

# Recurrent Pregnancy Loss



**Southern Ontario  
Fertility Technologies**

## Introduction

Early pregnancy loss (miscarriage or spontaneous abortion) is one of the most common events that can befall the reproductive-aged woman. Miscarriage occurs in **10%-40% of all “clinical pregnancies”**, and it may occur in up to 60% of all fertilization events. We consider a clinical pregnancy one in which there are signs of pregnancy other than just a positive pregnancy test. The term biochemical miscarriage is often used when the only indication of a pregnancy other than a late period, is a positive pregnancy test. Recurrent pregnancy loss (the loss of more than two pregnancies) occurs in 3% of reproductive age women.

**Sometimes, the many terms used to describe a miscarriage can be confusing. The important thing to remember is that any time a positive pregnancy test is registered, a pregnancy has occurred. It has the same emotional and prognostic significance no matter what form**

## Incidence of Pregnancy Loss

Miscarriage is more common in **older women**. The chance of a miscarriage at 20 years old is about 13% but at 40 years old is at least 40%. It is generally believed that miscarriage is **not generally more common in couples undergoing infertility treatment**. However, conditions such as polycystic ovary syndrome and severe male infertility may predispose to miscarriage.

A large clinical study looked at the risk of losing a pregnancy based on past reproductive history. In women with no prior pregnancy losses, the incidence of miscarriage was **12.6%**. For those with second pregnancies where the first pregnancy had been lost, the incidence was **16.6%**. Of women who had had two previous pregnancy losses, **37.5%** experienced a loss in their third pregnancy. The chance of a successful pregnancy is increased by 10 to 20% in women with at least one previous live birth.

Because pregnancy loss is so common, **the most common cause of more than one loss is the recurrence of non-repetitive cause**. In other words, bad luck two or three times in a row. Even after three miscarriages, the chance of finding a recurring cause is less than 10%.

## Genetics Component of Pregnancy Loss

The most common cause of miscarriage is an error occurring as the chromosomes from the mother and father first separate into half and then recombines to form the usual 46 chromosomes present in humans. **Loss of pregnancies with abnormal numbers of chromosomes is probably nature’s way of selecting out the pregnancies that should not go on.**

A laboratory test that examines the number of chromosomes is called a **karyotype**. Tissue from an aborted fetus, cells from the amniotic fluid around a baby or blood from a patient can be cultured. When the cultured cells are dividing, they can be stained and examined under the microscope and the number of chromosomes can be counted. Additionally, each chromosome can be identified and minor structural abnormalities found. Karyotypes are expensive to perform and are not generally thought to be helpful if performed on a couple before three miscarriages or on aborted material.

**Chromosomal mistakes of a random variety (I.E. unlikely to recur in the next pregnancy) are the most important contributor to all pregnancy losses.** The frequency of chromosomal abnormalities in miscarriages that occurred in the first third of the pregnancy (up to 13 weeks) is felt to be 40 to 60%. After 13 weeks, the frequency drops to about 10%; stillborn fetuses in the last third of pregnancy it is 5 to 10% and in live born babies it is just under 1%. Random miscarriages appear to often therefore be a system of biological “checks and balances” and may be responsible for maintaining the low rate of life-threatening congenital abnormalities encountered in liveborns.

**When karyotypes are performed on miscarriages, over half have an incorrect number of chromosomes.** Humans should have 46 chromosomes. Forty-four of these are termed autosomes and the remaining two are the sex chromosomes. A female has two X chromosomes and a male has an X and a Y chromosome. A large study found that 10% of miscarriages had 45 chromosomes, 44 autosomes and one X chromosome (45, XO). This is Turners Syndrome. Primary autosomal trisomies (an extra non-sex chromosome) occurred in 31%. An extra chromosome 21 is Down’s syndrome. The remainder had a variety of other chromosomal abnormalities.

The vast majority of these chromosomal errors are random events and are not likely to occur again. They are due to errors in cell division or fertilization occurring during the extremely complicated reproductive process. They do however occur randomly at a higher incidence in older women. The increased risk of Down’s syndrome in older women represents “the tip of the iceberg”. The incidence of miscarriage increases with increased female age, becoming between 40 and 50% over age 40. Most of these miscarriages are from the increased burden of chromosomal errors.

### **Causes of Recurrent Pregnancy Loss**

The vast majority of couples with recurrent pregnancy loss will have no identifiable recurrent cause. Even in a couple with three consecutive losses, over 90% will not have a diagnosable recurrent cause.

Because the chance of random losses is so high per pregnancy, especially if the female partner is older, **the risk of “bad luck” occurring three times in a row is much higher than a recurrent cause.** Recently, there has been some investigators who feel some couples may be more prone to these random loses, perhaps because they are more prone to

<b>Cause</b>	<b>Incidence (%)</b>
<b>Uterine abnormalities</b>	<b>10</b>
<b>Endocrine abnormalities</b>	<b>30</b>
<b>Chromosomal abnormalities in the parents</b>	<b>3</b>
<b>Infections</b>	<b>&lt;1</b>
<b>Abnormalities in immune status</b>	<b>5</b>
<b>Abnormalities in coagulation</b>	<b>3</b>

make a mistake sorting out their chromosomes during the reproductive process. Unfortunately, there is no way to diagnose this and no way to treat it.

However, investigations to rule out a recurrent cause are important, as identification of one of these causes will allow treatment. Some of the simpler investigations can be performed after two miscarriages with karyotypes on the parents being reserved for use after three miscarriages.

A table of the possible causes of recurrent miscarriages and their generally recognized frequency is presented. Many of the recognized frequencies are very controversial, as some physicians do not believe in some causes. However, each potential cause will be discussed.

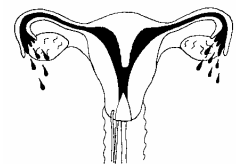
### **Uterine Abnormalities**

Anatomic defects of the uterus make up one of the largest definable categories of recurrent loss. It is likely that the absence of appropriate blood supply to the endometrium (the lining of the cavity of the uterus where the embryo must obtain a blood supply), the mechanical effects of compression or the failure of the uterine cavity to expand are the underlying reasons for such losses.

The most common anomalies associated with recurrent losses include large septum and uterine fibroids.

**A large septum** is associated with loss rates of between 40 and 80%. Septum can usually be divided surgically using a hysteroscope (a telescope which is placed through the cervix and allows the surgeon to operate inside the uterus without making an incision).

**Unicornate uteruses** (only one side of the uterus forms) and **bicornuate uteruses** (where the two sides of the uterus develop separately) are also associated with increased miscarriage rates (10 to 30%). They are much more difficult to surgically correct but this can be considered in severe forms.



A uterine septum is an example of a uterine abnormality contributing to pregnancy loss

**Uterine fibroids** can contribute to both infertility and recurrent pregnancy loss. Between 10 and 30% of women will have fibroids. Most fibroids do not cause problems. Only large fibroids or ones that protrude into the cavity of the uterus (submucous) are problematic. Submucous fibroids can be removed with the hysteroscope but extremely large fibroids may require a full abdominal operation.

**Asherman's syndrome** is the complete or partial obliteration of the uterine cavity and can have profound effects on dispensability, implantation site and blood supply in the uterine lining. The most common reason for the development of Asherman's syndrome is a D&C after a spontaneous pregnancy loss. Most experts feel that infection must be present. The miscarriage rate varies from 25% to 80% depending on severity. After hysteroscopic resection the loss rates are from 15 to 30%.

**Cervical incompetence** caused by surgery or injury can cause losses later in pregnancy. It is usually characterized by early delivery without apparent labour. It can be treated with cervical cerclage.

### **Chromosomal Rearrangements**

Chromosomal rearrangements are an important identifiable cause of recurrent pregnancy loss. Couples with this problem will have a normal chromosomal complement but part of it will be rearranged in either the mother or father. When the egg or sperm are formed, they may be missing or have an extra copy of some genetic information. Even after three consecutive miscarriages only about 4% of couples are found to have this problem.

Recently "fragile X" syndrome has been identified as a possible cause of recurrent pregnancy loss. This syndrome is due to repetitive duplication of genetic material in one arm of the X chromosome. It causes mental retardation in affected males in the family.

Chromosome abnormalities cannot be corrected. The importance of finding them is more to prevent the birth of severely abnormal babies. A balanced translocation could cause the potential offspring to have one, two or three copies of the misplaced part of the chromosome. Having two copies could result in a normal child, having one copy could result in a miscarriage but three copies could result in a pregnancy producing a severely abnormal child. It is more this third situation we are trying to avoid. Chromosome testing can take a long time. Usually we don't wait for it to be completed but if a pregnancy does occur we ask the lab to report it more quickly.

### **Progesterone Deficiency**

Progesterone is a critical hormone for the maintenance of early pregnancy. Preparation of the endometrium (the lining of the uterus) for implantation of the embryo is under the influence of progesterone. The methods of diagnosing and treating this are very controversial. Conclusive evidence of this problem as a cause of recurrent loss is lacking but many experts believe this occurs in 10 to 60% of couples experiencing recurrent losses.

Progesterone levels in the second half of the menstrual cycle or endometrial biopsies have been used to make this diagnosis. A newer method of assessment is a vaginal ultrasound and measurement of the endometrial thickness and structure. In the future, colour-flow Doppler and three dimensional ultrasound may be used to evaluate the endometrium.

At S.O.F.T we assess the reproductive hormones on day three of the cycle ruling out major endocrine problems and recognizing that the level of progesterone may vary from cycle to cycle. We will also suggest that Progesterone vaginal suppositories (200 mg) which are specifically compounded for S.O.F.T. are inserted in the vagina at bedtime or Prometrium 100 mg oral tablets are inserted in the vagina twice a day is started at day 14 (assuming a 28 day cycle) of the cycle and stopped if menstruation begins or at day 35 of the cycle after a negative pregnancy test.

Much of the literature on progesterone supplementation of the luteal phase of the cycle is contradictory but in reviewing this I do believe benefit is demonstrated if the progesterone is **started before implantation occurs and if it is used vaginally**. Implantation occurs 3 to 5 days after ovulation. Therefore, starting the progesterone in each cycle at approximately the time of ovulation is beneficial. The inconvenient part of this is that it has to be used in each cycle, many in which a pregnancy will not occur. Also, the biological effect of vaginal progesterone appears to be three to five times that of oral progesterone so the progesterone supplementation should be taken vaginally.



**This is an example of a normal “triple-layer” endometrium**

### **Systemic Disease**

Systemic diseases such as diabetes or thyroid disorders can produce recurrent pregnancy loss. In general, systemic diseases are only associated with recurrent pregnancy loss when the disease is **clinically evident**. However, both your thyroid and pituitary function will be checked with the initial day three blood work. Other systemic illnesses such as liver or kidney disease will be self evident as they cause other health problems long before they effect the ability to carry a pregnancy.

## **Infectious Diseases**

Bacterial colonization with Mycoplasma, Toxoplasma, Listeria, Chlamydia and Group B Streptococcus (GBS) has been suggested as causative of recurrent losses. Colonization with some of these organisms can be very high. There is **no good evidence to suggest an infectious etiology for recurrent losses**, however some physicians will prescribe antibiotics to both members of the couple as an empiric treatment. Infectious diseases may be more common causes of single pregnancy losses.

## **Immunologic Infertility**

**Autoimmune pregnancy loss** can be associated with diseases where the woman seems to make antibodies against her own body. Many of these individuals will have positive blood tests for antinuclear, anticardiolypin or antiphospholipid antibodies.

Several regimes have been proposed to treat people with this condition. These include aspirin, heparin gamma globulin injections and corticosteroids. Even without a demonstrated diagnosis, many experts will propose the use of low-dose ASA (81 mg). **Several recent studies have demonstrated an improved chance of a successful pregnancy using 81 mg ASA.** At S.O.F.T. we suggest all women who have had two losses should take 81 mg ASA and it is usually continued until week 35 of the pregnancy.

**Alloimmune origins** of pregnancy loss include maternal nonrecognition of paternal antigens, increased similarities of maternal and paternal antigen patterns, and paternal antigenic rejection. This cause of recurrent pregnancy loss is very controversial. Several treatments have been proposed but none have been proven effective. One treatment which has received widespread use is the injections of parental white cells into the female. The theory is that these injections allow the mother's immune system to recognize the potential father's cells and therefore allow her to produce blocking antibodies to suppress her immune response to their fetus. No prove that this is beneficial has yet been provided in our medical literature. Another approach is the use of gamma globulin. These treatments are available in Hamilton.

Some minor **coagulation abnormalities** are also linked to recurrent pregnancy loss. Factor 5 Leiden is a relatively newly discovered coagulation disorder that has been linked to recurrent losses. Testing for this is not generally covered by OHIP but is available at no cost to you through S.O.F.T.

## **The Investigation at S.O.F.T.**

Your basic investigation will include a history and physical examination if it has not been performed recently by your family doctor or gynecologist. Screening for infectious causes may be performed if they are suspected from history. A hysterosalpingogram, hysterosonogram or hysteroscopy will be suggested to rule out uterine abnormalities.

Blood tests will be ordered to investigate the possibility of autoimmunity or a coagulation disorder. These will include antinuclear, anticardiolypin, antiphospholipid antibodies and factor 5 Leiden. A karyotype will be ordered on both the male and female if three miscarriages have occurred.

## **Follow-up after Investigations**

Several treatments may be suggested even if positive results are not found. A cause of recurrent miscarriages is only found in about 10% of couples. This does not completely

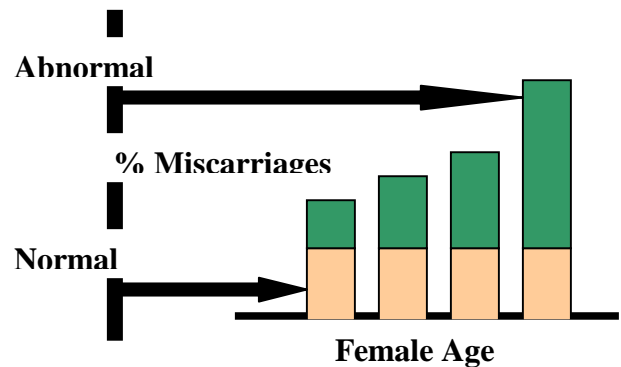
rule out a recurrent cause. We always suggest 81 mg ASA and progesterone vaginal luteal phase support. With a negative investigation, **over 50% of couples will experience a successful pregnancy in their next attempt.** Suggestions to optimize your health and reduce any negative factors will be presented (I.E. Smoking cessation, decreased alcohol consumption, folic acid supplementation). If a chromosomal error occurs in the next pregnancy, nothing can be done to correct it. However, if the fetus is normal, these maneuvers may help to maintain a normal pregnancy that would otherwise be lost.

**In our first three years of operation at S.O.F.T. the protocol presented here has been followed. Ninety one pregnancies have occurred and 79 (86.5%) of these have been successful or are ongoing past the point of miscarriage.**

If there is an indication of an autoimmune or coagulation difficulty we add Fragmin® (low molecular weight heparin) 5,000 IU per day as soon as a pregnancy is diagnosed. We also suggest this in couples with “high order” recurrent pregnancy losses (IE 4 or more). If positive results are found, appropriate treatment will be suggested. For instance, uterine septum should be resected and infections should be treated.

### Rational Behind Intervention

One way to look at pregnancy losses from a very simplified point of view is that all pregnancy losses occur because the **fetus is abnormal or the implantation is abnormal.** There is nothing we can or should do about the abnormal fetuses but it is the abnormal implantations we may be able to effect. We believe that the percentage of pregnancies that are lost because of abnormal implantation (therefore a normal fetus is 7 to 9%). The percentage lost because of abnormal fetuses varies with age, being very low in the 20’s (IE 5%) and much higher in the 40’s (IE 40%). A graph would appear like the one presented.



By using ASA and progesterone (perhaps fragmin ©) we can minimize the chance of a loss of a normal fetus. However, there is nothing we can or should do to prevent the loss of an abnormal fetus. We will provide you early diagnosis, support and early treatment to make going through this unpleasant experience as easy as possible.

An **early pregnancy ultrasound** will be offered as it may allow insights into some of the causes and allows early treatment of an unsuccessful pregnancy. After a positive pregnancy test, you will be asked to attend the clinic about 50 to 60 days after your last menstrual period for a vaginal ultrasound. By this time we should be able to clearly see the gestational sac (bag of waters) inside the uterus. At this point usually the fetal pole (the blob which will become the baby) and even a fetal heart beat can be seen. A multiple pregnancy can also be diagnosed. It also is possible to



**Normal “luteal day 40” ultrasound of a single pregnancy**

diagnose miscarriage or ectopic pregnancies.

Although a perfectly normal ultrasound cannot guarantee a normal pregnancy because it cannot predict the future, it is very reassuring. At least 90% will go on to be normal. However, often repeat ultrasounds are done past the point of lost pregnancies in the past. Another recourse which we provide you with at S.O.F.T. is the ability to return anytime you are concerned about the pregnancy should bleeding, spotting or pain occur.

When the ultrasound is done, your due date will be calculated and a report will be sent back to your referring physician informing them of your pregnancy and asking them to take over your obstetrical care.

It is at this time we will also remind you of the **Clinic Rules**. Rule one is you have to send us a birth announcement and rule two is that you have to bring the baby to visit us.

Jim Martin ©

Southern Ontario Fertility Technologies (S.O.F.T.)

555 Southdale Rd., E., Suite 107, London, Ontario, N6E 1A2.

Tel: 519-685-5559 Fax: 519-685-5519

**Check out our web page at: [www.soft-infertility.com](http://www.soft-infertility.com)**