



CIGNA HEALTHCARE COVERAGE POSITION

**Subject Recurrent Pregnancy Loss:
Diagnosis and Treatment**

Revised Date 2/15/2006
Original Effective Date 2/15/2004
Coverage Position Number 0284

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Coverage Position

CIGNA HealthCare covers the following tests as medically necessary for the evaluation of recurrent pregnancy loss (i.e., two or more consecutive pregnancy losses):

- peripheral-blood karyotyping of the parents*
- karyotype of the products of conception*
- pelvic ultrasound
- hysteroscopy
- hysterosalpingography
- endometrial biopsy
- lupus anticoagulant detection using standard assays
- anticardiolipin antibody detection (IgG, IgM) using standard assays
- factor V Leiden testing
- thyroid stimulating hormone (TSH)
- thyroid antibodies
- diabetic testing
- pre- and post-test genetic counseling

* Please note: All participants undergoing genetic testing should have both pre and post-test genetic counseling with a licensed or certified genetic counselor or physician trained in genetics and genetic counseling.

CIGNA HealthCare does not cover ANY of the following diagnostic tests for recurrent pregnancy loss, as they are considered experimental, investigational or unproven:

- antibodies to phosphatidylserine, phosphatidylethanolamine or other phospholipids
- antithrombin III, protein C or protein S deficiencies, prothrombin (G20210A) genetic mutation analysis
- TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus)
- antinuclear antibody (ANA) titers
- paternal human leukocytic antigen (HLA) testing
- natural killer (NK) cell testing
- testing for maternal antileukocytic antibodies
- testing for maternal serum blocker
- maternal antipaternal antibodies
- embryotoxicity assay (ETA)

CIGNA HealthCare covers the following treatments for recurrent pregnancy loss as medically necessary (this list may not be all inclusive):

- surgical treatment of structural uterine abnormalities
- cerclage
- administration of low-dose heparin and aspirin as a treatment for clearly established antiphospholipid syndrome

CIGNA HealthCare does not cover ANY of the following immunotherapy interventions for the treatment of recurrent pregnancy loss, because they are considered experimental, investigational or unproven:

- intravenous immunoglobulin therapy (IVIg, IGIV)
- paternal cell immunization/paternal leukocyte immunization
- third-party donor leukocytes
- trophoblast membrane infusion

General Background

Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA) or recurrent miscarriage may be defined as two or three or more consecutive pregnancy losses (American College of Obstetricians and Gynecologists [ACOG], 2001). The recurrent loss is distressing for the patient, and, in as many as half of the cases, the cause is unknown. Of clinically recognized pregnancies, 10-15% result in pregnancy loss, usually before 14 weeks gestation (Fausett, Branch, 2002). The risk of spontaneous abortion increases with the number of previous pregnancy losses. The chance of having a normal pregnancy is 30% in a woman who has had three recurrent spontaneous abortions, 25% after four losses and 5% after five losses. Recurrent spontaneous abortion may affect as many as 1-3% of childbearing women.

Potential Causes of Recurrent Pregnancy Loss

RSA 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 RSA:

- parental chromosomal anomalies
- 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 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. The most widely used test for genetic abnormalities is chromosome analysis. Cytogenetic examinations of both partners have been found to be helpful in predicting future recurrences. In addition, couples with a chromosome abnormality should receive genetic counseling.

Chromosomal analysis of the products of conception is debatable, as some conditions may occur spontaneously. ACOG (2001) suggests that there are no definite recommendations for routinely obtaining abortus karyotypes. Some authors have recommended karyotype analysis of abortus tissue for couples with a subsequent second or third pregnancy loss (Wolf, Horger, 1995; Hogge, et al., 2003; Royal College of Obstetricians and Gynaecologists [RCOG], 2003). Although not supported in the published literature, this recommendation is based on the premise that if the abortus is aneuploid, the physician and patient may then conclude that maternal cause is excluded (ACOG, 2001).

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. Two aPLs that have established assays are those for anticardiolipin and lupus anticoagulant. The effects of aPL antibodies on pregnancy are devastating: 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. The use of steroids is associated with maternal and fetal morbidity and is not recommended (RCOG, 2003).

Empson et al (2005) conducted a Cochrane review to examine the outcomes of treatments given to maintain pregnancy in women with prior miscarriage and aPLs. They reviewed 13 studies, none of which compared unfractionated heparin to LMW heparin. As a result, they were unable to determine the relative effects of unfractionated heparin versus low molecular weight heparin. The authors concluded that combined unfractionated heparin and aspirin may reduce pregnancy loss by 54%, and furthermore that randomized trials are needed to determine the difference between unfractionated heparin and LMW heparin.

Other Antigens: Further studies have shown relationships between autoantibodies and other phospholipid antigens, such as phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidylethanolamine, and phosphatidic acid, although their clinical implications are not well defined. Clinical studies are limited, and there is established 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, 2003).

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 (2003), 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 does 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. Much 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. A search of the available evidence does not lead to valid, consistent conclusions regarding testing, efficacy of treatment or improved pregnancy outcomes (ACOG, 2001).

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]). A current analysis of 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, 2003; Scott, 2003; Price, et al., 2005).

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 alloimmune 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. IgG is the principal immunoglobulin in human serum. IVIg contains immunomodulating peptides, antibodies against most exogenous antigens, many normal human proteins, and Fab, the antigen-binding region of autoantibodies. It is obtained from the pooled plasma of large numbers of healthy blood donors. The results of clinical trials for treatment of pregnancy loss have been conflicting due to differences in study design, patient selection, small patient populations and the administration of varying IVIg preparations (Clark, et al., 2001). The hypothesized effect of reducing the occurrence of spontaneous abortion has not been sufficiently demonstrated in the literature. Furthermore, the use of IVIg for recurrent spontaneous abortion is an off-label use, per the U.S. Food and Drug Administration (FDA).

Ober and associates reported the Recurrent Miscarriage (REMIS) Study (1999). The authors investigated whether paternal immunization improves the rate of successful pregnancies in women with unexplained recurrent miscarriage and possible alloimmune abnormalities. The study involved 91 women with three or more spontaneous abortions of unknown cause who received immunization with paternal mononuclear cells and 92 women who received immunization with sterile saline (control). An analysis of all randomized women who completed the trial resulted in a success rate (i.e., pregnancy continued to at least 28 weeks' gestation) in 36% of the treatment group and 48% of the control group. The authors concluded that there was no improvement in pregnancy outcome and that therapy should not be offered as a treatment.

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).

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. 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 submucous, 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. Surgical intervention may be warranted to correct the abnormality.

Cervical Incompetence: Cervical incompetence 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 a weakened cervix can sometimes be prevented by performing a cerclage.

Endocrine Disorders: From 10-23% of repeated pregnancy losses are attributed to endocrine disorders (Kalro, 2003). Polycystic ovarian (PCO) disease 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 believe 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. A review of the current scientific literature indicates that studies are inconclusive in providing strong evidence to support that suppression of elevated LH levels improves pregnancy rates. While the cause of miscarriage in women with elevated LH is poorly understood, treatment involving LH suppression may be considered a viable option.

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, findings from recent studies have generated controversy about that theory. A recent Cochrane review conducted by Oates-Whitehead et al (2005) reviewed 14 clinical trials to determine the efficacy and safety of progestogens as a preventative therapy against miscarriage. The authors concluded there was no statistically significant difference between women receiving progestogen and those receiving only placebo, or no treatment, when there was no provision made for obstetrical history. However, for subgroup analysis that included only women who had suffered three or more consecutive miscarriages directly prior to the studied pregnancy (i.e., three trials), there was a small statistically significant difference in favor of the progestogen group. Nevertheless, those findings should be approached with caution as the study group numbers were small and the confidence intervals wide.

Despite inconsistent evidence reported in the literature, treatment with progesterone supplements and human chorionic gonadotropin hormones is often employed as a method of preventing miscarriage. In addition, some clinical studies support the administration of 17-alpha-hydroxyprogesterone in preventing preterm labor (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 (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. 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 has been associated with recurrent pregnancy loss, most of the reported data indicate similar outcomes for gestational diabetes, frank diabetes and control groups. Several authors have 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). However, despite current trends in recommendations and clinical studies, glucose testing continues to be considered part of the evaluation for RSA.

Prothrombotic States: Inherited thrombophilic disorders are 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. This suggests 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 and antithrombin III. The scientific literature reports inconsistent findings in supporting any association with inherited thrombophilic disorders and recurrent early pregnancy loss, although some studies have shown a relationship with late pregnancy complications. 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 should be based on a risk/benefit assessment. Screening is reasonable in women with unexplained late or repeated pregnancy loss after exclusion of other causes (Kujovich, 2004). The ACOG practice bulletin 2001 does not recommend testing for inheritable thrombophilias, as their role in recurrent early pregnancy loss is uncertain, and there is no evidence that antithrombotic therapy effectively prevents miscarriage. A recent Cochrane review conducted by Di Nisio et al (2005) 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 or one later intrauterine fetal death, without causes other than inherited thrombophilia is too limited to recommend the use of anticoagulants in this setting. They indicated that further randomized clinical trials are needed.

Although it is unclear whether factor V Leiden causes risk of first trimester miscarriage, poor pregnancy outcomes and other possible serious maternal complications have been associated with factor V Leiden mutation. Several authors recommend testing in women with recurrent pregnancy loss (Gordy, et al, 2001; Rai, et al 2002; Bloomenthal, et al, 2002; Cleary-Goldman, et al, 2003). The recommendations by the RCOG (2003) state, "In the absence of randomized trials, the poor pregnancy outcome associated with factor V Leiden mutation, coupled with the maternal risks during pregnancy, may justify routine screening for factor V Leiden and offering thromboprophylaxis for those with the mutation and evidence of placental thrombosis."

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 (2003), the role of infection as a cause of RSA is unclear, and therefore routine testing is not recommended.

Embryotoxicity: A new area of study 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). A review of 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; cytogenetic 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).

The ACOG guidelines (2001), "Management of Early Pregnancy Loss," 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 6-8 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.

The Royal College of Obstetricians and Gynaecologists (RCOG, 2003) recommends the following for diagnosis and treatment of recurrent pregnancy loss:

- All couples with a history of recurrent miscarriage should have peripheral-blood karyotyping performed. The finding of an abnormal parental karyotype should prompt referral to a clinical specialist.
- In all couples with a history of recurrent miscarriage, cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.
- All women with recurrent miscarriage should have a pelvic ultrasound to assess uterine anatomy and morphology.

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 and administration of human chorionic gonadotropin in pregnancy to prevent miscarriage. In addition, the current guideline, "The Investigation and Treatment of Couples with Recurrent Miscarriage" (updated 2003) does not recommend any of the following:

- suppression of high levels of LH hormone
- routine screening for thyroid antibodies
- use of steroids in treating miscarriage associated with aPL syndrome
- paternal cell immunization
- third-party donor leukocytes
- trophoblast membrane infusion
- intravenous immunoglobulin
- TORCH screening
- screening for bacterial vaginosis

Summary

Recurrent spontaneous abortion (RSA) is a heterogeneous condition and may result from several underlying factors, such as anatomic, hormonal, thrombotic, autoimmune, alloimmune, genetic and infectious causes. It has been reported that no explanation is found in as many as 50-75% of couples with RSA. Maternal age and previous number of miscarriages are considered two independent risk factors for further miscarriage. Couples who experience RSA may benefit from extensive medical evaluation and in some cases genetic counseling, although many tests and treatments remain unproven in the peer-reviewed, published scientific literature. Some authors have reported as many as 60-70% of couples who experience RSA go on to have successful pregnancy.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
86147	Cardiolipin (phospholipid) antibody, each Ig class
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
74740	Hysterosalpingography, radiological supervision and interpretation
58100	Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)
86900	Blood typing; ABO
86901	Blood typing; Rh (D)
76856	Ultrasound, pelvic (nonobstetric), B-scan and/or real time with image documentation; complete
58555	Hysteroscopy, diagnostic (separate procedure)
58558	Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C
85705	Thromboplastin inhibition; tissue
84443	Thyroid stimulating hormone (TSH)
82947	Glucose; quantitative, blood (except reagent strip)

HCPCS Codes	Description
J1644	Injection, heparin sodium, per 1,000 units
S0265	Genetic counseling, under physician supervision, each 15 minutes

ICD-9-CM Diagnosis Codes	Description
646.33	Habitual aborter, antepartum condition or complication

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
86021	Antibody identification; leukocyte antibodies
86039	Antinuclear antibodies (ANA); titer
86148	Anti-phosphatidylserine (phospholipid) antibody
86357	Natural killer (NK) cells, total count
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85301	Clotting inhibitors or anticoagulants; antithrombin III, antigen assay
90283	Immune globulin (IgIV), human, for intravenous use

HCPCS Codes	Description
J1564	Injection, immune globulin, 10 mg
J1563	Injection, immune globulin, intravenous, 1 g

***Current Procedural Terminology (CPT®) ©2005 American Medical Association: Chicago, IL.**

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