Prenatal diagnosis of chromosomal disorders

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Indication for prenatal testing

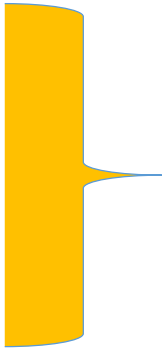
- Advanced maternal age
- Previous child with a chromosomal abnormality
- Family history of a chromosome abnormality
- Family history of a single-gene disorder
- Family history of congenital structural abnormalities
- Abnormalities identified in pregnancy
- Other high-risk factors

Prenatal screening (non-invasive)

- Maternal serum screening
  - Neural tube defects (NTD)
  - Down syndrome and other chromosome abnormalities
    - First-trimester screening (between 11 and 13 weeks of gestation)
    - Second-trimester screening (between 16 and 18 weeks of gestation)
    - Noninvasive prenatal screening by analysis of cell-free fetal DNA (NIPT)
- Ultrasonography

Invasive tests

- Amniocentesis
- Chorionic villus sampling
- Cordocentesis
- Fetoscopy
- Preimplantation Genetic Diagnosis (PGD)



Prenatal tanı

Neural tube defects (NTD)

- Anencephaly
- Spina bifida → open myelomeningocele

- Maternal serum AFP (MSAFP) multiples of the median (MoM)

2.5 MoM → ~75% of screened open spina bifida cases (the 95th centile)

Causes of Elevated Maternal Serum Alpha-Fetoprotein Concentration

- ✓Gestational age older than calculated
- ✓Spina bifida
- ✓Anencephaly
- ✓Congenital skin defects
- ✓Pilonidal cysts
- ✓Abdominal wall defects
- ✓Gastrointestinal defects
- ✓Obstruction
- ✓Liver necrosis
- ✓Cloacal exstrophy
- ✓Cystic hygroma
- ✓Sacrococcygeal teratomas
- ✓Renal anomalies
- ✓Urinary obstruction
- ✓Polycystic kidney
- ✓Absent kidney
- ✓Congenital nephrosis
- ✓Osteogenesis imperfecta
- ✓Low birth weight
- ✓Oligohydramnios
- ✓Multiple gestation
- ✓Decreased maternal weight

Thompson & Thompson, *Genetics in Medicine*, 8th ed. 2016.

Screening for Down syndrome and other chromosome abnormalities

	First-Trimester Screen			Second-Trimester Screen			
	Nuchal Translucency	PAPP-A	Free β-hCG	uE_3	AFP	hCG	Inhibin A
Trisomy 21	↑	↓	↑	↓	↓	↑	↑
Trisomy 18	↑	↓	↓	↓	↓	↓	-
Trisomy 13	↑	↓	↓	↓	↓	↓	-
NTD	-	-	-	-	↑↑	-	-

Thompson and Thompson Genetics in Medicine, 8th ed. 2016.

Non-Invasive Prenatal Testing (NIPT)

- After 6-7 weeks of gestation fetal DNA (+) in maternal plasma
- 2% to 10% of the cell-free fetal DNA in maternal blood
- Sensitivities and specificities approaching 99% for trisomy 21
- The test has false-positive and false-negative rates in the 1% to 2% range

Ultrasonography

- To detect fetal anomalies
- As a guide during invasive procedures

Ultrasonographic scanning

- fetal viability
- gestational age
- the number of fetuses
- volume of amniotic fluid
- fetal anatomical structures
- position of the fetus and placenta
- the optimal position for needle insertion

Prenatal USG findings suggestive of a chromosome abnormality

Feature	Chromosome abnormality
Cardiac defect	Trisomy 13, 18, 21
Cleft palate-lip	Trisomy 13
Clenched overlapping fingers	Trisomy 18
Cyctic hygroma or fetal hydrops	Turner syndrome, Trisomy 21
Duodenal atresia	Trisomy 21
Horseshoe kidney	Turner syndrome
Exomphalos	Trisomy 13, 18
Polydactyly	Trisomy 13, Triploidy
Rocker-bottom foot	Trisomy 13, 18
IUGR	Trisomy 13, 18*, 21

	Percent of Fetuses with Abnormal Karyotype	
Abnormality	If Isolated Abnormality	If Multiple Abnormalities
Ventriculomegaly	2	17
Choroid plexus cysts	≪1	48
Cystic hygroma	52	71
Nuchal edema	19	45
Diaphragmatic hernia	2	49
Heart defects	16	66
Duodenal atresia	38	64
Exomphalos	8	46
Renal abnormalities	3	24

Thompson & Thompson, Genetics in Medicine, 8th ed. 2016.

Ultrasonographic 'Soft' Markers

- Choroid plexus cysts → trisomy 18 ?
- Increased echogenicity of the fetal bowel → CF
- Cardiac echogenic focus → cardiac anomaly?

Radiography

- from 10th weeks onwards
- to diagnose inherited skeletal dysplasias

Amniocentesis

- The 16th and 20th weeks of gestation
- 10 to 20 mL of amniotic fluid
- The concentration of AFP in the amniotic fluid
- The success of chromosome analysis → 99% ↑
- 1 in 300 to 1 in 500 risk of miscarriage

Chorionic Villus Sampling (CVS)

- The 10th and 13th weeks of pregnancy
- *The major advantage of CVS →early diagnosis*
- *DNA is extracted → direct mutation test*
- The success of chromosome analysis → 99% ↑
- The risk of miscarriage 1% - 3%
- ~ 1% of CVS samplings → chromosomal mosaicism

Cordocentesis

- fetal blood sampling
- from 20th weeks onwards
- mosaicism in CVS or amniocentesis samples
- the risk of miscarriage 1% - 2%

Fetoscopy

- visualization of the fetus by means of an endoscope
- specific biopsy samples; for example the skin, the liver
- 3% to 5% risk of miscarriage

Special problems in prenatal chromosome analysis

- Mosaicism
- Cultural failure
- Other unusual chromosome finding
  - Different numerical chromosomal anomalies
  - Structural chromosomal rearrangement
  - Marker chromosome

Preimplantation Genetic Diagnosis (PGD)

- **blastomere** biopsy (at the 3 days after IVF) → single cell
- **blastocyst** biopsy /at the 5 to 6 days after IVF) → ~5 cells

Embryos → the genetic abnormality in question Ø

transferred to the uterus

Further reading

- Thompson&Thompson, Genetics in Medicine, eighth ed. 2016.
- Emery's Elements of Medical Genetics, 15th ed. 2017.