Prenatal diagnosis of frequently seen fetal syndromes (A-Z) 😊

Ibrahim Bildirici, MD
Professor of OBGYN
ACIBADEM University SOM
Attending Perinatologist
ACIBADEM MASLAK Hospital
Amniotic band sequence:

Amniotic band sequence refers to a highly variable spectrum of congenital anomalies that occur in association with amniotic bands.

The estimated incidence of ABS ranges from 1:1200 to 1:15,000 in live births, and 1:70 in stillbirths.
Anomalies include:

Craniofacial abnormalities — eg, encephalocele, exencephaly, clefts, which are often in unusual locations; anencephaly.

Body wall defects (especially if not in the midline), abdominal or thoracic contents may herniate through a body wall defect and into the amniotic cavity.

Limb defects — constriction rings, amputation, syndactyly, clubfoot, hand deformities, lymphedema distal to a constriction ring.

Visceral defects — eg, lung hypoplasia.

Other — Autotransplanted tissue on skin tags, spinal defects, scoliosis, ambiguous genitalia, short umbilical cord due to restricted motion of the fetus.
Arthrogryposis

• Multiple congenital joint contractures/ankyloses involving two or more body areas
• Pena Shokeir phenotype micrognathia, multiple contractures, camptodactyly (persistent finger flexion), polyhydramnios
  *many are AR
  *Lethal due to pulmonary hypoplasia
• Distal arthrogryposis
  Subset of non-progressive contractures w/o associated primary neurologic or muscle disease
Beckwith Wiedemann Syndrome

- Macrosomia
- Hemihyperplasia
- Macroglossia
- Ventral wall defects
- Predisposition to embryonal tumors
- Neonatal hypoglycemia
- Variable developmental delay
85% sporadic with normal karyotype

10-15% autosomal dominant inheritance

10-20% with paternal uniparental disomy (Both copies of 11p15 derived from father)

***Imprinting related disorder

1/13 000.
Binder Phenotype

a flat profile and depressed nasal bridge. Short nose, short columella, flat naso-labial angle and periallar flattening

Isolated Binder Phenotype transmission would be autosomal dominant
Binder Phenotype can also be an important sign of chondrodysplasia punctata (CDDP)
1. Chromosomal abnormalities: As Trisomy 21/4p del
2. Metabolic congenital abnormalities: As Zellweger syndrome.
3. Disruption of vitamin K metabolism: caused by inherited or extrinsic factors
   3.1 Inherited etiology: X-linked recessive brachytelephalangic type of chondrodysplasia punctata = CDPX1 caused by mutations of ARSE, localized in Xp22. ARSE codes Aryl Sulfatase Enzyme, a system Golgi enzyme. His activity is inhibited in vitro by Warfarin.
   3.2 Extrinsic factors:
      - Prenatal exposure to Phenytoin and Alcohol
      - Prenatal exposure to Coumarin derivatives: especially between 6th and 9th weeks.
      - Maternal chronic disease: with important vitamin K deficiency during first trimester.
CHARGE Association

CHARGE is a mnemonic for
coloboma,
heart defects,
choanal atresia,
retarded growth and
development,
genital abnormalities, and
ear anomalies.

TE fistula +/- esophageal atresia,
anal atresia

CHARGE syndrome, caused
by mutation of CHD7, is inherited in an autosomal
dominant manner.
Cornelia de Lange Syndrome

Abnormal facies
Growth and mental retardation
Limb defects
Gastrointestinal defects
Cardiac defects
Hypertrichosis

IUGR
Upper limb reduction defects
Micrognathia with protruding upper lip
CDH
AD
Most sporadic, rare familial cases
NIPBL mutations
Cri du Chat Syndrome (5p- syndrome)

Microcephaly
Facial dysmorphic features: hypertelorism, micrognathia, low-set ears
Intrauterine growth restriction
Cardiac defects (ventricular, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot)

Occasional abnormalities: Cleft lip and palate, myopia, optic atrophy, preauricular skin tag, bifid uvula, clinodactyly, absent kidney and spleen, cryptorchidism and hemivertebra.
Absent nasal bone:
Amniocentesis: 5 p-
Cystic fibrosis

AR multisystem disorder: dysfunctional chloride ion transport across epithelial surfaces

>1000 CFTR mutations possible

1/2000-5000

Best diagnostic clue:
Echogenic bowel in 2nd trimester progressing to bowel dilation in 3rd trimester
A fetus with echogenic bowel seen using normal ultrasound gain settings (1A). Image at right (1B) is the same finding demonstrated on a lower gain.
DiGeorge Syndrome
Prenatal diagnosis of chromosomal abnormalities in fetuses with abnormal cardiac ultrasound findings: evaluation of chromosomal microarray-based analysis.


Out of the 276 pregnancies with abnormal cardiac ultrasound findings, karyotyping revealed a chromosomal abnormality in 44 (15.9%).

Of fetuses with normal karyotype in which 22q11.2 deletion syndrome studies were performed, 6.4% (5/78) had this microdeletion syndrome.

Among fetuses with abnormal cardiac findings, normal karyotype and negative or no 22q11.2 deletion syndrome study that underwent CMA, the detection rate of pathogenic copy number variants not detected by conventional cytogenetics was 2.0% (1/51)
Down Syndrome:
<table>
<thead>
<tr>
<th>Isolated Marker</th>
<th>LR Nyberg et al</th>
<th>LR Nyberg et al</th>
<th>LR Smith-Bindman et al</th>
<th>LR Bromley et al</th>
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<tbody>
<tr>
<td>Major Anomaly</td>
<td>25</td>
<td>ND</td>
<td>ND</td>
<td>3.3</td>
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<tr>
<td>Nuchal Fold</td>
<td>18.6</td>
<td>11</td>
<td>17</td>
<td>NC</td>
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<tr>
<td>Short Humerus</td>
<td>2.5</td>
<td>5.1</td>
<td>7.5</td>
<td>5.8</td>
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<tr>
<td>Short Femur</td>
<td>2.2</td>
<td>1.5</td>
<td>2.7</td>
<td>1.2</td>
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<tr>
<td>Hyperechoic bowel</td>
<td>5.5</td>
<td>6.7</td>
<td>6.1</td>
<td>Not seen isolated</td>
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<tr>
<td>Pyelectasis</td>
<td>1.6</td>
<td>1.5</td>
<td>1.9</td>
<td>1.5</td>
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<tr>
<td>EIF</td>
<td>2</td>
<td>1.8</td>
<td>2.8</td>
<td>1.4</td>
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</table>
Edwards syndrome (Trisomy 18)

1st trimester
Increased nuchal translucency

2nd trimester
Multiple major anomalies
Single major anomaly + Trisomy 18 marker
Choroid plexus cyst + other anomalies
Early IUGR
IUGR
Cardiac defects
Musculoskeletal findings
- Clenched hands + overlapping index finger
Arthrogryposis
Rocker bottom foot
Clubfoot
Radial ray malformation
Cystic hygroma
Brain anomalies
Strawberry shaped calvarium
Meningomyelocele
Facial anomalies
GI anomalies
SUA
<table>
<thead>
<tr>
<th>2D Measurements</th>
<th>AUA</th>
<th>Value</th>
<th>m1</th>
<th>m2</th>
<th>m3</th>
<th>Meth.</th>
<th>GP</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD (Hadlock)</td>
<td></td>
<td>48.63mm</td>
<td>48.63</td>
<td></td>
<td></td>
<td>avg.</td>
<td>25.7%</td>
<td>20w5d</td>
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<tr>
<td>OFD (HC)</td>
<td></td>
<td>60.51mm</td>
<td>60.51</td>
<td></td>
<td></td>
<td>avg.</td>
<td></td>
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<td>HC (Hadlock)</td>
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<td>175.10mm</td>
<td>175.10</td>
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<td></td>
<td>avg.</td>
<td>3.9%</td>
<td>20w0d</td>
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<tr>
<td>HC* (Hadlock)</td>
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<td>17.21cm</td>
<td>17.21</td>
<td></td>
<td></td>
<td></td>
<td>&lt;2.3%</td>
<td>19w5d</td>
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<tr>
<td>AC (Hadlock)</td>
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<td>129.49mm</td>
<td>129.49</td>
<td></td>
<td></td>
<td>avg.</td>
<td>&lt;2.3%</td>
<td>18w3d</td>
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<td>FL (Hadlock)</td>
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<td>29.92mm</td>
<td>29.92</td>
<td></td>
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<td>avg.</td>
<td>&lt;2.3%</td>
<td>19w2d</td>
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<td>HL (Jeanty)</td>
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<td>28.10mm</td>
<td>28.10</td>
<td></td>
<td></td>
<td>avg.</td>
<td>&lt;5.0%</td>
<td>19w0d</td>
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</table>

2D Calculations

| CI (BPD/OFD)     | 80% (70 - 86%) | HC/AC (Campbell) | 1.35 (1.06 - 1.25) |
| FL/BPD           | 62% (GA: OOR)  | FL/HC (Hadlock)  | 17% (17 - 20%)     |
Fryns Syndrome

Perinatal lethal disorder
CDH with pulmonary hypoplasia
Micrognathia
Orofacial cleft
Cardiac defects
Polyhydramnios
Distal digital hypoplasia (typically not apparent on ultrasound)

***AR inheritance
Gene not known
Meckel-Gruber Syndrome

Renal cystic dysplasia 95-100%
Encephalocele 60-80%
Postaxial polydactyly 55-75%

2nd trimester oligohydramnios
Significantly increased abdominal circumference

***AR =25% recurrence risk
MKS1 17q21-24, MKS2 11q13, MKS3 8q24
Noonan Syndrome

The prenatal ultrasound findings reported in Noonan syndrome include accumulation of nuchal fluid, femur lengths at or just below the lower end of the normal range, pleural effusions, and renal anomalies.

The most common prenatal features are polyhydramnios (58%), cystic hygroma (42%), increased thickness of the nuchal translucency and fetal hydrops (33%).

Cardiac anomalies are present in 60% of cases: including left ventricular hypertrophy (25%), pulmonary stenosis (19%), atrial septal defect (10%) or dysplastic pulmonary valve in 7%.
Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings.

*Eur J Hum Genet*. 2013 Sep;21(9):936-42

In recent studies on prenatal testing for Noonan syndrome (NS) in fetuses with an increased nuchal translucency (NT) and a normal karyotype, mutations have been reported in 9-16% of cases. In this study, DNA of 75 fetuses with a normal karyotype and abnormal ultrasound findings was tested in a diagnostic setting for mutations in (a subset of) the four most commonly mutated NS genes. A de novo mutation in either PTPN11, KRAS or RAF1 was detected in 13 fetuses (17.3%). Ultrasound findings were increased NT, distended jugular lymphatic sacs (JLS), hydrothorax, renal anomalies, polyhydramnios, cystic hygroma, cardiac anomalies, hydrops fetalis and ascites. A second group, consisting of anonymized DNA of 60 other fetuses with sonographic abnormalities, was tested for mutations in 10 NS genes. In this group, five possible pathogenic mutations have been identified (in PTPN11 (n=2), RAF1, BRAF and MAP2K1 (each n=1)). We recommend prenatal testing of PTPN11, KRAS and RAF1 in pregnancies with an increased NT and at least one of the following additional features: polyhydramnios, hydrops fetalis, renal anomalies, distended JLS, hydrothorax, cardiac anomalies, cystic hygroma and ascites. If possible, mutation analysis of BRAF and MAP2K1 should be considered.
Prenatal Noonan Spectrum Disorders Panel

Genes:
BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, SOS1
Patau Syndrome (Trisomy 13)

- Small head
- Absent eyebrows
- Cleft lip and/or palate
- Dysplastic, or malformed ears
- Clenched hands and polydactyly, or extra fingers
- Undescended or abnormal testes
1st trimester
Increased NT

2nd trimester
Multiple major anomalies (>90%)
Holoprosencephaly
Midline facial anomalies
Cardiac defects
Polydactyly
Early IUGR
Smith-Lemli-Opitz Syndrome

Disorder of cholesterol biosynthesis characterized by IUGR
Multiple congenital anomalies
Developmental delay

IUGR
Microcephaly (90%)
Cardiac defects: AV canal defect, VSD, Hypoplastic LH
Postaxial polydactyly
Genital ambiguity, cystic renal disease
Facial malformations: Hypertelorism, short up-turned nose, low-set ears, micrognathia
Increased NT in the 1st trimester

*AR
Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessive disorder of endogenous cholesterol biosynthesis caused by deficiency of 7-dehydrocholesterol reductase (DHCR7).

DHCR7 mutation is a rapid and reliable method for prenatal diagnosis of SLOS, and provides an alternative to specialized biochemical tests for elevated 7DHC in amniotic fluid or CVS.

***Up to 7% of stillbirths may be due to SLOS
Wolf Hirschorn Syndrome (4p-)

Severe intrauterine growth restriction

Facial dysmorphic features, midline defects (hypertelorism, labial or labio-palatine defects, corpus callosum agenesis)

Cardiac septal defects

Urinary tract malformations

Brain anomalies***microcephaly***
Wolf-Hirschhorn syndrome is caused by deletion of the WHSCR of chromosome 4p16.3 by one of several genetic mechanisms.
Severe early onset IUGR with normal doppler findings
‘Greek helmet’ facial appearance w prominent glabella, rectangular nose, downturned mouth, hypospadias, cardiac and urinary tract defects
These children have severe developmental delays. Other significant problems can include heart defects, cleft lip and/or palate, hearing impairment, and eye problems. Most children who have WHS have seizures (approximately 90%).

array-CGH is the way to go!
TEŞEKKÜRLER