CLINICAL RESEARCH

Prenatal fetal karyotyping and maternal serum alpha-fetoprotein screening

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Abstract

Prenatal karyotyping was undertaken in 569 consecutive amniotic fluid samples where the indication for amniocentesis was two sequential raised maternal serum alpha-fetoprotein concentrations. In 475 successful cultures five chromosome abnormalities were found—four constitutional anomalies (47,XXY; 47,XYY; an inherited inv(8) (p23q11); and a de-novo translocation t(6;7) (p11;p22)) and a culture-derived anomaly (trisomy 2) found in amniotic fluid cells but not in the fetus aborted because it had spina bifida. Of the pregnancies complicated by constitutional abnormalities, only the pregnancy in which the de-novo translocation was detected was terminated. No chromosome abnormalities were detected in the 17 pregnancies which miscarried after amniocentesis.

These results provide little justification for including fetal karyotyping as an essential part of maternal serum alpha-fetoprotein screening programmes.

Introduction

The advent of wide-scale maternal serum α -fetoprotein (AFP) screening programmes has generated a new category of amniocentesis samples. Such samples are procured primarily with the objective of confirming or excluding a fetal neural-tube defect by the technically easy AFP¹ and acetylcholinesterase assays.² The question whether fetal karyotype analysis should also be carried out remains open. Since as many as 2% of all preg-

nancies may be subjected to amniocentesis because of raised maternal serum AFP concentrations,³ the more complex process of chromosome analysis would throw a considerable load on antenatal diagnostic services. The principal justification for karyotyping these samples is the possibility that chromosomal abnormalities causing congenital malformations or mental retardation occur more often in mothers with raised serum AFP concentrations than in an unselected population. We review the results of karyotype analysis in a series of amniotic fluid samples where the indication for amniocentesis was two sequential high maternal AFP values.

Patients and methods

The patients studied were all those on whom amniocentesis was performed between January 1976 and December 1979 because of high maternal serum AFP values. Women whose risk of fetal abnormality justified amniocentesis whatever the serum AFP value were excluded. Those with two sequential AFP concentrations above the 95th percentile of the normal range were referred for further clinical investigations and possible ultrasound scanning.³ A total of 570 patients who showed no clinical signs of threatened abortion, whose gestational age was confirmed by ultrasonic investigations of biparietal diameter, and who appeared not to have a twin pregnancy were referred for amniocentesis. One patient had oligohydramnios, and three attempts at amniocentesis at 19 weeks failed to produce fluid. At 25 weeks she aborted a fetus with Potter's syndrome. From the remaining 569 women samples of amniotic fluid adequate for AFP estimation, karyotype analysis, and studies of cellular morphology were obtained.

Fetal chromosome studies—Amniotic fluid cells were cultured in glass medical flats or Falcon tissue culture flasks in Hams's F10 medium supplemented with 25% fetal calf serum and subcultured when necessary by trypsinisation. When sufficient dividing cells were available they were harvested for cytological study using standard chromosome preparation techniques. Six to eight slides were made from each culture. Slides were stained for conventional analysis as well as G and C banding. When a fetus had an apparently female karyotype the amniotic fluid cells and preparations of cultured maternal leucocytes (when available) were stained for Q-band polymorphism comparison to eliminate the possibility of maternal contamination. Chromosome studies were carried out on fetal organ fibroblasts, cardiac blood and embryonic membrane from aborted fetuses, or on cord blood samples from infants at delivery.^{4 5}

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Determination of amniotic fluid and blood cell numbers and culture of rapidly adhering cells—Total and viable amniotic fluid cell numbers and red cell contamination together with the origin of the red cells were ascertained according to the methods of Gosden and Brock.⁶⁻⁸

Results

CHROMOSOMAL ANALYSIS OF AMNIOTIC FLUID SAMPLES

Karyotyping was attempted on all samples, irrespective of the volume available, viable cell numbers, or whether blood clot was present in the fluid. Volumes of fluid varied from 3 to 18 ml and the viable count from 100 to 84 000 cells per ml. The greatest problems encountered in culture occurred when the number of maternal blood cells exceeded 50×10^6 /ml of fluid (so that blood clots formed and bound viable cells), when viable cell numbers were less than 2000/ml, and when the proportion of viable cells was less than 10% of the total amniotic fluid cells. In these cases either there were insufficient cells to establish a culture or cell settling was impeded by dead cells or red blood cells. Blood contamination was present in 219 (38.5%) of the samples: this may have been because these women had a high risk of fetal abnormality and that, as they had already reached at least 17-18 weeks' gestation, there was not time to postpone the amniocentesis even if the placental position was unfavourable. Prenatal karyotyping was completed in 475 (83%) of the specimens.

The low overall success rate (83%) for the amniotic fluid cell cultures was worrying. Apart from the blood contamination and samples with very low viable cell counts, an additional factor affecting the success rate was the quality of fetal bovine serum.⁹ During one phase of our survey unsatisfactory batches of fetal calf serum were encountered. Although these had proved adequate in their growth-promoting ability for established amniotic fluid cell cultures, they proved to be disastrous for the initial stages of cellular adhesion. As a result several cultures failed. Viable cell counts were useful in pinpointing cases where problems were likely to occur and required only 0.1 ml of fluid. Studies for rapidly adhering cells, which helped in the differential diagnosis of fetal defects, used only 0.5 ml of fluid, so that removing 0.6 ml of fluid from an average volume of almost 13 ml of liquor was very unlikely to have contributed to the culture failures. As the indication for amniocentesis in these pregnancies was a high maternal serum AFP concentration (risk of neural-tube defect) we did not request repeat tap for chromosome studies if the culture failed.

Chromosome abnormalities were detected in five amniotic fluid samples (table I). Both fetuses with sex chromosome aneuploidy (47,XXY and 47,YYY) proceeded to term. Male infants of normal

birth weight were delivered and the karyotypes confirmed from cord blood cultures. Also allowed to proceed to term was a pregnancy in which a pericentric inversion of chromosome 8 was detected, 46,XY, inv(8) (p23q11). Chromosome studies of parental blood showed that the mother also had inv(8). Our unit cytogenetic registry contains five pedigrees (including two which are very extensive) of inv(8) with identical breakpoints. The inversion chromosome in all pedigrees appeared to have normal familial transmission and was not associated with any abnormalities or increased risk of fetal loss. A normal male infant was delivered and the karyotype confirmed.

In one amniotic fluid sample an apparently balanced translocation between chromosomes 6 and 7 was detected. Neither parent carried the translocation (full testing of markers was carried out for paternity), and so this was a de-novo rearrangement. The risk for people carrying de-novo translocations was ascertained by studies in the unit registry and found to be about one in six for mental retardation; no specific congenital abnormalities were implicated. The parents requested termination of pregnancy because of the chance of mental retardation: a phenotypically normal fetus was aborted. The presence of the 46,XX, t(6;7) (p11;p22) translocation karyotype was confirmed in all the fetal tissues studied—blood, lung, kidney, thymus, adrenal, ovary, skin, and muscle.

In the only case of autosomal aneuploidy an extra chromosome 2 was detected in the cultured amniotic fluid cells. Nevertheless, the amniotic fluid AFP concentration was grossly raised, an acetylcholinesterase band was seen on gel electrophoresis, and rapidly adhering cells suggested a fetus with a neural-tube defect. The pregnancy was terminated to yield a female fetus with a large thoracolumbar myelocoele. Chromosome studies of fetal tissues showed a 46,XX karyotype. Trisomy 2 occurs in amniotic fluid cell culture but may be a special culture-derived selection of extraembryonic cells.^{10 11} With the exception of this case the remaining four prenatally detected chromosome anomalies were all present in either the terminated fetus or confirmed in cord blood at delivery.

Chromosomal analysis in spontaneous abortions—Of the 569 pregnancies subjected to amniocentesis, 17 (3.0%) resulted in spontaneous abortion. Table II shows the developmental anomalies and fetal karyotypes. Only one fetus had a developmental abnormality (urogenital atresia), and none had a chromosomal abnormality.

Discussion

The main scientific justification for carrying out fetal karyotyping on amniotic fluid taken because of raised maternal serum AFP concentrations would be if there were a higher incidence of

TABLE I—Details of pregnancies in which karyotype abnormalities were found in cultured amniotic fluids cells

Pregnancy	Karyotype of amniotic fluid cells	Maternal age (years)	Parity	Social class	Outcome of pregnancy	Fetal/newborn karyotype
A	47,XXY	30	1 + 1	III	Live-born boy, 2740 g	47,XXY
B	47,YYY	30	1 + 1	III	Live-born boy, 3300 g	47,YYY
C	46,XY, inv(8)	26	0 + 0	II	Live-born boy, 3550 g	46,XY, inv(8) (p23q11)
D	46,XX, t(6;7)	28	2 + 0	III	Termination of female fetus (risk of mental retardation)	46,XX, t(6;7) (p11;p22)
E	47,XX,+2	31	1 + 0	III	Termination of female fetus for neural-tube defect (thoracolumbar myelocoele); chromosome mosaicism in culture	46,XX

TABLE II—Details of spontaneous abortions after amniocentesis

Case No	Fetal chromosomes	Maternal age (years)	Parity	Social class	Week of gestation at abortion	Size at abortion (in weeks of gestation)	Fetal abnormalities	Details
1	46,XY	21	1 + 0	III	23	23	None	Mother had carcinoma cervix
2	46,XY	30	0 + 0	I	25	25	Urogenital atresia	—
3	46,XX	35	3 + 2	IV	22	16	None	Macerated
4	46,XX	23	0 + 0	IV	22	21	None	—
5	46,XY	25	0 + 0	III	26	26	None	Twins
6	46,XY	20	1 + 0	III	27	24	None	—
7	46,XX	31	0 + 1	I	25	25	None	—
8	46,XX	32	3 + 1	III	22	15	None	Macerated
9	46,XX	26	0 + 1	III	27	27	None	—
10	46,XX	19	0 + 0	IV	25	24	None	Macerated
11	46,XX	33	0 + 0	IV	27	19	None	Macerated
12	46,XY	24	—	—	—	—	—	Lost to follow-up
13	Failed	29	1 + 1	V	20	13	None	Evacuation for missed abortion
14	46,XX	24	1 + 1	II	21	18	None	Macerated
15	46,XY	22	0 + 0	III	21	18	None	Macerated
16	46,XX	22	1 + 0	III	25	17	None	Macerated
17	46,XY	19	0 + 0	III	26	18	None	Macerated

chromosome abnormalities in this group of mothers than in an unselected population. One reason for expecting this is that increased amniotic fluid AFP concentrations have been reported in cases of Turner's syndrome,¹² trisomy 18,¹³ and trisomy 13.¹⁴ In Turner's syndrome, however, a raised amniotic fluid AFP value apparently depends on cystic hygromas in the fetus,¹⁵ whereas in the two autosomal trisomies it is an atypical finding. Furthermore, there is no evidence that maternal serum AFP values are invariably increased in these conditions. A more plausible reason for anticipating chromosome abnormalities is the known association between raised maternal AFP values and subsequent spontaneous abortion. Wald *et al*¹⁶ showed that in mothers with raised second-trimester serum AFP concentrations subsequent spontaneous abortion is six times as probable as in those with normal concentrations. Brock *et al*¹⁷ found that nearly 10% of all pregnancies with two sequential AFP values above the 95th percentile end in spontaneous abortion.

In our series five abnormal karyotypes were detected in the successful analysis of 475 amniotic fluid samples. One of these was an artefact of tissue culture, not confirmed in the aborted fetus with spina bifida. Careful follow-up of the 94 cases in which amniotic fluid karyotype analysis was unsuccessful disclosed no other obvious chromosome abnormalities. Thus the overall rate of chromosome anomaly per 1000 cases lay between 7.0 (4/569) and 8.4 (4/475). Nevertheless, the rate of termination of pregnancy for chromosomal reasons was 2.1/1000 (1/475).

The importance of these figures must be seen in relation to other amniocentesis samples where there was no prior risk of chromosome abnormality and to the results from newborn surveys. The largest prenatal study was that of Milunsky,¹⁸ who reported 2198 cases where the indication for amniocentesis was a family history of neural-tube defect or hydrocephalus; 11 chromosome abnormalities were found, giving a rate of 5.0/1000. In the Medical Research Council study on the risks of amniocentesis¹⁹ four chromosome abnormalities were detected in 1282 pregnancies where the indication for amniocentesis was the risk of a neural-tube defect, a rate of 3.1/1000. Hook and Hamerton²⁰ summarised six series of consecutive newborn surveys comprising 56 952 infants, with an overall birth prevalence of chromosome abnormality of 6.2/1000 and an individual series range of 4.7 to 6.7/1000. The rate of chromosome abnormalities of "definite or probable" clinical significance in the summed series was between 2.27 and 2.91/1000, the higher risk including XYY and XXY males.

When a fetus with a sex chromosome aneuploidy is diagnosed prenatally several dilemmas arise. A major problem is that among the sex chromosome anomalies (47,XXY, 47,XYY, 47,XXX, and 45,X) different degrees of abnormality are found; individuals vary from those with little or no handicap to those who are quite severely handicapped.

From debate in the *BMJ* on "What is to be done with the XYY fetus?"²¹⁻²⁴ it is clear that no consensus of opinion exists. Some clinicians think that in cases of sex chromosome aneuploidy termination of the pregnancy is not justified, and they do not tell the parents. Others, for medicolegal reasons, do tell the parents but have very varied views about the risks involved, some placing much emphasis on the age and fertility of the parents and their social circumstances. A third group think that the evidence about sex chromosome anomalies is equivocal, but that if the parents are told social problems might be caused by the adult expectations of the child's behaviour, and for this reason they do not tell the parents. Ratcliffe and Axworthy²⁴ did not regard the small reduction in IQ of XYY males as reason for selective abortion, but their longitudinal study had covered only the first 12 years of life, and thus any pronouncement on the rate of social deviance would be premature. Similar problems exist when the diagnosis of Klinefelter's syndrome (47,XXY) is made prenatally. It is important to consider the data about 47,XXY males drawn from the widest possible population (S G Ratcliffe, D G Axworthy, J Bancroft, W McLaren, findings submitted for publication) rather than from selected populations (such as mental subnormality hospitals).

The consultant obstetricians in both cases of sex chromosome abnormality in our study decided not to tell the parents, and the pregnancies continued.

Of the 570 mothers subjected to amniocentesis, 17 (3.0%) subsequently miscarried. Karyotype analysis was successful in 16 of these cases, and there were no chromosome abnormalities. The one unsuccessful case was probably a missed abortion, as indicated by the size of the evacuated fetus (table II). Hence miscarriages after amniocentesis in maternal serum AFP screening programmes are probably not the consequence of segregating out a group of pregnancies carrying chromosomally abnormal fetuses. Furthermore, our rate of miscarriage was closely similar to that reported in a large collaborative study,¹⁹ in which virtually all (96.5%) of the amniocenteses were carried out for indications other than high maternal serum AFP values. Our results, however, are at variance with other reports of miscarriage after amniocentesis in serum AFP screening programmes.²⁵⁻²⁸ As reported,²⁷ this probably follows from using a comparatively low serum cut-off point and excluding mothers from amniocentesis who have clinical signs of threatened abortion.

Many laboratories cannot undertake karyotyping in all pregnancies complicated by high serum AFP concentrations because of their work load. We, however, think that they might make some contribution if they could karyotype a proportion of these pregnancies where the risk of chromosome abnormality appears to be increased. Some laboratories carry out fetal karyotyping in pregnancies complicated by high serum AFP values where the mother is over 25 or 30 years old. Can these age limits be justified?

In our series two of the mothers with karyotypically abnormal fetuses were 30 years old and the other was 28. Analysis of the age distribution of the whole population with raised serum AFP values showed that there were 59 women (10.4%) aged 16-19 years, 190 (33.4%) aged 20-24 years, 217 (38.1%) aged 25-29 years, 90 (15.8%) aged 30-34 years, and 13 (2.3%) aged 35-38 years. Thus if fetal karyotyping had been implemented in those aged 30 or more 18.1% of the women would have been included. If the limit had been reduced to 25 years 56.2% would have had fetal karyotyping. This would have meant that 320 fetal karyotypes would have had to be carried out to detect two sex chromosome abnormalities and one (terminated) de-novo translocation.

Another argument used to justify karyotyping all amniotic fluid samples is that it is unethical to deny a mother all available information on her baby after she has been subjected to the risks of amniocentesis. This ignores the fact that chromosome analysis is expensive and requires highly trained laboratory personnel and that many laboratories are already overextended. We find that amniotic fluid from mothers with high maternal serum AFP values are often bloodstained and technically difficult to karyotype. Even if analysis is successful on fluid samples in this category (up to 2% of all pregnancies) it will make virtually no impact on the incidence of children born with severe chromosome abnormalities. For example, in the study period there were 19 live-born infants with Down's syndrome (18 trisomy 21, and one translocation), two with trisomy 18, and one with trisomy 13 in the hospitals participating in AFP screening, despite most mothers aged 35 or more being offered amniocentesis. Furthermore, the error rate on prenatal cytogenetic analysis in a world-wide survey of 32 443 cases was reported as 1.4/1000 samples.²⁸ This is almost certainly an underestimate but even so is not too different from the rate of chromosome abnormalities giving rise to congenital malformations and mental retardation in unselected populations. Thus, although prenatal karyotyping of all amniotic fluid samples will probably continue in those laboratories which have adequate capacity, it would be unwise to make it an essential component of a maternal serum AFP screening programme.

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Natural history of autoimmune thyroiditis

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Abstract

One hundred and sixty-three asymptomatic people with thyroid antibodies or raised serum thyrotrophin (TSH) concentrations, or both, and 209 age-matched and sex-matched controls without either marker of thyroid disorder were followed up for four years to determine the natural history of autoimmune thyroiditis. Mildly raised TSH concentrations alone and the presence of thyroid antibodies alone did not significantly increase

the risk of developing overt hypothyroidism during the four years compared with the controls. Overt hypothyroidism developed at the rate of 5% a year in women who initially had both raised TSH concentrations and thyroid antibodies.

Prophylactic treatment with thyroxine may be justified in women found to have both markers of impending thyroid failure. The cost effectiveness of screening the adult population remains to be evaluated.

Introduction

Overt hypothyroidism is a common condition that develops insidiously and is often not recognised until it has been present for a considerable time. The clinical features are not specific, and the diagnosis is often made only when there is a full range of the symptoms and signs that are associated with myxoedema. In overt primary hypothyroidism serum thyrotrophin (TSH) concentrations are invariably raised, thyroxine concentrations are depressed, and thyroid antibodies are usually present, reflecting the underlying autoimmune process that is believed to be the usual cause. Raised TSH concentrations and thyroid antibodies are present before the clinical features become apparent and may be used to identify people at risk of progression to overt hypothyroidism.

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