Medical Policy

**MP 4.02.510**  
Genetic Testing for Recurrent Pregnancy Loss

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**Last Review:** 08/20/2018  
**Effective Date:** 11/15/2018  
**Section:** OB/GYN Reproduction

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**DISCLAIMER/INSTRUCTIONS FOR USE**

Medical Policy provides general guidance for applying Blue Cross of Idaho benefit plans (for purposes of Medical Policy, the terms “benefit plan” and “member contract” are used interchangeably). Coverage decisions must reference the member specific benefit plan document. The terms of the member specific benefit plan document may be different than the standard benefit plan upon which this Medical Policy is based. If there is a conflict between a member specific benefit plan and the Blue Cross of Idaho’s standard benefit plan, the member specific benefit plan supersedes this Medical Policy. Any person applying this Medical Policy must identify member eligibility, the member specific benefit plan, and any related policies or guidelines prior to applying this Medical Policy. Blue Cross of Idaho Medical Policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the member specific benefit plan coverage. Blue Cross of Idaho reserves the sole discretionary right to modify all its Policies and Guidelines at any time. This Medical Policy does not constitute medical advice.

**POLICY**

The following tests may be considered medically necessary for evaluation of patients with recurrent pregnancy loss (defined as two or more consecutive spontaneous abortions):

1. Karyotype (cytogenetic analysis) of parents to detect balanced chromosomal anomalies;
2. Prenatal genetic diagnosis for all couples in which one partner has been found to have a balanced translocation or inversion;
3. Karyotype of abortus tissue when a couple with recurrent pregnancy loss experiences a subsequent spontaneous abortion;
4. Measurement of anticardiolipin (IgG or IgM) antibodies and lupus anticoagulant, using standard assays, for diagnosis of antiphospholipid syndrome.

The following tests/studies are considered investigational because they have been shown to be of no value in the evaluation of recurrent pregnancy loss:

1. Annexin A5 promoter haplotype M2 testing;
2. Angiotensin converting enzyme (ACE) gene polymorphisms testing;
3. Antibodies to phosphatidylyserine, phosphatidylethanolamine, phatidylinositol, phosphatidylglycerol, phosphatidic acid or other anti-phospholipid antibodies other than anticyclophosphamide and lupus anticoagulant;
4. Antiadrenal antibodies;
5. Antinuclear antibody (ANA),
6. Antiovarian antibodies;
7. Cytokine polymorphisms analysis (Th1/Th2 intra-cellular cytokine ratio);
8. Determination of the percentage of circulating natural killer (NK) cells and NK activity;

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9. Embryo toxicity assay (ETA) or embryo toxic factor;  
10. Estrogen receptor beta gene polymorphisms testing;  
11. Expression of peroxisome proliferator activation receptors (PPARs) and tumor necrosis factor alpha (TNFα) in placenta tissues;  
12. Genetic association studies of inflammatory cytokine polymorphisms;  
13. Inhibin B;  
14. Interleukin-18 gene polymorphisms testing;  
15. Inter-α trypsin inhibitor-heavy chain 4 (ITI-H4) (as a biomarker for recurrent pregnancy loss);  
16. Luteal phase biopsy to determine the status of natural killer (NK)-like cells;  
17. Maternal antiparental antibodies;  
18. Maternal antileukocytic antibodies to paternal leukocytes;  
19. Methylenetetrahydrofolate reductase (MTHFR) testing;  
20. Mitochondrial DNA variations analysis;  
21. Mixed lymphocytotoxic antibody tests;  
22. Mixed lymphocyte culture reactions;  
23. Molecular cytogenetic testing using comparative genomic hybridization (CGH) for chromosomal analysis (e.g., parental blood and products of conception);  
24. Molecular genetic testing for highly skewed X-inactivation patterns;  
25. Parental human leukocyte antigen (HLA) status;  
26. Plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms testing;  
27. Plasminogen activator inhibitor-I (PAI-1) antigen;  
28. Plasminogen activator inhibitor-I activity;  
29. Pre-implantation genetic screening (PGS);  
30. Prolactin receptor gene polymorphism testing;  
31. Reproductive immunophenotype (CD3+, CD4+, CD5+, CD8+, CD16+, CD19+, CD56+);  
32. Serum anti-heat shock protein antibodies (e.g., anti-HSP60 and anti-HSP70) levels;  
33. Serum anti-Mullerian hormone levels;  
34. Serum “blocking factor”;  
35. Routine preimplantation embryo aneuploidy screening;  
36. X-chromosome inactivation study;  
37. Tests for inherited thrombophilic disorders: antithrombin III antibody; antithrombin III antigen; factor V Leiden (genetic testing); factor V Leiden coagulation (ACPR); prothrombin G20210A mutation, serum homocysteine, protein C activity, protein C antigen, protein S activity, protein S antigen, prothrombin (Factor II) mutation, and deficiencies of the anticoagulants protein C, protein S, and antithrombin II.

POLICY GUIDELINES

No applicable information.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (e.g., FEP) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only on the basis of their medical necessity.
BACKGROUND

Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA) or recurrent miscarriage, has been defined by the American College of Obstetricians and Gynecologists (ACOG) as two, three, or more consecutive pregnancy losses (ACOG, 2001). In 2008, American Society for Reproductive Medicine (ASRM) redefined recurrent pregnancy loss as two or more failed pregnancies (ASRM, 2008). According to ASRM, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination. In contrast, sporadic pregnancy loss is nonconsecutive pregnancy loss that occurs randomly during a woman’s reproductive years. Recurrent pregnancy loss is distressing for the patient and, in as many as half of the cases, the cause is unknown. Ten to 15% of clinically recognized pregnancies will result in pregnancy loss, pregnancy loss usually occurs before 14 weeks of gestation. The risk of spontaneous abortion increases with an increase in the number of previous pregnancies lost.

The need for formal assessment and testing for recurrent pregnancy loss varies among individuals. Traditionally couples are offered evaluation after three losses; however, couples who are in their forties may elect to be evaluated after two recurrent pregnancy losses.

RATIONALE

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS AND ROYAL COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS RECOMMENDATIONS

This policy is based on the recommendations of the American College of Obstetricians and Gynecologists (ACOG, 2001) and the Royal College of Obstetricians and Gynecologists (RCOG, 2011).

The ACOG guideline Management of Recurrent Early Pregnancy Loss reached the following conclusions: 'Women with recurrent pregnancy loss should be tested for lupus anticoagulant and anticardiolipin antibodies using standard assays. If test results are positive for the same antibody on two consecutive occasions 6-8 weeks apart, the patients should be treated with heparin and low-dose aspirin during her next pregnancy attempt. Mononuclear cell (leukocyte) immunization and IVIG are not effective in preventing recurrent pregnancy loss' (ACOG, 2001).

An association between the luteal phase defect and recurrent pregnancy loss is controversial. If a diagnosis of luteal phase defect is sought in a woman with recurrent pregnancy loss, it should be confirmed by endometrial biopsy. Luteal phase support with progesterone is of unproven efficacy.

Couples with recurrent pregnancy loss should be tested for parenteral balanced chromosome abnormalities. Women with recurrent pregnancy loss and a uterine septum should undergo hysteroscopic evaluation and resection. Cultures for bacteria and viruses and tests for glucose tolerance, thyroid abnormalities, antibodies to infectious agents, antinuclear antibodies, antithyroid antibodies, paternal human leukocyte antigen status, or maternal antiparental antibodies are not beneficial and, therefore, are not recommended in the evaluation of otherwise normal women with recurrent pregnancy loss. Couples with otherwise unexplained recurrent pregnancy loss should be counseled regarding the potential for successful pregnancy without treatment.

The Royal College of Obstetricians and Gynaecologists (2011) are consistent with ACOG Guidelines. RCOG recommends the following workup for recurrent pregnancy loss:

- peripheral blood karyotyping in both partners

The American College of Obstetricians and Gynecologists (2001) state that tests for thrombophilias are not required as part of the evaluation of recurrent pregnancy loss, but may be considered in cases of
Genetic Testing for Recurrent Pregnancy Loss

otherwise unexplained fetal death in the second or third trimesters. “The role of thrombophilia in recurrent pregnancy loss is a controversial subject of current research interests. Tests for factor V leiden, the prothrombin G20210A mutations, or deficiencies of protein C, protein S, or antithrombin III should be considered in cases of otherwise unexplained fetal death in the second or third trimesters. However, the role of these heritable thrombophilias in recurrent early pregnancy loss is uncertain at present, and tests for these thrombophilias are not required as part of the evaluation. Whether antithrombotic treatment improves subsequent pregnancy outcomes in women with evidence of thrombophilia is uncertain.”

Updated guidelines from the American College of Obstetricians and Gynecologists (2013) state that testing for inherited thrombophilias in women who have experienced recurrent fetal loss is not recommended because it is unclear if anticoagulation therapy reduces recurrence. Although there may be an association in these cases, there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin (LMWH) prevents recurrence in these patients. Investigators have also found evidence of significantly higher serum homocysteine levels among women with a history of recurrent miscarriage (Krabbendam, et al., 2005; Hague, 2003). Routine folate supplementation is recommended during pregnancy to prevent neural tube defects (USPSTF, 2017). This supplementation should also reduce serum concentrations of homocysteine that may be associated with recurrent pregnancy loss.

A systematic evidence review found insufficient evidence for plasminogen activator inhibitor 4G/5G polymorphism testing in recurrent miscarriage (Augustovski, et al., 2006).

The RCOG recommends that in women with recurrent miscarriage who have undergone the above investigations should undergo the following management:

- those with karyotypic abnormalities should be seen by a clinical geneticist;
- that women with persistently positive tests for antiphospholipid antibodies are offered treatment with low dose aspirin together with low dose heparin during pregnancy (also the subject of on-going research);
- that treatments of unproven benefit should be abandoned;
- that all future treatment options are evaluated in randomized controlled trials.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE RECOMMENDATIONS

The Practice Committee of the American Society for Reproductive Medicine (2004) concluded that the use of IVIG for the management of recurrent spontaneous pregnancy loss is an experimental treatment.

RECURRENT PREGNANCY LOSS

In a review on genetics for recurrent pregnancy loss, Sierra and Stephenson (2006) stated that recent research has generated interest in genetic markers for recurrent pregnancy loss such as skewed X-chromosome inactivation and human leukocyte antigen-G polymorphisms. Assisted reproductive technologies (specifically, pre-implantation genetic diagnosis) have been offered to couples with recurrent pregnancy loss; however, more research is needed before routine use of these new approaches can be advocated.

Stephenson and Kutteh (2007) stated that recurrent pregnancy loss affects up to 5% of couples trying to establish a family. Evaluation classically begins after 2 consecutive miscarriages of less than 10 weeks of gestation, but may be warranted earlier if a prior miscarriage was found to be euploid, or if there is concomitant infertility and/or advancing maternal age. The evaluation begins with an extensive review
of medical history and thorough physical examination, followed by a diagnostic screening protocol. The authors noted that management must be evidence-based; unproven treatments should be avoided.

**MISCELLANEOUS TESTS**

**Embryo Toxicity Assay**

Embryo toxicity assay (ETA) is a laboratory test performed on a woman who has had recurrent early pregnancy loss. A blood sample from the woman is used to furnish a culture medium for growing mouse embryos. The culture is then examined under microscopy to determine if there are any circulating factors in the blood specimen that are toxic to the developing mouse embryos. There is a lack of adequate evidence in the peer-reviewed published medical literature on the effectiveness of this test in improving clinical outcomes.

**Mitochondrial DNA Variations Analysis**

Azadi and associates (2017) stated that cases with 3 or more consecutive spontaneous abortions before the 20th week of gestation are termed as RPL. Problems in implantation of the fetus and any retarded growth of the fetus in the uterus can be correlated to RPL. Possible causes of RPL would include the genetic variations in the regulatory enzymes of the crucial metabolic pathways, clotting factors, hormones and hormone receptors. This defect of the mitochondrial respiratory chain is recognized as a major cause of human disease. These researchers examined 73 women with RPL and 100 healthy normal controls. By using the direct sequencing method, the amplified products including the mtDNA complex I genes were analyzed. Overall, 7 variations in mitochondrial complex I genes were found (T4216C, A5153G, C10142T, C12062T, A12662G, G14179A and T14263C) using direct sequencing technique. The RPL group had significantly higher proportions of the different variants than those observed of the control group. The authors concluded that more research is needed to understand the effect and role of the mitochondrial variations in the progress of RPL, which may vary among individuals and different ethnic groups.

**Prolactin Receptor Gene Polymorphism Testing**

In a case-control study, Kim and colleagues (2018) examined the role of the prolactin receptor gene C/T polymorphism in 311 Korean women with RPL and 314 controls. Genotyping for prolactin receptor gene intron C/T polymorphism was performed using a TaqMan assay. The significance of difference in the genotype distribution was assessed using a Chi-square test, and continuous variables were compared using a Student's t-test. The genotype distribution of the prolactin receptor gene C/T polymorphism in the RPL group did not differ from that in the control group (CC/CT/TT rates were 49.8%/41.5%/8.7% and 52.5%/37.6%/9.9% for the RPL patient and control groups, respectively, p = 0.587). When the analysis was restricted to patients with 3 or more consecutive spontaneous miscarriages or patients without prior live-birth, there were also no differences in the genotype distribution between these subgroups and controls. The authors concluded that the findings of the current study suggested that the prolactin receptor gene intron C/T polymorphism was not a major determinant of the development of RPL. Many studies have examined if there is a genetic component for the risk of RPL. Recently, 1 study examined if genetic polymorphisms involved in the regulation of the hypothalamic-pituitary-ovarian axis would be associated with recurrent miscarriage. Among 35 polymorphisms in 20 candidate genes, genotype distribution with regard to the prolactin receptor gene intron C/T polymorphism (rs37389) differed between the recurrent miscarriage and the control groups. Since this study reporting the candidate association between the prolactin receptor gene and recurrent miscarriage, no replication study has been performed. The genotype distribution of the prolactin receptor gene C/T polymorphism in the recurrent miscarriage group did not differ from that in the control group. The authors stated that
the findings of this study may be useful in that it is the first replication study since the initial report of
the association of prolactin receptor gene polymorphism with recurrent miscarriage. They noted that
although no association was found, the potential role of prolactin in pregnancy loss needs to be further
investigated because prolactin and its receptor have been postulated to play an important role in the
maintenance of normal pregnancy.

**Serum Anti-Heat Shock Protein Antibodies Levels**

Matsuda and associates (2017) noted that vascular dysfunction has been reported in women with
RPL. These investigators examined the severity of vascular dysfunction in non-pregnant women with
RPL and its correlation with anti-heat shock protein (HSP) antibodies that are known to induce
arteriosclerosis. They measured the serum anti-HSP60 antibodies, anti-HSP70 antibodies, and anti-
phospholipid antibodies (APA) in 68 women with RPL and 29 healthy controls. Among the women with
RPL, 14 had a diagnosis of antiphospholipid syndrome (APS), and in the remaining 54, the causes for RPL
were unexplained. Compared to the controls, the brachial-ankle pulse wave velocity (baPWV), carotid
augmentation index (cAI), and uterine artery pulsatility index (PI) were all significantly higher in the
women with both APS and unexplained RPL. Compared to the controls, the anti-HSP60 antibody levels
were significantly higher in the APA-positive group of women with unexplained RPL, and the anti-HSP70
antibody levels were significantly higher in APS and APA-positive group of women with unexplained
RPL. However, the anti-HSP60 and anti-HSP70 antibody levels did not correlate with the values of
baPWV or cAI. The authors concluded that these findings showed that anti-HSP60 and anti-HSP70
antibodies were increased in women with unexplained RPL. They stated that further studies are needed
to elucidate the roles of anti-HSP antibodies and their pathophysiology in unexplained RPL.

**Serum Anti-Mullerian Hormone Levels**

In a retrospective, cohort study, Pils and colleagues (2017) correlated anti-Mullerian hormone (AMH)
levels and other parameters for ovarian reserve to the gestational age at the time of pregnancy loss in
women with idiopathic RM. A total of 79 patients had suffered a total of 266 miscarriages. When
comparing women with an "unembryonic" to those with an "embryonic" most recent miscarriage, there
was no difference in median age (36.3 years, inter-quartile range [IQR] of 31.6 to 40.1 versus 34.2 years,
IQR of 29.9 to 38.0; p = 0.303); but in median AMH levels (0.7, IQR of 0.2 to 18, versus median 1.8, IQR
of 1.3 to 3.3, respectively, p = 0.044) and in the rate of patients with an AMH less than or equal to 1
ng/ml (23/37, 62.2 %, versus 8/42, 19 %; p < 0.001). The authors concluded that AMH might add to the
diagnostic process in RM in the future. They stated that to their best knowledge, this was the first study
to compare markers of ovarian reserve with age at pregnancy loss in women with RM. These findings
suggested that AMH might be a valuable parameter in addition to chronological age in the
future. However, these investigators stated that they could not provide reliable data on these issue in
the present study because of its retrospective design and the small sample size (n = 79) that must be
considered general study limitations. They stated that larger prospective trials are needed to prove the
finding that lower AMH levels were associated with earlier gestational age at miscarriage and to further
evaluate the value of AMH in the diagnostic process of RM.

**SUPPLEMENTAL INFORMATION**

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.
MEDICARE NATIONAL COVERAGE

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ESSENTIAL HEALTH BENEFITS

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntary offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES


**CODES**

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<td>whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-hyphenlike episodes [MELAS], myoclonic epilepsy with ragged-hyphenlike fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmyn detection</td>
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Genetic Testing for Recurrent Pregnancy Loss

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**POLICY HISTORY**

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<td>Replace policy</td>
<td>Reviewed with literature search; policy statement revised to define pregnancy loss as 2 or more consecutive losses.</td>
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<td>01/15/16</td>
<td>Replace policy</td>
<td>Changed policy statement: tests for inherited thrombophilic disorders (please reference MP 2.04.82 for genetic thrombophilia tests which are eligible for coverage).</td>
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<td>04/25/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review; no change to the policy.</td>
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<td>08/30/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to title, list of genetic tests, updated literature review, and added references 1-11. Effective date is November 15, 2017.</td>
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<td>04/30/18</td>
<td>Update only</td>
<td>Medical policy renumbered from 4.02.10 to 4.02.510</td>
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<tr>
<td>08/20/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted additional investigational tests, effective 11/15/2018: (1) mitochondrial DNA variations analysis; (2) prolactin receptor gene polymorphism testing; (3) serum anti-heat shock protein antibodies (e.g., anti-HSP60 and anti-HSP70) levels; and (4) serum anti-Mullerian hormone levels. Added codes: 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81460, 83516, and 82397. References 5, 7, 9, and 10 added.</td>
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