



Dr. Richard Bronson's clinical interests include providing treatment for couples who have experienced delays in planned conception or repeated pregnancy loss, and developing tests to evaluate immunologically-mediated infertility, with special focus on immunities to spermatozoa. He has studied the biologic basis of fertilization failure, and his work has led to discoveries that provided a better understanding of sperm-egg interactions leading to successful fertilization. Dr. Bronson is a past president of the American Society of Reproductive Immunology and associate editor of the journal *Human Reproduction*.

## WHY DOES A PREGNANT WOMAN MISCARRY?

This is the first of a three part series. Reprinted from fall 2007

BY RICHARD BRONSON, MD, FACOG

Approximately one in every seven pregnancies ends in miscarriage. The usual cause of sporadic pregnancy loss is due to an embryo possessing an abnormal number of chromosomes—either one too many or one too few. All of the cells of our body, except our eggs or sperm, possess 46 chromosomes (23 different pairs, one derived from the mother and one from the father).

During formation of the gametes (eggs and sperm), the number of chromosomes each possesses is halved, so that when these two cells join at fertilization, the normal number 46 is restored. Unfortunately, during that halving process (termed meiosis), things can go wrong, leading to a small percent of eggs or sperm that contain not 23 chromosomes, but some other number such as 24 or 22. This problem increases with the woman's age and may be the result of the man's age as well. Some embryos with an abnormal number of chromosomes will fail to grow beyond a few days after fertilization, while others will die some time during the first or second trimester of pregnancy. Occasionally, a fetus possessing an abnormal number of chromosomes survives through gestation and a child may be born with abnormalities due to this "aneuploidy." One common example of this is seen in children born with an extra chromosome 21.

The majority of embryos possessing an abnormal set of chromosomes die very early in the first trimester of pregnancy. Most of the time, having had a miscarriage does not indicate that there will be difficulties in the future. In fact, the likelihood of a second pregnancy loss following a first loss is approximately 20 to 25 percent, and, even following a subsequent second loss, the odds of a miscarriage in the next pregnancy are about 25 to 30 percent. This does not mean, however, that a couple should not consider determining whether there is anything that may predispose them to a greater risk of pregnancy loss.

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Those factors that increase the risk of miscarriage can be divided systematically into several large groups: abnormalities of the uterus, hormonal disorders, certain infections, alterations in blood clotting, immunologic abnormalities, and genetic causes. A thorough examination will address all of these issues. The usual recom-

mendation is to perform an evaluation after a woman has experienced three losses, as the likelihood of successful pregnancy remains high until this time. However, it is often difficult for a couple to attempt to conceive again, after experiencing two pregnancy losses without the reassurance that there is no predisposition to miscar-

riage for them, or that any problem detected has been addressed. Also, in the face of delayed conception, an evaluation following two pregnancy losses is advised as well as in the case for women who are over the age of 35, when the chances of conceiving start to diminish significantly. ■

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**BY RICHARD BRONSON, MD, FACOG**

**T**he causes of pregnancy loss are often different when miscarriage occurs early in the first trimester, rather than late in that trimester, or within the second trimester. Most commonly, miscarriages that happen early in the first trimester result from either a genetic cause, due to the embryo having an abnormal number of chromosomes (human cells normally contain 23 pairs of chromosomes), or a hormonal cause, due to the pregnant woman not having enough of the hormone progesterone. This hormone is essential for allowing the embryo to grow within the uterus, and if there is not enough of it, miscarriage will occur. After an egg is released from an ovary in the process called ovulation, the ovary produces progesterone, which helps to create the “fertile bed” in which the embryo grows to establish a normal pregnancy. To determine the best treatment if low progesterone is suspected, the first step is to evaluate

its cause. It can be associated with an abnormal increase in the hormone prolactin, which normally plays a role in getting the body ready for milk production during pregnancy. Prolactin can be abnormally high in non-pregnant women with hypothyroidism in which the amount of hormones produced by the thyroid are low; during use of certain medications; and in the presence of a “benign” tumor of the pituitary gland that in itself is not dangerous to health.

It is possible to measure the level of progesterone in the blood during a pregnancy to confirm that there is enough of this hormone. It is also essential to measure the level of another hormone, called hCG (human chorionic gonadotropin), at the same time. This hormone is produced by cells that form the placenta within the uterus, in which a fetus would later grow. The rate of increase in its level provides a measure of the health of

the embryo. The hCG hormone makes the ovary produce large amounts of progesterone to help maintain pregnancy. Low levels of progesterone may be a reflection of a poorly developing embryo that is destined to miscarry, rather than being the cause of the miscarriage. If hCG levels do not rise normally when measured over several days, there is a strong likelihood that the embryo itself is not healthy. Measuring the levels of both hormones, hCG and progesterone, helps to distinguish cause and effect.

If a second miscarriage occurs, it is very important to send any pregnancy tissue (whether passed on its own at home or at the time of the cleaning of the uterus in an operating room) for chromosome analysis. This will help to determine whether the miscarriage was associated with an embryo containing an abnormal set of chromosomes or not. At times, the

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pregnancy tissue obtained under these circumstances may no longer contain living cells and, unfortunately, no information may be obtained. If the chromosomes of the embryo are normal, it becomes important to look for non-genetic causes that may create conditions leading to miscarriage.

Women can be born with an abnormally shaped uterus that makes them inclined to have a miscarriage. When an embryo destined to be a female grows, the uterus forms when two primitive tubes—the Mullerian ducts—grow together and are joined. Sometimes this fusion of tissue is incomplete. A wall (septum) then may be present within the middle of the uterus that can result in abnormal development of an embryo, leading

to its loss. This septum can be removed by a relatively simple operation, performed under anesthesia in an ambulatory surgery center. Other abnormalities of the uterus may also lead to miscarriage, in either the first or second trimester, such as a single- or double-horned uterus that is misshaped. These congenital (present at birth) abnormalities of the uterus cannot be easily corrected by surgery. It is known that they may be associated with a weakening of the lower end of the uterus, called the cervix, which may open on its own in the second trimester and lead to pregnancy loss. Monitored by repeated ultrasound examinations during pregnancy, the cervix can be closed with a stitch, if necessary.

Sometimes, a miscarriage may lead to future miscarriages. This happens when the uterus does not completely empty its contents after a miscarriage, resulting in persistent bleeding and possible infection, and the need for a subsequent D&C (dilation and curettage). These circumstances might cause scarring within the uterus that prevents the uterus from growing normally during a subsequent pregnancy, leading to early or later miscarriage. This scarring needs to be removed before a woman attempts to become pregnant again. An x-ray study can be performed to diagnose the presence of scars within the uterus, as well as to confirm whether the uterus has a normal shape. ■

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**BY RICHARD BRONSON, MD, FACOG**

Fibroids, benign growths of the muscle of the uterine wall, can cause miscarriages in several ways. They may change the shape of the uterus and push into the embryo. They may also grow quickly during the pregnancy because of the hormones produced by the placenta, which can lead to pain or may induce premature labor. Fibroids are easily found by ultrasound examination, and a decision can be made about whether they should be removed before a woman tries to become pregnant.

Some women have mutations in their immune system that lead to the presence of antibodies that can cause miscarriage. Autoimmunity is the term given when a person has antibodies to his or her own tissues. Most thyroid problems are caused by such antibodies, which can lead to either an underactive thyroid (hypothyroidism) or an overactive thyroid (hyperthyroidism), depending on the type of antibodies present. Both of these conditions are associated with an increased risk of

pregnancy loss, and need to be treated before conception. Other hormonal conditions, such as diabetes and polycystic ovary syndrome, can also influence miscarriage.

Some women may develop antibodies to lipids that are present in cells that form the placenta. If these antibodies are consistently present at high levels, they may damage the placenta and limit its ability to nourish the embryo. This can result in the death of the embryo in the

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late first trimester or the second trimester of pregnancy. At other times, the fetus may survive, but grows at a slower than normal rate. Women who develop these antibodies are also at risk for developing high blood pressure and toxemia during pregnancy, as well as deep vein thrombophlebitis, placing them at increased risk of blood clots passing into the lungs (pulmonary embolus). Thrombophilia, a tendency for the blood to clot, can also lead to miscarriage in the second trimester. Blood tests can be done to confirm if a woman has this condition, and, if so, whether blood thinners should be prescribed.

In a small percentage of couples who experience miscarriages repeatedly, embryos often have an abnormal set of chromosomes, which can contain an extra chromosome, for example chromosome number 47. Sometimes, the cause is that the wife or husband has chromosome abnormalities, which leads to the need for genetic studies of the couple. Recent evidence indicates that men, no matter what their age, who have very low sperm counts, or whose vast majority of sperm are abnormally shaped, may have increased numbers of sperm with abnormal chromosome numbers. Tests are now available to determine if

this is the case in instances where the routine semen analysis is severely abnormal. These couples often also experience long delays in conceiving, as well as repeated pregnancy losses.

Despite thorough evaluation, the cause for repeated miscarriage may not be determined. Although the odds of a successful pregnancy are greater than 60 percent for couples experiencing repeated miscarriages, conceiving again is often emotionally trying. Early and frequent monitoring of the pregnancy can often provide reassurance to a couple who has experienced multiple pregnancy loss. ■