Chromosomal abnormalities detected after an abnormal ultrasound in pregnancy

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Summary: Improvements in ultrasound technology have resulted in an increasing number of requests for prenatal chromosome testing because of fetal abnormalities detected in utero. Between January 1990 - January 1991, 388 tissue samples were referred to our laboratory for cytogenetic analysis, of which 202 were amniotic fluids samples, 157 chorionic villus biopsies and 29 fetal blood specimens. Of these 54 were referred for fetal abnormalities detected prenatally on high resolution ultrasound. Chromosomal analysis was successful in 50 cases, and included 6 (12%) chromosomally abnormal fetuses: 2 trisomy 21, 2 trisomy 18, one 45, X and one unbalanced translocation. The maternal age for three of the four cases of autosomal trisomy were below 35 years (the cut-off for amniocentesis for advanced maternal age). In contrast, 273 prenatal chromosome studies performed for advanced maternal age (AMA) produced only 4 (1.5%) chromosomally abnormal fetuses. These abnormalities detected on ultrasound indicate a significant population of fetal choromosomal aberrations which would otherwise not be detected prenatally.

Key words: Ultrasound; Prenatal Diagnosis; Karyotyping; Aneuploidy.

INTRODUCTION

An increasing number of fetal malformations can be detected by ultrasound examination during the second or third trimester of pregnancy ([1]). In one series of 425 pregnancies out of 2372 referrals, 55 different fetal anomalies were identified with 95% sensitivity ([2]). These included various craniospinal defects, anomalies of the gastrointestinal and urinary tracts, cardiac malformations, skeletal dysplasias, non-immune hydrops and cystic hygromata. Many such fetal abnormalities are known to be associated with chromosome abnormalities, particularly cystic hygromata cardiac anomalies, and omphalocoeles ([3, 4]). Because of such associations many authors have stressed the need for prenatal chromosome analysis in cases of abnormal ultrasound findings ([5-7]). Knowledge of the fetal karyotype facilitates optimal perinatal counselling and management options include termination of pregnancy, invasive fetal therapy, decisions regarding mode of delivery and postnatal management.

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Samples for cytogenetic studies can be obtained by amniocentesis, late placental biopsy, fetal blood sampling most commonly at the placental cord insertion site and more recently at the intrahepatic portion of the umbilical vein. Amniocentesis is widely available, relatively safe and an effective diagnostic technique, although cytogenetic investigation routinely takes 2-3 weeks to complete. Late placental biopsy can produce a quick result (1-5 days), but discrepancies between placental and fetal karyotypes have been documented ([8]) and results must be interpreted with caution. Fetal blood sampling allows rapid karyotyping using methods derived from routine blood culture, but remains at present a technique available to a restricted number of centres. To identify those referred because of abnormalities detected on ultrasound, we received all cases for prenatal diagnosis processed by our laboratory during the period January - December, 1991. Our experience of prenatal karyotyping for fetal malformation is compared with findings in other common indications for prenatal chromosome investigations.

METHODS

Patients were referred primarily from two main centres as part of routine antenatal care. Indications for cytogenetic analysis included advanced maternal age (defined as greater than 35 years), pregnancies "at risk" because of known parental chromosome abnormalities, maternal anxiety, maternal serum AFP levels outside the reference range, a previous history of chromosome aneuploidy, follow up studies of other tests and ultrasound detected fetal abnormalities.

Fetal abnormalities were detected on ultrasound either as a result of a routine scan at 18 weeks gestation, or as part of fetal growth or fetal biophysical assessment for a variety of indications in late gestation. Specimens for cytogenetic investigation included chrionic villus, amniotic fluid and fetal blood specimens. These were obtained and processed by standard techniques ([9]). To assess the likely impact of such referrals on routine cytogenetic laboratory services; maternal age, gestational age, specimen type, reason for referral and cytogenetic findings were documented.

RESULTS

Specimens received for prenatal chromosome diagnosis during 1991 consisted of 201 amniotic fluid samples, 157 chorionic villus biopsies and 29 fetal blood specimens. Of these 388 referrals, 273 (70.5%) were performed for advanced maternal age, 54 (13.7%) for abnormalities detected on ultrasound, 8 (2.1%) for parental chromosome abnormalities and 53 (13.7%) for other reasons. Of the combined number of amniotic fluid and chorionic villus specimens received ($n = 359$), 76% were tested for advanced maternal age, and only 7.2% for abnormalities detected on ultrasound. By contrast, 96% of fetal bloods sent for cytogenetic studies were because of abnormal ultrasound findings, and these specimens comprised over half of all referrals in this category. The only fetal blood karyotype requested for a reason other than an ultrasound detected malformation was from a 19 week pregnancy in a woman with a previous trisomy 18. Referrals for "known parenteral chromosome abnormality" have been tabulated separately because the high risk of chromosome abnormality resulting from segregation of the parental abnormality would otherwise give a spuriously high rate of chromosome abnormality in the "others" category.

The mean maternal age in the AMA cohort was 38.6 ± 2.1 years ($n = 273$), reflecting the selection by age implicit in this category of referrals. The mean maternal age of the abnormal ultrasound group, and those with known parental chromosome aberrations (27 years) reflect the population mean maternal age at confinement. The slightly, but not statistically significant, higher mean maternal age in the "others" category can be attributed to (i) repeat of follow up procedures in patients originally referred for advanced maternal age, (ii) cases of maternal anxiety in women approaching 35 and (iii) cases

Table 1. — *Comparison of prenatal diagnosis by reason for referral.*

Reason for referral	No. of patients	Maternal age	Amniotic fluid	Chorionic villus	Fetal blood	Aneuploidy No. (%)
AMA	273	38.6±2.1	145	128	—	4 (1.5)
US	54	27.5±5.5	16	10	28	6 (11.3)
KCPA	8	27.4±3.4	3	5 NG	—	5 (62.5)
Other	53	31.9±5.7	38	14	1	0 (0)

Legend: AMA = maternal age > 35 years; US = abnormalities detected on ultrasound; Other = other reasons for referral; KCPA = known parental chromosome abnormality, the group at greatest risk of aneuploidy (n = 15). The one fetal blood which was not referred because of abnormal ultrasound findings was from a patient with a previous trisomy 18.

aged 35-36 with indications for amniocentesis additional to age alone, such as a previous history aneuploidy.

With referrals for advanced maternal age and "other" reasons the mean gestational age at the time of chorionic villus sampling was 11-12 weeks (range 9-17 weeks), and at the time of amniocentesis 16-17 weeks (range 14-23 weeks). This contrasts with chorionic villus sampling at circa 15 weeks (range 11-19 weeks) and amniocentesis at circa 22 weeks (range 15-23 weeks) in cases with abnormal ultrasound findings. Fetal blood samples were obtained between 19 and 35 weeks gestation (mean = 28.9 weeks).

Table 2 lists the major categories of abnormal ultrasound findings. The largest category of ultrasound abnormality was IUGR in 7 referrals. In 4, IUGR was "severe", i.e. ≤ 3rd centile for gestational age and included a growth retarded twin

Table 2. — *Categories of abnormal ultrasound findings.*

	Gest. man	Age range	No. cases	Abnormal karyotype
Intrauterine Growth Retardation .	32.0	(28-35)	7	—
Cystic Hygroma	13.3	(11-15)	5	2
Multiple Fetal Anomalies . . .	23.3	(18-33)	5	3
Hydrops	21.0	(15-30)	4	—
Suspected trisomies		NG	4	—
Hyperechogenic Bowel	17.0	(17)	3	—
Gastroschisis	31.0	(30-32)	3	—
Holoprosencephaly	26.0	(19-35)	3	—
Others	23.9	(11-35)	19	1+
Total			53	6

Legend: Only those categories giving three or more referrals are listed separately. The "others" comprise a heterogenous group of anhydramnios (n = 1), hydrocephalus (n = 2, with one abnormal karyotype), diaphragmatic hernia (n = 2), hydronephrosis (n = 2), hydranencephaly (n = 1), agenesis of the corpus callosum (n = 1) and haemorrhage into a fetal ovarian cyst (n = 1). Three suspected trisomies (2 trisomy 21 and 1 trisomy 18) were referred without specification of the ultrasound basis of the diagnosis. The third was a suspected Down syndrome on the basis of increased nuchal fold and low AFP. Otherwise, all abnormalities are the sole finding noted.

Table 3. — *Cytogenetically abnormal fetuses referred for ultrasound anomalies.*

Case	Karyotype	Mat. age	Ultrasound
91-1025	46, XX, −13, +der (13) t (13; 18)	27	Hypotelorism, low set ears, micrognathia, polyhydramnios, ventricular septal defect (VSD)
91-0717	47, XX, +18	32	Absent radii left arm, agenesis of the corpus callosum, choroid plexus cysts, small VSD
91-1347	47, XX, +18	18	Diaphragmatic hernia
91-1361	47, XX, +21	34	Cystic hygroma
91-1602	47, XY, +21	41	Choroid plexus cyst, 2 vessel cord, hydronephrosis
91-0513	45, X	19	Cystic hygroma

however, its co-habitant demonstrated normal growth. Cystic hygromata were found in five pregnancies. Two were chromosomally abnormal; one with 45, X and another with trisomy 21. In both the cystic hygromata occurred in isolation. Multiple fetal anomalies were detected in 5 pregnancies. In 2 (twins; both with acardia acephaly), culture failed. In the remaining 3, an abnormal karyotype was detected in all cultures.

Four cases of suspected trisomies were referred. Three with suspected trisomies 21 and one with a suspected trisomy 18. One patient was referred because of increased nuchal fold thickness at 18 weeks on prenatal ultrasound associated with a low AFP. Details regarding the prenatal findings in the remaining 3 cases were not available. No chromosome abnormality was detected in these pregnancies. Ultrasound findings of a hyperechogenic bowel, gastroschisis and holoprosencephaly occurred in 3 pregnancies. No chromosome abnormality was detected in these cases. The remaining 19 referrals were for a variety of reasons, detailed in the footnote in table 2. In this group a case of trisomy 18 in association with a diaphragmatic hernia was detected. The other referral with a diaphragmatic hernia revealed a normal karyotype.

DISCUSSION

The selection of cases for cytogenetics based on abnormal ultrasound findings influences the aneuploidy detection rate. In this study, karyotyping for fetal abnormality detected on prenatal ultrasound yielded 6 out of 52 (11.5%) with chromosomal aberrations compared with 7 abnormal forms out of 273 (2.5%) from studies performed for advanced maternal age during the same period. The maternal ages of all four cases of autosomal trisomy in the ultrasound group were well below 35 years, the cut off for prenatal diagnosis for AMA.

Since the first report of detection of a fetal anomaly leading to termination of pregnancy ([10]), a wide variety of major malformations detected prenatally have been described. With the advent of high resolution ultrasound in the 1980's an increasing number of minor fetal malformations have also been described. Routine ultrasound has been recommended in United Kingdom ([11]) and this examination is delayed until 18-19 weeks gestation when the fetal anatomical development is "complete". Routine screening detects 55% of major and 35% of minor congenital malformations ([12]) and thus prenatal chromosomal analysis of all ultrasonographically detected fetal malforma-

tions potentially involves 1.5% of pregnancies. This contrasts with the 25% detection rate in the "indication based" system in the United States of America ([13]).

Pregnancies with multiple fetal malformations have a higher incidence of associated chromosomal abnormality when compared to isolated defects and in this series aneuploidy following successful culture was detected in the three cases with multiple fetal anomalies. The isolated fetal anomalies detected prenatally with a strong association with an abnormal karyotype include cystic hygromata and omphalocoeles. In Bernstien et al's series ([14]) two thirds of cases of isolated cystic hygroma were aneuploid (8 of 13) and thus, tissue typing is strongly recommended. In our series abnormal karyotype forms were detected in 2 out of five cases with cystic hygromata. These abnormalities detected on ultrasound indicate a significant population of fetal chromosomal abnormality which would otherwise not be detected prenatally.

Tissue for karyotype may be obtained from amniotic fluid, chorionic villi or fetal blood. Factors determining the choice of tissue sample include maternal preference, gestational age, uterine and placental position, maternal rhesus status, and liquor volume. The safety of the procedure, reliability of the results and the time required for laboratory processing are also important considerations. In our series fetal blood was the sample of choice in approximately half of the cases. Blood sampling was performed in the majority of cases from the fetal intrahepatic vein which appears to have less associated complications in particular, vessel tamponade, spasm and haemorrhage from the puncture site ([15]).

Prenatal sampling is no longer confined to cases of early prenatal diagnosis with a view to termination of pregnancy in the event of aneuploidy. Combined cytogenetic and ultrasonographic assessment of the fetus facilitates differentiation of lethal from minor fetal abnormalities. In centres where facilities exist prenatal invasive procedures including surgery may be entertained on confirmation of normal karyotype. The mode of delivery may also be dictated by fetal karyotype thus avoiding unnecessary operative intervention in the presence of fetal malformation associated with lethal fetal genotype. The ability to perform prenatal diagnosis from a variety of tissues at different gestational ages increases the scope of the service which can be provided. So that resources are not overloaded, it is important to establish when to karyotype and the urgency of the result, which will influence the tissue selected for karyotyping. A cohesive management team is thus essential to obtain the optimum benefit for the patient ([16]).

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