Fertility in 47,XXX and 45,X patients

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SUMMARY Female patients with a sex chromosome abnormality may be fertile. In patients with a 47,XXX cell line there appears to be an increased risk of a cytogenetically abnormal child but the extent of this risk cannot yet be determined; it is probably lower in the non-mosaic 47,XXX patient than the mosaic 46,XX/47,XXX one. Patients with a 45,X cell line rarely become pregnant, and when they do they appear to have a high risk of an abnormal child or repeated unsuccessful pregnancies; this risk is certainly exaggerated by the method of reporting; when the poor reproductive performance is first identified leading to the recognition of the maternal cytogenetic fault, the reproductive failure rate is naturally high; when the maternal fault is first identified and the reproductive history then established far better results are evident.

Patients with sex chromosome anomalies usually present in clinical practice as examples of gonadal dysgenesis with primary amenorrhoea, streak gonads, and absolute sterility. There are exceptions, however, notably individuals with a 47,XXX karyotype who are known to be fertile (Barr *et al.*, 1969) and certain patients with a mosaic karyotype or with deletions or isochromosomes who develop a degree of ovarian differentiation compatible with secondary sexual development, menstruation, or rare fertility (Dewhurst and Lucas, 1971). The reproductive performance of the 47,XXX group is surprisingly good though a small number of children who are cytogenetically abnormal have been described. The reproductive performance in the latter group is alarming, the outcome being an abortion or an abnormal child in a high percentage of reported cases. A thorough review of the subject seemed appropriate in an attempt to clarify the picture and to determine with greater certainty the risk of an abnormal child or an unsuccessful pregnancy in such patients.

47,XXX and 46,XX/47,XXX patients

Barr *et al.* (1969), in a comprehensive review of patients with the above karyotypes, reported on 28 women who had had 67 children, 2 abortions, and 2 terminations of pregnancy. Twenty-nine children had been examined cytogenetically and 24 were found to be normal. The 5 women who bore abnormal children were one with a 47,XXX karyotype, and 4 with a 46,XX/47,XXX karyotype (Table 1) (Rosenkranz, 1965a,b; Fujita and Yamamoto, 1967; Williams, 1969). It is interesting that there were 4 cyto-

genetically abnormal children among the 14 offspring from only 8 patients with a mosaic karyotype and only one cytogenetically abnormal child from the remaining patients whose karyotype was 47,XXX. Since the report of Barr *et al.*, Kadotani *et al.* (1970) have reported one 47,XXX patient who gave birth to a child with trisomy 21 Down's syndrome; 4 other abnormal children have, however, been reported who were born to mosaic 46,XX/47,XXX patients (Table 2) (Baikie *et al.*, 1972; Geisler *et al.*, 1972; Tsuang *et al.*, 1975; Zizka *et al.*, 1975).

These data indicate a greater liability to abnormal offspring in mosaic than non-mosaic patients but suggest that patients with either may have an increased risk of bearing an abnormal child. From the information at present available it is not possible to determine how great this risk might be. 47,XXX or mosaic 46,XX/47,XXX women show no characteristic clinical features and many who bear a normal child will undoubtedly escape recognition unless a deliberate search is made for them (Lucas *et al.*, 1971), while those who bear an abnormal child are by contrast more likely to be recognised and reported. Indeed a careful scrutiny of the cases referred to above in which abnormal children were born to mothers with a 47,XXX cell line shows that in every case the discovery of the abnormality in the child led to the recognition of the abnormal karyotype in the mother, thus exaggerating the apparent risk. All that can be concluded at present, therefore, is that a mosaic 46,XX/47,XXX mother may possess an increased risk of fetal anomaly; we do not know how great this risk is but it is probably greater than that run by a 47,XXX non-mosaic mother. We cannot conclude as was

Received for publication 31 August 1977

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Table 1 47,XXX and 47,XX/47,XXX patients (Barr et al., 1969)

Authors	Mother	Child
Rosenkranz (1965a,b)	1 47,XXX 2 46,XX/47,XXX 3 46,XX/47,XXX	Klinefelter's syndrome 46,XX/47,XXX Klinefelter's syndrome; Normal son Klinefelter's syndrome; Normal son; 3 normal daughters Klinefelter mosaic (46,XY/47,XXY)
Fujita and Yamamoto (1967)	4 46,XX/47,XXX	
Williams (1969)	5 46,XX/47,XXX	

Table 2 46,XX/47,XXX patients

Authors	Mother	Child
Baikie et al. (1972)	46,XX/47,XXX	Klinefelter's syndrome; 3 other children
Geisler et al. (1972)	46,XX/47,XXX	Klinefelter's syndrome; 2 normal boys
Tsuang et al. (1975)	46,XX/47,XXX	Klinefelter's syndrome; Normal boy and girl
Zizka et al. (1975)	46,XX/47,XXX	48,XXYY

recently done by Gerald (1976) that as many as one-sixth of the offspring of mothers with a 47,XXX cell line will be abnormal cytogenetically. Amniocentesis and chromosome analysis in early pregnancy appear to be indicated in those rare occasions when a known 47,XXX or mosaic patient becomes pregnant.

Patients with a 45,X cell line

A review of the literature reveals reports of pregnancies in 5 patients with a 45,X karyotype (Bahner et al., 1960; Nakashima and Robinson, 1971; Grace et al., 1973; Groll and Cooper, 1976; Philip and Sele, 1976), 7 who were 45,X/46,XX (Kava and Klinger, 1968; Bomers-Marres, 1966; Predescu et al., 1969; Bishun et al., 1969; Mackay et al., 1971; Siegelman, 1972; Lieber and Berger, 1973), 4 who were 45,X/46,XX/47,XXX (Briggs et al., 1963; de Toni et al., 1965; Armendaris et al., 1967; Nielsen and Thomsen, 1968; Giraud, 1970; Hsu et al., 1972; Kim et al., 1975). The outcome of the pregnancy in these patients is set out in Tables 3, 4, 5, and 6 from which it may be seen that 54 pregnancies have occurred resulting in 16 miscarriages, 1 termination, 12 abnormal children, 3 children who were stillborn without sufficient details to

Table 3 45X patients

Authors	Offspring
Bahner et al. (1960)	Male: chromatin negative
Nakashima and Robinson (1971)	Female: 46,XX
Grace et al. (1973)	Female: 46,XX
Groll and Cooper (1976)	Female: stillborn, cord
Philip and Sele (1976)	Female: normal Macerated hydrocephalic 26 weeks Male: 46,XY

Table 4 45,X/46,XX patients

Authors	Offspring
Kava and Klinger (1968)	Male: normal Miscarriage
Predescu et al. (1969)	4 miscarriages Abnormal child? Down's
Mackay et al. (1971)	Normal female growth retarded in utero
Bomers-Marres (1966)	Female: normal Male: normal
Bishun et al. (1969)	Male: gross malformations Male: spina bifida; Spina bifida and hydrocephalus
Lieber and Berger (1973)	Termination
Siegelman (1972)	3 miscarriages; Male 45,XY Female 45,X/46,XX

Table 5 45,X/47,XXX patients

Authors	Offspring
Lewis et al. (1963)	3 males: normal
Maclean et al. (1968)	(a) 1 child: no details (b) 1 child: no details
Reyes et al. (1976)	Female 46,XX

decide the reason, and 22 who were born alive and are now either well or have died for other reasons. Abnormalities encountered in the 12 abnormal children are set out in Table 7.

This is an appalling reproductive performance and gives rise to considerable concern. However, if the reports are divided into those in which the abnormal child or the poor reproductive performance led to the recognition of the maternal faults and those in which the mother's abnormality was discovered first and her fertility record then established, a different picture emerges (Table 8). It is clear that when the mother is identified first her reproductive performance is far better than the impression given by the review of the patients as a whole. Indeed, as with the group of 47,XXX women, the apparent risk of abnormality is considerably exaggerated by the method of reporting.

Table 6 45,X/45,XX/47,XXX patients

Authors	Offspring
de Toni et al. (1965)	Female: 45,X/46,XX Twins: 45,X 45,X/46,XX/47,XXX
Giraud (1970)	Macerated child 7/12; 45,X/46,XY with congenital heart disease 46,XX: congenital heart disease
Briggs et al. (1963)	Normal female
Nielsen and Thomsen (1968)	Male: died 3/12 age
Armendaris et al. (1967)	Down's syndrome, trisomy 21 Male: 46,XY
Kim et al. (1975)	Stillbirth: no details 2 miscarriages
Hsu et al. (1972)	(a) 2 miscarriages (b) 3 miscarriages Male: died leukaemia Male: Down's syndrome Male: normal

Table 7 *Nature of abnormality*

Spina bifida	2
Down's syndrome	2
? Down's syndrome	1
Gross malformations	1
Congenital heart defect	2*
45,X/46,XX	2
45,X	1
45,X/46,XX/47,XXX	1
Total	12

* I also 45,X/46,XY.

Table 8 *Outcome of pregnancy related to manner of discovery of abnormal maternal karyotype*

	<i>From abnormal child or repeated miscarriages</i>	<i>Secondary amenorrhoea or mental hospital survey, etc.</i>
Miscarriages	14	2*
Termination	0	1
Abnormal children	12	0
Other stillborn	2	1
Alive ?well or died other reasons	5	17
Total	33	21

*One a macerated hydrocephalic.

None the less in the present state of our knowledge pregnant patients with a 45,X cell line must constitute a high risk group in which amniocentesis to detect fetal abnormality might be undertaken. It must be pointed out, however, that this technique may not detect all the abnormalities reported in Table 7, though the majority would be recognised.

Discussion

This review suggests that the chances of a normal child in those patients with an abnormal sex chromosome complement who are capable of reproduction is greater than it appears to be at first sight. More data are clearly required, however, before any realistic assessment of the risk of abortion or of fetal anomaly can emerge.

One paper has not been included in the review and its omission requires comment. Arakaki and Waxman (1970) successfully cultured endometrium from 68 women who had a spontaneous abortion; 59 endometria were cytogenetically normal, 9 abnormal. They compared the cytogenetic findings in the abortus in the normal and abnormal endometrial groups and found the abnormal endometrial group to have a higher rate of cytogenetically abnormal abortus though there were abnormalities in each. They did not establish the karyotype of the mother by examining the peripheral blood or other tissue and we cannot say whether the chromosome complement obtained from the endometrium was characteristic of the patient's karyotype or not. The paper was not included here,

therefore, though further work in this field would clearly be interesting.

Brief mention will be made of the manner in which a woman with a 45,X cell line might retain her reproductive capacity. It is known that the primitive gonads of 45,X women contain germ cells (Singh and Carr, 1966); these are destroyed almost totally by the time of birth or soon afterwards, probably because of the failure of pre-granulosa cells to surround the germ cell and form primary follicles; germ cells not surrounded in this fashion, but left exposed to ovarian stroma, are quickly destroyed (Baker, 1963). This destruction is to some extent a normal process during intrauterine development and results in a reduction in the number of oocytes from almost 7 000 000 at the fifth month to around 2 000 000 at birth. In the 45,X/46,XX patient, especially one with a high proportion of 46,XX cells, survival until adult life of sufficient germ cells to permit fertility is clearly a possibility. Even in patients without a large preponderance of 46,XX cells a favourable distribution of these cells during early embryonic development might have the same effect. In a 45,X patient we may consider that very rarely germ cell survival could occur permitting fertility in exceptional circumstances. The alternative explanation is that the fertile 45,X patients reported are in reality unrecognised mosaics. This seems likely in several cases since only one tissue has been examined cytogenetically; moreover in the case reported by Groll and Cooper (1976) for example, the patient's height (5'11½") strongly suggests the possibility of a normal cell line since it is extremely uncommon for a 45,X patient to be so tall. In other patients, however, such as that reported by Philip and Sele (1976), mosaicism is far less likely since four tissues were cultured.

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