The Women's Natural Health Clinic

Failed Implantation and Recurrent Miscarriage

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Overview

This fact sheet combines information from sources at the forefront regarding recurrent miscarriage and implantation failure including the Center for Reproductive Immunology & Genetics – Los Gatos USA, the Rosalind Franklin University – Chicago USA and St May's Hospital recurrent miscarriage unit – London UK

Miscarriage is the most common complication of pregnancy. Approximately 15% of all pregnancies end in a miscarriage and 25% of women who become pregnant will experience at least one miscarriage Recurrent miscarriage is usually defined as the loss of three or more consecutive pregnancies, and fortunately only 1% of couples fall into this group. If we include women who have experienced two miscarriages in the definition of recurrent miscarriage, the scale of the problem increases considerably and 3% to 5% of couples will be affected by this problem. We also now know that 50% of early pregnancy failures are caused by chromosomally abnormal female eggs and are increasingly learning more about the other 50%.

The difference between sporadic and recurrent miscarriage is important. It helps us to predict the chance of a successful pregnancy in the future, and the likelihood of there being a recurring cause for the loss of the pregnancy. A woman who has suffered a single sporadic miscarriage has an 80% chance her subsequent pregnancy will be successful and a woman with three consecutive miscarriages a 60% chance of her next pregnancy being successful.

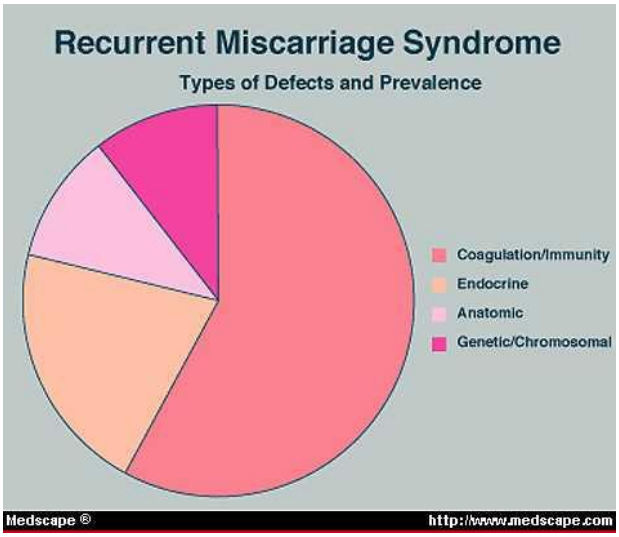
One in six pregnancies in women under the age of 30 will end with a miscarriage. For women between the age of 30 and 40 the number increases to one on five and over the age of 40 to one in four. One in two hundred couples will experience two or more consecutive miscarriages. Many of these miscarriages are the result of Mother Nature's quality assurance system preventing abnormal fetal development continuing where there are chromosome abnormities which would prevent survival of the baby if born. Probably the most common cause of any pregnancy loss is a chromosome abnormality in the conception. The contribution of the inappropriate number of chromosomes usually comes from the egg, although recent research has demonstrated more come from abnormal sperm than we thought just a few years ago. Best estimates are today that only about one half the eggs a woman has in her reproductive lifetime are capable of a successful pregnancy. Most of these chromosomally abnormal eggs are never identified as pregnancies. Either they do not divide to produce an embryo or fetus, or the conception is lost very soon after implantation of the early embryo. A woman is a few days late for her menstrual period and thinks nothing of it. However, in cases of repeated serial miscarriage the cause is pathological where something is wrong with the mother's physiology. The same causes have now been proven to exist in many cases of repeated failed assisted conception treatment cycles.

These are broadly described as immunological causes, where the either the mother or the father's immune system incorrectly identifies the fetal cells as interlopers and attacks them in the same way as a viral, bacterial or parasitic interloper.

There is a certain overall or background risk to pregnancy loss. The risk increases with age. Below is a table published in Fertility and Sterility. Many syndromes associated with recurrent fetal loss include anatomic anomalies, endocrine/hormonal abnormalities, genetic/chromosomal abnormalities, and blood coagulation protein/platelet defects (Bick RL; Madden J; Heller KB; Toofanian A (1998))

Maternal age (years)	Risk of Miscarriage (%)
15-19	9.9
20-24	9.5
25-29	10.0
30-34	11.7
35-39	17.7
40-44	33.8
44 & older	53.2

Fertility and Sterility: vol.46, p 989; 1986



Many syndromes associated with recurrent fetal loss include anatomic anomalies, endocrine/hormonal abnormalities, genetic/chromosomal abnormalities, and blood coagulation protein/platelet defects (Bick RL; Madden J; Heller KB; Toofanian A (1998).

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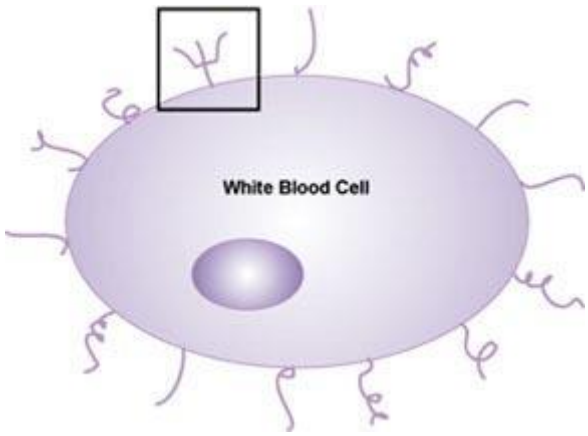
Immunological Causes of Implantation Failure and Early Miscarriage

There are six common categories of reproductive immunology problems that can cause recurrent miscarriage and failed implantation. Category 1 is the least severe, while Category 5 and 6 are the most severe. Without treatment, a woman with Category 1 problems can experience recurrent miscarriage, which may activate other categories of immune problems from Category 2, 3, 4 or 5

Category 1 - HLA compatibility
Category 2 – Blood clotting disorders
Category 3 - Positive antinuclear antibody (ANA)
Category 4 - Autoimmune response to sperm antigen
Category 5 - Abnormal natural killer cells (NK cells)
Category 6 – Abnormal Leukocyte Antibodies (LA)

Reproductive Immunology Background

All cells of the body have on their surfaces proteins or peptides called HLA (human leukocyte antigens). These are depicted in the figure below. These antigens serve as an early warning system that identifies foreign invaders - such as germs, viruses or cancer cells-that get into our bodies. With the new captured information, these cells signal the immune system to make antibodies (IgM, IgG and IgA) against the invader.



HLA Antigens: serve as antennae to identify foreign germs or viruses entering the body. Communicate this and initiate an immune response.

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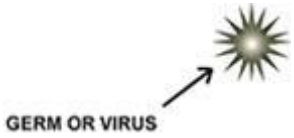

HLA Antigens: serve as antennae to identify foreign germs or viruses entering the body. Communicate this and initiate an immune response. A pregnancy must also be recognised as a foreign being (father puts HLA antigens on the placenta that are different from those of the mother). When this applies, the mother makes an antibody called a blocking antibody that attaches to the placenta and effectively cloaks the pregnancy from the mother's immune system. The antibody she makes in this circumstance does not kill; it protects the baby and makes the placental cells grow faster. When the father's HLA antigens placed on the placenta are too similar to the mother's HLA antigens, she does not make the antibody. In this circumstance the baby is not protected, the placental cells are not stimulated to grow and the baby dies. She interprets the pregnancy as "altered self" (i.e., a cancer cell). Therefore, when the cells of the baby die, she activates other immune problems from Category 2, 3, 4 or 5 where the natural killer cells that she was born with are now misinterpreting the baby as a cancer. This occurs in couples sharing DQ alpha HLA antigens.

Immune response to pregnancy - Alloimmunity

This serves to alert the mother to react to the baby as a baby, not as an infection. Which results in blocking antibody production

Immune response to infection - Infectious immunity

This initiates antibody production (gamma globulins) that destroys the bacteria or virus and remains in the body as a memory if the invader returns.

Category 1 - HLA compatibility

The HLA antigens on the placenta cells made by the father are called HLA-G. When the couple shares DQ alpha antigens in common, the G molecule put on the placental cells by the father is too similar to the G molecule that the woman's father put on her placenta to sustain her in her mother's uterus.

As a result, she does not make the blocking antibody, the baby dies, and her immune system recognises the placenta as "altered self" (i.e., a cancer cell) and category 1 problems move on to worsen to categories 2, 3, 4 and 5 (see diagram below).

HLA compatibility effects

1. Inadequate blocking antibody formation.

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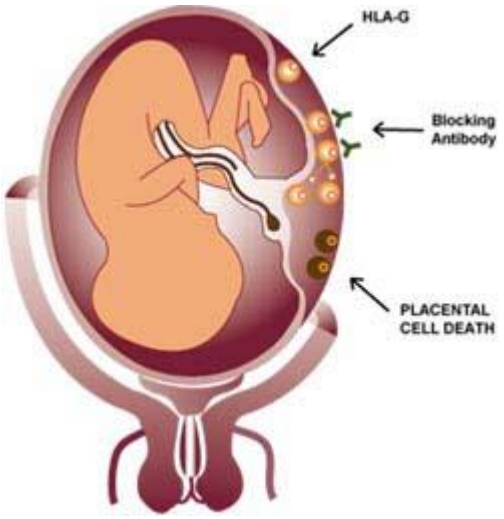
2. Ineffective camouflage of placenta.
3. Placental cells fail to grow and divide.
4. Death of placental cells.
5. Activation of category 2, 3, 4 and 5 immune problems.

HLA-G: Message sent from father to stimulate blocking antibody.

Blocking Antibody: Protects and stimulates the growth of placental cells.

Placental Cell Death: Consequences of low blocking antibody.



Category 2 – Blood Clotting Abnormalities

Whilst it has been known for a considerable time that a woman's blood becomes thicker in pregnancy, it has only recently been established that this process is more pronounced in some women compared with others. If blood clots occur in the blood vessels of the placenta the blood flow to the baby is decreased and this can lead to either miscarriage or, if the pregnancy proceeds, to the birth of a baby that is smaller than normal.

Repeated miscarriages, IVF failures, endometriosis and anything that causes tissue injury can lead to the formation of antibodies to phospholipids. These are called antiphospholipid antibodies. Phospholipids are important molecules in the membranes of all cells, and antibodies to these important molecules can derange cell function, cause inflammation and can cause blood to clot too quickly.

Many patients with autoimmune diseases also have tissue injury and make antiphospholipid antibodies. This is how antiphospholipid antibodies were discovered. Certain patients with lupus made antibodies that caused their blood to clot too quickly. This antibody is now called the "lupus anticoagulant antibody." When the test for this antibody is positive, most people think they have lupus. However, the majority of patients with this antibody have produced it because of infertility, IVF failures or recurrent miscarriage, not because they have lupus or other autoimmune diseases.

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Today, 22% of women with recurrent miscarriage have antiphospholipid antibodies. The incidence of this problem increases in women by 15% with each pregnancy that is lost. It is a significant consequence of infertility, implantation failures and recurrent miscarriage.

Antiphospholipid antibodies, the two most important of which are the lupus anticoagulant and the anticardiolipin antibodies, cause blood to clot more easily. Women with a history of recurrent miscarriage who have persistently positive tests for either lupus anticoagulant and/or anticardiolipin antibodies are said to have the Primary Antiphospholipid Syndrome (PAPS).

It has been shown in a recent large treatment trial conducted at St Mary's Hospital London, that 15% of women with a history of recurrent miscarriage have PAPS. In pregnancies in which no drug treatment is given, women with PAPS have a 90% miscarriage rate. The trail also found that women with PAPS have a 40% chance of a successful pregnancy when they are treated with aspirin alone but a 70% chance when treated with aspirin blood thinning drugs. Subsequent studies have confirmed this high live birth rate with aspirin and blood thinning drugs and as a result this has become, both nationally and internationally, the established treatment for recurrent miscarriage sufferers with PAPS.

There are six different phospholipid molecules that have very important functions in cell membranes and intracellular organelles. The phospholipid molecules are:

1. Cardiolipin
2. Ethanolamine
3. Glycerol
4. Inositol
5. Phosphatidic Acid
6. Serine

Cell death or cell injury can lead to the production of antibodies to all or any one of these molecules. These antibodies disrupt cell functions and increase the clotting speed of blood. This can cause major problems in the first few weeks of pregnancy.

As shown in the diagram, Serine and Ethanolamine are phospholipids that serve as glue molecules in allowing the placenta to be securely attached to the uterus during implantation. They also allow the cytotrophoblast to change into a new cell, the syncytiotrophoblast, which begins to feed the baby by transporting nutrition from the mother's blood into the baby.

Antibodies to these phospholipids prevent secure attachment or often totally prevent attachment. In addition, antibodies to these phospholipids prevent the cytophoblast from forming into the syncytiotrophoblast, which is needed to develop the fetus.

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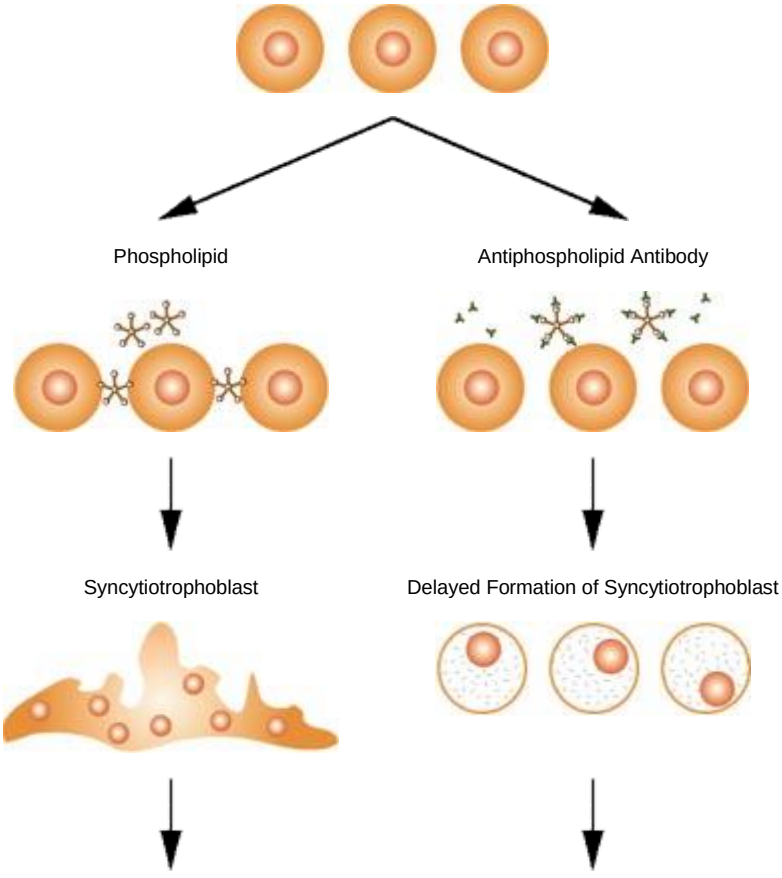
Cytotrophoblast Placental Cell
Attaches placenta to uterus.



Feeds the baby.
Produces ß-hCG and progesterone.
Grows throughout pregnancy.

Pregnancy loss or implantation failure.

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The three major gene mutations that lead to Inherited Thrombophilia's are:

Factor V Leiden mutation.

Factor II (Prothrombin) G20210 gene mutation.

Methylene-tetrahydrofolate reductase (MTHFR) mutation, leading to hyperhomocytseinemia

The most common cause of APC resistance arises from the point (one DNA based-pair) mutation at the cleavage site of factor V, called factor V Leiden. It is the most common of the Inherited Thrombophilia's, with a prevalence of 10% in the Caucasian population. The mutation has been discovered in 60% of patients who have clot formation during pregnancy and is also a major cause of blood clots associated with oral contraceptive use. The Prothrombin (factor II) gene mutation has been shown to occur in 7.8% of women who experienced fetal loss due to a clotting disorder. Factor II is one of the major factors in the human clotting pathway. Homocysteine is normally present in low levels in the bloodstream. It is derived from dietary methionine, an amino acid. A gene mutation for the enzyme methylene-tetrahydrofolate reductase (MTHFR), will lead to build up of homocysteine in the bloodstream. This condition, called hyperhomocytseinemia, results in blood clot formation and hardening of the arteries, even in childhood. Nutritional lack of vitamins B6, B12 and folic acid aggravate the problem. Women who have the homozygous form of the MTHFR gene mutation (both of her alleles having the mutation) are more than a two-fold increased risk for a miscarriage.

Although there are numerous risk factors for venous thromboembolic disease, the term *thrombophilia* refers only to those familial or acquired disorders of the hemostatic system that result in an increased risk of thrombosis.

The *inherited thrombophilia's* include

Antithrombin III deficiency,
Resistance to activated protein C (factor V Leiden),
Protein C and protein S deficiencies,
Prothrombin gene mutation,
The MTHFR gene mutation, as well as some rare forms of dysfibrinogenaemia.

In contrast, antiphospholipid syndrome is the only genuine *acquired thrombophilic* state and this acquired syndrome is far more common in women with recurrent pregnancy losses and implantation failures than the inherited thrombophilia's.

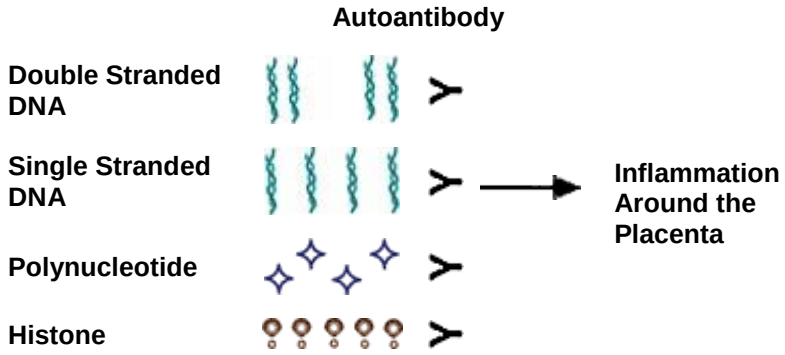
Women with the following should be investigated for thrombophilia:

Recurrent pregnancy losses
Infertility
Know implantation failures
IVF failures
Thromboembolic disease at a young age
Positive family history

Antiphospholipid antibodies (aPL) are a family of autoantibodies with specificity for negatively charged phospholipids, or more accurately for their complex to phospholipid binding proteins. Their presence is associated with arterial/venous thrombosis and recurrent pregnancy losses. These clinical manifestations with the persistence of aPL are recognised as antiphospholipid syndrome (APS), one of the most common acquired thrombophilia. Beta 2-glycoprotein I (beta 2GPI) bears the epitope(s) for anticardiolipin antibodies (aCL) on its molecule, and lupus anticoagulant activity depends on the presence of beta 2GPI or prothrombin. Thus, phospholipid binding proteins may have some crucial roles in the pathophysiology of thrombotic events in APS. It has been hypothesized that aPL bind to cells and induce procoagulant activity via phospholipid binding proteins.

Category 3 - Positive antinuclear antibody (ANA)

Category 3 immune problems occur in 22% of women with recurrent pregnancy losses and nearly 50% of women with infertility and IVF failures. Women with this problem make antibodies to DNA, or DNA breakdown products in the embryo or in the pregnancy. These antibodies form first in the blood as IgM. As the problem gets worse they appear as IgG and live in the lymphatic system and lymph nodes. With more losses they form IgA antibodies which have their home and action in the organs including the uterus. These antibodies can be against pure double stranded DNA (ds DNA), single stranded DNA (ss DNA), or smaller molecules called polynucleotides and histones that make up the single strands.



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Antinuclear antibody effects

Antinuclear Antibody (ANA) positive, speckled pattern.
Autoantibody to DNA leads to inflammation in the placenta.
Autoimmune disease screening in the woman is negative

The test is reported as a titer and a pattern. Any titer above 1:40 is significant. The titers can get into the thousands such as 1:2,500. This simply means that the test is positive when the blood serum is diluted many times. These same antibodies appear positive in women with lupus, rheumatoid arthritis, Crohn's disease and other autoimmune diseases.

They are usually in high titers. Pregnancy losses, infertility and IVF failures cause the titers to be much lower and a low positive titer does not mean that you have or are getting an autoimmune disease; however, this is ruled out during the testing. In women with autoimmune diseases these antibodies cause inflammation in joints and organs. In women with no autoimmune diseases but a positive antibody, the antibody causes inflammation around the embryo at the time of implantation or in the placenta after implantation. This inflammation is the same as occurs with cuts or scratches or splinters.

Category 4 - Autoimmune response to sperm antigen

Ten percent of women with infertility, implantation failures and recurrent miscarriage have produced antibodies to sperm. When this happens, a couple is unable to conceive normally, even if they had no problems with conception in the past. The antibody to sperm is often associated with antiphospholipid antibodies to the phospholipids serine and ethanolamine.

Antibodies to sperm should be suspected in:

Women who have antibodies to serine and or ethanolamine,
Women with poor post coital tests (sperm are dead or not moving in the cervical mucus)
Women whose partners have anti-sperm antibodies.

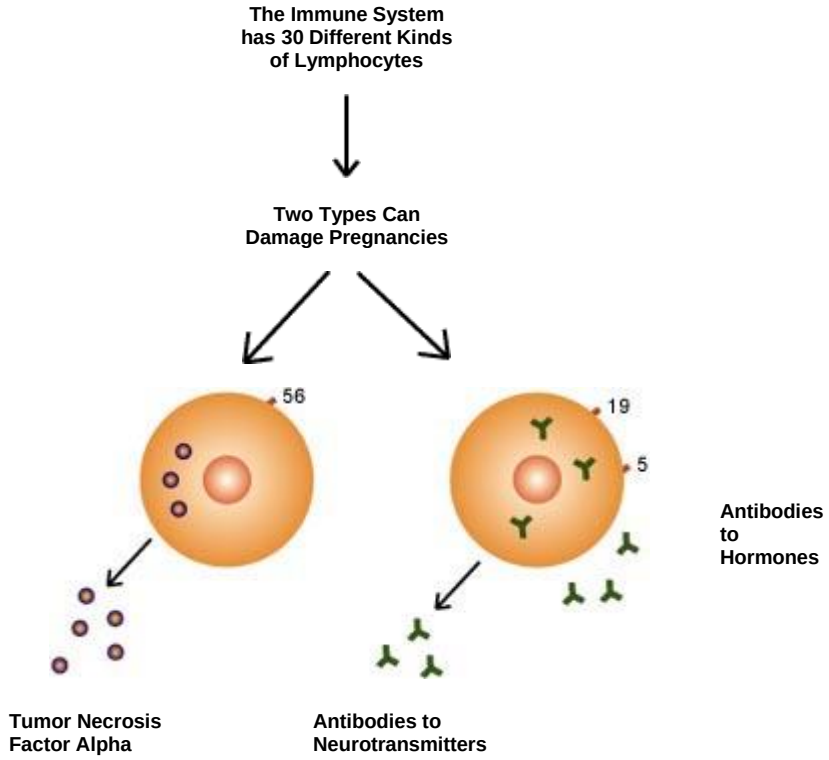
Being exposed to antibody coated sperm dispensed by the male seems to encourage women to make antisperm antibodies on their own. When anti-sperm antibodies develop, they will inactivate or attack sperm from the partner and any donor (i.e., they are not partner specific). Testing for anti=sperm antibodies in women is done from a blood sample. The presence of anti-sperm antibodies in women strongly predicts that she will also have category 5 immune problems.

Anti-sperm antibodies effects

Sperm antibody test positive.
Couple is unable to conceive normally.
Multiple failed pregnancy through IVF or IUI

Category 5 - Abnormal natural killer cells (NK cells)

There are 30 different types of lymphocytes (CD designations) that make up the immune system. A balanced functioning of these white blood cells keeps a person healthy. Three of these cell types can cause infertility, implantation failures and miscarriages. Women are born with these cell types. In some women, they increase in numbers and activity and result in reproductive failures.



Types of white blood cells include the following:

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1. TH-2 ("T Helper 2")
   The response is a balanced correct response during pregnancy (Category 1).

2. TH-1 ("T Helper 1")
   The response is a cyto-toxic autoimmune response that can lead to infertility, implantation failure and miscarriage (categories 2, 3, 4 and 5).

3. CD3, CD4, CD8
   Control production of blocking antibody response; a correct response.

4. $CD19^{+}$ 5^{+}
   Produce antiphospholipid antibodies (Category 2) and anti-DNA and histone antibodies (Category 3). It also produces anti-sperm antibodies.

5. $CD56^{+}$, $CD57^{+}$, CD69
   Are natural killer cells which attack pregnancy sites.

CD-3 (Pan T-Cells)

These cells are the most important in our immune system. They are low when the immune system is weak (suppressed) and normal when the immune system is healthy. Infertile patients and patients with recurrent pregnancy losses have values in the high normal range. These individuals have immune systems that are strong - even overactive. A strong overactive immune system is associated with a 5% incidence of autoimmune diseases for example, thyroiditis, lupus, rheumatoid arthritis.

CD-4 (T-Helper Cells)

These cells are CD-3 lymphocytes and are essential for all lymphocytes to know what to do. They cannot function without the road map provided by the CD-4 T Helper cells. For example: CD-4 cells are killed by the HIV virus and as a result the immune system falls into disarray. In women with infertility or miscarriage these cells can also be high normal because they are helping the many CD3 Pan T cells. They are rarely low in number. If they are low, the patient needs a further immunological evaluation to study the aetiology of this deficiency.

CD-8 (T-Cytotoxic-Suppressors)

These cells are the referees of the Pan T and the T Helper interactions. They coordinate how strongly or how weakly the immune system reacts. In women with miscarriage and or infertility these cells are often on the low side. "They get tired arbitrating the hyperactive Pan T cells and the T Helpers." They are rarely high. These three cell types comprise the 'engine' of the immune system. AIDS and immunological deficiencies affect these cell populations and as a result they are low in number. In

patients with infertility and recurrent pregnancy losses, the CD3 and CD4 cells are usually high with the T- cytotoxic suppressors a little low from overwork.

CD-19 (B Cells)

These lymphocytes are plasma cells that produce antibody of all classes. IgM is the first antibody produced to anything that enters our body. This antibody stays in the blood and then as the immunity progresses it produces IgG (Gamma globulin G) that resides in the lymph system. One IgM molecule has the immune capacity of 5 IgG molecules. IgG lives and repopulates itself in the lymph gland system. IgA (Gamma globulin A) is the last antibody made in an immune response and it resides in and protects the organs, skin and GI tract. When this antibody appears, it means that the immune response is completed and cannot go any further. When IgA responses (organ immunity) are present in any test for reproductive failure it usually means that the patient has an autoimmune process such as lupus, rheumatoid arthritis or other autoimmune disorders.

CD-19 B cells are almost always high normal or very elevated in women with an immune cause for their infertility or recurrent pregnancy losses. There is often a greater than 12% elevation. This is one of the most important indicators of an immune problem and that the immune system is working overtime. Endometriosis must also be considered as it stimulated the immune system into hyper-reactivity.

CD56+ CD16+ natural killer cells

Natural Killer cells of this type are produced in the bone marrow and these cells produce a chemotherapy molecule called TNF (Tumor Necrosis Factor). This molecule is involved in eliminating cancer cells that may develop in normal individuals. Tumor Necrosis Factor also causes joint damage in women with rheumatoid arthritis. These Natural Killer cells are often elevated in women with infertility and recurrent miscarriage.

The Tumor Necrosis Factor produced by these cells kills the rapidly dividing cells of the embryo and placenta often resulting in IVF failure, blighted ovum or a chemical pregnancy where the BhCG elevates slightly and then quickly returns to non-pregnant levels. Normal levels for this cell population are 3-12%. The CD 56 and the CD16 molecules on the surface of these cells are special glue (adhesion) molecules that allow the Natural Killer Cells to attach to cancer, placental and embryonic cells. Once glued to the placental cell, it sprays Tumor Necrosis Factor on the cell and kills it.

CD 56+ natural killer cells

These Natural Killer (NK) Cells include CD56+/16+ Natural Killer Cells and CD56+ Natural Killer cells with lack of a CD16 molecule. Natural Killer Cells are activated by a pregnancy that fails or a fertilized embryo that degenerates. CD56+/16+ Natural Killer Cells are produced in the decidua and they are even more geared up to kill than those from the bone marrow. They produce large quantities of Tumor Necrosis

Factor locally that kills the placental cells and the fetal cells. The normal range of CD56+ Natural Killer cells is 3-12%. Levels of 18% or greater correlate with poor reproductive outcome.

CD 56+ natural killer cells

1. Increase in number 2-12% normal. Above 12% see infertility and pregnancy losses.
2. Increase in cytotoxicity in NK assay. Cytotoxicity above 15% at 50:1 can damage the embryo.
3. These cells usually reside in the blood; however, in 2% of women they are so activated they live in the uterus. This is determined by an endometrial biopsy
4. They produce toxic Cytokines (TH-1 cytokines) including Tumor Necrosis Factor (TNF) Alpha.

CD 56+ natural killer cells effects

1. Prevent implantation.
2. Cause miscarriages by damaging the placental cells, causing decidual necrosis, damage the yolk sac.
3. Later in pregnancy they cause slowness of the heart rate of the baby, cause an irregular shaped gestational sac that is smaller than normal and amniotic fluid volume that is too small.
4. They induce sub chorionic haemorrhages which can cause spotting, bleeding and can be seen easily on ultrasound.
5. In some women they can affect the DNA in the eggs so that fragmentation, slow cell division, arrested cell division and poor-quality embryos are seen.

CD $19^{+}5^{+}$ B Cells

1. Normal numbers are 2% - 10%. Women with problems have increases in cell numbers above 10%.
2. These cells produce antibodies to hormones necessary for pregnancies to develop safely. These antihormone antibodies are against oestradiol, progesterone, and human Chorionic Gonadotropin (hCG).
3. These antibodies lower hormone levels and lead to luteal phase deficiencies, slow rising hCG levels when pregnant, poor stimulation during ovulation induction cycles and poor lining development by ultrasound evaluation.

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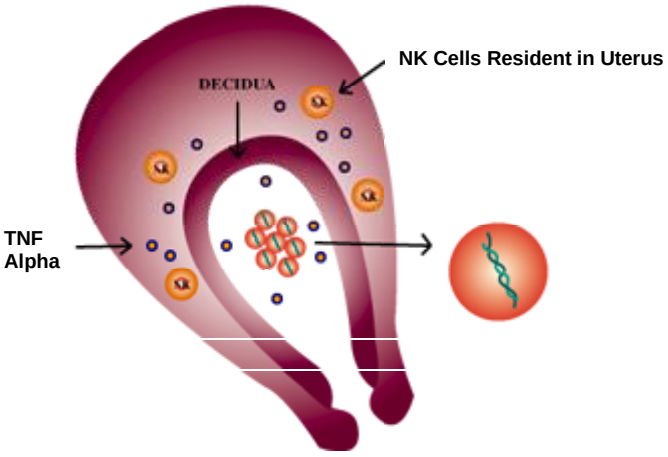
CD 69 Cells

CD69 is a functional triggering molecule on activated NK cells and is one of the earliest cell surface activation markers expressed and is capable of inducing toxicity. CD 69 levels are a helpful simple test that gives a window into overall reproductive NK cell levels.

Before Implantation



Causes Apoptosis of the DNA in the Embryo Leading to Spot Welding of the DNA

↓

Embryo Grows Slowly and Dies. Embryo Never Attaches. Placental Tissue Grows With No Embryo Seen.

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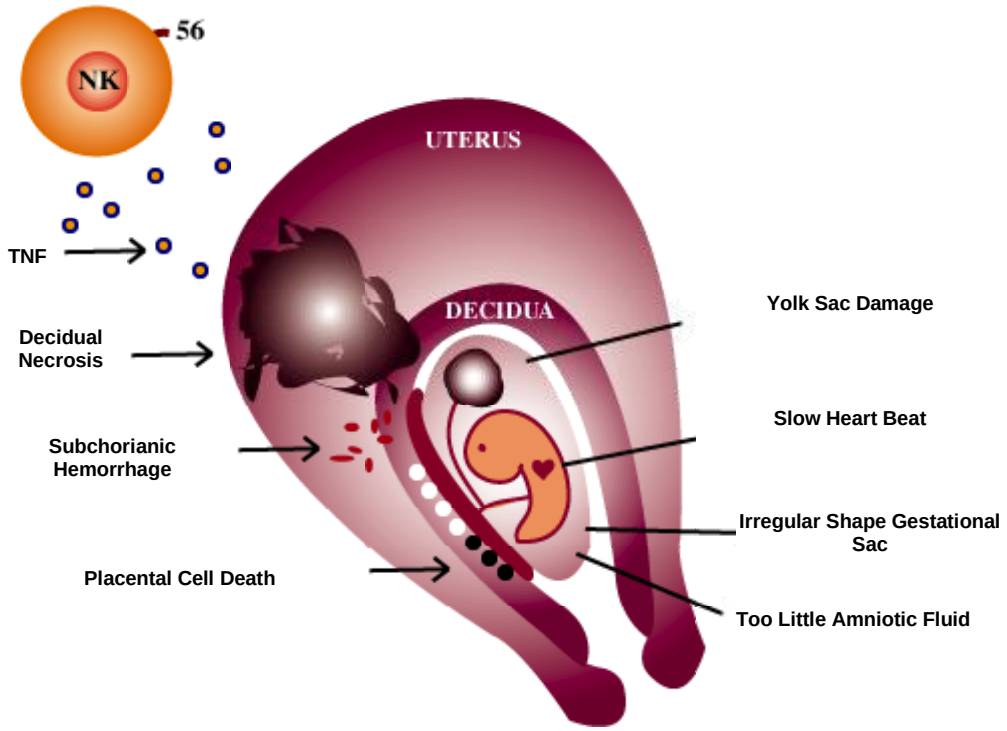
Immune pathology studies of a biopsy of the endometrium (uterine lining) in women with recurrent pregnancy losses, IVF failures and implantation failures show that lymphocytes can damage the lining as well as the embryo. These lymphocytes are not seen in the uterus of fertile women. To find if a woman has this problem an endometrial biopsy is done 7-9 days post ovulation.

These unwanted immigrant cells that take up house-keeping in the uterus are:

1. Activated macrophages that secrete IL-1 (toxic to the lining and to the embryos);
2. CD 56+ Natural Killer cells that secrete tumor necrosis factor alpha (toxic to the embryos and uterine tissue). These cells can cause stromal haemorrhages, sub chorionic haemorrhages and early premenstrual spotting
3. Mast cells (associated with hives and rashes in the skin of allergic individuals), when present in the uterus, cause stabbing pains, bad premenstrual syndrome, severe cramping and ill feelings after intrauterine insemination or embryo transfer.

After Implantation TNF Alpha Damage



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Women who are at risk for having NK cells in the uterine tissue

1. Women with a known autoimmune disorder such as fibromyalgia, lupus, rheumatoid arthritis, Crohn's Disease, thyroiditis, chronic fatigue syndrome, Raynaud's disease, mixed connective tissue disorder and ulcerative colitis
2. Women with a history of dysplasia of the cervix, carcinoma in situ of the cervix or papilloma virus infections (HPV)
3. Infertile women with endometriosis prior to their first assisted reproductive technology (ART) or IVF cycle
4. Women with recurrent spontaneous abortions who lose their pregnancies earlier and earlier or who have secondary infertility
5. Women with two more IVF failures
6. Women with repeated natural implantation failures
7. Women who experience flu like symptoms with implantation, transfer or implantation failure
8. Women who experience stabbing pelvic pains or intense cramping with inseminations or embryo transfers
9. Women who experience strange symptoms in abdomen, pelvis and legs of cramping, jitteriness, jerking or strange travelling sensations in the skin post intrauterine insemination or post transfer

Category 6 - Abnormal Leukocyte Antibodies (LA)

Leukocyte antibodies are cells in the body that attack leukocytes and pregnancy they moderate NK cell activity. Leukocytes are found in blood, bone marrow, and lymph tissues, they are responsible for attacking foreign bacteria and other invaders that enter the body. NK cells are programmed (by the thymus) leukocytes. In order to maintain pregnancy, the female body creates antibodies to leukocytes triggered by male antigens carried by sperm. Normal healthy pregnant women should test positive for a certain level of protective leukocyte antibodies in the presence of a normal level of NK cells. When leukocyte antibodies are low or not present implantation and early miscarriage occurs even in the presence of normal levels of NK cells. These are related to Category 1 as in the unusual case that a couple have a partial or complete phenotype match the woman's immune system is not triggered to produce protective leukocyte antibodies.

Recurrent Miscarriage and Implantation Failure Tests

The Women's Natural Health Clinic

Natural Killer Cell assay

The Natural Killer research test simply separates NK cells from the patient and asks them to perform their aggressive roles in the test tube. Varying concentrations of IVIg are added to the test tube to determine how much is necessary to prevent killing.

Leukocyte Antibody Detection assay

The ability of a woman to produce protective antibodies that cloak the pregnancy implantation site is tested by exposing her white blood cells to her partners antigen removed from his blood sample. If the result shows a woman is producing a very low level of antibodies or a complete absence of antibodies than a further test for phenotype matching is indicated. This is called an DQ-Alpha test.

Clotting factor assay

A blood test for women to determine the activity level of inherited and acquired factors that cause blood clotting in pregnancy in female blood.

Anti-sperm Antibodies assay

A semen analysis for the male partner and a blood test for the female partner identifies if either partner has developed Anti-sperm antibodies which would reduce sperm ability to achieve conception in the male and can cause early implantation failure in the female partner. Now commonplace in semen tests in the UK. A further, more advanced test called a SEED tests may also be indicated if ASAB's are negative and no other cause for unexplained infertility can be identified.

Evaluation of the Endometrium

An endometrial sample taken at implantation time (7-9 days post ovulation) in a normal non-conception cycle. This will be then analysed for immune overactivity, sub-clinical infection, cellular staging and histology.

Recurrent Miscarriage and Implantation Failure Treatments

Conventional medicine treatment

In conventional medicine the know causes of recurrent miscarriage or IVF failure fall into three

categories. Firstly, chromosomal defects, where no treatment exists at this time. Secondly, acute infections, endocrine disorders, treatments for all these is routine and well understood.
Usually Antibiotics, Progestogen or hCG hormones are administered. The third category is auto immune disorders where immune system suppressing, systemic steroids, intralipids or IVIG and blood thinning drugs are used. The therapy is started before pregnancy occurs and continued though pregnancy.

Natural medicine treatment

We recommend that patients start taking 400mcg/day folic acid before and during first 12 weeks of pregnancy.

Patients who are homozygote positive for the MTHFR C677T mutation a raised homocysteine level, but this can be reversed by giving the patient 5mgs of folate supplement daily.

Patients with raised natural killer cells (CD69 - CD56 – CD19+5) respond well with treatment by medicines refined form pharmaceutical mushrooms. These have been well proven in Japan to moderate the immune system of HIV and autoimmune disease patients and form a mainstream part of conventional medicine treatment in japan. The same action has been observed in women with raised NK cell levels.
Patients are given a combination of mushroom types (Cordyceps, Mesima and Coriolus) in tablet form. Which type of mushroom medicine depends on the exact nature of abnormal immune activity

In TCM three or more recurrent miscarriages is termed 'slippery fetus syndrome'. Women with a history of infertility or early menstrual periods due to luteal phase deficiency are far more likely to suffer from this condition. This syndrome is most common in women in their mid to late 30's and early 40's where kidneys are starting to weaken. This condition is often compounded by the stress of demanding careers and often, the emotional frustration of dealing with infertility. These emotional pathologies aggravate the underlying weakness increasing the probability of repeated miscarriages even further.

Post conception additional care

We recommend that our patients have a series of ultrasound examinations during their pregnancies. This is because although our patients may have different immune problems, they are all similar in at least one respect: the problem leads to abnormal blood flow from the mother to the placenta. This may adversely affect the developing pregnancy. This is called a vasculitis; i.e., an inflammation of the blood vessels. The way to determine if inflammation is present is through the regular ultrasound examinations. If an abnormal result is obtained, treatment may be altered to allow blood to flow more easily. Because it is such a critical period ultrasound examination should be carried out every two weeks during the first trimester. Thereafter, ultrasound examinations are performed monthly, unless

there is a reason to perform them more frequently. After the first trimester examinations, we perform different ultrasound tests during each scan in addition to the fetal blood supply tests.

Our Female Healthcare Philosophy

At the Women's Natural Health Clinic, we specialise in providing comprehensive natural reproductive, gynaecological, obstetric and general healthcare for females from adolescence to post-menopause. Our approach is to integrate techniques in both oriental and western medical diagnosis to formulate a naturally oriented treatment plan combining acupuncture, herbal medicine, naturopathic medicine, nutritional therapy, exercise and lifestyle. Each treatment plan is tailored specifically to each individual woman maximizing results.

Please email us at enquiries@naturalgynae.com with questions, we are more than happy to provide any information via email that will assist you in deciding which treatment approach would be best for you

For more information, contact details and appointments click here www.naturalgynae.com

References and Bibliography

1. Dr. Alan Beer and his associates, in an award winning 1995 study presented to the 6th International Congress of Reproductive Immunology, reported that 86.6% of women with elevated Natural Killer Cells had a successful pregnancy outcome when treated with preconception IVIg, aspirin and heparin.
2. Dr. Carolyn Coulam finished a double blind study on IVIg therapy for immune problems resulting in infertility. Her results were published in the December 1995 issue of The American Journal of Reproductive Immunology. Her study showed a 3:1 ratio of increased births to women receiving IVIg vs. a placebo. These results are now being presented to the FDA to support the approval and the use of this drug for reproductive immunology purposes.
3. In 1994, an article was published by Coulam, C.B., Krysa, L.W., and Bustillo, M. in Human Reproduction 9, 2265 - 2269, entitled "Intravenous Immunoglobulin for In-Vitro Fertilization Failure".
4. DePlacido, G., Zullo, Mallo, A. Capieio, F., Nazarro, A., Colarcurci, N., Palumbo, G. published in 1994 in the Annals of the New York Academy of Science, 734, 1 - 3 an article entitled, " Intravenous Immunoglobulin (IVIg) in Prevention of Implantation Failures".
5. Kleinstein, J., Khanaga, O., Gips, H. and Kunzel, W. published the article entitled, "Intravenous Immunoglobulin Increase Clinical Pregnancy Rates in IVF Program in 1994 in the Society Gynecological Invest, 41st Annual Meeting, Abstract #P108.
6. In a 1994 article in the American Journal of Reproductive Immunology, the Recurrent Miscarriage Immunologist Trialist Group published the results of a Meta-Analysis of White Blood Cell Immunizations that was organized by the American Society of Reproductive Immunology Ethics Committee. Two different analyses showed an increase in live births (a ratio of 1.16 in one analysis and a ratio of 1.21 in the second). When the

analysis was limited to women with primary miscarriages it increased to a ratio of 1.46. These results were significant at the p=.006 level. The studies that used subcutaneous immunization vs. intravenous with white blood cell (LIT) immunizations showed better results. Also, those studies included in the Meta-Analysis that screened out the women with other immune problems showed better results (example APA and Natural Killer Cells). The presence of these additional problems seemed to cause pregnancy losses even when LIT was given.

7. Most of the studies on reproductive immunology concern miscarriage. The thinking now is that a good portion of infertility is simply very early miscarriage. This theory was reported in the American College of Gynecology (ACOG) September 1995 Bulletin. "Approximately 50-70% of pregnancies end in spontaneous abortion. Most of these pregnancy losses are unrecognized because they occur before, or at the time of, the expected menses". When these patients are studied carefully, 15% show an unexpected pregnancy per menstrual cycle that did not take.

8. A study by Geoffrey Sher was published in Human Reproduction, vol. 9, no. 12 PP 2279-2283, 1994, "High fecundity rates following in-vitro fertilization and embryo transfer in antiphospholipid seropositive women treated with heparin and aspirin". This study showed a 49% viable pregnancy rate for women positive for antiphospholipid antibodies and treated with heparin and aspirin vs. 16% of seropositive women not treated with heparin and aspirin.