# Chapter 8
# Prenatal Invasive Procedures


**What does prenatal diagnosis mean?**

- Prenatal diagnosis is the detection of hereditary diseases, congenital anomalies, and some infections in the early stages of pregnancy after ninth week of gestation.

**Which families are recommended to apply prenatal invasive procedures?**

- Mothers aged 35 and over.
- If the family has a child with chromosomal anomaly and/or congenital anomaly.
- Family risk for metabolic diseases.
- Stillbirth and/or recurrent miscarriage with unknown cause.
- If one parent has chromosomal translocation.
- If the family has blood diseases such as hemophilia, sickle cell anemia, thalassemia.
- If the mother has anxiety, prenatal diagnosis is performed.
- The probability of fetus with anomaly in pregnant women at risk for genetic diseases varies between 1 and 50%. In these families, the risk is 10–15 times higher than non-risky families.
- All genetic diseases and congenital anomalies cannot be detected by prenatal diagnosis, and no guarantee can be given for a completely healthy child.

**What is the meaning of aneuploidy?**

- Aneuploidy is defined as having one or more extra or missing chromosomes, leading to an unbalanced chromosome number in a cell.

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**What are the prenatal diagnostic methods?**

1. *Noninvasive methods, in maternal blood*
   (a) Double test (11–14 week) {Free Beta human chorionic gonadotrophin (βhCG), Pregnancy associated plasma protein A (PAPP-A), nuchal translucency (NT) measurement}
   (b) Triple test (15–20 or 22 week) {alpha fetoprotein (msAFP), estriol (uE3), and free or total hCG}
   (c) Quadruple test (15–18 or 22 week) {msAFP, uE3, dimeric inhibin A (DIA), and hCG}
   (d) Penta test (15–20 weeks) {msAFP, uE3, DIA, hCG, and hyperglycosylated hCG (HhCG)}
   (e) Extracellular DNA (noninvasive prenatal test-NIPT, cell free DNA)
2. *Invasive methods*
   (a) Amniocentesis
   (b) Chorionic villus biopsy (CVS)
   (c) Cordocentesis
   (d) Fetal biopsy (muscle-skin-liver-kidney)

**What is the meaning of preimplantation genetic diagnosis (PGD)?**

- PGD is a method for selecting embryos that do not have chromosomal abnormalities and certain genetic diseases for their transfer to the uterus and combine them with in vitro fertilization (IVF).
- PGD can be performed during the cycle of embryo development (IVF) by combining eggs and sperm in the laboratory.

**Especially on which situations PGD can be suggested to the families?**

- Studies have shown that 50% of spontaneous abortions are caused by a chromosomal abnormality.
- Chromosomal abnormalities may occur by chance in the fetus and may be due to balanced chromosomal abnormalities (translocation, inversion) that have no effect on the mother or father.
- Chromosome analysis and prenatal diagnosis are recommended to these families in their pregnancy.

**What are the indications for cell-free DNA (Non invasive prenatal test-NIPT) screening?**

- Maternal age greater than 35 years at delivery
- Ultrasonographic findings indicating increased aneuploidy risk
- History of prior pregnancy affected by a trisomy
- Parental balanced robertsonian translocation increasing risk of trisomy 13 or 21
- High-risk first trimester or second trimester aneuploidy screening results

**What are the features of alpha fetoprotein (AFP)? In which prenatal tests can we use it?**

- AFP: A glycoprotein-oncofetal protein produced in the liver of the fetus that can be detected in the mother's blood from the 12th week of pregnancy. First trimester measurement is not recommended due to low sensitivity. Ideally it is suitable to be measured during 16th–18th gestational weeks. There is no clinical role in measuring AFP in fetal plasma. Fetal AFP is filtered through the kidney and passes to amniotic fluid.
- Neural tube defects (NTDs) such as spina bifida, especially in the nervous system anomalies, AFP levels increase above normal. Since AFP in the fetal serum is easy to pass from the vessels to amniotic fluid through the neural defect, AFP levels increase in the amniotic fluid and then passes to the mother by diffusion through the amniotic membrane. Since this transition is less than transplacental transition, the expected increase in msAFP may not always occur.
- Therefore, measurement of msAFP is a screening test, not a diagnostic test.
- msAFP value $\geq$2.0 or 2.5 multiples of the median (MoM) measurement is interpreted as high. If the measurement is repeated and similar results are obtained, ultrasonography and if necessary AFP and acetyl cholinesterase activity in amniotic fluid is measured by amniocentesis.

**What are the conditions that may affect the levels of msAFP?**

- Misdating
- NTD
- Fetomaternal bleeding
- Abdominal defects
- Nephrosis
- Intrauterine fetal loss
- Amniotic band sequence
- Cantrell pentalogy
- Dermatological diseases (fetal)
- Chorioangioma
- Cystic hygroma
- Hydrops fetalis
- Sacrococcygeal teratoma
- Triploidy
- Maternal: DM, obesity, hepatoma, teratoma, liver diseases

**What are the features of the triple test (TT)?**

- Triple test: In maternal blood, msAFP, unconjugated estriol, and hCG are evaluated, and the risk is calculated by adding the age factor. If the value is above 1:250, there is a risk. It is a screening test for Down syndrome. The definitive diagnosis is made by fetal chromosome analysis.

- Triple test of pregnancy performed between 15th and 20th gestational weeks.
- In Down syndrome, msAFP decreased, uE3 decreased and hCG increased

**What is the meaning of spina bifida?**

- Spina bifida is a congenital malformation in which the spinal column is split (bifid) as a result of failed closure of the embryonic neural tube, during the fourth week post-fertilization.

**What is the commonest and most severe form of spina bifida?**

- Myelomeningocele (MMC) is the most severe form of spina bifida characterized by protrusion of the spinal cord and the meninges through a defect in the vertebral column and a spectrum of clinical manifestations including hindbrain herniation, hydrocephalus, sensory and motor neurological deficits, bowel dysfunction, and urinary dysfunction.

**What is the meaning of lemon and banana signs? In which gestational weeks can we observe those changes?**

- The lemon sign: Loss of the convex outward shape of the frontal bones with mild flattening, is present in virtually all fetuses with MMC between 16 and 24 weeks gestation
- The banana sign: Shape of the cerebellum looks like banana and is thought to be due to tethering of the spine with downward traction on the cerebellum (the Chiari II malformation). It can be mostly detected from 14 to 24 gestational weeks.
- Those changes occur due to vacuum effect, namely skull is trying to push the brain matter out of foramen magnum.

**What is the probability of exitus of a live born infant with MMC?**

- Live born infants with myelomeningocele have a death rate of approximately 10%.

**What is the management of MMC?**

- Surgery should be performed within 48 h of birth. However, an earlier intervention involving fetal surgery is now considered as a good method with reduced need for shunting and improved motor outcomes. Also another new method, fetoscopic repair is a promising alternative to open fetal myelomeningocele repair with a lower risk of uterine dehiscence.

**In which other conditions, prenatal invasive interventions can be used besides cytogenetic analysis?**

- Fetal transfusion
- Selective termination
- Balloon atrial septostomy
- Cord strangulation
- Balloon valvuloplasty
- Shunt operations
- Fetoscopy
- Twin-twin transfusion syndrome (TTTS) laser therapy

**In which weeks is prenatal invasive interventions performed for cytogenetic analysis?**

- CVS: 12 weeks (9–15 weeks)
- Amniocentesis: generally after 15th weeks (early amniocentesis is not preferred; complications like club foot)
- Cordocentesis > 18 weeks (ideal—can be done from 16th week)
- 0.5–1% pregnancy loss rate

**Describe amniocentesis, what are the indications?**

- Amniocentesis is performed between 15th and 21th pregnancy weeks. A small amount of amniotic fluid is taken with a fine needle with ultrasonography. Cells belonging to fetus poured into amniotic fluid are cultured and produced in special media, and chromosome, enzyme, and DNA analyzes are performed in cells. The risk of abortion is 0.5%. It is called early amniocentesis if administered before 14 weeks, since it is more risky and complications such as club foot (talipes) may occur currently, early amniocentesis is not a preferred method.
- Transvaginal amniocentesis is also possible after 11 weeks, after chorion–amniotic fusion.
- No risk of mosaicism. In addition to culture, enzyme and DNA studies can also be performed.
- Culture success is 97–99%.
- Determination of lung maturation.
- Rh/rh isoimmunization.
- Genetic diagnosis (prenatal diagnosis).
- Diagnosis of amnionitis.
- Amnioinfusion.

**What are the complications and disadvantages of amniocentesis?**

- Bleeding, infection, amniotic leak-oligohydramnios, and preterm labor are the most important complications.
- The main disadvantage of the procedure is the length of the culture stage, which is 15–30 days after the procedure.

**What are the main features of cordocentesis?**

- Cordocentesis is the collection of 1–4 mL blood from the umbilical cord of the fetus, karyotyping, whole blood analysis, and blood gas measurement.
- Cordocentesis is performed after the 18th week of pregnancy. Is used in the diagnosis of hereditary blood and metabolic diseases in case of anomaly detection by ultrasound, late admission, failure of previous prenatal diagnostic methods, or in doubtful results.
- It is used in the evaluation of blood gases in infants with cordocentesis developmental retardation, in the diagnosis of infectious diseases (rubella, toxoplasmosis), and to recognize hemolytic anemia in infants of Rh-negative pregnant women during intrauterine period.
- The risk of abortion is 1.5–4.8%.
- Bleeding, infection, and preterm labor are the most important complications.

**What are the indications for cordocentesis?**

- In hereditary blood and metabolic diseases (hemoglobinopathies, hemophilia, thrombocytopenia)
- Rh/rh Isoimmunization
- Fetal infection
- Karyotyping

**What are the main features of the chorionic villus sampling (CVS)? In which situations can it be used?**

- CVS is a prenatal test, removal of 5 mg of tissue from the placenta by ultrasound control. It is preferred in diseases that can be diagnosed by DNA analysis (thalassemia, phenylketonuria, cystic fibrosis, Duchenne muscle dystrophy, sickle cell anemia, fragile X send).
- There two methods of CVS: transcervical and transabdominal.
- CVS is performed during 9–15th gestational weeks.
- The risk of abortion is 2–3%. The risk of miscarriage in the transabdominal method is 0.5–1%.
- DNA studies other than chromosome analysis can be done, some enzyme deficiencies can be detected.
- The rate of fetal loss and anomaly (limb deformities) increases in earlier cases (due to vasoconstriction caused by prostaglandins during CVS).
- Adequate material rate is 95%, culture success is 95%.
- The size of the fragment is more important than the total amount of tissue removed during the procedure.
- Direct karyotyping without culturing chorionic villus cells is the most important advantage, but CVS culture is essential for diagnosis.
- The disadvantage of CVS is mosaicism, which is 1%. In the other two techniques (amniocentesis or cordocentesis) this ratio is close to zero.
- Bleeding is the most common complication.
- Infection, especially in transcervical applications, is rare.

**How is fetoscopy and fetal biopsy performed? Describe its characteristics.**

- Amniotic sac shown with light source and 15–30° optics by fetoscopy.
- Fetal skin, muscle, liver biopsy can be taken.
- Skin biopsy is more common currently.
- It is used in the diagnosis of skin diseases such as ichthyosis, epidermolysis bullosa, Sjögren's syndrome.
- Fetal mortality rate is 3–5%.

## Suggested Reading

1. Cunningham F, Leveno KJ, Bloom SL, et al. Prenatal diagnosis. In: Williams obstetrics. 25th ed. New York: McGraw-Hill; 2018. p. 277–300.

2. Messerlian GM, Palomaki GE. Down syndrome: overview of prenatal screening. UpToDate (09 Nov 2018). https://www.uptodate.com/contents/down-syndrome-overview-of-prenatal-screening.
3. ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. 2007;109:217.
4. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol. 2007;110:1459.
5. Palomaki GE, Messerlian GM, Halliday JV. Prenatal screening for common aneuploidies using cell-free DNA. UpToDate (21 Sept 2018). https://www.uptodate.com/contents/prenatal-screening-for-common-aneuploidies-using-cell-free-dna.
6. Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine. Practice Bulletin No. 163: screening for fetal aneuploidy. Obstet Gynecol. 2016;127:e123.
7. Committee Opinion No. 640: cell-free DNA screening for fetal aneuploidy. Obstet Gynecol. 2015;126:e31. Reaffirmed 2017.
8. Ghidini A. Diagnostic amniocentesis. UpToDate (25 Sep 2017). https://www.uptodate.com/contents/diagnostic-amniocentesis.
9. Dukhovny S, Wilkins-Haug L. Open neural tube defects: risk factors, prenatal screening and diagnosis, and pregnancy management. UpToDate (18 Dec 2018). https://www.uptodate.com/contents/open-neural-tube-defects-risk-factors-prenatal-screening-and-diagnosis-and-pregnancy-management.
10. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 187: neural tube defects. Obstet Gynecol. 2017;130:e279.
11. Palomaki GE, Neveux LM, Knight GJ, Haddow JE, Pandian R. Maternal serum invasive trophoblast antigen (hyperglycosylated hCG) as a screening marker for Down syndrome during the second trimester. Clin Chem. 2004;50:1804–8.
12. Kabagambe SK, Jensen GW, Chen YJ, Vanover MA, Farmer DL. Fetal surgery for myelomeningocele: a systematic review and meta-analysis of outcomes in fetoscopic versus open repair. Fetal Diagn Ther. 2018;43(3):161–74.
13. Farmer DL, Thom EA, Brock IIIJW, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Gupta N, Adzick NS, Management of Myelomeningocele Study Investigators. The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. Am J Obstet Gynecol. 2018;218(2):256–e1.
14. Adzick NS, Thom EA, Spong CY, Brock JW III, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993–1004.
15. Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev. 2017;9(9):CD003252. https://doi.org/10.1002/14651858.CD003252.pub2. PubMed PMID: 28869276; PubMed Central PMCID: PMC6483702.
16. Carlson LM, Vora NL. Prenatal diagnosis: screening and diagnostic tools. Obstet Gynecol Clin North Am. 2017;44(2):245–56. https://doi.org/10.1016/j.ogc.2017.02.004. PubMed PMID: 28499534; PubMed Central PMCID: PMC5548328.