CLINICAL PRACTICE

Ultrasonographically detectable markers of fetal chromosomal abnormalities

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Screening for fetal chromosomal abnormalities on the basis of maternal age has not resulted in a substantial fall in the proportion of infants born with an abnormal karyotype. Most fetuses with major chromosomal abnormalities have defects that can be recognised on detailed ultrasonographic examination. Therefore, provided the cardinal signs of each chromosomal syndrome are recognised, it is possible that screening by ultrasound examination could have a greater impact.

We karyotyped 2086 fetuses after ultrasonographic examination had revealed fetal malformations, growth retardation, or both. Chromosomal abnormalities were detected in 301 (14%) cases and were more common among fetuses with multisystem malformations (29%) than among those with isolated defects (2%). The commonest chromosomal abnormality was trisomy 18, followed by trisomy 21, triploidy, Turner's syndrome, unbalanced chromosomal rearrangements, and trisomy 13. Trisomy 18 was associated with strawberry-shaped head, choroid plexus cysts, facial cleft, micrognathia, heart defects, exomphalos, malformations of hands and feet, and growth retardation. In trisomy 21, the associated defects were subtle and included nuchal oedema, macroglossia, atrioventricular septal defects, mild hydronephrosis, clinodactyly, and sandal gap. The frequency of autosomal abnormalities increased with maternal age, but if fetal karyotyping had been restricted to mothers older than 35 years, large proportions of chromosomally abnormal fetuses would not have been diagnosed prenatally (64–97%).

Our findings provide guidelines as to which defects to search for in screening studies for the detection of chromosomal abnormalities.

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Introduction

Chromosomal abnormalities are important causes of perinatal death and childhood handicap. A high risk of a cytogenetic disorder is the commonest indication for invasive prenatal diagnosis. However, despite the availability of such diagnostic methods, there has been only a small reduction in the proportion of infants born with chromosomal abnormalities in England and Wales.[1] The main reasons for this relative failure are that less than 3% of chromosomally abnormal pregnancies have any risk factor that can be identified before conception (such as parental translocation), that screening on the basis of maternal age will identify only about 30% of autosomal trisomies,[2] and that there is poor uptake (generally less than 50%) of invasive fetal testing among the at-risk group.[3] Although screening on the basis of maternal age and serum biochemistry could potentially identify more than 50% of pregnancies with fetal trisomy 21,[4] the uptake of invasive fetal testing will not necessarily increase. Furthermore, trisomy 21 is only one of many chromosomal abnormalities.

Another, complementary, method of screening for fetal chromosomal abnormalities is ultrasonography. Most fetuses with cytogenetic abnormalities have either external or internal defects[5] that can be recognised on detailed ultrasonographic examination. Many of these defects are easily detected at routine examination, but others need to be looked for specifically. Therefore, before any study can be done to assess the usefulness of ultrasonography in screening for fetal chromosomal abnormalities, it is essential to establish the types of chromosomal abnormalities associated with each malformation, and the ultrasonographically detectable phenotypic expression of the different types of chromosomal abnormalities. We aimed to achieve these two objectives by examining cytogenetic findings in 2086 fetuses with a wide range of malformations, growth retardation, or both, detected at ultrasound examination.

Patients and methods

Between 1983 and 1991, fetal karyotyping was done in 2086 patients referred to our unit because detailed ultrasonography showed fetal malformations, growth retardation, or both. Parents were counselled about the possible association of these features with chromosomal abnormalities and the risks and benefits of the various sampling procedures. Data are presented from those who chose to have fetal karyotyping, which was done by cytogenetic analysis of chorionic villi in 20 cases, of amniotic fluid in 110, and of fetal blood

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TABLE I—GESTATION AT REFERRAL AND FREQUENCY OF CHROMOSOMAL ABNORMALITIES FOR ULTRASONOGRAPHICALLY DETECTABLE FETAL MALFORMATIONS AND GROWTH RETARDATION

Defect	Median (range) gestation at referral (wk)	No with chromosome abnormality/total with defect (%)		Chromosomal abnormalities					
				Trisomy			Triploidy	Turner's syndrome	Other†
		Isolated*	Multiple	21	18	13			
Brachycephaly	23 (17–38)	..	43/114 (38)	7	19	5	3	8	1
Strawberry-shaped head	24 (16–39)	..	44/54 (82)	..	43	..	1	..	..
Microcephaly	22 (18–37)	0/1	8/51 (16)	1	1	3	..	..	3
Ventriculomegaly	23 (16–38)	2/42	40/144 (28)	7	12	3	12	3	5
Holoprosencephaly	22 (17–36)	0/7	15/51 (29)	..	3	11	..	..	1
Choroid plexus cyst	21 (16–38)	1/49	33/72 (46)	2	30	1	..	..	1
Posterior fossa cyst	22 (16–38)	0/1	21/44 (48)	..	8	6	3	..	4
Facial cleft	22 (17–37)	0/8	31/56 (55)	1	10	15	1	..	4
Micrognathia	23 (17–37)	..	37/56 (66)	..	21	3	9	..	4
Macroglossia	24 (20–37)	..	10/13 (77)	9	..	..	..	..	1
Nuchal oedema	21 (16–38)	0/12	53/132 (40)	31	5	7	2	3	5
Cystic hygromata	19 (16–35)	0/4	35/48 (73)	1	1	..	..	33	..
Hydrops	26 (16–39)	7/104	18/106 (17)	14	1	2	2	2	4
Diaphragmatic hernia	21 (17–38)	0/38	17/41 (41)	..	10	2	1	..	4
Heart defect	23 (17–39)	0/4	101/152 (66)	21	37	14	4	16	9
Exomphalos	21 (16–39)	1/30	41/86 (48)	..	32	7	1	..	2
Duodenal atresia	32 (20–36)	1/6	9/17 (53)	10	..	..	..	..	..
Oesophageal atresia	27 (20–37)	0/1	18/23 (78)	1	17	..	..	..	..
Renal defects	22 (16–40)	9/482	87/360 (24)	23	25	20	5	8	15
Abnormal extremities	23 (16–40)	0/18	195/457 (43)	35	71	21	38	22	8
Growth retardation	28 (17–39)	4/251	133/424 (31)	13	48	15	40	9	12

*1 trisomy 8, 9 trisomy 21, 2 trisomy 22, 1 duplication marker; 1 each deletion of 2q, 3p, and 5p, 4 deletions of 4p; unbalanced translocations (1,1) and (11,12), 2 Turner's syndrome; 2 47XXY, 1 47XYY

†1 trisomy 8, 2 each trisomies 9 and 22, 2 isochromosome 12p, 1 each duplications 4q, 11p, marker; 1 each deletion of 3p, 5p, 5q, 6p, 7q, 8q, 8p, 9p, 13q, 14q, 21q, 3 deletions of 2q and 5 of 4p, unbalanced translocations (1,1), (11;12), (4;15), and (17,19), 3 47XXY, 2 47XYY

in 1956. Details of the karyotyping methods and malformations have been described previously.[6-16] During that time, we saw 1252 other patients who either did not want fetal karyotyping or were not offered it because the defects present (in most, limb shortening due to skeletal dysplasias, such as osteogenesis imperfecta, and spina bifida in the absence of multisystem defects) are not related to cytogenetic abnormalities.

The main reasons for referral of patients were detection of fetal malformation (1466) or growth retardation (458) at the referring hospital, risk of hereditary blood or metabolic disorders (11), maternal rubella or toxoplasma infection (3), advanced maternal age (23), low (22) or high (29) maternal serum alphafetoprotein, and risk of fetal anaemia due to red cell isoimmunisation (19).

In every case, a systematic ultrasound examination was undertaken and all fetal defects were recorded. The diagnosis of fetal malformations was based on the demonstration of well-described anatomical defects,[6-16] abnormal fetal biometry, or both. Abnormal biometry was defined by measurements above the 97·5th or below the 2·5th centiles for gestation of our reference ranges, derived from a cross-sectional study of 1010 normal fetuses. The defining measurements used were the ratio of the biparietal and occipitofrontal diameters for brachycephaly (>97·5th), the ratio of the anterior and/or posterior cerebral ventricle to hemisphere diameters for ventriculomegaly (>97·5th), and femur length (<2·5th) and the ratio of head circumference to femur length for short femur (>97·5th) and microcephaly (<2·5th). Fetal growth retardation was judged to be present if the abdominal circumference was below the 5th centile. However, in fetuses with malformations affecting the abdominal circumference (eg, exomphalos, dilated bladder, or ascites) growth retardation was diagnosed when both the head circumference and femur length were below the 5th centiles of the respective reference ranges.

TABLE II—FREQUENCY OF CHROMOSOME ABNORMALITIES AND NUMBER OF ULTRASOUND-DETECTED DEFECTS

No of defects	No with chromosome abnormality/total with defect (%)	Autosomes				Sex chromosomes		Triploidy
		Trisomy			Other	Turner's syndrome	Other	
		21	18	13				
Any	301/2086 (14)	69	83	31	33	38	5	42
≥2	276/958 (29)	60	83	31	21	36	2	42
≥3	223/468 (48)	37	79	28	12	33	..	34
≥4	153/248 (62)	19	64	24	10	18	..	18
≥5	93/133 (70)	5	50	16	5	8	..	9
≥6	58/80 (72)	..	36	12	4	2	..	4
≥7	33/40 (82)	..	26	5	1	..	..	1
≥8	22/24 (92)	..	17	4	1	..	..	..

Results

The fetal karyotype was abnormal in 301 of 2068 (14%) cases tested. Table I provides data on the frequency of different types of chromosomal abnormalities for the defects most commonly found at ultrasound examination. The frequency of chromosomal abnormality increased with the number of defects per fetus detected by ultrasound (table II). The commonest chromosomal abnormality was trisomy 18; the associated malformations included choroid plexus cysts, strawberry-shaped head, facial cleft, micrognathia, heart defects, exomphalos, overlapping fingers, clubfoot, and growth retardation. In trisomy 13, defects included holoprosencephaly, facial cleft, cardiac defects, hydronephrosis, polydactyly, overlapping fingers, and clubfoot. Many of the defects associated with trisomy 21 were more subtle—nuchal oedema, macroglossia, atrioventricular septal defects, mild hydronephrosis, sandal gap, and clinodactyly. Turner's syndrome was associated in many cases with nuchal cystic hygromata, general oedema, brachycephaly, and cardiac defects. Triploidy was characterised by early-onset severe asymmetrical growth retardation, ventriculomegaly, and syndactyly; a molar placenta was found in only 6 of the 42 cases.

The frequency of autosomal abnormalities increased with maternal age (table III). However, the majority of chromosomally abnormal fetuses (74%) were found among women younger than 35 years; this group also had higher frequencies of fetal sex chromosome abnormalities and triploidy than did older women. If fetal karyotyping had been restricted to mothers of 35 years or older, the

TABLE III—FREQUENCY OF CHROMOSOMAL ABNORMALITIES IN RELATION TO MATERNAL AND GESTATIONAL AGE

—	No with chromosomal abnormality *(%)*	Autosomes				Sex chromosomes		
		Trisomy						
		21 (n=69)	18 (n=83)	13 (n=31)	Other (n=33)	Turner's syndrome (n=38)	Other (n=5)	Triploidy (n=42)
Maternal age (yr)								
15–24	57/584 *(10)*	7	15	6	8	9	1	11
25–34	165/1197 *(14)*	32	38	17	21	24	4	29
35–44	79/305 *(26)*	30	30	8	4	5	..	2
Gestational age (wk)								
15–23	190/1125 *(17)*	40	45	22	13	37	3	30
24–31	66/591 *(11)*	14	24	5	9	1	1	12
32–39	45/370 *(12)*	15	14	4	11	..	1	..

percentages of affected fetuses identified would have been only 36% for trisomy 21, 31% for trisomy 18, 19% for trisomy 13, 11% for Turner's syndrome, and 3% for triploidy.

Although in most cases malformations were detected by ultrasound at 15–23 weeks' gestation, 18% were detected after 31 weeks. The frequency of autosomal abnormalities did not change with gestation at detection (table III). By contrast, 85% of cases of triploidy and Turner's syndrome were detected at 15–23 weeks.

TABLE IV—FREQUENCY DISTRIBUTION OF CHROMOSOMAL ABNORMALITIES IN THIS STUDY COMPARED WITH THAT AT MID-TRIMESTER AMNIOCENTESIS AND IN LIVEBIRTHS

—	This study % (n)	Amniocentesis[18]	Livebirths[19]
Autosomal chromosomes			
Trisomy 21	23 (69)	62%	36%
Trisomy 18	27 (83)	12%	4%
Trisomy 13	10 (31)	4%	1%
Other	11 (33)	10%	16%
Sex chromosomes			
Turner's syndrome	13 (38)	2%	3%
47,XXY	1 (3)	8%	20%
47,XYY	1 (2)	2%	20%
Triploidy	14 (42)	..	..

The frequencies of trisomy 18, trisomy 13, triploidy, and Turner's syndrome were higher and the frequencies of sex chromosome abnormalities other than Turner's syndrome were lower than those previously reported among liveborn infants and among fetuses karyotyped in the second trimester of pregnancy because of advanced maternal age (table IV).[18,19]

Discussion

The frequency of chromosomal abnormalities in fetuses with ultrasonographically detectable fetal malformations, growth retardation, or both (14%) is much higher than the reported prevalence in screening studies based on advanced maternal age. Even for a 45-year-old woman, the risk that her fetus will have any chromosomal abnormality is only 7·2% and the risk of Down's syndrome alone is 4·5%.[18] Since karyotyping is advocated for advanced maternal age or abnormal maternal serum biochemistry, when the risk of abnormality is often less than 1%, women whose ultrasound examinations detect certain fetal defects, even apparently isolated, should be offered the option of fetal karyotyping since the risk of chromosomal abnormality is more than 1% for many defects. However, for many of the isolated defects, the exact maternal-age-independent risk for chromosomal abnormalities remains to be established by large prospective studies of unselected populations.

Each of the fetal malformations was associated with a distinct pattern of chromosomal abnormalities (table I). Our findings show that both substantial defects and more subtle ones are markers of fetal chromosomal abnormalities. We found that, for a given malformation, the risk of a chromosomal abnormality may be inversely related to the apparent severity of the defect. For example, among fetuses with exomphalos, those with extra-abdominal herniation of bowel only were more likely to have chromosomal abnormalities than those with herniation of liver and bowel.[15,20] Another example is ventriculomegaly; chromosomal abnormalities were usually found in association with mild rather than severe dilatation of the lateral cerebral ventricles.[9]

Ultrasonographic detection of one defect associated with a specific chromosomal abnormality should stimulate a search for other associated defects; if they are present, the parents can be counselled that the risk of the fetus being chromosomally abnormal is much greater (table II). An ultrasonographically detectable defect is not just a potentially useful marker of a chromosomal abnormality but, in the presence of a normal karyotype, it may also lead to the diagnosis of further important defects or a genetic syndrome. For example, the finding of nuchal oedema may unmask a cardiac abnormality, and the detection of clubfoot may lead to the detection of other features associated with arthrogryposis syndrome.

Turner's syndrome and triploidy were more common in fetuses of women younger than 35 than in older women (table III). Furthermore, the proportion of chromosomal abnormalities due to Turner's syndrome and triploidy was much higher than that at second-trimester amniocentesis for advanced maternal age.[18] Possible explanations for these findings are that the frequency of Turner's syndrome and triploid conceptions in younger women is higher or that the rate of conception is similar for all age groups, but that younger women can sustain pregnancies with highly lethal abnormalities for longer gestations. Nevertheless, these chromosomal abnormalities were rarely found in fetuses of women referred after 24 weeks' gestation, which is consistent with the low frequency among liveborn infants.[19]

In lethal abnormalities, the risk of intrauterine death is high and autolysis may render necropsy impossible. Therefore, antenatal karyotyping is essential for differential diagnosis to allow accurate counselling of parents about the aetiology of the disorder and the risk that future fetuses would be affected. Even when defects are initially judged to be minor or potentially correctable, fetal karyotyping and early diagnosis of chromosomal abnormalities provides the parents with the option of pregnancy termination. When defects are diagnosed in the third trimester, knowledge of a

serious chromosomal abnormality may affect the management of labour and delivery.

Although serious defects, such as holoprosencephaly, can be diagnosed easily by ultrasound, others, such as facial cleft or rocker-bottom feet, need to be specifically looked for. Ultrasonographers should be aware of the syndromal pattern of defects associated with each chromosomal abnormality. In the UK, the Royal College of Obstetricians and Gynaecologists has recommended that more resources for high-quality ultrasound machines and for staff training should be provided to all obstetric departments,[21] and that every pregnant woman should be offered a proper ultrasound scan at about 20 weeks' gestation both for fetal biometry and for a systematic search for defects.[22] Prospective studies are needed to assess the sensitivity of ultrasound screening for chromosomal defects in unselected populations and in high-risk groups.

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PUBLIC HEALTH

HIV infection at outcome of pregnancy in the Paris area, France

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The prevalence of HIV infection in women at end of pregnancy, irrespective of outcome, was determined in a comprehensive survey of both women and medical centres during successive 4-week periods in four areas of the Paris region, France. Blood samples were tested anonymously for antibodies to human immunodeficiency virus (HIV)-1 and HIV-2. Of the 11 593 blood samples 0·40% (95% confidence interval [CI] 0·28–0·51) were positive for HIV-1 and 0·02% (95% binomial interval [BI] 0·002–0·065) for HIV-2. Seroprevalence was higher among women with ectopic pregnancy (2%) (95% BI 0·24–7·04); the rate in women having an elective or therapeutic abortion was more than twice that in those delivering babies (0·70% *vs* 0·28%, $p < 0·05$, relative risk 2·54, 95% CI 1·36–4·75). Studies with neonatal HIV seroprevalence as a surrogate for HIV prevalence in pregnant women would underestimate prevalence in these women.

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