The Reproductive Medicine and Immunology program is committed to helping couples who have experienced recurrent pregnancy losses, unexplained infertility, repeated IVF-ET failures, history of second or third trimester pregnancy losses of unknown etiology, or pregnancy with a history of or active autoimmune disease. We work with our patients to discover the cause of their pregnancy loss and help them achieve a successful pregnancy. The Reproductive Medicine and Immunology program was established at Rosalind Franklin University of Medicine and Science in 1987. For nearly 30 years, the program has provided evaluation and treatment to patients from across the country and around the world. While attempting pregnancy, we co-manage patients with their reproductive endocrinologist or primary gynecologist. Once pregnancy occurs, we co-manage with their obstetricians or high-risk obstetricians.

MISSION STATEMENT

We are committed to a complete understanding of the role of the immune system in pregnancy and in pregnancy loss by couples whose long journey toward parenthood has been unsuccessful thus far.

Our mission is to open the door to a new dimension through:
• Reproductive immunology research
• Patient education
• Physician education
• State-of-the-art immune testing
• Pregnancy risk assessment counseling
• Immunologic treatment tailored to the problem leading to infertility and pregnancy losses
• Pregnancy monitoring and management for couples experiencing reproductive failure
• Prevention of autoimmune consequence of infertility and pregnancy loss
• Specialized pregnancy monitoring tailored to the needs of reproductive immunology patients
JOANNE KWAK-KIM, MD, MPH
DIRECTOR Reproductive Medicine and Immunology at Rosalind Franklin University Health Clinics

Dr. Joanne Kwak-Kim has spent the last three decades serving women who suffer from recurrent pregnancy loss. Her expertise in Reproductive Medicine and Immunology is matched only by her deep compassion for her patients and dedication to their care.

Dr. Kwak-Kim helps patients from all walks of life and around the globe, providing knowledge and solace to women who have already endured many losses by the time they reach her door. Her patients speak freely of how she turned their lives around — their years of confusion and frustration ended thanks to Dr. Kwak-Kim’s consultation. A pioneer in her field, many of the treatments available in Dr. Kwak-Kim’s office today were developed based on decades of her own research and patient care as the Reproductive Immunology specialty emerged.

As a mentor to CMS students, Dr. Kwak-Kim is an outspoken advocate of the Reproductive Medicine and Immunology specialties. When asked what a Reproductive Immunologist needs in order to succeed, Dr. Kwak-Kim recommends a creative mind, a listener’s ear and a compassionate heart — attributes that have served Dr. Kwak-Kim well in her thirty years of exemplary care.

GIOVANNI JUBIZ, MD, PhD, FACOG

Dr. Giovanni Jubiz is a board-certified OB/GYN, specializing in minimally invasive advanced laparoscopy and robotic surgery for management of pelvic organ prolapse, urinary incontinence and hysteroscopy procedures. He also specializes in the medical management of pelvic pain, abnormal uterine bleeding, infertility and obstetrical care.

Dr. Jubiz completed his OB/GYN residency at Lincoln Hospital (affiliated with Cornell University) in New York. He earned his medical degree from Universidad del Norte and a master’s degree in medical genetics from Javeriana University in Colombia. In 2001, Dr. Jubiz specialized in clinical biochemistry with a major in inborn errors of the metabolism before completing his PhD in medical genetics and human genetics at Howard University in Washington, DC. He is fluent in both English and Spanish.

A fellow of the American Congress of Obstetrics and Gynecology, Dr. Jubiz is also a member of the American Medical Association and the American Association of Gynecologic Laparoscopists.
HEATHER MICHALIDES, RN, MSN, APN
WOMEN’S HEALTH CARE NURSE PRACTITIONER

Nurse practitioner Heather Michalides works collaboratively with the reproductive immunology team at RFU Health Clinics, providing patients with compassionate care and knowledge to help maintain a successful pregnancy and fulfill their dreams of having a child.

As a family nurse practitioner, Heather has more than 25 years of clinical experience in the areas of primary care and obstetrics and gynecology services, specializing in treating conditions such as infertility and endometriosis.

Heather received a bachelor of science in nursing from Valparaiso University in Valparaiso, IN, and a master of science in nursing from the University of St. Francis in Joliet, IL. She is certified by the American Academy of Nurse Practitioners.

MARGARET SULLIVAN, RN, MSN, APN
WOMEN’S HEALTH CARE NURSE PRACTITIONER

Margaret Sullivan received both her Bachelor of Science in Nursing and Master of Science in Nursing from Virginia Commonwealth University in Richmond, VA. She is also credentialed through the National Certification Corporation (NCC).

Margaret has over 15 years of clinical experience as a nurse practitioner. She has worked in busy obstetrics and gynecology practices managing patients in routine and problem-focused gynecological care and throughout pregnancy and postpartum.

Margaret joined Dr. Kwak-Kim’s team in 2012. Since that time, she has become an integral team member assisting women in fulfilling their dream of having a child. She believes in empowering women through knowledge and education. She strives to foster a compassionate, collaborative relationship with each patient, offering the best medical opportunities to succeed.

ALICE GILMAN-SACHS, PhD
DIRECTOR Flow Cytometry Laboratory

Dr. Alice Gilman-Sachs received her PhD in Microbiology and Immunology from the University of Illinois, Chicago. She joined Rosalind Franklin University of Medicine and Science in 1985 and is a founding member of the Reproductive Immunology program. She is an Associate Professor in the Department of Microbiology and Immunology. Dr. Gilman-Sachs has established new immune tests such as the flow cytometric crossmatch, the natural killer cell assay with reproductive immuno-phenotype and T helper 1/T helper 2 cytokine assay. She is an active collaborator in all laboratory research efforts in the department, and is recognized worldwide for her contributions in reproductive immunology.
KENNETH D. BEAMAN, PhD
DIRECTOR Clinical Immunology Laboratory

Dr. Beaman is a graduate of Colorado State University. He received his PhD in Medical Microbiology and Immunology at Ohio State University and served his postdoctoral fellowship in Immunology at Yale University. Dr. Beaman is a Professor of Microbiology and Immunology at Rosalind Franklin University of Medicine and Science. He was instrumental in developing the university’s Clinical Immunology Laboratory, an internationally recognized reference laboratory and a center of excellence.

Dr. Beaman is the recipient of a prestigious FIRST award from the National Institutes of Health and has published numerous articles in prestigious research journals. He has pioneered most of the laboratory testing that is now accepted as standard by reproductive immunologists. Dr. Beaman previously served as Editor-in-Chief of the American Journal of Reproductive Immunology.

SVETLANA DAMBAEVA, MD, PHD

Dr. Dambaeva received her doctor of medicine (MD) degree from Siberian State Medical University in Tomsk, Russia, and her PhD in immunology from the Institute of Immunology in Moscow. She completed her postdoctoral training in obstetrics and gynecology at the University of Wisconsin-Madison. To further her specialization in clinical diagnostics, Dr. Dambaeva completed a Medical Laboratory Immunology Fellowship program, accredited by the American Society of Microbiology, in the laboratory of Dr. Kenneth Beaman at Rosalind Franklin University.

She is board certified as a diplomate by the American Board of Medical Laboratory Immunology. Dr. Dambaeva currently serves as associate director of the Clinical Immunology Laboratory and research assistant professor in the Dept. of Microbiology and Immunology at Rosalind Franklin University. Her research interests include analysis of the immune response at the maternal-fetal interface. Dr. Dambaeva’s goal is to develop and validate novel diagnostic tests that will help physicians identify immune-related causes of pregnancy loss and infertility.

CONTACT US

REPRODUCTIVE MEDICINE AND IMMUNOLOGY
830 West End Court, Suite 400, Vernon Hills, IL 60061
PHONE 847.247.6900 | FAX 847.247.6951

Reproductive Medicine and Immunology has an integrated and highly experienced staff including registered nurses, nurse practitioners, sonographers, medical assistants and patient service representatives.

To send an email, please visit www.rfuclinics.com and click the “Patient Portal Login” link to log in to your patient account and send a message. The portal allows for secure, protected email communication between you and your provider.
WHO CAN BE A CANDIDATE FOR THE REPRODUCTIVE MEDICINE AND IMMUNOLOGY PROGRAM?

Women with:
- Recurrent pregnancy losses
- A pregnancy loss with unknown etiology
- A pregnancy loss after infertility treatment such as ovulation induction or IVF cycles
- Repeated implantation failures after assisted reproductive technology cycles
- Unexplained infertility
- A pregnancy or plan for a conception along with a history of or an active autoimmune disease
- A history of complicated pregnancy with unknown etiology, such as fetal growth restriction, placental abruption, preterm delivery, etc.
- A premature ovarian failure with unknown etiology

WHAT CAUSES RECURRENT PREGNANCY LOSSES?

There are many causes for recurrent pregnancy losses, such as:
- Anatomical causes
- Endocrine causes
- Immunologic causes
- Genetic causes
- Hematological causes
- Miscellaneous causes

The Reproductive Medicine and Immunology program can help couples who are conceiving normally but miscarry multiple times by providing proper assessment and treatment, which often results in significantly increased chances of a successful pregnancy. The Reproductive Medicine and Immunology program is an internationally renowned program in immunological and genetic evaluation and treatment for recurrent pregnancy losses and implantation failures.

RESULTS OF RESEARCH

There is growing evidence that implicates the immune system in pregnancy losses. During early pregnancy, some of the molecular messages from an embryo and maternal hormonal changes may stimulate maternal immune responses to suppress inflammatory (rejection) immune responses (T helper 1 immune response). If these inflammatory immune responses are not suppressed, the mother's immune system will reject the implanting embryo. Such a problem arises particularly in women with autoimmune abnormalities (dormant, active or undiagnosed).
Ultrasound evaluation is one of the most important tools in determining the reason for reproductive failures. Structural abnormalities of the ovary, tubes and uterus can be evaluated in 2-, 3- or 4-dimensional views. Recent advances in ultrasound technology enables physicians to measure blood flow patterns in structures such as the ovary, uterus, placenta, umbilical cord and vessels in the fetal brain. This technology is available as part of the Reproductive Medicine and Immunology program.

**UTERINE BIOPHYSICAL PROFILE**

The Uterine Biophysical Profile is used to predict the outcome of cycles in patients undergoing various infertility treatments. Below is an assessment test to determine uterine competence for implantation.

It is hoped that this biophysical scoring system will be a valuable aid to both patients and their doctors as they prepare for a cycle of conception following immune testing and treatment.

**WHAT DO WE MEASURE?**

- Endometrial layering
- Endometrial thickness
- Endometrial blood flow within zone 3 (inner layer of endometrium)
- Myometrial contractions
- Myometrial echogenicity
- Myometrial blood flow
- Uterine or radial artery blood flow, as measured by resistance index (RI) or pulsatility index (PI)

**WHEN SHOULD THIS EVALUATION BE PERFORMED?**

Three to four days prior to ovulation is the best time for the uterine biophysical evaluation.
WHAT ABOUT PREGNANCY ULTRASOUND FOLLOW-UP?

Since many of our patients are on medication during pregnancy, ultrasound evaluation plays a major role in monitoring the progress of their pregnancy. Fetal growth pattern, blood flow pattern and placental evaluation are some of the areas of major interest for women with reproductive failures. The Reproductive Medicine and Immunology program will determine your need for ultrasound evaluation using state-of-the-art ultrasound equipment.

MEDICATION PREGNANCY AND LACTATION LABELING

The U.S. Food and Drug Administration published a new rule that sets standards for how information about using medicines during pregnancy and breastfeeding is presented in the labeling of prescription drugs and biological products.

The new content and formatting requirements will provide a more consistent way to include relevant information about the risks and benefits of prescription drugs and biological products used during pregnancy and breastfeeding.

The final rule replaces the current product letter categories – A, B, C, D and X – used to classify the risks of using prescription drugs during pregnancy with three detailed subsections that describe risks within the real-world context of caring for pregnant women who may need medication.

The Pregnancy subsection includes information for a pregnancy exposure registry for the drug when one is available. Information in the Pregnancy subsection includes a Risk Summary, Clinical Considerations, and Data. Information formerly found in the "Labor and delivery" subsection is now included in the “Pregnancy” subsection.

The Nursing mothers subsection was renamed, the Lactation subsection, and provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant.

The Females and Males of Reproductive Potential subsection, new to the labeling, includes information, when necessary, about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

ASPIRIN

Low-dose aspirin, 78-81 mg/day, is often utilized for women with blood clotting tendencies like antiphospholipid antibody syndrome and inherited thrombophilia. Low-dose aspirin may be prescribed alone or combined with other treatment.

SIDE EFFECTS
The possible side effects of full dose aspirin, e.g., nausea, heartburn, upset stomach, decreased appetite and blood in stools, are not often seen with low-dose aspirin. On rare occasions, allergic reactions have been observed. Aspirin intolerance manifested by exacerbation of bronchospasm and rhinitis may occur in patients with a history of nasal polyps, asthma, allergic skin reactions or rhinitis. If you have a past history of any of the above, please notify the staff before starting aspirin. Enteric-coated aspirin is also available for women with a history of gastrointestinal side effects from plain aspirin or conditions requiring chronic or long-term aspirin therapy.

INTERACTION
When taking low-dose aspirin, moderation in the consumption of the following foods is recommended: curry powder, paprika, licorice, prunes, raisins, gherkins and tea. In addition, non-absorbable antacid and phenobarbital should be used in moderation.

PREGNANCY
The use of aspirin during pregnancy, in chronic or intermittent high doses, may affect maternal and neonatal blood clotting mechanisms, leading to an increased risk of bleeding. High-dose aspirin may be related to increased perinatal mortality, intrauterine growth restriction, and congenital defects. **Aspirin at low doses (less than 150 mg/day) does not carry these risks.** Doses in excess of 81 mg/day may have side effects, so make sure that medications prescribed for you during your pregnancy do not contain additional aspirin.

BREASTFEEDING
Aspirin is excreted into breast milk in low concentration. Altered platelet function is a potential risk to the nursing infant. If you choose to breastfeed your baby, discuss with your physician regarding the potential risk of aspirin treatment.
HEPARIN

Heparin is an injectable anticoagulant used in women with antiphospholipid antibodies (APA), inherited or acquired thrombophilia who are attempting a pregnancy. Heparin is a blood thinner that facilitates the movement of blood to the growing placenta in early pregnancy. Two forms of heparin are available: unfractionated and low molecular weight. Regular sodium heparin has high molecular weight, in contrast to low molecular heparin. Purified commercial preparations of heparin are nontoxic and side effects from the drug are infrequent.

DOSAGE
Prophylactic heparin dose is 5,000 units subcutaneously once or twice daily.

SIDE EFFECTS
Because heparin is obtained from animal tissue, you should be cautious when you start the injections, especially if you have any history of allergy. Allergic reactions include chills, fever, skin eruptions and, in rare cases, asthma, rhinitis, excessive eye tearing, headache, nausea, vomiting and anaphylactic shock. Before starting therapy, a skin test with 1,000 IU heparin subcutaneously may be done. Sodium heparin can be extracted from either beef or pork. Please inform us if you have an allergy to either.

Heparin can cause mild reduction of platelet count and bleeding. Very rarely, heparin can cause heparin-induced thrombocytopenia with thrombosis. Periodic aPTT, platelet count and hematocrit monitoring during heparinization is recommended. The usual prophylactic dosage for heparin administered during pregnancy rarely causes this problem. Almost all patients experience some bruising at the site of the heparin injection. If bruising occurs at other sites on your body, you must contact us. Heparin can also cause nosebleeds, or blood in the urine or stool. If any of these symptoms occur, stop heparin and contact our office immediately.

OSTEOPOROSIS
Long-term heparin therapy may induce osteoporosis (thinning of the bones) and spontaneous fractures in patients who have received 15,000 units or more of heparin daily for more than 6 months (Ailo, 1975). However, recent studies would indicate that 5,000 units of heparin twice daily has no increased risk of irreversible osteoporosis, when calcium and vitamin D are taken together. We also recommend increased dietary calcium in the form of milk, milk products and calcium supplements. Sun exposure and exercise such as water aerobics during pregnancy are also helpful.

CONTRAINDICATIONS
The following are contraindications to heparin use: heparin allergy, active bleeding, hemophilia, purpura (tissue hemorrhage), thrombocytopenia (low platelet count), bacterial endocarditis, active tuberculosis, ulcerative lesions of the gastrointestinal tract, diverticulitis, ulcerative colitis or severe hypertension. Caution should be made when taking heparin if you have mild hypertension, liver or kidney disease, or diabetes. This will be discussed with you by your physician.
PREGNANCY
Heparin does not cross the placenta and has not been related to congenital defects. It has been reported that heparin use during pregnancy has been associated with a 13 to 22% unfavorable pregnancy outcome, including premature delivery and stillbirth. However, these cases were in women with severe maternal diseases necessitating high-dose anticoagulant therapy.

Heparin is probably the preferred anticoagulant during pregnancy, but is not risk-free. The only statistically significant fact to date is that mothers on heparin deliver their babies at an average of 37 weeks instead of 40 weeks.

BREASTFEEDING
Heparin is not excreted in breast milk and is safe to use when breastfeeding your baby.

HEPARIN
Injection Instructions

HOW CAN I INJECT BY MYSELF?
Self-injection makes for more accurate timing for medication and is easier for daily life.

SUPPLIES
• 1 cc tuberculin or insulin syringe with 27-30 gauge needle (1/2-5/8” long)
• Alcohol wipes or isopropyl alcohol 70% (rubbing alcohol)
• Cotton balls
• Band-Aid (optional)
• Sodium heparin (concentration we recommend is 20,000 units/ml)

DRAWING INTO THE SYRINGE
1. Wash your hands.
2. Collect all equipment needed for injection and prepare it in a clean area.
3. Wipe top of heparin vial with alcohol.
4. Remove cap from needle and pull back on the plunger of the syringe to where it is equal to the amount you will be injecting. The syringe is now filled with only air.
5. Insert the needle of the syringe into the center of the rubber stopper of the heparin vial.
6. Push down on the plunger of the syringe and inject the air into the heparin vial. This is to help produce suction when drawing up the heparin.
7. While supporting both the heparin vial and syringe, invert them so that the syringe is below the heparin vial. Be sure not to remove the syringe from the vial.
8. Draw back the amount of heparin needed to inject. Look for air bubbles. If any air bubbles are in the syringe, flick them to the top and push on the plunger to release them.
9. Once you have removed all air bubbles and have obtained the exact amount of heparin needed for injection, remove the syringe from the heparin vial.
10. Cap the needle until you are ready for the injection.
TIME TO INJECT
It is called a subcutaneous injection, which means you are injecting the medication just under your skin.

1. Select a site for the injection that is free of bruising or visible blood vessels. For a twice-daily dose, use the opposite site for PM injection. The preferred injection sites are the upper and lower abdomen, 2 inches away from the umbilicus.
2. Wipe the area with alcohol. Do not rub!
3. Remove cap from the needle.
4. Gently pick up a well-defined fold of skin.
5. Hold the syringe in a dart fashion and insert the needle directly into the skin at a 45-90 degree angle just into the subcutaneous “fatty layer” of the skin.
6. Move hand or finger in position to direct plunger. Do not remove the needle once it is inserted and do not pull back on the plunger (this prevents damage to the small blood vessels which could lead to bleeding and bruising).
7. Push down on plunger slowly as far as it will go.
8. When all the heparin has been injected, slowly withdraw the needle at the same angle at which it entered, also releasing the skin roll as you withdraw.
9. Apply light pressure to the area with a cotton ball for a few minutes. Do not rub the area. Rubbing the area increases the chances for bruising and bleeding.
10. Apply a Band-Aid only if necessary. The site may be irritated by the removal of the Band-Aid and have increased bruising.
11. Remove the needle from syringe and discard instruments separately.

HEPARIN
Points to Remember

Preferred site of injection is the abdomen (see diagram on next page). If there is no other place in the abdomen due to bruising, you may use the thighs, buttocks or back to minimize bad bruises and other possible complications.

- Rotate your sites of injections. Never inject in the same place as a previous injection or in a bruised area.
- Some bruising at the injection site is normal (less than the size of a quarter). Applying ice before or after the injection may reduce bruising. Report any problems to your doctor or nurse.
- Notify your doctors that you are taking heparin before any medication or surgical procedure.
- Carry an identification card in your wallet stating that you are on heparin.
- Contact your doctor if any of the following symptoms occur:
  - Nosebleeds
  - Blood in the urine or stool
  - Excessive bleeding longer than 15 minutes and not controlled by direct pressure
  - Unusual bruising other than at the site of injection
**DOSING CHART**
For drawing 5,000 Units:

<table>
<thead>
<tr>
<th>Concentration of Heparin per ml</th>
<th>Amount to draw and inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,000 Units/1 ml</td>
<td>1.0 cc</td>
</tr>
<tr>
<td>10,000 Units/1 ml</td>
<td>0.5 cc</td>
</tr>
<tr>
<td>20,000 Units/1 ml</td>
<td>0.25 cc</td>
</tr>
</tbody>
</table>

Always check the concentration of heparin on the vial you are using when determining proper dosage.

Heparin is usually given 2 times per day at 10-14 hour intervals.

**HEPARIN**
Injection Site Diagram

HEPARIN
Low Molecular Weight

Low molecular weight (LMW) heparin is often prescribed for replacing heparin treatment for women with heparin allergy or inherited/acquired thrombophilia with presence of factor V (Leiden) mutation or abnormalities in Protein C or S. Several commercial preparations are available such as dalteparin sodium (Fragmin®), enoxaparin sodium (Lovenox®), etc. It is known that high molecular weight heparin does not cross the placenta in pregnant women. In contrast, LMW heparin has not been studied enough to know the possible long-term effects on babies.
CONTRAINDICATIONS
Patients with the following concerns should not use LMW heparin injections:
• Hypersensitivity to heparin or pork products
• Known hypersensitivity to LMW heparin
• Active bleeding
• Thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of enoxaparin sodium (Lovenox®).

WARNING
• LMW heparin is not intended for intramuscular administration.
• LMW heparin cannot be exchangeable with HMW heparin.
• Patients with a history of low platelet count either induced by heparin or other reason should use extreme caution.
• As with other anticoagulants, there have been rare cases of neuraxial hematoma reported with the concurrent use of enoxaparin sodium and spinal/epidural anesthetics resulting in paralysis.
• Thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of dalteparin sodium (Fragmin®).

SIDE EFFECTS
Mild local irritation, pain, hematoma and erythema may occur at the injection site.

MONITORING
Periodic CBC with platelet count, and stool occult blood tests if needed are recommended. No special monitoring of blood clotting times is indicated.

ENOXAPARIN SODIUM
Enoxaparin sodium (Lovenox® or Clexane®) is a sterile injectable LMW heparin derived from porcine intestinal mucosa. In humans, enoxaparin sodium is characterized by a higher ratio of anti-factor Xa to anti-factor IIa activity than unfractionated heparin. At the recommended doses, single injection of enoxaparin sodium does not significantly affect platelet aggregation or global clotting time such as PT or PTT.

Lovenox® is often prescribed as 30 to 40 mg, subcutaneously, once or twice daily based on a patient’s needs. Enoxaparin sodium (per 0.3 or 0.4 mL water, respectively) prefilled syringes contain either 30 or 40 mg enoxaparin sodium.

DALTEPARIN SODIUM
Dalteparin sodium (Fragmin®) is a sterile LMW heparin produced utilizing sodium heparin from porcine intestinal mucosa. Dosage and injection frequency are determined based on a patient’s needs. A 0.2 mL single syringe contains 2,500 or 5,000 anti-factor Xa IU.

PREDNISONE
Prednisone is an oral steroid that suppresses abnormal autoimmunity such as ANA and autoantibodies to DNA and/or histone. Steroid treatment is often combined with aspirin or heparin, or both. Drug dosage will be adjusted when indicated by follow-up blood testing.
SIDE EFFECTS
The principal complications resulting from prolonged therapy with prednisone are fluid and electrolyte disturbance, high sugar level (hyperglycemia), sugar in urine (glycosuria), increased susceptibility to infection, peptic ulcer, loss of bone density (osteoporosis), muscular disease related with prednisone, behavioral disturbances (such as nervousness, difficulty sleeping or changes in mood), opacity of the lens of the eye (cataract) and streaks on skin. Cushingoid features consisting of moon face, buffalo pads, central obesity, small bleeding spots, acne and abnormal hairiness will frequently occur. Rarely, it is also reported to cause aseptic necrosis of the hip joint.

Average and large doses of prednisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction, potassium supplementation and regular blood pressure monitoring are necessary.

These side effects can be frightening to couples. Please talk to your nurse and ask any questions you may have during your consultation.

OTHER CONCERNS
Prednisone should be used with caution if you have ulcerative colitis, an abscess or other pus-forming infection, inflammation in existing small herniated sacs or pockets in the intestinal surface (diverticulitis), ulceration of the surface of the esophagus, stomach or duodenum by stomach juice (i.e., peptic ulcer), high blood pressure, congestive heart failure, history of blood clots, loss of bone density, Cushing’s syndrome, or convulsive disorder. Bone density loss can be prevented by calcium supplementation.

WITHDRAWAL
Too rapid withdrawal of prednisone during the weaning process may cause nausea, fatigue, anorexia, dyspnea, hypotension, hypoglycemia, myalgia, fever, malaise, joint pain, dizziness, sloughing off of skin and fainting. If you have these problems, contact our clinic immediately.

PREGNANCY
There are a number of studies in which pregnant patients received prednisone. These corticosteroids apparently have little, if any, effect on the developing fetus. The drug does not readily cross the placenta to your baby. Corticosteroids should be used during pregnancy when the potential benefit justifies the potential risk to the fetus. Prolonged use of prednisone during pregnancy has been associated with an increased chance for prematurity and lower birth weight of the baby.

BREASTFEEDING
Trace amounts of prednisone have been measured in breast milk. It is doubtful if these amounts are clinically significant. If it is recommended that you continue any prednisone postpartum during your breastfeeding period, you should contact a pediatrician and have a consultation. Small amounts of prednisone in the breast milk can make your child excitable and disturb your child’s sleep patterns.
PROGESTERONE

Progesterone is first produced by the corpus luteum of the ovary during the first 8 weeks of pregnancy. After this and onward, the placenta takes over. Progesterone is necessary for the safe maintenance of pregnancy, and pregnancy will fail if progesterone is too low. Many women with infertility, implantation failures and/or miscarriages produce low levels of progesterone and benefit from progesterone supplementation.

SIDE EFFECTS
The most common side effects are dizziness, breast pain, abdominal pain, fatigue, viral infection, abdominal distention, musculoskeletal pain, emotional lability, irritability and upper respiratory tract infection.

PROGESTERONE FUNCTION
1. Blocks inflammation that can lead to scarring and damage to the placenta.
2. Blocks the T cells and the B cells (lymphocytes) that can cause rejection of the placenta.
3. Blocks the natural killer cells from releasing factors such as the tumor necrosis factor (TNF) that can damage the placenta and uterine lining.
4. Prevents lymphocytes from wandering into the placenta and doing damage.
5. Causes an increase in human chorionic gonadotropin (HCG) production by the placenta, and HCG and progesterone block the killing power of natural killer (NK) cells.
6. Prevents prostaglandin production by the uterus and stops contractions from occurring.
7. Causes the cervix to produce a cervical plug that is rich in antibodies, which prevents germs and viruses from gaining access to the baby and the placenta.

Progesterone supplements can be excreted rapidly into the urine. Various forms of progesterone supplementation are available commercially, such as vaginal cream, vaginal suppositories, oral and injectable forms. Please consult with your physician to determine the best choice for you.

Prior to conception, progesterone supplementation should begin after ovulation and stopped when menses start and/or pregnancy test is negative. With a positive pregnancy test, the dosage is adjusted based on serum progesterone levels, monitored regularly.
INTRAVENOUS IMMUNOGLOBULIN G

Based on some clinical and animal research, intravenous immunoglobulin G infusion treatment (IVIg) may promote a successful reproductive outcome. However, this form of treatment remains investigational until large-scale controlled clinical trials are conducted and their results confirm the benefit of IVIg. Because IVIg therapy for pregnancy losses is still investigational, the cost of treatment may not be covered by medical insurance and remains the responsibility of the patient. In order to decide whether or not you want to proceed, you should understand enough about its risks and benefits to make an informed decision. This process is known as informed consent. This consent form gives detailed information about the IVIg treatment, which will be discussed with you. Once you understand the nature of treatment, you will be asked to sign this form if you wish to proceed.

Intravenous immunoglobulin G infusion treatment is being used to possibly sustain your pregnancy and promote reproductive outcome. Intravenous immunoglobulin G consists of concentrated human immunoglobulin, primarily IgG, prepared from pooled human donors by pharmaceutical companies. Treatment is given intravenously and dosage and infusion protocols are determined based on laboratory testing and clinical responses. Treatment is usually given while you are attempting a pregnancy and during a pregnancy. In rare cases, IVIg treatment may continue even after the delivery.

IVIg therapy has gained FDA marketing clearance for other indications than pregnancy failure. The use of IVIg in the case of recurrent miscarriage or multiple implantation failures is considered investigational.

SIDE EFFECTS
The following are possible side effects of IVIg. There is the potential for headache, backache, muscle pain, fever, low blood pressure, chills, flushing and nausea usually beginning within one hour of the start of the infusion. True life-threatening allergic reactions (such as an anaphylactic reaction) may occur in patients with a history of prior systemic allergic reactions or seizure following the administration of human immunoglobulin preparation. Very rarely, a life-threatening allergic reaction may occur in patients with no prior history of severe allergic reaction to human immunoglobulin preparation. Persons with isolated immunoglobulin A deficiency have the potential for developing antibodies to IgA and could have unusual and exaggerated allergic reactions to subsequent administration of blood products that contain IgA. Since this is a blood product, there is a very remote chance of getting a viral infection such as hepatitis, HIV (the virus that causes AIDS) and Creutzfeldt-Jakob disease (a prion protein that destroys brain tissue).
Local pain or irritation can be present at the infusion site. Application of a warm compress to the infusion site alleviates local symptoms. These local symptoms tend to be associated with infusions via a hand vein, and their incidences may be reduced by infusions via the vein in front of the elbow (antebrachial vein). Blood clotting has been reported in IVIg infusion patients. The exact cause is unknown; therefore, caution should be made in patients with a history of cardiovascular disease or blood clotting episodes. Aseptic meningitis syndrome (AMS) has been reported to occur infrequently. AMS may occur more frequently in association with high dose (2 gm/Kg) IVIg treatment. Current protocol utilizes 400 mg/Kg dosing schedule to minimize this side effect. In the last 10 years of IVIg utilization, we did not have any patients who received a diagnosis of AMS while on this protocol. Periodic monitoring of renal function via testing and urine output is important in patients judged to have a potentially increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen and serum creatinine, should be assessed prior to the initial infusion and again at appropriate intervals thereafter.

Various minor reactions, such as headache, fatigue, chills, backache, leg cramps, lightheadedness, fever, hives, flushing, slight elevation of blood pressure, nausea and vomiting have been reported. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. Premedication with an antihistamine such as Benadryl® and additional fluid replacement therapy minimize these side effects. Immediate unusual allergic reaction is a remote possibility. Epinephrine will be available for treatment of any acute unusually exaggerated allergic reaction.

**METFORMIN**

Metformin hydrochloride (Glucophage®) is an anti-hyperglycemic drug that lowers blood sugar by keeping the liver from making too much sugar. It also improves insulin sensitivity and decreases intestinal glucose absorption. Metformin is increasingly being used to improve insulin sensitivity, decrease ovarian androgen production and improve fertility in anovulatory women with polycystic ovary syndrome.

**SIDE EFFECTS**

Metformin causes side effects which may include stomach pain, bloating, cramping, diarrhea and nausea. These side effects usually go away soon after the metformin is started and occur less frequently if metformin is taken with food. Another problem is a rare, but serious condition called lactic acidosis, which occurs when tissues do not get enough oxygen to survive. To avoid this problem, metformin should not be given to people with severe kidney or liver impairment, severe heart failure or a history of alcohol abuse.

**BREASTFEEDING**

Studies in lactating rats show that metformin is excreted into milk at levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Some of the immunological or genetic terms in this handbook are new to you. This glossary may help your understanding.

**Anti-DNA/Histone Antibodies:** These are antibodies to nuclear antigens such as single- or double-stranded DNA (ss-DNA, ds-DNA), histone proteins or Scl 70. These may be reported as negative; borderline; positive; and weak-, moderate- or high-positive.

**Anti-nuclear Antibody (ANA):** This blood test checks for autoimmunity to nuclear protein. It is usually reported as ANA positive when a titer is 1:40 or higher. A speckled pattern is most commonly associated with reproductive immune problems, in contrast to the nucleolar pattern seen in lupus or rheumatoid arthritis.

**Antiphospholipid Antibody (APA):** This 18 panel qualitative blood test involves 3 forms (IgM, IgG and IgA) of antibodies against 6 phospholipids (cardiolipin, phosphatidyl ethanolamine, phosphatidyl inositol, phosphatidic acid, phosphatidyl glycerol and phosphatidyl serine). Results may be reported as negative, borderline, positive, weak, moderate or high positive. Positive APA reflects increased blood clotting tendency.

**B Lymphocytes:** Lymphocyte that rearranges and expresses immunoglobulin genes.

**CD (Cluster of Differentiation):** System of cataloging surface molecules of leukocytes that distinguish the type of cells of its state of activation or differentiation.

**Cytokine:** One of several protein hormones synthesized by a variety of cells, used to communicate with other cells; typically made in minute amounts and intended to affect cells in a microenvironment.

**Factor II, DNA Analysis** (see Prothrombin Gene Mutation).

**Factor V Leiden:** A specific mutation in the Factor V gene that is associated with an increased risk of venous thromboembolism.

**Flow Cytometry:** Method to characterize or separate cells by size, density, and the ability to bind or internalize fluorescent antibodies or dye.

**Helper T (TH) Lymphocyte:** CD4+ T lymphocyte that enhances the activation, proliferation and differentiation of lymphocytes through the release of cytokines.

**HIV-1 and HIV-2 Antibody:** This antibody test is for diagnosis of human immunodeficiency virus (HIV) exposure.

**HTLV Antibody:** This antibody testing is for diagnosis of human T lymphotrophic virus exposure.
**Immunoglobulin (IgG):** Multimetric protein with antigen-binding properties produced by B lymphocytes and plasma cells, released into serum and other secretions.

**Immunoglobulin Class:** Immunoglobulin isotype determined by a difference in the constant region Fc portion of the molecule, such as IgG, IgM, IgA, IgD or IgE.

**Interferon (IFN):** Low molecular protein that protects cells from viral infection. Interferon gamma is the major cytokine that regulates lymphocyte cell responses and acts on macrophages to enhance inflammatory responses.

**Interleukin:** Generic term for soluble cytokines produced by leukocytes that act as growth factors and chemotactic agents, and can initiate and regulate innate immune and inflammatory responses.

**Lupus Anticoagulant:** This is IgG and IgM antibodies directed against negatively charged phospholipids. It is associated with increased risk of a thrombotic episode.

**Lymphocyte:** Cells that mediate antigen-specific immune responses. T, B and natural killer cells are the subsets.

**Methylene Tetra Hydro Folate Reductase (MTHFR) Mutation:** The MTHFR enzyme is responsible for creating the circulating form of folate. Folate is important in homocysteine regulation. The C677T mutation in this gene can cause elevated homocysteine levels, particularly when two mutations are present.

Elevated homocysteine levels are associated with heart muscle infarction, venous clots, stroke and coronary artery disease. Most importantly, pregnancy complications such as pregnancy losses, intrauterine growth restriction, placental abruption, preterm labor and an increased risk of fetal open neural tube defect have been reported.

**Natural Killer Cell:** Large granular lymphocytes lacking T- and B-lymphocyte antigen receptor gene arrangement. An important defense against infection and tumor cells. Exert cytotoxic effects with undefined specificity but without being major histocompatibility complex (MHC) restricted.

**Natural Killer (NK) Cell Assay:** This blood test, developed by the Clinical Immunology Laboratory at Rosalind Franklin University of Medicine and Science, has three parts. The first part measures NK cytotoxicity, or the killing capacity of a woman’s insolated NK (effector) cells when placed in a test tube with target cells in three different concentrations (50:1, 25:1, 12.5:1 effector/target cell ratios). Results are reported as a percentage of target cells killed.
Natural Killer Cell Assay—Immunoglobulin G Transformation: The second part of the NK assay checks whether Immunoglobulin G will reduce NK killing (IVIg suppression) in vitro. In a separate set of tubes, two doses of Immunoglobulin G (6.25 mg/ml and 12.5 mg/ml correspond to in vivo doses of 25 mg daily for one day and three consecutive days, respectively) are added to NK and target cells, and the percentage of cells killed are noted. This is usually part of the initial full NK panel and not the follow-up NK.

Natural Killer Cell Assay—Reproductive Immunophenotype: This is the third part of the NK assay. Various white blood cell subtypes are measured in percentages: CD3+ cells are T-cells while CD19+ cells are B-cells. CD56+ cells are natural killer cells. The CD19+/5+B-cells reflect B-cells which produce auto-antibodies to hormones, neurotransmitters and certain organs.

Prothrombin Gene Mutation: A point mutation in the prothrombin gene is the second most common reason for inherited thrombosis. Heterozygous mutation has a 3-fold increase in venous thrombosis risk. Homozygous mutations have even higher risk for thrombosis. Up to 40% of the factor II mutation carriers also carry the factor V Leiden mutation.

T Helper 1/T Helper 2 Cytokine Ratio: This new blood test designed by the Rosalind Franklin University of Medicine and Science Clinical Immunology Lab reflects the ratio between two opposing T helper immune responses. An elevated ratio reflects the dominance of TH-1 cells (represented by secreting TNF and IFN) which are cytotoxic and pro-inflammatory, as against the TH-2 cells (represented by secreting IL-10) which are important for implantation and pregnancy.

Tumor Necrosis Factor (TNF): TNF is a T helper 1 cytokine produced by activated macrophages, T cells and other cells, and has many biological activities on the immune and other systems. TNF is considered a major inflammatory mediator.
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