

## RECURRENT MISCARRIAGE

If you have had a previous miscarriage, it is very normal to be frightened and worried during your next pregnancy. It is important to understand that exercise, working and intercourse do not increase the risk of pregnancy loss. Likewise, staying at home and resting in bed probably do not prevent miscarriage. Video display terminals and computers do not increase the risk of miscarriage; neither does hair spray, hair color or permanents. However, smoking and drinking can increase the risk of pregnancy loss, so you should discontinue these activities before or at least during pregnancy.

It is really not known how often human pregnancies are lost. The most widely accepted rate of loss for a single spontaneous miscarriage in the general population is thought to be 15-20% (1 of every 5-6) of "clinically detected" pregnancies. Many pregnancies are lost prior to clinical detection, but the incidence of these very early losses is not clear. A number of studies have checked for pregnancy each month with a highly sensitive immunoassay from blood drawn in sexually active women not using contraception. This research consistently demonstrates a high rate of "unrecognized pregnancies". Some studies report a total pregnancy loss rate (non-clinical plus clinical) of more than 50% (1 in 2).

The chance of having a second spontaneous miscarriage with a history of only one isolated prior spontaneous miscarriage is generally considered to remain unchanged at 15-20%. However if there have been 2 spontaneous miscarriages in a row, then the most reliable information suggests that there is about a 35% chance (1 in 3) that the next pregnancy will be lost. Therefore the loss rate is approximately doubled. If there have been 3 spontaneous miscarriages in a row, then it appears that the couple has a roughly 45-50% chance of a loss of the next pregnancy.

There are reports indicating improvement in future pregnancy success for couples with recurrent pregnancy loss after there has been at least one prior live born for the couple (that is, a

40-45% loss rate if no live births and only a 30% loss rate with a history of prior live born. The spontaneous miscarriage rate rises as the woman's age increases, with a gradual increase starting at about age 30, more rapid increases after age 35, and much more rapid increases after age 40. The age related increases in spontaneous pregnancy loss appear to be predominantly due to chromosomal accidents around the time of fertilization. When older women are the recipients of donor eggs from younger women they do not have this increased spontaneous miscarriage rate. This suggests that the cause is related to the age of the egg, rather than uterine factors.

About 80% (4 in 5) of spontaneous miscarriages occur in the first trimester of pregnancy (the 1<sup>st</sup> 13 weeks). In couples without a history of recurrent losses, if a fetal heart beat is seen by ultrasound at 6 gestational weeks there is a reduced loss rate to about 5%. There is a further reduction if heart activity is seen at 8 weeks to about 3%. Unfortunately, in couples with recurrent losses, the loss rate is still about 4-5 times greater, even after seeing the heart beating. Because of this high level of uncertainty, many couples do not announce that they are "expecting" until seeing the heart beat or until completion of the first trimester.

### MANY CAUSES

Many couples mistakenly blame themselves (often harshly) for their pregnancy losses. In fact, it is rare that either member of the couple could have done anything that would result in a pregnancy loss. It is beneficial to be aware of the recognized causes for pregnancy loss.

**Fetal causes** are generally related to genetic and developmental abnormalities: That live born humans have a very low percentage of chromosomal abnormalities (about 1.6%) indicating that most chromosomal abnormalities are lethal and miscarried early in pregnancy. Maternal causes include abnormalities in the environment in which the embryo develops. Known **maternal causes** related to an action of

the mother are uncommon, but can include heavy smoking and alcohol abuse (both rare), irradiation or exposure to chemical toxins and medications known to cause fetal malformations.

**Other causes** which are not related to any conscious activity of the mother or couple would include: anatomic abnormalities (typically uterine), hormonal imbalances, immunologic abnormalities (autoimmune or alloimmune), infections, and serious or life threatening maternal diseases.

By far the most common causes for spontaneous pregnancy loss are fetal, not maternal. It is difficult for a woman with an undesired pregnancy to consciously create an unfavorable environment for the pregnancy to successfully force a miscarriage.

## EVALUATION

An evaluation for known causes of recurrent pregnancy loss is usually initiated after 2 or 3 consecutive pregnancy losses. The tremendous emotional impact of each loss may encourage an evaluation sooner than later. A full evaluation includes

- Demonstration of a normally shaped uterine cavity ( hysterosalpingogram or hysteroscopy)
- Evaluation for hormonal deficiency in progesterone production (by endometrial biopsy or serum progesterone levels)
- Analysis of both the maternal and paternal chromosomes (by blood work)
- Laboratory testing for immunologic causes of pregnancy loss (by blood work)
- Possible infectious causes (by cultures of uterus, cervix, etc.)
- Taking a history for maternal disease states, hormonal problems, environmental or other toxin exposure

If a full evaluation is completed on couples with either 2 or 3 consecutive losses, there will still be about 50% of couples with “unexplained” recurrent pregnancy loss. That is, roughly half of couples seem to have a reason for recurrent loss

that is beyond modern medicine’s ability to diagnose the cause. This is very frustrating for both the couple and the physician. In this situation, the couple will at least know that potentially repairable pathology has been ruled out.

## ANATOMIC CAUSES

An estimated 15% of couples with recurrent pregnancy loss have an anatomic abnormality of the uterus at the primary reason. The four categories of anatomic defects that cause recurrent pregnancy loss are abnormalities in

- The normal process of uterine fusion during embryonic development
- The development of the uterus and cervix due to maternal diethylstilbestrol (DES) ingestion
- The size or blood supply in the uterus due to fibroids, endometrial polyps or scar tissue (Asherman’s syndrome)
- The function of the cervix

Since fibroid tumors of the uterus are so common, we will address them specifically. About 75% of uterine specimens removed at hysterectomy contain fibroids. It is estimated that as many as 40-50% of women may have some fibroids by menopause. The role of uterine fibroids in reproduction is usually not clear. If the fibroid is presenting (bulging) into the uterine cavity (submucosal) then it may obstruct one of the fallopian tube entrances or it may present a mechanical or other barrier to implantation. If the fibroid occupies a substantial portion of the uterine wall, then it might interfere with the blood supply to the uterine structures around it or an embryo implanting near it. Occasionally during pregnancy, fibroids may grow and even outgrow their blood supply to a point that they may degenerate or become infected and this can lead to pain and irritability (contractions) of the uterus that can be associated with complications of pregnancy (preterm labor, severe pain, miscarriage). Most fibroids do not seem to interfere with fertility and for fertility purposes do not need to be removed unless a reproductive problem has been identified and all other

treatable causes for the reproductive problem have been evaluated and excluded. Exceptions would include intrauterine filling defects on HSG, fallopian tube compression by the fibroid or the creation of tremendous distortion of the uterine cavity. Uterine septa (a partial or total wall in the center of the upper uterus) are not uncommon and are a known cause for recurrent 1<sup>st</sup> trimester pregnancy loss. This abnormality is usually suggested by HSG, but is best confirmed by hysteroscopy. Most can be treated by removal of the septum through the hysteroscope. Endometrial polyps and intrauterine scar tissue can be diagnosed and treated in the same fashion. Cervical causes of recurrent loss typically occur in the 2<sup>nd</sup> trimester and most commonly are related to a weakness in the cervix (incompetent cervix) so that it is unable to support the weight of an advancing pregnancy. Treatment is usually by inserting a strengthening band in the cervix (circlage).

### **HORMONAL CAUSES**

To successfully implant into the uterus the embryo must be available during a window of time limited to a few days per cycle, referred to as the “window of uterine receptivity.” If this window of uterine receptivity is not properly timed with respect to ovulation then either infertility or pregnancy loss may occur. This appears to be regulated primarily by progesterone and abnormalities are called luteal phase defects. Known causes include inadequate luteal phase ovarian production of progesterone, inadequate progesterone from the ovary in early pregnancy and inadequate progesterone production by the placenta. An endometrial biopsy is the gold standard for diagnosis. Progesterone levels can be followed through the luteal phase and in early pregnancy. Treatment can be accomplished by supplementing progesterone after ovulation (by vaginal creams or suppositories, intramuscular injections or possibly oral micronized progesterone) or by giving serial HCG injections to stimulate increased ovarian production of progesterone. There do not appear to be any significant increased risk of fetal anomalies in taking natural progesterone supplementation during pregnancy. Polycystic ovary syndrome is

associated with ovulatory dysfunction, elevated levels of male hormones and increased miscarriage risk. Insulin sensitizing agents such as metformin have been shown to reduce this risk. Thyroid disease, endometriosis and disorders of prolactin production have also been implicated in miscarriages. Levels of Inhibin B and HCG during early pregnancy may be able to predict miscarriages before they occur, but currently there is no successful treatment.

### **GENETIC CAUSES**

At least 60% of the clinically recognized pregnancies that are lost in the first trimester have a major chromosomal abnormality and this may be as high as 82% in women over 35. Among couples with 3 or more pregnancy losses, the frequency of chromosomal abnormalities is about 50%. Chromosomal abnormalities may be of fetal origin that arise as spontaneous mutations or abnormalities resulting from breakage or abnormal duplication or division of chromosomes in the developing baby. These are not preventable, but it would be uncommon for the same mutations to recur. In recurrent pregnancy loss, the genetic abnormalities are typically parental, arising from genetic abnormalities in one or both parents (carriers). Diagnosis is by blood testing of husband and wife looking at the chromosomes and pattern of gene distribution. A family history of specific genetic defects would warrant specialized testing. Unfortunately there is no available treatment to “fix abnormal chromosomes” at this time.

### **IMMUNOLOGIC CAUSES**

Immunologic causes are poorly understood and this field is very complex and constantly changing. Many theories and treatments that have been proposed have been proven to be incorrect or inaccurate. The 2 major classifications of immunologic causes of recurrent pregnancy loss are: Autoimmune in which the woman’s immune system attacks her own organs and tissues (e.g. Lupus) and Alloimmune in which the immune system attacks tissues considered to be foreign (non-self). Autoimmune disease or dysfunction may play a

role in up to 10% of recurrent pregnancy losses. Anti-phospholipid antibodies, even in the absence of general disease have been shown to adversely affect pregnancy and are associated with recurrent pregnancy loss. There are numerous anti-phospholipid antibodies and screening for all would be prohibitively expensive. Maternal blood tests for anti-cardiolipins and lupus anticoagulant are usually adequate for screening.

The pregnancy is “foreign” to the mother in that ½ of the genetic material is from the father. The pregnancy seems protected for the usual immune rejection response by some unidentified “blocking factors”. It has been proposed that when the mother and father share many of the genes (HLA) that distinguish tissue as self so that blocking antibodies may not develop, allowing the rejection immune response (suppressor cells, natural killer cells, etc.) to attack the embryo. Prior immunization therapies are no longer recommended for treatment. Treatments for immune causes include low dose aspirin (81mg), heparin and steroid therapy. Other treatments such as IVIg, Enbrel and intralipids are unproven, expensive and some involve significant risks. Endometriosis is thought to have a possible immunologic basis.

### INFECTIOUS CAUSES

Infectious causes may be acute (recent) or chronic (long term). Very high fevers (>104) can be lethal to a developing embryo. Infections of the cervix or vagina such as Mycoplasma, Ureaplasma, Bacterial vaginosis, etc. have been associated with infertility and pregnancy loss. There may be infection and inflammation of the lining of the uterus (endometritis). Most bacterial infections are relatively easily treated with specific or broad spectrum antibiotics. Since treatment is usually easy, safe and inexpensive, it is often given to both partners as an arbitrary therapy. Viral infections (eg. CMV, Rubella, Chicken pox, hepatitis, etc) are sometime difficult to diagnose and their association with recurrent miscarriages less certain. There are no reliably successful treatments for these viral diseases.

### MISCELLANEOUS CAUSES:

Age is a major cause for individual and recurrent miscarriages.

Maternal age	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 & Sterility*:vol.46, p 989: 1986  
Other miscellaneous causes include severe maternal diseases (diabetes, obstructive pulmonary disease, asthma, colitis, lupus, malaria, TB, etc), substance abuse (heavy smoking, alcohol or drug abuse), irradiation or exposure to chemical or gaseous toxins (pesticides, poisons, nitrous oxide, lead, formaldehyde, ethylene oxide, etc.) and medications, especially teratogens (cause birth defects) and leutolytic agents (Lupron, etc.).

### THE EMOTIONAL ASPECTS OF MISCARRIAGE

After a miscarriage, it is normal to experience a period of grief. This process often creates feelings of shock, disbelief, anger, sadness, low self-esteem, loneliness and depression. You may also find yourself repeatedly asking why this has happened to you. As a result you could believe that you are being punished for something you did or did not do. Guilt and blame are emotions that prevent you from completing the grieving process and it is essential that you and your spouse openly discuss all of your feelings. It is also important to find emotional support from others who have had similar experiences. Talk with friends, join support groups, visit a professional counselor and study reading materials. In addition to emotional support, you may feel the need to symbolically acknowledge your loss. For example, you might give a donation to a special charity or have a memorial service.

If you have experienced recurrent miscarriage, you may feel hopeless and confused regarding a positive pregnancy outcome. It is important to realize that miscarriage is not an uncommon event. Your evaluation will focus on the known causes of recurring miscarriage. But knowledge of this problem is still limited, and no obvious cause is detected in up to 40% of couples with repeated pregnancy losses. The encouraging

news is that the spontaneous cure rate is very high and so is the chance of success in treating certain known causes. Even if your evaluation does not reveal a treatable cause and you do not undergo treatment, your chance of achieving a healthy pregnancy despite having had several miscarriages is still generally better than fifty per cent.

**Predicted percentage success rate of subsequent pregnancy according to age and previous miscarriage history**

Age	Number of Previous Miscarriages			
	2	3	4	5
20	86-98 <b>(92)</b>	83-97 <b>(90)</b>	79-96 <b>(88)</b>	74-96 <b>(85)</b>
25	82-95 <b>(89)</b>	79-93 <b>(86)</b>	75-91 <b>(82)</b>	68-90 <b>(79)</b>
30	77-90 <b>(84)</b>	74-86 <b>(80)</b>	69-83 <b>(76)</b>	61-81 <b>(71)</b>
35	69-85 <b>(77)</b>	66-80 <b>(73)</b>	60-75 <b>(68)</b>	51-74 <b>(62)</b>
40	57-82 <b>(69)</b>	52-76 <b>(64)</b>	45-71 <b>(58)</b>	37-67 <b>(52)</b>
45	41-79 <b>(60)</b>	35-72 <b>(54)</b>	29-67 <b>(48)</b>	22-62 <b>(42)</b>

Values are percentages with 95% confidence intervals (%)

Human Reproduction (1999). 14(11):2868-2871