Miscarriages can be Prevented

An unexpected miscarriage can shatter dreams. Two more can be devastating. But now there is hope, and a solution. One in every 200 couples are too genetically similar to achieve successful pregnancy. And usually, they don't know it. That's why early detection is vital. Without intervention, the painful pattern of miscarriage occurs again and again.

Reproductive Immunology Associates of Los Angeles offers a proven, painless, highly sophisticated diagnosis and treatment method. By combining cell flow cytometry and immune enhancing vaccinations, our success rate is 80 percent. To date, we have had well over 500 births.

As the United States' only private physician group capable of performing all of the laboratory tests necessary to diagnose this condition, we can provide complete evaluation within 10 days. And we closely monitor each pregnancy, consulting with referring physicians every step of the way.

Introduction

One in two hundred couples will experience two or more consecutive miscarriages. There are five reasons for miscarriage which have been identified:

Cause	Percent
Infection	1
Anatomy abnormal	5 to 10
Progesterone level low	20
Chromosome abnormal	
Primary miscarrier (no live births)	7
Secondary miscarrier (one or more live births)	50
Immune mechanisms	50
Unknown	15

some women have multiple reasons for miscarriages. At Reproductive Immunology Associates we evaluate patients for immune related miscarriages. Your obstetrician will test for most other causes of pregnancy loss.

Immune Systems

Advances in immunology, the study of the body's defense systems, enable us to understand how during pregnancy, the mother's immune system is altered so that the fetus is not rejected by her body and allows the fetus to grow.

The immune system is comprised of white blood cells, also known as leukocytes, which make a variety of antibodies . Some of the antibodies protect us and others are harmful to our bodies. Some of the antibodies that are important to the reproductive system are:

Blocking (protective) antibodies	-alloimmune
Antiphospholipid antibodies	-autoimmune
Antinuclear antibodies	-autoimmune

When the immune system is the cause of miscarriage,

the chances of mother having a successful pregnancy without treatment after 3 miscarriages is 30%, after 4 miscarriages 25%, and after 5 miscarriages 5%. With proper treatment, overall success is 80%!

Blocking Antibodies

Early in pregnancy, the mother's immune system receives signals from the tiny fetus. Many of the signals are hormonal, but others come directly from genetic messages that the father has contributed. Some of the messages involve the tissue type, also known as the human leukocyte antigens (HLA) are the white blood cell (leukocyte) type. HLA are expressed on white blood cells. They are unique to each individual and allow the body to identify anything foreign to it such as infections, cancers, transplanted organs and fetuses. One half of the fetus's HLA type is contributed by mother and the other half by father. When a woman becomes pregnant, her body's immune system usually recognizes the father's HLA as different from her own, and the white blood cells in her uterus produce protective, blocking antibodies. These antibodies coat the baby's cells and protect the fetus from mother's killer cells (figure 1). If father's HLA is too similar to mother's, her cells may not recognize differences that are vital to the production of blocking antibodies.

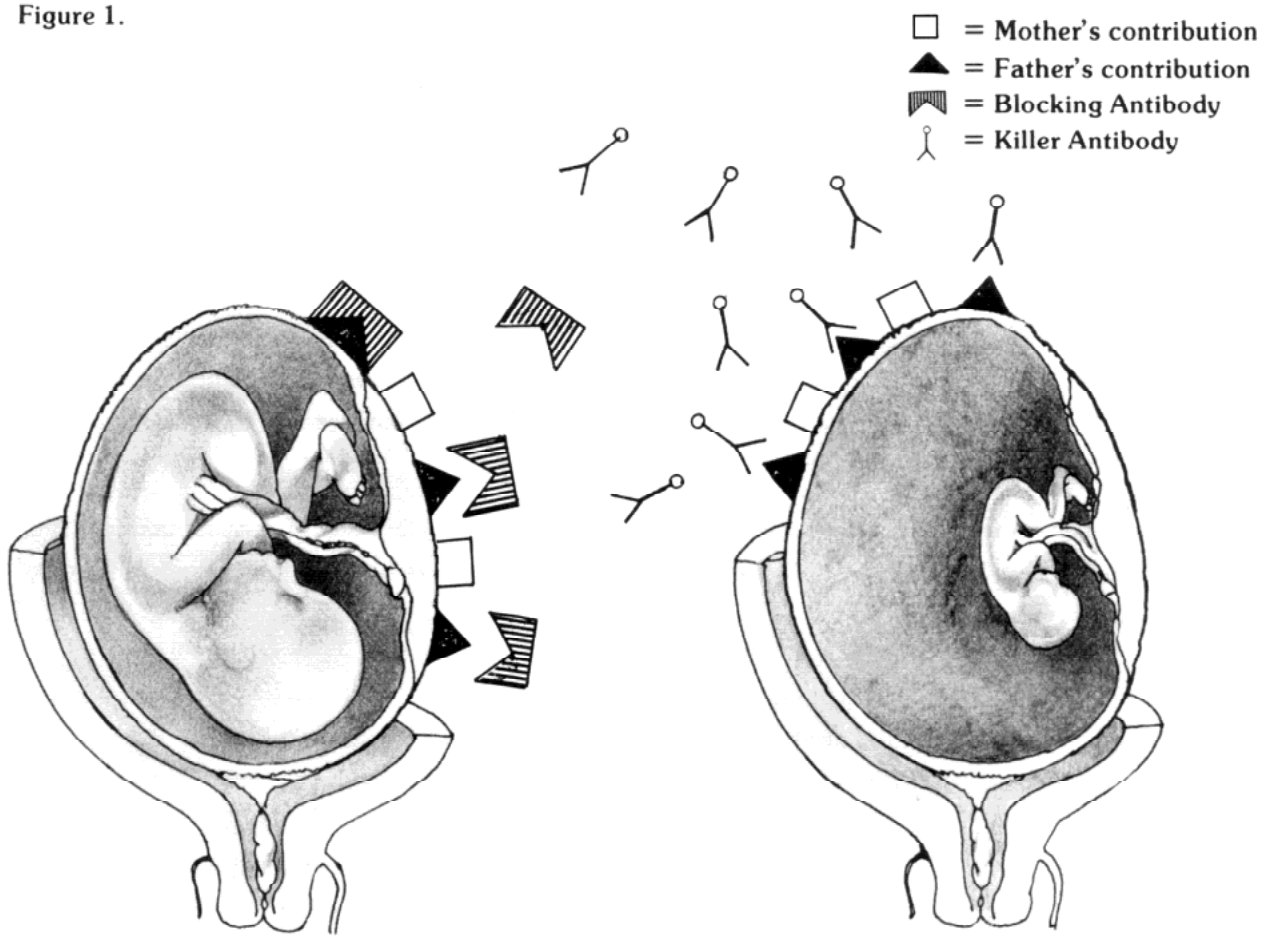
Women who have successful pregnancies and have no history of miscarriages normally, have high levels of blocking antibodies even in the non pregnant state vs women who miscarry and whose levels tend to be low even when pregnant.

table 1: Comparison of Blocking Ab level in women with vs women without RSA

Group	Blocking Ab Present Prior to Pregnancy	Delivered
Women with no miscarriage	YES (82/100)	100/100(100%)
Women with miscarriages (RSA)	NO (6/175)	0/175(0%)

Ab Antibody
RSA Recurrent spontaneous abortion

Figure 1.



Normal Levels of Blocking Antibodies

Low Levels of Blocking Antibodies

Table 2: success rate with varying treatment modalities in women with a history of RSA

Group PLI	Recieved ANA	APA &/or	Meds Given*	Delivered PT. NO. (%)
I	NO	NO	NO	8/40 (20.0%)
II	YES	NO	NO	72/88 (81.1%)
III	YES	YES	NO	4/24 (16.7%)
IV	YES	YES	YES (early)	130/160 (81.3%)
V	YES	YES	YES (late)	16/32 (50%)

* Medications for APAs and ANAs include low dose aspirin, heparin and prednisone when indicated.
ANA Antinuclear antibodies
APA Antiphospholipid
PLI Paternal leukocyte immunization

Through HLA tissue typing we can identify couples who look too much "alike" In addition we can measure the ability of a couple's cells to respond to each other i.e. level of blocking antibodies, using sophisticated equipment which combine computers and laser (cell flow cytometry).

Treatment involves immunizing mother with concentrates of father's white blood cells so that the HLA signal is amplified. When blocking levels are elevated, prior to conception, the rate of successful term pregnancy is approximately 80%.

The risk associated with white blood cell immunization is the possible transmission of infectious agents that the father's blood may be harboring. This can be avoided by testing his blood for any significant infections. Very

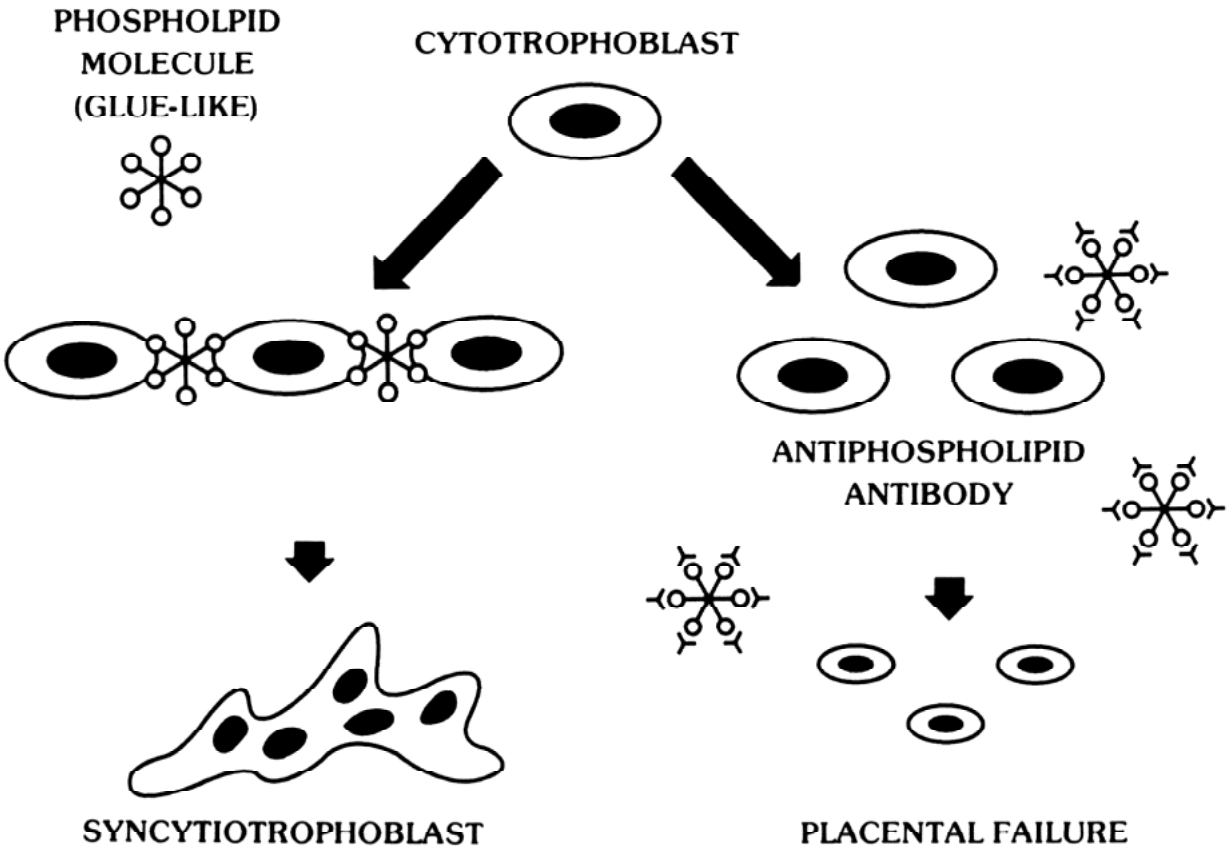


Figure 2.
Antibodies to Phoapholipid molecules can, therefore, interfere with the development of the placenta

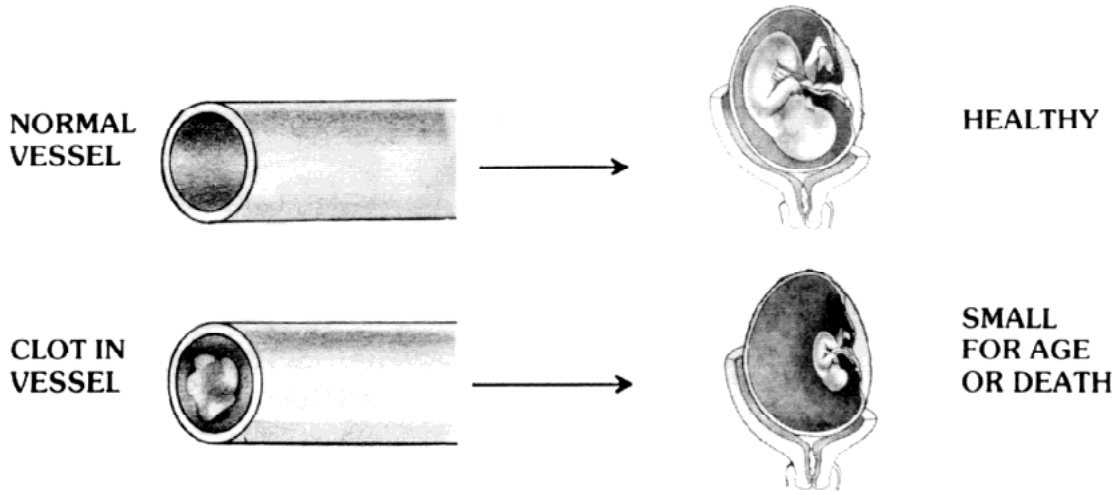


Figure 3.
Antiphospholipid antibodies can also cause blood vessels to constrict, causing decreasined blood flow throughout the curculatory system

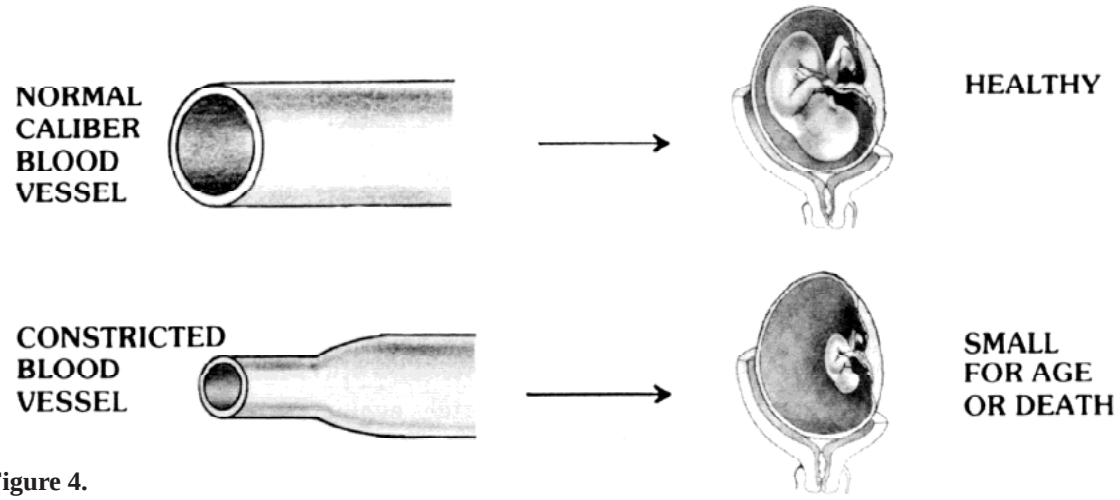


Figure 4.
The combination of blood clots and constricted blood vessels may impair blood supply to the fetus and placenta resulting in complete fetal demise or growth retardation.

uncommonly, there can be a local skin infection caused by bacteria on mother's own skin. This is easily treated.

Antiphospholipid Antibodies

Phospholipid molecules are normal components of all cell membranes. Some also have glue like properties and allow cells to fuse (as you will see later). Antibodies to phospholipid molecules can, therefore, cause problems. Specifically, they can damage the inside of the blood vessel wall. This allows blood cells to stick to the site f the injury and cause blood clots (figure 3 & 4).

Some phospholipid molecules have adhesion properties i.e. glue like, and allow cells to fuse. The formation of the normal placenta involves the fusion of small cells called cytotrophoblasts into giant cells known as syncytiotro-phoblasts. The syncytiotrophoblasts play a key role in the regulation of nutrients going to the baby.

With each pregnancy loss, there is a 10% chance that the mother will develop an antibody to a phospholipid molecule (figure 2). Most women with antiphospholipid antibodies are not sick. However, some have underlying autoimmune tendencies and should be appropriately evaluated. Women with underlying autoimmune diseases may have antiphospholipid antibodies even before they ever become pregnant.

The treatment for antiphospholipid antibodies involves the use of low dose (baby) aspirin and a blood thinner called Heparin. Heparin is a very large molecule and is unable to cross the placenta. Aspirin is able to cross the placenta but the dose used is so small that the fetus is unaffected. The effectiveness of treatment is mush greater when the medication, if indicated, is started prior to conception and continued throughout the pregnancy. All medication, if indicated should be discussed with one's

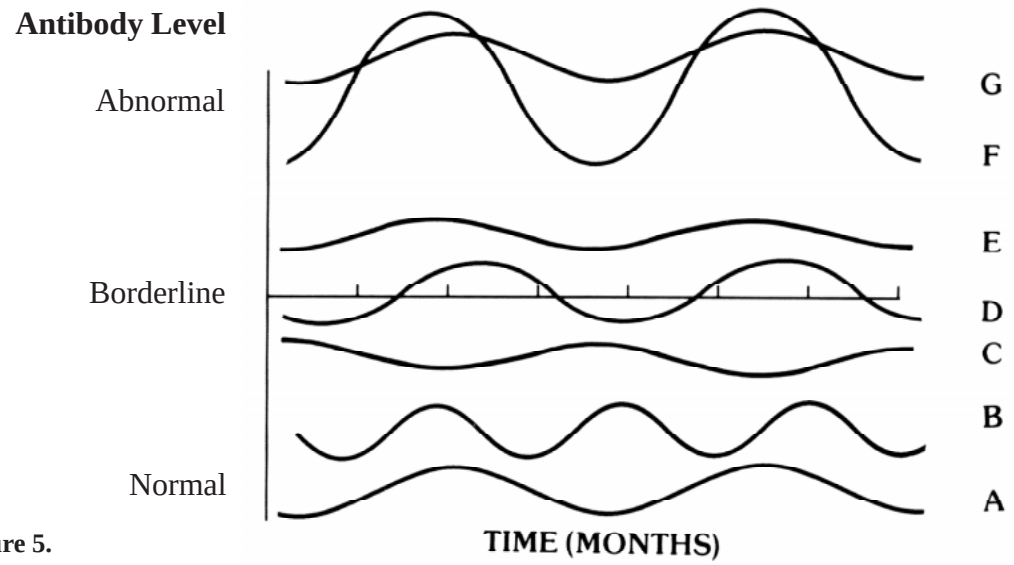


Figure 5.

physician.

Antinuclear Antibodies

The nucleus is the "brain" of the cell. It contains the information that regulates the function of the cell. Some people have antibodies to different nuclear components. What causes these antibodies to be made is currently under investigation but there appears to be a genetic susceptibility which may be reflected by the HLA tissue type (refer back to the section on blocking antibodies).

The disease that we typically associate with antinuclear antibodies is Systemic Lupus Erythematosus (SLE). The miscarriage rate in SLE patients is much higher than that of the general population. Although most women who suffer recurrent miscarriages do not have clinical signs of SLE, many exhibit autoimmune phenomena which is similar to that seen in SLE patients. The placentas in these women are inflamed and weakened.

The treatment for this problem is Prednisone, a corticosteroid, which suppresses the inflammatory process and stabilizes the cell. Prednisone does not pass through the placenta easily and is also broken down by enzymes in the placenta so that the fetus is exposed to only trace amounts. Additionally, the body produces the equivalent of 8 mg per day of this corticosteroid. When indicated, Prednisone should be started prior toconception.

As the body is dynamic, antibody levels may change over time. This is illustrated in the figure above. Most people have no antinuclear antibodies all of the time (A,B). Many women who miscarry have borderline (C,D,E) or abnormal levels of antinuclear antibodies (F,G) (figure 5).

Patients who develop new autoantibodies like antinuclear and antiphospholipid antibodies during pregnancy have a more guarded prognosis.

Laboratory Testing

Studies recommended include:

- Blocking Antibody level (by flow cytometry)
  - T cell IgG and IgM
  - B cell IgG and IgM
- Antiphospholipid Antibody Panel
  - Anticardiolipin antibodies IgG,IgM,IgA
  - Antiphosphoglycerol antibodies IgG,IgM,IgA
  - Antiphosphoserine antibodies IgG,IgM,IgA
  - Antiphosphoethanolamine antibodies IgG,IgM,IgA
  - Antiphosphatidic acid antibodies IgG,IgM,IgA
  - Antiphosphoinositol antibodies IgG,IgM,IgA
  - Activated partial thromboplastin time (APTT)
  - Lupus anticoagulant (LA)
  - VDRL
- Antinuclear Antibody Panel
  - ANA Titer
  - Double stranded DNA
  - SSA
  - SSB
  - RNP
  - SM
- HLA Tissue Typing
  - ABC
  - DR,DQ
- DQA DNA fingerprinting
- Chromosome analysis
- Immunophenotype
- Natural Killer Cell Activation Assay
- Quantitative Immunoglobulin

Reproductive Immunology Associates provides the most advanced medical technology, information and personalized care to couples experiencing immune related miscarriages

As innovators and leaders in the diagnosis and treatment of immune related miscarriages, the physicians, medical technologists and support staff have a unique and unduplicated experience in working with couples and their physicians. Our daily commitment is to provide and environment where people who have suffered the agony and frustration of frequent miscarriage can come for information, evaluation and results.

Additionally, we feel a continuing and ever-increasing responsibility to keep the medical community fully informed about the technological advances, applications and success we are creating in our highly specialized practice.

A significant aspect of our practice are the relationships we have developed with our referring physicians to provide maximum comfort, continuity of care and results.

Ultimately we exist to serve our patients in an extremely personal and supportive manner at a time when they are most frustrated, confused and vulnerable.

Enabling our patients the opportunity to experience the joy of childbirth of our greatest reward.

In order to help insure that the medical community and the public have the most complete and up-to-date information in this highly specialized field we have established the Reproductive Immunology Associates web site.

Our hope is that this web site will act as a valuable resource to all people affected by miscarriage and their physicians.

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