Chapter 10

Features of chromosomal defects

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PHENOTYPIC EXPRESSION

The commonest chromosomal defects are trisomies 21, 18 or 13, Turner syndrome (45,X), 47,XXX, 47,XXY, 47,XYY and triploidy. In the first trimester, a common feature of many chromosomal defects is increased nuchal translucency thickness. In later pregnancy, each chromosomal defect has its own syndromal pattern of abnormalities.

Trisomy 21

Trisomy 21 is associated with a tendency towards brachycephaly, mild ventriculomegaly, flattening of the face, nuchal edema, atrioventricular septal defects, duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the limbs, sandal gap and clinodactyly or mid-phalanx hypoplasia of the fifth finger.

Trisomy 18

Trisomy 18 is associated with strawberry-shaped head, choroid plexus cysts, absent corpus callosum, Dandy–Walker complex, facial cleft, micrognathia, nuchal edema, heart defects, diaphragmatic hernia, esophageal atresia, exomphalos, renal defects, myelomeningocele, growth retardation and shortening of the limbs, radial aplasia, overlapping fingers and talipes or rocker bottom feet.

Trisomy 13

In trisomy 13, common defects include holoprosencephaly and associated facial abnormalities, microcephaly, cardiac and renal abnormalities (often enlarged and echogenic kidneys), exomphalos and postaxial polydactyly.

Triploidy

Triploidy, where the extra set of chromosomes is paternally derived, is associated with a molar placenta and the pregnancy rarely persists beyond 20 weeks. When there is a double maternal chromosome contribution, the pregnancy may persist into the third trimester. The placenta is of normal consistency and the fetus demonstrates severe asymmetrical growth retardation. Commonly, there is mild ventriculomegaly, micrognathia, cardiac abnormalities, myelomeningocoele, syndactyly, and 'hitch-hiker' toe deformity.

Turner syndrome

There are two types of this syndrome, the lethal and non-lethal types. The rate of intrauterine lethality between 12 and 40 weeks is about 75%. The lethal type of Turner syndrome presents with large nuchal cystic hygromata, generalized edema, mild pleural effusions and ascites, and cardiac abnormalities. The non-lethal type usually does not demonstrate any ultrasonographic abnormalities.

Sex chromosome abnormalities

The main sex chromosome abnormalities, other than Turner syndrome, are 47,XXX, 47,XXY and 47,XYY. These are not associated with an increased prevalence of sonographically detectable defects.

Types of abnormalities

The following table describes the common chromosomal abnormalities in the presence of various sonographically detected defects.

Common chromosomal abnormalities in fetuses with sonographic defects

	Trisomy 21	***Trisomy 18***	***Trisomy 13***	***Triploidy***	***Turner***
Skull/brain					
Strawberry-shaped head	-	+	-	-	-
Brachycephaly	+	+	+	-	+
Microcephaly	-	-	+	-	+
Ventriculomegaly	+	+	-	+	-
Holoprosencephaly	-	-	+	-	-
Choroid plexus cysts	+	+	-	-	-
Absent corpus callosum	-	+	-	-	-
Posterior fossa cyst	+	+	+	-	-
Enlarged cisterna magna	+	+	+	-	-
Face/neck					
Facial cleft	-	+	+	-	-
Micrognathia	-	+	-	+	-
Nuchal edema	+	+	+	-	-
Cystic hygromata	-	-	-	-	+
Chest					
Diaphragmatic hernia	-	+	+	-	-
Cardiac abnormality	+	+	+	+	+
Abdomen					
Exomphalos	-	+	+	-	-
Duodenal atresia	+	-	-	-	-
Collapsed stomach	+	+	-	-	-
Mild hydronephrosis	+	+	+	-	+
Other renal abnormalities	+	+	+	+	-
Other					
Hydrops	+	-	-	-	+
Small for gestational age	-	+	-	+	+
Relatively short femur	+	+	-	+	+
Clinodactyly	+	-	-	-	-
Overlapping fingers	-	+	-	-	-
Polydactyly	-	-	+	-	-
Syndactyly	-	-	-	+	-
Talipes	-	+	+	+	-

RISK FOR CHROMOSSOMAL DEFECTS

Number of defects

Ultrasound studies have demonstrated that major chromosomal defects are often associated with multiple fetal abnormalities. The overall risk for chromosomal defects increases with the total number of abnormalities that are identified. It is therefore recommended that, when an abnormality/marker is detected at routine ultrasound examination, a thorough check is made for the other features of the chromosomal defect(s) known to be associated with that marker; should additional abnormalities be identified, the risk is dramatically increased.

Incidence of chromosomal defects in relation to number of sonographically detected abnormalities (Nicolaides et al., Lancet 1992;340:704–7)

Abnormalities	*n*	*Chromosomal defects*
1	1128	2%
2	490	11%
3	220	32%
4	115	52%
5	53	66%
6	40	63%
7	16	69%
8 or more	24	92%

Major defects

If the 18–23-week scan demonstrates major defects, it is advisable to offer fetal karyotyping even if these defects are apparently isolated. The prevalence of these defects is low and therefore the cost implications are small. If the defects are either lethal or they are associated with severe handicap, fetal karyotyping constitutes one of a series of investigations to determine the possible cause and therefore the risk of recurrence. Examples of these defects include hydrocephalus, holoprosencephaly, multicystic renal dysplasia and severe hydrops. In the case of isolated neural tube defects, there is controversy as to whether the risk for chromosomal defects is increased. Similarly, for skeletal dysplasias where the likely diagnosis is obvious by ultrasonography, it would probably be unnecessary to perform karyotyping. If the defect is potentially correctable by intrauterine or postnatal surgery, it may be logical to exclude an underlying chromosomal abnormality, especially because for many of these conditions the usual abnormality is trisomy 18 or 13. Examples include facial cleft, diaphragmatic hernia, esophageal atresia, exomphalos and many of the cardiac defects. In the case of isolated gastroschisis or small bowel obstruction, there is no evidence of increased risk of trisomies.

Minor defects or markers

For apparently isolated abnormalities, there are large differences in the reported incidence of associated chromosomal defects. It is therefore uncertain whether, in such cases, karyotyping should be undertaken, especially for those abnormalities that have a high prevalence in the general population and for which the prognosis in the absence of a chromosomal defect is good. Since the incidence of chromosomal defects is associated with maternal age, it is possible that the wide range of results reported in the various studies is the mere consequence of differences in the maternal age distribution of the populations examined. In addition, since chromosomal abnormalities are associated with a high rate of intrauterine death, differences may arise from the fact that studies were undertaken at different stages of pregnancy. For example, to determine whether apparently isolated choroid plexus cysts at 20 weeks of gestation are associated with an increased risk for trisomy 18, it is essential to know the incidence of trisomy 18 at 20 weeks, based on the maternal age distribution of the population that is examined. Therefore, we propose that, in the calculation of risks for chromosomal defects, it is necessary to take into account ultrasound findings as well as the maternal age and the gestational age at the time of the scan .

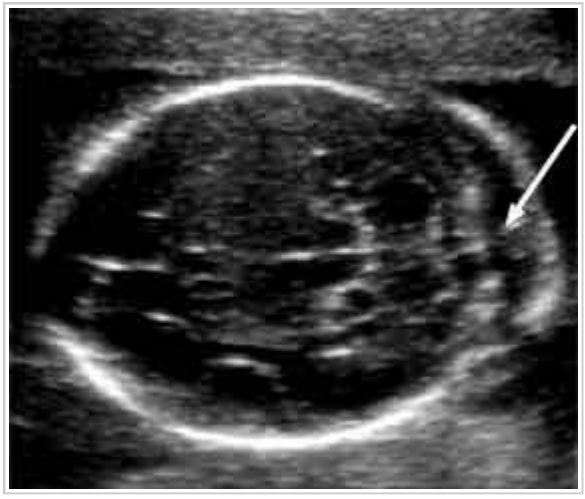
Association with maternal age and gestation

The risk for trisomies increases with maternal age and decreases with gestation; the rate of intrauterine lethality between 12 weeks and 40 weeks is about 30% for trisomy 21, and 80% for trisomies 18 and 13 (Appendix 1). Turner syndrome is usually due to loss of the paternal X chromosome and, consequently, the frequency of conception of 45,X embryos, unlike that of trisomies, is unrelated to maternal age. The prevalence is about 1 per 1500 at 12 weeks, 1 per 3000 at 20 weeks and 1 per 4000 at 40 weeks. For the other sex chromosome abnormalities (47,XXX, 47,XXY and 47,XYY), there is no significant change with maternal age and, since the rate of intrauterine lethality is not higher than in chromosomally normal fetuses, the overall prevalence (about 1 per 500) does not decrease with gestation. Polyploidy affects about 2% of recognized conceptions but it is highly lethal and it is very rarely observed in live births; the prevalence at 12 and 20 weeks is about 1 per 2000 and 1 per 250 000, respectively.

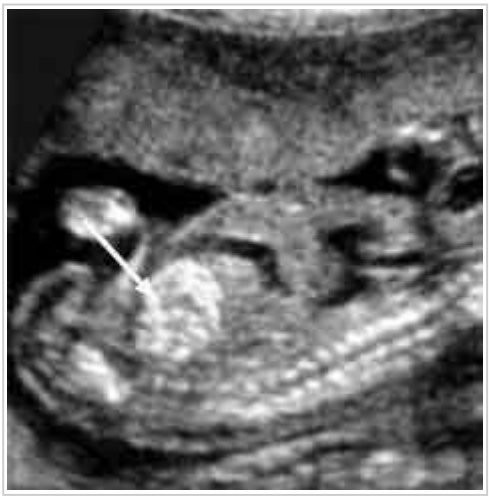
Type of defect

If there are minor defects, the risk for trisomy 21 is calculated by multiplying the background (maternal age- and gestation-related risk) by a factor depending on the specific defect. For the following conditions, there are sufficient data in the literature to estimate the risk factors.

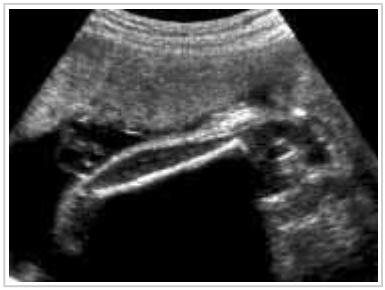
Nuchal edema or fold more than 6 mm This is the second-trimester form of nuchal translucency. It is found in about 0.5% of fetuses and it may be of no pathological significance. However, it is sometimes associated with chromosomal defects, cardiac anomalies, infection or genetic syndromes. For isolated nuchal edema, the risk for trisomy 21 may be ten-times the background risk.



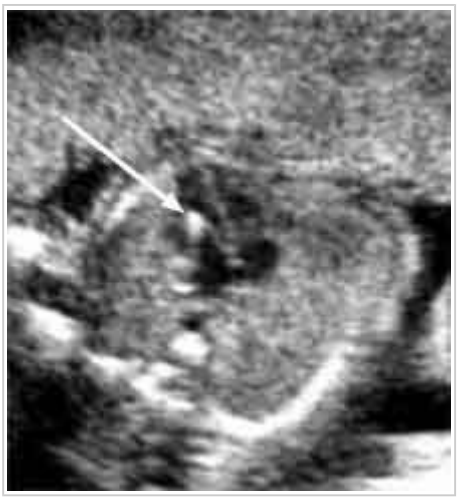
Hyperechogenic bowel This is found in about 0.5% of fetuses and is usually of no pathological significance. The commonest cause is intra-amniotic bleeding, but occasionally it may be a marker of cystic fibrosis or chromosomal defects. For isolated hyperechogenic bowel, the risk for trisomy 21 may be seven-times the background risk.



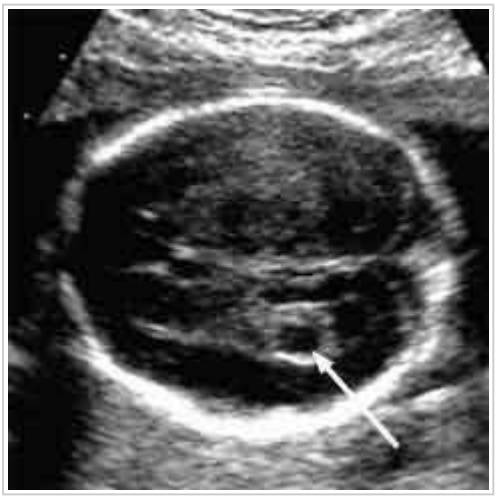
Short femur If the femur is below the 5th centile and all other measurements are normal, the baby is likely to be normal but rather short. Rarely, this is a sign of dwarfism. Occasionally, it may be a marker of chromosomal defects. On the basis of existing studies, short femur is found four-times as commonly in trisomy 21 fetuses compared to normal fetuses. However, there is some evidence that isolated short femur may not be more common in trisomic than normal fetuses.



Echogenic foci in the heart These are found in about 4% of pregnancies and they are usually of no pathological significance. However, they are sometimes associated with cardiac defects and chromosomal abnormalities. For isolated hyperechogenic foci, the risk for trisomy 21 may be three-times the background risk.



Choroid plexus cysts These are found in about 1–2% of pregnancies and they are usually of no pathological significance. When other defects are present, there is a high risk of chromosomal defects, usually trisomy 18 but occasionally trisomy 21. For isolated choroid plexus cysts, the risk for trisomy 18 and trisomy 21 is 1.5-times the background risk.



Mild hydronephrosis This is found in about 1–2% of pregnancies and is usually of no pathological significance. When other abnormalities are present, there is a high risk of chromosomal defects, usually trisomy 21. For isolated mild hydronephrosis, the risk for trisomy 21 is 1.5-times the background risk.