RECURRENT MISCARRIAGE
Habitual Abortion, Recurrent Pregnancy Loss, RPL, Repetitive Miscarriages

Three or more consecutive pregnancy losses before 20-24 weeks of gestation or below a fetal weight of 500 g.

 Diablo Diagnosis  Female

Related Diagnoses:
Uterine fibroids

About Recurrent miscarriage

Recurrent miscarriages are one or more pregnancy losses before 20-24 weeks of gestation or below a fetal weight of 500 g (Pic. 1). About 1% of women in reproductive age are affected by recurrent miscarriages. The majority of patients are counseled to try to conceive again, and chances are about 60% that the next pregnancy is successful without treatment. However, each additional loss worsens the prognostic for a successful pregnancy (Pic. 2) and increases the psychological and physical risks to the mother.

There are many causes of recurrent miscarriages:

- Maternal age

The prevalence of miscarriage increases with advancing maternal age (Pic. 3). The increase in the risk of miscarriage in this group is due to an increase in chromosomally abnormal embryos, probably as a result of poor oocyte quality, and a decline in uterine and ovarian function. Advanced paternal age is also a risk factor for miscarriage. The risk of miscarriage is highest in couples where the woman is older than 35 years and the man older than 40 years.

- Anatomical abnormalities

An accepted cause of recurrent pregnancy loss is uterine malformations that may be acquired or congenital. The latter include didelphic (double uterus), bicornuate (heart-shaped), arcuate (has a dip, or slight indentation at the top), and septate uterus (partially or completely divided uterus by septum). The diagnosis is made by MRI (magnetic resonance imaging) or a combined laparoscopy hysteroscopy of the uterus.

In the second trimester a weak cervix can become a recurrent problem. Such cervical incompetence leads to premature pregnancy loss resulting in miscarriages or preterm deliveries.

- Karyotypic disorders

A chromosomal abnormality in one partner is found in 3% to 6% of recurrent miscarriage couples, which is ten times higher than the background population. The most commonly encountered abnormalities include balanced translocations and inversions that do not have any consequences for the phenotype of the carrier (carries the trait but does not display it), but in pregnancy there is a 50% risk of a fetus with an unbalanced chromosomal abnormality that can result in a miscarriage. This risk is influenced by the size and the genetic content of the rearranged chromosomal segments.

Whether or not to screen couples with recurrent miscarriage for chromosomal abnormalities remains a topic of debate. The argument for performing this costly analysis is to optimize the counseling of recurrent miscarriage couples with respect to any subsequent pregnancy and to avoid the birth of a child with congenital defects and mental handicaps due to an unbalanced karyotype (the chromosomes of a cell) by offering appropriate prenatal diagnostic screening (PGS).
Immunological and immunogenetic causes

Since reproductive success is of utmost importance for the survival of a species, it is likely that redundant mechanisms (contain more degrees of freedom than are needed to perform a given task) have developed to prevent immune rejection of the embryo, and only when several mechanisms fail in a woman will recurrent miscarriage will occur. This complexity continues to feed the ongoing controversy regarding which immunological factors play a role in the pathogenesis of recurrent miscarriage. There is general agreement that a series of autoantibodies such as anti-phospholipid, anti-nuclear and anti-thyroid antibodies can be found with increased prevalence in recurrent miscarriage patients and may display a negative prognostic impact.

The antiphospholipid syndrome is an autoimmune disease that is a common cause of recurrent pregnancy loss. Around 15% of the women who have recurrent miscarriages have high levels of antiphospholipid antibodies. Women who have had more than one miscarriage in the first trimester, or a miscarriage in the second trimester, may have their blood tested for antibodies, to determine if they have antiphospholipid syndrome. Women diagnosed with antiphospholipid syndrome generally take aspirin or heparin in subsequent pregnancies, but questions remain due to the lack of high quality trials.

Natural killer (NK) cells, a type of white blood cell, are present in uterine tissue. High levels of these cells may be linked to RPL but high numbers or the presence of these cells is not a predictor of pregnancy loss in women who have not had a miscarriage.

Earlier studies that perhaps paternal sharing of human leukocyte antigen (HLA) genes would be associated with increased pregnancy loss have not been confirmed.

Immunization of mothers against male-specific minor histocompatibility (H-Y) antigens could be associated with the secondary recurrent miscarriage, that is, recurrent miscarriage in pregnancies succeeding a previous live birth. An example of this effect is that the male:female ratio of children born prior and subsequent to secondary recurrent miscarriage is 1.49 and 0.76 respectively.

Thrombophilias

Thrombophilic factors are associated with both sporadic (occasional) miscarriages and recurrent miscarriage and can be hereditary or acquired. It is suggested that the association is caused by an increased risk of thrombus formation in the nascent placental vessels resulting in placenta infarctions.

Hereditary factors include deficiency of antithrombin, protein C and protein S or carriage of the factor V Leiden or factor II gene mutations. Acquired factors include the presence of anti-phospholipid antibodies, lupus anticoagulant or anti-cardiolipin antibodies, which are deemed to be present when identified in repeated samples taken 3 months apart and outwith pregnancy.

It was noted that many women with thrombophilia go through one or more pregnancies with no difficulties, while others may have pregnancy complications. Thrombophilia may explain up to 15% of recurrent miscarriages.

Endocrinological causes

The prevalence of hypothyroidism (low thyroid function) with or without underlying thyroid autoimmunity is significant among fertile women in fertile age. There is evidence that thyroid dysfunction and thyroid autoimmunity is associated with infertility and pregnancy loss both in the situation where the woman is euthyroid (normal thyroid function) with thyroid antibodies and in a thyroid antibody negative woman with an elevated level of thyroid stimulating hormone (TSH). However, the true significance of thyroid dysfunction and the value of its correction in improving outcomes in recurrent miscarriage remains unclear.

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder of reproductive-age women. PCOS may be associated with ovulatory disorder and miscarriage when fertility is desired. Using strict criteria the prevalence of PCOS among women with recurrent miscarriage is estimated to be 8.3% to 10%. The mechanisms behind an increased miscarriage risk in women with PCOS remains partly unclear. The current view is that the main cause may be the associated obesity, which is dealt with in the section describing lifestyle factors.
Sperm DNA integrity is essential to reproduction, and measurement of sperm DNA fragmentation (SDF) was therefore first introduced as an additional tool in predicting male infertility. In general, DNA fragmentation is the separation or breaking of DNA strands into pieces. Indeed, there is a correlation between low semen quality and high sperm DNA fragmentation levels, but at present much controversy exists with regard to cut-off levels, which assay to use, and the clinical relevance of the tests in assisted reproductive technologies.

In contrast, there is a documented link between DNA damage in sperm and miscarriage. A recent meta-analysis including 16 studies found a highly significant increase in miscarriage rate in couples where the male partner had elevated levels of sperm DNA damage compared to those where the male partner had low levels of sperm DNA damage.

- **Lifestyle factors**

Women experiencing sporadic as well as recurrent miscarriage often have many questions regarding lifestyle factors. Even small amounts of alcohol increased the risk of a miscarriage significantly and further, the results suggested that the risk increased in a dose-related manner. Risky amount of alcohol is defined as drinking more than two units of alcohol per week – one unit is half a pint of bitter or ordinary strength lager, or a 25ml measure of spirits, and a small 125ml glass of wine is 1.5 units. Smoking-related complications in late pregnancy are substantial and well documented. In contrast, data are sparse and conflicting when it comes to smoking and miscarriage.

- **Infections**

A number of maternal infections can lead to a single pregnancy loss, including listeriosis, toxoplasmosis, and certain viral infections (rubella, herpes simplex, measles, cytomegalovirus, coxsackie virus). However, there are no confirmed studies to suggest that specific infections will lead to recurrent pregnancy loss in humans. Malaria, syphilis and brucellosis can also cause recurrent miscarriage.

- **Ovarian factors**

The issue of a luteal phase defect (abnormal length of luteal phase, for example shorter than 11 days) is complex. The theory behind the concept suggests that an inadequate amount of progesterone is produced by the corpus luteum (temporary endocrine structure in female ovaries producing progesterone) to maintain the early pregnancy. Assessment of this situation was traditionally carried out by an endometrial biopsy, however recent studies have not confirmed that such assessment is valid.

Regarding the assessment, transvaginal ultrasonography has become the primary method of assessment of the health of an early pregnancy. In non-pregnant patients who are evaluated for recurrent pregnancy loss the following tests are usually performed. Parental chromosome testing (karyogram) is generally recommended after 2 or 3 pregnancy losses. Blood tests for thrombophilia, ovarian function, thyroid function and diabetes are performed.

If the likely cause of recurrent pregnancy loss can be determined treatment is to be directed accordingly. It includes pharmacotherapy, surgical therapy for anatomy anomalies and psychological therapy to eliminate anxiety and stress.

Traditionally, the diagnosis of recurrent miscarriage is not made until a woman has lost at least three consecutive pregnancy losses. Diagnostic evaluation includes maternal and paternal karyotypes, assessment of the uterine anatomy, and evaluation for endocrine disorders, and thrombophilies. In some women, evaluation for insulin resistance (fail to respond normally to the hormone insulin) or ovarian reserve (the capacity of the ovary to provide eggs) may be indicated.

Therapy should be directed toward any treatable cause. It includes in vitro fertilization (IVF), surgical correction of anatomic uterine abnormalities, or treating of endocrine disorders.

**Associated diseases**

- coronary artery disease
- ovarian cancer
- cardiovascular complication
- diabetes mellitus
- polycystic ovary syndrome (PCOS)
- thyroid diseases
- genital tuberculosis
- hyperprolactinemia (high blood prolactin level)
- chronic endometriosis
Complications

As the number of miscarriages increases, the risk of chromosomal abnormalities decreases and the risk of underlying maternal cause increases. Women with a history of recurrent miscarriage are at risk of developing preeclampsia (pregnancy-associated high blood pressure) in later pregnancies. There is also significant, and often unrecognized, psychological and psychiatric trauma for the mother – for many, miscarriage represents the loss of a future child, of motherhood, and engenders doubts regarding her ability to procreate. Studies have shown a significant percentage of women experience grief, depression, and anxiety, and that there is an increased risk of major depressive disorder following a miscarriage. The psychological effects can persist for 6 months to 3 years and tend to deepen with additional miscarriages.

Risk factors

- advanced age of both parents
- genetic factors (chromosomal abnormalities)
- previous miscarriages
- antiphospholipid syndrome
- uterine anatomy anomalies (congenital, leiomyoma, intra-uterine adhesions,...)
- thyroid disorders
- trombophilia
- polycystic ovary syndrome (PCOS)
- endometriosis
- obesity
- negative Rh factor
- alcohol drinking
- cigarette smoking
- high caffeine intake
- stress

Impact on fertility

It has been reported that women whose first pregnancy resulted in miscarriage are at a higher risk of the second pregnancy resulting in miscarriage compared with women who had a live birth.

It is well known that early miscarriage is normally associated with low or suboptimally (below optimal level) increasing human chorionic gonadotropin (hCG) levels that promotes the maintenance of the corpus luteum (producing progesterone) during the beginning of pregnancy. The association between low hCG production and miscarriage can be interpreted in two ways:

1. the outer cell layer (trophoblast) growth may be delayed due to embryonal aneuploidy (abnormal number of chromosomes), immune or thrombophilic disturbances and low hCG production is a secondary phenomenon
2. placenta may secrete inadequate hCG due to a primary failure of the trophoblast to produce hCG, which will result in inadequate progesterone production and resulting embryonal death.

Some women with recurrent miscarriage may be allowing embryos of poor viability to implant inappropriately. In other words, women who experience recurrent miscarriage may not be rejecting healthy embryos, but rather permitting embryos of low viability to implant long enough to present as a clinical pregnancy before rather than being lost as a preclinical biochemical pregnancy.

It was showed that chromosomal abnormalities carrier couples with at least two previous miscarriages had the same chance of having a healthy child as non-carrier couples with at least two miscarriages (83% and 84%, respectively), and more importantly a low risk (0.8%) of pregnancies with an unbalanced karyotype surviving into the second trimester. Current clinical guidelines do recommend parental karyotyping as part of the evaluation in recurrent miscarriage couples with a high risk of carrier status but only if maternal age is low at the second miscarriage, or if there is a history of two or more miscarriages in first degree relatives.

Prevention

Prevention of miscarriage centers on decreasing risk factors. Identifying the cause of the miscarriage may help prevent future pregnancy loss, especially in cases of recurrent miscarriage.
Vitamin supplementation has not been found to be effective to prevent miscarriage. Lifestyle modification and stress reduction should be emphasized by pointing out that a healthier lifestyle, free from tobacco, alcohol, illicit drugs, and undue stress cannot hurt and may significantly improve the couple's chances for a successful pregnancy.

Close surveillance during pregnancy is generally recommended for pregnant patients with a history of recurrent pregnancy loss. Even with appropriate and correct treatment another pregnancy loss may occur as each pregnancy develops its own risks and problems.

Patients with insulin resistance should be advised to improve their insulin sensitivity through lifestyle change or medical intervention before infertility treatment to reduce their risk of spontaneous miscarriage. High-dose folic acid is considered with women with high BMI and diabetes during pregnancy.

Cervical surgery, vaginal progesterone, or pessary are equally efficacious in the prevention of preterm birth in women with a short cervix detected on sonography at the mid-trimester in singleton gestation.

Symptoms

Miscarriage is the spontaneous loss of a pregnancy before 12 weeks (early miscarriage) or from 12 to 24 weeks (late miscarriage) of gestation. The most common symptom of a miscarriage is vaginal bleeding. This can vary from light spotting or brownish discharge to heavy bleeding and bright red blood. The bleeding may come and go over several days. However, light vaginal bleeding is relatively common during the first trimester of pregnancy (the first 12 weeks) and does not necessarily indicate a miscarriage. Of those who seek clinical treatment for bleeding during pregnancy, about half will miscarry. Symptoms other than bleeding are not statistically related to miscarriage.

Miscarriage may be detected during an ultrasound exam (Pic. 4), or through serial human chorionic gonadotropin (hCG) testing. Those who became pregnant using assisted reproductive technology methods, and those with a history of miscarriage may be monitored closely, and may be diagnosed with miscarriage sooner.

Therapies

Self therapy

Chinese herbal medication

Though Chinese herbal medication is widely used for recurrent miscarriage in China and other eastern countries, it was indicated that Chinese herbal medication may have beneficial effect on increasing live birth rate and improving embryonic developmental state for women with recurrent miscarriage.

Unlike mainstream Western Medicine, Chinese Medicine has a unique medical theory to understand miscarriage. To make the diagnosis and guide the treatment, “Qi” and “Blood” are the two basic elements involved. The major causes of threatened miscarriage include “Kidney Deficiency,” “Qi Deficiency,” “Blood Deficiency,” “Blood Heat,” “External Injury,” and “Wei Jia” (refers to ectopic pregnancy, which is considered as a cause of threatened miscarriage in Chinese Medicine). The diagnosis and treatment are based on different causes and varied a lot in different patients.

The principle of treatments is to supplement and regulate the balance of maternal “Qi,” “Blood,” and the system concerned and enhance the survivals of fetuses, so as to relieve clinical signs, promote pregnancy, and prevent inevitable miscarriage. Besides its application as expectant management for threatened and recurrent miscarriages, Chinese Medicine is also used as active managements for missed, incomplete, and complete miscarriages, which mainly accelerate the blood circulation so as to stimulate uterine contractions and empty the uterus.
The management of recurrent pregnancy loss should be guided by the underlying cause. However, all couples should be treated sensitively, sympathetically, and with appropriate emotional support. Best practice is to refer couples to a specialist clinic.

There are currently no treatments for women with unexplained recurrent pregnancy loss. It is generally agreed that maternal endocrine disorders (e.g., diabetes, thyroid dysfunction) should be evaluated and treated.

**Pharmacotherapy**

**NT100**

There is currently one drug in development, NT100, which is in clinical trials for the treatment of unexplained recurrent miscarriage. The study investigates the role of NT100 in improving maternal-fetal tolerance for women with unexplained recurrent miscarriage.

**Clindamycin**

Treatment of asymptomatic abnormal vaginal flora and bacterial vaginosis with oral clindamycin early in the second trimester significantly reduces the rate of late miscarriage and spontaneous preterm birth in a general obstetric population.

**Anticoagulation therapy**

In pregnant women with a history of recurrent miscarriage, anticoagulants seem to increase the live birth rate among those with antiphospholipid syndrome and perhaps those with congenital thrombophilia but not in those with unexplained recurrent miscarriage.

**Progesterone supplementation**

Progesterone supplementation is immunoprotective for pregnancy. Administration of progesterone to women with sporadic miscarriages is ineffective. However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit.

**Acetylsalicylic acid and low molecular weight heparin**

Low doses of acetylsalicylic acid and low molecular weight heparin (LMWH) are the best solution in women suffering from recurrent spontaneous miscarriage with antiphospholipid syndrome. This treatment combination of low dose aspirin and low molecular weight heparin reduces the miscarriage rate by 54%.

**Aspirin**

Evidence is debatable. There is paucity of evidence to make any recommendation on aspirin for treating recurrent miscarriage in women without antiphospholipid syndrome. Few RCT suggested clear benefit of using aspirin for such women. Recent trial failed to support any role of Aspirin in unexplained recurrent miscarriage. Aspirin helps in improving uterine perfusion. Aspirin is useful in many undiagnosed implantation failure patients. However, in the absence of strong evidence, routine use of Aspirin is not recommended.

**Dopamine agonist**

Though elevated luteinizing hormone (LH) is associated with increased risk of miscarriage suppression of LH secretion with gonadotropin-releasing hormone (GnRH) agonist prior to ovulation induction yielded no difference in outcome. Hyperprolactinemia may be associated with recurrent pregnancy loss through alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and
Oocyte maturation, and/or a short luteal phase. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with recurrent pregnancy loss.

**Surgical therapy**

The clinical management of pregnancy-loss patients with uterine anatomy abnormalities is also controversial, and there is no conclusive evidence that surgical treatment reduces the risk of pregnancy loss. Minimally invasive surgeries are the better option for the treatment of structural defects due to scars.

**Cervical cerclage**

Cervical cerclage, also known as a cervical stitch, is a treatment for cervical incompetence or insufficiency, when the cervix starts to shorten and open too early during a pregnancy causing either a late miscarriage or preterm birth. Usually the treatment is done in the second trimester of pregnancy, for a woman who had either one or more late miscarriages in the past.

The treatment consists of a strong suture being inserted into and around the cervix early in the pregnancy, usually between weeks 12 to 14, and then removed towards the end of the pregnancy when the greatest risk of miscarriage has passed.

**Other therapies**

**Psychological support**

Stress itself is a risk factor for miscarriage and recurrent miscarriage is a stressful condition so that the vicious cycle can be broken by strong psychological support. Psychological support in the form of frequent discussions and sympathetic counseling are crucial to the successful evaluation and treatment of the anxious couple. When no etiologic factor is identified, no treatment started at 60% to 80% fetal salvage rate still may be expected. Therefore, couples with unexplained recurrent miscarriage should be offered appropriate emotional support and reassurance.

**Assisted reproduction**

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy. It is reproductive technology used primarily for infertility treatments, and is also known as fertility treatment. It mainly belongs to the field of reproductive endocrinology and infertility, and may also include intracytoplasmic sperm injection (ICSI) and cryopreservation. Some forms of ART are also used with regard to fertile couples for genetic reasons (preimplantation genetic diagnosis). ART is also used for couples who are discordant for certain communicable diseases; for example, HIV to reduce the risk of infection when a pregnancy is desired.

In certain chromosomal situations, while treatment may not be available, in vitro fertilization (IVF) with preimplantation genetic diagnosis/screening (PGD/PGS) may be able to identify embryos with a reduced risk of another pregnancy loss which then would be transferred. However, in vitro fertilization does not improve maternal-fetal tolerance imbalances. It is proposed as a faster method of conceiving a live child than natural conception, at least for translocation carriers with recurrent miscarriages. The new technologies such as trophoderm-laser-assisted blastocyst biopsy and molecular karyotyping via whole genome amplification and either comparative genomic hybridization (CGH) or single nucleotide polymorphism (SNP) arrays helped to revitalize the concept of PGS.

Intravenous immunoglobulin (IVIG) administration for treatment of recurrent miscarriage is also not justified outside the context of research. In the future, assays detecting sperm DNA damage may be introduced into the evaluation of couples who experience recurrent miscarriage, and in infertility setting the development of methods that select sperm without DNA damage may be helpful in reducing the risk of miscarriage.
Diagnoses

Uterine fibroids
The most common benign smooth muscle tumors of the uterus encountered in women of reproductive age.
Learn more at: www.fertilitypedia.org/therapy/diag/uterine-fibroids

Symptoms

Recurrent miscarriage
A disease distinct from infertility, defined by two or more failed pregnancies.
Learn more at: www.fertilitypedia.org/edu/symptoms/recurrent-miscarriage

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilitypedia.org/edu/therapies/egg-donation

ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

Gallery

Pic. 1: Risk of miscarriage at specific gestational ages

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Risk of miscarriage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 6 weeks</td>
<td>22 - 57</td>
</tr>
<tr>
<td>6 - 10 weeks</td>
<td>15</td>
</tr>
<tr>
<td>After 10 weeks</td>
<td>2 - 3</td>
</tr>
</tbody>
</table>

Pic. 2: Risk of miscarriage according to obstetric history

<table>
<thead>
<tr>
<th>Consecutive pregnancies</th>
<th>Risk of miscarriage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First pregnancy</td>
<td>5 - 13</td>
</tr>
<tr>
<td>After 1 miscarriage</td>
<td>14 - 21</td>
</tr>
<tr>
<td>After 2 miscarriages</td>
<td>24 - 29</td>
</tr>
<tr>
<td>After 3 miscarriages</td>
<td>31 - 45</td>
</tr>
</tbody>
</table>

Pic. 3: Miscarriage rate according to maternal age

<table>
<thead>
<tr>
<th>Maternal age at conception (years)</th>
<th>Miscarriage rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 24</td>
<td>9</td>
</tr>
<tr>
<td>25 - 29</td>
<td>11</td>
</tr>
<tr>
<td>30 - 34</td>
<td>15</td>
</tr>
<tr>
<td>35 - 39</td>
<td>25</td>
</tr>
<tr>
<td>40 - 44</td>
<td>51</td>
</tr>
<tr>
<td>&gt;45</td>
<td>75</td>
</tr>
</tbody>
</table>

Pic. 4: Delayed or missed miscarriage
An embryo without heartbeat, still in the uterus. The gestational age according to the last menstrual period was supposed to be 11 weeks, but the size of the embryo corresponded to 9 weeks, indicating that the embryo died 2 weeks earlier.
Sources

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