Patient Handbook

Find more patient resources like consent forms, injection training videos and more at:

www.RMAnetwork.com

1-855-RMA-inPA

Table of Contents

rma
Philadelphia

OFFICE INFORMATION

Operating as a group practice allows RMA of Philadelphia to be staffed 365 days a year in order to maximize the opportunity for a successful experience for each of our patients. As a result, you may be seen by a provider other than your primary physician for monitoring and procedures. However, your primary physician will oversee all your care.

CALL HOURS

Monday – Thursday	7:00 AM – 3:30 PM
Friday	7:00 AM – 3:00 PM

OFFICE HOURS

Monday – Friday	7:00 AM – 3:30 PM by appointment only
Saturday & Sunday	8:30 AM – 11:30 AM by appointment only (King of Prussia office)
Holidays	8:30 AM – 11:30 AM by appointment only (King of Prussia office)

Observed Holidays: New Year's Day, Memorial Day, 4th of July, Labor Day, Thanksgiving, day after Thanksgiving, Christmas eve and Christmas Day.

The King of Prussia office is open with limited hours on these holidays.

MONITORING HOURS

Monday – Friday	7:00 AM – 9:45 AM by appointment only
Saturday & Sunday	8:30 AM – 11:00 AM by appointment only (King of Prussia office)
Holidays	8:30 AM – 11:00 AM by appointment only (King of Prussia office)

Monitoring is for cycle blood tests and ultrasounds.

SEMEN ANALYSIS HOURS

Monday – Thursday	
Center City	9:00 AM – 9:30 AM by appointment only
King of Prussia	7:30 AM – 1:00 PM by appointment only
Langhorne	9:00 AM – 9:30 AM by appointment only
Abington	9:15 AM – 9:45 AM by appointment only

EMAIL COMMUNICATION

We use a secure gateway to protect the security and confidentiality of information being sent and received via email. The email address you have listed in your chart will be used for email communication. Please be sure you are comfortable receiving emails at the address you have given us. With each email you send please include your full name and date of birth. Emails on this gateway do expire. If you wish to keep them, please forward the message to your personal email. In addition to emails you can now communicate directly with your primary care team through portal messaging.

Any questions regarding email correspondence should be sent to info@ivirma.com.
A Patient Authorization Form must be signed to allow email communication.

FOR APPOINTMENTS AND QUESTIONS CALL (215)-938-1515

Center City
1015 Chestnut St., 8th Floor
Philadelphia, PA 19107
FAX: 215-922-1565

Langhorne
930 Town Center Dr., Suite G-75
Langhorne, PA 19047
FAX: 267-852-0786

King of Prussia
625 Clark Ave., Suite 17B
King of Prussia, PA 19406
FAX: 215-654-1543

Abington
1151 Old York Rd.
Abington, PA 19001
FAX: 215-938-8756

RMA Surgical Center
625 Clark Ave., Suite 17B
King of Prussia, PA 19406
FAX: 215-654-1543

Physicians
Arthur Castelbaum, MD
Martin Freedman, MD
Jacqueline Gutmann, MD
Allison Lange, MD
William D. Schlaff, MD
Jeffrey Thorne, MD

Director of Clinical Services
Marianne Kearney, RNC

Director of Clinical Services Surgery Center
Erlynn Gill Haberman, RNC, MSN

Director of Third Party Services
Dana Tillotson, RNC, BSN

Director of Embryology Lab
Jeanne Walters, BS, ELD (ABB)

Nurse Practitioners
Jennifer Guglielmi, MSN, FNP, CLC
Brooke Motyl, MSN, WHNP-BC

IVF Nurse Coordinator
Jill McDonald, RN, BSN

Laboratory Supervisor
Betty Ignas, MLT (ASCP)

GENERAL INFORMATION

CONNECTING WITH THE CLINICAL TEAM & PHYSICIANS

The Clinical Team is available to meet with you to answer questions, review your treatment cycle, and explain any instructions provided by the Physician after you have had your ultrasound.

When calling the office during normal business hours to speak with a member of our clinical team or a physician, a Patient Services Coordinator will forward your message. You may not receive a call back until after monitoring hours or until the end of the day. Please inform the Patient Services Coordinator if it is urgent.

If you are calling after hours with an urgent message, please follow the prompts to be connected with our answering service.

EXAMPLES OF URGENT CALLS:

- ✓ A medical emergency related to your treatment at RMA (e.g. severe cramps or bleeding)
- ✓ If you are undergoing treatment and are still waiting for instructions after 4:00 PM
- ✓ If you do not have a medication you must take that evening
- ✓ If you were instructed to come in on day 2 of your cycle

If you are calling after hours to report Day 1 of your cycle or to schedule an appointment, please leave a voicemail and we will return your call the next day.

OUTSIDE MONITORING

Based on your unique circumstances, you may choose to do your monitoring visits at an outside clinic. If you require outside monitoring, our clinical team will provide you with an order specifying what you need to have done at your visit. You will provide this order to the fertility clinic where you will be monitored. It is your responsibility to discuss costs and fees for the visit(s) with that clinic. After your visit, the outside clinic will forward your results to our office. Once the physician has reviewed your results, instructions will be communicated to you by our clinical team.

You will be responsible for a medical management fee if you are monitored elsewhere. The fee is $500 - $1,000 depending on your treatment cycle type. Our financial coordinators are available to review this information with you.

PROPER IDENTIFICATION

For the protection of our patients, a copy of a proper government issued ID will be kept on file. Your name, as it appears on your insurance card, will be used on all your records. You can upload a photo of your identification card into the documents section of the patient portal or email it to your home office. We require your social security number as a secondary identifier because it is unique to you. This identification system is necessary to ensure the proper identification of any specimens, medical records and consent forms.

CONSENT FORMS

We accept documents electronically signed using DocuSign. When a consent form is needed it will appear in the “What We Need from You” section of your portal. If DocuSign is not being used, we ask that all consent forms be signed in our office in front of a designated employee. If this is not possible, a notary public can also verify the signature of each individual signing a consent form. A notary stamp must accompany the notary signature. If you are dropping off notarized consent forms, please allow a few extra minutes to accommodate the review process.

OBTAINING MEDICAL RECORDS

If you have any outside medical records that pertain to fertility, please have them sent to your home office. We advise contacting your doctor's office to follow their Medical Record Request protocol. You may also utilize our request form. The necessary form to obtain your outside medical records can be found on our website as *Release of Outside Records to RMA*.

If you are requesting records from our office, you can find the record release form on our website. Each individual person requesting records MUST complete and submit their own Medical Record Release Form. It can take 10-15 business days for medical record requests to be processed.

INSURANCE COVERAGE & BILLING

As a courtesy, our Finance Team will contact your insurance company to review your benefits. This information will be presented to you during your Financial Phone Consultation. The time for this phone consult will be scheduled at your New Patient Visit. We do encourage you to contact your insurance company to ensure you are receiving all the benefits to which you are entitled. We have provided an Insurance Worksheet Flier in your folder to assist you when calling your insurance company about your benefits.

We work with our patients to help make treatment more affordable. In doing so, we can offer military and first responder discounts, treatment packages for IUI and IVF cycles, multi-cycle packages for IVF and a Refund Guarantee Program.

Your insurance company may require pre-authorization for injectable medications. Injectable medication treatments start on a very specific day of your menstrual cycle. Initiating the pre-authorization process as soon as possible will ensure you know the exact cost of your medications. Please do not wait until you are ready to begin your treatment to initiate this process, as it could take up to five business days for your insurance to confirm the level of coverage for self-injected medications. If pre-authorization is required and it was not obtained prior to the medication start date, you may need to pay for the medications out-of-pocket and apply for reimbursement directly with your insurance company or delay starting treatment until the following month.

All copays are due at the time of visit. Please check with a Patient Services Coordinator before leaving each appointment as you may have a COPAY or a PACKAGE PAYMENT due.

For BILLING inquiries please call (844)291-6688 Monday – Friday between the hours of 8:00 AM - 4:30 PM.

PATIENT SUPPORT PROGRAM

Whether the goal is to manage stress, cope with loss, help others understand, or confidently make treatment decisions, we have resources available to help. A Patient Support Program Flier is included in your folder with books, podcasts, social media accounts and more that our patients have recommended. We have also included a list of mental health professionals that have special expertise in working with individuals and couples undergoing fertility treatment. If you are interested in acupuncture, please speak with your physician or nurse for more information.

CANCELATION POLICY

Our goal is to provide quality care to all of our patients in a timely manner. No-shows, late cancellations and late arrivals can negatively impact the flow of our office. If you are unable to keep your appointment, please contact us no later than 1 business day prior to your scheduled appointment to avoid a cancellation/reschedule fee.

HEALTH & NUTRITION

There are no foods that have been proven to directly impact fertility. It is recommended that you maintain a healthy and well-balanced diet of fruits, vegetables, whole grains, lean meats, and dairy products to provide your body the recommended dietary allowance of vitamins and minerals. Avoiding food laden with chemicals can be helpful for your health. Unless you are diagnosed with Celiac disease, there is no evidence that restricting gluten from your diet will aid with fertility.

FEMALES

- ✓ Refrain from using tobacco products, recreational drugs and/or alcohol as these are environmental toxins that may negatively impact your fertility.

- ✓ Restrict your intake of the following:
  - Caffeine should be restricted to 16 ounces per day, as it can impede the body's ability to absorb iron and calcium
  - Vitamin A should be restricted to 3,000 IU per day
  - Vitamin D should be restricted to no more than 2,000 IU per day, unless otherwise directed

- ✓ Take folic acid to decrease the risk of spinal cord defects, such as Spina Bifida. Foods rich in folic acid include dark green leafy vegetables, citrus fruits, nuts, legumes, whole grains, fortified breads and cereals. We can also provide you with prenatal vitamins that will have at least the recommended daily dose (800mcg). Women who have had a child with Spina Bifida should take 4mg of folic acid daily.

- ✓ Acupuncture can be used during your fertility work-up or treatments with licensed professionals.

- ✓ Avoid *all* herbal medicines. Herbal medicines, preparations or supplements used separately or in conjunction with acupuncture can interact adversely with fertility medications. For example, fish oil has anti-coagulant (blood thinner) properties that could negatively impact your treatment protocols.

- ✓ Please inform your nurse or physician if you are taking any supplements, prescription medications or over the counter medications.

MALES

- ✓ Refrain from using tobacco products, recreational drugs and/or alcohol as these are environmental toxins that may affect your fertility.

- ✓ Avoid hot tubs and saunas for at least 3 months prior to treatment as sperm function can be negatively affected.

- ✓ Acupuncture can be used during your fertility work-up or treatments with licensed professionals.

- ✓ Please inform your nurse or physician if you are taking any supplements, prescription medications or over the counter medications.

Medications of importance that may affect sperm quality include (listed by generic name):

Amlodipine	Felodipine	Nitrofurantoin
Anabolic Steroids	Isradipine	Propecia
Androstendione	Methotrexate	Proscar
Cholchicine	Nicardipine	Spironolactone
Cimetidine	Nifedipine	Sulfasalazine
DHEA	Nimodipine	Testosterone
Diltiazem	Niradazole	Verapamil
Erythromycin	Nisoldipine	

FERTILITY EVALUATION

PRELIMINARY TESTING / DIAGNOSTIC TESTING

If you have had any of the tests listed below, please request those records be sent to your home office. Please note that your physician may want to repeat a test you have already had performed. Should you choose to have some of your testing done at an outside facility, it is your responsibility to have those results forwarded to the office.

FEMALE TESTING

Blood Tests:

FSH/LH/Estradiol: The combination of FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone), and Estradiol drawn on Day 2, 3 or 4 of your cycle reflects a woman's ovarian reserve and/or how well we can expect the ovaries to respond to stimulation. We generally test all women, regardless of age, because of the wide range of variation in ovarian function with infertility patients. These tests help us to determine which procedures and protocols are best for you.

AMH (Anti-Mullerian Hormone): This test is an additional way for us to evaluate your ovarian reserve and can be drawn at any time during the menstrual cycle.

Pre-Pregnancy Screen (Blood Type and Rh factor, Rubella titer, Varicella Titer, and Genetic Screening): Knowing your blood type and Rh factor is helpful if there are problems with a pregnancy. Rubella and Varicella are infections that can cause serious birth defects if acquired during pregnancy. In order to alleviate any potentially serious consequences of these preventable diseases, vaccination should be completed prior to beginning treatment. Inherited or genetic disorders can be associated with birth defects, miscarriage and illness in offspring.

Infectious Screen (Chlamydia, Hepatitis B and C, Syphilis, HIV, Gonorrhea): Having one of these infectious diseases could adversely affect the outcome of your procedure or your pregnancy.

TSH (Thyroid-Stimulating Hormone): This is the most sensitive test of thyroid function and can detect either over or under activity of the thyroid gland. This test screens for subtle abnormalities that could affect your treatment or pregnancy.

Other Testing: If your medical history, family history or test results suggest that you may be at risk for genetic, autoimmune diseases or other medical problems, appropriate tests will be ordered prior to initiating treatment.

RADIOLOGY EVALUATION

HSG (Hysterosalpingogram) or Saline Sonogram (Sonohysterography): These diagnostic tests are performed to evaluate the interior of the uterine cavity and the fallopian tubes.

Mammogram: A Mammogram is a screening test for breast cancer. The baseline mammogram for most women should be done at age 40. Some women may require more frequent mammogram testing depending on their medical and family histories.

OTHER EVALUATION

Baseline Ultrasound: Done at the initial visit, the baseline ultrasound enables assessment of the ovaries and uterus.

Pap Smear: The Pap smear is a screen for Cervical cancer and Human Papilloma Virus infections. A Pap smear should be performed routinely at the discretion of your gynecologist. Please contact your gynecologist for a Pap smear if you are not up to date.

Hysteroscopy: This is performed to evaluate the uterine cavity for any abnormalities that may prevent implantation or continuation of a pregnancy.

MALE TESTING

Semen Analysis: A Semen Analysis is required to assess male fertility status. The results help formulate appropriate treatment plans.

Blood Hormone Levels: The analysis of hormone levels can help determine the cause of seminal parameter abnormalities.

Karyotype: This test evaluates chromosomes. In men with severe seminal abnormalities, the likelihood of chromosomal abnormalities is increased.

Y-Deletion Testing: In some men with very low or no sperm counts, the problem can be due to structural abnormalities in the segment of the Y-Chromosome that controls sperm development. Y-Deletion is the second most common genetic defect that causes male infertility and the nature and severity of this genetic defect determines prognosis of fertility. The same Y-Chromosome micro-deletion could be passed to male children.

Genetic Screening: Inherited or genetic disorders can be associated with birth defects, miscarriage and illness in offspring.

SURGERY

Your physician may recommend surgery for diagnostic purposes to further evaluate the cause of infertility, or to correct a problem that may be contributing to infertility. If surgery is recommended, you will be referred to the surgical coordinator who will assist you with scheduling your pre-admission testing.

Physicians and Hospitals:

Arthur Castelbaum, MD:
Abington Memorial Hospital, Abington, PA
Holy Redeemer Hospital, Meadowbrook, PA
St. Mary Medical Center, Langhorne, PA
Thomas Jefferson University Hospital, Philadelphia, PA

Martin Freedman, MD:
Abington Memorial Hospital, Abington, PA
Holy Redeemer Hospital, Meadowbrook, PA
St. Mary Medical Center, Langhorne, PA

William D. Schlaff, MD:
Thomas Jefferson University Hospital, Philadelphia, PA

NON-IVF TREATMENT OPTIONS

MONITORING DURING TREATMENT

To allow us to maximize the likelihood of pregnancy while reducing the risk, particularly those associated with medications used to enhance ovulation, we perform close monitoring during your treatment with ultrasounds and blood tests. The information from the blood work and ultrasound findings allow us to adjust medications and time treatments. Most treatment cycles require several monitoring visits.

Please contact the office when your menstrual cycle begins to schedule your baseline evaluation appointment. If your menstrual cycle begins after hours, during the weekend, or on a holiday, please call the office and leave a voicemail with your name, date of birth, phone number and reason for calling. You will need an ultrasound and hormone blood test on days 2, 3 or 4 of your menstrual cycle before starting any medications. Blood tests and ultrasounds are performed in the morning in order to receive same-day results.

Ultrasound: An ultrasound is a test that uses sound waves to create a picture of the anatomy of the female pelvis. We use transvaginal ultrasound rather than transabdominal ultrasound because the vaginal wall is thinner than the abdominal wall. This allows for a clearer image, as the sound waves have a shorter distance to travel. During the ultrasound, you will lie on an examination table in a position like having a pelvic exam. The vaginal ultrasound transducer will be gently inserted into your vagina to evaluate the pelvic structures. As the sound waves strike the tissues, they reflect towards the transducer, projecting a white image on the screen. When passing through fluid, the sound waves appear black. The uterus appears in whites and grays, while the ovarian follicles, which contain the oocytes (eggs), will appear as black sacs. The oocytes themselves cannot be seen. With each ultrasound, the uterus, the uterine lining, and the number and size of the ovarian follicles are evaluated. A baseline ultrasound is required before starting the cycle to make sure the ovaries and uterus are at their "baseline state" and ready to begin ovarian stimulation. The procedure is not uncomfortable or painful. There are no known risks associated with the use of medical ultrasound. You may experience some vaginal discharge after your ultrasound due to leakage of the gel used on the vaginal probe.

Blood Tests (Estradiol/Progesterone/LH): Estradiol is a hormone that is produced by the growing follicle. Its main function is to cause the endometrium (uterine lining) to grow to a thickness that will support an early pregnancy. In normal menstrual cycles, estradiol is also responsible for helping to control the secretion of FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone). The estradiol level provides a reflection of how well the ovaries are responding to therapy. The level of estradiol also helps indicate how many follicles, as seen during ultrasound, are active. Progesterone is usually produced in small amounts by the growing follicle and large amounts by the corpus luteum after ovulation. After ovulation, the progesterone converts the endometrium to a secretory state in preparation for embryo implantation. LH matures the oocyte and will cause ovulation to occur. We monitor this level to make certain we properly time intercourse or insemination.

It is important that you are available to receive treatment instructions from the Clinical Team. We recommend that you provide a telephone number with an active voicemail and a signed consent form allowing nurses to leave detailed messages at this number. We also encourage patients to sign a consent form for email communication.

NATURAL CYCLES

Natural cycles are treatment cycles where no medications are taken but monitoring occurs. Baseline ultrasound and blood work is performed to evaluate your ovaries, uterine lining, and hormonal status. In order to determine when ovulation might be occurring, mid-cycle ultrasound and blood work are performed. The Clinical Team will advise you as to what day of your cycle you should come to the office for this ultrasound, as this day is dependent on your cycle length (the number of days between your periods). For example, if you have periods every 28 days, you would be scheduled for the mid-cycle ultrasound and blood work on cycle Day 12.

IUI (INTRAUTERINE INSEMINATION)

An IUI is a procedure done in the office. It involves the collection of a semen sample through masturbation. If it is not at all possible to collect a sample through masturbation, a seminal collection device can be worn during intercourse. The sample is then processed or "washed," which takes approximately 45 minutes. The same process holds true for those using donor sperm. Once ready, the sample is inserted directly into the uterus with a thin catheter. Your physician may recommend an IUI in conjunction with medication treatments or natural cycles.

ORAL OVULATION INDUCTION

Clomiphene Citrate (Clomid®, Serophene®): Clomiphene Citrate enables many women to ovulate by improving and coordinating the pituitary gland signals that cause a follicle in the ovary to mature and prepare the oocyte for release. Clomiphene Citrate is given to women whose pituitary gland can function but needs to be regulated in order to work effectively. It is also used to improve the quality and timing of ovulation in women who ovulate on their own.

If your physician prescribes Clomiphene Citrate, it is important that you understand the treatment, its effects, risks and benefits. Clomiphene Citrate is taken each month until you become pregnant or your physician determines that another kind of medication or treatment is preferable. Most women take Clomiphene Citrate for up to 3 months. It is typically recommended that you meet with your physician after 2-3 cycles of Clomiphene Citrate to discuss future treatment options should your last cycle not result in a pregnancy.

You will begin taking the medication on the third, fourth, or fifth day of your menstrual cycle after your baseline ultrasound and blood work. Clomiphene Citrate is typically taken for 5 days. Sometimes it is necessary to increase the dosage or number of days taking the medication. The amount of Clomiphene Citrate taken each day varies from woman to woman, depending on her hormonal status and her response to the medication. The goal is to induce ovulation with the minimal dose of Clomiphene Citrate. A mid-cycle ultrasound and blood work are typically performed on or about Day 12 of your cycle. You will be instructed on which day to return. This provides information about the growth of the follicle(s) and development of the uterine lining.

> **Potential Side Effects of Clomiphene Citrate:** The most common complaint is mood alteration, like PMS. Infrequently, women may experience hot flashes, decreased cervical mucus, headaches, and visual disturbances. Clomiphene Citrate antagonizes the effect of estrogen, which is the hormone that thins and increases the amount of mucus in the cervix and vagina. As a result, the potential decrease in the amounts of vaginal secretions and cervical mucus may make your vagina feel dry during sexual intercourse. You can use a lubricant called Pre-Seed. This effect on the estrogen receptors can also prevent thickening of the lining in the uterus. A thin uterine lining can reduce the chance of pregnancy. Clomiphene Citrate is associated with an increased risk of multiple pregnancies. Approximately 5-8% of pregnancies that occur with Clomiphene Citrate will be twins; triplets or more occur rarely. Approximately 5% of women develop benign cysts on their ovaries caused by the stimulation of the ovary by the Clomiphene Citrate. These cysts may cause a woman to have lower abdominal pain and a bloated feeling in the abdomen. These cysts almost always resolve after discontinuing the medication. It is recommended you decrease physical activity after ovulation. Symptoms usually occur 1 week after the last pill and continue for 1-2 weeks. Within 1 month of cessation of the treatment, any side effects from Clomiphene Citrate should disappear.

Letrozole (Femara®): Letrozole is an oral medication that inhibits the enzyme that is responsible for the production of estrogen. As a result of decreasing estrogen feedback, the pituitary gland is stimulated to produce hormones that can then stimulate the ovary to produce follicles. Its primary use and its indication for FDA approval has been for the treatment of breast cancer. Use for fertility is permissible by the FDA but is considered an "off-label" indication. As with Clomiphene Citrate, Letrozole is given to women whose pituitary gland can function but needs to be regulated in order to work effectively. It is also used to improve the quality and timing of ovulation in women who already ovulate. If your physician prescribes Letrozole, it is important that you understand the treatment, its effects, risks and benefits.

You should have a blood test performed to confirm that you are not pregnant prior to taking Letrozole. Letrozole can only be taken before ovulation. It is not advisable for women with liver disease to take Letrozole. As with Clomiphene Citrate, Letrozole is taken each month until you become pregnant or your physician determines that another kind of medication or treatment is preferable. Most

women take Letrozole for up to 3 months. It is typically recommended that you meet with your physician after 2-3 cycles of Letrozole to discuss future treatment options should that last cycle not result in a pregnancy.

You will begin taking the medication on the third or fourth day of your menstrual cycle after your baseline ultrasound and blood work. Letrozole is typically taken for 5 days. Sometimes it is necessary to increase the dosage or number of days taking the medication if there is a history of diminished response. The amount of Letrozole taken each day varies from woman to woman, depending on her hormonal status and her response to the medication. A mid-cycle ultrasound and blood work are typically performed on or about Day 12 of your cycle. You will be instructed on which day to return. This provides information about the growth of the follicle(s) and development of the uterine lining.

Potential Side Effects of Letrozole: Like Clomiphene Citrate, Letrozole is associated with an increased risk of multiple pregnancies by approximately 5%. Letrozole is typically tolerated well and may be associated with mild headaches. An initial study suggested that Letrozole might be associated with an increased risk of certain birth defects; however, subsequent studies have not found this to be true. Given how quickly Letrozole leaves the body, it is unlikely that Letrozole is truly associated with birth defects.

HCG (Human Chorionic Gonadotropin) (Profasi®, Pregnyl®, Ovidrel® or Novarel®): HCG is administered by subcutaneous injection and comes in a pre-filled syringe. The hCG injection will cause the final maturation and release of the oocytes from the follicles. The blood work and ultrasound monitoring determine the timing of the hCG injection. We recommend you obtain this medication ahead of time, as it often requires pre-authorization from your insurance company. You administer this injection at home. Since ovulation is expected 2 days after the hCG injection, you will be advised to have sexual intercourse during this time. If you are being inseminated, the insemination is scheduled for 2 days after the hCG injection.

GONADOTROPIN THERAPY

Gonadotropins are the hormones FSH and LH, which are both normally secreted by the pituitary gland. FSH is responsible for the selection and growth of developing follicles. By giving more FSH, more follicles can be selected to develop. LH is primarily responsible for the final maturation of the oocyte and for causing ovulation, but also contributes to the development of the follicle. Gonadotropins are administered by subcutaneous injection (injections given into the fatty tissue). The medication is administered daily for approximately 7-10 days. Response to the medication is monitored with frequent blood work and ultrasound.

There are 3 gonadotropins used for stimulating follicle growth. Your physician will select the medication or combination of medications that are most appropriate for you.

Menopur®
- ✓ equal amounts of FSH and LH
- ✓ subcutaneous injection

Follistim®
- ✓ only FSH
- ✓ subcutaneous injection

Gonal F®
- ✓ only FSH
- ✓ subcutaneous injection

Potential Side Effects of Gonadotropins: The use of gonadotropins is associated with an increased risk of multiples in a pregnancy. Approximately 15% of pregnancies that occur with gonadotropins are twins. Triplets or greater occur in 2-3% of pregnancies.

Approximately 5% of women develop benign cysts on their ovaries caused by the stimulation of the ovary by the gonadotropins. These cysts may cause a woman to have lower abdominal pain and a bloated feeling in the abdomen. These cysts almost always resolve after discontinuing the medication. It is recommended you decrease physical activity after ovulation. Symptoms usually occur prior to ovulation and continue for 1-2 weeks.

In less than 1% of women, the ovaries can get quite enlarged, and fluid can accumulate in the abdomen. This is called OHSS (Ovarian Hyperstimulation Syndrome). In rare cases, the fluid will need to be drained and hospitalization may be required. As a result of the fluid leaving the blood vessels, there is an increased risk of clotting problems, including deep venous thrombosis(DVT), pulmonary embolism, and stroke. The cause is unknown, but it is associated with high estrogen levels.

Frequent ultrasounds and hormone levels alert physicians to patients who are at increased risk for OHSS. Early symptoms may include weight gain (over 5 pounds), bloating, nausea, vomiting, diarrhea and shortness of breath. This typically improves within a few days. Other potential side effects include symptoms of estrogen excess, (dizziness, nausea, headaches, mood swings, irritability, fluid retention) and local irritation at the injection site. Ovarian enlargement with twisting of the ovary (torsion) can rarely occur. Any side effects from gonadotropins should disappear within 2-3 weeks of treatment.

HCG (Human Chorionic Gonadotropin) (Profasi®, Pregnyl®, Ovidrel® or Novarel®) is the "pregnancy hormone" and its actions are identical to LH but lasts longer in the body. HCG is necessary to cause the final maturation of the oocyte. HCG is administered by subcutaneous injection and comes in a pre-filled syringe. Additional information regarding hCG is provided in page 10.

MEDICATIONS USED AFTER OVULATION

Progesterone (Endometrin®, Crinone®): Progesterone is a hormone normally produced by the corpus luteum. The corpus luteum is what the ovarian follicle turns into after ovulation. Progesterone alters the lining of the uterus, providing an appropriate environment for the implantation of the embryo. Your nurse will tell you if progesterone has been recommended and, if so, what day to start the progesterone, the dosage, and when to stop. Progesterone supplementation can delay your period.

Potential Side Effects and Risks of Progesterone: Use of progesterone can be associated with breast tenderness, bloating, mild abdominal, and nausea. As we only use natural progesterone, there is no increased risk to the fetus for birth defects, miscarriage or other pregnancy complications.

POST-TREATMENT FOLLOW-UP

Should you get your period after a Clomiphene Citrate, Letrozole or a Gonadotropin cycle, you should call the office on the first day of your menstrual cycle for instructions.

If you do not get your period approximately 16 days after the hCG is administered, call the office to schedule a pregnancy test. If your pregnancy test is negative and you are not using progesterone, you should expect a period shortly. If you are using progesterone supplements you will be asked to discontinue the medication. If your pregnancy test is positive, a nurse will instruct you on how often you will need to continue monitoring and will be available to address any pregnancy-related issues or concerns. Pregnancy monitoring generally involves weekly blood tests and ultrasounds until you are discharged to your obstetrician at approximately 10 weeks gestation.

IVF (IN VITRO FERTILIZATION) TREATMENT

IVF (In Vitro Fertilization) is a method of assisted reproduction in which sperm and oocytes are combined outside the uterus in a laboratory dish. If fertilization occurs, one or two of resulting embryos are transferred into the uterus where one or more may implant in the uterine lining and develop.

PRELIMINARY TESTING

The tests described below are specific for preparation of an IVF cycle. Please review pages 6 and 7 for additional preliminary tests.

HSG (Hysterosalpingogram) or Saline Sonogram (Sonohysterography): These diagnostic tests are performed to evaluate the interior of the uterine cavity and the fallopian tubes.

Hysteroscopy: This is performed to evaluate the uterine cavity for any abnormalities that may prevent implantation or continuation of a pregnancy.

Infectious Screening: (HIV I/2, Syphilis, Hepatitis B and C, Chlamydia and Gonorrhea): Though recommended for all patients, this testing must be performed prior to IVF, per guidelines established by the American Society for Reproductive Medicine.

Mock Transfer: During the mock transfer, a catheter is inserted into your uterus to determine the direction and length of the uterine cavity. This is done to provide necessary information regarding the pathway into the uterus so that the embryo transfer can occur in the smoothest possible fashion. The mock transfer requires a full bladder.

IVF NURSE CONSULT

Prior to starting your cycle, you will have an IVF Nurse Consult. The consult will provide you with all the pertinent information you will need to go through an IVF cycle. If applicable, we encourage partners to attend the session. The consult reviews important information regarding your IVF treatment including how to mix and administer medications, possible side effects and risks involved with IVF treatment, how to prepare for oocyte retrieval and embryo transfer, an explanation of the required consent forms and other important information to help you through this process. The consult is a good opportunity to have your questions answered and for both partners, if applicable, to sign the consent forms.

Detailed consent forms providing information about the procedure(s) that you will be undergoing will be given to you prior to your consultation with the IVF Nurse. Please read the consent forms carefully and make sure that you bring your questions to our attention. All consent forms must be signed by both you and your partner (if applicable) prior to the start of your cycle. A designated employee or notary public must witness the signing of these consent forms or they must be completed via DocuSign.

MEDICATIONS USED IN AN IVF CYCLE

Below is a list of the medications that are generally used during an IVF cycle. Your physician will determine the appropriate medication choices for your treatment cycle. Please contact your IVF nurse if you have any questions regarding your medications.

Adjuvant Medications:

OCPs (Oral Contraceptives): are an oral medication that contains a synthetic estrogen and progesterone-like compound. OCPs offer several advantages for patients seeking IVF treatment, including allowing flexibility in scheduling and starting your IVF cycle. There are many different types of OCPs. Our physicians prefer the monophasic pills, which have a single dose of each hormone throughout the pack. If you have used birth control pills in the past that you tolerated well and fits the criteria, please let us know and we may prescribe this pill for you. OCPs may be used in several different ways, depending on your medical history.

Potential Side Effects and Risks of Oral Contraceptives: Nausea, breast tenderness, increased appetite, weight gain, acne, increased breast size, and headaches can occur with OCP use. The following are rare complications of OCPs: thromboembolic events (stroke, deep venous thrombosis, and pulmonary embolism), benign and malignant tumors of the liver, and high blood pressure. However, if you smoke heavily, are over 35 years old and smoke, or have serious heart disease you may be at an increased risk for these complications. The side effects and risks are uncommon, especially for the short duration that you will be on OCPs.

Estradiol (Estrace®): is a supplemental estrogen that can be used to prepare the body for an IVF cycle. It is also used in FET (Frozen Embryo Transfer) or OD (oocyte donation) cycles to ensure the development of a healthy uterine lining. Estrogen tablets are usually taken orally but may also be inserted vaginally. You will be instructed how to administer the estrogen, what day to start, the dosage, and when to stop. The estrogen we use is identical to the estrogen that your own body makes. While natural estrogen has been used since the 1980's to promote pregnancy in IVF, there is no official labeling available for this use. Do not be alarmed that the accompanying package inserts fail to mention the usage of natural estrogen and progesterone products to support pregnancy, as all estrogens (natural and synthetic) have identical package inserts.

Potential Side Effects and Risks of Estradiol: Breast tenderness and headaches can occur with estradiol use. The following are rare complications of estradiol: thromboembolic events (stroke, deep venous thrombosis, and pulmonary embolism). The side effects and risks are uncommon, especially for the short duration that you will be taking estradiol. It is important that you inform your physician if you have had a history of endometrial cancer, breast cancer, cardiovascular events (heart attack, stroke, venous thrombosis, pulmonary embolism), arterial vascular disease, or if you smoke cigarettes or use tobacco. Avoid taking estrogen with grapefruit juice, as the grapefruit juice may elevate the drug level of the medication.

GnRH Analogues (Gonadotropin-Releasing Hormone Analogues): GnRH analogues are used in IVF to prevent premature ovulation. GnRH is a small peptide hormone that normally is responsible for stimulating the release of FSH and LH from your pituitary gland. FSH and LH are responsible for follicular development and ovulation, respectively. In an IVF cycle, the goal is to develop multiple follicles so that multiple oocytes may be harvested. If ovulation was to occur and the oocytes were released from the follicles, oocytes would not be able to be collected. GnRH analogues prevent ovulation by blocking the pituitary gland's ability to secrete FSH and LH. There are two basic classes of these analogues: agonists and antagonists. Agonists have the same action as the natural hormone while antagonists block the natural hormone action.

Leuprolide Acetate or (Lupron® 14-day Kit) is a GnRH agonist. Leuprolide acetate can be used in several different ways. When used in higher doses after ovulation, it can suppress pituitary FSH and LH release and prevent premature ovulation. When used in micro-doses at the beginning of the cycle, it can stimulate FSH and LH release and assist in stimulating the ovaries, as well as prevent ovulation. If used dosage mid-cycle, it will act on the pituitary gland to stimulate hormone release and will trigger the final maturation and release of oocytes from the follicles.

Potential Side Effects and Risks of Leuprolide Acetate or (Lupron® 14-day Kit): Hot flashes, vaginal dryness, mood swings, vaginal bleeding/spotting, headache, and insomnia. All are short term and generally disappear shortly after the gonadotropins are started. Bone loss is also a side effect of prolonged use of the medication, but not short-term use, as with IVF.

Ganirelix Acetate® Injection and Cetrotide® are GnRH antagonists. They do not allow any FSH or LH release to occur at all. This property allows them to be introduced later in the stimulation, and still be effective in blocking ovulation.

Potential Side Effects and Risks of Ganirelix Acetate® Injection and Cetrotide®: Abdominal pain, headaches, vaginal bleeding/spotting, nausea, and injection site irritation. All are uncommon, short term, and generally disappear after the medication is stopped.

Stimulation Medications:

Clomiphene Citrate (Clomid®, Serophene®) enables many women to ovulate by improving and coordinating the pituitary gland signals that cause a follicle in the ovary to mature and prepare the oocyte for release. Though not frequently used, Clomiphene Citrate may be prescribed in an IVF cycle. Additional information regarding Clomiphene Citrate is provided on page 9.

Letrozole (Femara®) is a synthetic, oral medication that inhibits the enzyme that is responsible for the production of estrogen. As a result of decreasing estrogen feedback, the pituitary gland is stimulated to produce hormones that can then stimulate the ovary to produce follicles. Its primary use and its indication for FDA approval have been for the treatment of breast cancer. Use for fertility is allowable by the FDA but is considered an off-label indication. Though not frequently used, Letrozole may be prescribed in an IVF cycle. Additional information regarding Letrozole is provided in page 9.

Gonadotropins are the hormones FSH and LH, which are both normally secreted by the pituitary gland. FSH is responsible for the selection and growth of developing follicles. By giving more FSH, more follicles can be selected to develop. LH is primarily responsible for the final maturation of the oocyte and for causing ovulation. LH also contributes to the development of the follicle. Additional information regarding gonadotropin therapy provided on page 10.

Trigger Shots:

HCG (Human Chorionic Gonadotropin) (Profasi®, Pregnyl®, Ovidrel® or Novarel®) is the "pregnancy hormone" and its actions are identical to LH but lasts longer in the body. HCG is necessary to cause the final maturation of the oocyte. HCG is administered by subcutaneous injection and comes in a pre-filled syringe. Additional information regarding hCG is provided in page 10.

Lupron may be used in place of hCG on its own or in conjunction with Profasi®, Pregnyl® or Novarel® to trigger the final oocyte maturation.

Your aspiration procedure will be carefully timed to obtain maximum maturity, but retrieval is done before the oocytes are lost to ovulation. Therefore, it is imperative that you take the final medication at the precise time that you are instructed.

Other Medications:

Doxycycline is an antibiotic that reduces the risk of infection as the oocytes are retrieved with a needle through the vaginal wall. The antibiotic will be continued after oocyte retrieval. Tetracycline or Zithromax® may be substituted for doxycycline. Please advise your IVF nurse should you have any medication allergies.

> **Potential Side Effects and Risks of Doxycycline:** Gastrointestinal upset (nausea, vomiting, diarrhea), sensitivity to sunlight, and allergic reactions including: rash, itching, peeling of skin, asthma.

Dostinex (Cabergoline) is a medication that is typically used to decrease the production of the hormone prolactin. Dostinex has been shown to reduce the reduce the occurrence of ovarian hyperstimulation syndrome (OHSS). If used, it is administered after the trigger in those women who are at greatest risk for OHSS (high estrogen levels, very large number of follicles). It is an oral medication that is taken for 8 days.

> **Potential side effects and risks of Dostinex**: Gastrointestinal upset (nausea, vomiting, stomach pain, gas, indigestion, constipation), headache, dizziness, drowsiness, hot flashes, numbness or tingly feeling, dry mouth.

MONITORING

It is essential that close monitoring be performed using ultrasound and blood tests (for estrogen and progesterone) because of the potency of these medications and the risk of complications, particularly OHSS (Ovarian Hyperstimulation Syndrome). Additional information regarding monitoring is provided in page 8.

Most cycles will require approximately 7 visits. During these visits, the relationship between the blood work and ultrasound findings is being evaluated. Once individualized goals for follicle size and estrogen levels have been achieved, hCG and/or Lupron will be administered to complete the final maturation of the oocytes prior to the oocyte retrieval.

OOCYTE (EGG) RETRIEVAL

The oocyte retrieval is a minor surgical procedure performed at the RMA of Philadelphia Surgical Center in King of Prussia. The oocyte retrieval usually lasts less than 30 minutes. During the oocyte retrieval, you will lie on an examination table in a position like having a pelvic exam. Medications, given by the anesthesiologist or certified registered nurse anesthetist, will make you feel relaxed and sleepy. The vagina is thoroughly cleansed with sterile fluid. A long thin needle is passed through the wall of the vagina and into the ovary while ultrasound is used to visualize the pelvic structures and guide the needle. The oocytes are then aspirated from the follicles. This procedure is usually well tolerated but may cause mild discomfort. Rarely the ovaries are not accessible by the transvaginal route and transabdominal retrieval is necessary. Transabdominal retrieval will be discussed with you by your physician if applicable.

After the retrieval, you will stay in the recovery room for approximately 1 hour. When you have fully recovered from the anesthetic, you will be ready for discharge. The recovery room nurse will provide you with instructions on medications and activity level following the procedure. Please arrange for someone to take you home after your oocyte retrieval. Our policy requires that a patient cannot be discharged unless accompanied by an adult. You are NOT allowed to drive after your procedure.

Potential Side Effects and Risks of the Oocyte Retrieval:

- ✓ Injury to structures near the ovaries, such as the bladder, bowel or blood vessels, which requires further surgery
- ✓ Bleeding from the ovaries, possibly requiring surgical treatment with/without the need for transfusion
- ✓ Infection

Oocyte (Egg) Cryopreservation: Oocytes may be cryopreserved for later use. This may be performed prior to medical treatment such as radiation or chemotherapy that may harm the ovaries and oocytes. Oocyte cryopreservation may also be performed in women who wish to delay pregnancy.

INSEMINATION OF THE OOCYTES

Once the oocytes are retrieved, they will be evaluated and prepared for insemination (the combining of the sperm and oocytes to facilitate fertilization) by the embryology team. The semen specimen is also evaluated and prepared for use in the insemination process. Insemination of the oocytes can take place by either placing the sperm with the oocytes in the culture dish ("conventional insemination"), or by injecting a single sperm into an oocyte ICSI (Intracytoplasmic Sperm Injection). The Embryology Team will contact you the day after your retrieval to review your fertilization results. The number of oocytes retrieved and how many oocytes were fertilized will be discussed.

Semen Sample

On the day of the oocyte retrieval, a fresh semen sample is required. This sample could be from a male partner or sperm donor, as appropriate. It is preferred that all semen specimens be produced on-site. If there is concern that a semen specimen cannot be collected on-site, please discuss this matter with the clinical staff before the day of retrieval to make alternate arrangements.

Proper government issued ID must be provided at the time of the specimen collection or drop-off. If the semen specimen cannot be collected by masturbation, a non-toxic sterile SCD (seminal collection device) can be provided. On occasion a sample will be requested to supplement the first or the Embryologist and Physician will recommend using ICSI (Intracytoplasmic Sperm Injection) to increase the chances of fertilization.

Sperm Cryopreservation: If there are concerns regarding the ability to produce a specimen or having sufficient numbers of sperm available on the day of the oocyte retrieval, a specimen may be produced in advance and frozen for use as back-up. Sperm cryopreservation is also used as a way of fertility preservation for males undergoing radiation, chemotherapy treatment or prior to military deployment.

ICSI (Intracytoplasmic Sperm Injection) is the technique where one sperm is injected directly into one oocyte. The procedure is performed by piercing the zona pellucida (the glycoprotein "shell" around the oocyte) with a micro-needle containing a single sperm. This is done using a micromanipulator, which consists of four parts: a high-powered microscope, a glass micro-tool, a micro-tool holder, and a controlling device that translates the movement of a joystick into three dimensional movements of the micro-tool. The sperm is then injected into the cytoplasm of the oocyte. The goal of ICSI is to increase the chance of fertilization for those patients whose

sperm might otherwise be unable to penetrate the oocyte on their own. Only the oocytes found to be mature at the time of ICSI will be injected, as only these oocytes are ready to accept the sperm and be fertilized. Couples that may benefit from this technique are those with severe male infertility (low count, low motility, and low percentage of normal forms), male partners having undergone vasectomy reversal, sperm obtained from the testis or epididymis, prior unsuccessful fertilization, and prior ICSI.

Prior to the micromanipulation, the oocytes are treated with an enzyme that will remove the cumulus cells surrounding the oocyte, facilitating visualization of the oocyte. The oocyte is held in place with a holding pipette, while the micro-needle containing sperm is introduced through the zona pellucida into the oocyte. The sperm is injected into the oocyte and the micro-needle is removed. The micro-manipulated oocyte is then released by the holding pipette and washed with a fresh culture medium.

All subsequent treatment will be the same as for non-manipulated oocytes. Any embryos that develop normally after this procedure may be transferred to the uterus or frozen for transfer later.

Potential Risks Associated with ICSI:

- ✓ The oocytes may be damaged, which could threaten their viability
- ✓ Fertilization may not occur
- ✓ Cleavage (cell division) of the fertilized oocyte may not occur
- ✓ The embryo may not develop normally and therefore pregnancy may not occur
- ✓ Patients with very low sperm counts or without sperm in their semen may transmit the genetic cause of this problem to male offspring. These genetic abnormalities may occur in up to 10% of certain groups of patients
- ✓ The increased risk of sex chromosome abnormalities in children born through IVF with ICSI cannot be totally ruled out

Surgical Isolation of Individual Spermatozoa: is when men have severe Oligospermia (sperm only seen after centrifuging the specimen) or Azoospermia (no sperm in the ejaculate) the sperm can sometimes be obtained directly from the reproductive tract. If on the same day both partners are undergoing IVF related surgical procedures that require the use of intravenous anesthesia, arrangements should be made for a third party to escort both patients home.

MEDICATIONS USED AFTER OOCYTE RETRIEVAL (FRESH EMBRYO TRANSFER):

Progesterone is a hormone that is normally produced by the corpus luteum. The corpus luteum is what the ovarian follicle turns into after ovulation. Progesterone alters the lining of the uterus, providing an appropriate environment for the implantation of the embryo. After the oocyte retrieval, the female partner will be given natural progesterone to increase the chances for successful implantation, as the ovary's ability to secrete progesterone may be hindered by the GnRH analogs as well as by the aspiration itself. The progesterone is given vaginally or by daily intramuscular injection. If you become pregnant, you will continue to take it until 8 to 12 weeks of pregnancy, at which time the placenta is making sufficient amounts of progesterone and supplementation is no longer necessary. Your IVF nurse will instruct you what day to start the progesterone, the dosage, and when to stop.

Potential Side Effects and Risks of Progesterone: Progesterone use can be associated with breast tenderness, bloating, and nausea. As we use only natural progesterone, there is no increased risk to the fetus for birth defects, miscarriages or other pregnancy complications.

Estradiol (Estrace®) is a supplemental estrogen that can be used to help support the uterine lining after an embryo transfer. Estrogen tablets are inserted vaginally. For more information refer to page 13.

EMBRYO DEVELOPMENT

The embryos will remain in culture up to 7 days from the day of the oocyte retrieval (Day 0). During that time, they should progress from a 1-cell zygote, to an 8-cell embryo on Day 3, to a blastocyst (100+ cells) on Days 5, 6, or 7 in culture.

It is important to understand that not all embryos possess the potential to lead to a pregnancy. We normally expect some embryos to slow or stop their growth during the course of their development in culture. It is possible that in rare circumstances, no embryos will develop to reach the blastocyst stage.

Embryo transfer at the blastocyst stage allows us to transfer fewer embryos (to reduce the rate of multiple pregnancies) while maintaining high pregnancy rates.

Potential Risks of the Insemination and Culture of the Oocytes and Embryos Include:

- ✓ Not all the oocytes retrieved may be normal
- ✓ It is possible that none of the oocytes may fertilize or that they may fertilize abnormally
- ✓ Cell division after fertilization may not occur or the embryo(s) may not develop normally
- ✓ Inability of the male partner to produce a semen specimen or acquire sperm of sufficient quantity or quality to allow for normal fertilization

Assisted Hatching (AH) involves thinning the zona pellucida, the outer layer of the embryo. All embryos will undergo assisted hatching. The procedure involves the use of a micromanipulator to hold the embryo and a laser to thin one area of the zona pellucida. This creates an opening in the zona pellucida. As with all IVF procedures, every attempt is made to manipulate the embryo as carefully and gently as possible.

Potential Risks Associated with AH: Detrimental effects to the embryos are exceedingly rare; however, single cells within the embryo may be damaged. Information available currently indicates that this does not appear to affect the overall developmental potential of the embryo. The exact likelihood of success following the hatching process for a given embryo or patient cannot be predicted. However, the implantation rate per embryo rises. The micromanipulation itself may produce abnormal embryos or may cause immediate degeneration of the embryos. Technical problems may make successful micromanipulation impossible. The chances of having identical twins may be increased. Identical twins carry all the risks of any multiple pregnancy, as well as possibly sharing the placenta and a very small risk of umbilical cord accidents.

PGT (Pre-implantation Genetic Testing)

PGT can be used to ensure that embryos of the highest quality are being transferred. PGT is accomplished using micromanipulation techniques on embryos 5, 6 or 7 days after the retrieval. A few cells that are already hatching from the embryo are removed with a small suction pipette. These cells are then sent to an outside laboratory where the specific testing is done. The embryos themselves never leave the RMA of Philadelphia laboratory.

PGT-A (Aneuploid) is the process by which embryos are screened for chromosomal abnormalities prior to embryo transfer. Embryos that are found to be chromosomally abnormal are not eligible for transfer. PGT-A identifies the embryos most likely to achieve a pregnancy, thereby maximizing the likelihood of a successful outcome. It also reduces the risk of miscarriage.

PGT-M (Mutation) is the process by which embryos are evaluated for specific genetic abnormalities prior to embryo transfer. We apply this technology to couples with a known risk for passing on specific inherited diseases that are isolated to specific genes or chromosomes.

Other options currently available for the genetic testing of a conception include: chorionic villus sampling (done in the first trimester of pregnancy) and amniocentesis (done in the second trimester of pregnancy). There are other less sensitive but noninvasive testing options that can be performed once pregnant. The advantage of PGT is that a diagnosis may be made while the embryos are in the lab and therefore only normal embryos are transferred.

Over the last twenty years, over 50,000 cycles have been performed and over 10,000 babies have been born worldwide using PGT techniques. Currently, there appears to be no increased risk of fetal malformations or other identifiable problems with this procedure.

Detailed counseling and informed consent will be provided for couples requiring this therapy. This technology can only be performed if it is planned in advance.

Embryo Cryopreservation

It is RMA of Philadelphia's policy to transfer the fewest number of embryos possible during an IVF cycle in order to minimize the risk of multiple pregnancies. With your consent, we will freeze all high-quality embryos that reach the blastocyst stage of development. The embryos that are viable to be frozen are stored in liquid nitrogen. Liquid nitrogen is an inert gas that has been cooled to a liquid (nearly - 200˚C). The time an embryo can remain frozen, undamaged, appears to be indefinite.

Consent forms are required regarding the disposition of the frozen embryos under specific circumstances. At your request, they may also be discarded, donated, or shipped to another facility for storage or use.

Potential Risks of Embryo Cryopreservation Include:

- ✓ Some of the cryopreserved embryos may not survive the freeze/thaw process or may not resume normal growth when they are thawed.
- ✓ Some of the cryopreserved embryos may not successfully implant when they are replaced into the uterine cavity.

EMBRYO TRANSFER

Our IVF staff will notify you of the day and time of your embryo transfer. If you have a partner, they must be present at time of embryo transfer to complete necessary consent forms prior to the transfer.

Embryo transfer is the process whereby the embryos are removed from the culture media or thawed in the embryology lab and then placed within the uterus. All embryo transfers will be performed at the RMA of Philadelphia Surgical Center in King of Prussia.

The physician and embryologist will discuss the quality of your embryos and make a recommendation on the appropriate number to be transferred. Our goal is to optimize your chance of conception, while minimizing the risk of a multiple pregnancy, in particular, high order multiple pregnancies.

All the embryo transfers are ultrasound guided. This is done to ensure that the embryos are placed in the correct location within the uterine cavity. This ultrasound is transabdominal because using the transvaginal probe (like in the monitoring phase) would get in the way of the transfer. For this type of ultrasound to be effective, your bladder needs to be full. You will need to start drinking water at least an hour and a half prior to your arrival at the Surgical Center. During the embryo transfer, you will lie on an examination table in a position like having a pelvic exam. A speculum will be placed in the vagina. The cervix and vagina are then cleansed with a solution that may be pink or clear. During the actual transfer, a thin catheter will be passed through the cervix and into the uterine cavity. This will be monitored on the ultrasound screen. The embryo(s) will be placed in the uterine cavity when the catheter reaches the correct position. The transfer is a procedure of short duration and is very well tolerated. On occasion, a patient may experience some cramping and discomfort, and possibly a small amount of bleeding or spotting.

Possible complications of embryo transfers are rare, but may include:

- ✓ The embryo transfer may be technically difficult or impossible
- ✓ Infection

FROZEN EMBRYO TRANSFER (FET)

In a FET cycle, an embryo created in a prior IVF cycle is transferred into the uterus that has been specifically prepared in a manner to enhance implantation. During an IVF cycle in which the ovaries are stimulated to mature multiple eggs, levels of estrogen and often progesterone are higher than would be seen during a natural cycle. This often results in the uterine lining developing more quickly than usual, so that it is not as effective in supporting implantation of the embryo. As a result, pregnancy rates with a FET cycle may be higher than with an embryo transfer in a fresh cycle.

Medications used in an FET cycle:

OCPs (Oral Contraceptives): are an oral medication that contains a synthetic estrogen and progesterone-like compound. OCPs offer several advantages for patients seeking IVF treatment, including allowing flexibility in scheduling and starting your FET cycle. Additional information regarding OCPS is provided on page 12.

Estradiol (Estrace®): is a supplemental estrogen that can be used to prepare the body for an IVF cycle. It is also used in FET (Frozen Embryo Transfer) or OD (oocyte donation) cycles to ensure the development of a healthy uterine lining. Estrogen tablets are usually taken orally but may also be inserted vaginally. Additional information regarding estradiol is provided on page 13.

Progesterone is a hormone that is normally produced by the corpus luteum. The corpus luteum is what the ovarian follicle turns into after ovulation. Progesterone alters the lining of the uterus, providing an appropriate environment for the implantation of the embryo. Additional information regarding progesterone is provided on page 16.

Aspirin when used in FET cycles is taken daily as a low dose (typically 81 mg "baby aspirin"). The low dose aspirin may act by increasing blood flow to the uterus by reducing inflammation and the formation of small blood clots.

> **Potential Side Effects and Risks of Aspirin Include:** Increase risk of bleeding including stroke and gastrointestinal bleeding, and allergic reaction.

Embryo Transfer

Embryo transfer is the process whereby the embryos are removed from the culture media or thawed in the embryology lab and then placed within the uterus. All embryo transfers will be performed at the RMA of Philadelphia Surgical Center in King of Prussia. Our IVF staff will notify you of the day and time of your embryo transfer. If you have a partner, they must be present at time of embryo transfer to complete necessary consent forms prior to the transfer. Additional information regarding embryo transfer is provided on page 18.

PREGNANCY TEST

A pregnancy test will be done nine days after the embryo transfer. If your pregnancy test is positive, an IVF nurse will instruct you on how often you will need to continue coming in for monitoring and will be available to address any pregnancy-related issues or concerns that you may have. Pregnancy monitoring generally involves weekly blood tests and ultrasounds until you are discharged to your obstetrician (around 10 weeks) for the remainder of your obstetric care. If your pregnancy test is negative, you will be advised to discontinue your progesterone and to schedule a follow-up appointment with your physician.

PREGNANCY-RELATED INFORMATION

SPOTTING

Spotting is very common in early pregnancy and rarely leads to problems. However, if your spotting is accompanied by cramping pain, please call the office and ask to speak to a nurse.

BIRTH DEFECTS

Birth defects occur in 3% of all pregnancies, and complications that may occur in any pregnancy can occur in a pregnancy after fertility treatment or assisted reproduction. Recent medical studies have suggested that there may be a link between fertility treatments and some health problems. There is controversy surrounding whether IVF increases the risk of congenital malformations. However, even the authors of these studies concede that the relationship between the increased health risks and fertility treatment or IVF is unclear. It is still unknown whether it is the underlying cause of the couple's infertility or the specific treatments for the infertility that cause these increased risks.

MULTIPLE PREGNANCIES

Multiple pregnancies are the most common complication of fertility treatment. For ovulation induction, the risk is directly related to the number of mature oocytes released in the cycle. In IVF, the risk of a multiple pregnancies is directly related to the number of embryos transferred. It is also possible that embryos can split, resulting in identical twins and more implantations than embryos transferred. "High order multiples" refers to a pregnancy with triplets or more. When deciding the number of embryos to transfer, we strive to strike a balance between what provides the highest probability of pregnancy with the lowest probability of having a high order multiple pregnancies.

There are risks to both the mother and the fetus with multiple pregnancies. These risks increase with the number of fetuses in the uterus. Risks to the mother include increased miscarriage rate, pre-term labor, pre-term delivery, pregnancy-induced hypertension, and gestational diabetes. Risks to the fetuses arise primarily because of the maternal complications and include fetal death, cerebral palsy, brain damage, neurological damage, developmental delay and damage to virtually any organ system (eyes, lungs, gastrointestinal tract, in particular). Patients less than 35 years old have a greater risk of twins. We strive to have the highest singleton pregnancy rates, taking into consideration that even twin pregnancies can have many complications for both the mother and fetuses.

Multi-fetal pregnancy reduction is the process by which one or more fetuses are selectively terminated to reduce the number of fetuses. This has been demonstrated to decrease the risks and complications later in the pregnancy. The procedure is performed at about 12 week's gestation and involves potassium injections to terminate the development of one or more of the fetuses. Selective reduction carries a 5% rate of loss of the entire pregnancy. The procedure may not always protect pregnancy from prematurity. Multi-fetal reduction is a complex issue. While it may seem that this is a valid means to maximize the survival of the remaining fetuses, there are many issues for you to consider prior to undergoing this technique. If you are considering it, you will be offered counseling by our physicians and referred to a high-risk pregnancy specialist for further counseling.

ECTOPIC PREGNANCY

Ectopic pregnancies are pregnancies that implant outside the uterus. About 95-97% of them occur in the fallopian tubes. Ectopic pregnancies represent 1-2% of normally conceived pregnancies. In gonadotropin cycles, the ectopic rate is slightly increased. In IVF, the ectopic rate is around 1-3% of all pregnancies. Ectopic pregnancies can be treated with prescription medication or surgically, depending upon the situation. If left untreated, they can rupture and become a life-threatening condition. Our close monitoring of pregnancies enables us to make the diagnosis of ectopic pregnancy as early as possible.

MISCARRIAGE

During the first few weeks of pregnancy, about 80% of normal pregnancies will show doubling of the hCG levels every two to three days. It is important to realize that hCG levels that do not double this way are not always an indication that a pregnancy is not progressing as expected. If your hCG levels do not increase normally, there are several possibilities: you could have a normal pregnancy that is in the "slowest" 20%, the pregnancy could be abnormal and, in the uterus, or the pregnancy could be in the fallopian tube (ectopic). Your levels will be closely monitored until it can be determined which one of these apply.

A miscarriage is the loss of an early intrauterine pregnancy. Most of these early losses are due to an abnormal chromosome complement in the embryo. There is an increased pregnancy loss rate with increasing age. In general, women 35 or younger have about a 15-20% incidence of pregnancies ending in miscarriage. For women 35-40, the approximate rate is 20-25%. For women over 40, the risk is greater than 40%. Treatment options include a D&E (dilation and evacuation), using medication to facilitate passage of the tissue, or allowing the tissue to be passed naturally.