

Causes of Miscarriage

In approximately 50% of couples, extensive investigations fail to establish a cause for RM. Although it may disappoint some couples that their problem remains unexplained, in fact the outlook for such couples is often better than for those in whom a cause is found!

The known causes of RM can be classified as follows:

Immunological

Blood clotting disorders (thrombophilias)

Hormonal

Infection

Anatomic

Chromosomal

Environmental

Immunological causes of recurrent miscarriage:

Historically, a pregnancy has been compared to a heart, kidney or liver transplant. This is because the fetus derives half of its genetic information from its father, who is unrelated to the mother. Everybody knows that for a transplant to "take" attempts are made to match the tissue type of the donor to that of the recipient, and even when a match is close, powerful drugs still have to be given to the recipient to suppress the immune system to prevent the transplant being "rejected". In human pregnancy, not only is there no physical match, but no drugs are given, yet the pregnancy thrives. For decades this apparent paradox has fascinated immunologists, who have sought the Holy Grail which has enabled the fetus to elude the mother's immune system. We now know that the comparison of the fetus to a transplant is wholly simplistic and in fact inappropriate, but there is strong evidence that in some instances, the immune system, whose prime function is to protect the body against infections, can be implicated in recurrent miscarriage. It is, however, important to recognize that much of our knowledge in this area remains rudimentary.

Natural Killer (NK) cells

NK cells are part of the so-called innate immune system, which protects the body against viral and bacterial infection without the need for prior sensitization. A strong body of research has now shown that in normal pregnancy NK cells in the peripheral blood reduce both in number and in their capacity to kill. Further research has suggested that in women with recurrent miscarriage, and in those with implantation failure following IVF treatment, there are increased numbers and activity of NK cells. Unfortunately studies have either confined themselves to the peripheral blood or to the lining of the womb, but usually not to both. There are important subtle differences between those cells found in the womb and those in the peripheral blood, and further research is needed to clarify the role of NK cells in recurrent miscarriage. Treatments that cause suppression of the immune system such as steroids are promising, but have yet to be subjected to rigorous

evaluation. We offer NK cell testing and are evaluating the role of abnormal findings in recurrent miscarriage, and the outcome following treatment with prednisolone, heparin and aspirin.

Cytokines

Cytokines are small chemicals

Immunologic disease - eg SLE

Immunological diseases, especially auto-immune conditions (where the body's immune system turns on itself and attacks its own organs and other systems causing disease) may compromise fertility and pregnancy. Systemic lupus erythematosus is the best example of a disease that compromises pregnancy: this includes recurrent miscarriage, poor fetal growth, intrauterine death and pregnancy complications such as pre-eclampsia. Although it would be uncommon for a woman with SLE to present for the first time with recurrent miscarriage rather than with other features of the disease, the screening tests performed in the Recurrent Miscarriage Clinic would pick up the markers of SLE and suggest extended investigations to confirm the diagnosis. Treatment of active disease is usually with steroids, and if other markers such as the lupus anticoagulant or anticardiolipin antibody are also present, then heparin and aspirin may also be indicated. Patients with SLE and other connective tissue disorders require specialized care and so-operation between obstetricians, rheumatologists and sometimes renal physicians. The Recurrent Miscarriage Clinic has direct links to a joint Connective Tissue Disorders Clinic run by an Obstetrician (Mr Isaac Manyonda) and a Rheumatologist (Dr John Axford).

Blood clotting disorders (Thrombophilias)

Individuals with a thrombophilia are at increased risk of forming blood clots, leading to deep vein thrombosis (DVT) and /or pulmonary embolism (PE - clot on the lung) if the clot in the vein dislodges and is propelled in the blood stream to the lungs. This increased risk of clot formation is because the individual makes too much of a clot-promoting protein, or too little of a protein that promotes dissolution of clots. Pregnancy itself, even in women without a thrombophilia, increases the risk of clot formation 6-fold. So women with a thrombophilia are at significant risk of clot formation during pregnancy.

In recent years, research has shown that thrombophilias, some of which are acquired while others are inherited, are a significant contributor to recurrent miscarriage. While it is tempting to suppose that thrombophilias impair pregnancy by the formation of blood clots around the early after-birth, in reality the story is more complex. The good news is that once identified, there are effective therapeutic interventions for these disorders.

The Primary Antiphospholipid syndrome (PAPS) - this is an example of an acquired thrombophilia the most important markers of which are the lupus anticoagulant and the anticardiolipin antibodies. It is estimated that PAPS can be diagnosed in about 15% of women with recurrent miscarriage. Left untreated, women suffer a miscarriage rate of up to 90%. Earlier studies showed that treatment with a combination of low dose aspirin and low molecular weight heparin gave a 70% chance of successful pregnancy, while aspirin on its own

gave a 40% chance of success. Intriguingly, more recent reports have suggested that aspirin on its own can in effect achieve the high results achieved by the combination with heparin!

Factor V Leiden (FVL) mutation- this is an example of an inherited thrombophilia which, in the absence of treatment, is associated with recurrent miscarriage. FVL is carried by 5% of Caucasians, but is rarely found among Blacks people. Again the current approach is to treat carriers of this mutation with a combination of heparin and low dose aspirin.

Other thrombophilias - these include Protein C deficiency, Protein S deficiency, Antithrombin III deficiency, G20210A prothrombin gene mutation, hyperhomocysteinemia etc. These disorders are in fact rare, and because of the small numbers no conclusive studies have been conducted to prove that they in fact cause recurrent miscarriage. However, the pragmatic approach is to assume that if they are the only finding in a woman presenting with recurrent miscarriage, they may well be contributory. Treatment is similarly with heparin and aspirin, and if this is not given to "cure" recurrent miscarriage, it will at least protect the woman against blood clot formation!

Hormonal causes of recurrent miscarriage:

Polycystic ovaries (PCO):

Ultrasound finding of PCO is common in the general female population - 22-25% of women will be found to have slightly enlarged ovaries with small cysts arranged around the edge rather like a necklace. PCO may be entirely without symptoms, but can also be a cause of long and / or irregular menstrual cycles, infertility, acne, difficulty with keeping weight down and excessive body hair (hirsutism). When PCO are associated with symptoms or signs, the condition is referred to as the polycystic ovarian syndrome or disease (PCOS or PCOD). Hormonal abnormalities associated with PCOS include increased production of luteinising hormone (LH) and testosterone.

A link has been suggested between PCO and recurrent miscarriage because most studies have shown that PCO are over-represented in women with RM, reports ranging from 40-80%. Although it is thought that high levels of LH may interfere with the normal maturation of eggs in the woman, and in this way predispose to miscarriage, research has shown that high levels of LH are not a cause of miscarriage. Thus LH and / or PCO may simply be markers of another underlying cause. Various avenues of research are currently on-going to elucidate the possible mechanism(s) that may be involved in recurrent miscarriage in women with PCO.

Progesterone:

Progesterone is undoubtedly a key hormone in pregnancy maintenance, since the administration of drugs that abolish its activity, or removal before 6-7 weeks gestation of the corpus luteum, which produces most of the progesterone in early pregnancy, results in miscarriage. Progesterone appears to have many roles in pregnancy, including rendering the lining of the womb more receptive to the early embryo, and causing the womb to be less prone to contractions - keeping the

uterus in a quiescent state. It is although thought to alter the balance of the all important chemicals called cytokines in a way that tends to promote pregnancy. It should not be surprising therefore that it has been suggested that low levels of progesterone may be a cause of miscarriage, sporadic or recurrent. Linked to this has been the idea of "corpus luteum deficiency" whose diagnosis can only be made reliably by taking and carefully examining a biopsy from the lining of the womb in the second half of the menstrual cycle. For many women were given progesterone supplements as a treatment for recurrent miscarriage, but the practice was largely abandoned when a meta-analysis showed the treatment to be useful, and not without a small risk of virilizing a female fetus. Current views are that low levels of progesterone hormone reflect a pregnancy that is failing, rather than being a cause of the pregnancy failure. But these views are being challenged again. Many have criticized the meta-analysis that showed a lack of benefit from progesterone supplementation because of the poor quality of studies included in the meta-analysis. Others have pointed to recent research that has shown very clearly that progesterone supplementation prevents late miscarriage and preterm birth in women at risk. They have argued that some cases of late miscarriage and preterm birth represent a spectrum condition that starts in the first trimester of pregnancy, and progesterone supplementation may therefore benefit a select group of women, although nobody knows how that group of women is to be identified. This area is therefore ripe for further research. Some women, based on previous experience, are convinced that progesterone prevents recurrent miscarriage. Provided they understand the small risks, the pragmatic approach is to allow them to use progesterone supplements. It should be remembered that progesterone support is widely used in IVF treatment cycles, where it is essential.

Other hormones:

Poorly controlled diabetes mellitus or untreated over- and under-active thyroid gland can probably cause miscarriage. However, it would be highly unlikely that a woman with one of these diseases would present for the first time with a history of recurrent miscarriage, but be otherwise well.

Infection as a cause of recurrent miscarriage

While an acute infection causing high fever and general malaise may cause a sporadic miscarriage, chronic infection of the genital tract is rare, and therefore infection is not considered a common cause of recurrent miscarriage.

However, recent research has shown that bacterial vaginosis (BV) is strongly linked to a significant risk of late miscarriage (14-24 weeks) and preterm birth. BV is not considered an infection, but is a change in the normal bacterial flora in the vagina, when the healthy bacteria that are normally resident there are replaced by others that then cause a yellowish, "fishy" smelling discharge. Although the organisms that cause BV are known, it is not known why some women get BV, and it is a condition that comes and goes. It can be treated successfully with antibiotics, but often recurs.

Earlier research suggested that antibiotic treatment of BV did not reduce the risk of late miscarriage and preterm birth, but recent research from our own unit published in the Lancet in 1993 showed that early treatment of BV reduces both late miscarriage and preterm birth. We also have soon to be published data that

show that BV may increase the risk of early miscarriage. Perhaps even earlier treatment, pre-pregnancy when possible, may further diminish the risk of miscarriage posed by BV.

Anatomic causes of recurrent miscarriage:

It has for a long time been debated whether congenital abnormalities of the womb cause recurrent miscarriage. There is no doubt that women with a so-called double uterus, or uterine septum, often have successful pregnancies, but when it is the only abnormality found in a woman with RM, it leaves a doubt as to its potential role in the RM. Other abnormalities that occur later in life, such as polyps and fibroids, may also be linked to RM, but conclusive proof remains elusive. Many doctors are now offering excision of a septum in a woman with RM, especially if no other abnormality is found to account for the RM. Fibroid(s) inside the cavity of the womb are easily removed using key hole surgery (hysteroscopic resection), and so it is prudent that any such fibroids be removed. However, fibroids in other parts of the womb such as within the wall or hanging from the wall are unlikely to be the cause of miscarriage, and any decision for surgery must be weighed against the potential risks from surgery such as the formation of scar tissue and infertility.

Cervical weakness: Previously referred to as cervical incompetence, this condition causes late miscarriages (14 - 24 weeks gestation). Diagnosis is notoriously difficult, and is commonly based on a history of late miscarriages which are often painless and associated with minimal bleeding. Cervical weakness may be congenital, but the majority are acquired following trauma to the cervix such as with mechanical dilatation during repeated late pregnancy termination, or extensive biopsy of the cervix for abnormal smears. It is likely that cervical weakness is over-diagnosed, as there is no reliable method of diagnosing the condition. Treatment involves the insertion of a stitch around the cervix, usually performed at 12-14 weeks gestation.

Chromosome abnormalities

Approximately 60-70% of sporadic (one-off) miscarriages are caused by a chromosomal abnormality of the fetus. Chromosomes carry the genetic information of an individual, and the fetus inherits half from the mother and the other half from the father. Errors in the transmission and the division of the chromosomes can occur and lead to the fetus having either too few or too many chromosomes, which are often incompatible with life and the pregnancy miscarries. These chromosome errors occur randomly, and in rare instances may cause recurrent miscarriage. Most research shows that the likelihood of RM caused by chromosome abnormalities in the fetus is related to the age of the mother and increases from 19% at ages under 35 years to 47% in women over 35 years.

In approximately 5-7% of couples with RM one or other partner (more commonly the woman) possesses abnormal chromosomes which they repeatedly pass on to the fetus. The abnormality is usually not in the number of chromosomes, but in the way in which they are arranged. The commonest such re-arrangement is called a balanced translocation (an "inversion" is another example, but very rare). Obviously there is currently no cure for the chromosomal abnormality in the

parent, but when such a parental chromosomal abnormality is identified, a referral to a clinical geneticist is offered. S/he will be best placed to advise on the future prospects, and may also advise on the need for prenatal tests to detect the abnormality in any future pregnancy, as some abnormalities may be compatible with the birth of a live but incapacitated baby. The chances of a successful pregnancy in the future will depend on the specific type of chromosomal abnormality.

It should also be appreciated that current tests examine the chromosomes, but not the individual genes, of parents or fetuses. Thus standard techniques therefore do not pick up single gene mutations, which may nevertheless contribute to repeated miscarriage. The future is bright - with the rapid development of DNA technology, we will be better able to detect genetic causes for recurrent miscarriage.

Environmental causes of recurrent miscarriage

It is reasonable to suppose that any toxic substance that a woman consumes may cause miscarriage.

- . **Heavy smoking** - a consumption of >15 cigarettes/day increases the risk of miscarriage in a dose-dependent manner. It is advisable to give up smoking altogether.
- . **Alcohol** - heavy alcohol consumption is well known to cause the "fetal alcohol syndrome", but it is now generally believed that lower levels of alcohol consumption may also increase the risk of miscarriage, again in a dose-dependent manner.

Stress is generally thought to increase the risk of miscarriage, but the term "stress" can mean all sorts of things, and women have successful pregnancies in conditions which, on the face of it, should be highly stressful! Nevertheless it is prudent to avoid stress whenever possible.