Abnormal Pregnancy Sonogram: Selective Indication for Fetal Karyotype

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The inability to make a definitive diagnosis in the fetus with a sonographically identified abnormality often results in parental and physician uncertainty. An antenatal chromosome evaluation could resolve this uncertainty. Forty-one fetuses with an abnormal ultrasound examination were tested for karyotypic abnormality using a variety of specimens. Nearly one-third (13 of 41) of these fetuses had various chromosome abnormalities. There were only seven survivors in this series, underscoring the often poor prognosis when a significant ultrasound defect is detected antenatally. Knowledge of the fetal chromosome constitution in the setting of an abnormal ultrasound has important epidemiologic, cost-benefit, counseling, and pregnancy management implications. *(Obstet Gynecol 69:15, 1987)*

The widespread use of ultrasound during pregnancy has led to the antenatal detection of fetal abnormalities, often at an advanced stage of gestation. Their discovery elicits questions of cause, possible further diagnostic evaluation, prognosis, possibility of intrauterine intervention (surgery or termination), and, ultimately, recurrence risk. These questions can be answered definitively when the fetus has a chromosome abnormality. Six to 7% of major congenital malformations are associated with chromosome errors.[1] The rate may be higher if the anomalies co-exist with intrauterine growth retardation (IUGR).[2] Certain sonographic findings represent clear indications for a chromosome analysis. A cystic hygroma implies the Turner syndrome[3] but also can occur with other chromosome aberrations.[4] About 10% of fetuses with omphalocele,[5] 14% of fetuses with prenatally detected nonimmune hydrops,[6] and a similar proportion of fetuses with prenatally detected hydrocephalus[7] have abnormal chromosomes. Trisomy 21 is present in a third of infants with duodenal atresia.[8] Indeed, most abnormalities detectable by ultrasound imply a significant risk of a chromosomal anomaly as well. However, the magnitude of this risk over a wide spectrum of fetal malformations has been reported only once in a large series.[9]

We here report a series of prenatal karyotypes prompted by fetal abnormalities observed on ultrasound and we discuss their impact on obstetric management and genetic counseling.

Methods

A fetal karyotype was obtained for an abnormal ultrasound finding in 41 pregnancies from 1982 through mid-1985, of which 18 were in the last year of the study. The majority of these patients were referred after the identification of an abnormal sonogram elsewhere. Specimens were obtained from amniotic fluid (when available), cystic masses (in the presence of oligohydramnios or when drained for diagnostic purposes), and umbilical vessel puncture (when a rapid karyotype was considered important or when other fetal blood studies were desired). Each procedure was done under sonographic guidance using a needle guide.[10] Severe IUGR was defined as an abdominal circumference at the level of the umbilical vein of less than the 2.5 percentile for gestational age. Intrauterine growth retardation was considered early onset if it was detected before 28 weeks' gestation. Oligohydramnios was defined as no pocket of amniotic fluid exceeding 1 cm in all dimensions.[11]

Results

Table 1 details the anomalies felt to represent a significant risk for a chromosome error and which led to prenatal chromosome analysis. Each organ system (genitourinary, gastrointestinal, cardiopulmonary,

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Table 1. Indications for Fetal Karyotype and Chromosome Abnormalities Found

Indication	Number	Number abnormal
Before intrauterine or contemplated intrauterine surgical procedure		
Nonimmune hydrops	1	
Obstructive uropathy	3	1 (trisomy 18)
Hydrocephalus	1	
Fetal anomaly(ies), with or without IUGR, with associated polyhydramnios	8	2 (trisomy 18 and large marker chromosome)
Fetal anomaly(ies), with or without IUGR, with associated oligohydramnios	6	1 (trisomy 13)
Fetal anomaly(ies) with IUGR and normal fluid volume	3	2 (trisomy 13 and 8q-)
Multiple anomalies with normal fluid volume	2	
Nonimmune hydrops	6	
Cystic hygroma, fetal hydrops	3	3 (all 45,X)
Omphalocele	2	
Subcutaneous and scalp edema	1	1 (17q-; mother balanced 2;17 translocation car
Early onset IUGR, oligohydramnios	2	1 (triploidy)
Fetal death and anomalies	2	2 (trisomy 18 and trisomy 13)
"Double bubble"	1	
Total	41	13

IUGR = intrauterine growth retardation.

Table 2. Ultrasound Abnormalities and Comparative Autopsy Data of Fetuses With Chromosome Abnormalities

Karyotype	Utrasound findings	Major autopsy findings
8q-	Omphalocele	Omphalocele
	Hydrocephalus	Hydrocephalus
	IUGR	Ambiguous external genitalia
		Malrotation of gut
		Single umbilical artery
Large marker chromosome	Polyhydramnios	Absent corpus callosum
	Mild bilateral hydronephrosis	CHM, multiple
	Moderate posterior ventricular dilatation	Cleft lip/palate
		Bilateral hydronephrosis and hydroureter
		Ambiguous genitalia
		Digital abnormalities
Trisomy 18	Dilated bladder	Probable urethral valve with markedly d tended bladder
		Absent right kidney
		Lumbo-sacral NTD
		CHM, multiple
		Small right diaphragmatic hernia
		Laryngeal atresia
		Bilateral radial aplasia
		Herniation of right upper lung into left chest
		Malrotation of gut
		Adrenal hypoplasia
		Single umbilical artery
Trisomy 18	Polyhydramnios	Omphalocele
	Omphalocele	CHM, multiple
	Hydrocephalus	Horseshoe kidney with left ureteral dup cation
	IUGR	Brain autolyzed, ? hydrocephalus
		Bilateral radial aplasia
Trisomy 13	Severe oligohydramnios	Urethral stenosis with distended bladde
	Dilated bladder	Bilateral ureteral obstruction with left cy dysplasia and right hydronephrosis
	Bilateral hydronephrosis	Bilateral radial aplasia
		Cleft lip and palate, right
		Complex ocular anomalies

central nervous system, skeletal) was involved. Amniocentesis was successful in all patients, and a viable cell culture was obtained from 39 of 41 fluids. The two culture failures were associated with severe oligohydramnios. (In the first, an insufficient volume of fluid was aspirated. In the second, the amniotic fluid was too thick and mucoid to separate cells for analysis. A postnatal karyotype was normal in each.) In six cases of anhydramnios, a successful karyotype resulted from cells aspirated from fetal ascites (three), cystic hygroma (two), and the fetal bladder (one). In three instances culture material was obtained by percutaneous umbilical blood sampling.

The average maternal age for the entire series was 24.5 years. The average gestational age at amniocentesis was 24 weeks for those pregnancies with a chromosomally abnormal fetus (range 15–34) and 26 weeks for those with a chromosomally normal fetus (range 19–34).

Thirteen fetuses (32%) had abnormal chromosomes (Table 1). Two karyotypes were particularly unusual. One fetus with ultrasound evidence of severe IUGR, an omphalocele, hydrocephalus, and normal amniotic fluid volume had an interstitial deletion of the long arm of chromosome 8. Parental chromosomes were normal. The second fetus had polyhydramnios, mild bilateral hydronephrosis, and moderate dilatation of the posterior ventricular system at 31 weeks. A large marker chromosome was identified (Figure 1). In the latter case, premature labor at 33 weeks was not suppressed, and a cesarean section was avoided when fetal distress occurred. A live-born infant with multiple malformations died four days after birth.

The fetal anomalies were discovered before 24 weeks in eight of 13 fetuses with a chromosome abnormality, and the pregnancy was terminated. These terminations were done either at the time the fluid sample was obtained (six) or when the result returned (two). The

Table 2. *(Cont'd)*

Karyotype	Utrasound findings	Major autopsy findings
Trisomy 13	Holoprosencephaly	Autopsy not done
	IUGR	No omphalocele noted grossly
45,X	Cystic hygroma	Cystic hygroma
	Hydrops	Hypoplasia of transverse portion of aorta
		Left superior vena cava
		Gastrointestinal malrotation
		Generalized edema
45,X	Severe oligohydramnios	Cystic hygroma
	Large cystic hygroma	Tubular hypoplasia of aortic arch
	Hydrops	Gastrointestinal malrotation
		Generalized lymphedema and lymphocysts
45,X	Severe oligohydramnios	Cystic hygroma
	Large cystic hygroma	Generalized edema
	Hydrops	
17q-	Subcutaneous and scalp edema	Edematous
		Bilateral simian crease
		Neuronal layering abnormalities
Triploidy	Oligohydramnios	Autopsy not done
	IUGR	No omphalocele noted grossly
Trisomy 18	Fetal death	Acqueductal stenosis
	Hydrocephalus	Omphalocele
	IUGR	CHM, multiple
		Horseshoe kidney
		Bilateral aplasia of ulnae
		Single umbilical artery
Trisomy 13	Fetal death	Alobar holoprosencephaly
	Holoprosencephaly	Bilobed right lung
	IUGR	Hemivertebra, 12th thoracic
		Bicornate uterus
		Single umbilical artery

CHM = congenital heart malformation; NTD = neural tube defect; IUGR = intrauterine growth retardation.

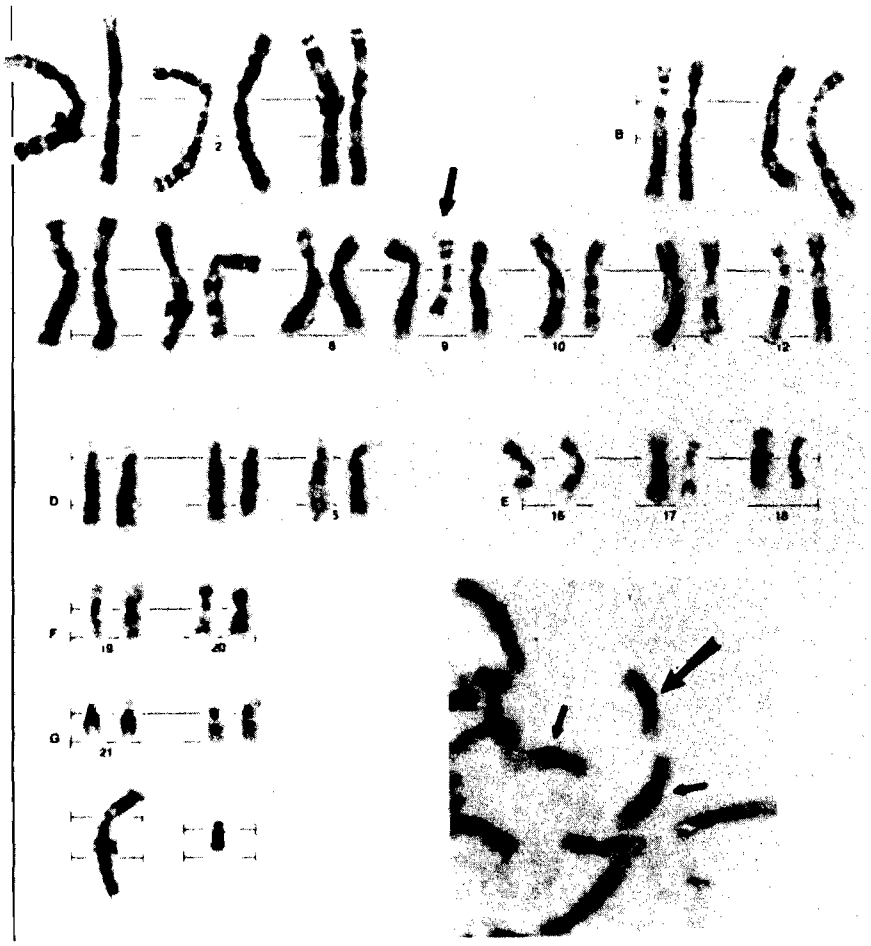

Figure 1. G-banded karyotype showing a large marker chromosome (*arrow*). This apparently represented extra chromosome 9 material with the region from band q22 to qter missing. It has the appearance of an isochromosome of either 9p or the deleted long arm. However, a C-banded karyotype (*insert, large arrow*) rules out this possibility, as there is continuity of the C-banded region. The normal 9s (*insert, small arrows*) also are shown.

remaining five abnormal karyotypes were associated with third trimester gestations: the large marker chromosome, a trisomy 18, triploidy, and trisomy 13 (two). The fetus with triploidy died at 37 weeks' gestation, three weeks after evaluation. In one case of trisomy 13, the fetus died one day before amniocentesis and in one case of trisomy 18 fetal death had occurred at least two days before amniocentesis.

Table 2 compares the ultrasound findings with final autopsy diagnoses in chromosomally anomalous fetuses. It is apparent that other anomalies amenable to sonographic detection were present. Often, the missed diagnoses were associated with oligohydramnios which obscured visualization. A surprising proportion of absent radii (three) and ulnae (one) was observed at autopsy in the six cases of trisomy 13 and 18. The range of other findings is also more extensive than that seen in newborns with the same trisomies.

Outcome data for those pregnancies associated with normal fetal chromosomes are given in Table 3. The seven survivors included two with omphalocele, one with a congenital heart defect, and one with the Beckwith-Weideman syndrome. A third infant with a prenatal diagnosis of IUGR and hydrocephalus has congenital cytomegalovirus infection and neurologic impairment secondary to hydrocephalus ex vacuo. Amniotic fluid viral cultures were negative. Two infants with idiopathic nonimmune hydrops have fared well after intensive neonatal treatment. A sixth fetus with "chylous" ascites, diagnosed after a fetal paracentesis showed a lymphocyte count of 2950/mm^3, also has done well. A seventh fetus with hydrocephalus underwent intrauterine shunt placement by members of the University of Colorado group.

Two fetuses with normal chromosomes died in utero one week after amniocentesis (one case of nonimmune hydrops of undetermined etiology and one severely IUGR fetus with oligohydramnios with congenital heart disease [hypoplastic left ventricle, atrial septal defect, mitral valve atresia] noted at autopsy). Twelve chromosomally normal infants died shortly after birth. Seven had multiple malformations inconsistent with a defined syndrome, including one with duodenal atresia. One of these seven had a normal co-twin. The pregnancies of seven fetuses with normal chromosomes were aborted (Table 3).

Table 3. Outcomes of Pregnancies With Karyotypically Normal Fetuses

Survivors	
Omphalocele	2
Cytomegalovirus	1
Nonimmune hydrops	2
Chylous ascites	1
Hydrocephalus, shunted in utero	1
Total	7
Intrauterine fetal death after amniocentesis	
Nonimmune hydrops	1
IUGR and oligohydramnios	1
Total	2
Neonatal death	
Multiple congenital anomalies, nonsyndromic	7
Endocardial fibroelastosis	1
Extralobar pulmonary sequestion	1
"Prune belly" syndrome	1
Cystic adenomatoid malformation	1
Severe IUGR, misshapen cranium and oligohydramnios (probable Seckel syndrome)	1
Total	12
Termination of pregnancy	
Sacrococcygeal teratoma with large intraabdominal component	1
Fetal ascites and severe oligohydramnios	2
Anencephaly and omphalocele	1
Omphalocele and sacral meningocele	1
Nonimmune hydrops, persistent fetal bradycardia	1
Obstructive uropathy, in utero surgery deemed inappropriate	1
Total	7

IUGR = intrauterine growth retardation.

Discussion

This series from a referral center found about a third of fetuses with a broad spectrum of ultrasound findings to have chromosome abnormalities. The scant literature relating to this observation suggests that a prenatal karyotype in these circumstances is an underused procedure. The prevalence of chromosome abnormalities seen in this series may be somewhat biased by the inclusion of three cases of cystic hygroma and one case of subcutaneous and scalp edema in a fetus of a known 2;17 balanced translocation carrier parent. The latter case is further evidence that fetal edema may be a nonspecific marker for aneuploid fetuses.[4] Excluding these patients, the proportion of abnormal karyotypes was still 24%. Bias in the other direction is incurred by including cases where the established or strongly suspected intrauterine diagnosis was not characteristic of an abnormal karyotype (eg, chylous or other forms of isolated ascites and nonimmune hydrops secondary to pulmonary extralobar sequestration). In addition, infants of diabetic mothers have an increased incidence of nonchromosomal malformations, and two such cases were included.

At least 25% of the time the karyotype was obtained, an obvious benefit was readily discernible. The fetus with the marker chromosome evidenced distress in labor, a common occurrence with abnormal fetuses,[12] particularly with severe chromosome abnormalities such as trisomy 18.[13] Additionally, many fetuses with anomalies die in utero and postmortem tissue cultures sometimes fail. In this series, fetal death followed the amniocentesis in three instances, one where the fetus was triploid. In two additional cases, recent death occurred before amniocentesis. The amniocytes from the latter two grew surprisingly well and revealed trisomies in both instances. Geographic location of delivery may be changed with knowledge of an abnormal karyotype. In one diagnosis of trisomy 13, the mother elected to deliver in her home town. On the other hand, in the two surviving cases of omphalocele and two of nonimmune hydrops, knowledge of chromosome normality facilitated early, aggressive treatment decisions.

There also are overriding economic considerations. During the time of this study a fetus was noted by ultrasound at 32 weeks to have a large meningomyelocele, co-existing polyhydramnios, and hydrocephalus with absence of midline structures. The findings should have prompted a prenatal karyotype, which unfortunately was not done. This infant with subsequently proven triploidy died at three days of life after shunt placement and meningomyelocele repair. The hospital bill for mother and infant would have paid for the cost of all 41 karyotypes in this series.

Several technical advances have contributed to the successful karyotyping of fetuses in this series. Ultrasound guidance allows precise placement of a needle into pockets of amniotic fluid less than 1 cm in diameter. In two cases of oligohydramnios, a culture failure resulted. Culturing success may be aided in this circumstance by injecting a physiologic solution into the space before obtaining a specimen. Other fetal fluid collections (eg, ascitic, urinary tract, cystic hygroma fluids) proved a valuable source of cells when amniotic fluid was absent. Further, in three instances percutaneous cord puncture permitted a karyotype within 72 hours,[14] helpful when decisions must be made in an advanced gestation. Fetal blood sampling will doubtless become a more important tool in the evaluation of the anomalous fetus.[9] The risk of cord blood sampling with ultrasound guidance appears to be acceptably low, probably in the range of a midtrimester genetic amniocentesis in experienced hands.[15] Another potential benefit of a cord blood karyotype is the opportunity to analyze chromosomes in a more extended state than

possible with amniocytes. This enhances the ability to detect rare but subtle deletions.[16]

Several other developments in prenatal diagnosis may increase the identified population in need of chromosome screening. First, a low maternal serum alpha-fetoprotein is associated with fetal trisomy.[17,18] As the application of this form of screening increases, more younger women, as characterized this series, will be referred for amniocentesis. Second, advances in ultrasound imaging technology will increasingly lead to detection of fetuses with heart defects.[19] It is estimated that 10% of heart defects are associated with a chromosome abnormality.[20] The rate is likely higher if the abnormality is detected prenatally.[21] Fetal bradycardia implies a heart defect in about 40% of cases,[22] and should prompt fetal echocardiography and/or a fetal karyotype.

The finding of a fetal abnormality on ultrasound presents a difficult challenge. Conflicting parental emotions combine with the known uncertainties of precise and complete ultrasound diagnoses.[23,24] To have determined that a major fetal ultrasound abnormality is or is not related to a chromosome aberration is an important, early step toward diagnosis and hence resolution. The findings may be important for future counseling and continued pregnancy management.

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