UNIVERSIDADE
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UNIVERSITY CENTRE OF LISBON

SCHOOL OF PSYCOLOGY AND LIFE SCIENCES

MASTER IN EMBRYOLOGY AND HUMAN REPRODUCTION

THE ROLE OF PLATELET-RICH PLASMA IN THE WORLD OF FERTILITY

USE OF PLATELET-RICH PLASMA IN THE ENDOMETRIUM: INICIAL OF CLINICAL TRIALS

Dissertation defended in public examinations for the degree of Master in Embryology and Human Reproduction, supervised by Prof. Dr Ignacio Santiago Alvarez Miguel

SANDRA SOUSA MOREIRA

2024

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FINAL VERSION

Dissertation defended in public examinations at Universidade Lusófona, Centro Universitário de Lisboa on 17/01/2025, before the jury appointed by Order of Appointment nº1050, of 2024, with the following composition:

Chair: Prof Dr Patrícia Carla Coelho Rodrigues;

Debater: Prof Dr Rocío Nuñez Calonge;

Advisor: Prof Dr Ignacio Santiago Alvarez Miguel.

SANDRA SOUSA MOREIRA

2024

None of us can know what we are capable of until we are tested.

Elizabeth Blackwell

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Resumo

Esta dissertação centra-se na preparação de um endométrio adequado para a realização de uma transferência embrionária, tendo como principal objetivo melhorar as taxas de implantação embrionária e de gravidez clínica utilizando algo que é fornecido pelo corpo da paciente, neste caso o plasma rico em plaquetas (PRP).

O estudo piloto foi iniciado e continua a ser realizado na clínica IERA de Badajoz, em Espanha. Os pacientes incluídos têm de ter pelo menos uma tentativa de transferência de embriões falhada e serem provenientes de ovodoação ou embriões geneticamente testados. Devido a critérios de inclusão rigorosos e a desafios de recrutamento, o tamanho da amostra foi limitado.

Devido a não haver dados suficientes de forma a concluir com resultados estatísticos que comprovam o objetivo do estudo até a defesa desta dissertação, foi considerado a necessidade de um estudo intensivo na literatura sobre o uso do PRP no endométrico, com dados estatísticos a comprovarem a sua eficácia. Foi realizada uma pesquisa sistemática de estudos publicados em inglês desde o início até junho de 2024 (sendo que os estudos apresentados consistem em datas mais recentes) em bases de dados como PubMed, The Cochrane Library, Embase, Web of Science, Science Diret e MEDLINE.

Palavras-chave: Plasma rico em plaquetas (PRP); endométrio; transferência de embriões; taxa de gravidez clínica; FIV

Abstract

This dissertation focuses on the preparation of a proper endometrium in other to do an embryo transfer, having the main purpose of improving embryo implantation and clinical pregnancy rates using something that is provide by the patient's bodies, in this case platelet-rich plasma (PRP).

The pilot study was initiated and continues to be conducted at the IERA clinic in Badajoz, Spain. Patients included in the study must have experienced at least one previous failure embryo transfer attempt and either be recipients of donated eggs or have genetically tested embryos. Due to strict inclusion criteria and recruitment challenges, the sample size was limited.

Because there was not enough data to conclude with statistical results that prove the aim of the study until the defence of this dissertation, the need for an intensive study in the literature on the use of PRP in the endometrium was considered, with statistical data to prove its effectiveness. A systematically review of studies published in English from inception until June 2024 was made (the studies presented consist of more recent dates) in databases such as PubMed, The Cochrane Library, Embase, Web of Science, Science Direct and MEDLINE.

Keywords: Platelet-Rich Plasma (PRP); endometrium; embryo transfer; clinical pregnancy rate (CPR); IVF

Abbreviations, acronyms, and symbols

- AI: Artificial Insemination
- AR: Assisted reproduction
- ART: Assisted Reproduction Technology
- bFGF: Basic fibroblast growth factor
- BMI: Body mass index
- CPR: Clinical pregnancy rate
- EA: Endometrial atrophy
- EGF: Epidermal growth factor
- FET: Frozen embryo transfer
- GnRH: Gonadotropin-releasing hormone
- hCG: Hormone chorionic gonadotropin
- HGF: Hepatocyte growth factor
- HRT: Hormone replacement therapy
- ICSI: Intracytoplasmic sperm injection
- IERA: Extremadura Institute of Health Assisted Reproduction Quirónsalud
- IGF: Insulin-like grow factor
- IL-1-β: Cytokine interleukin-1β
- IL-6: Interleukin 6
- IL-8: Interleukin 8
- IVF: *In vitro* Fertilisation
- LIF: Leukaemia inhibitory factor
- mm: millimetres
- PDGF: Platelet-derived growth factor
- PRP: Platelet-rich plasma
- RIF: Recurrent implantation failure
- TGF-β: Transforming growth factor
- TNF-α: Tumor Necrosis Factor Alpha
- UN: United Nations
- VEGF: Vascular endothelial growth factor
- µl: microlitres

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Chapter 1.

Introduction

1. Introduction

In recent years, Western nations have seen a concerning rise in infertility rates. This condition is defined by the inability to conceive after a year or more of regular, unprotected intercourse, affecting either the male or female reproductive system. (Chandra et al., 2013). In fact, based on the most recent UN-endorsed studies, it is estimated that about 17.5% of adults (i.e. about one in six) have fertility problems, making it urgent to increase access to affordable, quality infertility care for those in need (Njagi et al., 2023).

During the years of science development in human reproduction we discovered that the age of the patient is a factor but not the only reason for failure to obtain a pregnancy.

We see in many cases that it can occur because of the lifestyle of the patients; the quality of the sperm is not the best (we determine it by doing a spermogram); problems in the uterus; the quality of the embryo in the day of the transfer; failure in the implantation of the embryo; or others (Franasiak et al., 2021).

The human endometrium and its thickening are very important for embryo implantation, as its thickening provides an implantation site and a source of nutrition. Its thickening is a response to the secretion of oestrogen when there is maturation of the follicles, as it is the endometrium that provides the site of implantation of the embryo and the source of nourishment until the development of the placenta. It is also a tissue that goes through several cycles of development, differentiation, and detachment during the duration of a woman's fertility. A good indicator of receptivity by the endometrium is its thickness, as well as a prognostic marker of pregnancy outcome after embryo transfer (Aghajanova et al., 2018).

There is clinical controversy regarding endometrial thickness variation in assisted reproduction patients, but there are several studies correlating endometrial thickness and pregnancy.

So far, there is no consensus on the lower limit of endometrial thickness that is indicative of whether the endometrium is receptive for embryo implantation. Most studies consider satisfactory when the endometrial thickness is greater than 7 mm and when the endometrium is ready, with 10 mm or more being desired.

In recent years, methods used for endometrial stimulation in thin endometrium include high-dose, long-term oestrogen supplementation, vaginal oestrogen administration, GnRH analogues, vitamins, among others.

Nowadays, whenever we turn to the literature, there is scientific evidence that autologous platelet-rich plasma (PRP) is beneficial on the endometrium, where its effect on the endometrium can be interpreted as an increase in thickness and changes that favour embryo implantation, and it is something that has a lower risk of immunological reactions caused by its application because it comes from the patient's own blood. (Sfakianoudis et al., 2019).

2. Assisted reproduction

As stated by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, headquartered in Bethesda, Maryland, (U.S.A.), assisted reproduction is the set of treatments and procedures that facilitate pregnancy when it cannot be achieved naturally (NICHD, 2023). The first successful treatment within one of the best known of these techniques, in vitro fertilisation (IVF), in humans was performed in 1978 in the UK: a woman had an unstimulated menstrual cycle, and doctors performed a laparoscopic removal of a single oocyte from the ovary. The oocyte was then fertilised in vitro and subsequently transferred as an embryo into her uterus (Jain and Singh, 2023).

According to the definition in the online medical journal ‘Reproducción asistida org’, currently, approximately 12-18% of couples who wish to conceive a child discover that they are infertile. In 30 per cent of these cases, the underlying causes are attributable to male factors, while in another 30 per cent they originate from female factors. Approximately 20% of couples find themselves in a situation where both partners are infertile. The remaining 20% correspond to cases of infertility of unknown origin (EOD), where the underlying causes cannot be identified with certainty (Reproducción Asistida.org, 2023b).

ART (Assisted Reproductive Technology) refers to a range of methods aimed at treating infertility by manipulating sperm and oocytes. Before starting ART, it's essential to discuss maternal risks and pregnancy with the patient. Conditions like pulmonary hypertension and heart failure are contraindications for pregnancy, making preconception counselling and screening necessary (Jain and Singh, 2023). Once these conditions are addressed, the most suitable ART method can be selected for the patient.

2.1. Artificial Insemination (AI)

Artificial insemination involves placing a man's sperm into a woman's uterus through a long, narrow tube, similar to a thin straw. According to the American Society for Reproductive Medicine (ASRM, 2011), this technique is often used in combination with drugs that stimulate ovulation. It is a technique that is very effective for certain severe pathologies, including the following:

- Women who have scarring or cervical defects;
- Men who have a low sperm count;
- Men with low sperm motility;
- Men who are unable to have erections naturally;
- Men who have retrograde ejaculation, a condition in which sperm are ejaculated into the bladder instead of out of the penis;
- Couples who have difficulty having sexual intercourse.

It is known as Homologous Artificial Insemination (HAI) if both recipients are from the couple, whereas, if it is with donor sperm it is known as Donor Artificial Insemination (DI).

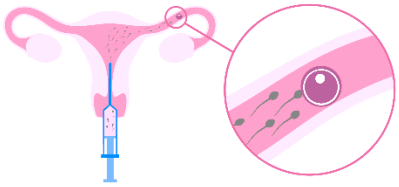


Figure 1. *Artificial Insemination (from the magazine Babygest, 2019)*

2.2. *In vitro* fertilisation (IVF)

In the technique *in vitro* fertilisation, the couple's oocytes and sperm are combined and incubated in a laboratory environment for the purpose of generating an embryo. This embryo is then placed in the woman's uterus by a medical professional, where it has a chance of implanting and thus leading to a successful pregnancy. For this technique to work properly, prior preparation must be carried out, and the following steps are strictly followed (ASRM, 2015):

I. Ovarian stimulation: In this first step, the woman receives drugs designed to activate the ovaries and encourage the simultaneous maturation of multiple eggs. These medications are administered through injections over a period ranging from 8 to 14 days. A health professional closely monitors the development of the eggs using

transvaginal ultrasounds and blood tests to assess both the growth of the ovarian follicles and the production of oestrogen by the ovaries. Once it is determined that the eggs have reached maturity, based on the size of the ovarian follicles and oestrogen levels, an injection of the hormone chorionic gonadotropin (hCG) is administered to initiate the ovulation process. Egg retrieval is carried out 34-36 hours after the hCG injection under the supervision of a health professional.

II. Egg retrieval: Like the name itself says, is a procedure to retrieve eggs from the ovaries, by suction, so that they can be fertilised. It is usually performed in a doctor's office as an outpatient procedure. During the procedure, a mild sedative and painkiller are usually administered for the patient's comfort, and the procedure itself takes about 30 minutes, as a needle is inserted through the wall of the vagina into the ovaries. Ultrasound is usually used to guide the placement of the needle.

III. Fertilisation: The man provides a semen sample. If the sperm are healthy, they undergo a centrifugation process to concentrate them and reduce their volume. They are then placed in a petri dish along with the egg and incubated overnight in a controlled environment. Fertilisation usually occurs naturally in this environment. However, occasionally a sperm cell fails to fertilise the egg on its own. In these cases, a technique called Intracytoplasmic Sperm Injection (ICSI) is used, where a specialist injects a sperm directly into the egg using a microscopic needle. The pregnancy rate resulting from IVF, whether through natural fertilisation or ICSI, are similar.

IV. Embryo transfer: is performed in a doctor's office and is generally considered painless, although some women may experience uterine spasms. A health professional carefully inserts a long, thin tube through the vagina and into the uterus, where the embryo is inserted. Implantation of the embryo into the membrane lining the uterus usually takes place 10 days after the initial retrieval.

Embryos that develop from IVF are transferred into the woman's uterus on days 3, 5 or 6 after the retrieval procedure.

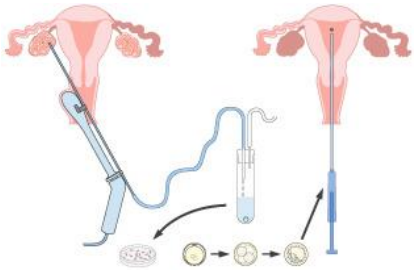


Figure 2. *A visualization of the process of an IVF (from The Lucky Egg, 2023)*

In some cases, embryos are subjected to a freezing process and then thawed for transfer. The patients normally have more than one fertilised embryo. This practice is often used when fresh embryos do not achieve the desired implantation or when a woman decides to preserve her eggs for use in future attempts at conception. To facilitate implantation, women may schedule it according to their ovulation cycle or receive medications containing oestrogen and progesterone to prepare the endometrium prior to implantation.

2.3. Egg donation

Egg donation is an alternative to IVF techniques and is an assisted reproductive method used in situations where a woman experiences difficulties related to the availability of her own eggs, leading her to resort to eggs donated by another woman. This approach is especially considered in women who lack ovarian function, either due to menopause or ovarian failure, and in those with ovarian function, but who present difficulties in assisted reproductive procedures (ASRM, 2023). Egg donation is an essential fertility treatment for women unable to produce their own eggs due to advanced age or at high risk of transmitting a genetic disease (Pennings et al., 2014).

Currently, we can say that egg donation, IVF and subsequent implantation are considered a great success in terms of quality and live birth rates. To achieve these success rates, the scientific community has determined a series of requirements for the woman who wants to be a donor to minimise risks and maximise success rates (SEF, 2018):

- Between 18 and 35 years of age.
- Without genetic, hereditary or congenital transmissible diseases.
- Women with piercings or tattoos performed 6 months prior to donation are ruled out.
- No family history of malformations linked to genopathies, chromosomopathies or metabolopathies.

- The number of children born from your oocyte donation must be less than 6.

2.4. Embryo donation

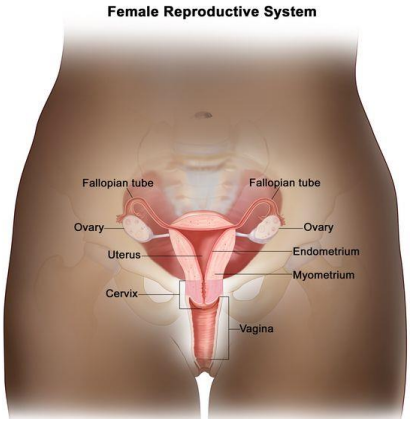
It is a treatment that consists of the transfer of an embryo that has been donated by a woman or a couple who have already completed their reproductive project and decide to make the surplus biological material available to third parties.

This procedure offers an opportunity for parenthood to couples or individuals who cannot use their own embryos due to fertility problems. In this process, donated embryos are transferred into the recipient's uterus with the goal of achieving a successful pregnancy. Embryo donation has become a valuable option for people who cannot conceive with their own embryos or who are at high risk of passing on serious genetic diseases to their offspring (ASRM, 2021).

3. Anatomy and histology of the Uterus and Endometrium

The uterus is the most important organ of the mammal's life. Is a hollow muscular organ located in the female pelvis, between the blader and the rectum, with a pear-shaped and has a muscular outer layer called the myometrium and an inner layer called endometrium.

The oocytes are produced in the ovaries, which travel through the fallopian tubes. Once the oocyte leaves the ovary it can be fertilised and implants in the walls of the uterus. This let's see that the main function of the uterus is to nourish the developing fetus before birth. Figure 3 shows the structure of the female reproduction system.



1. ***Figure 3.*** *Structure of the female reproductive system (NCI Dictionary of Cancer Terms)*

The endometrium is the inner layer of the uterus, which is the most important part for the 9 months of pregnancy. It consists of many glands embedded in surrounding tissue, where its structure changes depending on age and the stages of menstrual cycles, as it responds to the steroid hormones progesterone and oestrogen.

For us to understand more about its function, we need to separate the three different layers of the uterus (Assisted Reproduction ORG, 2024).

The perimetrium is the outermost layer, that partial covers the surfaces of the uterus up to the junction between the body of the uterus and the cervix of the uterus and is structurally derived from the peritoneum. The perimetrium has a role in the menstrual cycle. It helps prepare the uterus for implantation of a fertilised egg by thickening and thinning in response to hormonal changes.

The myometrium is the thickest uterine layer that divides in three different ones. The inner and outer layers lie in a longitude position that is parallel to the long axis of the uterus. While the middle layer that is known by the stratum vascular, is where we find blood vessels and lymphatics. The uterus contractions come from these layers when working together to expel any contents of the uterine lumen. It can expand during pregnancy, to allow the foetus to grow, and to contract so that childbirth can take place.

The endometrium is the inner layer, consisting of the most important layer of the female reproductive system, it's also known as the mucosal membrane. Provides the optimal environment for the implantation of the embryo.

It consists of a highly vascularised tissue, regenerative in nature, with a multitude of blood vessels and glands that are formed and destroyed during each menstrual cycle. Thus, we also find the division of the endometrium into two layers (Assisted Reproduction ORG, 2024):

- Basal layer: this contains the blood vessels and stem cells that generate the functional layer.
- Functional layer: corresponds to the part of the endometrium that grows during the menstrual cycle and is finally shed and expelled to the outside during menstruation.

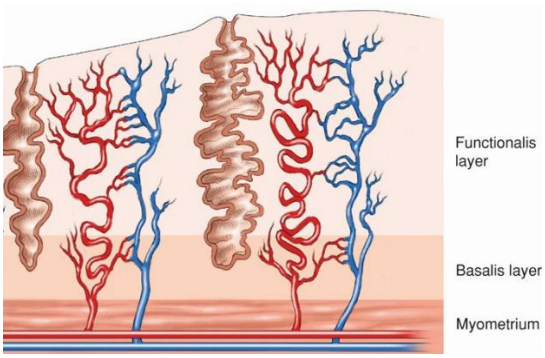


Figure 4. *The division of the endometrium (Obgyn Key, 2017)*

The menstrual cycle is when the woman has a vaginal bleeding that occurs by the shedding of uterine mucosa (menstruation), in other words, it's when occurs the shedding of the inner layer, the endometrium, goes through different changes, the walls get thicker and rich with blood during ovulation in other to provide the best environment to the implantation of the embryo, which will provide a pregnancy (Assisted Reproduction ORG, 2024).

Additionally, depending on the stage of the menstrual cycle, the endometrium can be classified into two main types (figure 3):

- Proliferative endometrium: Due to the production of estrogen, the functional layer of the endometrium starts to expand as cells from the basal layer multiply. New blood vessels and endometrial glands form. This phase, called the proliferative phase, lasts from the beginning of the menstrual cycle until ovulation.
- Secretory endometrium: Following ovulation, the corpus luteum in the ovary releases progesterone, which helps the endometrium mature and become thicker. The endometrial glands grow larger and begin to secrete mucus and glycogen-rich substances, creating an ideal environment for implantation.

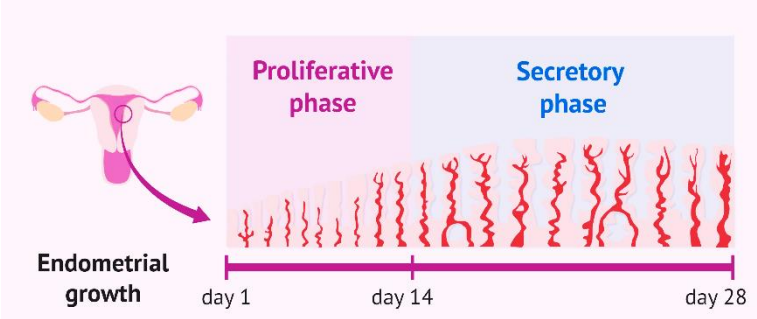


Figure 5. *Endometrial growth during the menstrual cycle (adapted from inviTRA, 2021)*

Any of these phases, aimed at preparing the endometrium to grow and strengthen for a successful pregnancy, but it can fail, potentially causing fertility issues.

Embryo implantation in the endometrium happens around 6 to 7 days after fertilization when the embryo reaches the blastocyst stage. For successful implantation, precise synchronization between the embryo and the endometrium is required, meaning the endometrium must be receptive to the embryo at that time. The ideal thickness of the endometrium for implantation is between 7 and 10 mm. An endometrium measuring less than 6 mm normally does not support embryo implantation.

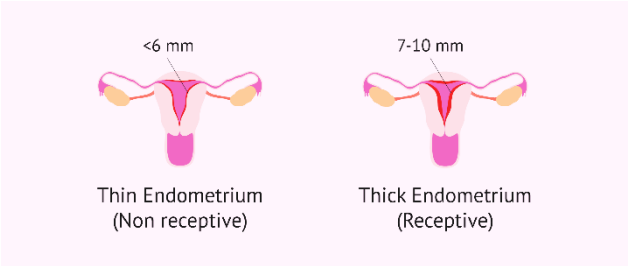


Figure 6. *The difference between a receptive and nonreceptive endometrium (from inviTRA, 2024)*

Using ultrasound, we can see the difference of the types of endometrium:

- Endometrium Type 0: During menstruation, the endometrium appears as a thin, pale line (<5 mm) and is hyperechoic.
- Endometrium Type I: In the proliferative phase, it has a trilaminar structure, but the inner line is faint.
- Endometrium Type II: The trilaminar pattern is clear, measuring 7–10 mm, and is seen before ovulation due to estrogen influence.
- Endometrium Type III: In the luteal phase, under progesterone, it becomes thick, and homogeneous, and contains fluid and glycoproteins.

4. Fertility-related uterine changes

Endometrial damage is a major cause of female reproductive problems, manifesting as endometrial atrophy (EA), menstrual abnormalities, infertility, recurrent miscarriage and other complications, infertility, recurrent miscarriages and other complications.

Endometrial atrophy (EA) is a condition in which the endometrium is too thin and never grows more than 5 mm thick. Factors that can cause EA include long-term use of oral contraceptives and tamoxifen, but in many cases the cause is unknown. The

prevalence of this pathology is 0.5% of infertile women who are undergoing assisted reproductive treatment (ART) (Esfandyari et al, 2020).

5. Endometrial assessment for implantation in ART

One of the most decisive steps in achieving pregnancy is the process of embryo establishment, which involves coordination of a series of complex interactions between the developing blastocyst and the maternal endometrium, i.e. oocyte quality and endometrial receptivity are the two fundamental factors in achieving good fertility results. A large proportion of implantation failures are related due to problems of the receptive endometrium, so we understand that solving these problems is one of the first steps towards success in terms of fertility, as well as improving maternal and perinatal morbidity associated with assisted reproduction techniques. Various maternal-fetal pathologies condition the evolution of implantation, of which we can highlight the absence of implantation, failed intrauterine implantation (clinical or preclinical abortion) and implantation in the wrong place (ectopic gestation), which is a potentially lethal obstetric emergency (Aguilar, 2013).

Uterine receptivity is defined as the state in which the endometrium allows apposition, penetration and the consequent induction of changes in the stroma that lead to embryo implantation. The standard technique for its study is its histological evaluation by biopsy, which is highly dependent on the tissue sample evaluated, as endometrial tissue is a very sensitive tissue.

The endometrium is a non-uniform tissue and asynchrony in histology can appear at any time during the cycle, as well as being an invasive technique and impossible to use in patients undergoing assisted reproduction treatment, so this method is not very standardised. This is why imaging techniques are also used and are increasingly gaining in popularity diagnostic imaging techniques. These techniques use parameters such as appearance or pattern, maximum endometrial thickness, demarcation, tissue perfusion and tissue perfusion (Doppler). In addition, recently, three-dimensional ultrasound has offered new ways of analysis with the new forms of analysis with the measurement of total endometrial volume and the study of endometrial vascularisation. the study of endometrial and sub endometrial tissue vascularisation (Aguilar, 2013).

6. The importance of embryo implantation

Embryo implantation or nidation is the most important factor in human reproduction. This process involves a highly coordinated and specific interaction called 'close dialogue: endometrium and embryo'. In this dialogue, the blastocyst, which has its own molecular program for cell growth and differentiation, interacts with the endometrium, a dynamic organ with a short period of receptivity called the 'window of implantation'. This complex interaction is regulated by several factors, including endocrine, paracrine and autocrine signals, which can originate from both the mother and the embryo. The aim is to ensure a successful union between the blastocyst and the endometrium, culminating in implantation and the onset of a healthy pregnancy (Reshef, 2022).

In all this process, the endometrium plays a fundamental factor, required to be in the proliferative phase of the menstrual cycle (Gutiérrez and Gutiérrez, 2019). At this stage, the process of decidualisation (morphological and functional transformation of the endometrium) is essential, which represents the differentiation of endometrial fibroblast-like stromal cells into specialised secretory decidual cells that provide a nutritional and immunosuppressive matrix vital for embryo implantation and placental development (Liu et al., 2020).

7. Factors that may alter endometrial receptivity

Several factors can impact endometrial receptivity, such as maternal age, uterine disorders, endometriosis, and hormonal imbalances. For women who have not responded to conventional treatments, alternative therapies like platelet-rich plasma (PRP) are being explore. These therapies aim to enhance endometrial receptivity and improve the chances of success in assisted reproductive technologies (ART). The goal is to create a more favourable environment for embryo implantation, potentially increasing pregnancy outcomes in patients facing reproductive challenges.

Many authors directly link a thin endometrium, measuring less than 7 mm, with unfavourable conception outcomes, including recurrent failure to implant (FIR) and decreased pregnancy rates (Dessolle et al., 2009). In fact, a thin endometrium observed on ultrasound is associated with low success rates after several IVF cycles, with a meta-analysis published in 2014 showing that the pregnancy rate when endometrial thickness is less than 7 mm is only 2.4% (Kasius et al., 2014).

Endometrial receptivity is regulated by a series of hormonal, molecular and cellular factors that interact in a complex and coordinated manner. During the menstrual cycle, oestrogen stimulates the growth and proliferation of the endometrium, while progesterone is responsible for differentiation and preparation for implantation. The timing of the implantation window depends on the interaction between these two types of hormones.

Besides the hormonal regulation, other factors can influence endometrial receptivity, such as inflammation, the presence of infections or exposure to toxic factors. When endometrial receptivity is compromised, the embryo may have difficulty to implant and develop properly, which can lead to infertility problems and miscarriages.

In summary, endometrial receptivity is a crucial process for reproductive success, and its study is important for improving assisted reproductive techniques and treating infertility problems.

8. Platelet-rich plasma (PRP)

8.1 What is PRP

The concept of PRP was first introduced by Kingsley in 1954 when he investigated blood coagulation and described thrombocyte clots. It was not until the 70's, when Matras used PRP to promote skin wound healing and treat thrombocytopenia (Verdugo-Martínez and Melo-Sánchez, 2022), that its application began to spread to various medical disciplines, with its main use in regenerative medicine today (Mouanness et al., 2021). With these considerations, over the years, PRP has been used in various medical conditions: in ophthalmology, orthopaedics, surgery and wound healing in injectable or gel form; it stimulates the regeneration of soft tissues such as fat, skin and mucous membranes, as well as hard tissues such as tendons and bones (Chang et al., 2015).

A brief introduction to platelets should be made in this section to highlight the relevance of PRP obtained from blood. These blood cells are derived from megakaryocytes and are short-lived, circulating in the bloodstream for only 7 to 10 days. As is well known, they help to prevent blood loss in the event of vascular injury. But platelets also transport substances that influence tissue repair processes such as angiogenesis, inflammation and immune response, and this activity is carried out thanks to different proteins contained in their granules (Nurden, 2008). Platelets secrete these

proteins with the aggregation process during clot formation. Of great relevance in this process is calcium, a cofactor necessary for aggregation and fibrin formation, and masterfully regulating tissue repair. Platelets can secrete a set of proteins at the site of injury, inducing tissue repair and remodelling of the extracellular matrix.

In addition to these proteins, platelets contain numerous growth factors, stored in intracytoplasmic granules (Puricelli, C. et al., 2023). Growth factors are a set of substances of a protein nature, whose physiological mission is to mediate the process of intercellular communication at the molecular level. They are therefore capable of modifying biological responses at the cellular level, as they directly regulate key processes such as cell migration, proliferation, differentiation and metabolism. Their main function is that of external control of the cell cycle, stimulating cell enlargement by increasing protein synthesis in the cells on which they act (Tam et al., 2007). The study of growth factors together with the discovery of their release by platelets has led to the development of an autologous platelet concentrate, useful to stimulate cell proliferation and differentiation in tissues where this is required, such as in wounds and tissue regeneration processes, or to combat cell involution that occurs with ageing (Rodríguez-Flores et al., 2012).

On this principle, PRP can be defined as a plasma fraction obtained from autologous blood that has a higher platelet concentration than plasma under basal conditions. In addition to a high concentration of platelets, it also contains high levels of GF, which are actively secreted by platelets. It is rich in proteins that act at the level of cell adhesion (such as fibrin, fibronectin and vitronectin), thus providing the structural support necessary for cell migration and for the proliferation and three-dimensional growth of the tissues on which it acts. PRP affects not only directly on target cells for growth factors, but also as an extracellular matrix for the stimulation of tissue repair and/or regeneration in a global manner (Mehta and Watson, 2008).

8.2 PRP in the fertility world

In recent years, methods used for endometrial stimulation in thin endometrium include high-dose, long-term oestrogen supplementation, vaginal oestrogen administration, GnRH analogues, vitamins, among others.

Nowadays, whenever we turn to the literature, there is scientific evidence that autologous platelet-rich plasma (PRP) is beneficial on the endometrium, where its effect on the endometrium can be interpreted as an increase in thickness and changes that

favour embryo implantation, and it has a lower risk of immunological reactions provoked by its application because it comes from the patient's own blood (Baum, 2021).

This idea arose after it was shown in the literature that PRP injection is an important factor in tissue repair and regeneration, such as in dentistry, ophthalmology, and muscle and bone trauma.

In the area of assisted reproduction, when we use PRP, it is because it contains growth factors and cytokines that help promote endometrial healing and growth, receptivity and embryo implantation and development (Anca et al, 2023).

The most common use of PRP in the endometrium is mainly used to improve its thickness so that the embryo has the best conditions for implantation. We apply PRP when the patient has an endometrium with a thickness between 6 and 9 mm, a thin endometrium, compared to endometrium with a thickness ≥ 9 mm. Hence, when the endometrium is less than 7 mm, it is defined as a refractory endometrium with compromised success rates.

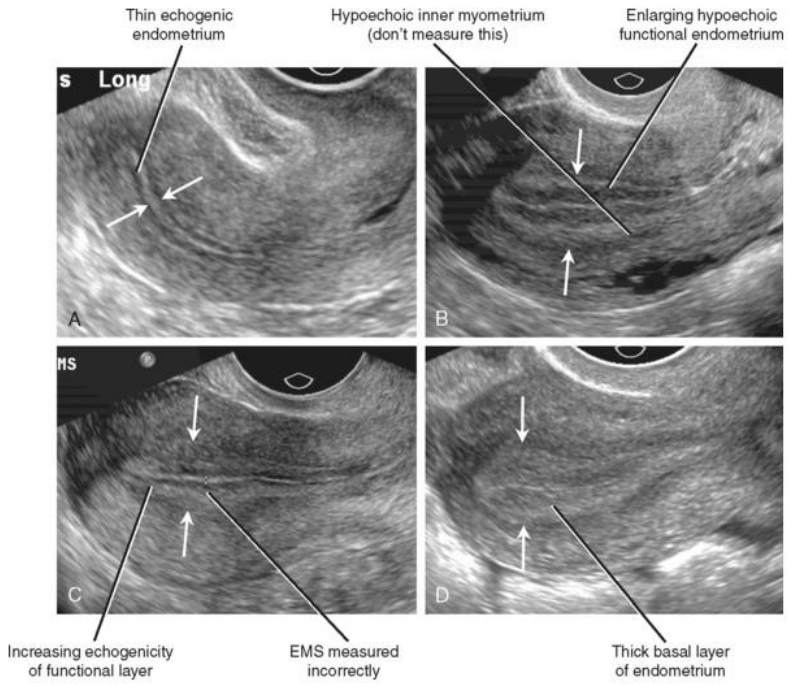


***Figure 7**. Cycle-related changes in the appearance of the endometrial stripe (EMS) on transvaginal ultrasound. A, Early proliferative endometrium. B, Late proliferative endometrium. C, Early secretory endometrium. D, Late secretory endometrium. Opposing Arrows on each image demonstrate correct cursor placement to measure thickness of the EMS. (Childs, 2016)*

The use of endometrial PRP is very promising, but when we look for information on how it is used in the endometrium, we do not obtain much information on the most appropriate protocols, quantity, periodicity, among others. Although it was initially

proposed for refractory endometrium, its usefulness can be extended, as there is nothing that says that it should only be used in endometrium with a thickness of less than 7 mm (Baum, 2021).

8.3 Mechanisms of action at endometrial level

PRP owes its great interest to the decisive role played by platelets in the process of healing and tissue repair. Three phases are distinguished: inflammation, proliferation and remodelling, in which platelets are involved. Platelets function as carriers of a wide variety of molecules in their alpha granules. These substances will be concentrated and deposited at the site of the damaged tissue, exposing and orienting a physiological concentrate of proteins that will intervene, accelerating and favouring the repair and regeneration process (Reyes et al., 2002).

Table 1. *The main molecules present in PRP with known functions at the endometrial level. Table prepared by the author (2024).*

Factor	Function	Reference
VEGF	Controls angiogenesis in the endometrium, resulting in an increased supply of oxygen and nutrients.	(Atkinson et al., 2021)
CSF-1	It is one of the signalling molecules present at the interface between mother and foetus during the implantation process.	(Gleicher et al., 2011)
PDGF	It stimulates chemotaxis, growth and specialisation of stem cells present in the endometrium, which contributes to the repair and remodelling process of endometrial tissue. This could lead to a possible improvement in endometrial receptivity and, consequently, in the likelihood of successful embryo implantation.	(Hajipour et al., 2021)
TGF-β	It stimulates endometrial regeneration and regulates its inflammatory response, which could potentially result in improved endometrial receptivity and, consequently, increased embryo implantation rates. In addition, TGF-β may play a role in human implantation by promoting trophoblast cell adhesion.	(Sfakianoudis et al., 2019) (Irving y Lala 1995)
TNF-α	Variation in TNF-α expression in the human endometrium, which is related to the menstrual cycle, suggests its role in the process of menstrual bleeding and tissue shedding. Successful implantation and placentation depend on a delicate balance between the expression of TNF-α and other cytokines produced by immune and trophoblast cells at the time of implantation.	(Alijotas-Reig et al., 2017) (Boudjenah et al., 2014)
bFGF	Induces endometrial angiogenesis and VEGF receptor expression in endometrium	(Hajipour et al., 2021)
EGF	It stimulates the multiplication of cells in the endometrium, leading to its restructuring. This effect could result in improved endometrial receptivity and, as a result, more successful embryo implantation.	(Hajipour et al., 2021)

IGF	Activates endometrial decidualisation (morphological transformation allowing embryo implantation and placenta formation).	(Hajipour et al., 2021)

Table 2. *(continuation of table 1) List of the main molecules present in PRP with known functions at the endometrial level. Table prepared by the author (2024).*

Factor	**Function**	**Reference**
LIF	LIF production occurs throughout the menstrual cycle, being most prominent in the mid- and late secretory phases, coinciding with the time of implantation. Mutations in the LIF gene have been observed in women experiencing unexplained infertility and repeated implantation failures. In addition, women undergoing IVF cycles who show high levels of LIF during the window of implantation have a higher chance of achieving pregnancy.	(Serafini et al., 2008)
HGF	It promotes cell growth in the endometrium and reduces inflammation by retaining the inactive form of nuclear factor kappa-B (NF-kB) in the cytosol.	(Lin et al., 2021)
IL-1- β	It plays an important role in angiogenesis through the induction of vascular endothelial growth factor (VEGF) and interleukin 6. In addition, it allows endometrial cells to escape immunosurveillance and not be destroyed.	(Baeriswyl y Glavic 2002)
IL-6	Its expression increases in the secretory and menstrual phases, raising the possibility that this cytokine may play a role in endometrial modifications related to the preparation for implantation and the process of menstrual shedding. Abnormal expression has been observed in patients experiencing recurrent miscarriages.	(Lim et al., 2000)
IL-8	It modulates the recruitment of neutrophils, which are known to invade the endometrium before menstruation and are probably involved in the breakdown and digestion of endometrial tissue.	(Arici et al. 1998)

These elements play a crucial role in the activation of fibroblasts and the recruitment of leukocytes to the site of injury. This, in turn, induces and regulates the multiplication and movement of other cell types involved in tissue recovery, such as smooth muscle cells and mesenchymal stem cells. In addition, they promote the process of angiogenesis, which is the formation of new blood vessels, thus contributing to tissue repair (Peerbooms et al., 2019; Rainys et al., 2019).

The use of PRP in animal models has shown promising results. A reduction in the expression of inflammatory markers and fibrosis has been observed, along with a marked increase in the rate of endometrial proliferation. In addition, a significant increase

in the expression of proliferation-related genes and an increase in pregnancy rates have been found in these studies. PRP has also been associated with increased proliferation of stromal and mesenchymal cells, increased expression of regenerative enzymes and improvements in cell migration. These findings support the therapeutic potential of PRP in improving endometrial receptivity.

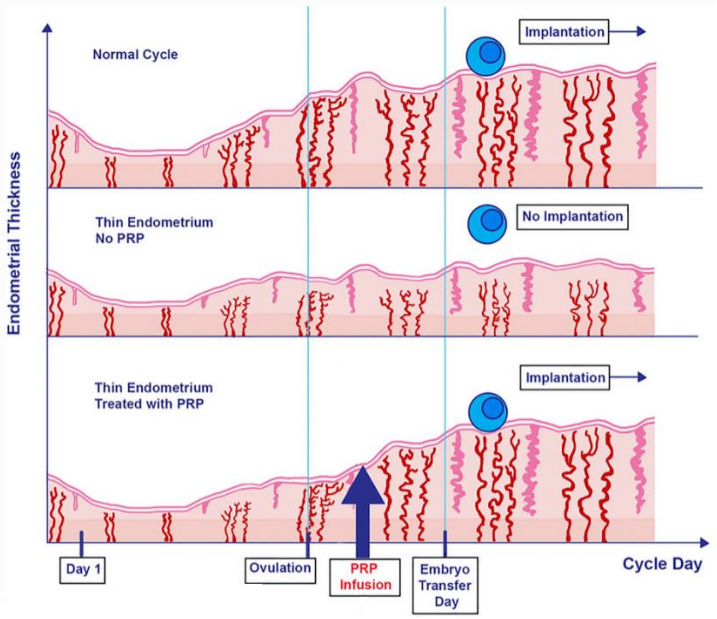


Figure 8. *Comparison of tissue development and embryo implantation between a normal endometrial cycle, an abnormal cycle (thin endometrium) without PRP infusion and a cycle treated by PRP infusion (taken and adapted from Mouanness et al., 2021).*

9. **Objectives**

The aim of this project is to explore the role of PRP in fertility treatments, specifically its application in enhancing endometrial receptivity in women who have experienced recurrent embryo transfer failures. The study focuses on women with at least one embryo transfer failure, as well as those with similar failures from egg donation cycles.

The key objective is to investigate new ways to provide the best possible outcome in achieving pregnancy. This dissertation examines the therapeutic potential of PRP by assessing its efficacy in improving endometrial receptivity, even when optimal endometrial conditions are present. Additionally, it aims to contribute to the development of novel treatments for women facing repeated embryo transfer failures, whether through natural conception or egg donation.

This study was designed as a pilot study, utilizing a recurring protocol of endometrial PRP application in a clinical setting. It was carried out with the assistance of laboratory members, doctors, and clinic directors. All participating patients were provided with a comprehensive consent form prior to their inclusion in the study, which will be attached at the end of this dissertation (annex A 1.).

Chapter 2.

Materials and Methods

2. Materials and Methods

Although this is a slight departure from the main objective of this study, it was considered relevant to carry out a brief review (if not exhaustive, at least to show the breadth of the field covered here) of the most frequent uses of this platelet concentrate in different therapeutic fields.

In addition to this review, the added value of this study was presented to all the professionals at the IERA clinic, and it was agreed by all to begin the pilot clinical trials to randomly select patients who met the criteria to be administered PRP before their transfers. A protocol, based on the protocol currently used in the clinic that will be describe in the next moment, and consent form were created to start the study (Annex A 1.).

However, due to the strict inclusion criteria and the day-to-day operations of the clinic, it was difficult to recruit a large number of patients, as many were undergoing other types of treatment or did not meet the eligibility requirements.

2.1. Methods of administration at uterine level

Although the literature is not very specific on this point, it seems that the most common way of administering PRP is by a method called uterine infusion or endometrial infusion. Some authors propose the intrauterine infusion of 0.5 ml PRP 48 hours prior to blastocyst transfer via a catheter (Nazari et al., 2022a), or via a catheter such as the intrauterine insemination catheter (Takwin, Iran). There are also no standards for platelet concentration, the volume of PRP injected and the frequency of injections, which makes it very difficult to compare meaningful results.

This procedure is not too invasive, which greatly reduces the potential risks that such a technique could cause. As well as embryo transfer, there may be discomfort with the placement of the speculum or urinary tract infection, although these are inconveniences that rarely occur.

2.2. Protocol used in the clinic

The protocol used in the clinic is provide by PRGF Endoret. The current protocol consists of administering PRP in 3 doses of 500 µl to 1000 µl, on days 6, 8 and 10 of the cycle in patients with endometrial thickness less than 7 mm.

2.2.1. Preparation of the product

I. Extraction of blood.

II. Centrifugation.
III. Generation of vacuum in the BTI tube (TP10).
IV. Fractionation using the plasma transfer device (PTD2).
V. Obtaining fractionated plasma, plasma supernatant or both.
VI. Activate the plasma by adding a precise quantity of ENDORET ACTIVATOR.
VII. Keep the activated plasma at 37ºC for at least 40min, until obtain the supernatant.
VIII. Use the Millex Sterile Filter to divide the plasma obtained in different aliquots (0.5 ml – 1 ml).
IX. Store the aliquots in cryotubes at -20°C or in liquid nitrogen.
X. If the first instillation is to be carried out on the day of product preparation, one of these aliquots is NOT frozen.

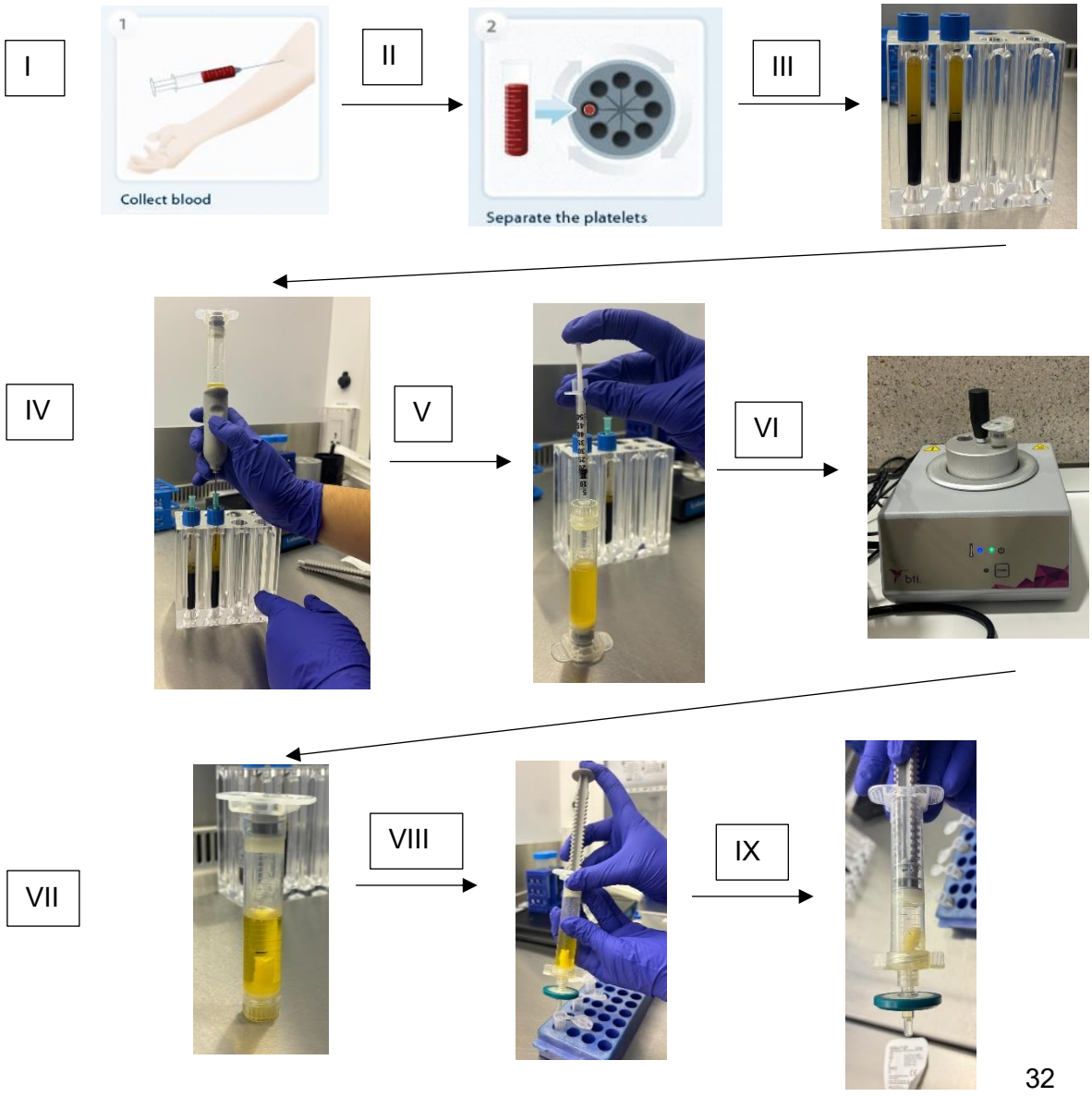


Figure 9. *PRP endometrial - Protocol used in clinic IERA*

The patient must NOT be on anticoagulant treatment. If she is, this treatment must be suspended until the blood is drawn. For example, if you take Adiro daily, you would have to stop taking it for 1 day and the next day you would have to take the blood and then the patient could take the medication. This is because, in order to eliminate the fibrin, we need the plasma to clot, and the presence of anticoagulants will prevent this clotting.

2.2.2. Instillation protocol

I. The product can be prepared at any time during the cycle.
II. The first instillation is usually performed between day 5 or 6 of the cycle. It is usually performed with an embryo transfer cannula, although there is no problem in doing it with a cannula of AI.
III. The second instillation is usually performed between day 8 and 9 of the cycle.
IV. The third instillation is usually performed between days 11 and 12 of the cycle.
V. The embryo transfer is normally carried out between 3 and 6 days after the last instillation (days 14 to 15 of the cycle).

2.3. Inclusion and exclusion criteria for the clinical trial

Inclusion criteria: patients with at least one failure embryo transfer. In those patients we included patients with PGT embryos, and patients with egg donation (independent of endometrial thickness).

Exclusion criteria: patients with uterine pathologies and will have a transfer of more than one embryo.

Chapter 3.

Analysis of studies and clinical trial

3.1. Analysis of study results

The table (table 3) shows a schematic and chronologically ordered review of the most recent studies in which PRP has been used to increase endometrial receptivity in women of different ages, showing the study population selected in each case, as well as the main results observed by the researchers.

Table 3. *Different studies and their results based on the use of PRP at the endometrial level targeting women with poor endometrial response and women with IRF. The table only shows the patients for whom it was possible to complete the full follow-up, which means that in some studies it does not coincide with the initial study populations. Table prepared by the author (2024).*

Authors	Study population	Results	Year
Tandulwadkar et al., 2017.	64 women aged 22-40 years with an endometrial thickness under 7 mm and no other associated cause of implantation failure.	The endometrial thickness media increased from 5 mm to 7.22 mm. The vascularisation pattern improved considerably, and the clinical pregnancy rate was 45.31%.	2016
Eftekhar et al., 2018.	83 women, aged 18-42 years, with poor endometrial response to standard hormone replacement therapy (HRT) (endometrial thickness < 7 mm) undergoing FET. Two groups were established, one control (n=40) and one group given PRP + HRT (n=43). There was no significant difference between the baseline parameters of the two groups.	Endometrial thickness, implantation rate and clinical pregnancy rate per cycle all improved significantly in the PRP group. In 10 women in the control group and 7 in the PRP group there was no endometrial improvement (non-significant statistics).	2016-2017
Kim et al., 2019.	20 women with an average age of 38.4 years and refractory thinned endometrium. Undergoing FET.	The thickness of the endometrium increased by a mean of 6 mm (non-significant). Implantation and clinical pregnancy rates increased, being 12.7% and 30%, respectively.	2019

Nazari et al., 2020.	97 patients under 40 years, BMI<30 kg/m2, with IRF and undergoing ECT. Two groups were established, one control (n=48) and one with PRP administration (n=49). There were no significant differences between the baseline characteristics of the two groups.	The chemical and clinical pregnancy rates were higher in the PRP group than in the control (53.06% vs. 27.08%; 44.89% vs. 16.66%, respectively) and were statistically significant.	2016-2017
Allahveisi et al., 2020.	50 women with RIF undergoing FET. They were divided into two groups, control (n=25), and PRP group (n=25).	No statistically significant differences were found between the chemical and clinical pregnancy rates of the control group compared to the PRP group.	2018-2019
Kusumi et al., 2020.	36 patients aged 20-50 years, with thin endometrium (≤7 mm) and IRF. 32 underwent FET. Hormone replacement therapy (HRT) with oestrogens was performed for 2 menstrual cycles, and PRP was administered on days 10 and 12 of the second HRT cycle together with FET.	The mean endometrial thickness increased, along with the clinical pregnancy rate, which was 15.6%. PRP therapy was safe and effective in increasing endometrial thickness and improving the potential pregnancy rate.	2018-2019
Zamaniyan et al., 2021.	98 women with IRF undergoing FET. Two groups were arranged, a control group, which wasn't administered PRP and a group which was administered PRP. No significant differences between the baseline characteristics of the two groups.	Clinical pregnancy and implantation rates were significantly higher in the PRP group (48.3% vs. 23.26%; 46.7% vs. 11.7%; 58.3% vs. 25%, respectively).	2016-2109

Nazari et al., 2022a.	393 patients aged 18-38 years, BMI ≤30 kg/m2 and serum FSH level ≤10 mIU/ml, with IRF, undergoing frozen embryo transfer (FET) cycles with ICSI. Two groups were established, one control (n=197) and one was given PRP (n=196). No significant differences between the parameters of the two groups were found.	The rates of chemical pregnancy, clinical pregnancy and live birth were higher in the PRP group than in the control group (51.53% vs 24.87%; 48.97% vs 19.28%; 39.28% vs 5.58%, respectively) with statistical significance. In contrast, there was no significant difference in multiple pregnancies (3.06% vs. 1.01%). The spontaneous miscarriage rate was significantly higher in the control group.	2018-2020
Nazari et al., 2022b.	40 patients under 40 years old with at least two previous pregnancy losses and BMI 20-30 kg/m2. Control group (n=20) and PRP group (n=20).	The clinical pregnancy rate was higher in the PRP group (35% vs. 20%). The live birth rate was 15% in the PRP group, but no live births were recorded in the control group.	2018-2019
Bakhsh et al. 2022.	50 control women and 50 women undergoing PRP therapy, all with a diagnosis of IRF.	Treatment with 0.5 ml PRP injection 48 hours after embryo transfer, pregnancy was confirmed in 13% of control women, compared to 20% in treated women (PRP).	2022
Dogra et al., 2022.	20 infertile patients under 38 years of age with refractory thin endometrium (<7mm). Mean BMI 25.6±4.14 kg/m2.	Mean endometrial increase of 1.07 mm. Clinical pregnancy rates of 20% were achieved	2018-2020
Pandey et al., 2023.	117 women aged between 21-37 years with persistent thin endometrium (<7 mm). Two groups were established, a control group (B) (n=51) and a group administered PRP (A) (n=59).	The mean endometrial thickness together with endometrial vascularity was significantly increased in group A compared to group B. The positive pregnancy rate and clinical pregnancy rate in group A were 23.73% and 18.64%, respectively, and significantly higher than those in group B.	2021-2023
Huniadi et al., 2023.	51 women aged 21-42 years with at least one failed embryo transfer cycle due to endometrial thickness less than 7 mm. BMI: 26.1 ± 3.7 kg/m2	With PRP administration the endometrial thickness improved from 6.7 ± 1.32 to 7.81 ± 0.71, as well as the pregnancy rate which increased by 0.5%.	2021-2023

Even though in many cases (such as, chemical pregnancies) conception is not obtained, it should not be forgotten that the main objective of most of these studies is to observe the role that PRP can play at the endometrial level and how it can contribute to an increase in endometrial thickness. This does not imply that, if conception does not occur, these data are unfavourable, as there are many factors independent of PRP that can complicate pregnancy.

The majority of the studies reviewed have obtained data that support the possible benefits of PRP at the endometrial level, in the case of the article cited, the data do not show any benefit from PRP. This fact highlights the importance of reaching a consensus and standardising these working methodologies to obtain robust data that the scientific community can reliably collect for their research and comparisons.

It is also worth noting that the exact mechanisms of action of PRP are not known, and these possible beneficial effects could be due to mechanical endometrial injury caused by the intrauterine catheter, as in most of the included studies, the control group did not receive any intervention beyond standard replacement therapy.

Finally, we will give an individual section to a study published this year (Liu et al., 2024), as it includes a systematic review and a meta-analysis containing a total of 6 different studies, comparing 487 patients. It has been decided to mention this meta-analysis not only because of its recent publication date, but also because it can provide a broader vision of the value that PRP can bring to the field of reproduction medicine. According to the data provide by this analysis, the administration of PRP clearly improves implantation, clinical pregnancy and endometrial thickness. Key findings include significant improvements in endometrial thickness and higher clinical pregnancy rates in the PRP-treated group. The results suggest that PRP could be a promising option for women with thin endometrium undergoing fertility treatments.

3.2. Analysis of the results from clinical trials

Table 4. *Control Group of the clinical trials IERA*

Date	Identification	Age	Reason	Num FET	Endometrium	Test Results
01/04/2024	L C	43	Egg Donation	2	8mm	Negative
05/04/2024	L M	35	PGT	2	-	Positive
05/04/2024	C J	36	Egg Donation	1	-	Positive with abortion
08/04/2024	A R	37	PGT	1	9,5mm	Negative
08/04/2024	R D	41	PGT	1	9,6mm	Positive
09/04/2024	E M	41	Egg Donation	2	8mm	Negative
23/04/2024	A D	43	Egg Donation	1	9,6mm	Positive

Table 5. *Trial group which had PRP, from the clinical trials IERA*

Date	Identification	Age	Reason	Num FET	Endometrium	Test Results
08/04/2023	C R	39	PGT	1	8mm	Positive with abortion
11/04/2024	M V	44	Egg Donation	1	12,9mm	Positive with abortion
25/04/2024	C Y	36	-	-	-	Cancelled
21/05/2024	M G	38	Abortions	3	8,5mm	Negative
18/07/2024	C S	31	PGT	2	9 mm	Negative

Due to the limitations of the data resulting from the strict inclusion criteria and the day-to-day operations of the clinic, which led to insufficient sample data and variability in the pilot study conditions, the results of this analysis do not provide statistically significant outcomes. Although it would be an interesting value for analysis there was no record of the endometrium thickness before the instillations of PRP.

As a result, the limited sample size posed a challenge in obtaining results that are both statistically significant and open to rigorous debate, making it harder to draw definitive conclusions regarding the efficacy of PRP administration in this context.

Chapter 4.

Conclusion

4. Conclusion

In view of the above, after a systematic review of the existing specialized literature on the subject, it is possible to reach the following conclusions:

- We understand that the endometrium is a complex tissue that plays a crucial role in fertility. However, various conditions can disrupt its ability to become receptive during the menstrual cycle, which is necessary for a successful embryo implantation, or it can lead to repeated failures in implantation and difficulty achieving pregnancy.
- Although there isn't full agreement, most of the scientific community defines recurrent implantation failure as occurring when at least three embryos have been transferred without a successful pregnancy.
- The platelet-rich plasma (PRP) has gained a lot more interest in various medical fields, which includes fertility treatments for recurrent implantation failure. Specifically, PRP is considered a safe and promising option to enhance endometrial receptivity. Its potential benefits have sparked significant scientific research and debate in current medical literature.

To fully understand the therapeutic potential of PRP, it is essential to standardize the methods of extraction and administration. This will ensure the most effective use of PRP and help maximize its therapeutic benefits.

In conclusion, research into PRP and other promising approaches could create new opportunities to improve fertility treatment outcomes, even when results are slow to appear. This could offer hope to couples struggling to conceive due to endometrial receptivity problems. Further research with a more robust sample size and standardized protocols is required to accurately assess the treatment's performance.

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Annex

Annex A 1. *Consent form; All participating patients were provided with this comprehensive consent form (written in Spanish)*

HOJA DE INFORMACIÓN

Título: *"Estudio sobre el uso de plasma rico en plaquetas (PRP) en el endometrio en pacientes que tienen una o mas transferencias fallidas con embriones de ovodonación o con embriones de PGT"*

El objetivo de este documento es informarte sobre el estudio en el que se le ha invitado a participar. Para ello, es necesario que previamente reciba la información correcta y suficiente, de este modo podrá evaluar y juzgar si quiere o no participar. Por favor, lea detenidamente este documento con atención, y no dude en ponerse en contacto con su médico para cualquier duda que le pueda surgir acerca de este documento.

Participación en el estudio

Debe saber que su participación en el estudio es totalmente voluntaria, por lo que es necesario que antes de su inclusión en el mismo haya dado su autorización mediante la firma de este consentimiento. Usted puede negarse a participar o retirar su consentimiento durante el estudio cuando lo desee, sin tener que dar ninguna explicación al equipo de investigación y sin que ello suponga ninguna alteración en la relación con su médico. Además, la atención medica que reciba siempre será la mejor para usted y sólo estará determinada por el criterio médico, independientemente de que su decisión sea la de participar o no.

Objetivo del estudio

El objetivo de este estudio es mejorar las tasas de embarazo.

Descripción del estudio

Este estudio se basa en la inoculación de PRP autólogo (de la misma paciente) en pacientes con una transferencia previa fallida (sin embarazo) con el fin de proporcionar las mejores condiciones uterinas para que el embrión se implante en su pared ya que el PRP favorece el crecimiento endometrial. Los resultados de este estudio se comparan con el mismo tipo de pacientes en las que no se realice la administración de PRP. La adición del PRP y por lo tanto el uso de esta técnica en este estudio es seguro pues el PRP proviene de su propia sangre y no pone en peligro tu salud ni la del embrión.

Confidencialidad

De acuerdo con la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de datos de Carácter Personal (LOPD), los datos personales y de salud que se recojan con motivo de este estudio son los necesarios para cubrir los objetivos del mismo.

Usted podrá ejercitar su derecho de acceso, rectificación, cancelación y oposición dirigiéndose al médico o colaboradores que le atiende en este estudio.

CONSENTIMIENTO INFORMADO

Yo, (nombre y apellidos del paciente).....
manifiesto que he sido informado del presente estudio y:

- He leído la información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con (nombre del investigador) .....
- Comprendo que mi participación es voluntaria.
- Comprendo los objetivos del estudio, así como las condiciones en las que se llevará a cabo.
- Comprendo que puedo retirarme del estudio:
  - Cuando quiera.
  - Sin tener que dar explicaciones.
  - Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas.

Firma de la paciente Fecha:

Firma del Investigador Fecha: