

# CREA. Medicina de la Reproducción S.L Services and Features

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Collaboration agreement  
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## CREA: experience, technology, quality and results

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CREA is a pioneering Spanish Fertility Center, with more than 25 years of experience in Reproductive Medicine. We offer a wide range of treatments for patients seeking parenthood, and we are reference in Andrology and Reproductive Genetics.

Our laboratories work with state-of-the-art technology, and we are known for implementing novel strategies under a steady quality management system.

Our Quality Management System follows the ISO9001 and UNE179007 standards and ensures that all procedures are carried out in a meticulous, safe and organized manner. We undergo regular external audits to guarantee that these standards are maintained over the years. Moreover, we voluntarily submit our IVF success rate to specific and independent inspectors to show to our patients that we work with total honesty and transparency.

We hold a high rate of success in IVF, with remarkable high pregnancy rates following a single embryo transfer policy.

## Our International department

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*We want our patients to feel right at home*

CREA has a tailor-made international department set up specially to take care of our visitors from abroad. Our mission is to forge a direct link between the patient's medical team in their home country, and the one in CREA. This allows for a smooth flow of information and lets the team deal with any unforeseen issues in good time.

CREA's International department looks after foreign patients who come to our clinic from many different countries. The department offers the utmost customized attention to patients to provide them with high quality assistance.

CREA's International department helps to ease out the process, as patients doubts, and queries are handled efficiently from their very first contact with us. Patients are in contact with our International Department's staff by email, phone or any online platforms such as Skype or Zoom. We keep this communication flow from the very first contact up until the very end of the treatment.

In addition to medical support during the treatment, our international department helps our patients with other needs during their staying in Valencia: airport transfer, hotels, city tour, restaurants, etc.

## Steps to start your IVF treatment in CREA

We know that the first appointment with fertility professionals is sometimes challenging for some couples. To relieve this possible anxiety, our patients follow a first appointment with CREA's international department, which aims for a first contact with us and to bring into line every particular case of infertility.

With this first contact we aim to ensure that the first appointment with one of our consultants will be fruitful, and it will develop in the most efficient way.

### First contact appointment (International department)

During the first contact appointment with the international department, patients will be informed about how to undergo a fertility treatment with us in CREA.

We offer fertility treatments to fulfill family projects for single mothers, lesbian and heterosexual couples.

Following an initial interview about patient's fertility status, the international department will inform about the tests and analysis that are required to undergo a first fertility consultation with one of our doctors. Our international department will also provide patients with some practical information about logistics and communication to coordinate the process between Sweden and Spain.

Some of the initial analysis we need for a first consultation:

- Female hormonal profile<sup>1</sup>.
- Genetic karyotype (female and male partners)<sup>1,2</sup>.
- Sperm analysis in CREA<sup>3</sup>.
- Other fertility analysis.

*Physical features will be registered in patients opting for egg or sperm donation.*

1. Exams such as hormonal blood tests and genetic karyotype can be performed in the country of origin. Anyway, we also offer the possibility to perform these tests in our clinic. To note, hormonal blood tests have one year of validity.
2. We request a blood karyotype in all our patients, as it is known that infertile patients present a higher risk of chromosomal abnormalities.
3. We would like to remark that in CREA it is essential to evaluate exhaustively both, female and male partners. In this line, a sperm analysis with us is always requested to the male partners.

### First consultation

We understand that travelling to us can be complex. However, we recommend to our patients to visit our clinic for a first fertility consultation. Thereafter, treatment preparation and further follow-ups can always be performed online.

During the first appointment our consultants will elaborate a complete review on patient's clinical history. They will evaluate blood analysis results, including hormonal profiles and genetic karyotypes, which will be requested in advance in the first contact appointment with our International Department.

## *In situ exams*

### 1. Female patients

In terms of *in situ* exams, female patients will undergo a transvaginal ultrasound to examine the status of the ovaries and the uterus. This evaluation will contribute to the fertility diagnosis with some valuable information:

- Ovarian size
- Ovarian reserve (antral follicles count)
- Uterine morphology

Depending on the medical history of the patient, doctors can request other analysis:

- Thrombophilia (mutation screening in blood coagulation factors)
- Repeated implantation failure and recurrent miscarriage: complementary tests

### 2. Male patients

A sperm analysis performed in our andrology laboratory is always requested to patients consulting in CREA.

Instructions for sperm sample collection will be provided in advance. The international department will coordinate the sperm analysis procedure between the patients and our andrology lab, to ensure the results are ready at the time of consultation.

A specialized andrologist from our Andrology department will evaluate the sperm analysis results and will indicate whether an andrology consultation or additional sperm tests are needed.

Sperm freezing could also be recommended. Patients visiting CREA from foreign countries are asked to freeze one sperm sample, which can be used to perform both: sperm analysis and freezing at a time. This anticipated step allows patients to save time and to reduce travel costs once the treatment is initiated.

### 3. Both partners

During the first consultation patients will be also informed about the possibility to perform a Genetic Matching. **Genetic Matching** is aimed for screening recessive genetic mutations in **healthy couples seeking to have a child**, also by natural means. Genetic Matching is also offered to patients using donor eggs or sperm, as all CREA's donors undergo this screening for recessive inherited severe diseases. *(We provide detailed information about genetic matching above).*

In CREA we do not hold any waiting list for any treatment. So, after the first consultation, and once the diagnosis phase and additional studies are fulfilled, the treatment could be scheduled. Then, patients will be provided with full information on treatment prices and informed consent forms to sign.

## Comments on "Steps to start your IVF treatment in CREA"

- STDs results are required to initiate a fertility treatment.
- Any treatment will be initiated only after the required informed consent forms are signed and sent, and the down payment for treatment has been done.

## Featured patient assistance in CREA

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*We are a multidisciplinary team*

CREA has a multidisciplinary team, formed by fertility consultants, surgeons, geneticists, clinical embryologists and psychologists. We always evaluate our patient's fertility profiles as a team. We believe in this strategy, as it enhances diagnostic certainty and offers the patients a broader interpretation of their fertility problems.

### ANDROLOGY DEPARTMENT

In most fertility centers the study of male partner for fertility diagnosis is eventually limited to a basic semen analysis. In consequence, any potential risk associated with male infertility is likely to be overlooked. However, it is important to remark that male infertility has been associated with several comorbid conditions, such as genetic disorders, cancer, diabetes and cardiovascular disease. These observations reveal the importance of performing comprehensive andrological exams to patients planning to enroll in an IVF program.

In CREA, our Andrology Department offers to our patients a comprehensive andrology evaluation with the aim to reduce any risk related to patient health, his future offspring and IVF treatment success.

#### *Male factors related to infertility*

- Low sperm quality (low sperm count, motility or morphology)
- Azoospermia (absence of sperm)
- Varicocele
- Pregnancy post-vasectomy
- Idiopathic male infertility: recurrent IVF failures or repeated miscarriages.
- Carriers of a genetic disorder  
(Ex. Y-chromosome microdeletions, *vas deferens* absence due to Cystic fibrosis mutations)
- Altered sperm DNA fragmentation
- Sperm aneuploidy (abnormal number of chromosomes in sperm)

## REPRODUCTIVE GENETICS: COUNSELLING AND DIAGNOSTIC TECHNOLOGY

We believe that Genetics is one of the most relevant aspects to investigate in infertile couples. Numerous genetic risk factors or other conditions such as advanced maternal age, have been associated with recurrent IVF failures, repeated miscarriages and higher risks of aneuploidy in newborn babies.

**Pre-implantation genetic test (PGT)** combined with IVF technology is a treatment option for couples showing **genetic risk factors** or **known genetic disease**. PGT is aimed to prevent the transmission of inherited severe diseases to the offspring.

### *Genetic risk factors related to infertility*

- Altered Karyotype
- Sperm chromosomal alterations (testicular failure)
- Advanced maternal age
- Recurrent IVF failures
- Repeated miscarriages

PGT methods:

1. **PGT-A for Embryo aneuploidy**, which involves a complete genetic screening to identify and discard embryos with an altered number of chromosomes (aneuploidy). Aneuploidy can lead to: embryo arrest, implantation failure, repeated miscarriage and genetic diseases such as: Down syndrome, Turner syndrome, Edwards syndrome, etc.
2. **PGT-SR for structural chromosomal abnormalities**, which involves a genetic screening to identify and discard embryos with an unbalanced chromosomal rearrangement. Structural chromosomal abnormalities can lead to aneuploidy or repeated miscarriages.
3. **PGT-M for known inherited severe disease**, which involves direct targeting towards a specific mutation causing a known genetic disorder. Some examples of common inherited diseases are: Cystic Fibrosis, Neurofibromatosis or Muscular dystrophies.

*Patients aiming for PGT will be further informed in detail by a consultant when necessary.*

### *Genetic counselling and Family project*

All our patients are offered with the possibility to undergo a **Genetic Matching**. We know that genetic disorders cannot be cured, but they can be prevented. Advances in Genetics now allow to detect the risk of inheritance of genetic diseases, also in healthy carriers.

**Genetic Matching** is aimed for screening recessive genetic mutations in **healthy couples seeking to have a child**, also by natural means. When both partners carry the same mutation, they have 25 % chance of having a child affected by the genetic disease. Patients showing high risk of transmission of a specific severe genetic disease are offered with personal genetic counseling and with PGT-M treatment.

In CREA, **Genetic Matching** is also used during **donor selection process**. Hence, our donor-patient match is not only based on physical features, but also in genetic compatible backgrounds.

We offer the genetic package *Pre-Conception FOCUS* designed by our partner laboratory of genetics Sistemas Genómicos ([www.sistemasgenomicos.com](http://www.sistemasgenomicos.com)). *Pre-Conception FOCUS* is aimed to establish a carrier status in 363 inherited severe diseases, by analyzing 299 genes and 7.400 different mutations using the cutting-edge technology: directed massive sequencing.



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## SINGLE EMBRYO TRANSFER POLICY

In CREA, we care about our patients with honesty. We work following a risk management directive, which aims to reduce health risks for patients and their offspring. On this basis, we initiated **our single embryo transfer program** already in 2010 despite the Spanish law allowance, which permits transferring a maximum of three embryos per transfer.

Scientific community is aware that multiple pregnancies are associated with numerous health risk to mother and children. However, in Spain, twin and triplet iatrogenic pregnancy rate remains 16,6%. (Data Source: Spanish Society of Fertility (2017) [www.sefertilidad.com](http://www.sefertilidad.com) ).

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### *SINGLE EMBRYO TRANSFER POLICY REPRESENTS TEAM COMMITMENT & QUALITY*

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We believe that implementing a Single Embryo Transfer policy reflects our societal health compromise and self-demand beyond our legislation allowance. Moreover, we believe that, working under a Single Embryo Transfer program reflects the trust that a fertility center has in its team and laboratories.

#### *Our embryology lab is fully equipped for a SET policy*

To implement a successful SET policy, the embryology lab must guarantee a successful extended embryo culture system and an effective embryo vitrification program. Embryo culture *in vitro* can be extended up to 5/6 days of development, when the best embryos reach a stage known as blastocyst. Embryos at their blastocyst stage have a higher implantation potential, which allow to transfer fewer embryos and, subsequently, to reduce the probability of multiple pregnancies.

- **Blastocyst culture.** CREA's embryology laboratory is equipped to undertake embryo culture up to blastocyst stage (5/6 days of development). We extend embryo culture up to blastocyst culture in all our cases, irrespective of the initial total number of embryos.
- **Low oxygen tension.** We use cutting-edge benchtop incubators and perform embryo culture in a low oxygen atmosphere. These culture conditions reduce hampering oxidative stress for embryos and improves embryo development rates up to blastocyst stage.
- **Time-lapse.** We monitor embryo development using Time-lapse technology, which offers an accurate embryo evaluation and selection.
- **Vitrification.** We have a successful embryo vitrification program since 2005, which was awarded already in 2007 in the IV Meeting of the Spanish Society of Reproductive Biology (ASEBIR). Our vitrification program guarantees embryo viability, with survival rates > 98 % after embryo thawing.

## Our Success rates

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*Our results are verified by an independent audit (SGS)*

Choosing a fertility center is a difficult task for patients seeking for IVF treatment. Among different aspects, such as team experience, location or financial details, the pregnancy success rate reported by the fertility center is a crucial fact to decide who to trust their family project.

The pregnancy success rate aims to inform the patients about their chances to get a pregnancy. However, and rather than be shown as a simple outcome, pregnancy success rate has itself several readings.

### How to read IVF results

CREA believes in transparency, and cares about a doctor-patient relationship built on trust. For this reason, we openly share our pregnancy success rates, which are verified data by an external and independent audit.

Our data is shown as **cumulative clinical pregnancy rate per treatment**, which helps our patients to estimate the effort to achieve an ongoing pregnancy after initiating one single IVF treatment.

This outcome informs about the **chance to get pregnant** following either IVF, ICSI or oocyte donation, and includes pregnancy chances following any embryo transfer performed with embryos produced in the same treatment.

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*IT IS IMPORTANT TO DISCERN BETWEEN "PREGNANCY RATE" AND "CLINICAL PREGNANCY RATE"*

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While *pregnancy rate* implies a positive pregnancy test (determined by urine or blood analysis at 4<sup>th</sup> week of pregnancy), the **clinical pregnancy rate** informs about an **ongoing pregnancy** (confirmed by an ultrasound around the 7<sup>th</sup> week of pregnancy).

Surely patients wonder why the results indicated as **clinical pregnancy rate** are lower than pregnancy rate data. This is due to a common misinterpretation of pregnancy rate values, which wrongly count number of biochemical pregnancies or early miscarriages as positive pregnancies. In this way, pregnancy rate returns inflate results.

**Clinical pregnancy rate** is therefore, the more faithful approach to echo prospective live birth outcomes.

### Laboratory certification and Data verification

Quality and safety are the two fundamentals in CREA's mission statement. In this line, CREA has shown its compromise along the years, being one of the first clinics in Spain to undergo the prestigious international audit by **Oozoa Biomedical Inc.** (2007). Moreover, we are one of the first fertility centers in Spain to obtain the quality certification **ISO 9001** (2008), and one of the first five embryology laboratories to implement the specific Spanish standard **UNE 179007** (2015).

However, our challenge goes further, and we recently **verified five-years period results**, to show confidently to our patients that we believe in our team experience and the quality of our laboratories.



We will like to remark the difference between a laboratory certification and data verification. Laboratory certifications, such as ISO9001 and UNE179007, indicate whether an IVF laboratory is allowed to performed medical assistance for infertility treatments following specific standards. **Data verification** audits evaluate the results shown by a fertility center to the public and verify that these data are real and not manipulated.

## Our Results

We show five-years period results, described as cumulative clinical pregnancy rate per treatment. Only data from single embryo transfer (SET) were included. Our results are verified by an independent audit (SGS)

### WE FOLLOW A SET POLICY IN > 85 % OF OUR PATIENTS



*More than 70% of our patients achieve a pregnancy with only one attempt*

Cumulative clinical pregnancy rate following SET (all ages)

IVF / ICSI (own oocytes)

73,24 %

Egg Donation

77,02 %



### WE CARE ABOUT OUR PATIENTS WITH HONESTY. PREGNANCY SUCCESS RATE DEPENDS ON MATERNAL AGE.

Cumulative clinical pregnancy rate  
(ranged by age in IVF/ICSI following SET with own oocytes)

< 35

89, 23 %

35-39

66, 33 %

>39 \*

40,85 %

*\*PGT-A can improve IVF outcomes in patients of advanced maternal age.*

## Price list

### Consultations

|                           |       |
|---------------------------|-------|
| First contact appointment | *     |
| First consultation        | 110 € |

|                         |      |
|-------------------------|------|
| Follow-up consultations | 60 € |
|-------------------------|------|

|                      |       |
|----------------------|-------|
| Gynaecology revision | 150 € |
|----------------------|-------|

### IVF Treatments

|  |       |
|--|-------|
| IUI (Artificial Insemination with husband sperm) | 790 € |
|--|-------|

|  |        |
|--|--------|
| AID (Artificial Insemination with donor sperm) | 1160 € |
|--|--------|

|          |        |
|----------|--------|
| IVF/ICSI | 4905 € |
|----------|--------|

|              |        |
|--------------|--------|
| Egg Donation | 7320 € |
|--------------|--------|

### Includes:

*Free of charge*

Including consultation with Doctor and evaluation of previous analyses by gynaecologist and andrologist. Including assistance by International Department by conference call, phone call, e-mail and whatsapp from the very first contact until the very last step of treatment.

These can be by conference call and they will be charged only if are previous to treatment (to diagnose and evaluate results or to give treatment)

- Gynaecology examination and breast examination
- Transvaginal ultrasound scan
- Smear-test
- Results evaluation in a 2nd consultation (online)

- Treatment response monitoring and stimulation guidelines
- Hormone testing (E2 and P4) control during treatment cycle
- Sperm capacitation
- Insemination

- Treatment response monitoring and stimulation guidelines
- Hormone testing (E2 and P4) control during treatment cycle
- Donor sperm dose
- Sperm capacitation
- Insemination

- Treatment response monitoring and stimulation guidelines
- Hormone testing (E2 and P4) control during treatment cycle
- Follicle aspiration under sedation
- IVF/ICSI procedure
- Sperm analysis (day of oocytes insemination)
- Medium stay room on the day of follicle aspiration
- Embryo culture until blastocyst stage
- Time-lapse
- Embryo transfer
- Medium stay room on the day of embryo transfer
- Luteal phase hormone testings (P4, E2)
- Beta-hCG test
- Consultation after pregnancy test's result
- First early pregnancy scan (weeks 5-7 of gestation)

#### Egg donor

- Treatment response monitoring and stimulation guidelines
- Hormone testing (E2 and P4) control during treatment cycle
- Follicle aspiration under sedation
- Medium stay room for the egg donor

- IVF/ICSI procedure
- Sperm analysis (day of oocytes insemination)
- Embryo culture until blastocyst stage
- Time-lapse
- Embryo transfer
- Medium stay room on the day of embryo transfer
- Luteal phase hormone testing (P4, E2)
- Beta-hCG test
- Consultation after pregnancy test's result
- First early pregnancy scan (weeks 5-7 of gestation)

#### Recipient

- Treatment response monitoring and endometrium preparation.
- Hormone testing (E2 and P4) control during treatment cycle

*\*The price is not including donor's medication*



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|   |                |   |
|---|----------------|---|
| <b>Embryo vitrification</b>                         | <b>1000 €</b>  | <ul style="list-style-type: none"> <li>Embryo culture to blastocyst stage (day 5) and embryos maintenance for current year plus 1 following year.</li> <li>Should a second additional vitrification be necessary on day 6 of development, the price is 310 €.</li> </ul>  |
| <b>Frozen embryo transfer</b>                       | <b>1640 €</b>  | <ul style="list-style-type: none"> <li>Treatment response monitoring and endometrium preparation.</li> <li>Hormone testings (E2 and P4) control during treatment cycle</li> <li>Embryo thawing</li> <li>Embryo transfer</li> <li>Medium stay room on the day of embryo transfer</li> <li>Luteal phase hormone testings (P4, E2)</li> <li>Beta-hCG test</li> <li>Consultation after pregnancy test's result</li> <li>First early pregnancy scan (weeks 5-7 of gestation)</li> </ul>  |
| <b>Fertility preservation</b>                       | <b>2500 €</b>  | <ul style="list-style-type: none"> <li>Treatment response monitoring and stimulation guidelines</li> <li>Hormone testing (E2 and P4) control during treatment cycle</li> <li>Follicle aspiration under sedation</li> <li>Medium stay room on the day of follicle aspiration</li> <li>Oocyte vitrification</li> <li>Oocytes maintenance for current year <u>plus four additional years</u>.</li> </ul>   |
| <b>ICSI after fertility preservation</b>            | <b>3685 €</b>  | <ul style="list-style-type: none"> <li>Treatment response monitoring and endometrium preparation.</li> <li>Hormone testing (E2 and P4) control during treatment cycle</li> <li>Oocytes thawing</li> <li>ICSI procedure</li> <li>Embryo transfer</li> <li>Medium stay room on the day of the transfer</li> <li>Luteal phase hormone testings (P4, E2)</li> <li>Beta-hCG test</li> <li>Consultation after pregnancy test's result</li> <li>First early pregnancy scan (weeks 5-7 of gestation)</li> </ul>   |
| <b>R.O.P.A. (Reception of Oocytes from Partner)</b> | <b>5790 €</b>  | <ul style="list-style-type: none"> <li>Treatment response monitoring and stimulation guidelines (both patients)</li> <li>Hormone testing (E2 and P4) control during treatment cycle</li> <li>Follicle aspiration under sedation</li> <li>ICSI procedure</li> <li>Donor sperm dose</li> <li>Medium stay room on the day of follicle aspiration and embryo transfer</li> <li>Embryo transfer</li> <li>Luteal phase hormone testings (P4, E2)</li> <li>Beta-hCG test</li> <li>Consultation after pregnancy test's result</li> <li>First early pregnancy scan (weeks 5-7 of gestation)</li> </ul> |
| <b>Additional procedures</b>                        |                |   |
| <b>Frozen embryo annual maintenance</b>             | <b>660 €</b>   | <ul style="list-style-type: none"> <li>Individual positions per patient.</li> <li>High technology containers, with parameters monitoring 24h, 365 days per year and connected to alarms directed to our staff.</li> </ul>   |
| <b>Assisted Hatching</b>                            | <b>200 €</b>   |   |
| <b>Time-Lapse</b>                                   | <b>500 € *</b> | *At CREA we include it to patients under this agreement for free  |

## Andrology

|  |        |
|--|--------|
| Sperm analysis                                 | 105 €  |
| Sperm freezing and maintenance                 | 180 €  |
| TESA   | 1925 € |
| Advanced sperm selection (MACS, Microfluidics) | 400 €  |

- Computer-assisted sperm analysis. It includes parameters of pre-diagnosis of chromosome alterations (ASHA), strict morphology evaluation according to Kruger's criteria.
- Result's evaluation by clinical andrologist.
- Sperm maintenance of current year included. 300 Euros maintenance per year for following years.
- Surgery and hospital fees
- Analysis of meiosis of the sample
- Anatomical pathology
- Freezing of testicular sperm

## Genetics

|   |        |
|---|--------|
| Karyotype   | 65 €   |
| PGT-A<br><i>(Pre-implantation genetic test for aneuploidies)</i>              | 1630 € |
| PGT-SR<br><i>(Pre-implantation genetic test for structural abnormalities)</i> | *      |
| PGT-M<br><i>(Pre-implantation genetic test for known inherited disease)</i>   | *      |
| Genetic Matching (FOCUS)  |        |
| Both partners   | 1000 € |
| Double donation   | 1000 € |
| Female partner + sperm donor  | 700 €  |
| Male partner + egg donor  | 800 €  |

- Analysis up to 3 embryos
- Prices to be consulted according to the pathology
- Prices to be consulted according to the pathology
- Promo pricing until December 2020 (800 €)
- Promo pricing until December 2020 (500 €)
- Promo pricing until December 2020 (350 €)
- Promo pricing until December 2020 (400 €)

### Comments on Price List

*The fees for embryos vitrification, additional embryos vitrification, frozen embryos maintenance, etc. will be charged only if there will be one or more embryo(s) of good quality to freeze, among the ones not selected for embryos transfer. Vitrification of exceeding embryo will depend on the quality of the embryos, thus it's not possible to guarantee that any embryo will be frozen.*