Medical Policy

MP 4.02.10
Diagnostic Testing for Recurrent Pregnancy Loss

Last Review: 8/30/2017
Effective Date: 11/15/2017
Related Policies: None

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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 phosphatidylserine, phosphatidylethanolamine, phatidylinositol, phosphatidlylycerol, phosphatidic acid or other anti-phospholipid antibodies other than anti-cardiolipin 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;
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. Methylene tetrahydrofolate reductase (MTHFR) testing;
20. Mixed lymphocytotoxic antibody tests;
21. Mixed lymphocyte culture reactions;
22. Molecular cytogenetic testing using comparative genomic hybridization (CGH) for chromosomal analysis (e.g., parental blood and products of conception);
23. Molecular genetic testing for highly skewed X-inactivation patterns;
24. Parental human leukocyte antigen (HLA) status;
25. Plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms testing;
26. Plasminogen activator inhibitor-I (PAI-1) antigen;
27. Plasminogen activator inhibitor-I activity;
28. Pre-implantation genetic screening (PGS);
29. Reproductive immunophenotype (CD3+, CD4+, CD5+, CD8+, CD16+, CD19+, CD56+);
30. Serum “blocking factor”;
31. Routine preimplantation embryo aneuploidy screening;
32. X-chromosome inactivation study;
33. 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 (eg, 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**

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 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.

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.

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.

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.

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.

REFERENCES


CODES

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### Diagnostic Testing for Recurrent Pregnancy Loss

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<th>Procedure Code</th>
<th>Description</th>
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<td>Molecular diagnostics</td>
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<td>Natural killer (NK) cells</td>
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**POLICY HISTORY**

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<th>Action</th>
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<tr>
<td>07/08/09</td>
<td>Add to OB/Gyn section</td>
<td>New policy</td>
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<tr>
<td>12/03/14</td>
<td>Replace local policy</td>
<td>Reviewed with literature search; policy statement revised to define pregnancy loss as 2 or more consecutive losses.</td>
</tr>
<tr>
<td>01/15/16</td>
<td>Replace local policy</td>
<td>Changed policy statement: tests for inherited thrombophilic disorders (please reference MP 2.04.82 for genetic thrombophilia</td>
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Original Policy Date: July 2009
## MP 4.02.10
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<table>
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<th>Date</th>
<th>Event Description</th>
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<tr>
<td>04/25/17</td>
<td>Replace local policy with BCI annual review; policy reviewed by consensus with plans for future literature search and policy update.</td>
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<tr>
<td>08/30/17</td>
<td>Replace local policy with BCI 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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