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Frequency of chromosomal abnormalities in miscarriages and perinatal deaths

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There is a very high mortality among human conceptuses before, during, and shortly after birth, which is known as reproductive loss or pregnancy wastage. Chromosomal abnormalities are among the most important causes, particularly in the developed countries. The expulsion from the uterus of a conceptus before it is potentially sufficiently mature to survive is described as a spontaneous abortion, miscarriage, or early fetal death. In the United Kingdom viability is conventionally assumed to be attained by the 28th week after the first day of the mother's last menstrual period, though in many other countries 22 or 24 weeks is considered a more realistic time. The delivery of a dead fetus after this stage of pregnancy is known as a stillbirth or late fetal death. The death of a stillborn fetus may have occurred before or during the delivery. Intrapartum death generally results in the delivery of a fresh fetus ('fresh stillbirth'), while fetuses which die antepartum show varying degrees of maceration ('macerated stillbirth'). The death of an infant within a week of birth is an early neonatal death, and stillbirth and early neonatal death combined are termed perinatal death.

Prevalence of chromosomal anomalies

Table 1 shows the prevalence of chromosome abnormalities in spontaneously aborted fetuses (Creasy *et al.*, 1976) in infants dying during the perinatal period (Bauld *et al.*, 1974; Machin and Crolla, 1974; Kuleshov, 1976) and in liveborn infants (Ratcliffe, 1975). There has been a considerable variation between the prevalence of abnormal karyotypes reported by different studies: the major factor influencing the proportion of abnormalities being the gestational age of the abortuses. Of the larger studies, those that included abortuses expelled up until the end of the second trimester revealed 20 to 30% abnormal karyotypes (Carr, 1967; Dhadial *et al.*, 1970; Creasy *et al.*, 1976) while those studies restricted to the earlier stages of pregnancy revealed 50 to 60% of abnormalities (Therkelsen *et al.*, 1973; Arakaki and Waxman, 1970; Kajii *et al.*, 1973; Boué *et al.*, 1975). From these reports it appears that the prevalence of chromosomal abnormalities in abortuses decreases from over 60% in the earliest detectable stages of pregnancy to below 5% by the end of the sixth month. About half of the chromo-

Table 1 *Number and type of chromosomal anomalies found in spontaneous abortions, stillbirths, neonatal deaths, and livebirths of known karyotype*

	*Spontaneous abortions**		*Stillbirths†*				*Neonatal† deaths*		*Livebirths‡*		
			Macerated		*Fresh*						
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Prevalence per 1000*
Total number karyotyped	983	—	61	—	222	—	551	—	43558		
Total abnormal	287	100	7	100	10	100	31	100	247	100	5·69
45, X	68	23·7	0		0		2	6·5	2	0·8	0·05
Other sex aneuploidy	3	1·0	3	42·9	2	20·0	3	9·7	91	36·8	2·09
Autosomal trisomy	143	49·8	3	42·9	7	70·0	17	54·8	52	21·1	1·19
Triploidy	38	13·2	1	14·3	0		1	3·2	1	0·4	0·02
Tetraploidy	12	4·2	0		0		0		0		0
Structural:											
balanced	1	0·3	0		1	10·0	2	6·5	80	32·4	1·84
unbalanced	9	3·1					5	16·1	8	3·2	0·18
Others	13	4·5	0		0		1	3·2	13	5·3	0·30

*Creasy *et al.*, 1976.
†Machin and Crolla, 1974; Bauld *et al.*, 1974; Kuleshov, 1976.
‡Adapted from Tables 5-9 (Ratcliffe, 1975).

somally abnormal abortuses are trisomic for an autosome. Trisomies of all the autosomes except numbers 1 and 17 have been reported, though they occur with very different frequencies: trisomy 16 alone accounting for about one-third of the condition (Kajii *et al.*, 1973; Therkelsen *et al.*, 1973; Ikeuchi *et al.*, 1975; McConnell and Carr, 1975; Creasy *et al.*, 1976). Sex chromosome monosomy constitutes about a fifth of the abnormal karyotypes, but other sex chromosome abnormalities are very rare in abortuses. Triploidy occurs in about 10 to 15% of the abnormals, while the remainder are mostly tetraploids, unbalanced translocations, double trisomies, and mosaics.

The chromosome abnormalities found in perinatal deaths are similar in type to those found in newborns, but are about 10 times more common. The highest prevalence is among the macerated stillbirths, 11·5%, which is more than double that of the fresh stillbirths, 4·5%, and early neonatal deaths, 5·6%. The abnormalities reported have been predominantly trisomy 18, 13, and 21, sex chromosome aneuploidy and unbalanced translocations. One macerated stillbirth was trisomic for chromosome 22, and another macerated stillbirth and an early neonatal death were triploid.

The figures in Table 2 represent an attempt to extrapolate from these studies to the situation in a cohort of 1000 conceptions. Retrospective studies indicate that about 15% of clinically recognised pregnancies abort spontaneously (e.g. Warburton and Fraser, 1964), though studies employing life table techniques suggest the true figure may be 24 to 27% (French and Bierman, 1962; Erhardt, 1963). Table 2 is based on the more conservative assumption that from 1000 diagnosed pregnancies, 150 abort spontaneously, 10 are stillborn, and of the 840 remaining livebirths, 10 die during the first week of life. Fifty per cent of the spontaneous abortions are assumed to be chromosomally abnormal and the prevalence among perinatal deaths and livebirths is as shown in Table 1. These calculations suggest that in at least 8% of the diagnosed pregnancies the conceptus is chromosomally abnormal.

From these figures estimates of the previable mortality and the perinatal mortality were made for each type of chromosome abnormality (Table 3). These estimates are subject to large errors because of the assumptions made and, in the case of perinatal mortality, the small numbers that have been studied. All chromosome abnormalities have a very high *previable* mortality, with the exception of sex chromosome abnormalities other than sex chromosome monosomy, and balanced structural anomalies. The mortality of autosomal trisomies varies from about 70% for trisomy 21, to over 90% for trisomies 13 and 18, and virtually 100% for all others.

The estimates of *perinatal* mortality are, as stated, based on a small number of infants. Sex chromosome monosomy again has a much higher death rate than other sex chromosome abnormalities. This is in line with a report by Robinson (1974) who found a 33% early neonatal mortality for 45,X infants (3/9) compared with 13% for those with sex chromosome trisomy (4/31) detected by sex chromatin analysis of neonates. The perinatal mortality of trisomy 13 and, particularly, 18 is much higher than that of trisomy 21, being over 90% for the two former and only about 12% for the latter trisomy. In fact, the perinatal mortality of trisomy 18 was estimated as over 100%, which has been interpreted by Machin and Crolla (1974) as indicating that this condition is more common at term than is generally believed. The estimate for triploidy may be too low, as only one non-mosaic

Table 2 *Estimated numbers of abnormal fetuses which are aborted, stillborn, liveborn, and which die neonatally from a cohort of 1000 pregnancies by karyotype*

	1 *Spontaneous abortions*	*Stillbirths*		*4* *Neonatal deaths (incl. in LB)*	*5* *Livebirths*
		2 *Macerated*	*3* *Fresh*		
Number assumed to be derived from 1000 pregnancies	150	5	5	(10)	840
Total abnormal	75·0	0·57	0·23	(0·56)	4·78
45, X	17·77	0	0	(0·036)	0·039
Other sex aneuploidy	0·78	0·25	0·05	(0·05)	1·76
Autosomal trisomy	37·37	0·25	0·16	(0·31)	1·00
Triploidy	9·93	0·08	0	(0·02)	0·02
Tetraploidy	3·14	0	0	(0)	0
Structural:					
balanced	0·26	0	0·02	(0·04)	1·55
unbalanced	2·35	0	0	(0·09)	0·15
Others	3·40	0	0	(0·02)	0·25
Normal	75·0	4·43	4·77	(9·44)	835·22

LB, livebirths.

Table 3 *Previable mortality and perinatal mortality* derived from figures in Table 2†*

	Previable mortality %	*Perinatal mortality %*
Assumed overall mortality	15	2·4
Total abnormal	93·1	24·4
45, X	99·8	94·2
Other sex aneuploidy	27·5	17·0
Autosomal trisomy	96·4	51·1
Triploidy	98·8	98·8
Tetraploidy	100·0	—
Structural:		
balanced	14·2	3·8
unbalanced	94·0	60·0
Others	93·2	8·0
Estimated normal	8·16	2·2

*Large standard errors due to small numbers, particularly for perinatal deaths.

†Previable mortality $= \frac{\text{col } 1}{\text{col } 1 + 2 + 3 + 5} \times 100$

Perinatal mortality $= \frac{\text{col } 2 + 3 + 4}{\text{col } 2 + 3 + 5} \times 100$

triploid has survived beyond the early neonatal period, and that died at 9 days (de Grouchy *et al.*, 1974). As with the abortuses the unbalanced translocations have a much higher mortality than those that are balanced.

Conclusion

In spite of the approximations involved in these calculations it is clear that the chromosome abnormalities detected in liveborn infants are only a small fraction of all aberrant conceptions, most of which die in the early stages of gestation. The low mortality of balanced structural abnormalities seems reasonable, and the Lyon hypothesis explains the relatively high survival of sex chromosome polysomies (Lyon, 1961). However, in the case of abnormalities which are sometimes compatible with survival into adult life, such as sex chromosome monosomy or trisomy 21, we have no explanation why most zygotes are aborted, but some survive.

These estimates of the viability of various chromosomal abnormalities show that if an environmental hazard were to increase their incidence at conception uniformly only a few would reflect this in their birth prevalence, and most affected individuals would be unlikely to reproduce. Any factor which were to affect the relation between incidence and prevalence could have a very serious effect on the number of affected survivors. Heritable abnormalities, such as balanced translocations, while not producing abnormal individuals directly, could have a much greater long-term effect on the population, and would mostly evade the screening mechanism of abortion and perinatal death.

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