THE OHIO STATE UNIVERSITY
HEALTH PLAN

Subject: Evaluation of Recurrent Pregnancy Loss

Effective Date: 4/16
Revision Date: 8/22

DESCRIPTION

Clinically recognized pregnancy loss is common, occurring in approximately 15-25% of pregnancies. The majority of sporadic losses before 10 weeks' gestation result from random numeric chromosome errors, specifically, trisomy, monosomy, and polyploidy. In contrast, recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed chemical pregnancies. It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.

The challenge for clinicians is to differentiate sporadic miscarriage from RPL. Self-reported losses by patients may not be accurate. For the purposes of determining whether evaluation for RPL is appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical evaluation may proceed following two first-trimester pregnancy losses.

DEFINITIONS

Recurrent Pregnancy Loss (RPL):

- Two or more failed consecutive clinical pregnancies as documented by ultrasonography or histopathologic examination; or
- Three consecutive pregnancy losses, which are not required to be intrauterine.

INDICATIONS FOR NURSE APPROVAL

OSU Health Plan considers the following tests medically necessary for the evaluation of members with recurrent pregnancy loss who meet the above definition:

- Karyotypic analysis of the parents to detect any balanced structural chromosomal abnormalities
- Screening for lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), and anti-β_2 glycoprotein I, for diagnosis of antiphospholipid syndrome
- Karyotypic analysis of products of conception
- Diagnostic evaluation for uterine anatomic anomalies:
    - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy
    - Ultrasound
    - MRI
- Pelvic ultrasound
- Screening for thyroid or prolactin abnormalities
- Genetic counseling for cases of RPL associated with parental chromosomal abnormalities
- Endometrial biopsies for evaluation of luteal phase defect
- Factor V Leiden genetic testing for members with RPL and one or more of the following:

- An abnormal activated protein C (APC) resistance assay result; or
- Recurrent, unexplained late fetal loss (after 9 weeks of gestation) associated with evidence of placental ischemia/infarction and maternal vessel thrombosis

EXCLUSIONS

The OSU Health Plan considers the following tests experimental and investigation for the evaluation of members with recurrent pregnancy loss:

- Routine testing of women with RPL who do not meet the above criteria for inherited thrombophilias (specifically, factor V Leiden and the prothrombin gene mutations, protein C, protein S, and antithrombin deficiencies)
- Testing for spermploidy (e.g., fluorescence in situ hybridization [FISH]) or DNA fragmentation
- Alloimmune factors (e.g., embryo-toxic factors, decidual cytokine profiles, blocking or anti-paternal antibody levels, HLA-G polymorphism)
- Antinuclear antibody (ANA)
- Methylene tetrahydrofolate reductase (MTHFR) testing
- Preimplantation genetic testing for aneuploidy (PGT-A)(formerly called Preimplantation genetic screening (PGS))
- ACE I/D and PAI-1 4G/5G polymorphism testing
- Annexin A5 promoter haplotype M2 testing
- Angiotensin converting enzyme (ACE) gene polymorphisms testing
- Determination of the percentage of circulating natural killer (NK) cells and NK activity
- Embryo toxicity assay (ETA) or embryo toxic factor
- Estrogen receptor beta gene polymorphisms testing
- Expression of peroxisome proliferator activation receptors (PPARs) and tumor necrosis factor alpha (TNFα) in placenta tissues
- Expression of pinopodes, thrombomodulin and ezrin in the endometrium
- Genetic association studies of inflammatory cytokine polymorphisms
- Inhibin B
- Interleukin genes polymorphisms testing (including IL-1β, IL-6, IL-10, IL-17, IL-18, IL-21)
- Inter-α trypsin inhibitor-heavy chain 4 (ITI-H4)
- Mitochondrial DNA variations analysis
- Mixed lymphocytotoxic antibody tests
- Mixed lymphocyte culture reactions
- Molecular cytogenetic testing using comparative genomic hybridization (CGH) for chromosomal analysis
- Molecular genetic testing for highly skewed X-inactivation patterns
- miRNA gene polymorphism testing
- Placental-specific protein1 (PLAC1)
- Placental expression of pentraxin 3 (PTX3)
- Products of Conception (POC) test (Igenomix)
- Serum anti-heat shock protein antibodies (e.g., anti-HSP60 and anti-HSP70) levels
- Sperm DNA fragmentation
- Tumor necrosis factor alpha gene polymorphisms testing
- X-chromosome inactivation study
- Whole exome sequencing

RELATED CPT/HCPC CODES

CPT codes covered if selection criteria are met:

58100	Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography
58555 - 58563	Hysteroscopy, diagnostic or surgical
74740	Hysterosalpingography, radiological supervision and interpretation
76831	Saline infusion sonohysterography (SIS), including color flow Doppler, when performed
76856 - 76857	Ultrasound, pelvic (non-obstetric)
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81402 - 81408	Molecular pathology
83890 - 83914	Molecular diagnostics [not covered for preimplantation genetic screening]
84443	Thyroid stimulating hormone (TSH)
85307	Activated Protein C (APC) resistance assay
85335	Factor inhibitor test
85337	Thrombomodulin
85705	Thromboblastin inhibition, tissue
86146	Beta 2 Glycoprotein I antibody, each [IgG or IgM]
86147	Cardiolipin (phospholipid) antibody, each Ig class
86800	Thyroglobulin antibody
86828 - 86829	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, flow cytometry); qualitative assessment of the presence or absence of antibody(ies) to HLA Class I and/or Class II HLA antigens
86830 – 86831	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); antibody identification by qualitative panel using complete HLA phenotypes, HLA Class I or HLA Class II
86832 – 86833	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); high definition qualitative panel for identification of antibody specificities (eg, individual antigen per bead methodology), HLA Class I or HLA II
86834 – 86835	Antibody to human leukocyte antigens (HLA), solid phase assays (eg, microspheres or beads, ELISA, Flow cytometry); semi-hyphenquantitative panel (eg, titer), HLA Class I or HLA Class II
88230 - 88239	Tissue culture
88245 - 88269	Chromosome analysis for breakage syndromes [not covered for preimplantation genetic screening]
88271 - 88275	Molecular cytogenetics [not covered for preimplantation genetic screening]
88280 - 88289	Chromosome analysis (additional karyotypes, specialized banding techniques, cells counted, high resolution study) [not covered for preimplantation genetic screening]
88291	Cytogenetics and molecular cytogenetics, interpretation and report [not covered for preimplantation genetic screening]

89325	Sperm Antibodies

CPT codes not covered for indications listed in this policy:	
0252U	Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicisms and segmental aneuploidy
81228	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, bacterial artificial chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81400	Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [angiotensin converting enzyme (ACE) gene polymorphisms testing], [plasminogen activator inhibitor-1 (PAI-1) gene polymorphisms testing]
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [highly skewed X-inactivation patterns]
81415 – 81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome)
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON], genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
82397	Chemiluminescent assay [inhibin B]
83090	Homocysteine
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method [serum anti-heat shock protein antibodies (e.g., anti-HSP60 and anti-HSP70) levels]
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified[cytokine polymorphisms analysis (Th1/Th2 intra-cellular cytokine ratio]
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85301	Clotting inhibitors or anticoagulants; antithrombin III, antigen assay
85302 - 85306	Clotting inhibitors or anticoagulants; protein C and protein S
85415	Fibrinolytic factors and inhibitors; plasminogen activator
86021	Antibody identification; leukocyte antibodies

86148	Ant-phosphatidylserine (phospholipid) antibody
86255	Fluorescent noninfectious agent antibody; screen, each antibody [antiadrenal antibodies]
86256	titer, each antibody
86353	Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis [mixed lymphocyte culture reactions]
86357	Natural killer (NK) cells, total count
86805	Lymphocytotoxicity assay, visual crossmatch; with titration
86807	Serum screening for cytotoxic percent reactive antibody (PRA); standard method
86812 - 86817	HLA typing
86825	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (eg, using flow cytometry); first serum sample or dilution
86826	each additional serum sample or sample dilution
88142	Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; manual screening under physician supervision [reproductive immunophenotype CD3+, CD4+, CD5+, CD8+, CD16+, CD19+, CD56+]
88184	Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker [NK activity]
88185	each additional marker (List separately in addition to code for first marker) [NK activity]
88189	Flow cytometry, cell cycle or DNA analysis [reproductive immunophenotype CD3+, CD4+, CD5+, CD8+, CD16+, CD19+, CD56+]
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody strain procedure; manual
88361	using computer-assisted technology
89290 - 89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than, equal to, or greater than 5 embryos [for recurrent pregnancy loss]

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