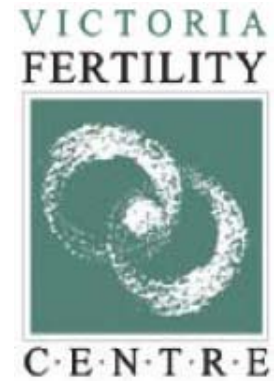


Heparin and Aspirin use in assisted reproduction



INTRODUCTION

The implanting conceptus (the embryo, the placenta, and the fetus) is immunologically foreign to the mother and it is indeed surprising that all pregnancies are not summarily rejected. In fact, the ability of the mother to successfully host a pregnancy is entirely dependent upon a complex interaction of sophisticated immunologic adjustments that are designed to prevent immunologic rejection of the conceptus.

The placenta and the fetus carry imprints of the father's immunologic make-up, which differ substantially from that of the mother. These imprints are referred to as HLA antigens. This immunologic difference between the conceptus and the mother causes the mother to produce blocking antibodies against the HLA antigens. The blocking antibodies produce a protective barrier around the fetus which is designed to quarantine the baby from rejection by the mother's immune system, thereby transforming the uterus into a "privileged site" for implantation. The production of such blocking antibodies is referred to as an allo-immune response. In some cases, where the father and mother share some of the same HLA antigens, blocking antibodies fail to develop and the required allo-immune response does not take place, thereby exposing the conceptus to a rejection process. Many repeated miscarriages and/or late pregnancy losses are believed to occur in such circumstances. Damage caused to the placenta as a result of such immunologic rejection, often causes the body to produce antibodies to phospholipids (a component of its own cells). The production of these so-called auto-antibodies or more specifically, antiphospholipid antibodies, are part of a process referred to as an **autoimmune response**. The antiphospholipid antibodies combine with phospholipids and severely damage placental cells, often resulting in early miscarriages or later pregnancy losses.

A similar autoimmune response is also known to occur in association with a variety of disease states where antibodies are formed to the body's own tissues. Examples include conditions such as Rheumatoid Arthritis, Hashimoto's Thyroiditis, Lupus Erythematosus, Myasthenia Gravis, etc. Not surprisingly, these are all diseases associated with a high incidence of repeated miscarriages or late pregnancy losses.

It has also been demonstrated that many women with organic pelvic disease (e.g., chronic pelvic inflammatory disease, endometriosis, and pelvic adhesions) also produce antiphospholipid antibodies and that such women find great difficulty in achieving pregnancy. In such cases, these antiphospholipid antibodies often destroy the root system of the very early placenta even before there is any indication that implantation has occurred. Such women are often erroneously labeled as being infertile when in fact they are simply rejecting their pregnancies so early (through an autoimmune process) even before it can be diagnosed.

In other words, reproductive failure associated with a failed allo-immunity as well as autoimmunity are ultimately most commonly a result of placental damage due to the influence of antiphospholipid antibodies.

In the past, the traditional approach to treating failed allo-immunity resulting in recurrent pregnancy loss, was to induce production of blocking antibodies by the immunization of the woman with her husband's (or donor's) white blood cells. As mentioned above, these blocking antibodies would quarantine the baby from the mother's immune system and thereby prevent the production of antiphospholipid antibodies. This treatment was often unsuccessful in spite of best efforts.

It has been demonstrated that the administration of mini-dose Heparin with aspirin (H/A), prior to initiating pregnancy through in vitro fertilization and embryo transfer counteracts the effects of antiphospholipid antibodies in most patients with autoimmune problems, resulting in a much higher success rate than that which could be achieved in the absence of such treatment

INFORMATION ABOUT HEPARIN

It is believed that Heparin inhibits the binding of antiphospholipid antibodies with the phospholipids of the placental root system thereby preventing damage. As such, Heparin therapy will not necessarily lower the concentration of antiphospholipid antibodies in the blood. In fact, because Heparin prevents the binding of the antibodies to phospholipids, the antiphospholipid antibody concentration might even rise.

When administered in large doses, heparin is an anticoagulant, and is commonly administered to people who have developed, or are at risk of developing thrombosis (blood clot formation in blood vessels). In very low doses prescribed for the treatment of ANA and APA, heparin with very rare exception, DOES NOT SIGNIFICANTLY AFFECT BLOOD COAGULATION (clotting). Moreover, heparin does not cross the placenta and enter the circulation of the fetus. Very rare complications to the patient include bleeding due to a decrease in the concentration of blood platelets, osteoporosis, gastrointestinal symptoms, and allergic-type reactions. These side-effects are rarely encountered in the low dose regimen recommended above. Moreover, the fact that we discontinue heparin therapy the night prior to the egg retrieval virtually eliminates the risk of bleeding during this procedure. By the time the egg retrieval is performed, there is no longer any heparin in your system. It is also safe to recommence heparin therapy immediately after the egg retrieval.

You will receive directions on how to self-administer low dose, subcutaneous heparin. A favorable site is the abdomen, around the belly-button (after numbing the area with ice). If you imagine the belly-button as being the center of a clock, then the daily injections can be given in each hour position, going around the face of the clock, approximately one to two inches from its center point. Local irritation, redness, mild pain, bruising or ulceration rarely follows deep, subcutaneous injections.

Heparin must be used with caution in individuals with GI ulcers, liver disease, impaired hemostasis (clotting), as well as in individuals using platelet inhibitors such as a high dose aspirin, Motrin, Advil, and other non-steroidal anti-inflammatory drugs. Significant elevation of two liver enzyme (SGOT and SGPT) levels have occurred in a small percentage of health patients. Signs of heparin overdose are nosebleeds, blood in the urine, tarry stools, and easy bruising (except at the injection site). A baseline CBC with platelet count will be performed and as long as the baseline lab values are within normal limits, the CBC with platelets will be repeated every few weeks. If these values remain stable after several weeks, then limited monitoring is necessary.

INFORMATION ABOUT ASPIRIN

Antiphospholipid antibodies increase the tendency for blood to clot in the vessels surrounding the root system of the placenta. Aspirin inhibits this effect.

Children's aspirin contains 81 mg. of aspirin per tablet. This is less than one-fourth the dosage of a regular adult aspirin tablet. Aspirin may cause gastrointestinal upset, heartburn, nausea, etc., and should not be taken by individuals with known gastrointestinal ulceration or by individuals who have a bleeding tendency. There is no evidence that the ingestion of aspirin during pregnancy causes fetal abnormalities. One of the side-effects of aspirin therapy that is of significant benefit to us, is that it causes platelets to be less able to form blood clots. It is for this reason that patients should discontinue aspirin therapy before surgery and restart its use thereafter. Clearly, it is our intent to strike a balance between optimal therapy and minimal risk.

Low dose aspirin has also been found to improve blood flow to the uterus and as such may improve the quality of the endometrium(uterine lining) and therefore the chance of successful implantation.