Diagnosis and Management of Pregnancy Loss

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Abstract

Recurrent pregnancy loss (RPL) is a multifactorial condition encompassing physical and emotional burdens. Several risk factors contribute to spontaneous miscarriage, most commonly through previous history and chromosomal abnormalities. Other etiologies include uterine anomalies, immunologic and endocrine factors, thrombophilias, and environmental pathogens. However, approximately half of all patients with spontaneous pregnancy loss have no reason for these miscarriages (ACOG practice bulletin, 2001). Those who experience two or more consecutive losses warrant further evaluation. Assessment of each patient starts with a comprehensive history and physical examination, karyotype testing, imaging of the pelvic structures, and detailed medical workup of possible conditions. If a definite cause is identified, treatment is focused on correcting the abnormality. Psychological support may be crucial and even therapeutic; patients should be comforted that a subsequent live birth is possible with great success.

Keywords

Recurrent miscarriage • Spontaneous abortion • Pregnancy loss • Antiphospholipid syndrome • Aneuploidy

Contents

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1 Introduction

Sporadic pregnancy loss is common, occurring in approximately 15–25% of all pregnancies (Hatasaka 1994). Normally, a miscarriage is not an anticipated event, and couples go through emotional, physical, and traumatic experiences as a result of this occurrence. Recurrent pregnancy loss is one of the more challenging and difficult aspects of reproductive medicine. According to the American Society for Reproductive Medicine (ASRM), recurrent pregnancy loss is a distinct disorder defined by two or more failed clinical pregnancies documented by ultrasonography or histopathological examination and not necessarily consecutive (Practice Committee of ASRM 2013). The European Society for Human Reproduction and Embryology (ESHRE) defines RPL as three consecutive losses, not necessarily intrauterine (Kolte et al. 2015). At very early gestational ages (<10 weeks), most losses, whether sporadic or recurrent, result from chromosomal errors (Wilcox et al. 1988; Practice Committee of ASRM 2012). As a result of increased prevalence of numerical chromosomal abnormalities with advancing maternal age, the prevalence of miscarriage increases with aging: <30 years of age (9–17%), at age 35 years (20%), at age 40 years (40%), and at age 45 years (80%). About 2% of pregnant women experience two consecutive miscarriages, while <1% experience three or more (Nybo Andersen et al. 2000). This chapter evaluates the etiology, evaluation, and treatment of recurrent pregnancy loss.

2 Etiology

Studies investigating RPL have identified several attributing factors including genetic, thrombophilic, anatomic, immunological, endocrine, infectious, and environmental causes. The overall risk of miscarriage in the first pregnancy is 11–13%, and this risk increases to 14–21% in the subsequent pregnancy after one miscarriage (Stirrat 1990). Advancing maternal age is associated with increased rates of pregnancy loss. Patients in this age group tend to have higher meiotic chromosomal errors and increased risk of aneuploidy, which contributes to higher rates of losses. In fact the sporadic miscarriage rate approaches 50% in patients above the age of 40 (Dunson et al. 2002).

2.1 Genetic Factors

More than half of all early pregnancy losses are associated with chromosomal abnormalities. Aneuploidies such as trisomies and monosomies are the most common chromosomal number errors found in sporadic miscarriages (Goddijn et al. 2004). Triploidies, or the duplication of an entire set of chromosomes, have been implicated in RPL as well. Other chromosomal anomalies include chromosomal rearrangements such as balanced translocations, reciprocal (60%) and Robertsonian (40%), which are observed in about 2–5% of couples with recurrent miscarriages (Franssen et al. 2005). These are more common in female fetuses, and translocations of maternal origin are more likely to result in pregnancy loss as compared to those of paternal origin. Less common chromosomal rearrangements consist of inversions. Recurrent pregnancy loss as a result of chromosomal anomalies is more common with: young maternal age at second miscarriage and/or a positive family history of two or more miscarriages (Goddijn et al. 2004).

2.2 Thrombophilic Factors

Pregnancy induces a hypercoagulable state as a physiologic mechanism to prevent postpartum bleeding. Fibrinogen and thrombin levels increase, while protein S decreases. Additionally, changes in hormone levels cause venous stasis as a result of enhanced compliance of the vessel walls. Procoagulant microparticles, such as procoagulant aminophospholipids, phosphatidylserine, and phosphatidylethanolamine, may contribute to the hypercoagulable state and as such may interfere with successful implantation and fetal growth. Microparticles also cause

apoptosis, platelet activation, and endothelial stimulation leading to increased incidence of pregnancy loss (Laude et al. 2001).

Although data on fibrinolytic factors and the effect of recurrent pregnancy loss is sparse, there seems to be a direct association between factor XII deficiency and RPL. In studies, women with recurrent miscarriage have shown decreased levels of factor XII activity and prolonged activated partial thromboplastin time. Decreased factor XII activity contributes to reduced fibrinolysis, increasing the likelihood of thrombosis (Sotiriadis et al. 2007).

2.3 Immunological Factors

During pregnancy there is a state of immune tolerance toward the fetus and placenta. When there is insufficient tolerance, spontaneous abortion or infertility may ensue. Embryos contain both maternally and paternally derived antigens. Paternal antigens and immunomodulatory factors present in semen are not recognized by the mother and are protected by trophoblasts. When the blastocyst is abnormal, paternal antigens are exposed, creating an immune response from the mother. Allogenic factors are thought to cause RPL in a similar fashion to a transplanted graft rejection (Hill and Choi 2000).

One particular immunological response that can contribute to RPL is the presence of antiphospholipid antibodies. Antiphospholipid syndrome (APS) is the only immune condition in which pregnancy loss is a diagnostic criterion for the disease. Five to twenty percent% of patients with recurrent pregnancy loss will test positive for antiphospholipid antibodies (Parke et al. 1991). Diagnosis of antiphospholipid syndrome is outlined in Table 1 (ACOG practice bulletin, 2001). These antibodies react directly with phospholipids; they affect the trophoblast by inhibiting villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua, inducing syncytiotrophoblast apoptosis, and initiating maternal inflammatory pathways on the syncytiotrophoblast surface. The decidua becomes infiltrated with tumor necrosis factor alpha (TNF-α) levels, complement C3, and neutrophils (Hill and Choi 2000). Overall, this alters the immune cell prolife at the maternal-fetal interface, causing pregnancy loss (Tong et al. 2015).

Table 1 Classification criteria for the diagnosis of antiphospholipid syndrome (Adapted from ACOG Practice Bulletin No. 132 with permission)

APS is present in one of the following clinical criteria and one of the following laboratory criteria are met
Clinical criteria
1. Vascular thrombosis
2. Pregnancy morbidity
(a) One or more unexplained deaths of morphologically normal fetuses after the 10th week of gestation by ultrasound or direct examination of the fetus
(b) One of more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia or recognized features of placental insufficiency
(c) Three or more unexplained consecutive spontaneous abortion before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
Laboratory criteria
1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or >99th percentile), on two or more occasions at least 12 weeks apart
3. Anti-β_2 glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions at least 12 weeks apart

2.4 Anatomic Factors

Congenital uterine anomalies are present in 2.7–16.7% of the general population (Devi et al. 2006). Relevant Müllerian tract anomalies include unicornuate, didelphic, bicornuate, septate, or arcuate uteri. Septate uterus, however, is the most common anomaly associated with pregnancy loss (Homer et al. 2000). In such case, spontaneous abortions may be related to impaired uterine distention or abnormal implantation. Alternatively, decreased vascularity, increased inflammation, or reduction in sensitivity to hormones in the defect may affect implantation.

Depending on their location, leiomyomas may alter the uterine cavity and impede implantation. This may be due to multiple factors including poor endometrial receptivity of the decidua overlying the myoma or due to degeneration and subsequent cytokine release. Submucosal leiomyomas are more commonly associated with recurrent pregnancy loss (Simpson 2007).

Intrauterine adhesions are created from granulation tissue after trauma to the basalis layer. The connective tissue formed may adhere to the uterine walls, creating a physical barrier to implantation in the uterine cavity. Also known as Asherman's syndrome, this anatomic deformity may lead to recurrent pregnancy loss (Pabuçcu et al. 1997).

2.5 Endocrinologic Factors

There appears to be an association between abnormal thyroid levels and pregnancy loss, mainly high serum thyroid antibody concentrations (thyroid peroxidase or thyroglobulin). Although no direct cause has been identified, excess thyroid hormone increases the risk of miscarriage (Stagnaro-Green et al. 2004; Bellver et al. 2008).

Poorly controlled diabetes mellitus causes hyperglycemia, maternal vascular disease, and adverse autoimmune factors. High values of hemoglobin A1C (values above 8%) increase the incidence of congenital fetal malformations and the frequency of miscarriage (Ylinen et al. 1984). Women with well-controlled blood sugars are not at an increased risk of spontaneous abortion (Mills et al. 1988).

Women diagnosed with polycystic ovarian syndrome (PCOS) have a higher miscarriage rate compared to the general population (20–40% vs. 10–20%) (Glueck et al. 2002). PCOS is known to be caused by sex hormone abnormalities leading to premature or delayed ovulation, poor endometrial receptivity, and disturbances in synthesis, secretion, and action of prostaglandins and ovarian growth factors. Serum luteinizing hormone levels, testosterone levels, and androstenedione concentrations are all elevated, causing adverse effects on the endometrium. Pregnancy loss is increased as a result of alterations in these hormone levels (Rai et al. 2000).

Normal levels of prolactin aid in maintaining early pregnancy and women with high circulating prolactin levels have higher rate of recurrent miscarriages. Hyperprolactinemia may cause alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation (Hirahara et al. 1998).

Successful implantation and maintenance of pregnancy requires progesterone (Practice Committee 2015). A possible but unproven cause of impaired progesterone production is a defect in corpus luteum function, also known as luteal phase defect, which leads to failure of development of a fully mature secretory endometrium (Practice Committee to ASRM 2015). Altered levels of progesterone may cause spontaneous abortions. Several underlying conditions including high prolactin levels and abnormal thyroid function may lead to diminished levels of progesterone (Daya et al. 1988).

2.6 Infectious Factors

Many pathogens including *Listeria monocytogenes*, *Toxoplasma gondii*, *Chlamydia trachomatis*, Ureaplasma *urealyticum*, *Mycoplasma hominis*, *Cytomegalovirus*, and herpesvirus among others may lead to sporadic miscarriages. However, there is no evidence proving that infections with these agents lead to recurrent pregnancy loss (Matovina et al. 2004). It is possible that an active infection may destabilize the balance of tolerance and rejection mentioned earlier in early pregnancy. That imbalance may cause multiple pregnancy losses in the form of rejections.

2.7 Male Factors

Sperm aneuploidy and DNA fragmentation are the main abnormalities found in sperm. Abnormal DNA fragmentation is present with advanced

paternal age and exposure to certain environmental factors (exogenous heat, varicoceles, increased reactive oxygen species in semen, and toxic exposures). However, cytogenetically abnormal sperm may be selected against during fertilization through routine conception (Gopalkrishnan et al. 2000).

2.8 Lifestyle, Environmental, and Chemical Factors

Cigarette smoking, obesity, alcohol consumption, illicit drug use, and caffeine intake have been associated with miscarriages. These factors seem to relate to pregnancy loss in a dose-dependent fashion. Smoking in particular has an adverse effect on trophoblastic function. Chemicals including anesthetic gases, arsenic, aniline dyes, benzene, ethylene oxide, formaldehyde, pesticides, lead, mercury, and cadmium are associated with sporadic spontaneous pregnancy loss (Christiansen et al. 2005).

3 Evaluation

Since spontaneous miscarriage can be a common, sporadic event, evaluation of patients for recurrent pregnancy loss should be initiated after two consecutive miscarriages or one second trimester loss. Evaluation must begin with a detailed history and physical examination with detailed description of all medical conditions, previous surgeries, and genetic and family disorders. Details of each previous pregnancy such as gestational age and isolated characteristics must be evaluated in addition to constructing a three-generation pedigree to identify possible heritable traits. Physical examination should be comprehensive with attention to pelvic organ abnormalities and signs of endocrinopathies (Christiansen et al. 2005). Due to the increased association of chromosomal abnormalities and miscarriage, some have argued that RPL evaluation should be selective rather than universal and only performed if the products of conception of the second miscarriage were euploid. Changes toward use of selective RPL evaluation seem to have more cost savings compared to universal evaluation (Foyouzi et al. 2012).

3.1 Genetic Assessment

In addition to obtaining a detailed history with a three-generation pedigree, karyotyping of couples is part of the evaluation for RPL. Parental karyotypes detect translocations or mosaic patterns that might be passed down to the fetus. Major chromosomal abnormalities are five to six times more likely to be detected in couples experiencing recurrent pregnancy loss than in the general population. Once identified as having a structural chromosomal rearrangement, affected couples may consider the option of assisted reproductive technologies with preimplantation genetic testing. Preimplantation genetic diagnosis (PGD) for specific translocations and then transfer of unaffected embryos or the use of donor gametes result in successful pregnancies in the absence of other identifiable cause of RPL.

Chromosomal analysis of the products of conception is of significant clinical value despite not being part of the initial RPL workup. An abnormal fetal karyotype may give psychological alleviation to the experiencing couple as the identifiable cause of the sporadic abortion. Normal karyotype in the products of conception may suggest maternal environmental factor as the cause of the spontaneous abortion. The possibility of maternal tissue contamination is present if cytogenetic analysis (G-banding karyotype) yields 46,XX karyotype. In these situations, reflex DNA extraction and microsatellite analysis of maternal blood can differentiate fetal versus maternal DNA, whereas SNP microarray technology is able to differentiate maternal versus fetal DNA in the products of conception. If karyotyping is not available, placental histology identifying trophoblast inclusions suggests genetic defects (De Braekeleer et al. 1990).

3.2 Thrombophilia Assessment

Inherited thrombophilias might be the cause of recurrent pregnancy loss, especially with evidence of placental ischemia and infarction and maternal vessel thrombosis. Screening for factor V Leiden, prothrombin gene mutations, and other

thrombophilias is justified with a positive personal history of venous thromboembolism or first-degree relative with high-risk thrombophilia (Practice Committee of ASRM 2012). If confirmed with thrombophilia, anticoagulant therapy with unfractionated heparin or low-molecular-weight heparin may be started immediately after conception.

Acquired thrombophilias such as antiphospholipid antibodies syndrome has a strong correlation with RPL as discussed earlier. The diagnosis is made on the basis of clinical vascular thrombosis or pregnancy morbidity along with laboratory findings of anticardiolipin antibody (IgG and IgM) and lupus anticoagulant (Table 1.). Serum tests for anticardiolipin antibody and lupus anticoagulant should be repeated 6–8 weeks apart to ensure no false-positive values due to viral illnesses. Lupus anticoagulant is detected based on an activated partial thromboplastin time, kaolin plasma clotting time, or dilute Russell viper venom test time. Standard treatment of patients diagnosed with APS consists of low-dose aspirin and heparin.

3.3 Anatomic Assessment

Müllerian anomalies are typically detected using sonohysterography and hysterosalpingography (HSG). Both methods provide additional information compared to sonography alone. Sonohysterograms delineate the internal contours of the uterine cavity while also providing visualization of the outer wall of the uterus. Additionally, sonohysterogram can distinguish between a septate and bicornuate uterus (Keltz et al. 1997). Hysterosalpingograms provide detailed information about the tubal anatomy and patency, similar to the sonohysterogram. However, an HSG cannot evaluate the outer contour of the uterus. In the recent years, the emergence of the three-dimensional ultrasound has proven to be an excellent noninvasive method for evaluating anatomic anomalies. In a comparison performed by Jerkovic and colleagues, the use of three-dimensional ultrasound identified the same congenital anomalies compared to hysterosalpingography (Jurkovic et al. 1995). Szkodziak and colleagues further concluded that three-dimensional transvaginal ultrasound might become the optimal method to diagnose uterine anomalies (Szkodziak et al. 2014). Detailed characterization of uterine defect may be identified with the use of magnetic resonance imaging (MRI), which allows for visualization of both uterine cavity and the external contour of the uterus, thus distinguishing septate from bicornuate uteri (Soares et al. 2000). Hysteroscopy and laparoscopy provide direct visualization of uterine anomalies with the additional benefit of correcting these anomalies as they are diagnosed, however both procedure are invasive compared with the aforementioned modalities. Hysteroscopy remains the gold standard for diagnosing and treating intrauterine lesions that may hinder embryo implantation.

3.4 Endocrine Assessment

Maternal endocrine disorders are usually routinely evaluated. Screening women for thyroid dysfunction is reasonable due to emerging associations with increased miscarriage risks and thyroid abnormalities. In the presence of elevated thyroid stimulating hormone (TSH) levels above 2.5 mIU/L, screening for antithyroid antibodies should be performed (Negro et al. 2010).

The presence of thyroid peroxidase (TPO) autoantibodies and anti-thyroglobulin antibodies increases the spontaneous miscarriage risk two to three times higher than those without these antibodies (even in euthyroid women). Recommendations for levothyroxine use toward treating patients with euthyroid or subclinical hypothyroid states and positive antithyroid antibodies are being favored (Thangaratinam et al. 2011).

Prolactin is another hormone routinely measured during the initial workup for recurrent pregnancy loss along with ovulatory dysfunction. If hyperprolactinemia is diagnosed, underlying cause such as a prolactinoma should be evaluated. Treatment with a dopamine agonist (bromocriptine) to normalize prolactin levels improves

pregnancy outcomes in those with recurrent pregnancy loss. Elevated prolactin may also result in a short luteal phase, diagnosed as luteal phase defect. In the past, endometrial biopsy (EMB) was used to diagnose luteal phase defect; however, histology is not reproducible, and thus EMB is no longer recommended for diagnosis. In those with suspected luteal phase defect, progesterone supplementation is beneficial with a history of three or more consecutive pregnancy losses.

4 Management

Although most therapeutic recommendations are based on clinical experience and data from observational studies, prognosis for successful future pregnancy is good. Goal of treatment depends on the underlying cause of RPL. Regardless of intervention, emotional support is important and, at times, will enhance therapeutic success.

4.1 Karyotype Abnormalities

The first step after diagnosis of chromosomal abnormalities of either parental or fetal origin is genetic counseling. The probability of future chromosomally normal and abnormal conception in addition to carriers of the chromosomal defect should be discussed. The magnitude of each specific chromosomal abnormality varies.

Prenatal genetic studies, including amniocentesis, chorionic villus sampling, and preimplantation genetic testing, all of which can determine fetal karyotype, however, cannot exclude the possibility of certain microdeletions. In vitro fertilization with preimplantation genetic diagnosis (PGD) can be used to transfer unaffected embryos. This treatment modality improves pregnancy outcome for translocation carriers with a history of RPL (Otani et al. 2006). If maternal or paternal chromosomal abnormalities are present, conception of an affected embryo can be bypassed using gamete donation, surrogacy, or adoption. This method of treatment depends on parental preference.

4.2 Thrombophilia

Aspirin given with heparin appears to improve pregnancy outcome in women with antiphospholipid syndrome. Current recommendations are to begin low-dose aspirin when conception is attempted and add prophylactic dose of unfractionated heparin or low-molecular-weight heparin once intrauterine pregnancy is confirmed. Anticoagulation improves maternal outcome in those with certain inherited thrombophilias up to 80% (Bates et al. 2012). However, those with thrombophilias still have an increased risk of complications relating to the pregnancy including preterm birth, preeclampsia, and fetal growth restriction.

4.3 Anatomic Abnormalities

Surgery is the best option for uterine abnormalities that are treatable (uterine septum, intrauterine adhesions, submucosal myoma). Several studies showed improved live birth rates in those surgically treated for the presence of a uterine septum, most easily done hysteroscopically. Performing a hysteroscopic metroplasty can double the incidence of live birth rate (Mollo et al. 2009). For women with irreparable uterine defects, a gestational carrier is an alternative option.

4.4 Endocrine Abnormalities

Women with elevated serum thyroid peroxidase antibody concentrations have higher rates of spontaneous abortion as mentioned earlier. These patients have higher risks of developing hypothyroidism in the first trimester and autoimmune thyroiditis during the postpartum period. Therapy with levothyroxine in euthyroid women with high TPO antibodies may reduce the risk of miscarriage from 13.8% to 3.5% (Negro et al. 2006). Diabetic women with poor glycemic control have a higher incidence of miscarriage than those with tight control. It is thus recommended to achieve a normal glycemic in diabetic patients with RPL.

Prolactin levels during early pregnancy are significantly higher in those with recurrent

miscarriage compared to the general population. In one study, 64 women with RPL and hyperprolactinemia who were randomized to treatment with bromocriptine or no bromocriptine, those receiving the dopamine agonist, had higher rates of successful pregnancy (82% vs. 52%) (Hirahara et al. 1998). Bromocriptine is thus recommended as treatment for RPL in women with hyperprolactinemia.

5 Conclusion

Recurrent pregnancy loss can be an emotional and physically traumatic occurrence. Many women suffer from feelings of guilt and self-blame, which may persist in subsequent pregnancies. The majority of miscarriages are due to abnormalities in chromosome numbers. Uterine anomalies, endocrine dysfunction, immunologic disease, thrombophilic disorders, and environmental factors are the remaining causes of pregnancy loss. A full workup for recurrent pregnancy loss is warranted after two miscarriages or one second trimester loss. Emerging reports suggest that a full RPL workup should be obtained only if the second miscarriage is chromosomally euploid; however, further research is needed before this approach becomes routinely adopted (Foyouzi et al. 2012). Although many times a specific cause of the pregnancy loss goes unknown, successful treatment and resulting pregnancies lead to patient satisfaction and overwhelming gratitude.

6 Cross-References

- Basic Management of Infertility
- Management of Recurrent Pregnancy Loss
- Workup and Management of Polycystic Ovary Syndrome

References

Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice duidelines. Chest. 2012;141:e691S.

Bellver J, Soares SR, Alvarez C, et al. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Hum Reprod. 2008;23:278.

Christiansen OB, Nybo Andersen AM, Bosch E, et al. Evidence-based investigations and treatments of recurrent pregnancy loss. Fertil Steril. 2005;83:821.

ACOG practice bulletin. Management of recurrent pregnancy loss. Number 24, February 2001, (Replaces Technical Bulletin Number 212, September 1995). American College of Obstetricians and Gynecologists.

Daya S, Ward S, Burrows E. Progesterone profiles in luteal phase defect cycles and outcome of progesterone treatment in patients with recurrent spontaneous abortion. Am J Obstet Gynecol. 1988;158:225.

De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. Hum Reprod. 1990;5:519.

Devi Wold AS, Pham N, Arici A. Anatomic factors in recurrent pregnancy loss. Semin Reprod Med. 2006;24:25.

Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. Hum Reprod. 2002;17:1399.

Foyouzi N, Huddleston HG, Cedars MI. Cost-effectiveness of cytogenetic evaluation of products of conception in the patient with a second pregnancy loss. Fertil Steril. 2012;98:1.

Franssen MT, Korevaar JC, Leschot NJ, et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. BMJ. 2005;331:137.

Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod. 2002;17:2858.

Goddijn M, Joosten JH, Knegt AC, et al. Clinical relevance of diagnosing structural chromosome abnormalities in couples with repeated miscarriage. Hum Reprod. 2004;19:1013.

Gopalkrishnan K, Padwal V, Meherji PK, et al. Poor quality of sperm as it affects repeated early pregnancy loss. Arch Androl. 2000;45:111.

Hatasaka HH. Recurrent miscarriage: epidemiologic factors, definitions, and incidence. Clin Obstet Gynecol. 1994;37:625.

Hill JA, Choi BC. Maternal immunological aspects of pregnancy success and failure. J Reprod Fertil Suppl. 2000;55:91–7. Review.

Hirahara F, Andoh N, Sawai K, et al. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril. 1998;70:246.

Homer HA, Li TC, Cook ID. The septate uterus: a review of management and reproductive outcome. Fertil Steril. 2000;73(1):1–14. Review.

Jurkovic D, Geipel A, Gruboeck K, Jauniaux E, Natucci M, Campbell S. Three-dimensional ultrasound for the assessment of uterine anatomy and detection of

congenital anomalies: a comparison with hysterosalpingography and two-dimensional sonography. Ultrasound Obstet Gynecol. 1995;5(4):233–7.
Keltz MD, Olive DL, Kim AH, Arici A. Sonohysterography for screening in recurrent pregnancy loss. Fertil Steril. 1997;67:670.
Kolte AM, Bernardi LA, Christiansen OB, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod. 2015;30:495.
Laude I, Rongières-Bertrand C, Boyer-Neumann C, et al. Circulating procoagulant microparticles in women with unexplained pregnancy loss: a new insight. Thromb Haemost. 2001;85:18.
Matovina M, Husnjak K, Milutin N, et al. Possible role of bacterial and viral infections in miscarriages. Fertil Steril. 2004;81:662.
Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med. 1988;319:1617.
Mollo A, De Franciscis P, Colacurci N, et al. Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertil Steril. 2009;91:2628.
Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006;91:2587.
Negro R, Schwartz A, Gismondi R, et al. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab. 2010;95: E44.
Nybo Andersen AM, Wohlfahrt J, Christens P, et al. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320:1708.
Otani T, Roche M, Mizuike M, et al. Preimplantation genetic diagnosis significantly improves the pregnancy outcome of translocation carriers with a history of recurrent miscarriage and unsuccessful pregnancies. Reprod Biomed Online. 2006;13:869.
Pabuçcu R, Atay V, Orhon E, et al. Hysteroscopic treatment of intrauterine adhesions is safe and effective in the restoration of normal menstruation and fertility. Fertil Steril. 1997;68:1141.
Parke AL, Wilson D, Maier D. The prevalence of antiphospholipid antibodies in women with recurrent spontaneous abortion, women with successful pregnancies, and women who have never been pregnant. Arthritis Rheum. 1991;34:1231.
Practice Committee of American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013;99:63.
Practice Committee of American Society of Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98:05.
Practice Committee of the American Society for Reproductive Medicine. Current clinical irrelevance of luteal phase deficiency: a committee opinion. Fertil Steril. 2015;103:e27.
Rai R, Backos M, Rushworth F, Regan L. Polycystic ovaries and recurrent miscarriage – a reappraisal. Hum Reprod. 2000;15:612.
Simpson JL. Causes of fetal wastage. Clin Obstet Gynecol. 2007;50:10.
Soares SR, Barbosa dos Reis MM, Camargos AF. Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography in patients with uterine cavity diseases. Fertil Steril. 2000;73:406.
Sotiriadis A, Makrigiannakis A, Stefos T, et al. Fibrinolytic defects and recurrent miscarriage: a systematic review and meta-analysis. Obstet Gynecol. 2007;109:1146.
Stagnaro-Green A, Glinoer D. Thyroid autoimmunity and the risk of miscarriage. Best Pract Res Clin Endocrinol Metab. 2004;18:167.
Stirrat GM. Recurrent miscarriage. Lancet. 1990;336:673.
Szkodziak P, Wozniak S, Czuczwar P, Paszkowski T, Milart P, Wozniakowska E, Szlichtyng W. Usefulness of three dimensional transvaginal ultrasonography and hysterosalpingography in diagnosing uterine anomalies. Ginekol Pol 2014;85(5):354–9.
Thangaratinam S, Tan A, Knox E, et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ. 2011;342:d2616.
Tong M, Viall CA, Chamley LW. Antiphospholipid antibodies and the placenta: a systematic review of their in vitro effects and modulation by treatment. Hum Reprod Update. 2015;21:97.
Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med. 1988;319:189.
Ylinen K, Aula P, Stenman UH, et al. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. Br Med J (Clin Res Ed). 1984;289:345.