Recurrent pregnancy loss

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Abstract

Miscarriage is the most common complication of early pregnancy. Most of clinically recognized pregnancies (over 15%) end in a miscarriage and, to a certain extent, the average prevalence of women nowadays with one miscarriage is up to 11%. The number of previous miscarriages a woman has suffered is a main determinant of miscarriage risk. This has a considerable effect on the physical and psychological well-being of the parturient. Recurrent pregnancy loss (RPL) – also referred to as recurrent miscarriage, recurrent spontaneous abortion or habitual abortion – is defined as the failure of two or more clinically recognized pregnancies (intrauterine pregnancy) before 20-24 weeks of gestation (168 days) or with a fetal weight below 500 grams. Recurrent miscarriage is part of the vast majority of discouraging conditions to deal with in the field of reproductive medicine, affecting around 1% of couples trying to conceive, being frustrating for both the couple involved and the physician, since the etiology is frequently unknown and the evidence-based diagnosis and treatment techniques are insufficient. This condition can lead to anxiety, depression, even symptoms of post-traumatic stress disorder (PTSD), symptoms that can persist, impacting the quality of life.

Keywords: *miscarriage, recurrent miscarriage, recurrent pregnancy loss, recurrent spontaneous abortion, habitual abortion, low progesterone*

Rezumat

Avortul spontan reprezintă cea mai frecventă complicație apărută în primele luni de sarcină. Majoritatea sarcinilor recunoscute clinic (peste 15%) se termină cu un avort spontan și, într-o anumită măsură, prevalența medie a femeilor din zilele noastre cu un avort spontan ajunge până la 11%. Numărul de avorturi spontane pe care le-a suferit o femeie reprezintă un factor determinant al riscului de avort spontan. Acest lucru are un efect considerabil asupra bunăstării fizice și psihologice a parturientei. Pierderea recurentă de sarcină – denumită și avort recurent, avort spontan recurent sau avort habitual – este definită ca eșecul a două sau mai multe sarcini recunoscute clinic (sarcină intrauterină) înainte de 20-24 de săptămâni de gestație (168 de zile) sau cu o greutate fetală sub 500 grame. Avortul spontan recurent face parte din marea majoritate a afecțiunilor descurajatoare în domeniul medicinii reproductive, afectând aproximativ 1% din cuplurile care încearcă să conceapă, fiind frustrant atât pentru cuplul implicat, cât și pentru medic, deoarece etiologia este frecvent necunoscută, iar tehnicile de diagnostic și tratament pe care se pot baza sunt insuficiente. Această afecțiune poate duce la anxietate, depresie, chiar și la simptome ale tulburării de stres posttraumatic (PTSD), simptome ce pot persista, influențând calitatea vieții.

Cuvinte-cheie: *avort spontan, avort spontan recurent, pierdere recurentă a sarcinii, avort habitual, progesteron scăzut*

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Avortul spontan recurent

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Introduction

Fertility and menstruation are largely controlled by hormones, and one of these hormones is progesterone. Changing progesterone levels can contribute to abnormal menstrual periods and menopausal symptoms. Progesterone is important for the establishment and maintenance of the gravidity state, preparing the uterus by triggering the endometrial lining to thicken. It also prohibits the muscle contractions in the uterus that would cause the body to reject the fertilized egg[(1)]. Progesterone – also called "the hormone of pregnancy" – is a steroid hormone belonging to a class of hormones called progestogens. It is secreted by the *corpus luteum*, a temporary endocrine gland that the female body produces after ovulation, during the second half of the menstrual cycle. These changes in the uterus allow for implantation of a developing zygote[(2,3)].

The *corpus luteum* develops from an ovarian follicle during the luteal phase of the menstrual cycle, following the release of a secondary oocyte from the follicle during ovulation. The follicle first forms a corpus hemorrhagicum before it becomes a *corpus luteum* (the term refers to the visible collection of blood, left after the rupture of the follicle, that secretes progesterone). While the oocyte (later the zygote, if fertilization occurs) traverses the fallopian tube into the uterus, the *corpus luteum* remains in the ovary. The corpus luteum is typically large relative to the size of the ovary; the size ranges from 2 to 5 cm in diameter[(2)].

Therefore, estrogens and progesterone secreted by the ovaries in a cyclical way induce morphological and functional adjustments in the endometrium, creating the ideal endometrial surroundings for implantation. Progesterone levels are lower in women with spontaneous miscarriage, that being the case when progesterone deficiency is connected with miscarriage[(2,4)].

Fertility also relies on a "receptive state" during the mid-secretory phase, when the endometrium is most receptive to blastocyst implantation, which undergoes periodic changes (throughout the menstrual cycle), influenced by hormonal and anatomical changes, as well as the immune system (local and systemic immunity is extremely influenced by the microbiota)[(5)].

Furthermore, fertility declines more rapidly with age. This decline is more commonly after the age of 35. There are a variety of reasons, but particularly the decline is in the quality of the oocyte released by the ovaries[6].

Moreover, congenital malformations of the Müllerian ducts or acquired uterine defects are strongly associated with adverse fertility and pregnancy outcomes[4].

On the genetic aspect, fetal aneuploidy is the leading cause of spontaneous miscarriage in the first 10 weeks of gestation. A chromosomal error is accountable for more than half of recurrent cases of pregnancy loss. Specific maternal physiologic adjustments and certain complex interactions between the new developing fetus and mother must take place in order to occur a successful pregnancy[7].

Methodology

PubMed database was used for this comprehensive review which was obtained from studies published from 2011 to 2021, studies searched using keywords such as "miscarriage", "recurrent miscarriage", "recurrent pregnancy loss", "recurrent spontaneous abortion", "habitual abortion" and "low progesterone", that analyzed the most common causes of recurrent pregnancy loss and also the strategy, assessment and management of this condition. However, studies are challenging to evaluate due to the nonstandardized definitions for RPL, the researchers including two instead of three consecutive miscarriages and others including women with three nonconsecutive miscarriages.

Incidence of early pregnancy loss

The incidence of spontaneous miscarriage cannot be determined with certainty, because the incidence of conception is unknown. In 10-15% of clinically recognizable pregnancies, spontaneous abortion can occur. Studies have shown that 75% of miscarriages occur before the 16th week of gestation and of these about 80% occur before the 12th week of pregnancy[8].

The term *biochemical pregnancy* refers to the presence of hCG levels in the blood of a woman, 7 to 10 days after ovulation, but in whom menstruation occurs when expected (conception has occurred, but spontaneous loss of the pregnancy takes place without the prolongation of the menstrual cycle). When both clinical and biochemical pregnancies are considered, evidence would suggest that more than 50% of all majority conceptions are lost in the following 14 days of conception[9].

Ultrasonography has been used to monitor the intrauterine events of the first trimester of gestation. If a live embryo is present at 8 weeks of gestation, the fetal loss rate over the next 20 weeks (up to 28 weeks) is mainly up to 3%[10].

Etiology

General etiological classes of miscarriage consist of genetic, anatomic, endocrine, immunological, thrombophilic, infectious and environmental factors. Couples struggling with recurrent miscarriage frequently choose to comprehend the reason and the threat of further recurrence[6].

The term *implantation window* was used for the interval in the course of the menstrual cycle when a developmentally ready embryo is permitted to attach, and sooner or later invade into the endometrium. Oocyte quality and normal karyotype are very important for normal implantation, more than the uterine factors[10]. The implantation window was first diagnosed by reproductive endocrinologists when they assessed the timing of an embryo transfer. According to studies like the one belonging to Navot et al., who documented 2-12 cell stage embryos 42-48 hour after insemination, transferred on cycle days 16 through 24, 14 being the ovulation day, the successful embryo implantation occurred only with the embryo transfers in the window of receptivity of the cycle (days 17 and 19). Earlier or later transfers did not result in any pregnancies. Further studies demonstrate that, with assisted reproductive technology, the window of implantation can be extended to cycle days 19-23.

The data gathered correlate with the observational study of 4.5-7-day-old embryos implanting in naturally cycling fertile women between cycle days 18.5 to 21. These results provide confirmatory evidence that the surface epithelium is a critical component of endometrial selectivity (trophoblast adhesion to exposed stroma), as well as ovarian reserve. In other words, the major determinants of female fertility and a successful pregnancy are oocyte quality, endometrial adequacy, and the synchronization of both[11,12].

Luteal phase defect

Early miscarriage can be a result of luteal phase defect, as implantation is not supported, the cause being the deficient progesterone secretion from *corpus luteum*, as well as poor endometrial response to progesterone[8]. It has been reported that the polymorphism of progesterone receptors can act as a risk-modulating factor in women with RPL that can cause alteration in the biological function of the progesterone and can be associated with an individual susceptibility to pregnancy loss. However, this concept has not been confirmed in a current meta-analysis[2].

The etiology is often complex and obscure. The three most common causes of RPL are parental chromosomal abnormalities (2-4% of RPL cases), structural uterine abnormalities (15% of RPL cases) and antiphospholipid antibody syndrome. However, no cause can be discovered in up to 50% of cases, in spite of multiple investigation[6].

The following factors (embryonic or parental) are important and should always be ruled out when the diagnosis and prognosis are needed.

We must distinguish between the two types of RPL:

1) Primary RPL refers to multiple pregnancy losses in a woman, without a previous ongoing pregnancy beyond 24 weeks of gestation.

2) Secondary RPL refers to multiple pregnancy losses in a woman after one or more previous pregnancies progressing beyond 24 weeks of gestation.

Table 1 Common causes of miscarriage[4,8]

Genetic	■ **Chromosomal alterations:** abnormal embryonic karyotypes ■ **Autosomal dominant disorders**
Endocrine and metabolic	■ Hypothyroidism ■ Diabetes mellitus ■ Polycystic Ovary Syndrome ■ Luteal Phase Defect = low progesterone levels and limited uterine lining growth, which can impede egg implantation and fetal development
Anatomic	■ **Uterine factors:** Müllerian anomalies **1. Congenital:** septate uterus, unicornuate uterus, bicornuate uterus, uterus didelphys **2. Acquired:** uterine myoma, intrauterine adhesions, endometrial polyps, Asherman syndrome ■ **Cervical incompetence**
Infection	■ *Mycoplasma* ■ *Ureaplasma* ■ *Chlamydia trachomatis* ■ *Listeria monocytogenes* ■ Herpes simplex virus
Immunological	■ Antiphospholipid syndrome ■ Systemic lupus erythematosus
Thrombophilias	■ Factor V Leiden mutation ■ Mutation in the promoter region of the prothrombin gene ■ Mutations in the gene encoding methylene tetrahydrofolate reductase (MTHFR)
Environmental and lifestyle factors	■ Smoking ■ Alcohol ■ Drugs ■ Stress
Other unexplained	

Genetic abnormalities

The most frequently recognized cause of miscarriage is fetal chromosomal error, the loss happening in most cases earlier than 10 weeks of pregnancy and worrying about 50-70% of couples. The cytogenetic research of miscarriage samples has proven that most of these abnormalities occur *de novo* in the first trimester. Studies on villous biopsies have verified that this percentage would possibly even reach 83%[7]. The majority of embryonic aneuploidies are due to meiotic chromosome segregation errors that occur in the oocyte and are well associated with the maternal age-related miscarriages. The risk of pregnancy loss rapidly increases after the age of 40 years old. Therefore, the risk of having a miscarriage is strongly influenced by age[4,7,13].

Anatomic uterine anomalies

The second most common anomaly associated with RPL is the bicornuate uterus that results from the incomplete fusion of Müllerian ducts, leading to a deep cleft on the fundal portion of the myometrium. Other congenital Müllerian tract anomalies that can cause RPL include unicornuate, septate and didelphys uteri[4,14].

In addition, the uterus with a normal outline but with an abnormal lateral wall shape of the uterine cavity (the term "dysmorphic" used to describe the cavity with abnormal morphology) has been associated with poor reproductive performance due to a narrow cavity with thick uterine walls, showing an increased risk of pregnancy loss. Lower rates of pregnancy have been observed in studies on females with dysmorphic uteri due to the lack of clear diagnostic criteria in distinguishing between various types of uterine malformations[15].

For many physicians, congenital uterine anomalies are challenging to differentiate between classes, making the diagnostic process confusing. On the basis of the evidence currently available, anatomic uterine anomalies are associated with low reproductive and obstetric outcomes, such as first- or second-trimester spontaneous abortion[15].

Uterine myomas, exceptionally submucosal myomas, endometrial polyps and intrauterine adhesions (or synechiae) are associated and may lead to RPL due to insufficient endometrium to support fetal growth[14].

Endocrine abnormalities

Thyroid diseases are known to have terrible repercussions on established pregnancies, especially the poorly managed ones, and may have an increased prevalence

in case of premature delivery, low birth weight, gestational hypertension, placental abruption, decreased IQ, congenital anomalies, and also fetal death[16].

Subclinical hypothyroidism described as a higher TSH than 2.5 and normal free thyroxine or free thyroxine index increase the chance of RPL. The incidence of antithyroid peroxidase antibodies (TPOAb) in female of reproductive age, independent of thyroid status, is 8-14% and numerous researches have investigated the link between TPOAb and RPL[16].

Immunological factors

Pregnancy is a known hypercoagulability state. This is probable an adaptive mechanism, lowering the risk for peripartum hemorrhage. Spontaneous pregnancy loss is often associated with maternal inflammation and systemic coagulopathies. A relationship between inflammation and hypercoagulability has been demonstrated in several studies. Also, maternal inflammation may cause coagulopathy and pathological changes in the placenta[17]. Whether thrombophilia is acquired (antiphospholipid antibodies) or inherited (factor V Leiden), they are associated with vascular thrombosis and with outcomes such as recurrent miscarriage and increased risk of developing venous thromboembolism. Thromboembolism is the main reason of maternal morbidity and mortality worldwide[17]. Four systematic reviews evaluated anticoagulant therapy with low-dose aspirin, heparin, or both[3].

Studies have shown multiple results on the positive association between recurrent pregnancy loss and antiphospholipid antibodies, the prevalence among women with RPL being about three times higher[18]. Antiphospholipid syndrome is found in 5-20% of women with RPL.

Infectious factors

The infectious diseases are not often a motive of early miscarriage. No factual affiliation has been determined between pathogens (bacterial and viral) and recurrent miscarriage, even though *Mycoplasma*, *Ureaplasma*, *Chlamydia*, *Listeria*, *Toxoplasma*, *Rubella*, cytomegalovirus and herpes virus have been related to spontaneous miscarriage[14].

However, studies have shown that altered uterine microbiota (considered for almost a century as a sterile environment maintained by the cervical plug) can have implications in tissue morphology by potentially modulating immune cells needed for implantation. Local and systemic immunity is influenced by microbiota[5].

A persistent inflammation of the endometrium (often asymptomatic) modifies the normal endometrial development that causes alteration of the local immune environment (resistance to progesterone at the endometrial level) and increased uterine contractility in the peri-implantation interval. All these alterations have a negative impact and can be associated with implantation failure. Therefore, a normal microbiota can be crucial in protection against uterine infections[5].

Evaluation and management of recurrent pregnancy loss

There are four predominant aspects that define RPL: defining being pregnant (*via* serum or urine biochemical markers and intrauterine pregnancy documented by ultrasonography), defining up to how many weeks the loss of pregnancy is considered a pregnancy loss, defining recurrence and finding out whether or not these habitual pregnancy losses have to be consecutive[19].

A complete medical history must be obtained, with special interest on personal and family history, more in-depth inquiry into the patient's medical issues which includes all diseases and illnesses currently being treated (history of thrombosis, autoimmune disorder, endocrine disorders or poor obstetric outcomes) and also a surgical history to include all invasive procedures the patient has undergone. The history should include: gestational age (fetal loss), due to the fact that recurrent miscarriage typically occurs at a similar gestational age in the following pregnancies[6].

An abortion is best managed by an ultrasound examination to determine the viability of the product of conception. The assessment of the uterine cavity should be performed, and imaging options may include sonohysterography or hysterosalpingography. The appropriate uterine imaging is important as it enables the prompt diagnosis and in evaluating different aspects for further treatments. Gynecological ultrasound is recommended in females with recurrent miscarriage, due to the fact that it is an available, noninvasive and low-cost technique for detecting uterine disorders.

To evaluate the uterus, the preferred method is transvaginal ultrasonography, particularly 3D, which has a high sensitivity and specificity, and can distinguish between septate uterus and bicorporeal uterus with a normal cervix[20].

As many scientific researchers have shown, it's no longer justified the systematic use of hysteroscopy, hysterosalpingography, CT or MRI, however if needed, hysteroscopy or hysterography should be performed to evaluate the uterine cavity[6].

Once a live embryo has been demonstrated on ultrasonography, the management consists essentially of reassurance and comforting and should be encouraged to undergo first-trimester screening for chromosomal abnormalities, such as trisomy 13, 18 or 21 (combined, triple or quadruple tests). After genetic counseling, couples with an atypical karyotype can be provided *in vitro* fertilization (IVF) accompanied by preimplantation genetic diagnosis[4].

Women with ≥2 primary RPLs or women with ≥3 secondary RPLs should be offered evaluation[10].

It is important to rule out the presence of systemic disorders (diabetes mellitus, systemic lupus erythematosus and thyroid disease) and it is necessary to test for the presence of a lupus anticoagulant. Additionally, paternal and maternal chromosomes should be evaluated[3].

Over 50% of couples with recurrent losses will have ordinary findings in the course of the general evaluation.

With the data now accessible on the function of vitamin D, it is encouraged that girls additionally be assessed for vitamin D deficiency[16].

When a specific etiologic component is found, the appropriate management frequently leads to reproductive success[3]. Overall, a meta-analysis on studies in women with altered vitamin D levels and vitamin D metabolism, both of which have been implicated in the pathophysiology of RPL, suggests the necessity and importance of screening vitamin D deficiency, given the repercussions in ongoing pregnancy, such as preeclampsia, gestational diabetes, preterm birth and small for gestational age newborn[16].

Early pregnancy is frequently perceived by clinicians as an "unstable structure" (the 'Jenga' hypothesis), effortlessly perturbed by a multitude of factors[21,22].

The purpose of investigations in couples with RPL is to observe the underlying threat factors contributing to the pregnancy losses. This can include the evaluation of lifestyle, genetic analysis, the evaluation of uterine anatomy, thrombophilia, immunologic and metabolic testing and the assessment of the male component. The following interventions can be considered: life-style advice, *in vitro* fertilization with preimplantation genetic trying out (PGT), aspirin and heparin, levothyroxine and surgical treatment for uterine anomalies[19].

Couples who struggle with RPL should be informed that obesity (BMI >30 kg/m^2) and the consumption of alcohol and smoking could have a negative impact on their chances of live birth[20]. Also, the most important aspect of the effective treatment for RPL is the clinical need for continuity of care and psychological support to manage stressful situations[13]. The psychological status of female with pregnancy loss, particularly those with four or more pregnancy losses, must be considered by healthcare specialists even though they are hospitalized for a short time[4,23].

The most important step in the management of obstetric antiphospholipid syndrome is understanding the pathogenic action of antiphospholipid antibodies that can be controlled with standard therapy which include combination treatment with prophylactic heparin dosage and low-dose aspirin during pregnancy[18].

Many women with systemic lupus erythematosus were identified to have antiphospholipid antibodies. The mechanisms by means of which antiphospholipid antibodies result in miscarriage are doubtful; however, they can be divided into three regularly occurring categories: inflammation, thrombosis and abnormal placentation[4].

Currently, there are frequently identified congenital (septate, bicornuate, unicornuate, didelphys and arcuate defects) and acquired (fibroids, polyps and adhesions) uterine defects in RPL patients[13]. Most uterine abnormalities can be effectively managed with surgical intervention.

The gold standard for the diagnosis of intrauterine abnormalities and the therapy of many intrauterine lesions throughout the procedure is hysteroscopy. Hysteroscopic metroplasty (also called Strassman metroplasty, uteroplasty or hysteroplasty) to correct a septate uterus may also have beneficial outcomes on pregnancy outcomes. The retrospective research persistently document decrease miscarriage rates in patients

Table 2 The evaluation and management of women with RPL[4,8,13,21]

	MANAGEMENT	OPTION TREATMENTS
GENETIC ■ Structural chromosomal rearrangements or errors ■ Embryonic chromosomal abnormalities	■ Genetic counseling + genetic tests ■ Karyotyping products of conception (informative) ■ Sperm DNA testing	■ Preimplantation genetics + IVF
ENDOCRINOLOGIC ■ Hypothyroidism ■ Poorly controlled diabetes mellitus	■ Screening for metabolic/endocrinological abnormalities ■ Antithyroid antibodies (TPOAb) ■ Fasting glucose, HbA1c	■ Levothyroxine treatment for TSH >4 mIU/L (*consider Levothyroxine for TSH > 2.5 mIU/L) ■ Metformin/insulin adjustment ■ Prophylactic vitamin D
IMMUNOLOGIC ■ Antiphospholipid syndrome ■ Inherited thrombophilia	■ ELISA to detect antiphospholipid antibody ■ Lupus anticoagulant	■ Unfractionated heparin + low- dose aspirin
ANATOMIC ■ Congenital genital tract anomalies ■ Fibroids, polyps and adhesions ■ Cervical Incompetence	■ 3D ultrasonography imaging ■ Hysterosalpingogram ■ MRI	■ Surgical treatment: hysteroscopic resection/ hysteroscopic adhesiolysis/metroplasty ■ Cerclage
HEALTH BEHAVIOUR	■ Lifestyle advice ■ Psychological support and counseling	■ Cessation of smoking ■ Limit alcohol consumption ■ Weight loss/normal range BMI

after metroplasty in contrast with untreated patients. A meta-analysis showed that the hysteroscopic resection of a uterine septum improved live birth rates from 6.1% earlier than surgical procedure to 83.2% after metroplasty[14].

Conclusions

After two consecutive miscarriages, the risk of another miscarriage increases to about 28%. Overall, RPL is a much less frequent phenomenon, and this is viewed as a distinct disease entity.

In many cases, the cause of RPL is unknown, therefore, after three or more losses, a thorough evaluation is recommended.

The individualized management of RPL is essential. Screening tests should not only discover the etiology, but also lead to effective interventions in increasing the incidence of upcoming pregnancy and live births. As therapy, the treatment alternatives for RPL are confined and rely on the results of the investigations.

There is no exceptional proof for any cure to stop miscarriages in a female with RPL. There is some evidence that progesterone could increase live birth rates in female with recurrent miscarriage, and also levothyroxine may limit the threat of miscarriage in women with hypothyroidism. The combination of aspirin and heparin in females with recurrent miscarriage and antiphospholipid antibodies should increase live births.

The impact of recurrent pregnancy loss is often underestimated, being a traumatic loss, not only of the pregnancy, but of a woman's self-image and self-worth that can build doubts regarding her ability to procreate and also maintaining the family integrity. A woman who has a miscarriage is at risk for depression and anxiety symptoms in the following period. The inability to have children negatively affects the psychological status of the couple, RPL being a devastating experience for most couples. Therefore, is it important that healthcare professionals support and help patients on their journey regarding the diagnosis and etiology of RPL, the psychological assessment and counseling being a key point which can be associated with successful live birth and delivery in RPL couples. ■

Conflicts of interests: The authors declare no conflict of interests.

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