

Miscarriages and Immunotherapy



Dear patients, now that you understand the immune mediated reasons for your miscarriages it is important that you follow any medication recommendations made to you unless you have had an allergic reaction, serious side effect or medical problem that precludes the use of the drug(s).

Some patients are uncomfortable about taking any medication during pregnancy. Rest assured that all medication and doses have been thoughtfully selected to minimize any drug related side effects.

As your pregnancy progresses your blood test results may change, justifying a modification in your medication regime. If changes are indicated, they will be communicated to you and initiated immediately.

If at any time you have questions regarding medications or suspect that you are having an allergic reaction or side effect, please call Reproductive Immunology Associates at (818) 781-5195.

Aspirin

Aspirin is an antiinflammatory and antiplatelet agent. Should you require low dose aspirin, the recommendation is 80 mg per day, which is equivalent to a baby aspirin.

Aspirin, like all medication, can cause allergic reactions. Manifestations of aspirin allergy may include dermatitis, rhinitis, bronchospasm and even anaphylaxis. People who have a history of asthma and nasal polyps are at increased risk for allergic reactions.

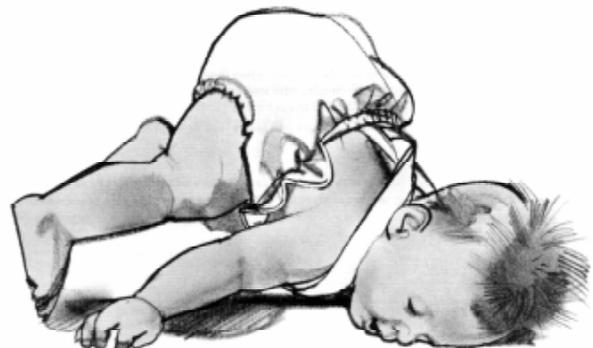
Side effects of low dose aspirin are infrequent but can include nausea, reflux esophagitis, abdominal discomfort, anorexia and gastrointestinal and urinary tract bleeding. Use of high dose aspirin during pregnancy may affect maternal and neonatal blood clotting mechanisms, leading to an increased risk of bleed. High dose aspirin may also impair maternal kidney function and has been causally related to increased perinatal mortality, intrauterine growth retardation and congenital defects. Aspirin at low doses has not been associated with these risks.

Aspirin is excreted into breast milk in low concentration ranging from 1.1 to 10 mcg/ml. Adverse effects of platelet function in the nursing infants have not been reported, but are a potential risk. If you choose to breast feed your baby you should not take aspirin at that time.

Routine laboratory testing while on aspirin should include complete blood count, chemistries, APTT and antiphospholipid antibody panel.

Heparin

Heparin, an anticoagulant, is a purified preparation derived from animal tissue. It is delivered as a subcutaneous injection and a typical dose would be 5000 IU twice a day.



Allergic reactions may include chills, fever, dermatitis, asthma and anaphylactic shock. Before a therapeutic dose is administered, a trial of 1000 IU would be prudent. Fortunately, allergy to heparin is rare.

Because of heparin's blood "thinning" property the user is more susceptible to bleeding (skin, nose, gastrointestinal tract, bladder, etc.). Almost all patients experience some bruising at the site where heparin is injected.

Long term heparin therapy has been associated with osteoporosis and spontaneous fractures in patients who have received in excess of 15,000 units per day for more than six months. One study of 117 patients on long term heparin (up to 15 years) report no spontaneous fracture when subjects received less than 10,000 units per day. Although our protocol utilizes low dose heparinization, supplementation (dietary) with calcium is recommended. Exercise and sun tanning may also prevent osteoporosis.

Heparin has not been related to congenital defects, nor does it cross the placenta. Heparin use during pregnancy has been associated with a 13 to 22% unfavorable pregnancy outcome including premature and still birth. Please note that the study group consisted of women who had severe maternal disease necessitating high dose anticoagulant therapy. Although heparin is the preferred anticoagulant during pregnancy it is not risk free.

Heparin is not excreted in breast milk.

Relative contraindications to the use of heparin are active bleeding, hemophilia, thrombocytopenia or other blood dyscrasia, endocarditis or tuberculosis. Caution should be exercised when there is underlying hypertension and liver kidney disease.

Routine platelet, hematocrit, APTT and antiphospholipid antibody panel monitoring during heparinization is recommended.

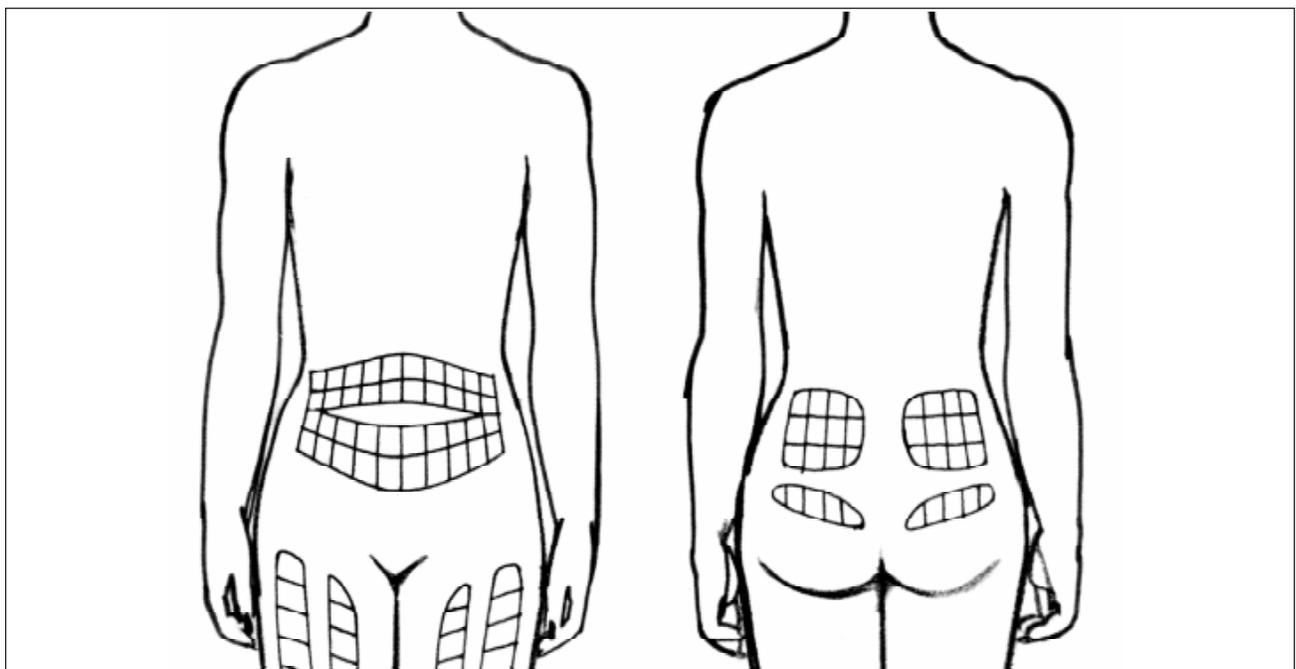
Administration of Heparin Subcutaneously

1. Wipe the area with alcohol. Do not rub!
2. Remove cap from needle and gently pick up a well defined fold of skin.
3. 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.
4. Push down on plunger slowly as far as it will go.
5. When all the heparin has been injected, slowly withdraw the needle at the same angle at which it entered, and also releasing the skin roll as you withdraw.
6. Apply bandaid only if necessary. The site may be irritated by the removal of the bandaid, thus causing increased bruising.

Important Points to Remember

1. Preferred site of injection is the abdominal area. Injections must be given 2 inches away from the umbilicus (see diagram). If you need another area to give your hep-

Rotation Site for Heparin Injection



arin, you may use your thighs or buttocks.

2. Rotate your sites of injections. Avoid injecting a bruised area.

3. Some bruising at the sight of injection is normal (less than quarter size). If increased bruising occurs, you may use ice before you clean the area for injection and/or after you have given yourself the injection.

4. Notify your doctors before any medication or surgical procedure that you are taking heparin.

5. Carry an identification card in your wallet stating that you are on heparin.

6. Contact your doctor if any of the following symptoms occur: nose bleeds, blood in the urine of stool, excessive bleeding lasting greater than 15 minutes and not controlled by direct pressure, unusual not at the site of injection.

Dosage Chart for Drawing Heparin 5000 IU

Concentration (IU/ml)	Amount to inject (cc)
a) 5,000	1.0
b) 10,000	0.5
c) 20,000	0.25
d) 40,000	0.125

***Always check concentration of Heparin on vial you are using.**

*Heparin is to be given 2 times per day at 10-14 hour intervals

*Depending upon the recommendation, Heparin will be started day 6 of the cycle of planned conception or 48 hours after ovulation

Prednisone

Prednisone is a corticosteroid. If indicated, you will be asked to take 5 or 10 mg orally twice a day upon confirmation of pregnancy (patients with immune mediated infertility may be on a different schedule). Drug dosage may be adjusted depending upon follow-up blood tests

Allergy to prednisone is rare, as the human body manufactures a similar compound. In fact prednisone is used to treat moderate to life threatening allergies.

Possible adverse reaction to moderate and high doses of prednisone include fluid and electrolyte imbalance; metabolic disturbances e.g. hyperglycemia or gestational diabetes and osteoporosis; susceptibility to infection; peptic ulcer; behavioral changes e.g. nervousness, insom-

nia, irritability and mood swings; myopathy; and cataracts.

Prednisone should be used with caution in people with hypertension, congestive heart failure, diabetes mellitus, osteoporosis, ulcerative colitis, ocular herpes and others (please consult with doctor if you have any chronic illness). Osteoporosis can be retarded with calcium supplementation and exercise.

Rapid withdrawal of prednisone may cause fatigue, myalgias, arthralgias, dizziness, hypotension, hypoglycemia and dyspnea. If you experience these symptoms, please contact your doctor.

There are a number of studies that review the use of prednisone during pregnancy and effects on the fetus. The fetus appears to be protected by at least three mechanisms: 1) enzymes in the placenta degrade the drug to an inactive form, 2) prednisone in maternal circulation is bound to a large protein making it harder to cross the placenta and 3) fetal liver is not able to activate prednisone until the end of the second trimester.

Trace amounts of prednisone have been measured in breast milk. Although these quantities are of doubtful clinical significance, your baby's pediatrician should be notified.

Laboratory studies to monitor while on prednisone include complete blood count, chemistries, electrolytes and antinuclear antibody panel.

Immunoglobulin G Infusion

Immunoglobulin G is a preparation of human derived antibodies. In some patients, conventional immunotherapy with aspirin, heparin and paternal white cell immunization may have to be supplemented with this medication. Patients at risk for developing intrauterine growth retardation, oligohydramnios, toxemia, or severe side effects of steroids, or have preexisting maternal disease are prime candidates. If you require this treatment, it is given intravenously three consecutive days monthly during pregnancy.

Immunoglobulin G is contraindicated in patients who are known to have had anaphylactic or severe systemic reaction to human immune globulin. Patients with IgA deficiency should not receive this product.

Side effects to immunoglobulin G include fever, chills, headache, nausea, malaise and back pain. Mild erythema following infiltration at the site of infusion has been reported.

Laboratory tests that need to be followed while on this treatment are quantitative immunoglobulins and immunophenotype.

Paternal Leukocyte Immunization

Paternal leukocyte immunization (PLI), a purified preparation of husband's white blood cell, is administered

intradermally. Because this is a blood product, the recipient (wife) risks acquiring infectious diseases that donor (husband) may harbor. Rh sensitization is also possible; however, extensive steps are taken to prevent this.

Most women will experience redness and itching at the site of immunization. Please notify your doctor if you have any unexpected or serious reaction.

Maternal antipaternal leukocyte antibodies (blocking antibodies), by flow cytometry, should be followed to monitor efficacy of treatment.

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