Puerto Rico Fertility Center

General Information of the In-Vitro Fertilization Program

Dr. Pedro J. Beauchamp

FIRST TEST-TUBE BABY IN PUERTO RICO Dr. Pedro Beauchamp with Adlin Román in his arms.
introduction

The very first baby that resulted from the fertilization of an egg outside of the mother’s body was born in England in 1978. Since then, the treatment of infertility by in vitro fertilization (IVF) has become common practice. Large IVF centers have been established in England, Europe, Australia and the United States. The experience gained in all these centers has been rapidly shared with the rest of the medical community; making IVF an international effort and collaboration rarely seen in the history of medicine. Worldwide, more than 750,000 babies conceived by this method have been born. According to 2012 statistics (www.cdc.gov/art), 176,275 women underwent this treatment that year, and of those, 51,294 (about 30%) became pregnant, giving birth to 65,179 babies. One out of every hundred babies born in the United States is now fertilized in a petri dish. In the United States there are more than 456 clinics offering in vitro fertilization treatment. Our in vitro fertilization program was inaugurated in July of 1985; it was the 35th to be implemented in the United States, and the first in Puerto Rico and the Caribbean. The first patients were treated in September, 1985, and the first pregnancy in our program occurred in the second patient undergoing our treatment.

particulars of in vitro fertilization treatment

During a menstrual cycle, the ovary develops an egg to maturity. At the right time in the cycle, this egg is expelled from the ovary (ovulation) into the fallopian tube. Millions of sperm enter the vagina, but only five to ten thousand manage to ascend to the distal, or farthest, portion of the tubes where the sperm and the egg meet and fertilization occurs. The fertilized egg stays in the fallopian tube three days, dividing and developing into an embryo. After the third day, the embryo enters the uterine cavity (the womb), where it floats for another three days. In human beings, the embryo is implanted in the inner layer of the uterus six days after ovulation.

The IVF technique basically substitutes the function of the fallopian tube in the laboratory. The events that normally occur in the fallopian tubes (egg fertilization and early embryo development) are performed at the laboratory because they cannot occur successfully in the woman’s tube. We bypass the normal process of reproduction so that the egg goes from the ovary to the in vitro lab instead of going into the fallopian tube. Once the egg has been fertilized (in three to five days) the embryo is placed in the uterus.
IVF Procedure

- Insemination
- Incubation
- Egg Aspiration
- Embryo Transfer
which patients are candidates for this treatment?

In vitro fertilization is a widely-accepted treatment and is indicated to treat infertility in the following cases:

A. Irreversible conditions of the fallopian tubes. These include missing fallopian tubes due to surgery, severe tubal injury for which reconstructive surgery is not advisable, and, in those patients who have undergone reconstructive surgery, not becoming pregnant within one year after surgery. Adhesions or significant pelvic scars that affect the anatomy and prevent normal functioning and the collection of the ovum in the fallopian tubes are also indications for IVF.

B. Low sperm count in the male partner. As mentioned above, relatively few sperm reach the fallopian tube to fertilize an egg (5,000 to 10,000 sperm, although more than 50,000,000 enter the vagina). IVF allows us to use a small number of sperm to fertilize an egg because the sperm are placed in direct contact with the egg in a petri dish. For this method, the ideal is to have a total of at least 5,000,000 mobile sperm. In cases where the sperm count is lower than this, there is the option of injecting sperm directly inside the egg using the ICSI (IntraCytoplasmic Sperm Injection) technique, described below. In men with a zero sperm count in the ejaculate (azoospermia) but whose testicles contain sperm, the sperm can be extracted by testicular biopsy (testicular sperm extraction, TESE), and the egg can then be fertilized by the ICSI method.

C. Untreatable cervical factor. Patients with cervical mucus problems who have not responded to the usual medical treatment or to intrauterine insemination are candidates for IVF treatment.

D. Endometriosis. Patients who have not become pregnant after medical or surgical treatment for pelvic endometriosis.

E. Long term, persistent, or unexplained infertility (without an apparent cause), despite standard medical treatment.

Other patients who can benefit from this technique are:

F. Couples with a family history of a genetic disease and those who have already had a child with a chromosomal or genetic anomaly, and who want to avoid giving birth to a baby with this particular condition. These couples are candidates for Preimplantation Genetic Diagnosis (PGD). It is possible to diagnose chromosomal or genetic abnormalities in the embryos before transferring them to the mother. Women whose age predisposes them to chromosomal abnormalities can also benefit from PDG and IVF.

G. Candidates for egg donation. Patients diagnosed with ovarian failure, premature menopause, or dysfunctional eggs can receive donated eggs and become pregnant.

H. Patients with an absent, abnormal or dysfunctional uterus are candidates to have their embryos carried to term by a surrogate mother.
how is the treatment administered?

In vitro fertilization is carried out in five main steps:

1. **Ovarian stimulation.**

   In a natural cycle, the ovary usually produces one mature egg. This is not the optimum number for IVF; more eggs increase the chances of a successful treatment. For this reason, it is necessary to over-stimulate the ovaries to produce three or more mature eggs. The patient is given a course of various fertility medications to stimulate the ovary to produce multiple mature eggs. The medication regimen depends on the specific conditions of each patient, such as her ovulation status, how many ovaries she has and the pretreatment small follicle count, her age, and her hormone levels at the beginning of the menstrual cycle. Most patients receive menopausal gonadotropic hormones (hMG, Menopur or Repronex injections) and/or follicle-stimulating hormone (FSH, Follistim, Gonal-F, Bravelle) for an average of ten (10) days (8-12). The average patient (under 40 years of age, with two ovaries) will produce eleven (11) eggs. Many patients also receive a pituitary agonist (Lupron injections or Synarel inhaler) or a pituitary antagonist (Cetrotide, Antagon). These drugs are given in addition to hMG and FSH, and are started one week before menstruation or on the second day of the menstrual cycle. The purpose of Lupron and Synarel is to shut down (inactivate) the pituitary gland so that the ovary can better respond to hMG and FSH, and to synchronize follicular development and prevent premature ovulation. Today, clomiphene citrate (Serophene or Clomid) is not used as frequently as before in IVF because this drug produces fewer mature eggs.

2. **Monitoring follicular development.**

   The response of the follicles (immature eggs in the ovary) is assessed through **blood tests** (estradiol, FSH, LH, progesterone) and **ultrasound**. The hormone levels in blood indicate whether the follicles are developing properly. The ultrasound examinations tell us the number, size, position, and degree of maturity of the follicles. Monitoring is important to determine when the follicles have reached adequate maturity. When the follicles are **mature**, the patient receives an injection of hCG (Novarel, Pregnyl, Profasi) to induce the ovary to ovulate (that is, expel) these eggs in 36 to 40 hours.
3. Retrieval of eggs from the ovary (IVF-ASP).

One or two hours before ovulation (34 to 35 hours after the hCG injection), the eggs are extracted directly from the ovary. Since the ovaries are normally situated one or two centimeters (half an inch to an inch) behind the vaginal wall, the follicular aspiration method used most often is the ultrasound-guided transvaginal technique. This is an out-patient procedure that takes place in the doctor’s office under intravenous sedation. It takes 15 to 30 minutes. A special needle is inserted through the vagina towards the ovary, guided by vaginal ultrasound. The trajectory and position of the needle is directed towards the follicles using this method of visualization.

![Ultrasound View](image)

Follicles are aspirated one by one. The follicular fluid and the cumulus (the mass of cells containing the microscopic egg) are removed.

In rare cases, when the ovaries are located very high in the pelvis, far from the vaginal wall and not accessible by transvaginal aspiration, follicular aspiration can be done by laparoscopy (a technique that utilizes a flexible fiberoptic instrument passed through a small incision in the abdominal wall). This procedure is done on an out-patient basis at the hospital. It requires general anesthesia or deep sedation, and takes about one hour. In addition, follicular aspiration by laparoscopy allows us to examine the pelvic anatomy and the condition of the pelvis (diagnostic laparoscopy) and to perform GIFT (gamete intrafallopian tube transfer) and ZIFT (zygote intrafallopian tube transfer).
4. **Fertilization of the eggs in the laboratory.**

After the eggs have been obtained from the ovary, the male partner must provide a semen sample. Sperm are prepared to enable them to fertilize eggs. Depending on the maturity of the eggs, they may be inseminated on the same day or the next morning. Usually, fertilization of the egg occurs within the first 18 hours after insemination; by the second day, the egg has already divided in two, four, or more cells [embryo stage].

In some cases it is necessary to inject the sperm directly inside the egg. This technique is called **intra-cytoplasmic sperm injection (ICSi)**. This procedure is done in cases where the sperm count or sperm motility are very low; when the zona pellucida [protein layer around the human egg] is very thick; when a high percentage of egg fertilization is not expected; when there is prior experience of inadequate egg fertilization, and in cases of infertility without apparent cause. Once the eggs are obtained at the laboratory, one sperm is injected inside the cytoplasm of the egg through microneedles.

Only completely mature eggs can be injected. Usually, two out of every three injected eggs are fertilized and continue their cell division. The percentage of pregnancies achieved with the method is about 50%, almost the same as for standard laboratory insemination.
5. **Embryo transfer (ET).**

Successfully fertilized and divided embryos are transferred to the mother. This transfer takes place **three to five days** after egg retrieval. It is done at the doctor’s office, and since it is a painless procedure, it requires no anesthesia. It consists of depositing the embryos inside the uterine cavity through the cervix (the neck of the womb or entrance to the uterus) through a very fine catheter (plastic tube). It is not necessary to dilate the cervix. The patient remains in absolute bed rest until she is released one hour after the transfer. The embryos are usually transferred between the third and the fifth day after aspiration. On the third day, the embryos usually have six (6) or more cells; on the fourth day, they are in the morula stage, and on the fifth day they are in the blastocyst stage. If there are three (3) or fewer embryos with good characteristics, they are usually transferred on the third day. If there are more embryos, or if the embryo development is to be assessed through the final stages, the embryos are transferred on the fourth or fifth day. The goal of prolonged incubation is to allow nature to select the embryos with the best potential to produce a pregnancy. The purpose of this later transfer is to maintain or increase the probability of a pregnancy by transferring fewer embryos and reducing the risk of a multiple pregnancy. It is recommended that **two or three blastocysts** be transferred on the fifth day, depending on patient’s age.

**It must be emphasized that not all the eggs obtained are mature enough (66-75%), not all mature eggs become fertilized (66-75%), and not all fertilized eggs (embryos) reach blastocyst stage. One of every four (25-33%) fertilized eggs has the genetic potential to reach the blastocyst stage and produce a pregnancy.**

Before transfer, the embryos (except blastocysts) undergo a procedure to reduce the thickness of the zona pellucida (the protein layer around the embryo). This procedure **(Assisted Zona Hatching, AZH)** entails making an opening in this zone to help the embryo come out of this surrounding layer, thereby increasing its probability of implantation in the uterus.

After the follicles are aspirated and the embryos transferred, hormone treatment with **progesterone** (progesterone in oil, Prometrium, Crinone, Endometrin) is initiated, usually, to prepare the endometrium (inner layer of the uterus) to receive the embryos and facilitate implantation.

![Pronucleus, day 1](image1)

![Two-cell embryo, day 2](image2)

![Four-cell embryo, zona hatching, day 3](image3)

![Morula, day 4](image4)

![Blastocyst, day 5](image5)
6. Cryopreservation (embryo freezing).

In many cases the ovaries have had an excellent response to drug stimulation, and many eggs and embryos are obtained. Ideally, the maximum recommended number of embryos is transferred to the uterus, depending on their stage of development and on the conditions of the woman (Table 5). Additional embryos may be frozen and stored for a definite time (up to 5 years) in liquid nitrogen. Only embryos with good characteristics and a high viability potential are frozen. The advantage of freezing embryos is not having to use all the embryos in one treatment cycle, and reducing the risk of multiple pregnancies present when many embryos are transferred. If the patient does not become pregnant during the in vitro treatment cycle, the embryos may be subsequently thawed and transferred to her uterus without the patient having to go through the whole in vitro process again. If the patient becomes pregnant, the embryos can be stored until the couple desires another pregnancy. The couple can also donate their eggs or embryos to an infertile couple to facilitate a pregnancy.

**what are the chances of success?**

The chances of success of in vitro fertilization depend on many factors. According to 2009 statistics reported to the Centers for Disease Control (CDC) by the 441 in vitro fertilization clinics in the United States and published in the Assisted Reproductive Technology National Summary, 31% (45,870) of the patients undergoing IVF became pregnant. These global figures include all IVF clinics and do not specify the patients’ age or the presence of male infertility issues. We know that the percentage of pregnancies in patients over 34 years of age progressively decreases compared to that in younger women. Men with decreased sperm counts and/or motility also have less success than those whose tests are normal. The effect of older age and low sperm count is additive. Today, thanks to technological advances, clinics with ample experience such as ours have achieved an average pregnancy rate of more than 50% per attempt at IVF (Tables 1, 3, and 4). Please refer to [www.cdc.gov/art](http://www.cdc.gov/art) for more information.

In the vast majority of patients (98.5% or more), one or more eggs can be obtained from the ovaries. In patients with a decreased ovarian response, it may be necessary to postpone treatment until the next cycle (12.5% of cases). Most mature eggs (75%) are fertilized and become embryos. An average of 25-33% of embryos becomes blastocysts. The probability of pregnancy depends partly on the number of embryos transferred to the woman. Therefore, it is best to transfer more embryos in order to achieve a higher percentage of pregnancies. However, the more embryos transferred each time, the higher the chance of a multiple pregnancy (Tables 3 and 4). The probability of congenital abnormalities in babies produced with this technique is not higher than in the general population. The overall incidence of miscarriage is 18%, and increases with the patient’s age (under 34 years = 12%, at age 40 = 28%, and it reaches 60% at the age of 43).
Puerto Rico Fertility Center
Dr. Pedro J. Beauchamp / In-Vitro Fertilization Program

Table 1 General Statistics by Age (PRFC 2007-2013)

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Pregnancy Rate</th>
<th>Live Birth Rate</th>
</tr>
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<tbody>
<tr>
<td>&lt; 35</td>
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<tr>
<td>35-37</td>
<td>54</td>
<td>56</td>
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<tr>
<td>38-40</td>
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<td>41-42</td>
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<tr>
<td>≥43</td>
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Table 2 Pregnancy and Live Birth Rates for ART Cycles Using Fresh, Nondonor Eggs or Embryos, by Age of Woman, 2009

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Pregnancy Rate</th>
<th>Live Birth Rate</th>
<th>PRFC [2007-13]</th>
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<tr>
<td>&lt; 35</td>
<td>68</td>
<td>54</td>
<td>8</td>
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<tr>
<td>35-37</td>
<td>56</td>
<td>39</td>
<td>16</td>
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<tr>
<td>38-40</td>
<td>39</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>41-42</td>
<td>27</td>
<td>27</td>
<td>8</td>
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<tr>
<td>≥43</td>
<td>16</td>
<td>16</td>
<td>8</td>
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Table 3 Puerto Rico Fertility Center IVF Results Age <35

<table>
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<tr>
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<tr>
<td>Percent</td>
<td>42</td>
<td>48</td>
<td>54</td>
<td>62</td>
<td>72</td>
<td>70</td>
<td>65</td>
<td>55</td>
<td>67</td>
<td>78</td>
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<tr>
<td>Live Birth Rate</td>
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<td>40</td>
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<td>66</td>
<td>54</td>
<td>66</td>
<td>65</td>
<td>63</td>
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Table 4 Pregnancy Outcomes 2007-13 Age < 40 Day 4-5 Transfer Morulas and Blastocysts

<table>
<thead>
<tr>
<th>Number Morula &amp; Blastocysts Embryos Transferred</th>
<th>Number Patients</th>
<th>Number Pregnancies (%)</th>
<th>Pregnancies</th>
<th>Number(%) Multiple Pregnancies</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (single)</td>
<td>2 (twin)</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>21 (46%)</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>358</td>
<td>248 (69%)</td>
<td>174</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>63 (63%)</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>Totals</td>
<td>504</td>
<td>332 (66%)</td>
<td>227</td>
<td>92</td>
</tr>
</tbody>
</table>

227 Singles (68%), 92 Twins (28%), 13 Triplets (4%), 0 Quads
Table 5  American Society of Reproductive Medicine
Recommended limit for Embryo Transfer
Guidelines 2013

<table>
<thead>
<tr>
<th>Day ET</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
</tr>
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<tbody>
<tr>
<td>2-3</td>
<td>2*</td>
<td>3*</td>
<td>4*</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>[2-8 cells]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>2*</td>
<td>2</td>
<td>3*</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>[Morula-Blastocyst]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Favorable Prognosis: consider transfer one less embryo
(First IVF, Previous pregnancy, Good embryo quality, Excess available for freezing)

Table 6  2010 National Statistics Pregnancy Rate Woman Age >40

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Pregnancy Rates (%)</th>
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<tbody>
<tr>
<td>40</td>
<td>26.7</td>
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<tr>
<td>41</td>
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<td>42</td>
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<tr>
<td>&gt;44</td>
<td>3.5</td>
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<td></td>
<td>3.2</td>
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<td>1.0</td>
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Pregnancy
Live birth
summary of the treatment

history of our in vitro fertilization program

9/85  First in vitro fertilization (IVF) in Puerto Rico *
5/86  First birth from IVF in Puerto Rico, the Caribbean, and Central America *
6/86  First GIFT birth *
5/87  First ambulatory transvaginal follicular aspiration *
8/88  First birth from combined IVF and GIFT *
3/90  First birth of twins from IVF *
10/92 First birth from IVF in the Lesser Antilles *
4/93  First triplets born from IVF
6/93  First birth from egg donation *
1/97  First quadruplets born from IVF
3/97  First birth from IVF with ICSI
8/97  First birth from frozen embryos
11/97 First birth from IVF with TESE
12/98 First birth in Venezuela from IVF with ICSI conducted in Puerto Rico *
11/01 First birth from IVF with donated frozen embryos *
2003 First and only IVF program in Puerto Rico approved by the Joint Commission *
3/05  First birth from IVF in a surrogate mother *
12/05 First birth from IVF by transmyometral embryo transfer *
10/08 First IVF pregnancy with preimplantation genetic diagnosis (PGD) *
10/13 First triplet pregnancy with cryopreserved embryos *

* First case reported in Puerto Rico
Habla la primera bebé “in vitro”

Al cumplir hoy 17 años Adlin Marie Román rompe el silencio

Marisol niega que corra para un cargo

La insólita historia del asalto al jefe de la Policía

Se gradúa de noveno grado a los 97 años

THE FIRST TEST-TUBE BABY SPEAKS OUT Today, on her 17th birthday, Adlin Marie Román breaks her silence.

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