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Chromosome variation in perinatal mortality: a survey of 500 cases

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SUMMARY The results of chromosome analyses on 500 cases of perinatal deaths are reported. It was found that 4·8% were chromosomally abnormal, but 90% of the chromosomally abnormal were either clinically malformed or macerated fetuses. Of the macerated fetuses, 9% were chromosomally abnormal and of these 33% had trisomy 21. The data suggest that the high loss of trisomy 21 fetuses in later stages of pregnancy is of an order sufficient to explain the discrepancy between the higher numbers of trisomy 21 detected during amniotic fluid sampling than found at birth in women of 35 years and over.

Perinatal mortality is known to be influenced by a large number of social, environmental, obstetric, and genetic factors. Chromosome abnormality forms an important component of the genetic factor but, to date, there is information only from four small surveys[1–4] to show its contribution to perinatal deaths and late abortions, the main emphasis on the influence of chromosome abnormality in fetal wastage and reproductive loss having been on early spontaneous abortions[5 6] and on the live newborn.[7]

Paucity of data on chromosome anomalies in the later stages of pregnancy has been partly the result of the difficulty of getting material, and largely because the material presents problems in establishing cell growth. However, the need for such information has been emphasised[8] because it may help to explain the apparent discrepancies between the higher number of chromosome abnormalities found in antenatal chromosome studies than expected from incidence figures from newborn data.[9 10]

Our survey of chromosome abnormalities in perinatal deaths and late abortions has been aimed at establishing an accurate picture of the frequency and pattern of chromosomal abnormalities in this group. In the present paper we report our results from a series of 500 cases.

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Materials and methods

The Lothians and Borders regions form a defined area in south-east Scotland and perinatal deaths from the area are sent routinely to the Pathology Department, Royal Hospital for Sick Children, Edinburgh, for necropsy. The present survey consists of a consecutive series which were referred during the period November 1978 to March 1981 and which fell into one of the following categories: (1) stillbirths with a gestation of 20 to 28 weeks; (2) perinatal deaths. Firstly, stillbirths with a gestational age (based on clinical estimation) of 28 weeks and over, and, secondly, livebirths in which death occurred within 7 days of birth; (3) neonatal deaths in which death was between 8 and 28 days after birth. Estimation of gestational age was based on a combination of menstrual age and a clinical assessment, which included radiological examination of biparietal diameter, thoracic spine length, and centres of ossification.

Tissue was taken at necropsy for chromosome studies and placed in tissue culture medium for transporting to the laboratory. Testis and ovary were the optimum tissues for culturing if the material was fresh; however, pericardium was also successful. If the fetus was macerated it was necessary to use amnion for culture, or fascia if amnion was not available. In seven cases a sample of blood was taken for chromosome studies before the death of the infant. In two cases the chromosome result was from an amniotic fluid culture taken at 16 weeks' gestation.

The tissue culture technique was as follows. Each

sample was cut into small explants, then set up on coverslips in tissue culture dishes using the plasma clot technique of Harnden.[11] Ham's F10 tissue culture medium with 25% fetal calf serum was used for culturing the cells and the cultures were grown and maintained in a 5% CO_2 atmosphere at 37°C.

Growth of cells onto the coverslip from the gonadal biopsies was usually observable after 2 to 3 days and there was usually sufficient outgrowth for harvesting after 8 to 10 days. Growth from amnion was slower and required 12 to 28 days of growth before harvesting, the length of time depending on the initial viability of the sample. The cells in mitosis were harvested in situ on the coverslips using standard cytogenetic techniques. Subculturing was carried out only if more material was required, for example, if growth was confined to one explant only of the 24 routinely set up.

Five cells from an unbanded Giemsa stained preparation and five cells from a G banded preparation were analysed routinely from each sample by one of two observers who had no previous knowledge of the clinical status of the case. Where non-modal cells were found, then further cells were analysed. A Q banded preparation was also examined from each case.

Results and discussion

During the period from November 1978 to March 1981, 595 cases which fell into the classifications required for our survey were referred for necropsy. Tissues from 585 were set up in culture, 10 not being attempted either because the sample had arrived in fixative (three cases), or the patient had a severe infection (two cases), or the sample was itself clearly infected (five cases). A chromosome result was obtained in 500 of the 585 (85% success).

Ovarian or testicular tissue from liveborns or fresh stillbirths grew successfully in 365 out of 383 cases (95%). Three of the 18 which did not grow had a severe yeast or bacterial infection. Amnion cultures set up from 192 macerated cases were successfully karyotyped in 132 (69%). Cultures from fascia from 10 macerated cases where amnion was not available produced a successful result in only three cases. The comparatively high success rate in amnion cultures from macerated fetuses was largely achieved by using a coverslip technique which enabled the cells to be harvested in situ. Several amnion cultures had feeble cell growth which would not have survived trypsinisation, but from which three or four mitoses could be salvaged in the original culture.

Cultures from testis and ovary from liveborns and fresh stillbirths showed a significant difference ($p<0.001$) in the average time required from setting up the tissue in culture until harvesting for chromosome analysis. Testis from liveborns averaged 8·7 days and ovary 11·3 days. Testis from fresh stillbirths averaged 10·6 days and ovary 15·9 days, suggesting that there was reduced viability in the stillborn material. Hassold *et al*[6] also observed a faster growth rate of 46,XY over 46,XX tissue, but thought that undetected maternal contamination might have been an influencing factor. Clearly such a problem does not exist in our material. Amnion cultures from macerated fetuses took longer to grow and the time in cultures was more variable. No significant difference was observed in growth rate between 46,XY and 46,XX cultures. Growth from amnion from three very macerated fetuses took longer than 28 days, and in each case growth arose from a single explant. The results in each case were 46,XX and our suspicions that these were maternal contaminations were confirmed in one case where the fetus had a normal male phenotype. This was the only case in the survey where a discrepancy arose between phenotypic sex of the fetus and chromosomal sex.

CHROMOSOME RESULTS

Frequency

The results of the survey are presented in table 1 according to age at death. They show that macerated fetuses are more likely to be chromosomally abnormal than non-macerated fetuses. In addition, in the macerated groups, the earlier gestational ages have a higher frequency of chromosome abnormalities, 20% of 20 to 28 weeks' gestation being chromosomally abnormal, compared with 6·9% in the 28 weeks and over gestation group. Chromosome abnormalities in unmacerated fetuses were negligible; in liveborn perinatal deaths, 4·3% were abnormal and the overall figure for perinatal deaths was 4·8% chromosomally abnormal. None was found in the neonatal group.

TABLE 1 *Results of chromosome findings in 500 stillbirths from 20 to 28 weeks, perinatal deaths, and neonatal deaths.*

Age at death	*No attempted*	*Success*	*46,XX*	*46,XY*	*Abnormal*
SB 20 to 28 weeks					
Macerated	38	20	10	6	4 (20%)
Non-macerated	92	86	34	52	– (0)
Total	130	106	44	58	4 (3·8%)
Perinatal deaths					
Macerated SB	164	115	53	54	8 (6·9%)
Non-macerated SB	63	57	26	30	1 (1·8%)
Livebirths	189	185	63	114	8 (4·3%)
Total	416	357	142	198	17 (4·8%)
Neonatal deaths	39	37	16	21	– (0)
Total	585	500	202	277	21 (4·2%)

Of the 500 cases in our survey, 357 were classified as perinatal deaths. When compared with similar surveys of perinatal deaths (table 2), the frequency of chromosome abnormalities in our data, together with that of Sutherland *et al*[4] which was carried out in the same department during the preceding 4 years, is lower than in the other series. Meaningful comparisons of the data from stillborns are not possible because of the widely differing success rates and the small numbers involved. However, comparisons of the perinatal liveborn figures where larger numbers have been studied are valid in view of the high success rate in each survey, and our figures for the department of 4·5%[4] and 4·3% (present survey) are significantly lower than the others. In the case of the present survey, had the grossly unbalanced chromosome abnormalities detected during antenatal chromosome screening and subsequently terminated been included, then the frequency would have been 5·6%, that is, in the same range as the earlier surveys which were carried out before antenatal diagnosis became a routine procedure. These results show that the programme of antenatal diagnosis of chromosome abnormalities being carried out in south-east Scotland is having a demonstrable effect on the frequency of chromosome abnormalities in perinatal mortality.

Type of error

Details of the chromosome abnormalities are presented in table 3. The majority are compatible with survival at least to birth, while a few are similar to those found in early spontaneous abortions which rarely survive to later gestational ages. When compared with the previous surveys of chromosome abnormalities in perinatal deaths (table 4), our results show broad similarities but some differences. About half the reported errors were trisomies for 21, 18, or 13 (64% in our survey), sex chromosome anomalies accounted for 11% of the errors (nil in our survey),

TABLE 2 *Comparison of frequency of chromosome abnormalities in perinatal death.*

Authors	*Perinatal deaths*									*Total*		
	Macerated SB			*Non-macerated SB*			*Liveborn*					
	Abnormal	*Total*	*%*	*Abnormal*	*Total*	*%*	*Abnormal*	*Total*	*%*	*Abnormal*	*Total*	*%*
Present survey	8	115	6·9	1	57	2	8	185	4·3	17	357	4·8
Machin and Crolla[1]	3	34	8·9	5	122	4	20	344	5·8	28	500	5·6
Bauld *et al*[2]	1	3	33	1	32	3	7	98	7·1	9	133	6·8
Kuleshov[3]	3	22	13·6	3	61	5	6	92	6·5	12	175	6·9
Sutherland *et al*[4]												
Edinburgh	6	49	12·2	5	146	3	14	311	4·5	25	506	4·9
Adelaide	1	7	14·3	0	11	0	0	48	0	1	66	1·5
Total	22	230	9·5	15	429	3·5	55	1078	5·1	92	1737	5·3

TABLE 3 *Summary of clinical and pathological data on chromosomally abnormal fetuses.*

No	*Age at death**	*Chromosome constitution*	*Gestation*		*Birth weight (g)*	*Maternal age*	*Parity*	*Malformation*
			Clinical age (wk)	*Menstrual age (wk)*				
1	*MSB 20–28 wk	45,X	20	24	186	17	0+0	+
2	MSB 20–28 wk	45,X	26	25	375	16	0+0	+
3	MSB 20–28 wk	69,XXX	27	33	310	26	1+0	+
4	MSB 20–28 wk	47,XX,+18	25	30	535	25	0+0	+
5	MSB	47,XY,+21	39	39	2350	37	0+0	+
6	MSB	47,XY,+21	34	34	2305	36	3+0	+
7	MSB	47,XY,+21	41	41	3675	30	1+0	
8	MSB	47,XY,+21	31	34	1575	21	0+0	+
9	MSB	46,XY,−14,+t(14q;21q)mat	40	40	2920	19	0+0	
10	MSB	47,XY,+18	29	36	1099	31	0+0	+
11	MSB	47,XY,+13	38	38	2630	23	0+0	+
12	MSB	69,XXX	28	36	850	27	2+1	+
13	NMSB	46,XX,inv(2)(p13q11)	33	33	1430	27	1+0	
14	LB	47,XY,+21	40	40	3273	25	1+0	+
15	LB	47,XY,+21	36	36	3990	40	3+1	+
16	LB	47,XY,+18	31	31	876	26	1+0	+
17	LB	47,XY,+13	34	34	2305	36	3+0	+
18	LB	47,XX,+13	32	32	1265	29	0+0	+
19	LB	47,XY,+r	31	31	1310	26	3+0	
20	LB	46,XX,−13,+mar	38	38	2856	21	1+0	+
21	LB	46,XY,4p−	34	34	2360	38	6+1	+

*MSB macerated stillbirth, NMSB non-macerated stillbirth, LB liveborn.

and structural rearrangements accounted for about 15% (12% in our survey). Triploidy and X monosomy, which together formed 35% of abnormalities in early spontaneous abortions,[6] accounted for only 7% of abnormalities in the perinatal deaths, but accounted for three out of the four abnormal stillbirths under 28 weeks' gestation in our survey. Cases where a normal chromosome variant was observed have not been included. For example, one perinatal liveborn was observed to have an exceptionally small Y chromosome. Subsequent examination of the father's chromosomes showed he carried an identical small Y.

Sex ratio

The well known excess of males in live newborns and non-macerated stillbirths was clearly demonstrated in our results. Macerated stillbirths, however, did not show a deviation from unity in the sex ratio. This reflects the presence of cases with congenital anomalies and, in particular, neural tube defects which are more prevalent in females.

The number of cases with any one type of chromosome abnormality was too small to detect any significant deviations in the sex ratios, but it is of interest that all six trisomy 21s were male. A male excess of trisomy 21 has now been reported in early spontaneous abortions[6] and there is a similar trend in newborn data.[12] The combined data suggest an increased proportion of males with trisomy 21 at conception or alternatively very early fetal loss of female trisomy 21.

Maternal age

The maternal age distribution of the 500 cases is shown in table 5. The mean maternal age of those with normal chromosomes was 25·18 years, and 36% had a maternal age of over 30 years. The mean maternal age of those with a regular trisomy was 28·83 years, and 42% were over 30 years. However, since the survey was being carried out concurrently with an antenatal chromosome screening service, there is a small selection against those with chromosome abnormalities in the maternal age group of 35 years and over.

Gestation

Classification of our cases in the survey was dependent on clinical including radiological estimation of gestational age. Table 3 shows a comparison of clinical estimation of gestation and gestation based on menstrual age in the cases with an abnormal karyotype. Clear discrepancies exist in cases with triploidy and trisomy 18. These fetuses were all severely macerated and it suggests that intrauterine death had occurred some time before the fetus was expelled. This illustrates one of the problems in collecting accurate information on the frequency of chromosome abnormalities in the 20 to 28 weeks' gestation period. Apart from problems of assessment of gestational age, the criteria of selection of material is also important. Thus, Hassold *et al*[6] found 45% abnormal karyotypes in products of conception weighing less than 500 g but which had a menstrual age of 20 weeks and over in their survey of spontaneous abortions. Their survey did not include fetuses over 500 g. By contrast, the survey of Creasey *et al*[13] found only 6·5% chromosomally abnormal in the over 20 weeks' gestation group, which included all spontaneous abortions irrespective of weight or gestation.

TABLE 4 *Types of chromosome anomalies in perinatal deaths.*

	Regular trisomies			*Triploidy*	*Sex chromosomes*		*Structural rearrangements*	*Other*	*Total*
	21	*18*	*13*		*45,X*	*Other*			
Present survey	6	2	3	1	—	—	2	3	17
Machin and Crolla[1]	3	8	3	1	1	4	8	—	28
Bauld *et al*[2]	1	5	—	—	—	1	1	1	9
Kuleshov[3]	2	2	1	1	1	3	1	1	12
Sutherland *et al*[4]									
Edinburgh	4	9	2	—	—	2	2	6	25
Adelaide	—	—	—	1	—	—	—	—	1
Total	16	26	9	4	2	10	14	11	92

TABLE 5 *Maternal age distribution in 500 stillbirths from 20 to 28 weeks, perinatal deaths, and neonatal deaths.*

Chromosome constitution	*Maternal age*						*No result*	*Total*
	15–19	*20–24*	*25–29*	*30–34*	*35–39*	*40+*		
Normal chromosomes	55	127	124	64	24	3	82	479
45,X	2	—	—	—	—	—	—	2
Regular trisomies	—	3	4	2	2	1	—	12
Other abnormalities	1	1	4	—	1	—	—	7
Total	58	131	132	66	27	4	82	500

Our own figure of 3·8% abnormal in the 20 to 28 weeks' gestation period is much lower and clearly reflects the fact that products of conception with a menstrual age of 20 weeks and over, but clinically less than 20 weeks' gestation, were not included.

CORRELATION OF CHROMOSOME RESULTS AND CLINICAL FINDINGS

The chromosome results for the whole survey in relation to the clinical findings at necropsy are shown in table 6. The classification according to cause of death is the same as that used by Sutherland *et al.*[4] The table shows that the chromosome abnormalities were virtually all confined to cases with severe malformations and macerated stillbirths. These two categories included about half of the cases in the survey but 90% of the chromosomally abnormal. Published surveys of perinatal deaths show similar findings. Those with malformations or maceration, or which had indications from appearances that a chromosome anomaly might be present, accounted for 86% of the chromosomally abnormal cases. The 14% of chromosome abnormalities found in association with other causes of death were generally different from the grossly unbalanced karyotypes found in the previous groups and were of a kind found in the general adult population, for example, 45,XY,t(13q;21q), 45,XX,t(14q;15q), 47,XXY, 46,XX, Gp−,[1] 47,XXX,[2] and 47,XYY.[3] It might be assumed that the association of perinatal death and chromosomal anomaly is simply coincidental in such cases.

INCIDENCE FIGURES

The total number of births in the Lothians, Fife, and Borders regions registered in the Annual Report of the Registrar General for 1979 and 1980 are respectively 15 182 and 15 089.[14] In 1979, 177 of the 223 registered perinatal deaths had necropsies and 147 were studied successfully for their chromosome constitution. In 1980, 160 out of 190 registered perinatal deaths had necropsies and 138 were successful chromosomally. Necropsies were not carried out if parents refused permission, or occasionally fetuses may not have been referred for necropsy if it was felt that the cause of death was already obvious. In both these situations there may well have been a slight bias towards those with malformations and, possibly, chromosome anomalies. In fact, we are aware of one trisomy 18 case during the period of the survey where parents refused permission for a necropsy. Therefore, the frequency of chromosome abnormalities in perinatal deaths may well be a slight underestimate.

Figures for the frequency of trisomies 13, 18, and 21 based on data from the present survey, together with data from the antenatal diagnosis survey in the same department, are shown in table 7 for south-east Scotland in 1979 and 1980. For trisomy 13, the frequency of 0·01% is of the same order as the frequency in consecutive live newborn populations.[7] A total of four trisomy 18 cases was detected giving a frequency of 0·1%, a gain of the same order as in consecutive liveborns, but not as high as found by Machin and Crolla[1] in their perinatal survey, where the frequency was 0·02%.

Data for trisomy 21, which included the number of liveborn as well, showed a total of 39 for the years of 1979 and 1980, that is, a frequency of 0·1%, also of the same order as in consecutive liveborn populations.[7]

Figures for the occurrence of trisomy 21 in women of 35 years and over for the same period are shown in table 8. In 1979 and 1980, 1280 livebirths occurred to women of 35 years and over. In the same period, adjusted back 0·4 year to allow for the fact that amniocentesis is carried out at about 16 weeks' gestation, 531 amniotic fluid analyses on women of 35 years and over were studied. In this group three with trisomy 21 were found, giving a frequency of 0·56%. In the 749 women of 35 years and over who did not have amniocentesis, there were two stillbirths

TABLE 6 *Chromosome results according to cause of death.*

Cause of death	*Chromosome results*			
	Total	*46,XX*	*46,XY*	*Abnormal*
Macerated stillbirths without malformation	114	55	56	3
Macerated stillbirths with malformation	21	8	4	9
Severe congenital malformation	53	23	23	7
Congenital heart malformation	17	9	8	—
Primary CNS malformation	21	15	6	—
Prematurity associated disease	119	33	85	1
Primary anoxia	71	25	45	1
Fresh stillbirths without malformation	61	23	38	—
Other	23	11	12	—
Total	500	202	277	21

TABLE 7 *No of cases of trisomy 13, 18, and 21 occurring in gestations over 16 weeks in south-east Scotland.*

		Trisomy 13		*Trisomy 18*		*Trisomy 21*		
	Total births	*Present survey*	*AF**	*Present survey*	*AF**	*Present survey*	*AF**	*LB**
1979	15 182	1	–	2	2	4	2	12†
1980	15 089	1	–	–	–	3	2	16†
Total	30 271	2	–	2	2	7	4	28

*AF, amniotic fluid, data adjusted back 0·4 year (see text); LB, liveborn.
†Source of data: Scottish Health Service.

TABLE 8 *Births, stillbirths, and trisomy 21 in women 35 years and over in south-east Scotland.*

	Stillbirths		*Amniotic fluid analyses**		*Livebirths*	
	Total	*Trisomy 21*	*Total*	*Trisomy 21*	*Total*	*Trisomy 21*
1979	5	2	240	1	637†	1
1980	13	–	291	2	643†	2
Total	18	2	531	3	1280	3

*Data adjusted back 0·4 year (see text).
†Source of data: Scottish Health Service.

with trisomy 21, an incidence of 0·27%, and three liveborn (0·40%). Although these numbers are very small, and the liveborn figures may be slightly influenced by under-reporting, they show that the incidence of trisomy 21 fetuses lost in the later stages of pregnancy in our data is sufficient to account for any discrepancy between the higher rate of trisomy 21 found at 16 to 18 weeks' gestation during antenatal diagnosis studies and that found in the liveborn. Hook[15] has also shown that there is a high incidence of stillbirths in women diagnosed as carrying a trisomy 21 fetus through amniocentesis but who had elected to continue their pregnancy.

Conclusion

Our survey, together with the previous surveys of chromosomal abnormalities in perinatal mortality, shows that the frequency of chromosome abnormalities lies between 4·8 and 6·9%. Our survey and that of Sutherland *et al*[4] have the lowest frequencies of abnormalities. They were both carried out in conjunction with an expanding antenatal chromosome diagnosis programme and, since almost half of the women of 35 years and over in the area are now being screened, it is not surprising that its effects are being reflected in the lower number of chromosome abnormalities now reaching the perinatal period.

It is clear in all the surveys that the majority of chromosome anomalies are found in malformed infants and malformed or macerated fetuses. Improved culture techniques for amnion cultures from macerated fetuses have now made it possible to get meaningful figures on the frequency of chromosome anomalies in this important group. Results from the 69% of successfully karyotyped macerated fetuses show that about 9% of these have a chromosome abnormality and 33% of these are trisomy 21. Data from our own survey suggest that the high loss of trisomy 21 in later stages of pregnancy is of an order sufficient to explain the discrepancy between the higher numbers of trisomy 21 detected during amniotic fluid sampling than found at birth in women of 35 years and over. The results of the survey also demonstrate the extreme difficulty found in diagnosing Down's syndrome on morphological features alone and emphasise the importance of cytogenetic studies in selected categories of fetal and perinatal wastage.

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