Phenotypic effects of mosaicism for a 47,XXX cell line in Turner syndrome

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Turner syndrome, gonadal dysgenesis with sex chromosome abnormalities, occurs in approximately 1/3000 live-born females. Of females diagnosed with the condition, half are monosomic for the X chromosome. Among the rest, a multiplicity of chromosomal aberrations has been described. The more frequent are the presence of an isochromosome of the long arm of the X (i(Xq)) and ring X and mosaicism for two or more normal or abnormal cell lines (for example, 45,X/46,XX; 45,X/46,X,i(Xq); 45,X/46,XY). A small proportion (3-4%)[1 2] of subjects with Turner syndrome are mosaic for a triple X (47,XXX) cell line. The triple X syndrome in the non-mosaic state is associated with a decrement in intelligence from that expected based on parental and sib accomplishment, normal stature, and normal fertility.[3–8]

Is the prognosis for females with Turner syndrome mosaic for a triple X cell line substantially different from that for females with 45,X? Does the presence of a third, normal 46,XX cell line in some of these females predictably affect phenotype? Is the risk for mental retardation or the likelihood of preserved fertility or normal stature greater in this category of people than in those with 45,X or 45,X/46,XX alone?

I have reviewed our experience with 17 patients with Turner syndrome mosaic for a triple X cell line (11 with 45,X/47,XXX and six with 45,X/46,XX/47,XXX), and that of an additional 80 published case reports (18 with 45,X/47,XXX and 62 with 45,X/46,XX/47,XXX).[1 9–64] These data are compared with those for the 227 girls and women with 45,X Turner syndrome and the 69 with 45,X/46,XX in our clinic database.

METHODS

Information gathered from medical records, direct examination, and self-report has been collected in a computer database as part of an ongoing, long term study of the natural history of Turner syndrome begun in 1977.[2 65 66] Subjects were ascertained through self-referral, advertisement, review of hospital records, and referral for diagnosis or management from paediatricians, obstetricians, perinatologists, endocrinologists, internists, and family practitioners.

All subjects have had karyotype confirmation of their clinical diagnosis. A minority has had two or more tissues analysed. In most of these, the two cell lines were amniotic fluid cells and confirmatory postnatal peripheral lymphocyte karyotyping.

I performed a search in PubMed using: Turner syndrome, sex chromosome, 47,XXX, triple X, and triple X females as search terms. I used the bibliographies from the citations generated to find case reports published before the inception of the electronic databases, as well as for any publications overlooked by the search strategy used. Reports in English, Italian, French, and Spanish were reviewed. I discarded any case reports without karyotype confirmation. Complete information was not available for all subjects. I analysed the results using the appropriate denominator for each feature.

RESULTS

Table 1 lists the ages and reasons for the diagnosis of Turner syndrome, comparing the subjects from our clinic population and those in the published reports to our clinic population with 45,X and 45,X/46,XX chromosome constitutions.

The women in the X/XX/XXX group described in the published reports were older than the subjects in the other groups. This is most likely because a significant proportion, one quarter, of these women were diagnosed in adult life, during evaluation of recurrent pregnancy loss. Among our clinic populations, prenatal diagnosis was a more common avenue of diagnosis than for the published cases. This reflects the nature of our clinic, which is a referral centre for such cases. We are less likely to be involved in the evaluation of recurrent pregnancy loss or fetal wastage and thus less likely to ascertain adult patients with Turner syndrome through this route.

Oedema is the primary reason for the diagnosis of Turner syndrome in infancy. Its absence as a clinical feature in the

Table 1 Comparison of subjects mosaic for a 47,XXX cell line with 45,X and 45,X/46,X Turner syndrome: data from clinic population and medical publications

	Clinic		Published reports		Clinic	
Karyotype	X/XXX	X/XX/XXX	X/XXX	X/XX/XXX	45,X	X/XX
No	11	6	18	62	227	69
Age range (y)	5–54	1.5–60	0–55	1–67	0–80	0–74
Mean age (y)	20.7	21.4	15.4	29.4	18.9	17.4
Reason for diagnosis (No)	11	6	11	56	224	65
Oedema	0	0	0	0	89 (40%)	4 (6%)
Short statute	8 (73%)	1 (17%)	4 (33%)	8 (14%)	66 (29%)	16 (24%)
Amenorrhoea	2 (18%)	1 (17%)	0	16 (29%)	44 (20%)	12 (18%)
Prenatal	1 (9%)	2 (33%)	0	2 (4%)	11 (5%)	24 (37%)
Other	0	2* (33%)	7† (66%)	30‡ (53%)	14§ (8%)	9¶ (14%)

*Recurrent pregnancy loss (1), behavioural problems (1).
†Mental retardation (3), secondary amenorrhoea (3), hypoplastic left heart (1).
‡Secondary amenorrhoea or fetal wastage (15), hypoplastic left heart (1), abnormal offspring (6), cancer (5), ambiguous genitalia (1), newborn screening (1), Hirschsprung disease (1).
§Mental retardation (1), failure to thrive ± developmental delay (3), unusual facies (4), congenital heart disease (3), multiple malformations (1), GI bleeding (1), premature ageing (1).
¶Mental retardation (1), failure to thrive (1), unusual facies (4), hirsutism (1), pregnancy loss (2).

Table 3 Height and ovarian function in subjects mosaic for a 47,XXX cell line compared with 45,X and 45,X/46,XX Turner syndrome

	Clinic		Published reports		Clinic	
Karyotype	X/XXX	X/XX/XXX	X/XXX	X/XX/XXX	45,X*	X/XX*
Height <3%	5/11 (45%)	2/6 (33%)	7/8 (87%)	27/46 (59%)	70/95 (74%)	17/28 (61%)
Spontaneous menses	4/7 (57%)	2/3 (67%)	11/13 (84%)	30/44 (68%)	13/123 (11%)	11/32 (34%)
Fertility	1/7 (14%)	1/3 (33%)	9/13 (69%)†	20/44 (45%)†	1/123 (0.8%)	6/32 (19%)
	G1P1	G2 SAB2	G10P9 SAB2	G76P34 SAB43 TAB1	G2P2	G1P1
						G2P2
						G2P2
						G2P1 TAB1
						G8P1 SAB7
						G4P1 SAB3

G, gravida; P, para; SAB, spontaneous abortion; TAB, therapeutic abortion.
*Includes only those women who have achieved final adult height.
†Some the result of medically induced ovulation.

females with a triple XXX cell line constitutes a major difference between these subjects and those with 45,X or 45,X/46,XX. Although oedema in the newborn period was not recognised, in utero oedema most likely had been present, based on the presence of nuchal webbing in a similar proportion of the subjects with mosaicism for a 47,XXX cell line and those with monosomy X alone.

Approximately a third of patients with Turner syndrome are diagnosed during evaluation for short stature. Among the published X/XX/XXX cases, short stature accounted for only 14% of diagnoses, despite the fact that almost two-thirds of the women were below the 3rd centile in height.

Tables 2 and 3 provide data regarding those features of Turner syndrome hypothesised most likely to be different in subjects with mosaicism for XXX: intellectual function, height, and fertility.

I did not try to establish the presence or absence of specific learning disabilities known to be associated with Turner syndrome, such as difficulties with spatial reasoning, processing, etc,[67–72] as there was inadequate information available for most of the published cases. Only frank mental retardation, as defined by a tested IQ below 70, inability to function independently in adult life, or as stated as such in the case reports, was considered. None of the females in our clinic population with a 47,XXX cell line are mentally retarded, compared with a prevalence of 8-9% in our "control" groups. However, the number of patients with mosaicism for 47,XXX is small. The proportion of published cases with mental retardation and 45,X/47,XXX (42.8%) is much higher than for the other groups. However, one was ascertained as part of a screening evaluation of residents in an institution for the mentally retarded,[45] one had a brother and a half sister with similar delays, both of whom had been extensively evaluated without a diagnosis,[44] and a third woman was karyotyped at the age of 25 during an evaluation for seizures, mental retardation, and structural brain malformations.[61] One subject was described as having normal mentality but was slightly slow[47] and two others were evaluated for pregnancy loss; normal intellectual function was implied but not clearly stated.[41 53] I did not include these three women in the analysis.

Short stature was seen in the majority of published cases. Some of our 45,X/47,XXX patients have received treatment with androgens or human growth hormone. Two of the three treated were above the 3rd centile in height. Three of eight who had not been treated were above the 3rd centile. None of our 45,X/46,XX/47,XXX patients had been treated with these agents; four of six were above the 3rd centile.

Spontaneous menarche is much more likely in subjects with mosaicism for an XXX cell line, with or without the presence of a normal 46,XX component (70%), than in women with 45,X without mosaicism (11%). Women with mosaicism for a 47,XXX cell line were also more likely to have spontaneous menarche than those with 45,X/46,XX (70% compared with 34%). A significant number of these women did not maintain normal menstrual cycles and secondary amenorrhoea or premature menopause were common occurrences.

Pregnancy is clearly more probable for women with the presence of either a 46,XX or a 47,XXX cell line or both, compared with those with monosomy X alone. Successful pregnancy outcome was least likely in the X/XX/XXX group, with less than 50% of pregnancies resulting in livebirths. Again, this may reflect how the subjects were ascertained, rather than a true a priori risk.

There was inadequate information provided for the published case reports to assess reliably the risk for other features known to be associated with Turner syndrome, including cardiac and renal malformations, thyroid disease, otological complications, etc. There were no obvious differences in the presence of these features between those with a 47,XXX cell line and those with monosomy X or 45,X/46,XX in our clinic population.

Establishing phenotype-karyotype correlations in Turner syndrome has been problematical. Many have been proposed

Table 2 Intellectual function in subjects mosaic for a 47,XXX cell line compared with 45,X and 45,X/46,XX Turner syndrome: comparison of clinic population and data from the medical publications

	Clinic		Published reports		Clinic	
Karyotype	X/XXX	X/XX/XXX	X/XXX	X/XX/XXX	45,X	X/XX
No	11	6	7	31	218	59
Normal intelligence	10 (91%)	5 (83%)	3 (42.8%)	23 (74%)	187 (86%)	52 (88%)
Mental retardation	0	0	3 (42.8%)*†	4 (13%)	19 (9%)	5 (8%)
Psychiatric diagnosis	1 (9%)	1 (17%)	2 (28.5%)*	4 (13%)	12 (5%)	2 (3%)

*One with psychiatric disease and mental retardation.
†One with half sister and brother with similar unexplained developmental delays.

and few confirmed. Overt chromosomal mosaicism for monosomy X and a second or third cell line occurs in almost 50% of patients with Turner syndrome and it is difficult to assess the relative contribution of each cell line to each organ system. All 45,X/46,XX subjects do not share the same proportion of normal:abnormal cells in all tissues and the proportion in one tissue does not necessarily predict that in others. Further, there may be selection in tissue culture for one cell line over another, so that the results in the laboratory do not represent the true in vivo situation. Moreover, occult mosaicism may mask differences conferred by the presence of cell lines with other X chromosome or Y chromosome abnormalities in ostensibly monosomic 45,X subjects. Most patients with Turner syndrome have been diagnosed based on karyotyping of only one tissue, usually peripheral blood. Thus, mosaicism for a chromosomally normal or differently aneuploid cell line may have remained undetected in the majority of cases.

Despite these limitations, the demand for prognostic counselling in Turner syndrome has increased, especially for the more uncommon karyotypes and in mosaicism, and even more so when the sex chromosome aneuploidy is detected prenatally.

DISCUSSION

In general, females with Turner syndrome, gonadal dysgenesis with sex chromosome aneuploidy, have oedema at birth or show physical evidence of in utero lymphoedema, are short, with adult height below the 3rd centile, and have streak gonads. These three features are the most consistently seen hallmarks of the condition. One-third of females with Turner syndrome are diagnosed at birth because of the presence of lymphoedema; two-thirds of those with a 45,X karyotype are so diagnosed.[2] Many of the infants without postnatal oedema show stigmata of prenatal oedema such as webbing of the neck and anteverted ears. Short stature is an almost invariable feature of the condition. Almost no predictions regarding final adult height can be made based on karyotype. Girls with mosaicism for a 46,XX cell line show a statistically insignificant taller mean adult height.[73] Those with a deletion of the long arm of the X (Xq−) are much more likely to have normal stature and to be diagnosed for primary amenorrhoea. Gonadal dysgenesis is a feature in almost all girls with Turner syndrome. Spontaneous menses occurs in approximately 10% of the entire population of girls with Turner syndrome. Almost 25% of girls who are mosaic for a normal 46,XX cell line will have spontaneous menarche.[2] A much smaller proportion in each group will maintain menses and even fewer will be fertile. Other physical features common to Turner syndrome, including congenital heart disease, kidney malformations, multiple naevi, etc, show no consistent relationship to karyotype.[2]

Triple XXX or 47,XXX occurs in 1/1000 of liveborn females.[74] Most of the information regarding these patients comes from several long term follow up studies of subjects ascertained through newborn screening programmes or from case reports.[3–8 75–80] Although there are relatively few studies, in general, it is believed that subjects with 47,XXX are more likely to have verbal processing deficits, a decrement in IQ predicted by sib achievement, and global delays. Height is usually normal and menses and fertility have not been recognised to be adversely affected. Caution must be used in making blanket predictions, as the total number of patients studied has been small, and most girls with 47,XXX are likely to go undetected or unreported.

In the subset of subjects with mosaicism for a monosomy X cell line who have been diagnosed with Turner syndrome, approximately 3-4% are mosaic for a 47,XXX cell line.[2] In our clinical experience, the recognition of this chromosome constitution prenatally can be particularly distressing for prospective parents and physicians. The most common reason for detection of 45,X/46,XX/47,XXX or 45,X/47,XXX prenatally is screening for Down syndrome. Prospective parents are usually concerned about the possibility of mental retardation and an increased likelihood of significant intellectual handicap associated with a 47,XXX cell line may be a pivotal factor in decisions regarding termination or maintenance of pregnancy. Thus, it seemed particularly worthwhile to try to establish phenotype-karyotype correlations based on postnatal survey for this subset of people.

On review of medical publications and our own clinic population, there are some major differences between those females with a 47,XXX cell line and those with 45,X only or 45,X/46,XX. The former are unlikely to present with perinatal oedema and more likely to be diagnosed in childhood for short stature, or later for primary or secondary amenorrhoea or during evaluation for pregnancy loss.

Despite the association of mental retardation with 47,XXX alone, there appears to be no significant difference in the risk for retardation in 45,X/47,XXX and 45,X/46,XX/47,XXX compared with monosomy X. None of our 16 patients is retarded. Although a much higher proportion (7/39, 18%) of published cases with 45,X/47,XXX or 45,X/46,XX/47,XXX had mental retardation, one had tubercular meningitis at the age of 11 months,[30] a second had neurofibromatosis,[12] another had Duchenne muscular dystrophy,[38] and a fourth woman had structural brain abnormalities including lissencephaly, cerebral atrophy, and pachygyria of the frontal lobe and cerebellar atrophy.[61] None of these is associated with 47,XXX specifically. A fifth subject was ascertained through screening of inmates in a mental institution.[45] Bias of ascertainment must always be considered a contaminant of published data.

Short stature is not invariable in this subset of women. There are no data to suggest that treatment with growth promoting agents in this subset is more or less effective than for other karyotypes associated with Turner syndrome. I believe it is reasonable and fair to counsel parents that approximately 60% of girls with 45,X/46,XX/47,XXX or 45,X/47,XXX will have short stature.

Gonadal dysgenesis and infertility are the primary features of Turner syndrome that are a major concern for parents and, in my opinion and experience, play a significant role in the weighing of consideration for termination or continuance of a pregnancy when the prenatal diagnosis of an X chromosome abnormality is made. It is clear that the presence of an XXX cell line carries with it a greater likelihood of residual ovarian function. However, it must be understood that while the development of secondary sexual characteristics may be normal, fertility may be impaired in the majority of these women.

Prenatal diagnosis of mosaicism for a sex chromosome abnormality always carries with it uncertainty of prognosis based on the limitations of the testing itself. The detection of mosaicism in chorionic villus cells or amniotic fluid may reflect placental rather than true embryonic/fetal mosaicism and the proportion of chromosomally abnormal cells in vitro may not represent the true proportion in the embryo/fetus, nor the specific tissue distribution of the mosaicism. It has been shown for both 45,X/46,XY mosaicism[81 82] and 45,X/46,XX mosaicism[83] that there is a much better prognosis and greater likelihood of normality when the diagnosis is made prenatally rather than postnatally. At this time, we do not have a sufficient number of patients with mosaicism for 47,XXX that have been ascertained prenatally to come to any useful conclusions. Our three prenatally diagnosed patients, while growing within normal parameters and intellectually unimpaired, are only 1½, 5, and 7 years old.

In summary, I recommend that prenatal and postnatal predictive counselling for subjects with 45,X/46,XX/47,XXX and 45,X/47,XXX Turner syndrome be essentially the same as for Turner syndrome in general with regard to likelihood of mental retardation, short stature, and structural abnormalities. For any particular infant, it is impossible to predict specific

outcome. It is fair to suggest that residual ovarian function is possible and to caution that premature ovarian failure is common. Those women who do become pregnant, with or without medication, are at higher risk for chromosomally abnormal offspring (7/44 livebirths, two with trisomy 21, the rest with sex chromosome aneuploidy[13 20 27 32 42]) and should be counselled appropriately.

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REFERENCES

1 **Kleczkowska A**, Dmoch E, Kubien E, Fryns JP, Van den Berghe H. Cytogenetic findings in a consecutive series of 478 patients with Turner syndrome. The Leuven experience 1965-1989. *Genet Couns* 1990;**1**:227-33.
2 **Sybert VP**. Turner syndrome. In: Cassidy SB, Allanson JE, eds. *Management of genetic syndromes*. 1st ed. New York: Wiley & Sons, 2001:459-84.
3 **Bender BG**, Harmon RJ, Linden MG, Bucher-Bartelson B, Robinson A. Psychosocial competence of unselected young adults with sex chromosome abnormalities. *Am J Med Genet* 1999;**88**:200-6.
4 **Harmon RJ**, Bender BG, Linden MG, Robinson A. Transition from adolescence to early adulthood: adaptation and psychiatric status of women with 47,XXX. *J Am Acad Child Adolesc Psychiatry* 1998;**37**:286-91.
5 **Linden MG**, Bender BG, Harmon RJ, Mrazek DA, Robinson A. 47,XXX: what is the prognosis? *Pediatrics* 1988;**82**:619-30.
6 **Pennington BF**, Bender B, Puck M, Salbenblatt J, Robinson A. Learning disabilities in children with sex chromosome anomalies. *Child Dev* 1982;**53**:1182-92.
7 **Rovet J**, Netley C. The triple X chromosome syndrome in childhood: recent empirical findings. *Child Dev* 1983;**54**:831-45.
8 **Rovet J**, Netley C, Bailey J, Keenan M, Stewart D. Intelligence and achievement in children with extra X aneuploidy: a longitudinal perspective. *Am J Med Genet* 1995;**60**:356-63.
9 **Bidot-Lopez P**, Matisoff D, Talner NS, Hsia YE. Hypoplastic left heart in a patient with 45,X/46,XX/47,XXX mosaicism. *Am J Med Genet* 1978;**2**:341-3.
10 **Antich J**, Ribas-Mundo M, Prats J, Frances JM. XO-XX-XXX mosaicism with Turner stigmata. *Lancet* 1967;**i**:1228-9.
11 **Armendares S**, Buentello L, Sanchez J, Ortiz M. XO/XX/XXX mosaicism without Turner stigmata. *Lancet* 1967;**ii**:840.
12 **Ayraud N**, Duplay J, Grellier P, Bezon A, Martinon J. 45,X-46,XX-47,XXX karyotype and tumor of the nervous system. 2 cases. *Nouv Presse Med* 1972;**1**:2902.
13 **Ayuso MC**, Bello MJ, Benitez J, Sanchez-Cascos A, Mendoza G. Two fertile Turner women in a family. *Clin Genet* 1984;**26**:591-6.
14 **Bijlsma JB**, James J, Drukker W. Triple mosaicism of the sex chromosomes in a phenotypical female. *Acta Endocrinol* 1964;**45**:336-40.
15 **Bortolini ER**, da Silva DM, Chequer RS, Vianna-Morgante AM, Zatz M. Duchenne muscular dystrophy in a girl with a 45,X/46,XX/47,XXX chromosome constitution. *Am J Med Genet* 1986;**25**:239-43.
16 **Briggs DK**, Stimson CW, Vinograd J. Leukocyte anomaly, mental retardation, and dwarfism in a family with abnormal chromosomes. *J Pediatr* 1963;**63**:21-6.
17 **Canlorbe P**, Toublanc JE, Borniche P, de Grouchy J. 45 X-46 XX-47 XXX mosaic with Turner phenotype and normal ovaries. Study of a case and review of the literature. *Ann Pediatr* 1972;**19**:861-6.
18 **Carr DH**, Morishima A, Barr ML, Grumbach MM, Luers T, Boschann HW. An XO/XX/XXX mosaicism in relationship to gonadal dysgenesis in females. *J Clin Endocrinol Metab* 1962;**22**:671-7.
19 **Couselo JM**, Ansede A, Noya M. Letter: 45, X-46, XX-47, XXX mosaicism. *Lancet* 1974;**1**:873.
20 **DeToni EJ**, Massimo L, Vianello MG, Podesta F. La casistica di un anno di attivita del Centro di Studi Cromosomici deela Clinica Pediatrica di Genova nel campo delle malformazioni sessuali. *Minerva Pediatr* 1965;**17**:578-84.
21 **Dzenis IG**, Antipina NN. An uncommon phenotypical variant in the Shereshevsky-Turner syndrome. *Hum Genet* 1979;**52**:275-9.
22 **Edwards JA**, Vance VK, Cohen MM, Schussler GC. XO/XX/XXX mosaicism with possible congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1970;**30**:666-71.
23 **Ferguson-Smith MA**, Alexander DS, Bowen P, Goodman RM, Kaufmann BN, Jones HJ, Heller RH. Clinical and cytogenetical studies in female gonadal dysgenesis and their bearing on the cause of Turner's syndrome. *Cytogenetics* 1964;**3**:355-83.
24 **Frasier SD**, Wilson MG. Growth pattern in 45,X-47, XXX mosaicism. *J Pediatr* 1972;**81**:187-8.
25 **Gagne R**. 45 X-47 XXX mosaicism and atypic Turner's phenotype: initial note. *Laval Med* 1969;**40**:280-1.
26 **Gemzell C**, Solish GI. Induction of ovulation and pregnancy in a woman with sex chromosomal mosaicism 45,X/46,XX/47,XXX. *Am J Obstet Gynecol* 1979;**134**:599-600.
27 **Giraud F**, Hartung M, Brusquet Y, Mattei JF, Sebahoun A, Serment H, Stahl A, Bernard R. Fertility of 45,X-46,XX and 45,X-46,XX-47,XXX women. *Ann Genet* 1970;**13**:255-8.
28 **Glaser D**, Nienhaus H, Kohler R, Walther G, Pawlowitzki IH. A sex cord stromal tumour in a woman with XO/XX/XXX-mosaicism. *Arch Gynecol Obstet* 1988;**243**:115-18.
29 **Grumbach MM**, Morishima A. An XXX/XX/XO sex chromosome constitution in gonadal dysgenesis and other examples of sex chromosome mosaicism in man. *Am J Dis Child* 1961;**102**:691-3.
30 **Hayward MD**, Cameron AH. Triple mosaicism of the sex chromosomes in Turner's syndrome and Hirschsprung's disease. *Lancet* 1961;**ii**:623-7.
31 **Hsu LY**, Hirschhorn K. Unusual Turner mosaicism (45,X-47,XXX;45,X-46,XXqi;45,X-46,XXr): detection through deceleration from normal linear growth or secondary amenorrhea. *J Pediatr* 1971;**79**:276-81.
32 **Hsu LYF**, Palo Garcia F, Grossman D, Kutinsky E, Hirschhorn K. Fetal wastage and maternal mosaicism. *Obstet Gynecol* 1972;**40**:98-103.
33 **Itoh K**, Igarashi T, Wakita H, Minamihisamatsu M. Sideroblastic anemia associated with multiple myeloma in Turner's syndrome. *Intern Med* 1992;**31**:483-5.
34 **Jacobs P**, Dalton P, James R, Mosse K, Power M, Robinson D, Skuse D. Turner syndrome: a cytogenetic and molecular study. *Ann Hum Genet* 1997;**61**:471-83.
35 **Jacobs PA**. Abnormalities involving the X chromosome in women. *Lancet* 1960;**1**:1213-16.
36 **Jacobs PA**, Harnden DG, Buckton KE, Court Brown WM, King MJ, McBride JA, MacGregor TN, Maclean N. Cytogenetic studies in primary amenorrhea. *Lancet* 1961;**i**:1183-8.
37 **Jaffe SB**, Loucopoulos A, Jewelewicz R. Cytogenetics of mullerian agenesis. A case report. *J Reprod Med* 1992;**37**:242-6.
38 **Jalbert P**, Mouriquand C, Beaudoing A, Jaillard M. Myopathie progressive de type duchenne et mosaique XO/XX/XXX: considerations sur la genese de la fibre musculaire striee. *Ann Genet* 1966;**9**:104-9.
39 **Jones HWJ**, Ferguson-Smith MA, Heller RH, Preston E, Stewart B. The pathology and cytogenetics of gonadal agenesis. *Am J Obstet Gynecol* 1963;**87**:578-600.
40 **Kheir S**, Ceballos R, Finley S, Vinson P. Gonadal dysgenesis in a neonate with 45,X/47,XXX karyotype. *South Med J* 1980;**73**:1402-4.
41 **Kivinen S**, Herva R. Twin pregnancy in woman with 45,X/47,XXX karyotype. *Obstet Gynecol* 1980;**56**:401-2.
42 **Lebel RR**, Elejalde BR, de Elejalde MM, Avila T. 45,X/46,XX/47,XXX phenotype. *Prenat Diagn* 1993;**13**:1165-6.
43 **Lews FJ**, Poulden RH, Eastham RD. Acute leukaemia in an XO/XXX mosaic. *Lancet* 1963;**2**:306.
44 **Lloyd IC**, Haigh PM, Clayton-Smith J, Clayton P, Price DA, Ridgway AE, Donnai D. Anterior segment dysgenesis in mosaic Turner syndrome. *Br J Ophthalmol* 1997;**81**:639-43.
45 **Maclean N**, Brown WM, Jacobs PA, Mantle DJ, Strong JA. A survey of sex chromatin abnormalities in mental hospitals. *J Med Genet* 1968;**5**:165-72.
46 **Massa G**, Vanderschueren-Lodeweyckx M, Malvaux P. Linear growth in patients with Turner syndrome: influence of spontaneous puberty and parental height. *Eur J Pediatr* 1990;**149**:246-50.
47 **Mornex R**, Orgiazzi J, Laurent C, Valencogne C, Mornex JF. Turner phenotype with menses, leucocytes 45,X and ovarian fibroblasts 45,X-47,XXX (author's translation). *Ann Endocrinol (Paris)* 1975;**36**:357-8.
48 **Muller P**, Clavert J, Rihm G, Gillet JY. XO-XX-XXX mosaic in two monozygotic girl twins: clinical and biological similarities and differences. *Ann Endocrinol (Paris)* 1970;**31**:1143-52.
49 **Nawroth F**, Foth D, Stute P, Schmidt T, Romer T. Possibilities of sterility therapy in a patient with a premature menopause due to an X-chromosomal anomaly - a case report. *Maturitas* 2000;**37**:129-32.
50 **Nielsen J**, Thomsen N. A psychiatric-cytogenetic study of a female patient with 45-46-47 chromosomes and sex chromosomes XO-XX-XXX. *Acta Psychiatr Scand* 1968;**44**:141-55.
51 **Park E**, Bailey JD, Cowell CA. Growth and maturation of patients with Turner's syndrome. *Pediatr Res* 1983;**17**:1-7.
52 **Reyes FI**, Koh KS, Faiman C. Fertility in women with gonadal dysgenesis. *Am J Obstet Gynecol* 1976;**126**:668-70.
53 **Rosen GF**, Kaplan B, Lobo RA. Menstrual function and hirsutism in patients with gonadal dysgenesis. *Obstet Gynecol* 1988;**71**:677-80.
54 **Rothenbuchner G**, Schober B, Egert H. Abnormalities of the chromosomes: a XO/XX/XXX mosaicism in a case of gonadal dysgenesia. *Human Chromosome Newsletter* 1964;**14**:20.
55 **Sarto GE**. Cytogenetics of fifty patients with primary amenorrhea. *Am J Obstet Gynecol* 1974;**119**:14-23.
56 **Schmidt CL**, Epstein JA, Sarosi P, Wolman SR, Weiss G. Isolated follicle-stimulating hormone deficiency in a woman with X chromosomal mosaicism. *Am J Obstet Gynecol* 1982;**144**:601-7.
57 **Schwartz S**, Raffel LJ. Prenatal detection of 45,X/46,XX/47,XXX mosaicism through amniocentesis: mosaicism confirmed in cord blood, amnion, and chorion. *Prenat Diagn* 1992;**12**:1043-6.
58 **Shokeir MH**. Pregnancy in five women with 45,X/46,XX and 45,X/47,XXX gonadal dysgenesis. *Birth Defects* 1978;**14**:171-84.
59 **Snider ME**, Solomon IL. Ultimate height in chromosomal gonadal dysgenesis without androgen therapy. *Am J Dis Child* 1974;**127**:673-4.