RMA of Philadelphia | Jefferson | RMA of Central Pennsylvania at PinnacleHealth | PINNACLEHEALTH

Highly Personalized Fertility Care

# PATIENT HANDBOOK

Find more patient resources including consent forms, injection training videos, and more at:
www.RMAspecialists.com

**Give Us a Call**
**1-855-RMA-inPA**

# THANK YOU FOR CHOOSING US

Thank you for choosing Reproductive Medicine Associates of Philadelphia and Central Pennsylvania (RMA) for your treatment. We hope your experience with our office is a positive and successful one. We have designed this booklet as a reference guide where you will find general information regarding the major aspects of your diagnostic work-up and therapies. We recommend that as you read each section, take notes of any questions or concerns you may have so that you will remember to address them with your physician or nurse.

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# SECTION ONE:
# GENERAL OFFICE INFORMATION

**Physicians**
Arthur Castelbaum, MD
Martin Freedman, MD
Jacqueline Gutmann, MD
William D. Schlaff, MD

**Nurse Practitioners**
Kelly Graves, RNC, MSN, CNM
Melissa Zegley, BSN, MSN, CRNP

**Director of Clinical Services**
Jennifer Hanna, RN, BSN

**Director of Nursing, Surgery Center**
Erlynn Haberman, RNC, MSN

**IVF Nurse Coordinator**
Jill McDonald, RN, BSN

**3rd Party Reproduction Coordinator**
Dana Tillotson, RNC, BSN

**Director, Embryology Lab**
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**Laboratory Supervisor**
Betty Ignas, MLT (ASCP)

## OFFICE HOURS

| | |
|---|---|
| Monday – Friday | 7:00 AM – 4:00 PM, by appointment only |
| Saturday, Sunday | 8:30 AM – 11:30 AM, by appointment only (King of Prussia Only) |
| Holidays | 8:30 AM – 11:30 AM, by appointment only (King of Prussia Only) |

- Observed Holidays: New Year's Day, Memorial Day, 4th of July, Labor Day, Thanksgiving Day, Christmas Day
  - The King of Prussia office is open with limited hours on these holidays.

## MONITORING HOURS

Monitoring hours are held between 7:00AM-9:45AM at all of our offices during the week. Our King of Prussia office offers monitoring hours between 8:30AM-11:00AM on weekends.

Monitoring refers to the time period blood tests and ultrasounds are performed. You will need to schedule an appointment for your monitoring. While your RMA physician will always try to perform your examination or procedure, operating as a group practice allows RMA to be staffed 365 days per year and provide each patient with the care that is timed to maximize the opportunity for success. As a result, you may be seen by an RMA provider other than your primary physician for monitoring or procedures.

## OUTSIDE MONITORING

Based on your own unique circumstances, you may choose to do your monitoring visits at a non-RMA clinic. For example, you may travel for work and not be able to attend visits in one of our offices. If you require outside monitoring, our clinical team will provide you with a script specifying what you need to have done at your visit. You will provide this script to the fertility clinic where you are monitoring. It is your responsibility to discuss costs and fees for the visit with the clinic. After your visit, our nursing team facilitates our office receiving the results so your physician can make decisions about your care. Once the physician has reviewed your results, instructions will be communicated to you by our nursing team.

RMA charges a medical management fee should you choose to have your monitoring visits done at an outside facility. The fee is $500-$1,000 depending on your treatment cycle type. Our Financial Counselors are available to review this information with you in further detail.

## MEETING WITH NURSES DURING MONITORING HOURS

The nurses are available to meet with you to answer questions, review your treatment cycles, and explain any new instructions provided by the physician after you have had your ultrasound. If you have any questions or concerns, please ask to see the nurse before you leave.

## LEAVING PHONE MESSAGES FOR NURSES OR PHYSICIANS

Our patient services coordinators will gladly take messages and forward them to the nurses or physicians during office hours. Because our nurses and physicians see patients throughout the day, you

may not receive a call back until the end of the day. Phone calls received after 3:45 PM may be returned the following day.

## ANSWERING SERVICE AFTER OFFICE HOURS

After normal business hours, calling our office number will offer the option to connect you to our answering service or give you the opportunity to leave a voice mail. If it is a weekend or holiday and you need to be contacted prior to Monday or the next regular work day, you will need to contact the answering service and they will contact the office or RMA doctor on call.

If your call is urgent, please follow the phone prompts to connect with the answering service. The service will take a brief message and contact number and forward calls to the office or on-call RMA physician. Urgent calls are calls that cannot wait until the next day for a response. Examples of urgent calls are:

- A medical emergency related to your treatment at RMA (e.g. severe cramps with bleeding)
- If you are undergoing treatment and are still waiting for instructions after 4:00PM
- If you do not have a medication you must take that evening

If your call is routine, such as making an appointment or reporting the first day of your menses (if you were instructed by a nurse to come in on day 2, you will need to contact the answering service), please call back during regular office hours. You can also call on weekend mornings by selecting the answering service option and asking to be connected to the weekend staff.

## REQUESTING MEDICAL RECORDS

All requests for copies of your medical records must be submitted in writing. You will need to complete the 'Authorization for Release of Medical Records. This form can be obtained from our patient services coordinators or on the website. Please note that any male records (e.g. semen analyses or lab results) will require a separate medical release to be completed by the male patient.

It may take 10-15 business days for medical records requests to be processed.

## INSURANCE COVERAGE

We are dedicated to helping you become familiar with insurance coverage options related to testing and treatment. Our finance department will contact your insurance carrier and review your coverage with you. However, we also encourage you to contact your insurance carrier directly to ensure you are receiving all the benefits to which you are entitled. At the end of this handbook you will find a valuable worksheet of questions that may help further your understanding of your benefits.

In addition, RMA offers a number of treatment packages for IUI cycles and IVF cycles. These discounted packages help you control the costs of your fertility treatment. For patients undergoing IVF, we offer multi-cycle packages, as well as a refund guarantee program. RMA offers military and first responder discounts and works with a number of organizations to help make treatment more affordable. Our financial counselors can provide you with information on all of these options and assist you in determining the best approach for you as you make your way down the path to parenthood.

The RMA finance department can be reached at 215-938-1515 Monday-Thursday from 7:00AM - 4:00PM and 7:00AM – 3:30PM on Friday.

## COMMUNICATING THROUGH E-MAIL

A patient authorization form for use of electronic mail must be signed before e-mail communication can commence.

To ensure that all communications are only to an e-mail address you have authorized, we ask that you provide us with the e-mail address you are most comfortable being used for communications with RMA. Please include your full name and date of birth whenever you send an e-mail to our office.

## THE NEED FOR PROPER IDENTIFICATION AT RMA

For the protection of our patients, RMA has a strict identity validation policy.

RMA requires a copy of a government issued photo identification (ID) card be kept on file. Your legal name, as spelled out on the ID, will need to appear on all of your records at RMA. We use your social security number as a secondary identifier because it is unique to you; in the absence of a social security number, your date of birth will be used. This duplicate identification system of your legal name and social security number (or date of birth) is necessary to ensure the proper identification and labeling of any specimens, medical records and consent forms.

We require that all consent forms be signed at RMA in front of a designated RMA employee and that your identity be verified with a government issued ID. A photocopy of your ID will be stored with the consent forms.

If you cannot come to our office, a notary public can also verify the signature for each individual signing a consent form. A notary stamp must accompany the notary signature. Only original, signed and notarized consent forms will be accepted if consent forms are completed outside of our office. Upon receipt of the original notarized consent forms, a nurse will review the consent forms to ensure all required fields are completed. If you are dropping off notarized consent forms, please plan accordingly and allow a few extra minutes to accommodate the review process.

# SECTION TWO:
# BASIC HEALTH INFORMATION

## NUTRITION AND BASIC HEALTH RECOMMENDATIONS FOR FEMALES

1. There are no foods that have been proven to affect fertility. Unless you are diagnosed with Celiac disease, there is no evidence that restricting gluten from your diet will aid with 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 the recommended dietary allowance of vitamins and minerals. Avoiding food that is laden with chemicals can be helpful to improve your health.

2. Refrain from smoking and recreational drug or alcohol use, as these are environmental toxins that may affect your fertility.

3. Restrict the amount of:
    - Caffeine to 16 ounces per day, as it can impede the body's ability to absorb iron and calcium.
    - Vitamin A (3,000 IU per day) and vitamin D (no more than 2,000 IU per day), as an excess of either could lead to toxicity affecting you or an early pregnancy.

4. Take folic acid to decrease the chances of spinal cord defects such as spina bifida. The United States Public Health Service has recommended that all women who are attempting to conceive consume a minimum of 400mcg *of folic acid daily.* This daily intake decreases the risk of spinal cord defects by 50%. Women who have had a child with spina bifida should take 4.0 mg of folic acid daily.

    Folic acid can be obtained naturally through dark green leafy vegetables, citrus fruits, nuts, legumes, whole grains, and fortified breads and cereals. To meet this folic acid requirement, RMA can provide you with a prescription for a prenatal vitamin, which contains the recommended maximum daily dose (1.0mg). Alternatively, you can choose to purchase folic acid at your local pharmacy or vitamin store and take it as a supplement to your multivitamin. This folic acid comes in 400 mcg doses and does not require a prescription.

5. Use acupuncture only though licensed professionals. Acupuncture is permitted during your fertility work-up or treatments. However, we recommend that only licensed acupuncturists be used at all times. At your request, our staff will provide you with a referral list of licensed acupuncturists. You may also call professional organizations or your insurance carrier for assistance with identifying licensed practitioners.

6. Avoid *all* herbal medicines. Do not use herbal medicines or preparations or supplements, separately or in conjunction with acupuncture, as they are known to interact adversely with fertility medications. If you are taking any supplements, please advise your physician, as they may have a negative impact on your treatment. For example, fish oil has anti-coagulant (blood thinner) properties that could affect your treatment protocols.

7. If you are on any prescription medication, please inform your nurse or physician.

## NUTRITION AND BASIC HEALTH RECOMMENDATIONS FOR MALES

1. There are no foods that have been proven to affect fertility. Unless you are diagnosed with Celiac disease there is no evidence that restricting gluten from your diet will aid with 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 the recommended dietary allowance of vitamins and minerals. Avoiding food that is laden with chemicals can be helpful to improve your health.

2. Refrain from smoking, recreational drug or alcohol use.

3. Avoid hot tubs or saunas for at least 3 months prior to treatment as sperm function may be negatively affected.

4. If you are on <u>any</u> prescription medications, please inform your physician.
   Medications of particular 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 | Verapamil |
| Diltiazem | Niradazole | |
| Erythromycin | Nisoldipine | |

## COMPLEMENTARY CARE

RMA understands the difficulties inherent in trying to build a family through infertility treatment. Our staff understands that individuals and couples often face emotional, family, or personal challenges that can affect them in many ways.

We are able to provide a list of counselors that offers a variety of services designed to assist patients through their personal journey to have a baby. Whether the goal is to manage stress, resolve conflicts with family and friends about disclosure, cope with pregnancy loss, or confidently make treatment decisions, resources are available to help.

# SECTION THREE:
# INFERTILITY EVALUATION

## PRELIMINARY TESTING / DIAGNOSTIC TESTING

If you have had any of the tests listed below, please provide us with those results. Please be aware that you may be required to undergo certain tests at RMA even if you have had them before. Should you choose to have some of your testing done at an outside facility, it is your responsibility to have these results forwarded to our 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 the cycle is a reflection of a woman's ovarian reserve, or how well we expect the ovaries to respond to stimulation. We generally test all women regardless of age because of the wide range of variation ovarian function in infertility patients. These tests help us to determine which procedures and protocols are most appropriate.

- **Anti-mullerian hormone (AMH):** This test is useful as an additional measure of 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 can be 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 the potentially serious consequences of these preventable diseases, vaccination should be completed prior to initiating treatment. Inherited or genetic disorders can be associated with birth defects, miscarriages 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**: TSH (thyroid-stimulating hormone) 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**

- **Hysterosalpingogram (HSG)** or **Sonohysterography (saline sonogram):** 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. ***Note:*** Some women may require more frequent mammogram testing, depending upon 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 determine if the male partner's sperm is normal. 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 the 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 is due to structural abnormalities in the segment of the Y-chromosome that controls sperm development. A 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, miscarriages and illness in offspring, with screening recommended as appropriate.

**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, the surgery, and the post-operative visit. The physicians at RMA have surgical privileges at the below hospitals:

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

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

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

# SECTION FOUR:
# TREATMENT OPTIONS (NON-IVF)

## MONITORING DURING TREATMENT

During treatment, it is essential that close monitoring be performed using ultrasound and blood tests. This allows us to maximize the likelihood of pregnancy while reducing the risk, particularly those associated with medications used to enhance ovulation.

When your menstrual period begins, please call the office where you would like to have your baseline evaluation performed. Should your menstrual period begin after RMA office hours or on a Saturday or Sunday, please call the office early the next morning. You will need an ultrasound and hormone blood tests on day 2, 3 or 4 of the menstrual cycle *before* starting any medications. Your monitoring must be performed in the morning to obtain the blood test results the same day.

**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 similar to 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 back 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 (oocytes), will appear as black sacs. The oocytes themselves cannot be seen. With each ultrasound, the uterus, the uterus 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 uterine lining (endometrium) 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 (uterine lining) 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.

Most treatment cycles require 3-5 monitoring visits. During these visits, the relationship between the blood work and ultrasound findings is being evaluated.

It is important that you are available to receive instructions from nursing. We recommend that you provide the office with a telephone number with active voicemail and sign a consent form allowing nurses to leave detailed messages at this number. We also encourage patients to provide an email address and consent to this form of communication. If you have not been contacted with your results by 3:30PM, please call our office.

## NATURAL CYCLES

Natural cycles are treatment cycles where no medications are taken but monitoring occurs. A 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 physician or nurse will advise you as to what day in 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.

## INTRAUTERINE INSEMINATION (IUI)

The IUI is a procedure done in the office by the provider. It involves the collection of a semen sample through masturbation or intercourse with the use of a seminal collection device. The sample is processed or "washed," which takes approximately 45 minutes. Once ready, the sample is inserted directly into the uterus by means of 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 (fluid filled sac that nurtures the oocyte) in the ovary to mature and prepare the oocyte for release. Clomiphene citrate is given to women whose pituitary gland is able to 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 doctor prescribes clomiphene citrate, it is important that you understand the treatment, its effects, its risks and its benefits.

Clomiphene citrate can also be used to perform a clomiphene citrate challenge test (CCCT), which can give your physician information about the functioning of your ovaries and your ovarian reserve. You will take clomiphene citrate (also known by brand names Clomid® and Serophene®) and have hormone blood tests on specific days of your cycle. An elevation in the hormone levels indicates an abnormal CCCT. If recommended by your doctor, the nurse will provide specific instructions for this test.

Clomiphene citrate is taken each month until you become pregnant or your doctor 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 that last cycle not result in pregnancy.

You begin taking the medication on the 3rd, 4th, or 5th day of your menstrual cycle after baseline ultrasound and blood work and continue it 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 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 is typically performed on or about day 12 of your cycle, 3-5 days after the last clomiphene citrate pill. The nurse will advise exactly which day to return to the office. This ultrasound provides information about the growth of the follicles, and development of the uterine lining. In addition to clomiphene citrate, this type of cycle typically requires a second drug, human chorionic gonadotropin (hCG) (Ovidrel®). Human chorionic gonadotropin (hCG) (Ovidrel®) is administered by subcutaneous injection and comes in a pre-filled syringe. The hCG (Ovidrel®) injection will cause the final maturation and release of the oocytes from the follicles. The blood work and ultrasound monitoring determines the timing of the hCG injection. We recommend you obtain this medication ahead of time, as it often requires prior 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 period. If you are being inseminated, the insemination is scheduled for two days after the hCG (Ovidrel®) injection.

**Potential Side Effects of Clomiphene Citrate**

The most common complaint is mood alterations, similar to PMS. Infrequently, women have 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 a multiple pregnancy. Approximately 5-8 percent of pregnancies that occur with clomiphene citrate will be twins. Triplet or greater pregnancies 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 the 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 one week after the last pill and continue for one to two weeks.

Within one month of cessation of the treatment, any side effects from clomiphene citrate should disappear.

**Letrozole** (Femara®)
Letrozole citrate 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. As with clomiphene citrate, letrozole is given to women whose pituitary gland is able to 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 doctor prescribes letrozole, it is important that you understand the treatment, its effects, its risks and its 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 doctor 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 pregnancy.

You will begin taking the medication on the 3$^{rd}$ or 4$^{th}$ day of your menstrual cycle after a baseline ultrasound and blood work and continue it 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.

As with treatment with clomiphene citrate, a mid-cycle ultrasound will be performed on or about day 12 of your cycle, 3-5 days after the last letrozole pill. The nurse will advise exactly which day to return to the office. This ultrasound provides information about the growth of the follicles, and development of the uterine lining. In addition to letrozole, this type of cycle typically requires a second drug, human chorionic gonadotropin (hCG) (Ovidrel®). Human chorionic gonadotropin (hCG) (Ovidrel®) is administered by subcutaneous injection and comes in a pre-filled syringe. The hCG (Ovidrel®) injection will cause the final maturation and release of the oocytes from the follicles. The blood work and ultrasound monitoring will determine the timing of the hCG injection. It is a good idea to purchase this medication. We recommend you obtain this medication ahead of time, as it often requires prior authorization from your insurance company. You administer this injection at home.

Since ovulation is expected within 2 days after the hCG injection, you will be advised to have sexual intercourse during this time period. If you are being inseminated, the insemination is scheduled for two days after the hCG (Ovidrel®) injection.

**Potential Side Effects of Letrozole**
Like clomiphene, letrozole is associated with an increased risk of multiple pregnancy, and is 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 the case. Given how quickly letrozole leaves the body, it is unlikely that letrozole is truly associated with birth defects.

## GONADOTROPIN THERAPY

Gonadotropins are the hormones FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone), which are both normally secreted by the pituitary gland. FSH is responsible for the selection and growth of developing follicles (fluid filled sacs that contain the oocyte). 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).

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

In addition to gonadotropins, this type of cycle typically requires a second drug, human chorionic gonadotropin (hCG) (Ovidrel®). HCG, Human Chorionic Gonadotropin, is used to simulate the normal mid-cycle LH surge, which is necessary to cause the final maturation of the oocyte and ovulation. Ovidrel® is administered by subcutaneous injection and comes in a pre-filled syringe.

As with the oral agents, letrozole and clomiphene citrate, you will be seen for baseline bloodwork and ultrasound. After the baseline tests, you will take the gonadotropins for 3-4 days, then return for an ultrasound and hormone levels. Based on these test results, your medication dosage may be adjusted and you will be informed when to return for repeat testing. It is vital that you know and understand your medication instructions. The average number of days you will take gonadotropins is 8-12 days.

As soon as your doctor discusses the use of injectable medications with your treatment cycle, we will arrange for you to meet with a nurse to learn about your injectable medications and how to administer them. You must schedule this appointment before you begin your period, as you will not be able to start if you have not met with the nurse for process, medication and injection instructions.

Your insurance company may require preauthorization for injectable medications. Injectable medication treatments start on a very specific day of your menstrual cycle. Initiating the pre-approval process as soon as possible will ensure you know exact the exact cost of your medications. As it could take up to five business days for the insurance carrier to confirm the level of coverage for self-injected medications, please do not wait until you are ready to begin your treatment to initiate this process. 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.

**Potential Side Effects of Gonadotropins**

The use of gonadotropins is associated with an increased risk of multiple pregnancy. Approximately 15 percent of pregnancies that occur with gonadotropins are twins. Triplet or greater pregnancies 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 the 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 one week after the last pill and continue for one to two weeks.

In less than 1 percent of women, the ovaries can get quite enlarged, and fluid can accumulate in the abdomen. This is called ovarian hyperstimulation syndrome (OHSS). In rare cases, the fluid will need to drained and hospitalization could be required. As a result of the fluid leaving the blood vessels, there is an increased risk of clotting problems, including deep venous thrombosis, 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 with 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.

## MEDICATIONS USED AFTER OVULATION

**Progesterone**

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. Progesterone options are Endometrin® and Crinone®. 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 cramping, 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 or gonadotropin cycle, you should call the office on the first day for instructions.

If you do not get your period approximately 16 days *after* the hCG (Ovidrel®) is administered, call the office to schedule a pregnancy test. If your pregnancy test is negative, you will be asked to discontinue your progesterone supplementation if you are using one. 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.

# SECTION FIVE:
# TREATMENT OPTIONS: IN VITRO FERTILIZATION (IVF)

IVF, or 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 woman's uterus where one or more may implant in the uterine lining and develop.

## PRELIMINARY TESTING

Please review the earlier section regarding testing (page 10). There are additional tests as described below that are specific for preparation for an IVF cycle.

**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.

**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.

## IVF NURSE CONSULT

Prior to starting your cycle, you will have an IVF Nurse Consult. The consult is protocol specific and will provide you with all the pertinent information you will need to go through an IVF cycle. We encourage partners to attend the session, if applicable. 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 also a good opportunity to have your questions answered and for both partners to sign the consent forms.

## 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. An RMA staff member, or notary public, must witness the signing of these consent forms.

## 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.

**Oral Contraceptives**

Oral contraceptives (OCPs or birth control pills) 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 oral contraceptives; the physicians at RMA prefer the monophasic pills, which have a single dose of each hormone throughout the pack. If you have used a birth control pill in the past that you tolerated well and fits this criteria, please let us know and we may prescribe this pill for you. The 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, 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. **Note:** The side effects and risks are uncommon, especially for the short duration that you will be on oral contraceptives.

**Gonadotropin-releasing (GnRH) analogs**

Gonadotropin-releasing hormone (GnRH) analogs are used in IVF to prevent premature ovulation. GnRH is a small peptide hormone that normally is responsible for stimulating the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) from your pituitary gland. FSH and LH are responsible for follicular development and ovulation, respectively. A follicle is a fluid filled sac in the ovary that contains an oocyte. 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 analogs prevent ovulation by blocking the pituitary gland's ability to secrete FSH and LH. There are two basic classes of these analogs: agonists and antagonists. Agonists have the same action as the natural hormone while antagonists block the natural hormone action.

The GnRH analogs used by RMA of Philadelphia are listed below:

**Lupron® (14-day Kit) or Leuprolide Acetate** is a gonadotropin-releasing hormone (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 in precise 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 Lupron® (14-day Kit) or Leuprolide Acetate:** 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.

**Estradiol (Estrace®)**

Supplemental estrogen (estradiol) can be used to prepare the body for an IVF cycle. It is also used in Frozen Embryo Transfer (FET) or Oocyte Donation (OD) 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 what day to start, the dosage, and when to stop, as well as the route of administration. The estrogen we use is identical to the estrogen that your own body is supposed to make. 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 insert fails to mention the usage of natural estrogen and progesterone products to support pregnancy, as all estrogens (natural and synthetic) have identical package inserts.

It is important that you inform your doctor 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.

**Clomiphene Citrate (Clomid®, Serophene®)**

Clomiphene citrate enables many women to ovulate by improving and coordinating the pituitary gland signals that cause a follicle (fluid filled sac that nurtures the oocyte) 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 in pages 13 and 14.

**Letrozole (Femara®)**

Letrozole 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 provided in page 15.

**Gonadotropins**
Gonadotropins are the hormones FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone), 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 pages 17-18.

The oocytes are retrieved at a precise time in their development. Various medications are used in the final maturation process to optimize maturation for the oocyte retrieval.

**hCG** - Human Chorionic Gonadotropin
Human Chorionic Gonadotropin is the "pregnancy hormone" and its actions are identical to LH, but it lasts longer in the body. hCG is necessary to cause the final maturation of the oocyte. There are several brand names for hCG (Profasi®, Pregnyl® or Novarel®). hCG is administered by subcutaneous injection and comes in a pre-filled syringe.

**Lupron**
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.*

**Doxycycline**
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.

## 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 ovarian hyperstimulation syndrome. Refer to page 12 and 13 for additional details regarding monitoring.

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 will be administered to complete the final maturation of the oocytes prior to the oocyte retrieval.

## OOCYTE (EGG) 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 similar to having a pelvic exam. Medications are given by the anesthesiologist or certified registered nurse anesthetist, which 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 very well tolerated, although, on occasion, can 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 doctor if applicable.

The oocyte retrieval is a safe surgical procedure, but potential rare risks include:

- Unsuccessful oocyte recovery.
- 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.

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.

**Semen Sample**

On the day of the oocyte retrieval, a semen sample is needed from the male partner, unless arrangements have been made in advance to use a partner's previously frozen specimen or frozen donor specimen. It is preferred that all semen specimens be produced on-site at the RMA of Philadelphia Surgical Center collection room. If there is concern that a semen specimen cannot be collected on-site, please discuss this matter with your IVF nurse before the day of retrieval to make alternate arrangements. The male partner must provide photo identification, such as a driver's license or passport, at the time of the specimen collection or drop-off. If the semen specimen cannot be collected by masturbation, a non-toxic sterile seminal collection device (SCD) can be provided. Sometimes the semen specimen collected on the day of the retrieval is poorer than expected and may not be adequate for conventional insemination. In these circumstances, either a second sample will be requested to supplement the first sample,

or the embryology and physician team will recommend using intracytoplasmic sperm injection (ICSI) to increase the chances of fertilization.

**Sperm Cryopreservation**
If there are concerns regarding the male partner's ability to produce a specimen or having sufficient numbers of sperm available on the day of retrieval, a specimen may be produced in advance and frozen for use as back-up.

Sperm may also be cryopreserved for much later use, for example prior to medical treatment such as radiation or chemotherapy that may harm sperm count, or prior to military deployment.

**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.

## MEDICATIONS USED AFTER OOCYTE RETRIEVAL

**Progesterone**
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 in an attempt 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 tell 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.

**Medrol® (methylprednisolone)**
Medrol® is a synthetic corticosteroid hormone. It is given to prevent the immune system from initiating an immune response against the embryos. The dose of Medrol® is small. The only notable side effect demonstrated in patients on this regimen has been the occurrence of vaginal yeast infection. Side effects and certain complications may occur with higher doses and prolonged usage.

**Estradiol (Estrace®)**
Supplemental estrogen (estradiol) is used in Frozen Embryo Transfer (FET) or oocyte Donation (OD) cycles to ensure the development of health uterine lining. Estrogen tablets are inserted vaginally. For more information refer to page 22.

## INSEMINATION

Once the oocytes are retrieved from the female partner, 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 produced by the male partner 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 (intracytoplasmic sperm injection or ICSI). The embryology team will contact you the day after your retrieval to review your fertilization results. The number of oocytes retrieved, whether or not ICSI was performed, and how many oocytes were fertilized will be discussed.

**Intracytoplasmic sperm injection (ICSI)**

ICSI 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 be benefit from this technique include those with severe male infertility (low count, low motility, low percentage of normal forms); male partners having undergone vasectomy reversal, sperm obtained from the testis or epididymis; prior unsuccessful fertilization; and prior ICSI.

The oocytes are obtained in the usual fashion for in vitro fertilization. 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 micromanipulated 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 at a later date.

**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**
When men have severe oligospermia (sperm only seen after centrifuging the specimen) or azoospermia (no sperm in the ejaculate), sperm can sometimes be obtained directly from the reproductive tract.

*If on the same day both partners are undergoing IVF related surgical procedures which require the use of intravenous anesthesia, arrangements should be made for a third party to escort both patients home. Our policy requires that under NO circumstances will a patient be discharged unless accompanied by an adult. Under NO circumstances should a patient recovering from anesthesia drive.*

## EMBRYO DEVELOPMENT

The embryos will remain in culture for 3 to 6 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 and 6 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. If a patient has a large number of normally growing embryos on day 3 of culture, the embryos will be placed into a special media and allowed to grow for 2-3 more days. During this extra time in culture, key metabolic steps are occurring within the embryo that can further separate embryos with potential to lead to a pregnancy from those without. 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 multiple pregnancy rate), while maintaining excellent pregnancy rates. Any extra embryos are cryopreserved. Many patients, however, produce only a small number of embryos. Again, over the initial three days in culture, some will be expected to slow or stop their development. With a limited number of embryos available for transfer, there may be little benefit from additional time in culture; therefore, the embryos may be transferred on day 3.

Risks of the insemination and culture of the oocytes and embryos include:
- Not all of 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)**
Assisted Hatching 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 at this time 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.
- This technology is relatively new, and unknown risks may exist for the baby or mother, although there is none reported to date. The hole in the zona pellucida may decrease its protective effect for the embryo. The higher implantation rate indicates that the overall effect of assisted hatching is likely beneficial.
- 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.

**Pre-implantation Genetic Testing (PGT)**
Preimplantation 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 or 6 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. The embryo(s) recommended for transfer based on the PGT results may be transferred on day 6 of the fresh cycle, if results are available, or during a subsequent frozen embryo transfer cycle if the results cannot be returned by day 6.

Over the last twenty years, over 50,000 cycles have been performed and over 10,000 babies have been born worldwide using PGD/PGS techniques. At this time, 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.

Pre-implantation genetic diagnosis (PGD), a type of PGT, is the process by which embryos are evaluated for genetic abnormalities prior to embryo transfer. RMA of Philadelphia applies this

technology to couples with a known risk for passing on specific inherited diseases that are isolated to specific genes or chromosomes.

Pre-implantation Genetic Screening (PGS), another type of PGT, 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. PGS identifies the embryos most likely to achieve a pregnancy, thereby maximizing the likelihood of a successful outcome. It also reduces the risk of miscarriage.

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). 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.

**Embryo Cryopreservation**

It is the policy of RMA of Philadelphia to transfer the fewest number of embryos possible during an IVF cycle in order to minimize the risk of multiple pregnancies. With your consent, RMA of Philadelphia will freeze all high quality embryos that reach the blastocyst stage of development. Some embryos may not develop to the blastocyst stage; only those with the greatest potential are frozen. The embryos that are available to be frozen are stored in special containers 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. You may elect to have the frozen embryos transferred back to your uterus at a later date in an attempt to initiate a pregnancy. At your request, they may also be discarded, donated, or shipped to another facility for storage or use.

Complications and 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.

There seems to be no greater risk to cryopreservation than for IVF.

Hormonal supplementation may be used to prepare your uterus for the embryos and to optimize the opportunity for a pregnancy in a Frozen Embryo Transfer cycle (FET). The transfer of the frozen embryos will occur in a manner similar to the fresh embryo transfer described below.

The IVF nurse will provide you with specific instructions regarding your regimen for the frozen embryo transfer cycle.

## EMBRYO TRANSFER

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

On the morning of your scheduled embryo transfer, you may receive a phone call informing you that your transfer has been postponed to allow the embryos more time in culture.

Embryo transfer is the process whereby the embryos are removed from the culture media in the embryology lab and then placed within the uterus. Embryo transfers usually occur 3, 5 or 6 days after oocyte retrieval, depending upon your specific embryo characteristics. 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 of 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 we did for 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 1 ½ hours to prior to arrival at RMA of Philadelphia Surgical Center in King of Prussia. During the embryo transfer, you will lie on an examination table in a position similar to 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 embryos will be deposited 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. After the procedure, you will remain resting flat for 10 minutes.

Complications of embryo transfers are rare, but may include:

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

## PREGNANCY TEST

A pregnancy test will be done 14 days *after* the oocyte retrieval. If the embryo transfer is from a frozen embryo or an oocyte donation cycle, the test will be either 9 or 11 days following the embryo transfer depending on the embryo development stage (nine days for blastocyst transfers, and 11 days for cell stage transfers). 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.

# SECTION SIX:
# 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 pregnancy 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.

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 proportion of twins. RMA of Philadelphia strives to have the highest singleton pregnancy rates, taking into consideration that even twin pregnancies can have many complications for both the mother and fetuses.

"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 pregnancy. With decreased number of cleaved embryos transferred and blastocyst culture and transfer, RMA of Philadelphia has aggressively decreased the percentage of high order multiples. Even though the rare successful births of these high order multiple pregnancies are widely publicized, most end in a complete loss or with infants having multiple medical problems due to their prematurity.

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 weeks of gestation and involves potassium injections to terminate the development of one or more of the fetuses. Selective reduction in itself 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.

## MISCARRIAGE

During the first few weeks of pregnancy, about 80% of normal pregnancies will show doubling of the hCG levels every 48 hours. It is important to realize that hCG levels that *do not* double every 48 hours 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, if any, 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 dilation and evacuation (D&E), using medication to facilitate passage of the tissue, or allowing the tissue to be passed naturally.

## 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.

# MEDICATION: SAFE USAGE DURING TREATMENT AND PREGNANCY

**What medications are safe to take during treatment or if I am pregnant and have (a):**

| Ailment | Name Brand Drugs (please note the generic equivalent is also safe) |
|---|---|
| Allergies | Benadryl®<br>Claritin® |
| Cold | Benadryl®<br>Robitussin DM®<br>Tylenol®, Extra-Strength Tylenol® |
| Constipation | Colace®<br>Dulcolax®<br>Fibercon®<br>Metamucil® |
| Headache | Tylenol®, Extra-Strength Tylenol® |
| Menstrual cramps | Advil®,<br>Aleve®<br>Motrin®<br>Tylenol®, Extra-Strength Tylenol® |
| Stomach virus (diarrhea) | Kaopectate®<br>Pepto-Bismol® |
| Urinary tract infection | Most antibiotics are safe in the first trimester. Cipro and tetracyclines, including doxycycline, are not recommended in pregnancy |
| Yeast infection | Monistat 3®, Monistat 7® (external use only during 1st trimester of pregnancy) |

**Pregnancy Category B (no adverse effect to fetus demonstrated) Antibiotics:**

- Amoxil (Amoxicillin)
- Ampicillin
- Augmentin
- Bicillin L-A (Penicillin)
- Ceclor CD
- Ceftin
- Cleocin (Clindamycin)
- Ery-Tab (Erythromycin)
- Flagyl (Metronidazole)
- Keflex (Cephalexin)
- Zithromax (Azithromycin)

# INSURANCE COVERAGE WORKSHEET

**Make sure to have all of the questions below answered when you contact your insurance company to determine your infertility benefits and medication coverage.**

1. Does my insurance cover any infertility treatment?

2. What is the level of coverage? (That is, what will you be responsible for? Are there separate deductibles or co-pays/ coinsurance for infertility treatment?)

3. Are there any specific criteria for coverage?

4. What procedures or treatments are covered? (Ask them specifically about any treatments your physician has discussed with you).

5. What services are covered?

6. Does my insurance cover any prescriptions and is there a specific pharmacy I must use?

7. Does it cover both oral and self-injected medications?

8. Are there any exclusions to the benefit?

9. Are there any limitations?

10. Will I need a referral? How does this process work?

11. What doctors/hospitals are participating providers with my plan? (You may need to ask this question if you are being referred for diagnostic testing elsewhere).

12. Does the treatment require an authorization or pre-approval?

13. Is there any written notification of approval or denial?

Highly Personalized Fertility Care

# RMA at Jefferson and
# RMA of Central Pennsylvania at PinnacleHealth

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**MECHANICSBUG**
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***On behalf of the entire staff at RMA at Jefferson and RMA of Central Pennsylvania at PinnacleHealth, we hope your experience with us is a positive one.***