RESEARCH SUBJECT OVARIAN PLATELET RICH PLASMA INJECTIONS INFORMATION & CONSENT FORM

Title: OVARIAN PLATELET-RICH PLASMA (OPRP) INJECTIONS FOR DIMINISHED OVARIAN RESERVE PATIENTS: A DOUBLE-BLINDED PLACEBO-CONTROLLED TRIAL

(IRB STUDY#: IORG0010499_202301)

Sponsor: Generation Next Fertility, Igenomix

Investigators: Jesse J. Hade MD, Janelle Luk MD, Edward Nejat MD, Alicia Broussard PhD

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Study Approved by GNF IRB Committee
First approved draft 2/13/2023
Approved Revised edits 3/16/2023

Patient Initials: _____

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INTRODUCTION

Patient Initials: _____

Before agreeing to participate in this research study, you must read and understand the following explanation of the proposed research study. This consent document describes the study's purpose, procedures, benefits, risks, discomforts, and precautions. It also describes the alternative procedures and your right to withdraw from the study at any time. No guarantees or assurances can be made as to the results of the study.

If you are not entirely truthful with your study doctor regarding your health history, you may harm yourself by participating in this study.

The study is being conducted for Generation Next Fertility PLLC. Generation Next Fertility employs your study doctor as a physician and a medical staff member.

Generation Next Fertility Institutional Review Board committee (GNF IRB) has approved the information in this consent document and has approved for the study doctor to do the study. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects; this does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

In case of emergency, please call Dr. Jesse J. Hade at (212) 641-0906

This consent form may contain words that you do not understand. Please ask the study doctors or staff to explain any word or information you do not clearly understand. You may take home an unsigned copy of this consent form to consider or discuss with family or friends before deciding.

You have been asked to participate in a research study involving undergoing surgery to inject your own ovarian serum with or without a concentration of platelets before taking hormonal drugs to undergo In-Vitro Fertilization (IVF) and embryo transfer. The following explanations have been provided for your benefit. You must clearly understand this information before initialing each page and signing your name on the final page.

PURPOSE OF THIS RESEARCH

This prospective double-blinded randomized placebo-controlled study aims to determine if In Vitro Fertilization (IVF) outcomes are improved by ovarian platelet-rich plasma injections (oPRP) for women diagnosed with diminished ovarian reserve (DOR). Women with DOR notoriously have the lowest chance of pregnancy and live birth compared to age-matched peers with a normal or robust ovarian reserve.

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IVF was first successfully employed on humans in 1978 during an unstimulated natural cycle. Due to the limited success of natural IVF cycles, gonadotropins were introduced to stimulate the growth and maturation of multiple antral follicles before oocyte retrieval. Over the years, this technique of ovarian stimulation before an oocyte retrieval has helped improve the success of IVF by increasing the number of mature oocytes collected and, ultimately, the chance of pregnancy and live birth. However, this process is expensive, and patients with DOR have little to no improvement in the number of mature oocytes retrieved and overall treatment success. For poor prognosis patients, oPRP is a novel therapeutic option with promising results.

Autologous platelet-rich plasma was introduced as a transfusion product by hematologists in the 1970s and prescribed as a therapeutic treatment for patients suffering from thrombocytopenia. PRP describes plasma with a platelet count above that of peripheral blood. Since its introduction, PRP has transcended its initial application and currently has many uses, including tissue regeneration and wound healing. PRP is utilized in various medical fields, including orthopedics, cardiothoracic surgery, plastic surgery, dermatology, dentistry, and diabetic wound healing.[i],[ii] The benefits of PRP on both ovarian and endometrial rejuvenation have been postulated based on data extrapolated from prior medical research.[iii] It is speculated that patients with diminished ovarian reserve, menopause, premature ovarian failure, and thin endometrial lining may benefit from autologous PRP injections and infusions. However, most of the information demonstrating the benefit of PRP on ovarian reserve and oocyte quality is limited to anecdotal evidence. To date, no large-scale randomized placebo control trial has been conducted to determine the true benefits and efficacy of ovarian PRP injections on patients undergoing in vitro fertilization (IVF) and embryo transfer.

This study is intended to evaluate the benefit of oPRP when compared to a placebo. Ovarian PRP is suspected to improve the antral follicle count (AFC) or number of immature follicles for ovarian stimulation, the number of oocytes retrieved during IVF, and the number of embryos and euploid blastocysts formed following fertilization.

Participants in this study will receive the following compensation:

- Two significantly reduced IVF cycles with intracytoplasmic sperm injection (ICSI) and preimplantation genetic testing for aneuploidy (PGT-A).
- At least one free frozen embryo transfer (FET) cycle when an embryo is available and deemed eligible for transfer.
- Freezing of all additional blastocyst embryos formed and not transferred, with up to 1 year of free storage.
- All additional FET cycles will be included for free, for up to 1 year following the initial ET or 12 months from the date of her oocyte retrieval if an embryo transfer is not performed.

Participants (with insurance if covered) will be responsible for the following:

- All fees and charges associated with embryo storage and embryo transfer (ET) starting one year after the initial ET or oocyte retrieval if no embryo transfer is performed.

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- All fees and charges associated with pregnancy, if it occurs, excluding the first pregnancy test.
- All IVF cycle medication costs and all charges incurred for non-study procedures and treatments including the initial consultation with ultrasound and bloodwork, uterine evaluation with hysteroscopy, and endometrial biopsy.

STUDY DESIGN

A randomized, double-blind, placebo-controlled trial comparing ovarian injection of platelet-rich plasma vs. placebo in women diagnosed with diminished ovarian reserve at-risk for a poor ovarian response (POR) between 35 to 42 years of age. Participants for this study include patients who are planning to undergo IVF with PGT-A followed by a frozen embryo transfer cycle. Only patients with either a euploid embryo or eligible mosaic embryo (following consultation with a geneticist), as determined by PGT-A, will be allowed to proceed with a single blastocyst FET cycle

All patients will have a baseline ultrasound and blood work at the time of menses, approximately one month before starting their initial IVF cycle. Routine monitoring will be required to determine the day of ovulation. Once an lutenizing hormone (LH) surge is detected or if a lead follicle on pelvic ultrasound is deemed significant enough to induce ovulation, a "trigger" shot with 250 mcg/0.5 mL of Ovidrel® (human chorionic gonadotrophin or hCG) will be self-administered subcutaneously (SQ). Based upon the patient's randomization, either oPRP or ovarian Serum (oS) injections will be performed under anesthesia and within 72 hours from the day of ovulation. Following their ovarian injections, all patients will return for monitoring with the onset of menses approximately 14 to 16 days from the date of ovulation.

A medication protocol will be determined at the start of each IVF cycle. Either a natural IVF protocol (nIVF), mild IVF protocol (mIVF), or conventional IVF protocol (cIVF) will be chosen by the treating physician. This determination will be based on findings from the repeat pelvic ultrasound with AFC and blood work for anti-mullerian hormone (AMH), follicle stimulating hormone (FSH), lutenizing hormone (LH), estradiol (E2), progesterone (P4), and beta-human chorionic gonadotrophin (B-hCG). Natural IVF will be considered for patients with only 1-2 antral follicles, mIVF for patients with 2-4 antral follicles observed, and cIVF for patients with four or more antral follicles visualized at the time stimulation started.

Patients will begin their designated protocol and return four to five days following medication start. A repeat pelvic ultrasound will be performed to measure the growth and size of all follicles visualized along with the endometrial thickness. Also, blood work for E2, FSH, LH, and P4 will be obtained. Monitoring for follicular and endometrial development will continue routinely and as needed, until the majority of all follicles observed have a mean diameter between 15 to 22 mm. Induction of ovulation

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will commence 35-and-a-half hours prior to oocyte retrieval, by self-administration of 10,000 IU hCG SQ.

The patient will receive deep sedation total IV anesthesia by a board-certified anesthesiologist for her oocyte retrieval and placement of either her second oPRP or oS injections. Using transvaginal ultrasound guidance, all follicles visualized under ultrasound will be aspirated using standard practices by patients undergoing IVF at GNF. Aspirates will be collected in 10 ml test tubes. All oocytes will be assessed for maturity two hours post-retrieval. All oocytes that are deemed mature (MII) will undergo intracytoplasmic sperm injection (ICSI), to maximize fertilization rates, 2-4 hours after identification of the first polar body. All immature (non MII) oocytes will be isolated under a stereomicroscope and transferred into maturation media and incubated further in a triple gas mixture (90% N2, 5% CO2, and 5% O2) for up to 24 hours to allow maturation prior to ICSI. Following the oocyte retrieval, either oPRP or oS will be performed as described previously.

Monitoring will recommence two weeks following the first oocyte retrieval to identify if any residual follicles or ovarian cysts are present. If the ovaries are deemed resting and no active ovarian cysts persist, then the patient will begin her second IVF cycle. Again, the medication protocol will be determined by findings observed on pelvic ultrasound including AFC and ovarian hormone testing. If the patient is deemed ineligible to start another IVF cycle, then she will return with the following menstrual period to begin her second IVF cycle. The process of monitoring patients, inducing ovulation, and collecting oocytes will be identical to the first oocyte retrieval. However, no additional oPRP or oS injections will be performed.

NUMBER OF SUBJECTS / LENGTH OF PARTICIPATION

The study population will be obtained from registered patients at Generation Next Fertility PLLC and include only those patients diagnosed with DOR based on the 2011 Bologna criteria[iv] and who are between the ages of 35 to 42 years old and who are candidates for IVF and oPRP. All patients enrolled in the study will meet the standard requirements of our IVF and oPRP program. No individual will be enrolled for more than two IVF cycles and all patients will sign a consent form in English.

In short, patients will be eligible if they have a history of regular menstrual cycles defined as menses occurring on a routine basis between 21 to 35 days with less than five days of variability between cycles and at least two of the following three criteria are present:

(1) Advanced maternal age (>40 years) or any other risk factor for poor ovarian response (POR).
(2) A previous POR (≤3 oocytes retrieved with a conventional stimulation protocol).
(3) An abnormal ovarian reserve test: antral follicle count (AFC) less than 7 follicles or an AMH below 1.1 ng/ml.

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To determine the number of participants for this study, we used the Stata 15 software (StataCorp, College Station, TX). Using a two-sided statistical test, a probability of Type I error (α) = 0.05 and a probability of Type II error (β) = 0.10, we calculated the minimum sample size needed to detect a difference between the experimental and control groups of 40% for average number of blastocysts formed as well as 50% or 60% for average numbers of immature oocytes (MI) and mature oocytes (MII) retrieved. Since these parameters are continuous variables, we assumed that we will be conducting independent sample t-tests. We relied on the preliminary data from the two retrospective studies performed at Generation Next Fertility (GNF) as well as data from GNF's clinical database to perform sample size calculations.

A maximum of 230 participants will be enrolled in the study. This study population will be divided into two groups of 115 patients and block-randomized based on age, AFC, and AMH. Patients will then be randomly selected and enrolled into either the study group, which receives oPRP injections or the control group, which receives only ovarian serum (oS) injections.

This study is intended to evaluate the potential benefit of oPRP when compared to a placebo. Ovarian PRP is suspected to improve the AFC formed for ovarian stimulation, the number of oocytes retrieved during IVF, and the number of embryos, blastocysts, and euploid blastocysts formed following fertilization. This study is designed and powered to analyze a suspected increase in the number of blastocyst embryos formed. Secondary parameters such as the number of euploid blastocysts formed and the number of pregnancies and live births will also be calculated for both groups. Participants in this study will be compensated by having two significantly reduced-cost IVF cycles with ICSI and PGT-A and at least one free FET cycle when an embryo is available and deemed eligible for transfer. They will also be eligible to freeze all additional blastocyst embryos formed and not transferred for up to 1 year for free. All additional FET cycles will be included for free for up to 1 year following the initial embryo transfer or 12 months from the date of her oocyte retrieval if no embryo transfer is performed. After this time, the patient will be responsible for all fees and charges associated with embryo storage and embryo transfer following the 1-year grace period. The patient will also be responsible for all fees and charges associated with pregnancy, if it occurs, excluding her first pregnancy test.

Following completion or termination of this study, and if oPRP is found to improve IVF success rates, then all control group patients who received ovarian serum injections will be eligible for up to two free oPRP injection treatments. This will only apply for patients that elect to proceed with at least one additional IVF cycle at the standard price and cost to patients undergoing IVF with or without PGT-A treatment at Generation Next Fertility.

WASHOUT

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You will be asked to stop taking any hormonal contraception or estrogen supplements for at least 30 days prior to starting treatment. This is called a washout period, during which the effects of these medications leave your body.

PROCEDURES & EXPECTATIONS

SCREENING TESTS:

Prior to entry into the study and starting treatment, all subjects diagnosed with DOR will undergo a consultation with a complete medical history and a targeted physical examination. A pelvic vaginal ultrasound will be performed to determine a baseline AFC and ascertain if the patient meets the entry criteria for participation in the study. If the patient meets the entry criteria, then additional bloodwork for a complete blood count (CBC) and ovarian reserve testing will be performed including Anti Mullerian hormone (AMH), follicle-stimulating hormone (FSH), and estradiol (E2) levels. Both the patient and her partner will require sexually transmitted disease testing for HIV, syphilis, Hepatitis B surface antigen (HBsAg), and Hepatitis C antibody (HcAb). The patient will also have urine cultures for both Gonorrhea and Chlamydia. In addition, ABO blood group identification, Rho typing & and genetic carrier screening will be offered to both the patient and her partner. Prior to embryo transfer, all patients will be screened for immunity against Rubella and Varicella. Patients not immune will be offered vaccination and then allowed to proceed with embryo transfer 1-3 months after completion of vaccination. A semen analysis will be performed for the patient's partner to determine if a male factor for infertility exists.

Because some of these tests are performed on specific days of your menstrual cycle, two to three visits to Generation Next Fertility may be required to complete the screening process. We require that you avoid excessive alcohol, vaping, cigarette smoking, and recreational drug usage during your participation in this study.

ALL DOR STUDY PATIENTS

INDICATIONS:

All study patients must meet the definition of DOR but may be married or single and may use their partner's sperm or anonymous donor sperm.

INITIAL CONSULTATIONS:

Prior to your acceptance into the study, you will be required to have an initial consultation, which will include a meeting with Dr. Jesse Hade to review your medical history, and at that time a physical examination will be performed. All potential study participants will undergo all the necessary screening required for both oPRP injections and IVF with embryo transfer (as outlined above). If you meet these requirements and are not excluded based on the below criteria, you will be notified of your acceptance into the study.

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EXCLUSION CRITERIA

Exclusion criteria include a prior or known diagnosis of premature ovarian failure or menopause, irregular menses (menstrual cycles <21 or >35 days or having more than 5 days of variability between menstrual cycles, history of a persistent ovarian pathology on pelvic ultrasound, history of recurrent pregnancy loss (defined as 2 or more consecutive pregnancy losses with no prior live birth) patients with known surgically untreated hydrosalpinx or a known history of uterine anomalies or endometrial pathology as deemed by hysteroscopy, any medical illness or condition where pregnancy is a contraindication, or any prior history of oPRP injections. Patients will also be excluded from participation if they have any factor in which PRP is contraindicated such as a history of any prior cancer including lymphoma, leukemia, breast or any gynecologic malignancy, or borderline ovarian tumors. Patients with a current or known history of any blood disorder including anemia, thalassemia, sickle cell disease, and any platelet dysfunction or disease including polycythemia will be excluded. Untreated or poorly controlled autoimmune diseases such as lupus, diabetes, and thyroid disease will also preclude enrollment. Patients whose partners have severe male factor infertility or with failed fertilization despite prior IVF and ICSI will also be excluded from this study.

Please remember that there are other forms of drugs, such as smoking & alcohol, which we discourage & that it is extremely important that you take medications as directed

IVF Protocols:

nIVF Protocol:

1. Prior to starting their first IVF cycle, all patients will be monitored from the onset of menses until ovulation occurs. Within 72 hours from ovulation, the first ovarian injection with either oPRP or oS will occur. The patient will have a hysteroscopy during this same procedure to identify and possibly treat any underlying endometrial abnormalities.
2. When the patient's next menses occurs, the first IVF cycle will commence, and the patient will return for baseline ultrasound and blood work.
3. Repeat monitoring of the patient will start 4-5 days following her baseline ultrasound and blood work and then roughly every 1-4 days to evaluate the growth of all follicles visualized. Once a lead follicle is found between 14-15 mm in diameter or if her LH rises ≥30% over baseline levels, a GnRH antagonist will be started to prevent premature ovulation along with 75 to 150 IU of Menopur® to allow folliculogenesis to continue.
4. 10,000 IU of HCG or 250 mcg of Ovidrel® will be self-administered SQ by the patient when a lead follicle of 17 mm or greater is visualized.
5. Approximately 35.5 hours after HCG administration, the patient will undergo an oocyte retrieval using a long 19-gauge aspiration needle followed by their second ovarian injection with either PRP or serum.

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6. All eligible oocytes following retrieval will undergo the ICSI procedure for fertilization.
7. Fertilization will be evaluated the following day to verify the number of polar bodies observed and if the normal pronuclear stage of embryonic development is reached. On day three of culture, all cleaving stage embryos will be evaluated and graded for cell number, fragmentation rate and overall cell symmetry. A grade of 1-4 will be assigned to each embryo at this time. Next, laser assisted hatching (LAZ) using ZILOS-tk® will be performed on the zona pellucida of all embryos. Incubation to the blastocyst stage will proceed using continuous culture in micro-drops with group cultivation. On days five through seven of embryonic culture, embryos reaching a blastocyst stage of 3BB or better, based on the Gardner grading system, will be biopsied for PGT-A analysis. Briefly, five to eight cells are biopsied using the ZILOS-tk® laser and the cells are then placed in microcentrifuge tubes per protocol by Igenomix® and later sent for analysis. All embryos biopsied are then vitrified using cryo-lock vitrification tubes. Remaining embryos which arrest in development and do not meet the above criteria for biopsy will be discarded.
8. Patients will next return for monitoring with the onset of menses, approximately two weeks following their first oocyte retrieval and ovarian injections. If eligible, a second IVF cycle will commence, and a stimulation protocol will be determined based on the above criteria.

<u>mIVF Protocol:</u>

1. Prior to starting their first IVF cycle, all patients will be monitored from the onset of menses until ovulation occurs. Within 72 hours from ovulation, the first ovarian injection with either oPRP or oS will occur. The patient will have a hysteroscopy during this same procedure to identify and possibly treat any underlying endometrial abnormalities.
2. When the patient's next menses occurs, the first IVF cycle will commence and the patient will return for a baseline ultrasound and blood work. Three days following the onset of menses the patient will begin a combination of medications including an oral medication of Letrozole and/or Clomiphene Citrate in conjunction with a daily SQ injection of FSH (Follistim® or Gonal-F®) at a dosage not to exceed 225 IU daily.
3. Repeat monitoring of the patient will start 4-5 days following her baseline ultrasound and blood work and then roughly every 1-4 days to evaluate the growth of all follicles visualized. Once a lead follicle is found between 14-15 mm in diameter or if her LH rises ≥30% over baseline levels, a GnRH antagonist will be started to prevent premature ovulation along with 75 to 150 IU of Menopur® to allow folliculogenesis to continue. All oral medication will be discontinued at this time and the dosage of FSH lowered so not to exceed the total daily dosage of 225 IU of FSH.

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4. 10,000 IU of HCG or 250 mcg of Ovidrel® will be self-administered SQ by the patient when the lead follicle has a mean diameter of 17 mm or greater and the majority of subordinate follicles have a mean diameter of ≥15 mm.
5. Approximately 35.5 hours after HCG administration, the patient will undergo an oocyte retrieval using a long 19-gauge aspiration needle followed by their second ovarian injection with either PRP or serum.
6. All eligible oocytes following retrieval will undergo the ICSI procedure for fertilization.
7. Fertilization will be evaluated the following day to verify the number of polar bodies observed and if the normal pronuclear stage of embryonic development is reached. On day three of culture, all cleaving stage embryos will be evaluated and graded for cell number, fragmentation rate and overall cell symmetry. A grade of 1-4 will be assigned to each embryo at this time. Next, laser assisted hatching (LAZ) using ZILOS-tk® will be performed on the zona pellucida of all embryos. Incubation to the blastocyst stage will proceed using continuous culture of micro-drops with group cultivation. On days five through seven of embryonic culture, embryos reaching a blastocyst stage of 3BB or better, based on the Gardner grading system, will be biopsied for PGT-A analysis. Briefly, five to eight cells are biopsied using the ZILOS-tk® laser and the cells are then placed in microcentrifuge tubes per protocol by Igenomix® and later sent for analysis. All embryos biopsied are then vitrified using cryo-lock vitrification tubes. Remaining embryos which arrest in development and do not meet the above criteria for biopsy will be discarded.
8. Patients will next return for monitoring with the onset of menses, approximately two weeks following their first oocyte retrieval and ovarian injections. If eligible, a second IVF cycle will commence, and a stimulation protocol will be determined based on the above criteria.

<u>cIVF Protocol:</u>

1. Prior to starting their first IVF cycle, all patients will be monitored from the onset of menses until ovulation occurs. Within 72 hours from ovulation, the first ovarian injection with either oPRP or oS will occur. The patient will have a hysteroscopy during this same procedure to identify and possibly treat any underlying endometrial abnormalities.
2. When the patient's next menses occurs, the first IVF cycle will commence, and the patient will return for baseline ultrasound and blood work. Three days following the onset of menses the patient will begin injectable medications with a daily SQ injection of FSH (Follistim® or Gonal-F®) at a dosage of 225 to 300 IU plus 75 to 150 IU of Menopur® with the total dosage of FSH not to exceed 450 IU daily.
3. Repeat monitoring of the patient will start 4-5 days following her baseline ultrasound and blood work and then roughly every 1-4 days to evaluate the growth of all follicles visualized. Once a lead follicle is found between 14-15 mm in diameter or if her LH rises ≥30% over baseline levels, a GnRH antagonist will be started to prevent premature ovulation.

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4. 10,000 IU of HCG or 250 mcg of Ovidrel® will be self-administered SQ by the patient when the lead follicle has a mean diameter of 17 mm or greater and the majority of subordinate follicles have a mean diameter of ≥15 mm.
5. Approximately 35.5 hours after HCG administration, the patient will undergo an oocyte retrieval using a long 19-gauge aspiration needle followed by their second ovarian injection with either PRP or serum.
6. All eligible oocytes following retrieval will undergo the ICSI procedure for fertilization.
7. Fertilization will be evaluated the following day to verify the number of polar bodies observed and if the normal pronuclear stage of embryonic development is reached. On day three of cultivation, all cleaving stage embryos will be evaluated and graded for cell number, fragmentation rate and overall cell symmetry. A grade of 1-4 will be assigned to each embryo at this time. Next, laser assisted hatching (LAZ) using ZILOS-tk® will be performed on the zona pellucida of all embryos. Incubation to the blastocyst stage will proceed using continuous culture of micro-drops with group cultivation. On days five through seven of embryonic culture, embryos reaching a blastocyst stage of 3BB or better, based on the Gardner grading system, will be biopsied for PGT-A analysis. Briefly, five to eight cells are biopsied using the ZILOS-tk® laser and the cells are then placed in microcentrifuge tubes per protocol by Igenomix® and later sent for analysis. All embryos biopsied are then vitrified using cryo-lock vitrification tubes. Remaining embryos which arrest in development and do not meet the above criteria for biopsy will be discarded.
8. Patients will next return for monitoring with the onset of menses, approximately two weeks following their first oocyte retrieval and ovarian injections. If eligible, a second IVF cycle will commence, and a stimulation protocol will be determined based on the above criteria.

EMBRYO TRANSFER:

Upon completion of both IVF cycles, and if the patient has an eligible embryo cryopreserved, she will proceed with her first frozen embryo transfer (FET) cycle. Patients will be treated with standard protocols used at Generation Next Fertility and will be required to have an elective single embryo transfer (eSET). All study participants will undergo a medicated hormone replacement cycle to reduce the variability between the time of embryo transfer in relation to progesterone exposure. After a minimum of 11 days of estrogen exposure and when the endometrial lining is visualized to be ≥7mm by vaginal ultrasound, 50 to 75 mg of intramuscular (IM) progesterone will be started daily. On the sixth day of progesterone exposure, the patient will have her embryo transferred.

A serum pregnancy test will be conducted nine to ten days after the embryo transfer. If this serum pregnancy test is positive, the second serum pregnancy test will be performed two to three days later. If the second serum pregnancy test is positive, a transvaginal ultrasound will be performed within two weeks to confirm the pregnancy placement and number of gestational sacs and yolk sacs. This will be repeated one to two weeks later. However, if the patient has a negative serum pregnancy test, then the FET cycle process can be repeated if and only if she has additional embryos deemed eligible

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for transfer. All patients with eligible embryos for transfer must transfer their embryos within 12 months of starting this study.

Embryo transfer is usually performed with the woman in a reclining position with legs up (as if having a PAP smear) using a sterile technique. You may eat and/or drink before the procedure unless directed otherwise. Following the embryo transfer you will be given an appointment for your pregnancy test. You should then go home and relax for the rest of the day.

RISKS & SIDE EFFECTS

The treatment used in this study may cause some or none of the side effects listed. In addition, there is always the risk that some uncommon or unknown side effects may occur including death.

Risks/Side Effects Associated with Estrogen and Progesterone Supplementation:
Side effects reported in women treated with hormones such as estrogen and progesterone include nausea and vomiting, breast tenderness or enlargement, enlargement of benign tumors ("fibroids") of the uterus, retention of excess fluid leading to worsening conditions such as asthma, epilepsy, migraine headaches, heart disease, or kidney disease. Patients may also experience a spotty darkening of the skin, particularly on the face. These hormones may increase the patient's ability to form blood clots and increase the chance of a blood clot developing in the blood vessels of the leg or pelvis.This can then lead to embolus formation (dislodging of the blood clot which then travels in the circulation) resulting in potentially serious damage to the lungs, heart, or brain. Hormones may also increase the risk for developing a stroke or heart attack and even death.

Risks/Side Effects Associated with gonadotropin and hCG:
Side effects reported in women treated with gonadotropins and or menotropins (Gonal-F, Follistim, and Menopur) include ovarian hyperstimulation syndrome, pulmonary and vascular complications (such as the collapse of the lungs, acute respiratory distress syndrome, blood clots which may lead to inflammation of the veins, obstruction of blood vessels in the lungs, damage to the lung tissues, stroke, and obstruction of the arteries resulting in loss of a limb), blood in the abdominal cavity, enlarged ovaries, dizziness, increase in heart rate, shortness of breath, rapid breathing, flu-like symptoms (fever, chills, musculoskeletal aches, joint pain, nausea, headache, and fatigue), breast tenderness, and dermatological (skin) reactions (dry skin, body rash, hair loss, and hives). In rare cases, pulmonary (lung) complications and/or thromboembolic (clots in blood vessels) events have resulted in death.

There have been infrequent reports of ovarian cancer in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established. In addition, ovulation induction medications have been used safely and without long-term adverse effects on most patients. However, the long-term safety of any one

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patient cannot be guaranteed. In addition, breast tenderness, mood swings, hot flashes, nausea, pain, and swelling at the injection site may occur.

The following side effects have been reported in some patients receiving Ovidrel (HCG) therapy: Headache, irritability, restlessness, depression, fatigue, swelling, and pain at the site of injection.

Risks Associated with Study Procedures:

In this study, participants will be required to have blood drawn on several occasions. This may lead to slight pain, bruising, swelling, and the possibility of local infection. Participants will also be required to take subcutaneous (SQ) or intramuscular (IM) injection of Follistim, Gonal-F, Menopur, HCG or Ovidrel (choriogonadotropin alfa). There may be risk of infection, bruising, swelling at the injection site and damage to the nerves with improper technique.

oPRP or oS injections like IVF is a surgical procedure that requires anesthesia and transvaginal ultrasound guided ovarian injections. Both processes are generally considered safe, but risks and complications have been reported from post procedural blood loss and infection. The performance of the ovarian oPRP or oS injections and the egg retrieval may be associated with infection, abscess formation, injury to abdominal organs, blood vessels, and subsequent death. Participants will be given oral antibiotics to be taken for a period of three days following the retrieval as prescribed by the physician to prevent risk of infection. Complications rarely require hospitalization and intervention with surgery, blood transfusion and IV antibiotic administration.

Anesthesia is required for the egg retrieval and ovarian injection procedures. The type of anesthesia administered, (I.V. deep Sedation), will be decided on an individual basis by the anesthesiologist physician. Side effects of anesthetic agents can include nausea and vomiting. Allergic reactions to anesthesia agents can include skin rash and in severe cases cardiac arrest and death.

oPRP although considered experimental, does not demonstrate any additional risks or complications during the retrieval of oocytes when compared to traditional IVF. Nor has there been any increased rate of fetal malformations or other adverse fetal events or ectopic pregnancies when compared to traditional IVF without oPRP.

Generation Next Fertility cannot guarantee future fertility or participants. Impaired fertility in the future may or may not be related to the egg retrieval process or injection of oPRP or oS. In addition, a participant's condition may not improve or may worsen while participating in this study.

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All subjects will be informed of all risks associated with the oPRP and oS injections and the IVF process. Immediate transportation and hospitalization for the management of a complication will be provided to all subjects who require such intervention following oocyte retrieval.

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If you do not understand any of the above risks, you may discuss them with Dr. Hade. If complications occur, Dr. Hade or his associate physicians and their team will monitor you closely and take appropriate medical action that may include stopping any or all medications and discontinuing the treatment cycle.

BENEFITS

This research may benefit you personally by assisting you in achieving pregnancy. However, pregnancy cannot be guaranteed and there may be no direct benefit to you especially if you are part of the control/placebo group. The information obtained from this study may have humanitarian benefits in enabling women with DOR undergoing IVF to achieve pregnancy with fewer treatments and lower cost.

COMPENSATION FOR PARTICIPATION

The goal of this study is to identify the true benefits of oPRP. Participants in this study will be compensated by having two significantly reduced IVF with ICSI and PGT-A cycles and at least one free FET cycle when an embryo is available and deemed eligible for transfer. They will also be eligible to freeze all additional blastocyst embryos formed and not transferred for up to 1 year for free. All additional FET cycles will be included for free for up to 1 year following the initial ET or 12 months from the date of her oocyte retrieval if no ET is performed. After this time, the patient will be responsible for all fees and charges associated with embryo storage and embryo transfer following the 1-year grace period. The patient will also be responsible for all fees and charges associated with pregnancy, if it occurs, excluding her first pregnancy test.

Following completion or termination of this study, and if oPRP is found to improve IVF success rates, then all control group patients who received ovarian serum injections will be eligible for up to two free oPRP injection treatments. This will only apply for patients that elect to proceed with at least one additional IVF cycle at the standard price and cost to patients undergoing IVF with or without PGT-A treatment at Generation Next Fertility.

Please be advised you will **NOT** receive any monetary compensation for your participation in this study.

ALTERNATIVE TREATMENT

You do NOT have to participate in this study as a Study or Control Patient.

Alternative therapy available to patients with DOR and infertility is to undergo artificial intrauterine insemination (IUI), traditional IVF with typical ovarian stimulation and embryo transfer protocols, or oocyte donation. You also have the right to have oPRP injections and not participate in this study. However, all the standard GNF fees and charges for oPRP injections under anesthesia will apply.

Patient Initials: _____

CONFIDENTIALITY

Records of your participation in this study will be held confidential except as disclosure is required by law or as described in this informed consent document (under "Confidentiality" or "Authorization to Use and Disclose Protected Health Information"). The study doctor, the sponsor or persons working on behalf of the sponsor, and under certain circumstances, the United States Food and Drug Administration (FDA) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify you by name. Therefore, absolute confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, you will not be identified.

COMPENSATION FOR INJURY

I understand that in order to participate in this study, I must have my own medical insurance and must provide documentation of such insurance. In the event that I should require additional medical treatment or hospitalization as a result of my participation in this study, either my insurance carrier or I will carry the financial responsibility for such care.

In the unlikely event that physical injury occurs as a direct result of your participation, immediate medical care will be available including hospitalization. Generation Next Fertility will help bill the appropriate insurance company for any additional expenses, but neither Generation Next Fertility nor any provider or sponsor will be directly responsible for the costs of such care.

SOURCES OF FUNDING

Funding for this research study will be provided by Generation Next Fertility.

EMERGENCY CONTACT/IRB CONTACT

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns, or complaints about the study, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

If you have any questions about this study, you are injured, or you experience a reaction to the study medication because of your participation in this study, contact:

- Dr. Hade, Dr. Luk or Dr. Nejat at (212) 641-0906

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, you should write to:

Patient Initials: _____

Generation Next Fertility IRB
115 East 57th Street
Suite 500
New York, NY 10022
Telephone: 212-641-0906

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all questions.

VOLUNTARY PARTICIPATION & WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. If you do participate, you may freely withdraw from the study at any time. Your decision will not change your future medical care at Generation Next Fertility.

You will be removed from the study without your consent if:

1. It appears to be medically harmful to you. You experience any side effects that, in the opinion of your study doctors or sponsors, will endanger your welfare with continued use of the medications. This includes risk of ovarian hyperstimulation syndrome (OHSS) and hypersensitivity reactions.

2. You develop an illness that increases risk of complication(s) from the oPRP, oS or IVF process and procedures.

3. You have to take an unacceptable medication during the study (other hormones, anti-inflammatory drugs, and drugs which act on the nervous system, such as tranquilizers), chemotherapy or other medication contraindicated in pregnancy.

4. You fail to follow directions for participating in the study.

5. It is discovered that you are ineligible.

6. The study is canceled or

7. For administrative reasons, including competitive enrollment - the target number of subjects has entered the treatment phase.

If you leave the study for any reason, the study doctor may ask to perform some end-of-study tests for your safety.

PRIMARY CARE PHYSICIAN / SPECIALIST NOTIFICATION OPTION

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

Patient Initials: _____

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ I do not have a primary care physician/specialist.

_____ The study doctor is my primary care physician/specialist.

NEW FINDINGS

You will be told about any new information that might change your decision to be in this study.

CONSENT

I/we have had ample opportunity to ask any questions concerning this study, and my participation is voluntary as reflected by the signed statement below.

I/we have read this consent form and have heard the verbal explanations of these procedures from my study doctor. I/we understand the information about this study. I/we freely give my consent to participate in this research. I/we understand that I/we have the right to ask questions and may refuse to continue participation at any time during the study.

During the course of the research, I/we will be informed of any new significant findings that may relate to my willingness to continue to participate.

I/we further understand that at any time during treatment, I/we are free to discuss with my study doctor or the study doctor's designee or a GNF Review Board, Inc. (GNF IRB) representative, my rights as a subject and any side effects that might occur.

I/we are deciding whether to participate in this study. My/our signature(s) indicates that I have decided to participate, having read (or been read) the information provided in this consent form.

I/we authorize the release of my medical records for research or regulatory purposes to the sponsor, the FDA, DHHS agencies, governmental agencies in other countries, and Schulman Associates Institutional Review Board, Inc. (Schulman).

I/we understand that existing laws do not fully address the legal issues which may be raised by the performances of this procedure, including but not limited to the legality of the procedure itself, the right and obligations of the parties participating, and the legality and enforceability of any contract between the embryo recipient, her partner, and the

ovum donor with respect to custody and parentage of any child which may be born as a result of this procedure. I/we have been advised to seek individual legal counsel prior to participation into this procedure. Because of the newness of egg donation, this is an area with limited legal precedence and the Diamond Institute cannot assure recipients or donors of the enforceability of this situation.

I/we understand and agree that all medical records pertaining to testing and treatment performed on me/my partner as part of the egg donation process are the property of the Diamond Institute and will not be released to me.

I/we understand that Generation Next Fertility, its physicians, and their associates have not made or implied any guarantee or warranty to me regarding the outcome of the Egg Maturation process. I/we release Generation Next Fertility from any liability or responsibility for the physical or mental nature of any child or children produced, or loss or damage, including any complication, which may result from my/our participation in this procedure or from the application of the law to this procedure or any agreement between the parties. This release is intended to and shall apply to the fullest extent permitted by law to any rights or claims which may be held or assisted by any third party, including any children which may result from this procedure.

I/we acknowledge that I/we have an adequate understanding of the ovarian platelet-rich plasma/ovarian serum injections and the In-Vitro Fertilization process as described above and that the physicians and their associates have provided me/us with all the required information that I/we have requested. I/we have been made aware of the usual and most frequent risks and hazards inherent in the procedures and the treatment associated with it. I/we understand that there may be some risks that are not known at this time. I/we have had the opportunity to ask all pertinent questions, and these have been answered to my satisfaction. If I/we choose to withdraw from the study or if the study doctor finds it is in my best interest to withdraw, I/we acknowledge that I/we am expected to return for a final visit.

My partner (if applicable) and I freely consent to my voluntary participation as a Study or Control Patient. As a subject of the study, I will be randomly selected to undergo either oPRP or oS injections prior to the IVF procedure and embryo transfer. I fully understand this procedure and accept its risks and limitations as explained to me. This study is designed to identify the true benefits of oPRP prior to the IVF process. I understand that I must undergo several surgeries to have both ovarian injections of either oPRP or oS followed by IVF and surgery to recover mature eggs from my ovaries. Following the removal of my eggs, I/we understand that they will be fertilized in the laboratory with sperm from my partner or chosen sperm donor. I/we understand that only embryos that form a viable and eligible blastocyst, as determined by the embryology staff at GNF, will be biopsied to determine the chromosomal normalcy prior to transfer. Only embryos that are deemed "normal" or "suitable" for transfer will be transferred back to my uterus. All embryos ineligible for transfer will be discarded.

Patient Initials: _____

I/we understand and authorize and consent to the performance of micromanipulation on all of the mature egg(s) retrieved from the IVF process. Micromanipulation procedures such as ICSI involve some risk to the oocyte and/or embryo. With the ICSI technique, only one sperm is injected into the cytoplasm of the egg. This procedure may reduce the risk of abnormal fertilization. However, even with this procedure abnormal egg(s) and sperm may be inseminated resulting in anomalous embryos. All embryos that are identified as abnormal will be discarded and not used for transfer.

I/we understand and agree that I/we are fully responsible for any and all offspring regardless of the outcome of the pregnancy.

I/we understand that once the egg(s) are removed from my body and have been inseminated with the sperm of the male partner (or chosen donor), the resulting embryo(s) are my/our sole responsibility. I/we understand and agree that I/we are legally responsible for the resulting embryos.

I/we do understand that no guarantee can be given to me/us about the success of this procedure. I/we realize that at any time the physician may cancel the procedure based on his/her judgment and experience. I/we also realize that the possibility exists that no eggs may be retrieved from my follicles, that the retrieved eggs may not fertilize or that fertilized eggs may not develop into blastocyst embryos. Finally, the blastocyst embryos may not be eligible for either biopsy or transfer and may not implant into the uterus following embryo transfer. I/we understand that there is the possibility of complications of childbirth or delivery, or the birth of an abnormal infant or infants, or undesirable hereditary tendencies of such issue, or other adverse consequences, and will not hold Generation Next Fertility or any of its employees responsible should such complications occur. Generation Next Fertility cannot guarantee future fertility or participants. I/we understand that impaired fertility in the future may or may not be related to the egg retrieval process or injection of oPRP or oS. I/we acknowledge that my condition may not improve or may worsen while participating in this study.

In consideration of the matters set forth above, I/we release Generation Next Fertility and its employees from any liability or responsibility for the physical or mental nature of any child or children produced and any loss or damage which may result from participation in this procedure, including any complications which may result from participation in this procedure or from the application of the law to this procedure or any agreement between the parties.

This release is intended to and shall apply to the fullest extent permitted by law to any rights or claims which may be held or asserted by any third party, including any children which may result from this procedure. I/we release Generation Next Fertility and its employees from any financial responsibility due to complications incurred to us or our offspring from this procedure. I/we also understand that if pregnancy should occur, further testing with either amniocentesis or chorionic villous sampling (CVS) is recommended to help identify all possible offspring(s) with chromosomal abnormalities.

Patient Initials: _____

If I/we or any of my/our offspring should require medical treatment as a result of participation in this procedure, the financial responsibility for such care will be mine/ours.

Patient Initials: _____

CONSENT

I/we have read and understand the information in this informed consent document. I/we have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I/we voluntarily agree to participate in this study until I/we decide otherwise. I/we do not give up any of my legal rights by signing this consent document. I/we will receive a copy of this signed consent document.

_____
Subject's Printed Name

_____ _____
Subject's Signature Date

___
_____
Subject Partner's Printed Name (if applicable)

_____ _____
Subject Partner's Signature (if applicable) Date
Date

_____
Printed Name of the Person Conducting the
Consent Discussion

_____ _____
Signature of the Person Conducting the Date
Consent Discussion

CONSENT FOR SUBJECTS WHO CANNOT READ

The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness* Date

*Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance

Patient Initials: _____

AUTHORIZATION TO USE AND DISCLOSE

PROTECTED HEALTH INFORMATION

During your participation in this research study, the study doctor **Jesse Hade, M.D., Janelle Luk, M.D., Dr Edward Nejat, M.D. or another designated physician** and study staff will collect or create personal health information about you (for example, medical histories and results of any tests, examinations, or procedures you undergo while in the study) and record it on study documents. The study doctor will keep this personal health information in your study-related records (that we will refer to as "your study records"). In addition, the study doctor may obtain and include in your records, information regarding your past, present, and/or future physical or mental health and/or condition. Your study doctor may ask you to sign a separate authorization to obtain some or all of your medical records from your doctor. Your study records may include other personal information (such as social security numbers, medical record numbers, date of birth, etc.), which could be used to identify you. Health information that could identify you is called Protected Health Information (or PHI). Other PHI that may be used includes laboratory data, photos, and images of ultrasounds, oocytes, and embryos. Information regarding test results for a resulting pregnancy including but not limited to birth date, gestational age of delivery, birth weight, size, complications of pregnancy and delivery, fetal malformations if it occurs, and method of delivery applies as well.

Under federal law (the "Privacy Rule"), your PHI that is created or obtained during this research study cannot be "used" to conduct the research or "disclosed" (given to anyone) for research purposes without your permission. This permission is called an "Authorization." Therefore, you may not participate in this study unless you give your permission to use and disclose your PHI by signing this Authorization. By signing, you are agreeing to allow the study doctor **Jesse Hade, M.D. or another GNF physician** and staff to use your PHI to conduct this study.

By signing this Authorization, you also are agreeing to allow the study doctor Jesse Hade, M.D. or another GNF physician to disclose PHI as described below:

- The sponsor of this study and anyone working on behalf of the sponsor to conduct this study (referred to as "the sponsor"). The sponsor will analyze and evaluate the PHI and may use it to develop new tests, procedures, and commercial products. The study staff will assign a code number and/or letters to participant records, which means that they will not ordinarily be identified in the records sent to the sponsor. The sponsor may, however, look at complete study records that identify participants. In addition, the sponsor may visit the study site to oversee the way the study is being conducted and may review participants' PHI during these visits to make sure the information is correct.
- The Institutional Review Board ("IRB") may have access to your PHI in relation to its responsibilities as an Institutional Review Board.

Patient Initials: _____

- Your medical insurance company or other third-party payer and legal boards and other legal representatives of your choosing may request access to your PHI.

The study doctor or sponsor may disclose your PHI to the United States Food and Drug Administration ("FDA") or similar regulatory agencies in the United States and/or foreign countries.

These disclosures also help ensure that the information related to the research is available to all parties who may need it for research purposes.

Except for the disclosures described above, your PHI will not be shared with others unless required by law. If your PHI is given to the parties listed above and/or to others who are not required to comply with the federal law, your PHI will no longer be protected by this law and could possibly be used or disclosed in ways other than those listed here.

You have a right to see and make copies of your PHI. You are agreeing, however, by signing this document, not to see or copy some or all of your PHI until the sponsor has completed all work related to this study. At that time, you may ask to see your complete records.

This Authorization will expire 50 years from the date you sign it unless you revoke (cancel or withdraw) it sooner.

You have a right to revoke your Authorization at any time. If you revoke it, your PHI will no longer be used for this study, except to the extent the parties to the research have already taken action based upon your Authorization or need the information to complete analysis and reports for this research. To revoke your Authorization, you must write to the study doctor **Jesse Hade, M.D. or another designated GNF physician**, stating that you are revoking your Authorization to Use and Disclose Protected Health Information. If you revoke this Authorization, you will not be allowed to continue to be in this study.

You will receive a copy of this Authorization after you have signed it.

_____ ____
Signature of Subject Date

_____
Printed Name of Subject

_____ _____
Signature of the Person Obtaining the Authorization Date

_____
Printed Name of the Person Obtaining the Authorization

FOR SUBJECTS WHO CANNOT READ

The study subject has indicated that he/she is unable to read. This Authorization document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness* Date

*Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance

[i] Conde Montero E, Fernandez Santos ME, Suarez Fernandez R: Platelet-rich plasma: applications in dermatology. Actas Dermosifiliogr 2015; 106: 104–111.
[ii] Sommeling CE, Heyneman A, Hoeksema H, Verbelen J, Stillaert FB, Monstrey S: The use of platelet-rich plasma in plastic surgery: a systematic review. J Plast Reconstr Aesthet Surg 2013;66:301–311.
[iii] Sills E, Rickers N, Li X, Palermo G. First data on in vitro fertilization and blastocyst formation after intraovarian injection of calcium gluconate-activated autologous platelet rich plasma. Gynecol Endocrinol. 2018;34:756–60.
[iv] Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund, G, Gianaroli L, et al. ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26:1616-24.

Patient Initials: _____