Medical Coverage Policy

Effective Date..... 2/15/2020
Next Review Date..... 2/15/2021
Coverage Policy Number 0284

Recurrent Pregnancy Loss: Diagnosis and Treatment

Table of Contents

Related Coverage Resources

Comparative Genomic Hybridization (CGH)/Chromosomal Microarray Analysis (CMA) for Autism Spectrum Disorders, Developmental Delay, Intellectual Disability and Congenital Anomalies
Genetic Counseling
Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis
Hydroxyprogesterone Caproate Injection
Immune Globulin
Infertility Services

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses recurrent pregnancy loss. Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA), is a heterogeneous condition and may result from several underlying factors, such as anatomic, hormonal, thrombotic, autoimmune, alloimmune, genetic or infectious causes.

Coverage Policy

For information regarding coverage for intravenous immunoglobulin therapy (IVIg, IGIV) for the treatment of recurrent spontaneous abortion, refer to the Cigna Drug and Biologic Coverage Policy Immune Globulin. For information regarding coverage for parental preimplantation genetic diagnosis, chromosomal abnormalities, karyotyping, molecular cytogenetics, and other genetic related conditions,

please reference Cigna Coverage Policy: **Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis**.

Please refer to the applicable pharmacy benefit to determine benefit availability and the terms and conditions of coverage for medications for recurrent pregnancy loss.

Diagnostic Testing

The following tests are considered medically necessary for the evaluation of recurrent pregnancy loss (i.e., two or more consecutive pregnancy losses):

- anticardiolipin antibody detection (IgG, IgM) using standard assays
- anti-β2-glycoprotein I of IgG and/or IgM isotype (serum or plasma)
- testing for uncontrolled diabetes
- endometrial biopsy
- hysterosalpingography
- hysteroscopy
- lupus anticoagulant detection using standard assays
- pelvic ultrasound
- saline infusion sonohysterography/hysterosalpingography

Each of the following diagnostic tests for recurrent pregnancy loss is considered experimental, investigational or unproven:

- antibodies to phosphatidylserine, phosphatidylethanolamine or phospholipids other than anticardiolipin or lupus anticoagulant
- antiovarian antibodies
- antithrombin III, protein C or protein S deficiency testing using standard assays
- antinuclear antibody (ANA) titers
- antiprothrombin (phospholipid cofactor) antibody, each Ig class
- embryotoxicity assay (ETA)
- homocysteine levels
- inhibin B
- lymphocytotoxicity assay
- maternal antipaternal cytotoxic antibodies
- mixed lymphocyte culture reactivity
- natural killer (NK) cell testing
- paternal human leukocytic antigen (HLA) testing
- peroxisome proliferator activation receptor (PPARs) and cytokine tumor necrosis factor-α (TNFα) in placenta tissues
- testing for maternal antileukocytic antibodies
- testing for maternal serum blocker
- TORCH panel (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus)

Treatment

The following treatments are considered medically necessary for recurrent pregnancy loss:

- administration of low-dose heparin and aspirin as a treatment for clearly established antiphospholipid syndrome
- antenatal transvaginal cervical cerclage
- antenatal transabdominal cervical cerclage for an individual with a prior failed or contraindication to transvaginal cerclage

- surgical treatment of structural uterine abnormalities

Each of the following interventions is considered experimental, investigational or unproven for the treatment of recurrent pregnancy loss:

- intravenous immune globulin (IVIG)
- intralipid infusion
- paternal cell immunization/paternal leukocyte immunization
- third-party donor leukocytes
- trophoblast membrane infusion
- prophylactic cervical cerclage (e.g., transvaginal, transabdominal) performed on a non-pregnant woman

General Background

According to the American Society for Reproductive Medicine (ASRM), pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination. Miscarriage is defined as spontaneous loss of pregnancy before the fetus reaches viability (i.e., 24 weeks gestation) (Royal College of Obstetricians and Gynaecologists [RCOG], 2017). Early pregnancy loss generally occurs prior to 20 weeks gestation. Sporadic pregnancy loss is nonconsecutive pregnancy loss that occurs randomly during a woman's reproductive years. Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA) or recurrent miscarriage, is defined as two or more failed pregnancies (ASRM, 2008; 2013) and may affect as many as 1–3% of childbearing women.

The need for formal assessment and testing for recurrent pregnancy loss varies among individuals depending on age and personal choice, although traditionally couples are offered evaluation after three losses (Simpson, Jauniaux, 2012). Infertile couples who are in their fourth decade (i.e., age ≥40) may elect to be evaluated after two losses.

Potential Causes of Recurrent Pregnancy Loss
Recurrent pregnancy loss is a heterogeneous condition and may result from several underlying factors, such as anatomic, hormonal, thrombotic, autoimmune, alloimmune, genetic, infectious or other unknown causes. The following conditions may be associated with recurrent pregnancy loss:

- parental chromosomal anomalies and genetic disorders
- autoimmune disorders (e.g., antiphospholipid syndrome, systemic lupus erythematosus)
- alloimmune disorders
- structural uterine anomalies (e.g., bicornuate uterus, uterine septum, fibroids, intrauterine adhesions)
- cervical incompetence
- endocrine disorders (e.g., polycystic ovarian disease, luteal phase defect, thyroid disease)
- prothrombotic states (e.g., antithrombin III deficiency, protein C or protein S deficiency/resistance, thrombocythaemia, factor V Leiden)
- infectious diseases
- embryotoxicity

Parental Chromosomal Abnormalities: Structural chromosomal abnormalities are generally accepted as possible causes of RSA; balanced translocations are the most common abnormality in which there are either duplications or deficiencies of chromosome segments. Chromosome inversions account for a small percentage of abnormalities. Analysis suggests that aneuploidy (i.e., an incomplete set of chromosomes) is very common in recurrent miscarriage.

Karyotyping: Karyotyping is a type of cytogenetic test commonly used for chromosome analysis to detect aneuploidy and displays the arrangement of chromosome pairs. In general, the utility of cytogenetic analysis of the products of conception (e.g., chorionic villus, fetal membranes, fetal tissues) has been debated, as some conditions resulting in RSA may occur spontaneously. The American College of Obstetricians and Gynecologists (ACOG) (2001) suggest that published evidence is lacking and there are no definite recommendations for

routinely obtaining abortus karyotypes. However, karyotype analysis of abortus tissue for couples with a subsequent second or third pregnancy loss has been recommended (Wolf, Horger, 1995; Hogge, et al., 2003; RCOG, 2017). This recommendation is based on the premise that if the abortus tissue is aneuploid, the physician and patient may then conclude that maternal cause is excluded (ACOG, 2001). Karyotpying of the products of conception (e.g., chorionic villus, fetal membranes, fetal tissues) and examinations of parental blood to detect balanced chromosome rearrangement (e.g., translocation, inversion) is supported by professional specialty organizations and have been found to be helpful in predicting future recurrences of chromosome abnormalities.

Molecular Cytogenetics: Another method of cytogenetic chromosomal analysis involves molecular techniques for studying chromosomes such as fluorescence in situ hybridization (FISH) and comparative array genomic hybridization-type (CGH) studies. FISH is well established and is a commonly used test utilizing a fluorescent dye to label deoxyribonucleic acid (DNA) and view the chromosomes. FISH is limited however in that it can only test a subset of chromosomes and is not useful for detecting all aneuploidies. Microarray analysis (CMA), using CGH or single-nucleotide polymorphism (SNP), has also been used in the prenatal setting. Comparative genomic hybridization (CGH) is a type of technology that allows the expression and analysis of numerous genes and may be referred to as gene expression profiling. SNP, another type of microarray analysis, is a DNA sequence variation where a single nucleotide in the genome sequence may be changed, which may or may not be pathogenic (ACOG, 2013). Both forms of testing detect copy number variants, identifying different types of genetic variations. In comparison with traditional karyotyping, these advanced molecular techniques are thought to provide more specific results and may assist with identifying more subtle abnormalities. CGH is sometimes used as an additional diagnostic test for a known genetic syndrome when conventional testing is negative. Various types of microarray analysis tests are available, some of which include comparison of parental genomic information.

Autoimmune Disorders: Pregnancy loss is common among women with systemic lupus erythematosus (SLE). Most women with SLE also have elevated levels of antiphospholipid (aPL) antibodies. Treatment for women with SLE and aPL antibodies is similar to treatment for antiphospholipid syndrome.

Antiphospholipid Syndrome: Antiphospholipid (aPL) syndrome is characterized by moderate-to-high levels of aPLs and other clinical features, including recurrent pregnancy loss, fetal death, and thrombosis. The aPL antibodies are a group of antibodies directed against phospholipids or phospholipid binding proteins. The aPL antibodies specifically are associated with recurrent pregnancy loss, preeclampsia, intrauterine growth retardation, premature labor and placental abruption. Commonly used tests for testing of aPLs that have established assays are those for anticardiolipin, lupus anticoagulant and anti-B2 glycoprotein I (ASRM, 2012; ACOG, 2011). The effects of aPL antibodies on pregnancy are significant: Prospective fetal losses rise from 25–34% in the absence of aPL to 90% in cases of untreated aPL (Bose, et al., 2004). Most experts recognize aPL syndrome as a treatable cause of recurrent pregnancy loss. Administration of maternal heparin or low molecular weight (LMW) heparin, with or without low-dose aspirin, is the treatment of choice. Unfractionated heparin and aspirin may also reduce pregnancy loss (Empson, et al., 2005).

Other Antigens: Studies have supported relationships between autoantibodies and other phospholipid antigens, such as phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidyl-ethanolamine, and phosphatidic acid, including antiprothrombin antibodies, although their clinical implications are not well-defined. Clinical studies are limited, and there is concern regarding technical aspects of the assays and selection of controls. Due to controversial data, testing involving other than lupus anticoagulant and anticardiolipin assays is not recommended (ACOG, 2001; Fausett, 2002; RCOG, 2017).

Some women with recurrent pregnancy loss have detectable antinuclear antibodies (ANAs). The ANA test is a screening tool for many immunological conditions, although the antibodies may be present in the normal population. According to RCOG (2017), the presence of ANAs has no effect on pregnancy outcome. Clinical studies do not support improved outcomes with treatment for positive ANA titers (Laskin, et al., 1997; ACOG, 2001; Fausett, 2002). Therefore, current scientific data do not support testing of ANA titers for recurrent pregnancy loss.

Alloimmune Disorders: It has been hypothesized that RSA is related to an alloimmune disorder that prevents the mother from developing an immune response that will protect the developing fetus from immune rejection. Controversy exists regarding the roles of parental human leukocyte antigen (HLA) sharing; maternal antibodies to paternal leukocytes; maternal embryotoxic antibodies; antisperm antibodies; the production of serum blocking factor by the female partner; and natural killer cell assays. The available evidence is not sufficient to permit valid, consistent conclusions regarding testing, efficacy of treatment or improved pregnancy outcomes (ACOG, 2001).

Additionally, the diagnostic value of testing for other immunologic-mediated causes of RSA such as lymphocytotoxic antibodies against paternal cells (antipaternal antibodies), mixed lymphocyte cultures for the detection of blocking antibodies, testing for peroxisome proliferator activation receptor (PPARs) and cytokine tumor necrosis factor-α (TNFα) in placenta tissues, and antiovarian antibody testing, has not been supported in the peer-reviewed published scientific literature.

Several methods of inducing immunity have been investigated and include immunotherapy from white blood cells from the woman's partner or donor (e.g., paternal leukocyte immunotherapy, third-party donor leukocyte), products derived from early embryos (e.g., trophoblast membrane infusions), or antibodies derived from blood (e.g., intravenous immunoglobulin [IVIg]). Evidence in the published, peer-reviewed scientific literature and professional society recommendations suggests that these treatments do not provide significant beneficial effect over placebo in preventing miscarriages and therefore remain unproven therapies (ACOG, 2001; RCOG, 2017; Price, et al., 2005). Additionally, the authors of a Cochrane review of 20 randomized trials (Porter, et al., 2006; Wong, et al., 2014) indicated there was no improvement in live births when either paternal cell immunization, intravenous immune globulin, or other immunotherapy regimens were utilized.

Intervention employing IVIg is suggested for individuals with antiphospholipid syndrome who have failed anticoagulant therapy, as well as for recurrent pregnancy loss as a result of autoimmune or alloimune factors. Typically, IVIg therapy is aimed at providing passive immunity to alter the immune response by increasing an individual's antibody titer and antigen-antibody reaction potential. IVIg contains immunomodulating peptides, antibodies against most exogenous antigens, many normal human proteins, and fragment, the antigen-binding region of autoantibodies (Fab). Data evaluating IVIg is limited, and significant differences between treatment and placebo groups have not been consistently demonstrated in the published scientific literature. The results of an early randomized trial (Ober, et al., 1999) did not demonstrate improvement in pregnancy outcome as a result of paternal immunization. Per the FDA's Center for Biologics Evaluation and Research (CBER), leukocyte immune therapy in humans as therapy for recurrent miscarriage can only be performed as part of clinical investigations and then only if an Investigational New Drug (IND) application is in effect (CBER 013002, 2002). For information regarding coverage for intravenous immunoglobulin therapy (IVIg, IGIV) for the treatment of recurrent spontaneous abortion, refer to the Cigna Drug and Biologic Coverage Policy Immune Globulin.

Intralipid infusions are administered as a source of fat/calories for individuals who require parenteral nutrition. More recently, intralipid infusion has been investigated as an alternative to IVIg for treatment of women experiencing recurrent pregnancy loss and who have an abnormal uterine natural killer (NK) cell level. Some researchers hypothesize the administration of intravenous lipids may enhance implantation and maintenance of pregnancy when NK cells are elevated by reducing the NK cell levels and endometrial immune activity. Although studies are currently underway, at present evidence in the peer-reviewed published scientific literature evaluating the efficacy of intralipid infusion for treatment of recurrent pregnancy loss is limited primarily to animal studies and published reviews with few retrospective or prospective human trials (Toth, et al., 2014; Bansal, et al., 2012; Coulam and Acaio, 2012; Martini, et al., 2018). Randomized controlled clinical trials are lacking. As a result, strong evidence based conclusions cannot be made at this time regarding safety, efficacy, and the clinical benefit of improved pregnancy and live birth rates.

Structural Uterine Abnormalities: Structural uterine abnormalities such as intrauterine adhesions, septum formation, and fibroids can interfere with implantation and early pregnancy during the first or second trimester. Most often, abnormalities that are congenital are associated with second trimester loss. Adhesions may result from such factors as intrauterine surgery, endometritis, and previous dilation and curettage. If adhesions are suspected, then appropriate treatment consists of lysis of adhesions under hysteroscopy. Incomplete Mullerian fusion (i.e., septate uteri) most often results in second trimester losses and complications but may result in some first trimester losses due to poor implantation. Fibroid uterus, primarily submucus, may also lead to spontaneous

abortion. Researchers theorize that pregnancy loss results from thinning of the endometrium over the fibroid, rapid fibroid growth caused by the hormones of pregnancy, and/or lack of space for the developing fetus. Diagnostic studies typically include hysteroscopy, hysterosalpingography (i.e., radio opaque dye), or saline infusion sonohysterography (i.e., saline infusion combined with ultrasound assessment). In some cases, surgical intervention may be warranted to correct the abnormality.

Cervical Incompetence: Cervical incompetence may be due to previous trauma, shortened cervical length, or a congenital weakness of the cervix. It usually results in pregnancy loss during the second trimester, at 16–18 weeks' gestation. The cervix is dilated and effaced, leading to early pregnancy loss. Repeated miscarriage due to cervical incompetence can sometimes be prevented by performing a cerclage. The insertion of the cervical stitch varies depending on whether it is elective, urgent or emergent. According to the ACOG practice bulletin, elective cerclage should be performed at 13 to 16 weeks of gestation after ultrasound evaluation has demonstrated the presence of a live fetus with no apparent anomalies (ACOG, 2003, reaffirmed 2008). The cerclage is most often performed through a transvaginal approach; however, the procedure may be performed through a transabdominal approach. Transabdominal approach may be recommended for women who have failed vaginal cerclage or for women who have short, scarred cervices that may make cerclage difficult (Gabbe, 2012; Alfirevic, et al., 2017). Cerclage performed in a non–pregnant individual has been described in the literature however the data is insufficient to allow evidence-based conclusions regarding safety and efficacy. In addition, ACOG (2003/2008) does not support scheduled early or first-trimester cerclage in patients with suspicious clinical history.

Polycystic Ovarian Syndrome (PCO): Repeated pregnancy losses may also be attributed to endocrine disorders (Toth, et al., 2010; Kalro, 2003). Polycystic ovarian (PCO) syndrome is a condition in which there is elevation of leutenizing hormone (LH) in the follicular phase of the menstrual cycle. Studies have shown that recurrent spontaneous abortion has a higher than average incidence in women with PCO. The exact mechanism has not been determined, but authors report it may be due to a direct effect on the ovaries, causing premature aging of the oocyte, or perhaps a direct effect on the endometrium, adversely effecting implantation. Evidence in the scientific literature is inconsistent and does not provide strong conclusions to support that suppression of elevated LH levels improves pregnancy rates. Nonetheless, while the cause of miscarriage in women with elevated LH is poorly understood, treatment involving LH suppression may be considered a viable option for some women.

Luteal Phase Defects (LPDs): Progesterone is the hormone responsible for preparing the endometrium for implantation. Luteal phase defect is a term used to describe an endometrium that lacks adequate progesterone effect. Progesterone secreted by the corpus luteum is required to support the endometrium until the trophoblast produces sufficient progesterone to maintain the pregnancy.

Although LPD was historically thought to be a cause of RSA clinical outcomes from published studies have generated controversy regarding that theory. Haas et al. (2018) reported on an updated Cochrane review to assess the efficacy and safety of progestogens as a preventative therapy against recurrent miscarriage. The study included 12 randomized or quasi-randomized controlled trials that compared progestogens with placebo or no treatment given in an effort to prevent miscarriage. In five trials women had had three or more consecutive miscarriages and in seven trials women had suffered two or more consecutive miscarriages. Routes, dosage and duration of progestogen treatment varied across the trials. Ten trials (1684 women) contributed data to the analyses. The meta-analysis of all women, suggests that there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 1.00, 10 trials, 1684 women, moderate-quality evidence). A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials, trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences between subgroups for miscarriage. The authors concluded that for women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in subsequent pregnancies.

Despite inconsistent evidence reported in the literature, treatment with progesterone supplements and human chorionic gonadotropin hormones is often employed as a method of attempting to prevent miscarriage. In

addition, some clinical studies support the administration of 17-alpha-hydroxyprogesterone in preventing preterm delivery (Meis, et al., 2003).

Thyroid Disease: There is inconclusive evidence regarding thyroid dysfunction as a cause of RSA. Antithyroid antibodies and mild thyroid disease have been associated with recurrent spontaneous abortions in some studies, while the connection has been refuted in others. Decreased pregnancy rates and increased fetal losses have been associated with hypo- and hyperthyroidism (Tulandi, 2019; Gabbe, 2002). It is believed that high titers of the antibodies result in thyroid dysfunction, but the association of antithyroid antibodies and recurrent pregnancy loss is not clear and may be related to other disorders. Professional organizations such as ACOG (2001), ASRM (2008) and the RCOG (2017) indicate there are no proven benefits for testing antithyroid antibodies for evaluation of recurrent miscarriage. While there is no strong evidence that thyroid disorders cause recurrent pregnancy loss, thyroid disorders in early pregnancy may lead to grave consequences, and therefore testing may be appropriate (Kalro, 2003).

Diabetes: The data linking diabetes to recurrent miscarriage are controversial. Although uncontrolled diabetes mellitus (e.g., symptomatic diabetes) has been associated with recurrent pregnancy loss, most of the reported data indicate similar outcomes for gestational diabetes, frank diabetes and control groups. It has been reported that metabolically controlled diabetes is not a cause of recurrent miscarriage. ACOG recommendations indicate that there is no evidence to support glucose intolerance as a cause of recurrent pregnancy loss (2001). The ASRM (2012) supports testing in the presence of uncontrolled diabetes.

Prothrombotic States: Inherited thrombophilic disorders are well-established causes of systemic thrombosis, and may be associated with an increased risk of pregnancy loss. Research shows that thrombophilic disorders are also found in 20% of women with normal pregnancies suggesting that additional risk factors may be required for complications to develop. The most common inherited thrombotic disorders are factor V Leiden and prothrombin G20210A mutation. Other, less common deficiencies include anticoagulant protein C, protein S, antithrombin III and methylene tetrahydrolfolate reductase (MTHFR) gene. The scientific literature reports inconsistent findings for supporting any association with inherited thrombophilic disorders and recurrent early pregnancy loss, although some studies have shown a relationship with late pregnancy complications. A combination of thromobophilias may further increase the risk for recurrent fetal loss (Laurino, et al., 2005), and identification of one or more of the more common thrombophilias in a woman with RSA may warrant further investigation for other risk factors. However, the probability of having a successful pregnancy outcome remains high despite the presence of thrombophilic disorders. Routine screening of all pregnant women is not recommended. Decisions on testing and prophylactic treatment for thrombophilic disorders are based on a risk/benefit assessment.

ACOG (2011; 2018) does not recommend testing for inherited thrombophilias for women with recurrent fetal loss. According to a ACOG Practice Bulletin (2018) although there may be an association in these cases, the evidence is insufficient to support that antepartal prophylaxis with unfractionated heparin or LMWH prevent recurrence. ACOG specifically notes that concerning inherited thrombophilias in pregnancy, there is no definitive causal link between inherited thrombophilias and adverse pregnancy outcomes. Most of the available studies are small case-control and cohort studies assembled in heterogeneous populations, are frequently contradictory, and display potential reporting biases. Furthermore ACOG does not recommend screening with-fasting homocysteine levels because there is a lack of association between testing results and negative pregnancy outcomes (ACOG, 2018).

The RCOG does not recommend testing for inherited thrombophilia for early pregnancy loss (RCOG, 2017). Updated guidelines for the investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage does however recommend women with second-trimester miscarriage undergo screening for inherited thrombophilias including factor V leiden, factor II (prothrombin) gene mutation, and protein S. The RCOG notes a meta-analysis of retrospective studies (Rey, et al., 2003) supports a strong association between second-trimester miscarriage and these inherited thrombophilias.

The National Society of Genetic Counselors for Recurrent Miscarriage (Laurino, et al., 2005; reaffirmed April 2010) reported that the evidence supports testing for factor V Leiden and prothrombin G20210A genotypes for RSA; that no significant association was found between protein C deficiency and recurrent pregnancy loss; and

association with protein S deficiency was questionable. Consequently, the panel does not recommend routine testing. Protein C deficiency, protein S deficiency, and antithrombin III should be reserved for those with a personal and/or family history of venous thromboembolic disease. The data for hyperhomocysteinemia are conflicting; pregnant women with and without MTHFR appear to have similar homocysteine levels, and there does not appear to be an association between MTHFR and RSA.

The American College of Chest Physicians published clinical practice guidelines for antithrombotic therapy and prevention of thrombosis. Within these guidelines the ACCP notes there is convincing evidence from clinical studies linking antiphospholipid antibodies (APLAs) with an increased risk of pregnancy loss. The ACCP recommends that for women with recurrent early pregnancy loss or unexplained late pregnancy loss screening for APLAs should be performed. Antepartal anticoagulant therapy is recommended for women with pregnancy loss who test positive for APLAs (Gordon, et al., ACCP, 2012). Although other thrombophilias, acquired and inherited, have been associated with pregnancy loss, due to uncertainties regarding the magnitude of risk, benefit of prophylaxis and effect on anxiety and well-being, the overall clinical utility of screening remains uncertain.

Information provided by The American Society for Reproductive Medicine (ASRM) states that inherited disorders which raise a woman's risk of serious blood clots, such as thrombosis, may also increase the risk for fetal death in the second half of pregnancy; however, there is no proven benefit to testing or treatment of women with thrombophilias and recurrent miscarriage in the first half of pregnancy (ASRM, 2005; revised 2008; ASRM 2012).

A Cochrane review reported that the evidence for safety and efficacy of thromboprophylaxis with aspirin and heparin for women with a history of at least two spontaneous miscarriages without apparent causes other than inherited thrombophilia. is too limited to recommend the use of anticoagulants in this setting. There is a paucity of studies evaluating efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. The two trials reviewed evaluated different treatments and only one study was placebo-controlled. Neither of the studies showed a benefit of one treatment over the other. The Cochrane group indicated that further randomized clinical trials are needed (Di Nisio et al.; 2005; Kaandorp, et al, 2009 [update]).

A consensus report and recommendation for prevention and treatment of venous thromboembolism and adverse pregnancy outcome (Duhl, et al., 2007) was published November 2007 (Pregnancy and Thrombosis Working Group). The authors acknowledged that no clear conclusions can be drawn from the studies they reviewed regarding an association between inherited thrombophilias and adverse pregnancy outcomes—some studies show a positive relationship, and other studies show no relationship. Studies addressing a possible relationship with pregnancy loss, in particular, demonstrate variable outcomes which may be related to varying definitions used for miscarriage and fetal death, varying methods of patient selection, and lack of appropriate ethnicity-matched controls. Most of the research, however, shows that antithrombin III deficiency, protein C or S deficiency, factor V Leiden, prothrombin G20210A, and MTHFR (methylene tetrahydrofolate reductase [associated with hyperhomocysteinemia]) are not typically associated with pregnancy loss prior to 10 weeks gestation and that more evidence exists suggesting that a loss after 10 weeks gestation may be associated with these disorders. Based on their findings, the panel recommended thrombophilia screening for patients with unexplained fetal loss at 20 weeks gestation or longer. The basic screening tests include factor V Leiden mutation, prothrombin G20210A mutation, protein C and S deficiencies, antithrombin III deficiency, lupus anticoagulant, homocysteine level and anticardiolipin antibodies.

Based on evidence in the published, peer-reviewed scientific literature, a practice bulletin from ACOG, and other professional specialty organizations, the clinical utility of testing for inherited thrombophilia disorders is not recommended for unexplained early recurrent pregnancy loss. Although there may be an association with pregnancy loss that occurs after the first trimester, the clinical utility of screening in this population and benefit of treatment remains unclear.

Infectious Disease: Some infectious agents, such as Listeria monocytogenes, toxoplasma gondii, rubella, herpes simplex, measles, cytomegalovirus, and coxsackievirus, may lead to infrequent RSA. The presence of bacterial vaginosis has shown some relationship to second trimester miscarriage and preterm labor. According to ACOG (2001) and RCOG (2017), the role of infection as a cause of RSA is unclear, and therefore routine testing

is not recommended. The ASRM (2012) noted there are no convincing data that infections such as ureaplasma, mycoplasma, Chlamydia and other types of pathogens result in recurrent pregnancy loss and testing for these organisms is not supported.

Embryotoxicity: Another area under investigation is the effect of positive and negative circulating embryotoxins as a cause of recurrent pregnancy loss. A sample of the patient's serum is obtained and cultured with mouse embryos. The embryos are then evaluated at 72 hours to determine embryotoxic effects (i.e., atretic embryos). Nonetheless, evidence in the published scientific literature does not support the validity of embryotoxicity assays for recurrent pregnancy loss.

Medical Management for Recurrent Pregnancy Loss
Medical management of recurrent pregnancy loss typically includes diagnosis and treatment by a reproductive endocrinologist and/or a high-risk obstetrician/gynecologist. Genetic counseling concerning the potential for successful pregnancy without treatment, in addition to a discussion of the uncertainties of diagnostic and treatment options and their safety and efficacy, may also be appropriate. Tests that are usually performed to determine the cause of RSA include blood testing for chromosome abnormalities, hormonal problems, and immune system abnormalities; karyotype analysis of the products of conception if available; ultrasound examination of the uterus; hysteroscopy; hysterosalpingography; and endometrial biopsy. ACOG no longer recommends routine screening for bacteria or viruses or testing for glucose tolerance and thyroid abnormalities, as these assessments are not beneficial and thus not recommended in the evaluation of otherwise healthy women with recurrent miscarriages (ACOG, 2001).

Professional Societies/Organizations
American Congress of Obstetricians and Gynecologists (ACOG): Although there is no recent update, the ACOG guidelines (2001), "Management of Recurrent Early Pregnancy Loss," addresses repetitive loss of recognized pregnancies during the first or early second trimester, (i.e., <15 weeks gestation), and recommend the following:

- Women with recurrent pregnancy loss should be tested for lupus anticoagulant and anticardiolipin antibodies, special protein substances made by the body's white cells for defense against foreign substances. These antibodies can alter the clotting process and lead to strokes, blood clots and low platelet counts, as well as miscarriages. If positive for the same antibody on two consecutive occasions six to eight weeks apart, the patient should be treated with heparin and low-dose aspirin in her next pregnancy attempt.
- Couples with recurrent miscarriage should be tested for genetic abnormalities.
- Women with recurrent miscarriage and a double uterus (uterine septum) should undergo hysteroscopy evaluation and reparative surgery.
- Couples with otherwise unexplained recurrent miscarriage should be counseled regarding the potential for successful pregnancy without treatment.

ACOG does not recommend mononuclear cell immunization and IVIg for prevention of RSA. The guidelines also indicate the association between luteal phase defect and RSA is controversial, and the efficacy of luteal phase support with progesterone is considered unproven. In addition, the guidelines do not support any of the following testing:

- cultures for bacteria /viruses
- glucose intolerance
- thyroid abnormalities
- antibodies to infectious agents
- antinuclear antibodies
- antithyroid antibodies
- paternal human leukocyte antigen status
- maternal antipaternal antibodies

American Society for Reproductive Medicine (ASRM): The ASRM committee (2012) published the following recommendations for the evaluation and treatment of recurrent pregnancy loss:

- evaluation of RSA can proceed after two consecutive clinical pregnancy losses
- assessment of RSA focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anomaly, hormonal and metabolic factors, and lifestyle variables. These may include:
  - peripheral karyotypic analysis of parents
  - screening for lupus anticoagulant, anticardiolipin antibodies, and anti-B2 glycoprotein I
  - sonohysterogram, hysterosalpingogram, and/or hysteroscopy
  - screening for thyroid or prolactin abnormalities
  - karyotypic analysis of products of conception in the setting of ongoing therapy for RSA
  - women with persistent to moderate-to-high titers of circulating antiphospholipid antibodies can be treated with a combination of prophylactic doses of unfractionated heparin and low dose aspirin
  - psychological counseling and support

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCDs): no NCD found
- Local Coverage Determinations (LCDs): no LCD found

Use Outside of the US

The Royal College of Obstetricians and Gynaecologists (RCOG): in the guideline for recurrent miscarriage, investigation and treatment of couples the RCOG (2017) recommends the following for diagnosis and treatment of recurrent pregnancy loss:

- Women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies.
- Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriages(s).
- All couples with a history of recurrent miscarriage should have peripheral-blood karyotyping performed where testing of products of conception reports an unbalanced structural chromosomal abnormality.
- All women with recurrent first trimester miscarriage and all women with one or more second-trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy and morphology.
- Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V leiden, factor II (prothrombin) gene mutation and protein S.

RCOG also does not recommend routine screening for occult diabetes and thyroid disease with oral glucose tolerance and thyroid function tests in asymptomatic women presenting with recurrent miscarriage. The society indicates that there is insufficient evidence to evaluate the effect of progesterone supplementation, administration of human chorionic gonadotropin, or metformin supplementation in pregnancy to prevent miscarriage. In addition, the most current guideline, (updated 2017), “The Investigation and Treatment of Couples with Recurrent Miscarriage” does not recommend any of the following:

- suppression of high levels of luteinizing hormone
- screening for thyroid antibodies
- use of steroids in treating miscarriage associated with aPL syndrome
- testing for peripheral blood or uterine natural killer cells
- cytokine testing
- paternal cell immunization
- third-party donor leukocytes
- trophoblast membrane infusion
- intravenous immunoglobulin
- TORCH screening

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Diagnostic Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
58100	Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography
58555	Hysteroscopy, diagnostic (separate procedure)
58558	Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C
74740	Hysterosalpingography, radiological supervision and interpretation
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76856	Ultrasound, pelvic (nonobstetric), real time with image documentation; complete
82947	Glucose; quantitative, blood (except reagent strip)
83036	Hemoglobin; glycosylated (A1C)
85130	Chromogenic substrate assay
85597†	Phospholipid neutralization; platelet
85598†	Phospholipid neutralization; hexagonal phospholipid
85705†	Thromboplastin inhibition, tissue
86146	Beta 2 Glycoprotein I antibody, each
86147	Cardiolipin (phospholipid) antibody, each Ig class
86900	Blood typing, serologic; ABO
86901	Blood typing, serologic; Rh (D)
88233	Tissue culture for non-neoplastic disorders; skin or other solid tissue biopsy

†**Note: Considered Medically Necessary when used to report lupus anticoagulant detection using standard assays.**

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
83090	Homocysteine
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85301	Clotting inhibitors or anticoagulants; antithrombin III, antigen assay
85302	Clotting inhibitors or anticoagulants; protein C, antigen
85303	Clotting inhibitors or anticoagulants; protein C, activity
85305	Clotting inhibitors or anticoagulants; protein S, total
85306	Clotting inhibitors or anticoagulants; protein S, free
85307	Activated Protein C (APC) resistance assay
86021	Antibody identification; leukocyte antibodies
86039	Antinuclear antibodies (ANA); titer
86148	Anti-phosphatidylserine (phospholipid) antibody
86255	Fluorescent noninfectious agent antibody; screen, each antibody
86353	Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis
86357	Natural killer (NK) cells, total count

86805	Lymphocytotoxicity assay, visual crossmatch; with titration
86812	HLA typing; A, B, or C (eg, A10, B7, B27), single antigen
86813	HLA typing; A, B, or C, multiple antigens
86816	HLA typing; DR/DQ, single antigen
86817	HLA typing; DR/DQ, multiple antigens
86821	HLA typing; lymphocyte culture, mixed (MLC)
86825	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (eg, using flow cytometry); first serum sample or dilution
86826	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (eg, using flow cytometry); each additional serum sample or sample dilution (List separately in addition to primary procedure)

Considered Experimental/Investigational/Unproven when used to report antiprothrombin (phospholipid cofactor) antibody, each Ig class or embryotoxicity assay:

CPT®* Codes	Description
86849	Unlisted immunology procedure

Considered Experimental/Investigational/Unproven when used to report inhibin B, peroxisome proliferator activation receptor (PPARs) or cytokine tumor necrosis factor-α (TNFα) in placenta tissues:

CPT®* Codes	Description
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

Considered Experimental/Investigational/Unproven when used to report TORCH panel:

CPT®* Codes	Description
86592	Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART)
86593	Syphilis test, non-treponemal antibody; quantitative
86644	Antibody; cytomegalovirus (CMV)
86645	Antibody; cytomegalovirus (CMV), IgM
86694	Antibody; herpes simplex, non-specific type test
86695	Antibody; herpes simplex, type 1
86696	Antibody; herpes simplex, type 2
86762	Antibody; rubella
86777	Antibody; Toxoplasma
86778	Antibody; Toxoplasma, IgM
86787	Antibody; varicella-zoster

Treatment

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
58558	Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C
58559	Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method)
58560	Hysteroscopy, surgical; with division or resection of intrauterine septum (any method)
58561	Hysteroscopy, surgical; with removal of leiomyomata
59320	Cerclage of cervix, during pregnancy; vaginal
59325	Cerclage of cervix, during pregnancy; abdominal

HCPCS Codes	Description
J1644	Injection, heparin sodium, per 1,000 units

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
57700	Cerclage of uterine cervix, nonobstetrical
86950	Leukocyte transfusion
90281	Immune globulin (Ig), human, for intramuscular use
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

HCPCS Codes	Description
B4185	Parenteral nutrition solution, per 10 grams lipids
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1460	Injection, gamma globulin, intramuscular, 1 cc
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1560	Injection, gamma globulin, intramuscular, over 10 cc
J1561	Injection, immune globulin, (Gamunex-c/gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (Vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/Flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (hyqvia), 100 mg immuneglobulin
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

Considered Experimental/Investigational/Unproven when used to report trophoblast membrane infusion:

CPT®* Codes	Description
96379	Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion

References

1. Altintas A, Pasa S, Akdeniz N, Cil T, Yurt M, Ayyildiz O, Batun S, Isi H. Factor V Leiden and G20210A prothrombin mutations in patients with recurrent pregnancy loss: data from the southeast of Turkey. Ann Hematol. 2007 Oct;86(10):727-31.

2. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017 Jun 6;6:CD008991.

3. American College of Chest Physicians. Antithrombotic therapy and prevention of thrombosis. Ninth edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Quick reference guideline for physicians. Copyright © 2012 by the American College of Chest Physicians. Accessed December 17, 2019. Available at URL address: http://www.chestnet.org/Guidelines-and-Resources/CHEST-Guideline-Topic-Areas/Pulmonary-Vascular

4. American College of Obstetricians and Gynecologists (ACOG). ACOG Committee Opinion No. 430: Preimplantation genetic screening for Aneuploidy. Obstet Gynecol. 2009 Mar;113(3):766-7.

5. American College of Obstetricians and Gynecologists (ACOG)/The Society for Maternal-Fetal Medicine. ACOG Committee Opinion 581: The use of chromosomal microarray analysis in prenatal diagnosis. December 2013.

6. American College of Obstetricians and Gynecologists (ACOG). Management of recurrent early pregnancy loss. ACOG practice bulletin no. 24. Washington, DC: American College of Obstetricians and Gynecologists (ACOG); 2001 Feb 12.

7. American College of Obstetricians and Gynecologists (ACOG). Early Pregnancy Loss. Practice Bulletin 150. May 2015. Obstet Gynecol 2015;125:1258-67.

8. American College of Obstetricians and Gynecologists (ACOG). Early Pregnancy Loss. Practice Bulletin 200. August 29, 2018. Interim update. Accessed December 17, 2019. Available at URL address: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Early-Pregnancy-Loss

9. American College of Obstetricians and Gynecologists (ACOG). Cervical Insufficiency. Practice Bulletin No. 48. American College of Obstetricians and Gynecologists. August 2003, reaffirmed 2008.

10. American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Practice Bulletin No. 124 American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:730-40.

11. American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Practice Bulletin No.197. June 25, 2018.

12. American College of Obstetricians and Gynecologists (ACOG). Antiphospholipid syndrome. ACOG Practice Bulletin No. 118. Washington, DC: ACOG; January 2011.

13. American Society of Reproductive Medicine (ASRM).Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertility and Sterility® Vol. 98. Nov 2012.

14. American Society of Reproductive Medicine (ASRM). Practice Committee Report. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2008 Jun;89(6):1603.

15. American Society of Reproductive Medicine (ASRM). Practice Committee Report. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2013 Jan;99(1):63. doi: 10.1016/j.fertnstert.2012.09.023. Epub 2012 Oct 22.

16. American Society of Reproductive Medicine (ASRM). Practice Committee. Intravenous immunoglobulin (IVIG) and recurrent spontaneous pregnancy loss. Fertil Steril. 2006 Nov;86 Suppl 5:S226-7.

17. Audibert F, Wilson RD, Allen V, Blight C, Brock JA, Désilets VA, et al.; Genetics Committee. Preimplantation genetic screening. J Obstet Gynaecol Can. 2009 Aug;31(8):761-75.

18. Bansal AS, Bajardeen B, Thurn MY. The basis and value of currently used immunomodulatory therapies in recurrent miscarriage. J Repro Immun. 2012-01-01Z,93 (1):41-51.

19. Bose P, Black S, Kadyrov M, Bartz C, Shlebak A, Regan L, Huppertz B. Adverse effects of lupus anticoagulant positive blood sera on placental viability can be prevented by heparin in vitro. Am J Obstet Gynecol. 2004 Dec;191(6):2125-31.

20. Branch DW, Peaceman AM, Druzin M, Silver RK, El-Sayed Y, Silver RM, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. Am J Obstet Gynecol. 2000 Jan;182(1 Pt 1):122-7.

21. Brenner B. Thrombophilia and adverse pregnancy outcomes. Obstet Gynecol Clin North Am. 2006 Sep;33(3):443-56,ix.

22. Brenner B, Aharon A. Thrombophilia and Adverse Pregnancy Outcome. Clin Perinatol. 2007 Dec;34(4):527-41.

23. Brenner B, Bar J, Ellis M, Yarom I, Yohai D, Samueloff A; Live-Enox Investigators. Effects of enoxaparin on late pregnancy complications and neonatal outcome in women with recurrent pregnancy loss and thrombophilia: results from the Live-Enox study. Fertil Steril. 2005 Sep;84(3):770-3.

24. Carp HJ. Thrombophilia and recurrent pregnancy loss. Obstet Gynecol Clin North Am. 2006 Sep;33(3):429-42.

25. Carter JF, Soper DE. Laparoscopic abdominal cerclage. JSLS. 2005 Oct-Dec;9(4):491-3.

26. Christiansen OB. Evidence-based investigations and treatments of recurrent pregnancy loss. Curr Opin Obstet Gynecol. 2006 Jun;18(3):304-12.

27. Cleary-Goldman J, Nakhuda GS, Zimmerman RC, Sauer MV. The role of factor V Leiden mutation in recurrent pregnancy loss. J Am Med Womens Assoc. 2003 Summer;58(3):165-72.

28. Coppens M; Kaandorp SP; Middeldorp S. Inherited thrombophilias. Obstet Gynecol Clin North Am. 2006 Sep;33(3):357-74.

29. Coulam CB, Acacio B. Does immunotherapy for treatment of reproductive failure enhance live births? Am J Reprod Immunol. 2012 Apr;67(4):296-304.

30. Coulam CB, Jeyendran RS, Fishel LA, Roussev R. Multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for recurrent miscarriage. Am J Reprod Immunol. 2006 May;55(5):360-8.

31. Davenport WB, Kutteh WH. Inherited thrombophilias and adverse pregnancy outcomes. Obstet Gynecol Clin North Am. 2014 Mar;41(1):133-44.

32. Debbs RH, DeLa Vega GA, Pearson S, Sehdev H, Marchiano D, Ludmir J. Transabdominal cerclage after comprehensive evaluation of women with previous unsuccessful transvaginal cerclage. Am J Obstet Gynecol. 2007 Sep;197(3):317.e1-4.

33. Dentali F, Crowther M. Acquired thrombophilia during pregnancy. Obstet Gynecol Clin North Am. 2006 Sep;33(3):375-88.

34. Di Nisio M, Peters LW, Middeldorp S. Anticoagulants for the treatment of recurrent pregnancy loss in women without antiphospholipid syndrome. Cochrane Database of Systematic Reviews. In: The Cochrane Library, Issue 2, 2005. Copyright © 2007 The Cochrane Collaboration.

35. Duhl AJ, Paidas MJ, Ural SH, Branch W, Casele H, Cox-Gill J, Hamersley SL, Hyers TM, Katz V, Kuhlmann R, Nutescu EA, Thorp JA, Zehnder JL; Pregnancy and Thrombosis Working Group.

Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am J Obstet Gynecol. 2007 Nov;197(5):457.e1-21.

36. D'Uva M, Di Micco P, Strina I, Alviggi C, Iannuzzo M, Ranieri A, Mollo A, De Placido G. Hyperhomocysteinemia in women with unexplained sterility or recurrent early pregnancy loss from Southern Italy: a preliminary report. Thromb J. 2007 Jul 11;5:10.

37. Edlow AG, Srinivas SK, Elovitz MA. Second-trimester loss and subsequent pregnancy outcomes: What is the real risk? Am J Obstet Gynecol. 2007 Dec;197(6):581.e1-6.

38. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002859.

39. Etiology and clinical evaluation of repetitive abortions. In: Gabbe SG, Niebyl JR, Simpson JL, editors. Obstetrics: normal and problem pregnancies. 4th ed. New York, NY: Churchill Livingstone, Inc.; 2002. p. 622-44.

40. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. Obstet Gynecol. 2002 Sep;100(3):408-13.

41. Fausett MB, Branch DW. Autoimmunity and pregnancy loss. Immunol Allergy Clin North Am. 2002 Aug;22(3):599-621.

42. Gabbe: Obstetrics: Normal and Problem Pregnancies, 6th edition. Ch 27. Cervical Insufficiency. Copyright ©2012 Saunders.

43. Gonen R, Lavi N, Attias D, Schliamser L, Borochowitz Z, Toubi E, Ohel G. Absence of association of inherited thrombophilia with unexplained third-trimester intrauterine fetal death. Am J Obstet Gynecol. 2005 Mar;192(3):742-6.

44. Goodman CS, Coulam CB, Jeyendran RS, Acosta VA, Roussev R. Which thrombophilic gene mutations are risk factors for recurrent pregnancy loss? Am J Reprod Immunol. 2006 Oct;56(4):230-6.

45. Gordon H. Guyatt, Elie A. Akl, Mark Crowther, David D. Gutterman, Holger J. Schuünemann, and for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis: Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2)(suppl):7S-47S.

46. Groom KM, Jones BA, Edmonds DK, Bennett PR. Preconception transabdominal cervicoisthmic cerclage. Am J Obstet Gynecol. 2004 Jul;191(1):230-4.

47. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2013 Oct 31;(10):CD003511.

48. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev.2018 Oct 8;10:CD003511.

49. Hogge WA, Byrnes AL, Lanasa MC, Surti US. The clinical use of karyotyping spontaneous abortions. Am J Obstet Gynecol. 2003 Aug;189(2):397-400; discussion 402.

50. Hogge WA, Prosen TL, Lanasa MC, Huber HA, Reeves MF. Recurrent spontaneous abortion and skewed X-inactivation: is there an association? Am J Obstet Gynecol. 2007 Apr;196(4):384.e1-6; discussion 384.e6-8.

51. Khangura SD, Visintini S. Off-Label Use of Intravenous Immunoglobulin for Recurrent Spontaneous Abortion: A Review of Clinical Effectiveness [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 May 11. Accessed January 3, 2020. Available at URL address: https://www.cadth.ca/label-use-intravenous-immunoglobulin-recurrent-spontaneous-abortion-review-clinical-effectiveness

52. Jeve YB, Davies W. Evidence-based management of recurrent miscarriages. J Hum Reprod Sci. 2014 Jul;7(3):159-69.

53. Jivraj S, Rai R, Underwood J, Regan L. Genetic thrombophilic mutations among couples with recurrent miscarriage. Hum Reprod. 2006 May;21(5):1161-5.

54. Kaare M, Painter JN, Ulander VM, Kaaja R, Aittomäki K. Sex chromosome characteristics and recurrent miscarriage. Fertil Steril. 2008 Dec;90(6):2328-33.

55. Kalro, BN. Impaired infertility casued by endocrine dysfunction in women. Endocrinol Metab Clin North Am. 2003 Sep;32(3):573-92.

56. Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD004734.

57. Karaer A, Karaer K, Ozaksit G, Ceylaner S, Percin EF. Y chromosome azoospermia factor region microdeletions and recurrent pregnancy loss. Am J Obstet Gynecol. 2008 Dec;199(6):662.e1-5. Epub 2008 Sep 25.

58. Katano K, Suzuki S, Ozaki Y, Suzumori N, Kitaori T, Sugiura-Ogasawara M. Peripheral natural killer cell activity as a predictor of recurrent pregnancy loss: a large cohort study. Fertil Steril. 2013 Dec;100(6):1629-34.

59. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. Arch Intern Med. 2004 Mar 8;164(5):558-63.

60. Kujovich JL. Thrombophilia and pregnancy complications. Am J Obstet Gynecol. 2004 Aug; 191(2):412-24.

61. Kumar P, Mahajan S. Preimplantation and postimplantation therapy for the treatment of reproductive failure. J Hum Reprod Sci. 2013 Apr;6(2):88-92.

62. Kutteh WH. Novel Strategies for the Management of Recurrent Pregnancy Loss. Semin Reprod Med 2015; 33(3):161-168.

63. Kutteh WH, Triplett DA. Thrombophilias and recurrent pregnancy loss. Semin Reprod Med. 2006 Feb;24(1):54-66.

64. Laskin CA, Bombardier C, Hannah ME, Mandel FP, Knox Ritchie JW, Farewell V, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. N Engl J Med. 1997 Jul; 337(3):148-53.

65. Laurino MY, Bennett RL, Saraiya DS, Baumeister L, Doyle DL, Leppig K, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2005 Jun;14(3):165-81. Reaffirmed April 2010.

66. Li L, Dou L, Leung PC, Chung TK, Wang CC. Chinese herbal medicines for unexplained recurrent miscarriage. Cochrane Database Syst Rev. 2016 Jan 14;(1):CD010568.

67. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA. 2006 Mar 1;295(9):1050-7.

68. Mahjoub T, Mtiraoui N, Tamim H, Hizem S, Finan RR, Nsiri B, Almawi WY. Association between adverse pregnancy outcomes and maternal factor V G1691A (Leiden) and prothrombin G20210A genotypes in women with a history of recurrent idiopathic miscarriages. Am J Hematol. 2005 Sep;80(1):12-9.

69. Martini AE, Jasulaitis S, Fogg LF, Uhler ML, Hirshfeld-Cytron JE. Evaluating the Utility of Intralipid Infusion to Improve Live Birth Rates in Patients with Recurrent Pregnancy Loss or Recurrent Implantation Failure. J Hum Reprod Sci.2018 Jul-Sep;11(3):261-268.

70. Medley N, Vogel JP, Care A, Alfirevic Z. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev. 2018 Nov 14;11:CD012505.

71. Meis PJ, Klebanoff M, Dombrowski MP, Sibai B, Moawad AH, Spong CY, et al. Prevention of recurrent preterm delivery by 17-alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun;348(24):2379-85.

72. Mingione MJ, Scibetta JJ, Sanko SR, Phipps WR. Clinical outcomes following interval laparoscopic transabdominal cervico-isthmic cerclage placement: case series. Hum Reprod. 2003 Aug;18(8):1716-9.

73. Moffett A, Regan L, Braude P. Natural killer cells, miscarriage, and infertility. BMJ. 2004 Nov;329(7477):1283-5.

74. Oats-Whitehead RM, Haas Dm, Carrier JAK. Progestogen for preventing miscarriage. Cochrane Database of Systematic Reviews 2007 Issue 4. In: The Cochrane Library, Issue 4, 2003. Copyright © 2007 The Cochrane Collaboration.

75. Papamitsou T, Toskas A, Papadopoulou K, et al. Expression of peroxisome proliferator activation receptors (PPARs) and TNFα in placenta tissues in unexplained recurrent pregnancy loss: An immunohistochemical study. Histol Histopathol. 2016 Feb 12:11734.

76. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD000112.

77. Prakash A, Laird S, Li TC, Ledger WL. Preliminary prospective study of the endocrinology of conception cycles and early pregnancy in women with antiphospholipid syndrome treated with low molecular weight heparin. Fertil Steril. 2006 Jan;85(1):165-70.

78. Price M, Kelsberg G, Safranek S, Damitz B. What treatments prevent miscarriage after recurrent pregnancy loss? J Fam Pract. 2005 Oct;54(10):892, 894.

79. Rasmark Roepke E, Hellgren M, Hjertberg R, Blomqvist L, Matthiesen L, Henic E, et al. Treatment efficacy for idiopathic recurrent pregnancy loss - a systematic review and meta-analyses. Acta Obstet Gynecol Scand. 2018 Mar 30.

80. Recurrent spontaneous abortion. In: Stenchever MA, Droegemueller W, Herbst AL, Mishell D Jr., editors. Comprehensive gynecology. 6th ed. St. Louis, MO: © 2012 Mosby, Inc.; CH 16.

81. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet. 2003 Mar 15;361(9361):901-8.

82. Royal College of Obstetricians and Gynaecologists. Recurrent Miscarriage, Investigation and Treatment of Couples. Guideline No 17. Updated Feb 2017; published initially 1998. Accessed December 18, 2019. Available at URL address: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg17/

83. Said JM, Higgins JR, Moses EK, Walker SP, Borg AJ, Monagle PT, Brennecke SP. Inherited thrombophilia polymorphisms and pregnancy outcomes in nulliparous women. Obstet Gynecol. 2010 Jan;115(1):5-13.

84. Shahine L, Lathi R. Recurrent pregnancy loss: evaluation and treatment. Obstet Gynecol Clin North Am. 2015 Mar;42(1):117-34.

85. Shetty S, Ghosh K. Anti-phospholipid antibodies and other immunological causes of recurrent foetal loss--a review of literature of various therapeutic protocols. Am J Reprod Immunol. 2009 Jul;62(1):9-24.

86. Silver RM, Zhao Y, Spong CY, Sibai B, Wendel G Jr, Wenstrom K, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (NICHD MFMU) Network. Prothrombin gene G20210A mutation and obstetric complications. Obstet Gynecol. 2010 Jan;115(1):14-20.

87. Simpson JL, Jauniaux ERM. Pregnancy loss. In: Gabbe: Obstretrics: Normal and problem pregnancies, 6th ed. Copyright © 2012 Churchill Livingstone, CH 24.

88. Sottilotta G, Oriana V, Latella C, Luise F, Piromalli A, Ramirez F, Mammi C, Santoro R, Iannaccaro P, Muleo G, Lombardo VT. Genetic prothrombotic risk factors in women with unexplained pregnancy loss. Thromb Res. 2006;117(6):681-4.

89. Stephenson M, Kutteh W. Evaluation and management of recurrent early pregnancy loss. Clin Obstet Gynecol. 2007 Mar;50(1):132-45.

90. Stephenson MD. Recurrent early pregnancy loss. Semin Reprod Med. 2011 Nov;29(6):461-2. doi: 10.1055/s-0031-1293199.

91. Toth B, Jeschke U, Rogenhofer N, Scholz C, Würfel W, Thaler CJ, Makrigiannakis A. Recurrent miscarriage: current concepts in diagnosis and treatment. J Reprod Immunol. 2010 May;85(1):25-32.

92. Toth B, Kuon RJ, Goeggl T, Holschbach V, Daniel V, Weber M, et al. Lipid infusion in RSA and RIF patients with elevated uterine natural killer cells. J Rep Immun. 2014-03-01Z, Volume 101-102, P35.

93. Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, et al. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis Rheum. 2003 Mar;48(3):728-31.

94. Tulandi T, Al-Fozan HM. Management of couples with recurrent pregnancy loss. UpToDate Inc., Waltham, MA. last updated: Oct 21, 2019. (accessed December 18, 2019).

95. Tulandi T, Al-Fozan HM. Definition and etiology of recurrent pregnancy loss. UpToDate Inc., Waltham, MA. Last updated: Nov 11, 2019. (accessed December 18, 2019).

96. Wang BT, Chong TP, Boyar FZ, et al. Abnormalities in spontaneous abortions detected by G-banding and chromosomal microarray analysis (CMA) at a national reference laboratory. Molecular Cytogenetics. 2014. 7-33.

97. Warburton D, Kline J, Kinney A, Yu CY, Levin B, Brown S. Skewed X chromosome inactivation and trisomic spontaneous abortion: no association. Am J Hum Genet. 2009 Aug;85(2):179-93.

98. Wolf GC, Horger EO. Clinical opinion: Indications for examination of spontaneous abortion specimens: a reassessment. Am J Obstet Gynecol. 1995 Nov;173(5):1364-8.

99. Wong LF, Porter TF, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev. 2014 Oct 21;(10):CD000112.

100. Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, Walker ID, Langhorne P, Brenkel I, Regan L, Greer I. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Health Technol Assess. 2006 Apr;10(11):1-110.

101. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstet Gynecol. 2010 Jun;115(6):1256-62.