



IMPLANTATION FAILURE AND RECURRENT MISCARRIAGE

INSTITUTO BERNABEU



ABOUT INSTITUTO BERNABEU

Since its founding in the 1980's, Instituto Bernabeu has been committed to providing its patients the highest level of comprehensive medical care, making it a leader in Reproductive Medicine.



Over the years, we have achieved more than 25,000 births through in vitro fertilization, and cared for 121,026 patients coming from over 167 countries. Each of our 9 clinics, in Alicante, Madrid, Mallorca, Cartagena, Albacete, Elche, Benidorm and Venice, are equipped with state of the art technology to perform the most advanced treatments available. Over 48,427 treatments have been carried out for patients who chose us for their personal journey in creating a family, trusting in Instituto Bernabeu because of our results, strong values, commitment to research, as well as our comprehensive patient care, both medical and emotional.

Our main goal is to achieve the best results and to promote the advancement of medical science. Because of this our medical practice is tied into our **investigations and teaching work**. These activities feed into each other, and materialize in the **University Chair** of the Reproductive Medicine with the University of Alicante and Community Medicine and Reproductive Health professorship of Miguel Hernández University. To date we have written

over 200 research projects, product of striving for individualized treatment for our patients. Along these lines, with the Rafael Bernabeu Charitable **Foundation** we are dedicated to developing a wide range of social outreach programs. We aim to make assisted reproduction treatments more accessible to patients with limited means, offer scholarships for young scientists in **Reproductive Medicine**, as well as support foundations that help underprivileged children, among other outreach programs.

This commitment to our patients, together with the professionalism and experience of our medical team, make Instituto Bernabeu a center of prestige in Reproductive Medicine world wide.



1. Exceptional medical care **in reproductive medicine**
2. First clinic in Europe **to offer a pregnancy guarantee**

WHY WE ARE DIFFERENT



3. Personalized care **individualized for all treatments**

4. 35 years' experience **support our work**



5. Clear, fixed prices **all included, no surprises**
6. The most innovative techniques **For fertility and reproductive genetics**

7. A full team of professionals **Gynecologists, biologists, geneticists, biochemists, endocrinologists, urologists, pharmacists**



8. Practical research
So that we can tailor your
treatment for you

9. State of the art facilities and
infrastructure
to make your stay as comfortable as
possible



10. In-house laboratories and
specialized technology
which offer efficiency in results and
control over the entire process

11. Teaching and research
programs
Pioneers in reproductive medicine



Excellent results
audited by two external
accredited agencies



12. 9 specialized clinics
in Alicante, Madrid, Mallorca,
Cartagena, Albacete, Elche,
Benidorm and Venice



WE LEAD THE WAY TO YOU

Implantation Failure Unit



IMPLANTATION FAILURE AND RECURRENT MISCARRIAGE UNIT AT **INSTITUTO BERNABEU**

Embryo implantation

It's the miracle of life: fertilization and human reproduction. A meticulous and perfect process that allows two cells to come together and create another that will develop until transforming into a new being.

Since the beginning of mankind, the ability to create life has been considered an object of worship. Similarly, the difficulty in achieving motherhood, especially when there are failed attempts, is a source of frustration for parents. But science once again progresses to offer answers and solutions. And nowadays, thanks to technological advances and innovation in assisted reproduction, we know precisely each step of fertilization, a fact that helps us to understand the reasons why occasionally and sometimes repeatedly it does not end in a healthy and viable pregnancy.

It all starts when out of hundreds of thousands of sperm only one successfully reaches the egg in one of the fallopian tubes and fertilizes it, creating a new cell: the zygote. During the following days, it begins to slowly descend into the uterus where it must pass a crucial test of extraordinary complexity: embryo implantation.

Implantation is the adherence to the uterus, which allows the future fetus to obtain oxygen and nutrients from the mother for its proper development and growth. But in order for this implantation to be effective, the zygote must be strong enough to attach, the uterus must be prepared to receive it and also the communication between them must be adequate. Therefore, sometimes if one of these steps does not occur, the implantation may not take place successfully. Only 1 out of 4 embryos successfully implants in the uterus, so this first test for the embryo is "the great unknown challenge", as explained by the specialists of Instituto Bernabeu Alicante.

IMPLANTATION FAILURE UNIT AT INSTITUTO BERNABEU

We may be facing a case of implantation failure if, after several consecutive attempts, the objective is not achieved. That is, both in patients who do not get pregnant following various courses of assisted reproduction treatment (In Vitro Fertilisation (IVF), egg donation, embryo adoption) and in those who do get pregnant but then suffer recurrent pregnancy loss. There are several reasons for this. The answer may, on the one hand, be in the embryo itself and in its composition. It is important to take into account that it is a foreign body for the mother's immune system because it does not have the same proteins and constitution as the mother's tissues since it also contains the father's cells. The embryo should, therefore, resist the potential attack from the mother's immune system which can, in some cases, refrain it from implanting and, therefore, from leading to a pregnancy. As well as the embryo, there are also factors in the mother and in the father which are at the origin of implantation failure or recurrent pregnancy loss.

Science, research and technological progress have now come together to improve those factors and apply specific treatments and solutions in order to overcome them. It is for this reason that Instituto Bernabeu set up the pioneering specific unit to deal with each particular case with a trained team of doctors, embryologists, geneticists and molecular biologists. It has also set up a program with specific protocols for treating recurrent pregnancy loss and failed courses of assisted reproduction treatment. By dealing with issues from an interdisciplinary point of view, we can diagnose and, therefore, successfully treat many of them.



THE MOTHER AND FATHER'S CONTRIBUTION

The Implantation Failure Unit at Instituto Bernabeu studies the uterus and rules out any factor which may affect uterine receptivity. Additionally, and thanks to a new ultrasound scan, endometrial volume, endometrial vascularity and contractions in the uterus are measured. These are essential in determining implantation capacity and for locating the most appropriate place for depositing the embryo during transfer and helping it to develop. The ovaries are also checked in order to rule out any conditions that might impede embryo implantation. A search for any conditions such as endometriosis or adenomyosis, causes of many implantation failures, is also carried out.

However, immunology analyses rarely help and any treatment derived from these analyses often fails to have a positive impact of any kind. That said, and taking into account the fact that this field is in continuous development, we have a Reproductive Immunology Department at IB that assesses this factor and carefully monitors any progress that is made.

Our most recent research work has demonstrated the impact of the microbiome (the microorganisms that live around the genitalia) on fertility. This prompted us to begin analysing it so that measures can be taken if abnormal results are obtained. We also assess the option of placing substances that stimulate the endometrium inside the uterine cavity days before transfer in order to increase biological competence.

In addition, we perform a study called IBgen RIF that includes a genetic, immunological and haematological factor panel, meaning that a single test can provide us with information about different causes.

In terms of the male partner, understanding the percentage of spermatozoa with fragmented DNA and their chromosomal make-up, means we can go into minute detail on the father's contribution to the future embryo. Endocrinological factors exposed to the environment and to toxins that may affect correct embryo implantation are studied.

Your gynaecologist may recommend a testicular meiosis study if you have abnormal semen parameters that are potentially the cause of previous unsuccessful attempts at in vitro fertilisation, implantation failure or spontaneous pregnancy loss.

In meiosis, spermatozoa precursor stem cells split their genetic load in half and change from having 46 chromosomes to 23. If there are abnormalities during this phase, they can affect the gamete's chromosomal make-up and, consequently, cause fertilisation failure, abnormal embryo development, implantation failure and premature pregnancy loss.

The procedure generally entails taking a small testicular biopsy although analyses can sometimes be performed on ejaculate. The result helps to ensure that the most suitable decision regarding reproduction can be taken.

Furthermore, observations are also carried out on both the mother and the father's chromosomes since they are the source of what the embryo will inherit. Following this, the genetic make-up of the third parent is taken into account: the embryo prior to transfer. Transfer of chromosomally normal embryos means that the risk of abortion decreases dramatically. With this in mind, we use a new technique consisting of PGS/PGT-A/CCS using array-CGH and NGS. This detects any abnormality in DNA to a much greater and precise degree and means that diagnosis levels 100 times greater than previous tests can be achieved. In order to guarantee the quality of the entire process, we use in-house technology and geneticists so that no outsourcing is required.

Cutting-edge tests, detailed DNA information, increasingly specialised experts and new and precise assisted reproduction techniques are combined with just one aim in mind: ensuring that the embryo finds its place in the uterus, develops and becomes a new human being.

PRICE LIST LINKED TO IMPLANTATION FAILURE AND RECURRENT PREGNANCY LOSS

At Instituto Bernabeu we are transparent. Our prices are clear and fixed, so that you know the cost of treatment from the very beginning.

■ Cycle of In Vitro Fertilization

5,000€

DESCRIPTION OF SERVICES INCLUDED

- Personalised treatment. Necessary scans and blood tests during the treatment. Embryo transfer (private room, operating theatre and fertilisation laboratory).
- Ovarian stimulation: clinical controls, ultrasounds and blood tests. Ultrasound-guided egg retrieval, post-retrieval check up and pain-relievers until final discharge and health insurance in case of any complications.
- All laboratory in vitro fertilisation processes required in order to optimise chances of success: ICSI, assisted hatching, time-lapse incubator, etc.
- Embryo cultivation for the entire time required including up to day six.
- Embryo storage for the first year, if cryopreservation is required.
- If you have not already had them, we will perform the following analyses free of charge:
 - Full gynaecological check-up and embryo transfer test including the smear test, if required.
 - β-HCG (blood test to determine pregnancy) and ultrasound to check gestation, if needed.

Subsequent In Vitro Fertilization cycles when an ongoing pregnancy has not been achieved

4,000€

■ Cycle of egg donation adapted to implantation failure and repeat miscarriage 7,200€

DESCRIPTION OF SERVICES INCLUDED

Egg donor treatment:

- Egg donor selection and preparation process, within which we might highlight the following.
 - Psychological and social assessment, fertility study, comprehensive medical and gynaecological check-up.
 - Infectious diseases blood test, screening of the 10 most common sexually transmitted diseases and cytomegalovirus (CMV).
 - Karyotype and analysis of genetic diseases including, amongst others, cystic fibrosis, fragile X, alpha thalassaemia, beta thalassaemia and muscular spinal atrophy and nonsyndromic hearing loss (GJB2).
 - Genetic Compatibility Test (GCT). Genetic compatibility screening for more than 600 or 3,000 genetic diseases, depending on the modality.
- Ovarian stimulation of donor: clinical controls, ultrasounds and blood tests. Ultrasound-guided egg retrieval, post-retrieval check up and pain-relievers until final discharge and health insurance in case of any complications.
- Storage of donor DNA for 20 years

Recipient treatment:

- Medical consultation with a specialist gynecologist to design your personalized treatment plan.
- Personalised treatment. Necessary scans and blood tests during the treatment. Embryo transfer (private room, operating theatre and fertilisation laboratory).
- All laboratory in vitro fertilisation processes required in order to optimise chances of success: ICSI, assisted hatching, time-lapse incubator, etc.

- Embryo culture for the entire time required including up to day six (in 99% of our egg donation treatments, transfer is done in blastocyst stage).
- If you have not already had them, we will perform the following analyses free of charge:
 - Full gynaecological check-up and embryo transfer test including the smear test, if required.
 - β -Hcg test (pregnancy test performed using a blood sample) and initial pregnancy ultrasound scan, if applicable.
- Session with a clinical psychologist from our egg donation department to inform you about the process of assigning and selecting the most suitable egg donor.

Subsequent Egg donation cycles when an ongoing pregnancy has not been achieved

5,700€

NOT INCLUDED (SHOULD THEY BE NECESSARY, THEY WILL BE INVOICED INDIVIDUALLY)

- The cost of the donor's medication: **1,000€**
- The cost of the recipient's medication.
- Any subsequent treatment using vitrified embryos from this cycle, or any other service not specified in the description of the treatment.
- Surgery (testicular biopsy, TESA, etc), if needed.
- Cryopreservation of embryos and maintenance during the first year: **600€**
- Annual storage of embryos after the first year, if desired: **300€**
- Genetic Compatibility Test (GCT) studies more than 3,000 hereditary diseases thanks to the testing of 2,306 genes, plus Cystic Fibrosis, Alpha Thalassemia, Beta Thalassemia, Fragile-X, Spinal Muscular Dystrophy and Non-Syndromic deafness (GJB2) of the future father: **1,175€**
- Genetic Compatibility Test (GCT) studies more than 600 hereditary diseases thanks to the testing of 555 genes, plus Cystic Fibrosis, Alpha Thalassemia, Beta Thalassemia, Fragile-X, Spinal Muscular Dystrophy and Non-Syndromic deafness (GJB2) of the future father: **850€**
- GCT Basic: genetic compatibility test to study 50 disorders: **350€**
- Sperm donor, if required: **500€**

■ **PGS/PGT-A/CCS** (Comprehensive Chromosome Screening): First embryo biopsied **550€**

PGS/PGT-A/CCS: Additional embryos biopsied **400€**

■ **Vaginal microbiome + chronic endometritis bacteria** **400€**

■ **PRP "Platelet Rich Plasma"** **950€**

DESCRIPTION OF SERVICES INCLUDED

Intra-uterine administration of platelet-rich plasma from the patient's blood

■ **IBGen RIF** **295€**

DESCRIPTION OF SERVICES INCLUDED

Analysis of the **variants in genes** associated with implantation failure and recurrent pregnancy loss. These include variants of the genes that are linked to thrombotic risk factors (prothrombin, factor V Leiden and MTHFR), immunology factors (IL-11 and APOE) and factors that modulate endometrial receptivity (p53 and VEGF)

■ IBGen RIF + vaginal microbiome

645€

DESCRIPTION OF SERVICES INCLUDED

- Analysis of the **vaginal microbiome** and **chronic endometritis bacteria**
- Analysis of the **variants in genes** associated with implantation failure and recurrent pregnancy loss. These include variants of the genes that are linked to thrombotic risk factors (prothrombin, factor V Leiden and MTHFR), immunology factors (IL-11 and APOE) and factors that modulate endometrial receptivity (p53 and VEGF)

■ RIF microbiome and endometrium

535€

DESCRIPTION OF SERVICES INCLUDED

- **Endometrial biopsy** and functional study of the endometrium and CD138 antibody marker for specific analysis of chronic **endometritis** (should there be an abnormal result, a second analysis will be performed at no additional cost in order to check if the condition has improved following treatment)
- **Vaginal microbiome** and **chronic endometritis bacteria** analysis (should there be an abnormal result, a second analysis will be performed at no additional cost in order to check if the condition has improved following treatment)
- **3D ultrasound scan**

■ RIF microbiome, endometrium and hysteroscopy

1,045€

DESCRIPTION OF SERVICES INCLUDED

- **Endometrial biopsy** and functional study of the endometrium and CD138 antibody marker for specific analysis of chronic **endometritis** (should there be an abnormal result, a second analysis will be performed at no additional cost in order to check if the condition has improved following treatment)
- **Vaginal microbiome** and **chronic endometritis bacteria** analysis (should there be an abnormal result, a second analysis will be performed at no additional cost in order to check if the condition has improved following treatment)
- **3D ultrasound scan**
- Diagnostic **hysteroscopy**

DURATION AND MEANS OF PAYMENT

- The entire cost of the selected course of treatment must be paid when treatment begins. The clinic reserves the right to cancel treatment should payment not be made within the established period.
- This price quotation is valid for 6 months from when it is signed. Payment may be made by bank transfer or credit card. Should embryos that are not transferred be cryopreserved, payment must be made when vitrification takes place.
- Should embryo transfer not take place, a refund of €200 will be made.
- Should embryo transfer be cancelled due to a decision taken by the recipient patient, no refund of any kind will be given.
- The price reduction for a second course of treatment and for PGS/PGT-A or possible cycles of oocyte accumulation and its vitrification may not be used in conjunction with agreements of any kind with any entity.
- In compliance with Law 7/2012 on measures to combat fiscal fraud, residents in Spain may not make cash payments for amounts equal to or above € 1,000. This amount increases to €10,000 should the payee not have fiscal residency in Spain.

FINANCING

If you live in our country, financing options are available to you. Please do not hesitate to ask about this.

DOCTOR'S INSTRUCTIONS AND/OR CANCELLATION

- Should the patient fail to adhere to the doctor's instructions or should treatment be cancelled or interrupted for medical reasons or at patient request, patients must pay for all services already provided. Therefore, the signees expressly understand and accept the costs and all the other financial information that has been explained to them by our members of staff, they have understood this information completely and have had the opportunity to ask any relevant questions, and they affirm that they fully comprehend and accept this price quotation.
 - The patient's right to refusal covers entitlement to refuse acceptance of this price quotation by failing to undergo treatment during the validity period. Should this be the case, the price quotation will be considered no longer valid.
 - If for whatever reason the cycle is cancelled before finishing the monitoring phase, the amount paid will be reimbursed, except the initial consultation fee and the number of ultrasounds/medical consultations done up until the point of cancellation 100€ each.
 - Should there be any surplus embryos following embryo transfer, they must be cryopreserved and the patients must pay the additional cost of this service that includes storage of the embryos for a period of one year. From the first year on, the valid storage cost must be covered by the patient unless they decide on a different destination for the embryos as permitted by Law.
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- The price quotation has been explained to us by staff at the clinic and we understand its content and scope.
 - We, the patients, have received a copy of this information detailing costs. It will be attached to the informed consent for the corresponding course of treatment.

DATE: _____

SIGNATURES: _____

PATIENT'S NAME: _____

The parties recognise that the stipulations and commitments within this contract have been made according to the Spanish and European legislation that is in force at the time of signing. Any modification to the legislation and in particular to Law 14/2006 regarding assisted reproduction, that prohibits or regulates in a different manner to that which is foreseen in a certain stipulation or clause, will leave said stipulation or clause without effect according to the terms and timeframes in which said modification were to be applied, while the rest of the agreements regulated in this contract will remain unaltered.

Basic information on personal data protection: Instituto Bernabeu SL is responsible for treating your personal information so that our contractual/healthcare relationship, the economic obligations stemming from that contract and the necessary communications that give the contract its substance are formalised. Execution of a specialist healthcare contract involving the interested party legitimises treatment of your data. This is performed in compliance with article 9.2 h) of the General Data Protection Regulation (GDPR). Your personal data shall not be transferred unless it is necessary for matters of legal obligation, when your consent to do so has been provided or in order to protect your vital interests. You have access, rectification, cancellation, opposition, transfer and limitation rights that you may exercise at our offices or by e-mail: lopd@institutobernabeu.com. Additional information on the treatment of your personal data can be accessed under the Privacy Policies/Patients section on our website: www.institutobernabeu.com

This Contract, including the annexes and all matters related thereto, shall be governed by and shall be construed in accordance with Spanish law. For any action or proceeding derived from or in relation to this assignment, the parties, expressly waiving any other jurisdiction that may correspond to them, submit to the jurisdiction of the courts of the state of the clinic in which the treatment was pursued.

According to the Spanish law 14/2006 of May 26, the donation is anonymous, voluntary, informed and unpaid.



SPAIN

Alicante

Madrid

Mallorca

Cartagena

Albacete

Elche

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ITALY

Venice

+34 965 50 40 00

www.institutobernabeu.com