Recurrent pregnancy loss, also referred to as recurrent spontaneous abortion (RSA) or recurrent miscarriage has been defined as two, three or more consecutive pregnancy losses by the American College of Obstetricians and Gynecologists (ACOG) (ACOG, 2001). More recently, the American Society for Reproductive Medicine (ASRM) redefined recurrent pregnancy loss as two or more failed pregnancies (ASRM, 2008). According to the 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. Of clinically recognized pregnancies, 10-15% results in pregnancy loss, usually before 14 weeks’ gestation. 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 pregnancy loss may affect as many as 1-3% of childbearing women. The need for formal assessment and testing varies among individuals depends on age and personal choice, although traditionally couples are offered evaluation after three losses. Couples who are in their fourth decade may elect to be evaluated after two recurrent pregnancy losses.

Policy

The following tests may be considered **medically necessary** for evaluation of members with recurrent pregnancy loss (defined as three 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. Antibodies to phosphatidylserine, phosphatidylethanolamine, or other antiphospholipid antibodies other than anticardiolipin and lupus anticoagulant; or

2. Parental human leukocyte antigen (HLA) status; or

3. Maternal antiparental antibodies; or

4. Tests for serum “blocking factor”; or

5. Tests for maternal antileukocytic antibodies to paternal leukocytes; or

6. Luteal phase biopsy to determine the status of natural killer (NK)-like cells; or

7. Tests for embryotoxic factor; or

8. Determination of the percentage of circulating NK cells; or

9. Embryo toxicity assay (ETA); or

10. X-chromosome inactivation study.

Policy Guidelines

No applicable information

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, 2001).

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 antiparenteral 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 Guidelines on Management of Recurrent Miscarriage (2001) are consistent with ACOG Guidelines. RCOG recommends the following workup for recurrent pregnancy loss:

- peripheral blood karyotyping in both partners
- karyotyping of all fetal products
- a pelvic ultrasound scan to assess ovarian morphology and the uterine cavity
- screening tests for antiphospholipid antibodies (both the lupus anticoagulant and anticardiolipin antibodies) performed on two separate occasions at least six weeks apart. Discordant results should prompt the performance of a third test.

The RCOG guidelines conclude that 'the place of all other investigations including a search for newly described thrombophilic defects is unproven and such tests should only be performed in the context of research studies.'

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.'

Investigators have also found evidence of significantly higher serum homocysteine levels among women with a history of recurrent miscarriage (Krabbe, 2005; Hague, 2003). Routine folate supplementation is recommended during pregnancy to prevent neural tube defects (USPSTF, 2006). 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).

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;

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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 3 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.

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