**PREG Minimal IVF Comparison and Consent**

**Minimal IVF** is an alternative IVF treatment in which less medication and less aggressive ovarian stimulation is performed mimicking a more **“natural”** cycle as well as being a less costly alternative to a **Standard IVF cycle** especially for those patients without insurance coverage.

In a S**tandard IVF cycle**, daily injectable medications **(gonadotropins; Gonal-F, Follistim, Bravelle, Menopur, Repronex)** are used for about 8 to 12 days to aggressively stimulate the ovaries to produce as many mature eggs (follicles) as possible. In addition, a medication called **Lupron** (an injectable daily medication used to suppress the body from ovulating) is given in combination with the gonadotropins to help prevent a spontaneous ovulation. During the stimulation cycle, multiple transvaginal ultrasounds (follicle scans) and blood work (usually 4 to 6 visits) are needed to monitor the growth of the ovaries and their response to the daily medications. Once there are an adequate number of mature follicles (egg sacs), an injection of **hCG (Ovidrel, Novaryl)** is given to finish maturing the eggs and allow for ovulation to occur. Prior to the ovaries releasing the eggs (usually 36 hours after the hCG injection) egg retrieval is performed to aspirate the eggs (done with ultrasound guidance and a needle placed through the back of the vagina into the ovaries) and isolate them in the embryology lab. During the egg retrieval, you will be deeply sedated so as not to feel any discomfort during the procedure. A sperm sample from the partner is then washed and prepared to allow insemination (placing sperm directly with the eggs in a petri dish) in the embryology lab or in some cases **Intracytoplasmic Sperm Injection or ICSI** is performed where the embryologist can pick a normal sperm and inject it directly into the egg to increase chance of fertilization (for fertilization to occur, a sperm must penetrate the outer shell of the egg and enter it). **ICSI** is generally recommended if there are severe sperm abnormalities present or if there is concern for fertilization problems or issues such as in “unexplained infertility” and severe endometriosis cases. In general, only 65-80% of mature eggs will fertilize normally and become embryos even when ICSI is performed for male factor. Once the eggs are fertilized, they will grow in the lab for 3 to 5 days before an embryo transfer (ET) is performed with use of a thin catheter to place the embryo(s) into the uterine cavity through the cervix (like an intrauterine insemination or IUI) under ultrasound guidance to ensure proper placement.

The day of ET **(Day 3 transfer versus Day 5 or blastocyst transfer)** is determined by the number of good quality embryos available. In general, there needs to be at least 4 to 5 good quality embryos available on Day 3 to consider growing the embryos out to Day 5 or blastocyst stage (a highly developed embryo with a high potential for pregnancy success). This also allows us the ability to select the best embryo(s) to transfer to the uterus. In cases where there are only a few embryos available, a Day 3 ET is performed since the uterus is a better incubator than the embryology lab. In general, 2 to 4 embryos are transferred on Day 3 and usually only 2 embryos or blastocysts on Day 5 due to their higher quality. If there exists remaining high quality blastocysts available after the embryo transfer then **freezing or cryopreservation** can be done for future frozen embryo transfer(s) and attempts at pregnancy. In addition, patients will need **progesterone supplementation** often in the form of daily intramuscular injections (IM) for about 2 weeks and an additional 2 to 3 weeks if pregnant.

In a **Minimal IVF cycle**, medications such as **Clomid or Letrozole (Femara)** which are oral medications are taken on cycle days 3 through 7 initially and then several days (3 to 6) of gonadotropins (injections) are then added to help gently stimulate the ovaries to produce several mature eggs (2 to 5 follicles) versus in a **Standard IVF cycle** where often there can be 10 to 15 follicles or more (aggressive ovarian stimulation). Another medication called **Antagon or Cetrotide** may be given to prevent ovulation as well if needed. Usually there will be 2-4 monitoring visits (ultrasounds, bloodwork, urine LH testing) needed to determine timing of hCG injection and egg retrieval as in a Standard IVF cycle.

If only 1 or 2 dominant (mature) follicles develop during Minimal IVF stimulation, it might be necessary to cancel the IVF cycle. In cases where the tube(s) are open or patent, then an intrauterine insemination (IUI) can be performed rather than proceed with the egg retrieval since there would only be 1 or 2 possible eggs retrieved, and fertilization must still occur (at the usual rate of 65-80%) for the eggs to become embryos, resulting in very low numbers of embryos (1 or 2 or possibly none). If the woman has tubal factor (blocked or missing tubes), the cycle probably should be cancelled and a **Standard IVF cycle** be attempted later. Since no medications (Lupron) are given to prevent the natural LH surge (spontaneous ovulation), there exists the possibility that up to 30% of **Minimal IVF cycles** may have a spontaneous LH surge on their own which could result in the early release of the eggs before the retrieval can be performed. This could result in fewer eggs retrieved or even in some cases no eggs obtained since they would have already been ovulated or released. A lighter sedation can also be used for the egg retrieval since there are generally fewer eggs to aspirate. Once the eggs are fertilized, a Day 3 embryo transfer will usually be performed since there is generally lower number of embryos available. Embryo freezing is also less likely to occur since there will be fewer eggs resulting in fewer embryos to work with. In addition, **progesterone vaginal suppositories** are used instead of IM injections for pregnancy support (since **Lupron** is not used for suppression) and can result in less injections and discomfort.

**Advantages of Minimal IVF versus Standard IVF** includes less medications, daily injections and monitoring visits as well as overall costs (see table below). In addition, minimal IVF usually causes less discomfort from enlarged ovaries and significantly less incidence of Ovarian Hyperstimulation Syndrome due to less medication being used.

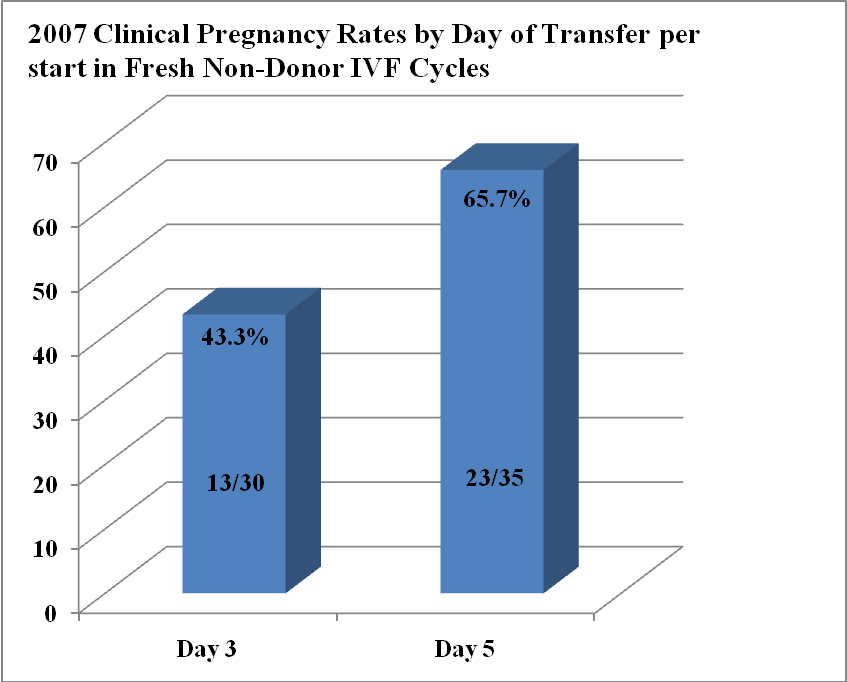
**Disadvantages of Minimal IVF versus Standard IVF** includes higher cycle cancellation rate (25-30%) because of lower ovarian response to less medications (fewer large follicles), increased risk (25-30%) of spontaneous LH surge (ovulation) leading to cycle cancellation or fewer or no eggs successfully retrieved, less eggs available for fertilization, less embryos available for use. Generally a Day 3 embryo transfer will be performed and there is significantly lower possibility of excess embryos to freeze. In addition, Minimal IVF pregnancy rates are usually less than half as successful as Standard IVF pregnancy rates due to these above factors.

**It is very important to realize that not all ovarian “follicles” will contain an egg, that not all eggs are “good” eggs and that not all eggs will fertilize to form embryos. In addition, not all embryos will be “good” embryos and not all “good” embryos will become pregnancies.**

**Previous studies have shown that only 20% to up to 50% of embryos may make it to the blastocyst stage. This will also affect the number of embryos that may be available for freezing (cryopreservation) since we only freeze embryos that have developed to the Full or Expanded blastocyst stage.**

The graph below depicts our Fresh Non-Donor **Standard IVF** clinical pregnancy rates by day of transfer.

(In general, the decision to attempt a day 5 transfer is considered if there are at least four high-grade embryos on day 3, otherwise a day 3 embryo transfer is performed.)



\*The clinical pregnancy rate is the percent of IVF cycles per cycle start resulting in a pregnancy with **fetal cardiac activity** within the uterus at 7 weeks of pregnancy as visualized by ultrasound.

\*\*A comparison of clinic success rates may not be meaningful because patient medical characteristics and treatment approaches may vary from clinic to clinic.

**Treatment Specific Pregnancy Rates:**

* Successful Pregnancy Rates for a “normal, fertile” couple is around 20 to 25% chance per month with timed intercourse. However, pregnancy rates in women decrease with advancing age and miscarriages and risks of abnormal pregnancies (Down’s and Turner’s syndrome) increase with age.
  + Fertility rates are highest in women in their late teens to late twenties (30% chance per month)
  + >35 years of age: 15% chance per month
  + >40 years of age: 5 to 10% chance per month
  + >43 years of age: <5% chance per month
  + Background miscarriage rates for any pregnant couple is around 15 to 20% chance
  + Age 35, miscarriage rate if >25%
  + Age 40, miscarriage rate is >30%
  + Age 45, miscarriage rate is >50%
* Couples who are infertile have less than a 5% chance of pregnancy per month without treatment but this does depend on the infertility factors present (no sperm, blocked tubes or ovarian failure have a zero% chance).
* Most infertility treatments are designed to try and improve the <5% chance per month to closer to the normal rate (20%) if possible (depends on female age and other infertility factors such as ovulation disorders, sperm abnormalities, tubal disease, pelvic adhesions, endometriosis, etc.).
* **These below quoted pregnancy rates are based on female age <35 years old. In women over age 35, these quoted pregnancy rates will be lower, especially in women over age 40 (unless using Donor eggs).**
  + No treatment: <5% chance per month
  + Ovulation induction (Clomid or Femara and hCG injection): 5 to 12% chance per cycle
    - Day 12 mid-cycle follicle scan
  + Ovulation induction and intrauterine inseminations (IUI): 8 to 15% chance per cycle
  + Stimulated Ovulation and IUI (SOIUI; using injectable gonadotropins): 10 to 25% chance per cycle
  + Minimal IVF: 20 to 35% chance per cycle
  + Standard IVF: 40 to 60% chance per cycle
    - Frozen embryo transfer (if had excess available embryos to freeze):
    - 40% chance per transfer cycle
  + Donor Egg IVF: 50-70% chance per cycle
  + PREG IVF Refund Program: Qualifying program with inclusion and exclusion criteria.
    - 3 full Standard IVF cycles with all frozen embryo transfers and if no successful pregnancy then a 90% refund returned (medications are not included in this program)

**NOTE: Costs of all medications and treatments are approximate and subject to change.**

**HOW MANY EMBRYOS TO TRANSFER??**

**Our goal at PREG is to help you have a healthy pregnancy.**

This goal is met by trying to give you the highest pregnancy rate possible with the lowest multiple pregnancy rates possible. The complications associated with multiple pregnancies are the biggest risk associated with IVF. Any pregnancy with more than 1 baby is considered high risk and the greater the number of babies the more the risk. Multiple pregnancies commonly result in premature deliveries. Premature delivery is fraught with potential short-term complications. Short-term problems may include breathing difficulty requiring ventilation, feeding difficulties and increased chance of infection. Long-term complications may include cerebral palsy, vision loss, lung problems and death. In addition, increased complications exist during the pregnancy such as high blood pressure, pregnancy-associated diabetes and early labor and need for confined bed rest with any multiple pregnancy.

In general, multiple pregnancies occur in approximately 30% of all IVF pregnancies with the majority of these being twins. However, there is about a 5 - 8% risk of triplets or higher, depending on the number of embryos transferred back (3 embryos or more). This multiple birth rate holds even true for the older female patient despite usually transferring back more embryos. Although a couple may always choose to transfer less embryos than recommended, a request to transfer more embryos than recommended will generally not be honored unless there exists very special circumstances.

**To maximize pregnancy rates and minimize multiple pregnancies, PREG strictly follows the recommendations of the Society of Assisted Reproduction (SART) for the number of embryos to be transferred.** These are the recommendations for the maximum number of embryos to be transferred in a patient undergoing her first IVF attempt or a patient with a previous successful IVF attempt. If a patient has had several failed attempts at IVF, then these figures may not apply. Note that the older the age of the female, the more embryos transferred back due to the age-associated decrease in pregnancy rates.

**Age** **Maximum # of “good quality” embryos to be transferred**

**< 30 1-2**

**< 35 2-3**

**35-40 2-4**

**> 40 up to 5**

A “good quality” embryo is usually defined by the number of cells (how many cells that have divided) in the embryo and the amount of fragmentation (small pieces or fragments of cells present in the embryo) **or** the extent of development of the embryo into the blastocyst stage. The quality of your embryos will be discussed with you prior to transfer. The recommended number of embryos to be transferred may increase in patients with previously failed attempts at IVF or couples with poor quality embryos, but transferring more than 5 embryos is essentially never done at PREG.

**Day 3 embryo quality grading:**

* Graded from 1 to 5
* Grade 1 and 2 are considered excellent to good quality embryos
* Grade 3 and 4 considered average to fair quality
* Grade 5 considered poor quality

**Blastocyst (Day 5 or 6 embryo) quality grading:**

* An Expanded Blastocyst is consider the most highly developed embryo
* Full blastocysts and early blastocysts are still very high quality embryos
* Morulas are compacting embryos that can continue development to the blastocysts stage by cavitation (forming a blastocoele cavity)
* In general, it is recommended to transfer between 1 to 2 blastocysts (usually 2) depending on the patients’ age, infertility factors and history as well as the development of the blastocyst stage
* **In general, only Full and Expanded blastocysts are cryopreserved (frozen)**

**Normal embryo development:**

The Zygote (fertilized egg) divides to become a two-cell embryo then a four-cell to an eight-cell embryo. Continued cell development and division will lead to a Morula (cells start compacting together) then cavitation begins with formation of blastocoele cavity (now considered an early blastocyst). Further development leads to a Full blastocyst (with formation of Inner Cell Mass or ICM which will eventually become the fetus) then continuing growth to an Expanded Blastocyst (a highly developed embryo). All these events happen usually within the first 5 to 6 days after fertilization of the egg.

The day of embryo transfer (Day 3 versus Day 5 or blastocyst transfer) is generally dependent on the number of embryos formed and their quality. Our embryology laboratory is a good place for embryos to grow (temperature, humidity, pH, culture medias, etc.) but the uterus is by far a much better place. If there appears to be low numbers of embryos available (usually less than 3) for transfer then your embryo transfer will usually be performed on Day 3. In order to have a blastocyst embryo transfer (Day 5) there generally needs to be at least four (4) high quality embryos (see definition of embryo quality above) available on Day 3. This will allow us to be able to choose the best quality embryo(s) for transfer.

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**Previous studies have shown that only 20% to up to 50% of embryos may make it to the blastocyst stage. This will also affect the number of embryos that may be available for freezing (cryopreservation) since we only freeze embryos that have developed to the Full or Expanded blastocyst stage (see above for definitions).**

**RISKS OF IN VITRO FERTILIZATION AND OVARIAN HYPERSTIMULATION SYNDROME**

The medical risks of IVF depend upon each specific step of the procedure. The following are some of the primary risks of IVF procedures.

Ovarian stimulation carries with it a risk of hyperstimulation, where the ovaries become swollen and painful. Fluid may accumulate in the abdominal cavity and chest, and the patient may feel bloated, nauseated, and experience vomiting or lack of appetite. Up to 30% of patients undergoing ovarian stimulation have a mild case of *ovarian hyperstimulation syndrome (OHSS)* that can be managed with over-the-counter painkillers and a reduction in activity. In moderate OHSS, patients develop or accumulate fluid within the abdominal cavity, and gastrointestinal symptoms may occur. These women are monitored closely, but generally do very well with simple outpatient management. The condition tends to resolve without intervention unless pregnancy occurs, in which case recovery may be delayed for several weeks. Up to 2% of patients develop severe OHSS characterized by excessive weight gain, fluid accumulation in the abdomen and chest, electrolyte abnormalities, over-concentration of the blood, and rarely the development of blood clots, kidney failure or death. It may be medically necessary to drain fluid from the abdomen with a needle if breathing becomes difficult. Patients with severe OHSS require hospitalization until the symptoms improve. If pregnancy occurs, OHSS can worsen. Occasionally, termination of pregnancy must be considered in the most severe cases.

Although initial reports suggested that women who use fertility drugs have an increased risk for ovarian cancer, numerous recent studies support the conclusion that fertility drugs are not linked to ovarian cancer. Nevertheless, there is still uncertainty whether a risk exists and research continues to address this question. An annual gynecologic visit is recommended for all women, with examination of the ovaries, regardless of prior use of ovulation medications.

There are risks related to the egg retrieval procedure. Removing eggs through an aspirating needle entails a slight risk of bleeding, infection, and damage to the bowel, bladder, or a blood vessel. This is true whether the physician uses laparoscopy or ultrasound to guide the needle. Less than one patient in 1,000 will require major surgery to repair damage from complications of the egg retrieval procedure. In rare cases, infection may occur from the retrieval or embryo transfer.

The chance of multiple pregnancies is increased in all assisted reproductive technologies when more than one embryo is transferred. Although some would consider twins a happy result, there are many problems associated with multiple births; and problems become progressively more severe and common with triplets and each additional fetus thereafter. Women carrying a multiple pregnancy may need to spend weeks or even months in bed or in the hospital in an attempt to delay premature delivery. The risk of premature delivery in multiple pregnancies is high, and babies may be born too early to survive. Premature babies require prolonged and intensive care and risk lifelong handicaps due to premature birth. Some couples may consider *fetal pregnancy reduction* to decrease the risks due to multiple pregnancy, but this is likely to be a difficult decision. For more information on this topic, refer to the ASRM patient information booklet titled *Multiple Gestation* and the ASRM patient fact sheet, *Complications of Multiple Gestation*. Data also suggest that IVF conceptions, even singletons, have a slightly increased risk of premature delivery or low birth weight.

First trimester bleeding may signal a possible miscarriage or *ectopic pregnancy*. If bleeding or pain (before 13 weeks) occurs, a medical evaluation is needed to determine the cause. Some evidence suggests that early bleeding is more common in women who undergo IVF and is not associated with the same poor prognosis as it is in women who conceive spontaneously.

Miscarriage may occur after IVF, even after ultrasound identifies a pregnancy in the uterus. Miscarriage occurs after ultrasound in nearly 15% of women younger than age 35, in 30% at age 40, and in 35% at age 42 following IVF procedures. In addition, there is approximately a 5% chance of ectopic pregnancy with IVF.

It is not clear whether the risk of birth defects is increased with IVF. Most studies do not show an increased risk, but several studies do show a slight increase risk (2-4% increase). Research is ongoing to determine the magnitude, if any, of this risk. Furthermore, when ICSI is used in cases of severe male factor infertility, a genetic cause of male infertility may be passed on to the offspring.

Assisted reproductive technologies involve a significant physical, financial, and emotional commitment on the part of the couple. Psychological stress is common; and some couples describe the experience as an emotional roller coaster. The treatments are involved and costly. Patients have high expectations, yet failure is common in any given cycle. Couples may feel frustrated, angry, isolated, and resentful. At times, frustration can lead to depression and feelings of low self-esteem, especially in the immediate period following a failed IVF attempt. The support of friends and family members is very important at this time. Couples are encouraged to consider psychological counseling as an additional means of support and stress management. Many programs have a mental health professional on staff to help couples deal with the grief, tension, or anxieties associated with infertility and its treatment.

**Minimal IVF Cycle Consent**

I\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(Wife/Partner) and\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Husband/Partner) in conjunction with our physician and staff at PREG have determined that we are candidates for an IVF treatment cycle and we choose the Minimal IVF cycle stimulation. We are fully aware that we have other possible alternatives available to us including regular or standard IVF using a full stimulation with gonadotropins, other forms of infertility treatments, adoption or choice of no children. We have also read and signed the standard IVF consent forms and understand that NOT all information in the standard IVF consent form will apply in a Minimal IVF cycle.

We give our full consent to participate in a Minimal IVF treatment cycle. We have read all of the above, or it has been read to us. We have been given the opportunity to ask questions about this treatment procedure and all of our questions have been answered to our complete satisfaction. A copy of this consent form has been provided to us.

**NAME OF PATIENT (Please print and sign) DATE**

**NAME OF SPOUSE OR PARTNER (Please print and sign) DATE**

**NAME OF PERSON OBTAINING CONSENT (Please print and sign) DATE**

**NAME OF PHYSICIAN (Please print and sign) DATE**