Early Pregnancy Loss – Etiology and Evaluation

There may be several motivations for clinicians and patients to undertake an evaluation for the cause of a single or recurrent early pregnancy loss. The knowledge that an early pregnancy loss is secondary to a sporadic genetic abnormality may provide parents with reassurance that there was nothing that they did or did not do that contributed to the loss, although the magnitude of this benefit is difficult to quantify. For couples with recurrent pregnancy loss and evidence of a structural genetic abnormality in one of the parents, preimplantation genetic diagnosis with transfer of unaffected embryos or the use of donor gametes might be considered for therapy. These therapies might be considered for couples with recurrent pregnancy loss without evidence of a structural genetic abnormality in one of the parents; guidelines on the management of recurrent pregnancy loss from ASRM state that “treatment options should be based on whether repeated miscarriages are euploid, aneuploid, or due to an unbalanced structural rearrangement and not exclusively on the parental carrier status.” Finally, among patients who are found to have a potential nongenetic underlying cause of recurrent pregnancy loss, such as antiphospholipid syndrome, cytogenetic analysis of pregnancy losses may provide evidence that the miscarriages were not due to treatment failure.

Genetic testing of products of conception, if possible, is recommended by several reproductive health organizations. A committee opinion from the ASRM recommends that the assessment of recurrent pregnancy loss include peripheral karyotyping of the parents, and states that karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss. The National Society of Genetic Counselors convened a multidisciplinary Inherited Pregnancy Loss Working Group which provided recommendations for the genetic evaluation of couples with recurrent pregnancy loss that stated that, when possible, chromosomal analysis on fetal tissue from products of conception should be pursued.

Late Pregnancy Loss

Fetal loss that occurs later in pregnancy, after 20 weeks gestation, may be referred to as IUFD, stillbirth, or intrauterine fetal death. In 2004, IUFD occurred in 6.2 of 1000 births in the United States, representing about 60% of perinatal mortality. IUFD may be related to a range of disorders, including genetic disorders in the fetus, maternal infection, coexisting maternal medical disorders (e.g., diabetes, antiphospholipid antibody syndrome, heritable thrombophilias) and obstetric complications, although in many cases, the precise cause is unable to be identified. Chromosomal or
Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

Genetic abnormalities can be found in 8% to 13% of IUFD, most commonly aneuploidies. In 1 large series of IUFD (N=1025), cytogenic abnormalities were detected in 11.9%.

The American College of Obstetrics and Gynecology recommends that evaluation after an IUFD includes examination of the stillborn fetus, along with examination of the placenta and umbilical cord, along with genetic testing for all IUFD (after parental permission is obtained). Other evaluation should be based on maternal history and may include evaluation for thyroid disorders, systemic lupus erythematosus, and infections.

Some of the motivations for evaluation for a cause of IUFD are the same as for earlier pregnancy loss. Although both early and later pregnancy losses may cause grief for the mother and her family, IUFD can be particularly devastating. Information about the cause of the pregnancy loss may be important in counseling women about their recurrence risk. In low-risk women with an unexplained IUFD, the risk of recurrence is 7.8 to 10.5 of 1000 live births, but this increases to 21.8 per 1000 live births in women with a history of fetal growth restriction. Identification of a heritable genetic mutation in a fetus may prompt testing in the parents; if a heritable mutation is identified, parents may pursue preimplantation genetic diagnosis in future pregnancies.

Genetic Abnormalities in Miscarriage and IUFD

Genetic disorders are generally categorized into 3 main groups: single gene, chromosomal, and multifactorial. Single gene disorders (also known as monogenic disorders) result from errors in a specific gene, whereas those that are chromosomal include larger aberrations that are numerical or structural. Evidence about specific abnormalities in miscarriages and IUFD is somewhat limited. However, it is estimated that 60% of early pregnancy losses are associated with chromosomal abnormalities, particularly trisomies and monosomy X. For later pregnancy losses, aneuploidies are most common in the 8% to 13% of tested IUFD that have an identified chromosomal or genetic abnormality. Karyotypic abnormalities are identified in 6% to 12% of IUFD. Rates of single gene disorders in IUFD are less well-quantified. However, of stillborn fetuses who undergo autopsy, 25% to 35% are identified to have single or multiple malformations or deformations; of these, 25% have an abnormal karyotype, but other single gene disorders are suspected to occur in a high proportion of stillborn fetuses with malformations.

Traditionally, genetic evaluation of the products of conception after a miscarriage is conducted by karyotyping of metaphase cells after cells are cultured in tissue. Karyotyping can identify whole chromosome aneuploidies and large structural rearrangements. However, only visible rearrangements are likely to be identified using this method (down to a resolution of 5-10 Mb), so smaller genetic variants may not be detected. In addition, karyotype requires culturing of the target cells, which may fail or be infeasible, particularly for formalin-preserved samples. In addition, there is the potential for maternal cell contamination, which may occur if the products of conception tissue is not separated from the maternal decidua before culturing, or if there is poor growth of noneuploid cells from the products of conception tissue, thereby allowing maternal cell overgrowth. The potential for maternal cell contamination makes it impossible to know if a normal female (46 XX) karyotype testing results is due to a normal fetal karyotype or a maternal karyotype. In 1 study that included 103 first trimester miscarriages, culture failure occurred in 25% of cases.

Chromosomal Microarray (CMA) Testing

There has been interest in using alternative genetic testing methods, particularly array comparative genomic hybridization, to detect chromosomal or other genetic abnormalities in the evaluation of miscarriages and IUFD.

Several types of microarray technology are in current clinical use, primarily array comparative
Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

genomic hybridization (array CGH) and single nucleotide polymorphism (SNP) microarrays. CGH CMA analysis detects copy number variants (CNVs) by comparing a reference genomic sequence to the patient (“unknown”) sequence in terms of binding to a microarray of cloned (from bacterial artificial chromosomes) or synthesized DNA fragments with known sequences. The reference DNA and the unknown sample are labeled with different fluorescent tags, and both samples are cohybridized to the fragments of DNA on the microarray. Computer analysis is used to detect the array patterns and intensities of the hybridized samples. If the unknown sample contains a deletion or duplication of genetic material in a region contained on the reference microarray, the sequence imbalance is detected as a difference in fluorescence intensity.

In SNP-based CMA testing, a microarray of SNPs, which may include hundreds of thousands of SNPs, is used for hybridization. In contrast to array CGH, a reference genomic sequence is not used. Instead, only the “unknown” sample is hybridized to the array platform, and the presence or absence of specific known DNA sequence variants is evaluated by signal intensity to provide information about copy numbers. In some cases, laboratories confirm CNVs detected on CMA with an alternative technique, such as fluorescence in situ hybridization (FISH) or flow cytometry.

Microarrays also vary in breadth of coverage of the genome that they include. Targeted CMA analysis provides coverage of the genome with a concentration of sequences in areas with known, clinically significant CNVs. In contrast, whole-genome CMA allows the characterization of large numbers of genes, but with the downside that analysis may identify large numbers of CNVs of undetermined significance.

CMA has several advantages over karyotyping, including improved resolution (detection of smaller chromosomal variants that are undetectable using standard karyotyping) and therefore can result in potentially higher rates of detection of pathogenic chromosomal abnormalities. Array CGH can detect CNVs for larger deletions and duplications, including trisomies. However, CMA based on array CGH cannot detect balanced translocations or diploid, triploid and tetraploid states or sequence inversions because these are not associated with fluorescence intensity change. SNP-based CMA analysis, in addition to detecting deletions and duplications, can detect runs of homozygosity, which suggests consanguinity, triploidy, and uniparental disomy.

CMA also has the advantage of not requiring successful cell culture, so may be more likely to yield a result in cases where karyotyping is technically unsuccessful due to failed culture. In the case of testing of specimens from early miscarriage, CMA may also be used to rule out maternal cell contamination, if a fetal sample is compared with a maternal sample.

CMA has the disadvantage of higher rates of detection of variants of uncertain significance. The American College of Medical Genetics has published guidelines regarding the interpretation and reporting of CNVs in the postnatal setting that recommend that laboratories that perform array-based assessment of CNVs track their experience with CNVs and document pathogenic CNVs, CNVs of uncertain significance, and CNVs that have been determined to represent benign variation based on comparisons with internal and external databases.

Commercially Available Tests

Natera, Inc. (San Carlos, CA) offers the Anora™ miscarriage test, which uses a SNP-based array system for testing of products of conception. The test includes the company’s proprietary “Parental Support Technology,” which uses a DNA sample from 1 or both parents as a reference to the products of conception sample. This comparison can identify maternal cell contamination, uniparental disomy, and the parent of origin of a fetal chromosome abnormality. According to a description of the “Parental Support” algorithm, the algorithm uses the “SNP array data to calculate the relative amounts of each of the 2 alleles at each SNP. At heterozygous loci, disomic...
Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

Chromosomes are expected to have SNP ratios of approximately 50%, trisomic chromosomes are expected to have SNP ratios of approximately 33% and 66%, and monosomic chromosomes are expected to have only homozygous loci. For each chromosome, the algorithm compares the observed SNP data to each of the expected alleles for the possible ploidy states and determines which is most likely."

According to the manufacturer’s website, the test reports the following abnormalities, including the parent of origin of any anomaly when a parental sample has been submitted:

- Any whole chromosome aneuploidy.
- Triploidy.
- Tetraploidy where 1 parent contributed 1 set of chromosomes and the other parent contributed the other 3. Tetraploidy when parental contribution is equal cannot be detected.
- Uniparental disomy.
- Interstitial deletions and duplications greater than 5 Mb.
- Any terminal deletion or duplication, as it could be an indication for a balanced translocation.
- Deletions of 1 Mb or greater and duplications of 2 Mb or greater are reviewed individually by a genetic counselor/geneticist and reported if the potential cause of a miscarriage or recurrence risk implications are identified.
- Any of the following deletions and duplications, when identified:
  - 1p36 deletion
  - 1q21.1 deletion (epilepsy)
  - 2q37 deletion
  - 3q29 terminal deletion
  - 4p16.3 deletion (Wolf-Hirschhorn syndrome)
  - 5p15.2 deletion (Cri du Chat)
  - 7q11.23 deletion (Williams syndrome)
  - 8q23.2-8q24.1 deletion (Langer-Giedion)
  - 9q34 deletion
  - 11p13-14 deletion (WAGR)
  - 11q24.1 deletion (Jacobsen syndrome)
  - 10p13-p14 deletion (DiGeorge 2)
  - 15q11-q13 deletion (Prader-Willi/Angelman region)
  - 16p11.2 deletion (epilepsy)
  - 17p11.2 deletion (Smith-Magenis)
  - 17p13.3 deletion (Miller-Dieker)
  - 17q21.31 deletion
  - 22q13 deletion (Phelan-McDermid syndrome)
  - 22q11.2 deletion (DiGeorge/VCFS)
  - 22q11.2 duplication
  - Xq28 deletion (MECP2 deletion)
  - Xq28 duplication (MECP2 duplication)

CombiMatrix (Irvine, CA) offers 2 SNP-based microarray systems for testing products of conception, the CombiSNP™ Array for Pregnancy Loss, which is used for testing fresh tissue samples, and the CombiBAC™ Array, which is used for testing formalin-fixed, paraffin-embedded tissue samples. According to the manufacturer’s website, the CombiSNP Array is a high resolution SNP microarray that can detect triploidy, numeric chromosome abnormalities, unbalanced structural rearrangements, microdeletion/ duplication syndromes, long stretches of homozygosity, which can indicate shared ancestry or uniparental disomy and maternal cell contamination. The CombiBAC Array is an array CGH method that can detect numeric chromosome abnormalities, unbalanced structural rearrangements and microdeletion/microduplication syndromes.
Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

GeneDx offers the Whole Genome Chromosomal Microarray for Products of Conception test, which is a SNP- and CGH-array that has whole-genome CGH-array coverage with oligonucleotide probes for the detection of CNVs and SNP probes to detect runs of homozygosity, which may indicate uniparental disomy.

Multiple laboratories offer CMA testing for prenatal samples that is not specifically designed for testing of products of conception.

Regulatory Status

The Anora™ miscarriage test, the CombiSNPTM Array for Pregnancy Loss, the CombiBACTM Array, and the GeneDx Whole Genome Chromosomal Microarray for Products of Conception, along with other CMA testing platforms currently available, are laboratory-developed tests. Laboratory-developed tests performed by laboratories licensed for high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) act do not require clearance from the U.S. Food and Drug Administration (FDA) for marketing.

Many academic and commercial laboratories offer CMA testing. These tests should be performed in a CLIA-certified laboratory.

Related Policies

Genetic Testing for Evaluation of Developmental Delay/Autism Spectrum Disorder

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Chromosomal microarray analysis of fetal tissue may be considered medically necessary for the evaluation of intrauterine fetal demise that occurs after the second trimester (after 26 weeks and 6 days gestation). Chromosomal microarray analysis of fetal tissue in cases of miscarriage or intrauterine fetal demise is considered investigational for losses that occur during the first and second trimesters (up to 26 weeks and 6 days gestation) and in all other situations not addressed above as medically necessary. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise is covered

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Policy Guidelines

This policy does not address the use of chromosomal microarray testing (CMA) for preimplantation genetic diagnosis or preimplantation genetic screening, or the evaluation of suspected chromosomal abnormalities in the postnatal period.

Genetic Counseling

The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, in most cases, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family and future reproductive planning. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Definitions

Fetal tissue may consist of fetal tissue, a formed fetus, or placental tissue derived from the fetal genotype, depending on the stage of pregnancy at the time of the fetal loss.

Early pregnancy loss or miscarriage is considered to be a pregnancy loss that occurred at or before 20 weeks gestational age.

Intrauterine fetal demise (IUFD) is defined as delivery of a nonliveborn fetus after 20 weeks gestational age.

The evaluation of both recurrent and isolated miscarriages and IUFD may involve genetic testing of the products of conception. Such testing has typically been carried out through cell culture and karyotyping of cells in metaphase. However, this technique is limited by the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination. Chromosomal microarray analysis (CMA) of fetal tissue or placental tissue derived from the fetal genotype has been proposed as a technique to evaluate the cause of isolated and recurrent early pregnancy loss (miscarriages) and later pregnancy loss (IUFD).

The evidence related to the use of CMA in the evaluation of miscarriage and IUFD is primarily from studies that compare CMA test results with conventional karyotyping; these studies suggest that CMA has a high rate of concordance with karyotyping. For both early and late pregnancy loss, CMA is more likely to yield a result than karyotyping. Other studies have reported that CMA detects a substantial number of abnormalities in patients with normal karyotypes, but these studies are small and the precise yield is uncertain. Rates of variants of unknown significance on CMA testing of miscarriage samples are not well characterized.

Potential benefits from identifying a genetic abnormality in a miscarriage or IUFD include reducing
Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

emotional distress for families, altering additional testing that is undertaken to assess for other causes of pregnancy loss, and changing reproductive decision making for future pregnancies. No studies were identified that identify whether or how patient management is changed based on CMA testing of products of conception from early or late pregnancy losses, or how patient outcomes are improved. There was strong support from clinical input that CMA testing is medically necessary for the evaluation of IUFD and likely offers incremental benefits over testing with karyotyping for genetic evaluation in pregnancy loss. Although there was not consensus about a specific gestational age at which CMA testing for pregnancy loss should be used, the American College of Obstetrics and Gynecology supports the use of CMA testing for pregnancy losses in the third trimester. Therefore, CMA testing may be considered medical necessary in the evaluation of IUFD in the third trimester when fetal genetic evaluation is desired, either as an alternative to conventional karyotyping or when conventional karyotyping is normal or unable to be performed (i.e., in case of cell culture failure or maternal cell overgrowth).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

There is no specific CPT code for this test.

According to the Natera’s products of conception (POC) testing physician fact sheet (available at: http://www.natera.com/pdf/POC-Physician-Fact-Sheet.pdf), this testing is reported using 99 units of CPT code 88271.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Policy retitled Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise


Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise


Policy Implementation/Update Information

9/30/14  New policy developed. Chromosomal microarray analysis of products of conception (fetal tissue or placental tissue derived from the fetal genotype) is considered investigational for the evaluation of early pregnancy loss. Senior Medical Director review. Notification given 9/30/2014 for policy effective date 12/9/2014. (sk)

Policy retitled Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise

5/26/15  Policy updated with scope expanded to include late pregnancy losses. CMA testing of fetal tissue may be considered medically necessary for 3rd trimester pregnancy losses. Title changed to “Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise”. Reference added. Specialty Matched Consultant Advisory Panel review 3/25/2015. (sk)

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