycle** (oligomenorrhea) or **absence of ovulation** (anovulation), due to the metabolic alterations that have been described, may make it difficult to achieve pregnancy naturally. In addition, the risk of endometrial cancer may increase in patients who have not menstruated during many months, particularly in those who are obese.

- **Ultrasound pattern of the polycystic ovary**. This pattern is defined as a larger than usual ovaries with more than 12 antral follicles in each ovary. It is important not to confuse this pattern with an ovary with a good ovarian reserve, which is typical of young women.

Customised treatment

Treatment of PCOS must be individualised and sometimes involves several specialists, such as a gynaecologist, endocrinologist, dermatologist or nutritionist. As a general rule -- and especially in patients who are obese or overweight -- the recommendation is to have **healthy lifestyle habits**, a healthful diet and to exercise regularly. This will improve insulin sensitivity and decrease the production of male hormones, and **promote ovulation**, a regular menstrual cycle and an improvement in the hirsutism or acne. Several studies show that a loss of 5% to 10% of the initial weight is capable of improving metabolic parameters and restoring menstrual rhythm and ovulation in patients in which they were altered.

When establishing a therapeutic strategy, patients should be differentiated into two groups: those who do not wish to be pregnant, and those who do. Combined **hormonal contraceptives** may be used in patients who do not wish to become pregnant and have irregular rules, provided that there are no contraindications. They will help regulate the menstrual cycle, reducing the risk of endometrial cancer, and will reduce male hormone levels and their clinical manifestations. There are some specific preparations with antiandrogenic effects such as dienogest, cyproterone acetate and drospirenone.

Other treatment options for these patients are the use of **progesterone** in the second part of the menstrual cycle, contraceptives containing only progesterone, or the progesterone releasing IU.

On the other hand, **drugs for inducing ovulation**, such as clomiphene citrate, metformin, letrozole or gonadotropins will be used for women do wish to become pregnant. If the pregnancy is not achieved naturally after these drugs are administered, **assisted reproduction techniques** such as artificial insemination or in vitro fertilization may be used, depending on the characteristics of the patient or the couple. Special interest will be given to avoiding complications during treatment, such as ovarian hyperstimulation syndrome.

Why don't I get pregnant if everything is fine?

Ana Serrano
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UR HLA Moncloa

It is not uncommon to meet a woman at the clinic who, because of personal, professional or other circumstances, consider becoming mothers at an age that has nothing to do with the age at which our grandmothers and great-grandmothers had their first children.

These women have normal gynaecological check-ups, take care to stay young and healthy, and are independent and professionally successful women. **In other words, "everything is fine"**. It's difficult and understandable that, in these circumstances, they don't understand that it is not easy to become pregnant.

Added to all of this is the "normality" with which it is accepted that there are women who decide to become mothers when they believe that it's the best time for them, without taking into account their age, and without being aware that the evolution of our eggs cannot be managed in the same way.

And why are the eggs no longer the same? Why do fewer become pregnant, even if everything is okay?

There is something very important that conditions, to a great extent, the viability of an oocyte becoming fertilised and developing into a healthy embryo that will result in a healthy newborn. We're talking about genetics. The material that will contain all the information that our parents transmit to us and that is characteristic of each individual -- our DNA or genome -- is packed into structures we call chromosomes.

This is what makes up what we call the karyotype, which, in the human species, consists of 46 chromosomes in pairs.

Each of the cells that makes up our body must have that specific number of chromosomes, i.e. 23 pairs, including those that determine sex. Likewise, the embryo must have this genetic information.

How are chromosomes in the embryo formed?

Each gamete -- the egg and sperm -- must transmit only one copy of each chromosome so that the embryo will end up with the **23 pairs of chromosomes**, one from the mother and the other from the father.

In physiological terms, beginning at the age of 35 and as we approach the age of 40, the woman's ovary begins to experience changes. As a result, many eggs may have an incorrect provision of the chromosomes that they would have to transmit. Consequently, many of these eggs will not be fertilised and, if they are, they will often lead to an anembryonic pregnancy or to pregnancies that could have alterations in the number of chromosomes, for instance, Down syndrome or trisomy 21.

Added to this are the changes experienced in this DNA. There may not be an alteration in the number of copies of the chromosomes, but rather in the way they are expressed. This is what we call epigenetics, a word of Greek origin that means "on top of the genome".

The German scientist **Thomas Jenuwein** explains it this way:

> *"The difference between **genetics and epigenetics** can be compared with writing and reading a good book. When it has been written (all the genes that are stored in the DNA), it will be the same in all the copies that are distributed. However, every person who reads it can interpret the story differently. Similarly, epigenetics can allow different interpretations of the same genetic code, and can result in various readings, depending on all the conditions in which the mould is interpreted."*

In this sense, lifestyle habits and the environment are very important: a healthy diet, exercise, avoiding tobacco, alcohol, pollutants...; all of this will have an impact on the epigenome of the embryo and on the future newborn.

The diet is one of the most studied environmental factors that influence the epigenome. Humans metabolise the nutrients from the food and thus get molecules, such as the methyl groups. These methyl groups are one of the molecules that epigenetics uses to modulate DNA, producing the activation or suppression of certain genes.

We know that nutrition, the environment and aging affect the pattern of DNA methylation in our cells, including the eggs. It seems that these age-related changes in DNA methylation could contribute to the deterioration of egg quality, and thus affect the development of the embryos or the placenta.

The molecules secreted by the mother can affect the development and health of the future child, both physically and mentally. This is why we sometimes are surprised by the resemblance between mothers and children born from oocyte donations, where the role of epigenetics is increasingly seen.

Questions and answers

The expert responds...

How effective are current fertility treatments?

Dr. Luis Martínez
Medical Director of RU HLA Immaculada

It depends on the treatment and on the basic parameter that is the patient's age. If we are speaking of in vitro, a patient under the age of 35 has a pregnancy rate of **45%** with a single transfer; if she is 40 years old or older, her pregnancy rate is **20%**. Treatment effectiveness is based on the couple you are treating and, at this point, the age of the woman age and egg reserve are fundamental. If there are sufficient eggs of good quality, the pregnancy rate is high. However, not only is it necessary to think about the pregnancy rate on the first transfer, but also whether embryos have been frozen.

If we are dealing with women over 40, obviously the rate of pregnancy with their eggs is lower. If they resort to oocyte donation, we raise the pregnancy rates again for each transfer we make.

This may be increased if the genetics of all embryos are studied to **select only those that have normal chromosomes**. If we can also define the ideal time in the endometrium, pregnancy rates will be favoured in the future.

What advantage do time lapse incubators have in optimising embryo selection?

Teresa Rubio
Head of the Embryology Laboratory at RU HLA La Vega

These innovative incubators that perform real time **recording of images of each embryo** using video, which makes it possible to fully monitor and obtain all the details of embryo development. This technique immortalises the moments of cellular divisions that are imperceptible to the human eye during the different stages of embryo culture. Therefore, the information obtained allows us to categorise which embryos are best for implantation, thereby increasing the success of in vitro fertilisation treatments. This information makes it possible to assess the ability of each embryo to achieve a successful pregnancy, and eliminates the subjectivity factor that exists when it comes to traditional assessment.

Time lapse incubators **improve the conditions of embryo culture**, since they include a microscope that describes morphological characteristics without having to remove the embryos from their culture environment, removing environmental stress from the embryo and making it more competent, thus raising the rates of success. They also provide a **film record** that allows us to keep the video of the biological beginnings of the future baby, capturing the first moments of the beginning of life.

Why are customised treatments more effective and why do they raise the success rate?

Each of us is unique and different, this fact is also true in assisted reproduction.

Dr. Miguel Barea
Medical Director of RU IMED Valencia

Each of us is unique and different to the rest; this fact is also true in medicine and in assisted reproduction.

People have different demographic or genetic factors and, in the same way, each woman has different markers, such as age, ovarian reserve, anti-mullein hormone, antral follicle count. The solution to diversity is to **individualise and customise** treatments. Our different specialised units provide specific solutions for each of our patients.

The goal is to **administer the precise medication and the appropriate dose to each patient** at the time established, significantly increasing effectiveness and success rates. Markers indicate the biological state, and help to obtain real prognostic information about the possibilities of conception. Therefore, individual markers are necessary to avoid both overtreatment in women with a high ovarian response, and undertreatment in women with a decreased ovarian response.

What is the profile of women and men who need to preserve their fertility?

Dr. José López Gálvez
CEO of UR Group

Thanks to the great advances in the reproductive medicine used in assisted reproduction, it's already possible to decide when the right time to start a family is. Research and high technology are answers to the infertility problems presented by today's society.

We must bear in mind that fertility drops from the age of 35 and that, from the age of 40, **75% of the eggs have some genetic alteration**, which increases the probability of miscarriage by 40%. Similarly, semen quality dropped by **40% compared to 10 years ago**, both in concentration and mobility. It's essential to be familiar with the alternatives that exist today and that allow a 42-year-old woman to use her own eggs to become a mother, with the guarantee that these eggs are in perfect condition and fertile.

According to this, women who, before the age of 35, decide to delay their motherhood due to personal, work or financial circumstances; young patients, diagnosed with cancer, autoimmune diseases, or with bone marrow transplants or endometriosis (pathologies that required treatments that threaten fertility), or women and men who are single but wish to become mothers or fathers in the future, require information and professional advice to preserve their fertility and have children when they wish, without dealing with the obstacle of infertility.

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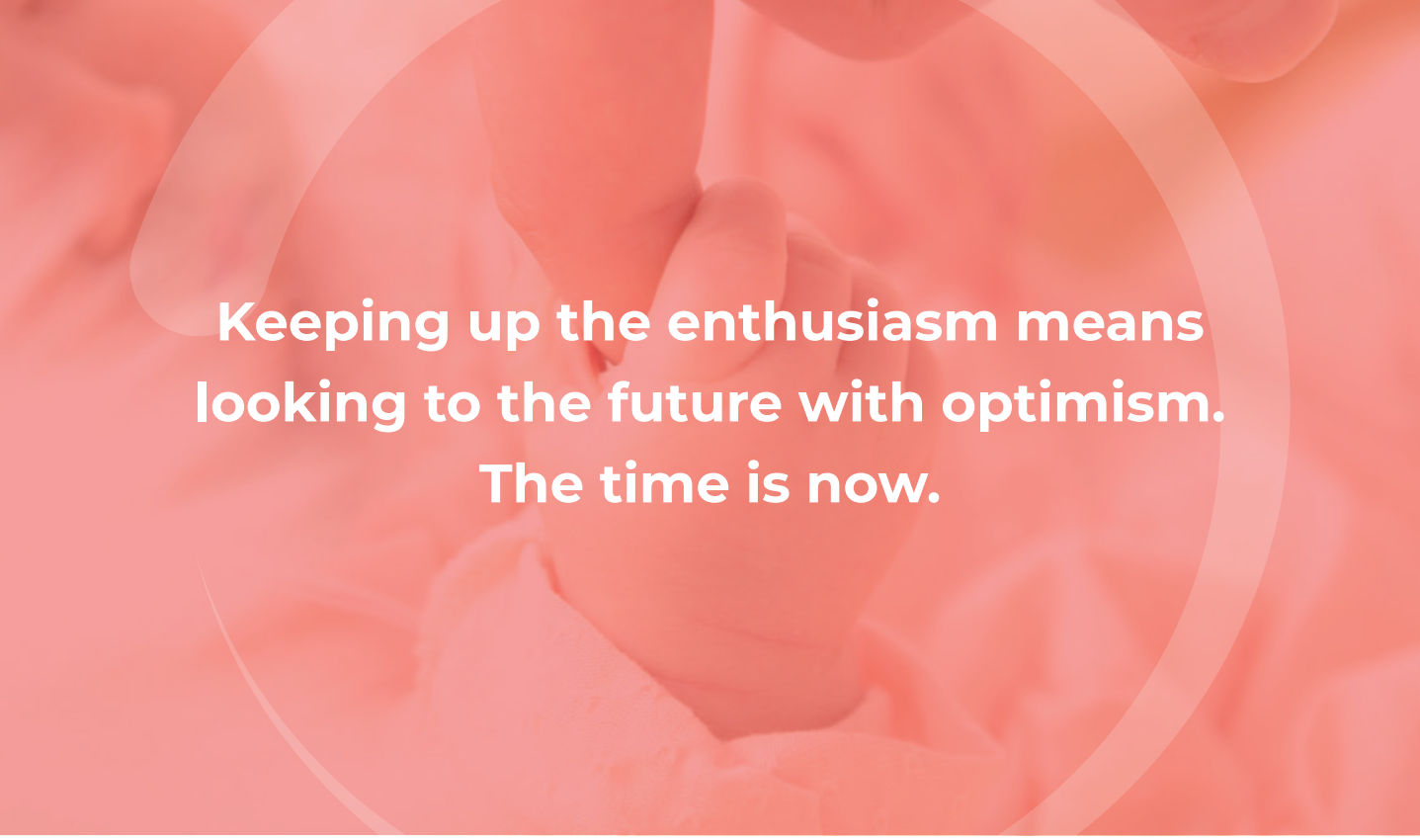

Keeping up the enthusiasm means looking to the future with optimism. The time is now.

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