Medical Coverage Policy

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Coverage Policy Number..... 0284

Recurrent Pregnancy Loss: Diagnosis and Treatment

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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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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

Each of the following diagnostic tests for recurrent pregnancy loss is considered not medically necessary:

- inhibin B
- peroxisome proliferator activation receptor (PPARs) and cytokine tumor necrosis factor-α (TNFα) in placenta tissues

The following diagnostic test for recurrent pregnancy loss is not covered or reimbursable:

- natural killer (NK) cell testing

Treatment

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

- antenatal (during pregnancy) transabdominal/laparoscopic cervical cerclage for an individual with **ANY** of the following conditions:
  - prior failed history-indicated transvaginal cervical cerclage
  - prior cervical trauma (e.g., cone biopsy, cervical laceration during delivery)
  - shortened cervical length
- cerclage performed on a non-pregnant individual with **ANY** of the following conditions:

- prior failed history-indicated transvaginal cervical cerclage
- prior cervical trauma (e.g., cone biopsy, cervical laceration during delivery)
- shortened cervical length

Each of the following interventions is considered not medically necessary for the treatment of recurrent pregnancy loss:

- paternal cell immunization/paternal leukocyte immunization
- third-party donor leukocytes

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Early pregnancy loss (miscarriage, spontaneous abortion) is the loss of a pregnancy before 13 completed weeks gestation. Sporadic pregnancy loss is nonconsecutive pregnancy loss that occurs randomly during an individual'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 (ACOG, 2024; ASRM, 2020) 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 (Jauniaux and Simpson, 2021). 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

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 individual'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; Price, et al., 2005). Additionally, the authors of a Cochrane review of 20 randomized trials (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.

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.

Cervical Incompetence: Cervical insufficiency is defined as the inability of the uterine cervix to retain a pregnancy in the second trimester in the absence of clinical contractions, labor, or both (ACOG, 2014). 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. 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 (ACOG, 2014; Alfirevic, et al., 2017). In a 2023 consult series endorsed by the American Association of Gynecologic Laparoscopists (AAGL) and the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM) states that "transabdominal cerclage (TAC) is a more morbid and complicated surgery than transvaginal cerclage, as it involves abdominal access and dissection with potentially

increased bleeding risks". "In addition, TAC placement typically necessitates cesarean delivery, exposing the patient to another abdominal surgery." For these reasons, TAC is not offered as a first-line treatment but rather is reserved for individuals in whom a transvaginal cerclage would be difficult to place due to anatomic reasons or in individuals with a history of unsuccessful vaginal cerclage in a prior pregnancy.

According to the ACOG practice bulletin, indications for cervical cerclage in women with singleton pregnancies (ACOG, 2014):

- History: history of one or more second trimester pregnancy loses related to painless cervical dilation and in the absence of labor or abruptio placentae OR prior cerclage due to painless cervical dilation in the second trimester
- Physical Examination: Painless cervical dilation in the second trimester
- Ultrasonic finding with a history or prior preterm birth: current singleton pregnancy, prior spontaneous preterm birth at less than 34 weeks gestation, and short cervical length (less than 25 mm) before 24 weeks gestation

In addition, the ACOG Practice Bulletin (ACOG, 2014) notes that cerclage should be limited to pregnancies in the second trimester before fetal viability has been achieved and that transabdominal cervicoisthmic cerclage generally is reserved for patients in whom a cerclage is indicted based on the diagnosis of cervical insufficiency but cannot be placed because of anatomical limitations or in the case of failed transvaginal cervical cerclage procedures that resulted in second trimester pregnancy loss.

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. The SMFM (2023) reported that a TAC can be placed early in pregnancy or before pregnancy. Placing a TAC before pregnancy has the advantage of a smaller uterus and surgical risks do not have the potential to affect pregnancy. The following weak recommendation was given for the use of TAC performed before pregnancy based on low-quality evidence with uncertainties in the estimates of benefits, risks, and burdens, evidence from observational studies, unsystematic clinical experience, or RCTs with serious flaws:

- We suggest that TAC can be performed before pregnancy or in the first trimester of pregnancy with similar fetal outcomes (Grade of Recommendation: 2C).

Eleje et al. (2020) reported on a Cochrane review to assess whether antibiotics administration, vaginal pessary, reinforcing or second cerclage placement, tocolytic, progesterone, or other interventions at the time of cervical cerclage placement prolong singleton gestation in women at high risk of pregnancy loss based on prior history and/or ultrasound finding of 'short cervix' and/or physical examination. The review included one study (involving 53 women/data from 50 women) compared cervical cerclage in combination with a tocolytic (indomethacin) and antibiotics (cefazolin or clindamycin) versus cervical cerclage alone. The study was generally at a low risk of bias, apart from issues relating to blinding. The authors concluded that there is insufficient evidence to evaluate the effect of combining a tocolytic (indomethacin) and antibiotics (cefazolin/clindamycin) with cervical cerclage compared with cervical cerclage alone for preventing spontaneous PTB in women with singleton pregnancies. They note that future studies should recruit sufficient numbers of women to provide meaningful results and should measure neonatal death and numbers of babies discharged home healthy, as well as other outcomes.

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:

- 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.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
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 Not Medically Necessary 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

Not Covered or Reimbursable:

CPT®* Codes	Description
86357	Natural killer (NK) cells, total count

Treatment

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

CPT®* Codes	Description
57700	Cerclage of uterine cervix, nonobstetrical
58578†	Unlisted laparoscopic procedure, uterus
58999††	Unlisted procedure, female genital system (nonobstetrical)
59325	Cerclage of cervix, during pregnancy; abdominal

†Note: When used to represent laparoscopic approach for transabdominal cerclage, during pregnancy or for non-pregnant uterus.
††Note: When used to represent approach for transabdominal cerclage for non-pregnant uterus.

Considered Not Medically Necessary:

CPT®* Codes	Description
86950	Leukocyte transfusion
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	Removed multiple policy statements in both the diagnostic testing and treatment sections of the policy.	2/15/2025
Focused review	• Revised the policy statements in the treatment section of the policy by adding the words '(during pregnancy)' to clarify the word 'antenatal'. • Revised the policy statement for 'prior failed or contraindication to transvaginal cerclage' in the transabdominal cervical cerclage treatment section of the policy by adding specific examples instead.	4/15/2024