Recurrent Pregnancy Loss: Diagnosis and Treatment

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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,
Medical Coverage Policy: 0284

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-\(\beta_2\)-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
- antivarian 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-\(\alpha\) (TNF\(\alpha\)) 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). Karyotyping 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 phosphatic 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 [IVlg]). 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 IVlg 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 alloimmune factors. Typically, IVlg therapy is aimed at providing passive immunity to alter the immune response by increasing an individual’s antibody titer and antigen-antibody reaction potential. IVlg contains immunomodulating peptides, antibodies against most exogenous antigens, many normal human proteins, and fragment, the antigen-binding region of autoantibodies (Fab). Data evaluating IVlg 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 (IVlg, 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 IVlg 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 uterus) 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 tetrahydrofolate 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 thrombophilias 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 thrombophilia 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 ureaplasm, 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 miscarriages 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:

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

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

#### Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83090</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>85300</td>
<td>Clotting inhibitors or anticoagulants; antithrombin III, activity</td>
</tr>
<tr>
<td>85301</td>
<td>Clotting inhibitors or anticoagulants; antithrombin III, antigen assay</td>
</tr>
<tr>
<td>85302</td>
<td>Clotting inhibitors or anticoagulants; protein C, antigen</td>
</tr>
<tr>
<td>85303</td>
<td>Clotting inhibitors or anticoagulants; protein C, activity</td>
</tr>
<tr>
<td>85305</td>
<td>Clotting inhibitors or anticoagulants; protein S, total</td>
</tr>
<tr>
<td>85306</td>
<td>Clotting inhibitors or anticoagulants; protein S, free</td>
</tr>
<tr>
<td>85307</td>
<td>Activated Protein C (APC) resistance assay</td>
</tr>
<tr>
<td>86021</td>
<td>Antibody identification; leukocyte antibodies</td>
</tr>
<tr>
<td>86039</td>
<td>Antinuclear antibodies (ANA); titer</td>
</tr>
<tr>
<td>86148</td>
<td>Anti-phosphatidylserine (phospholipid) antibody</td>
</tr>
<tr>
<td>86255</td>
<td>Fluorescent noninfectious agent antibody; screen, each antibody</td>
</tr>
<tr>
<td>86353</td>
<td>Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis</td>
</tr>
<tr>
<td>86357</td>
<td>Natural killer (NK) cells, total count</td>
</tr>
</tbody>
</table>
Considered Experimental/Investigational/Unproven when used to report antiprothrombin (phospholipid cofactor) antibody, each Ig class or embryotoxicity assay:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>86849</td>
<td>Unlisted immunology procedure</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
</tr>
</tbody>
</table>

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

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

Treatment

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58558</td>
<td>Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D &amp; C</td>
</tr>
<tr>
<td>58559</td>
<td>Hysteroscopy, surgical; with lysis of intrauterine adhesions (any method)</td>
</tr>
<tr>
<td>58560</td>
<td>Hysteroscopy, surgical; with division or resection of intrauterine septum (any method)</td>
</tr>
<tr>
<td>58561</td>
<td>Hysteroscopy, surgical; with removal of leiomyomata</td>
</tr>
<tr>
<td>59320</td>
<td>Cerclage of cervix, during pregnancy; vaginal</td>
</tr>
<tr>
<td>59325</td>
<td>Cerclage of cervix, during pregnancy; abdominal</td>
</tr>
<tr>
<td>HCPCS Codes</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>J1644</td>
<td>Injection, heparin sodium, per 1,000 units</td>
</tr>
</tbody>
</table>

**Considered Experimental/Investigational/Unproven:**

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

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

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96379</td>
<td>Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion</td>
</tr>
</tbody>
</table>


**References**


