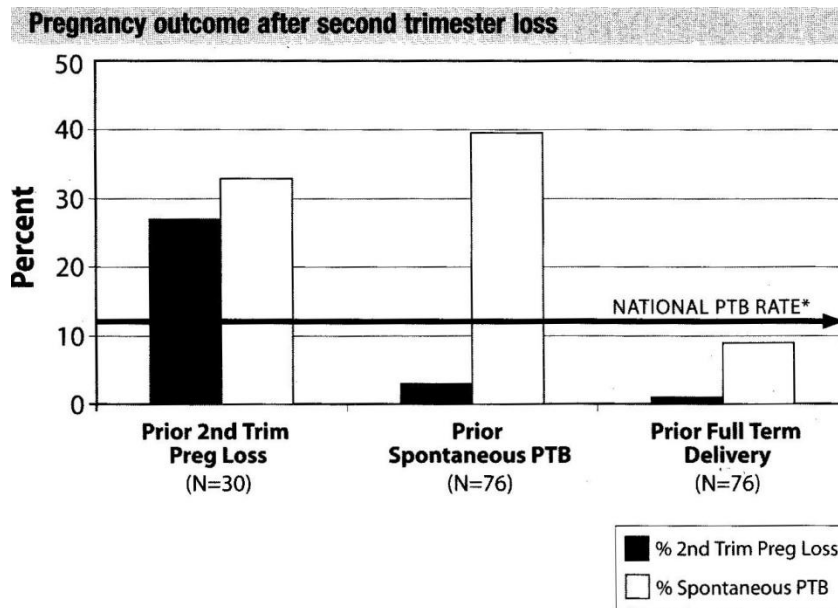


REPETITIVE PREGNANCY LOSS

Repetitive Pregnancy Loss is defined as combination of pregnancy losses, often involving three consecutive first trimester losses or a single second trimester loss. Approximately 15 percent of pregnant women experience sporadic loss of a clinically recognized pregnancy. Just 2 percent of pregnant women experience two consecutive pregnancy losses and only 0.4 to 1 percent have three consecutive pregnancy losses¹. In a patient's first pregnancy, the risk of miscarriage is 11 to 13 percent². After one miscarriage, the likelihood of subsequent loss increases to 14 to 21 percent. After two or three miscarriages, the rate is 24 to 29 percent and 31 to 33 percent, respectively. The same relationship holds true for pregnancy losses later in pregnancy³.

At Desert Women's Care we offer evaluation to healthy women after three consecutive first trimester losses or a single second trimester loss.



Subsequent pregnancy outcome in women with prior second trimester loss, prior spontaneous preterm birth, and prior birth at term.

Reproduced, with permission, from Edlow et al.³²

Iams. Care for women with prior preterm birth. Am J Obstet Gynecol 2010.

In counseling patients the risk of recurrence and the cause of pregnancy loss are the two most important issues to address.

In only about forty to fifty percent of cases is the etiology of pregnancy loss actually identified⁴. Anatomic, immunologic and endocrinologic causes each account for approximately 20% of cases with known cause while infection and genetic account for about five percent each.

Anatomic

Uterine anomalies such as septate uterus are a significant cause of repetitive pregnancy loss⁵⁻⁶. Septate uterus is the uterine condition most associated with repetitive loss acting through either decreased vascularity, decreased sensitivity to hormones or increased inflammatory response. The longer the septum the poorer the outcome with greater than a 60% miscarriage rate with unoperated uterine septum⁷.

Acquired anatomic deformation from submucosal myomas is related to pregnancy wastage⁸. Speculated mechanisms are similar to those of uterine septum including decreased blood supply available through the myoma, decreased receptivity of the endometrium overlying the myoma or to possible degeneration of the myoma. Endometrial polyps operate similarly.

Adhesions within the endometrial cavity involve denudation of the normal endometrium and predispose to repetitive pregnancy loss⁹. Diminished endometrial receptivity is an increasingly understood etiology¹⁰. Finally, cervical incompetence is known to result in loss later in pregnancy.

Immunologic

Pregnancy is an allograft and is fifty-percent non-self antigenic determinants presented to the mother's immune system. Autoimmune factors are implicated in recurrent pregnancy loss. It is speculated that when a blastocyst is intact it is not exposed to the maternal immune system. Oppositely, when the blastocyst is deformed it is exposed to the maternal immune system leading to miscarriage. Dysregulation of the normal immune mechanism probably operates at the maternal-fetal interface and may involve increased activity of uterine natural killer (uNK) cells, which appear to regulate placental and trophoblast growth, local immunomodulation, and control of trophoblast invasion¹¹⁻¹³.

Anti-Phospholipid Antibody Syndrome is the best understood mechanism for recurrent pregnancy loss¹⁴. Between 5 and 15% of cases of recurrent loss are ascribed to Anti-Phospholipid Antibody Syndrome.

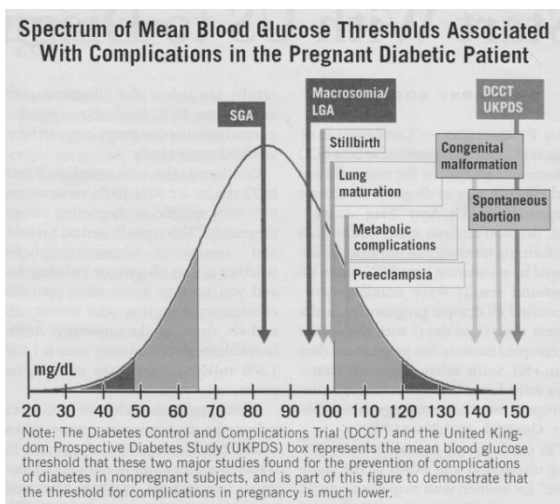
Thyroid Antibodies have also been implicated in autoimmune-mediated recurrent pregnancy loss. Studies have reported an increased rate of fetal loss in women with high serum thyroid antibody concentrations (thyroid peroxidase or thyroglobulin), including those who are euthyroid¹⁵⁻¹⁶.

Endocrinologic

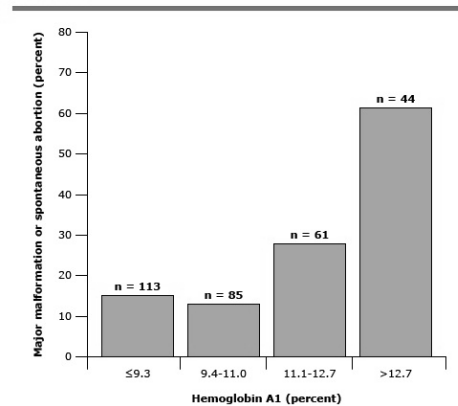
Endocrinologic factors suggested to relate to increased incidence of recurrent pregnancy loss include diabetes, polycystic ovarian syndrome, hyperprolactinemia and inadequate luteal phase.

Diabetes—

Although there is no increased risk of miscarriage in women with well-controlled diabetes mellitus¹⁷. Poorly controlled diabetes mellitus is associated with early pregnancy loss. Increasing hemoglobin A1C values early in pregnancy are related (particularly values above 8 percent) to increased frequencies of miscarriage and congenital malformations¹⁸⁻²⁰. The increased risk of miscarriage in poorly controlled diabetic women is believed to be secondary to hyperglycemia, maternal vascular disease inhibiting early perfusion, or immunologic factors.



Deleterious effect of poor glycemic control on fetal outcome



Combined incidence of major malformation and spontaneous abortion according to the hemoglobin A1 (HbA1) value during the first trimester of pregnancy in 303 women with type 1 diabetes. The risk rose markedly at HbA1 values above 11 percent (approximately equivalent to a HbA1c value of 8.5 percent). Other studies have found an increase in risk at HbA1c values above 9.5 percent.
Data from: Greene MF, Hare JW, Cloherty JP, et al. *Teratology* 1989; 39:225.

Polycystic Ovarian Disease--

The miscarriage rate in women with polycystic ovary syndrome (PCOS) may be as high as 20 to 40 percent, which is higher than the baseline rate in the general obstetric population (10 to 20 percent)²¹⁻²². The mechanism for excess pregnancy loss in these patients is unknown, but may be related to elevated serum luteinizing hormone (LH) levels, high testosterone and androstenedione concentrations (which may adversely affect the endometrium), or insulin resistance²³.

The sex hormone abnormalities in women with PCOS may cause premature or delayed ovulation, poor endometrial receptivity, and disturbances in synthesis/secretion/action of prostaglandins and ovarian growth factors or cytokines²⁴. In one study, a menstrual cycle longer than 34 days, which is common in women with PCOS, was the most important predictor for a recurrent pregnancy loss²⁵.

Hyperprolactinemia--

This hypothesis was supported by a study of 64 hyperprolactinemic women with RPL randomly assigned to bromocriptine therapy or no bromocriptine²⁶. Treatment to lower prolactin concentration was associated with a higher rate of successful pregnancy (86 versus 52 percent). Prolactin levels during early pregnancy were significantly greater in women who miscarried

Inadequate Luteal Phase--

Progesterone is essential for successful implantation and maintenance of pregnancy; therefore, disorders related to impaired progesterone production or action are postulated to affect achievement and maintenance of ongoing pregnancy. A defect in corpus luteum function (ie, luteal phase defect) is hypothesized as a potential cause of impaired progesterone production²⁷. Inadequate level of progesterone production, too short a period of adequate progesterone production or insufficient progesterone activity are all felt to be responsible for pregnancy loss prior to the placenta taking over production from the corpus luteum. Studies demonstrate that serum progesterone level does not correlate with pregnancy outcome²⁸. Endometrial biopsy for endometrial dating to infer progesterone effect also has no relationship to pregnancy outcome²⁹. Because of these facts Luteal Phase Defect has an uncertain relationship to recurrent miscarriage.

Coagulation Factors

A systematic review of the association between fibrinolytic defects and recurrent miscarriage found a significant association for factor XII deficiency (OR 18.11, 95% CI 5.52-59.4; five studies, 1096 women)³⁰. Numerous studies have demonstrated thrombophilias are not related to recurrent pregnancy loss³¹⁻³⁷. This position is shared by the American College of Obstetrician Gynecologists³⁸.

Genetic

Various chromosomal disorders have long been known to contribute to pregnancy loss. Abnormalities of chromosome number or structure are the most common cause of sporadic early pregnancy loss, accounting for at least 50 percent of such losses in multiple studies³⁹⁻⁴⁰. A significant proportion of habitual miscarriages may also be associated with structural or numerical chromosomal abnormalities (eg, aneuploidy, mosaicism, translocation, inversion, deletion, fragile sites)⁴¹⁻⁴².

There appears to be an increased risk of recurrent miscarriage in first degree relatives of women with unexplained recurrent miscarriages⁴³⁻⁴⁴. This may be related to shared HLA types, coagulation defects, immune dysfunction, or other undefined heritable factors.

Aneuploidy--

The risk of aneuploidy increases as the number of previous miscarriages increases⁴⁵. The relationship between the karyotype of the abortus and risk of RPL requires further study to better define which abnormalities are likely to be recurrent.

In some series, having one chromosomally abnormal spontaneous abortion appeared to increase the risk of a subsequent loss associated with a chromosomal abnormality⁴⁶⁻⁴⁹. As an example, one study reported that the frequency of an abnormal karyotype in a second abortus after a first aneuploid or euploid abortus was 70 and 20 percent, respectively⁵⁰. Another study involving preimplantation genetic diagnosis reported 532 of 764 embryos (70 percent) were abnormal in couples with RPL versus 97 of 215 embryos (45 percent) among controls⁵¹.

Rearrangement of chromosomes—

Three to 5 percent of couples with RPL have a major chromosomal rearrangement (versus 0.7 percent of the general population); usually a balanced translocation or an inversion⁵²⁻⁵⁴. One or both partners may harbor lethal genes in a heterozygous or balanced combination that does not affect them, but causes pregnancy loss when inherited by the embryo in a homozygous or unbalanced state. Balanced translocations are more common in the female than the male and more likely to result in pregnancy loss if the translocation is of maternal origin.

The likelihood that RPL is related to parental karyotypic abnormality appears to be higher when one or more of the following characteristics are present: young maternal age at second miscarriage, a history of three or more miscarriages, or a history of two or more miscarriages in a sibling or the parents of either partner⁵³.

Ovarian Reserve

Women with diminished ovarian reserve have lowered fecundability and a higher likelihood of repetitive miscarriage. Ovarian reserve can be evaluated by measurement of antral follicle count (AFC), basal serum follicle stimulating hormone (FSH), anti-müllerian hormone (AMH), or inhibin-B. At DWC we measure day 3 FSH concentration to assess ovarian reserve. If measurement of FSH levels was limited to women over 34 years of age, one quarter of those with elevated values would be missed⁵⁵. Generally speaking, women with diminished ovarian reserve will benefit from assisted reproduction with donor oocytes.

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DESERT WOMEN'S CARE RPL ORDER SHEET

ORDER ACTION

Office Based:

_____	GC and CT probes
_____	CBC with differential
_____	Fasting glucose
_____	2-hour Glucose Challenge with 75 grams of glucose
_____	Fasting prolactin
_____	TSH, Free T3 and Free T4
_____	Thyroid peroxidase antibodies
_____	Thyroid thyroglobulin antibodies
_____	Antiphospholipid Antibodies
	--Lupus Anticoagulant
	--Anti-Cardiolipin Antibodies
	--Anti B2 Glycoprotein 1 Antibodies
_____	factor XII
_____	Maternal blood for Karotyping

Imaging Studies:

_____	Ultrasound
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Surgery:

_____	Schedule Hysteroscopy and D&C
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