Clinical Policy Title: Amniocentesis for diagnosis of fetal chromosomal abnormalities

Clinical Policy Number: 12.01.04

Effective Date: October 1, 2016
Initial Review Date: July 20, 2016
Most Recent Review Date: July 3, 2018
Next Review Date: July 2019

Related policies:

CP# 02.01.01 Maternal genetic testing

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of diagnostic amniocentesis procedures for fetal chromosomal abnormalities to be clinically proven and, therefore, medically necessary when the procedure is performed between 14 and 18 weeks of gestation (can be performed at any later gestational age) for both singleton and multiple pregnancies (American College of Obstetricians and Gynecologists, 2016a; 2016b; Wilson, 2013).

In addition, the procedure is medically necessary to document the existence and severity of chromosomal abnormalities, genetic abnormalities, or neural tube defects if any of the following is documented:

1. The mother is over 35 years of age
2. A chromosomal or genetic abnormality occurred in a previous pregnancy
3. A chromosomal or genetic abnormality exists in either parent
4. A chromosomal or genetic abnormality exists in a blood relative
5. An abnormal result has been found from an ultrasound, alpha-fetoprotein test, or multiple marker screening tests
6. An abnormal result from DNA sequencing of gestational maternal plasma

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.

All other uses of diagnostic amniocentesis procedures are not medically necessary, including those meeting the above criteria prior to the 14th week of gestation.

Alternative covered services:

Non-invasive screening.

Background

Birth defects are the leading cause of infant mortality in the United States, accounting for more than 20 percent of the 473,582 infant deaths in the U.S. from 1999-2016 (Centers for Disease Control, 2018). Although the causes of approximately 70 percent of all birth defects are unknown, many birth defects can be attributed to chromosomal abnormalities. Older women are at increased risk for delivering a baby with any chromosomal disorder. The risk of delivering an infant with a birth defect due to a chromosomal abnormality is about 1 in 525 at age 20 years, 1 in 385 at age 30 years, 1 in 200 at age 35 years, and 1 in 65 at age 40 years (American College of Obstetricians and Gynecologists, 2017). The expectation for effective fetal assessment has increased in the last few decades. In the United States, the number of births to mothers 35 and older has risen nearly 48 percent, from 453,722 to 669,671, from 1995 to 2016 (CDC, 2017; Martin, 2016).

Pregnant women who have a high risk of fetal chromosomal disorders are generally offered chorionic villus sampling or amniocentesis, which allows the karyotype of the fetus to be determined. However, these tests are invasive and can cause miscarriage, and are not indicated as screening tests for women at average risk. Therefore, a number of noninvasive prenatal tests have been developed to screen for fetal abnormalities and to determine the need for additional diagnostic testing. Pregnant women typically undergo prenatal screening during the second trimester with tests that evaluate specific hormone levels in the serum and/or ultrasonographic examination of the fetus.

Amniocentesis is a diagnostic procedure performed on pregnant women that looks for genetic and chromosomal abnormalities (birth defects) in the fetus. It is a sterile technique that uses a 22-gauge spinal needle, guided with continuous ultrasonography, producing a sample of 20 to 30 milliliters (American College of Obstetrics and Gynecology, 2016a).
Some common conditions that may be detected include Down syndrome (trisomy 21), cystic fibrosis, and neural tube defects (spina bifida). This test is generally performed between weeks 14 and 20 of pregnancy, but may be performed in the third trimester to look for certain conditions, such as infection and fetal lung maturity. It is highly accurate (98-99 percent) and is usually recommended by obstetricians if the fetus is at a higher risk for any of the health problems mentioned above. Doctors determine that risk by taking into account some laboratory findings, such as the triple screen test. The biggest risk involved in amniocentesis is that of miscarriage. Over time, the rate of miscarriage related to the procedure has declined; a recent meta-analysis of 180,000 pregnant women calculated a percentage of 0.11, or 1 in 900 (Akolekar, 2015). Because amniocentesis involves guiding a needle very close to the fetus, it can potentially be a source of trauma that triggers a miscarriage.

Evidence from past experience shows that amniocentesis performed at 10 – 13 weeks gestation results in a much higher loss of pregnancy, membrane rupture, or club foot. Minor complications occur in about 1 – 2 percent of the cases, mostly transient vaginal spotting or amniotic fluid leakage, and thus the procedure is not recommended before week 14 of gestation (American College of Obstetrics and Gynecology, 2016).

Amniotic fluid can be evaluated for fetal lung maturity, genetic evaluation, evidence of spina bifida (a birth defect in spinal cord development) or other neural-tube defects, the presence of infection, or fetal chromosomal analysis. Chromosomes are structures which contain all of the genetic information within our cells. Amniotic fluid contains numerous free-floating fetal cells that can be grown in the laboratory. When these cells multiply and reach a certain number, their chromosomes are extracted and analyzed. It takes approximately two weeks to perform chromosomal analysis. The fluid also contains proteins, minerals and other compounds that can be tested. These additional studies may require 1 to 7 days to perform. Data obtained from amniotic fluid can help women make informed decisions regarding their pregnancies.

Noninvasive screening based on biochemical analysis of maternal serum or urine, or fetal ultrasound measurements, allows estimates of the risk of a pregnancy being affected and provides information to guide decisions about definitive testing. However, no test can predict the severity of problems a person with Down’s syndrome, or other congenital anomaly will have.

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- United Kingdom National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on May 7, 2018. Search terms were: “amniocentesis diagnostic tests, routine, female, genetic testing, pregnancy, and prenatal diagnosis [all MeSH].”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

In 2016, the American College of Obstetrics and Gynecology updated guidelines on prenatal diagnostic testing for genetic disorders and fetal aneuploidy (American College of Obstetrics and Gynecology, 2016a; 2016b). Both of these publications include recommendations for identifying risk factors suggesting amniocentesis may be helpful, and for pre-test counseling on risks and benefits.

The National Society of Genetic Counselors practice guideline on prenatal screening and testing for chromosome aneuploidy recommends criteria for necessity, after counseling on risks and benefits from a physician and genetic counselor; amniocentesis tests are not recommended prior to 14 weeks gestation (Wilson, 2013).

A review of 299 women undergoing amniocentesis at 16 to 20 weeks gestation revealed that most (84.9 percent) were performed because the mother was over 35 years old. Other reasons were a family history of hereditary disease (7.9 percent), positive biochemical markers (5.6 percent), and positive ultrasound markers (1.6 percent) (Izetbegovic, 2013).

A study of detection rates in 12,365 women with indications for genetic amniocentesis documented abnormal karyotype in 57.4 percent in cases where the mother or father had a chromosomal abnormality. Other detection rates of abnormal karyotype were 8.5 percent in women with an abnormal ultrasound, 2.79 percent in women over age 35, and 2.23 percent of women with abnormal maternal serum tests. The percent of amniocentesis procedures that found fetal abnormal karyotype and trisomy 13/18/21 were 3.46, and 1.25, respectively (Xiao, 2016).

In a three-year screening program of Dutch women referred for testing for advanced maternal age, the positive predictive values to detect trisomy 21, also known as Down syndrome, were 1.0 and 1.8 percent for those undergoing amniocentesis and chorionic villus biopsy, respectively. Rates were higher for those undergoing both tests. About half of women with a high risk score from the combined tests chose no further invasive testing, and 90 percent of those with a diagnosis of trisomy 21 elected to terminate the pregnancy (Siljee, 2014).

The risk of pregnancy loss (twin pregnancies) for pregnancies with genetic amniocentesis at 14 to 22 weeks
gestation was compared with chorionic villus sampling and genetic amniocentesis. In four case-control studies, the risk was significantly higher for the amniocentesis group (2.59 versus 1.53 percent) after 24 weeks; however, the lack of randomized studies limits the value of this finding (Agarwal, 2012). Another systematic review of 17 studies of twin pregnancies calculated the 24 week mortality after amniocentesis at 3.5 percent; in seven of the studies, the odds ratio was a significantly high 1.8 compared to pregnancies with no amniocentesis (Vink, 2012).

Another systematic review of singleton pregnancies comparing amniocentesis in women more than 14 weeks gestation and chorionic villus sampling from 10 to 14 weeks included 29 and 16 studies of the two techniques, each with at least 100 pregnancies. No significant differences between amniocentesis and chorionic villus sampling were observed for pregnancy loss at 24 weeks or less (0.9 versus 1.3 percent) and all pregnancies (1.9 versus 2.0 percent) (Mujezinov, 2007). Maternal obesity made no difference in risk of fetal loss after amniocentesis (Harper, 2012).

The issue of unnecessary amniocentesis was addressed in a study of 1386 Austrian women who underwent the procedure. Of these, 49 percent were found to have negative polymerase chain reaction results for congenital toxoplasmosis, indicating that these were performed without clinical justification, making treatment of these women unnecessary (Prusa, 2015). On the other hand, a study from Wessex, England found that from 1991 to 2010, the number of amniocentesis procedures needed to diagnose one case of trisomy 21 fell from 53 to 15, a reflection in the improvement of the procedure’s ability to detect disease (Renshaw, 2013).

A Cochrane review examined three studies, each with a different amniocentesis technique, for risk reduction, namely intramuscular progesterone, hexoprenaline and selecting high or low puncture sites for late 'blind' procedure. No conclusive evidence for a benefit for any of these techniques was found (Mujezinovic, 2012).

Other studies have reviewed effects of amniocentesis on outcomes. Of 174 women with threatened preterm labor, 67 underwent amniocentesis. Of infants born at 22 to 28 week gestation, the amniocentesis group had better neonatal outcomes, both short- and long-term (Maki, 2015).

Complication rates of amniocentesis have also been studied. A review of 1569 procedures in Austria from 2003 to 2010 showed the percent of cases that led to complications resulting in miscarriage or ruptured membranes were 0.75, 2.00, and 3.13 for amniocentesis, trans-abdominal chorionic villus sampling, and trans-cervical chorionic villus sampling, respectively (Kollmann, 2013). Another study of complications in 188 twin pregnancies (half with amniocentesis, half without) found insignificantly greater rates of fetal loss, late miscarriage, and intra-uterine growth restriction in the group with amniocentesis (Sassi, 2016). A group of 2990 women who had amniocentesis had an insignificantly higher fetal loss rate than a group of 487 women with no amniocentesis, i.e. 1.0 versus 0.8 percent (Corrado, 2012).

Policy updates:
A total of five guidelines/other and 16 peer-reviewed articles were added to this policy in 2017, while eight peer-reviewed articles were deleted. The coverage policy section was shortened, to reflect the content of the appropriate clinical guidelines.

In 2018, six guidelines/other publications were added to the reference list and one guideline, which has been withdrawn, was removed from the reference list. One peer-reviewed paper was added to both the reference list and the summary of clinical evidence.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
<th>Key points:</th>
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<tbody>
<tr>
<td>Beta (2018)</td>
<td></td>
<td><strong>Key points:</strong></td>
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| Procedural risk from amniocentesis and chorionic villus sampling |                         | • This systematic review searched for studies published from 2000 - 2017. The analysis included ten studies of amniocentesis and six of chorionic villus sampling.  
• The final calculation showed that the procedure-related risk of miscarriage from amniocentesis was 0.35% (95% confidence interval [CI]: 0.07 to 0.63). The risk from chorionic villus sampling was 0.35% (95% CI: -0.31 to 1.00). The authors concluded that these statistics are lower than those which are commonly quoted to women. |
| Xiao (2016)     |                                   | **Key points:**                                                              |
| Detection rates of abnormal karyotype by reason for amniocentesis |                           | • Karyotype analysis of amniotic fluid performed on 12,365 pregnant Chinese women  
• Detection rates of abnormalities were 57.4% for cases where the mother or father had chromosomal abnormalities; 8.5% in pregnant women with pathological ultrasound finding; 2.79% in pregnant women age 35 and over; and 2.23% in women with abnormal maternal serum screening tests  
• 3.46% had abnormal fetal karyotype, 1.25% had trisomy 13, 18, or 21 |
| Prusa (2015)    |                                   | **Key points:**                                                              |
| Rate of unnecessary amniocentesis |                           | • Review of 1386 Austrian women with amniocentesis, birth cohort 1992-2008  
• Study of toxoplasma-specific polymerase chain reaction (PCR) on amniotic fluid to detect congenital toxoplasmosis  
• Only 51% of women had acute maternal infection confirmed serologically  
• Greater efforts needed to reduce unnecessary amniocentesis |
| Kollmann (2013) |                                   | **Key points:**                                                              |
| Comparison of complication rates, amniocentesis and chorionic villus sampling |                           | • Outcome of 1,903 Austrian women who underwent genetic amniocentesis or chorionic villus sampling during 2003-2010  
• Percent complication rates were 0.75 amniocentesis, 2.00 after transabdominal chorionic villus sampling, 3.13 after transcervical chorionic villus sampling |
| Agarwal (2012)  |                                   | **Key points:**                                                              |
| Risk of pregnancy loss after amniocentesis |                           | • Risk of pregnancy loss after first trimester chorionic villus sampling (9-14 weeks gestation) and second trimester genetic amniocentesis (14-22 weeks gestation)  
• In four case-control studies, the risk of pregnancy loss before 24 weeks after amniocentesis was higher (2.59% versus 1.53%) |
<p>| Vink (2012)     |                                   | <strong>Key points:</strong>                                                              |</p>
<table>
<thead>
<tr>
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<th>Content, Methods, Recommendations</th>
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| Risk of pregnancy loss after amniocentesis | • Systematic review of 17 studies  
• The 24 week gestation pooled procedure-related mortality rate was 3.5%  
• In 7 studies, the odds ratio was a significant 1.8 for those undergoing amniocentesis |

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not
an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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