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CLINICAL REPORT

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Ovarian reserve evaluation in a woman with 45,X/47,XXX mosaicism: A case report and a review of literature

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Abstract

Background: Turner syndrome (TS) is a common chromosomal disorder affecting approximately 1:2,500 live female births. Mosaic 47,XXX karyotype is found in 3%–4% of TS patients. TS phenotype in rare 45,X/47,XXX mosaicism patients is milder than in classic TS, however their ovarian function, especially in the mature age, has not been described in detail.

Methods: A case report and literature review.

Results: A 30-year-old woman with menstrual irregularity and primary infertility presented with short stature and multiple nevi on the face without other common TS clinical features. She had spontaneous puberty and menarche but diminished ovarian reserve at the age of 30. Fluorescence in situ hybridization (FISH) indicated 45,X/47,XXX mosaicism, which was once misdiagnosed as 45,X monosomy. Literature review revealed the prevalence of short stature in only 64.3% of 45,X/47,XXX mosaicism cases, that is, much less frequently than in pure 45,X monosomy. The risk of premature ovarian insufficiency in 45,X/47,XXX mosaicism patients is higher, and ovarian failure is usually observed at around 30 years of age.

Conclusion: FISH should be recommended to evaluate low proportion mosaicism in similar cases. Due to the risk of ovarian failure, fertility preservation for patients with 45,X/47,XXX mosaicism at a younger age must be considered.

KEYWORDS
45,X/47,XXX mosaicism, fertility, karyotype, primary ovarian insufficiency, Turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is a common chromosomal disorder affecting approximately 1:2,500 live female births. Affected females possess 45,X karyotype with 45%–50% of TS patients having 45,X monosomy. Other karyotypes, which may be mosaic with 45,X, most commonly include 46,X,i(Xq); 46,XX/47,XXX; 46,X,del(Xp); or 46,XY (Zhong & Layman, 2012). Primary or premature ovarian insufficiency (POI) occurs more frequently in TS patients than in the general population. The classic phenotypes of TS most commonly include short stature and primary amenorrhea, which are present in over 90% of individuals with 45,X monosomy (Lim, Kil, & Koo, 2017).

The triple-X syndrome occurs in 1:1,200 female births, and the phenotypes include taller stature, earlier menopause age, lower intellectual ability, and higher probability of psychiatric problems. Renal and genital tract malformations have

been reported occasionally (Brambila-Tapia, Rivera, Garcia-Castillo, Dominguez-Quezada, & Davalos-Rodriguez, 2009).

Three to four percent of the patients with TS have mosaicism for 47,XXX, including 45,X/47,XXX; 45,X/46,XX/47,XXX, etc. The 45,X/47,XXX karyotype is extremely rare in TS (~1.5%) (Lim et al., 2017). Previous reports have summarized the puberty and fertility characteristics of young 45,X/47,XXX mosaicism patients and found that their phenotype is less severe than that of common TS (Lim et al., 2017; Mavridi, Ntali, Theodora, Stamatelopoulos, & Michala, 2018). Such individuals may develop normally through puberty without estrogen therapy. However, the ovarian function and prevalence of POI in 45,X/47,XXX mosaicism in an older age group have so far remained uncertain. Here, we describe a case of a 30-year-old woman with 45,X/47,XXX TS mosaicism who presented with ongoing diminished ovarian reserve (DOR), which had been previously misdiagnosed as 45,X monosomy. We also review all available published studies that described 45,X/47,XXX mosaicism cases or case series, summarizing the incidence of short stature, pubertal features, changes in ovarian function, and other TS-related presentations in this rare syndrome.

1.1 | Ethical compliance

Informed consent was obtained from the patient according to the protocol approved by the Institutional Review Board of Peking Union Medical College Hospital.

2 | CASE PRESENTATION

A 30-year-old woman was referred to our clinic because of irregular menstrual periods. The patient had spontaneous thelarche and menarche at 13 years with regular menses. At the age of 20, the menses became irregular, and cycle duration increased to about 4–6 months. She had been to a clinic and was prescribed progesterone for 10 days per month. She had regular withdrawal bleedings with progesterone. When she stopped progesterone, her menstrual periods returned spontaneously, became regular for several months, and then turned irregular again. The irregular menses apparently indicated poor ovarian function. However, the ovarian function and sex hormone levels were not evaluated at that time. She underwent hysteroscopy for amenorrhea at the age of 25, and the pathology showed multiple endometrial polyps and foci of endometrial complex hyperplasia. She got married at the age of 25 years but failed to get pregnant for two years despite having sex without contraception. Then, a diagnosis of primary infertility was considered, and she divorced at the age of 28.

The woman had short stature. Physical examination showed height 1.45 m, weight 50.0 kg, and multiple nevi on the face. The Tanner stages were breast V, pubic hair I, and axillary hair I. She had no cardiac murmur, and her thyroid function was normal. The patient stopped the use of medications about half a year before the visit to our clinic, and her regular natural menses recovered. Sex hormone levels at our clinic (cycle day 3) were as follows: follicular stimulation hormone (FSH), 10.5 mIU/mL (3.85–8.78 mIU/mL); luteinizing hormone, 1.65 mIU/mL (2.12–10.89 mIU/mL), estradiol, 74.0 pg/mL (27–122 pg/mL). The anti-Müllerian hormone (AMH) level was 0.43 ng/ml (0.67–7.55 ng/ml). AMH had been also measured 18 months ago, and its level was 0.96 ng/ml. Elevated FSH and low AMH levels suggested DOR. A pelvic ultrasound examination revealed uterus of $5.2 \times 4.8 \times 4.6$ cm, right ovary of 1.3×0.8 cm, and left ovary of 1.8×1.1 cm. Ovarian antral follicle count (AFC) was measured with 3 in the right ovary and 2 in the left.

The karyotype in G-banded lymphocyte metaphase cultures revealed 45,X (50 cells). Thus, the diagnosis of 45,X monosomy was considered. However, typical 45,X monosomy presents with primary amenorrhea or POI at an early age, whereas this patient had not reached menopause at 30 years of age. Considering the inconsistence between the symptoms and initial diagnosis, we suspected the presence of occult mosaicism and reexamined the karyotype. The result showed TS mosaicism with 45,X[22]/47,XXX[8]. Fluorescence in situ hybridization (FISH) with the dual probe for the X-centromere (DXZ1) and the SRY locus in the nuclei confirmed the mosaicism. The proportion was (DXZ1 × 1)[95]/(DXZ1 × 3)[5]; and the SRY gene probe did not hybridize in any nucleus. Therefore, the modified diagnosis of 45,X[95]/ 47,XXX[5] mosaicism was established. In further evaluations, renal ultrasound and cardiac echo examinations were normal. Physical examination did not show any typical TS signs other than short stature and multiple nevi.

The family history was unremarkable. The heights of the family members, mother, father, and sister were 156 cm, 167 cm, and 165 cm, respectively. Her sister was married and had five pregnancies that ended with artificial abortion. None of the family members had fertility problem or early menopause. The woman has regular menses and no fertility requirement now, so we suggested that she attends our clinic for regular follow-up for 3–6 months. The ovarian function apparently continued to decline. We will monitor the ovarian reserve of this patient closely.

3 | DISCUSSION

We revealed a rare case of 45,X/47,XXX mosaicism in a woman who had been initially misdiagnosed with 45,X monosomy. Due to the discrepancy between the clinical presentation and karyotype, the latter was retested and 45,X/47,XXX mosaicism was confirmed using FISH. The 45,X/47,XXX

mosaicism is extremely rare in TS. Recently, the frequency of patients with 45,X/47,XXX among all individuals with TS was estimated to be 1.5% (Lim et al., 2017). The exact incidence of 45,X/47,XXX may be slightly higher than 1.5% because the standard cytogenetic analysis may fail to detect mosaic aneuploidy at a very low level or exclude the possibility of tissue-specific mosaicism in patients.

The common clinical features of TS include short stature, delayed puberty (both seen in over 95% of affected individuals), congenital cardiac and renal anomalies, susceptibility to autoimmune diseases, acquired metabolic syndrome, edema of hands or feet, webbed neck, low posterior hairline, nail dysplasia, rotated ears, small mandible, nail hypoplasia, multiple pigmented nevi, broad shield chest, cubitus valgus, short fourth metacarpal, and high-arched palate (Zhong & Layman, 2012). However, TS phenotype varies, depending on the specific karyotype. Spontaneous puberty appears in 5% to 10% of girls with TS monosomy, and spontaneous pregnancies have been reported in 2%–10% (Bryman et al., 2011). 45,X/47,XXX mosaicism has a milder phenotype than 45,X monosomy (Gravholt et al., 2017). Apparently, the clinical consequences of haploinsufficiency of the genes in the 45,X cells are ameliorated by the 47,XXX cell line. Previously, more frequent incidence of spontaneous puberty (83%), menarche (57%–67%), and fertility problems (14%) had been reported (Blair, Tolmie, Hollman, & Donaldson, 2001; Lim et al., 2017; Sybert, 2002), whereas occurrence of cardiovascular and renal anomalies (<5%), as well as skeletal anomalies (<4%) are less frequent compared to that in 45,X patients without mosaicism (Tauchmanova et al., 2001). In line with data from previous reports, our patient also showed mild TS phenotype with short stature, spontaneous puberty, spontaneous menarche, and no structural anomalies. In addition, our patient presented with decreased ovarian function at 20 years of age because she had irregular menses. At the age of 30, her ovarian function became extremely poor (AMH: 0.43 ng/ml; AFC < 4). However, she has not reached menopause, and we will continue to follow her up.

Typical TS patients may be diagnosed at birth with symptoms such as edema, whereas correct diagnosis of subjects with 47,XXX mosaicism is usually made at a later stage. Therefore, clinicians should recommend karyotype analysis in any woman who has the following conditions: (a) short stature or delayed puberty at adolescent; (b) poor ovarian reserve or even developed POI before fourth decade. Our patient had indication for karyotype analysis. However, she was characteristically misdiagnosed. The initial karyotyping result was 45,X, but very few patients with 45,X monosomy still maintain ovarian function at the age of 30. If there is a concern about the result of initial chromosome analysis, such as the one described in the present report, an extended FISH analysis should be performed to check for low-level mosaicism. Actual karyotype of this patient was 45,X[95]/47,XXX[5], which means that the proportion of 47,XXX cells was very small. One advantage of utilizing FISH to identify low-level mosaicism is that it is of great importance to determine whether mosaicism containing Y fragment is present. Current guidelines recommend gonadectomy in TS women with detectable Y chromosomal material due to the elevated risk of gonadal neoplasia development (approximately 12%) (Gravholt et al., 2017).

To further evaluate the characteristics associated with 45,X/47,XXX mosaicism, we searched the Pubmed database and retrieved all published reports related to 45,X/47,XXX mosaicism. Those not written in English or in which the relevant information was largely missing were excluded. Finally, 26 articles that described 45 patients were selected (Acharya, Jonsrud, van der Hagen, & Maltau, 2003; Akbas et al., 2009; Alves & Silva, 2012; Blair et al., 2001; Bouchlariotou et al., 2011; Eblen & Nakajima, 2003; Everest et al., 2015; Hadnott, Gould, Gharib, & Bondy, 2011; Hishimura-Yonemaru et al., 2017; Improda et al., 2012; Kivinen & Herva, 1980; Kristesashvili, Chipashvili, Jorbenadze, & Greydanus, 2012; Lim et al., 2017; Liu et al., 2013; Lunding et al., 2015; Maciejewska-Jeske, Czyzyk, & Meczekalski, 2015; Martin, Smith, Hughes, & Morrison, 2018; Mavridi et al., 2018; Palmer & Reichmann, 1976; Sahinturk et al., 2015; Saikia, Sarma, & Yadav, 2017; Sybert, 2002; Tauchmanova et al., 2001; Terao, Hashimoto, Nukina, Mannen, & Shinohara, 1996; Venkateshwari et al., 2012; Wang, Yang, Li, & Mu, 2015). Characteristics related to puberty, menstruation, fertility, ovarian function, and karyotypes of the previously reported patients and those of the present case are summarized in Table 1. In the literature, short stature is statistically defined as height ≥2 standard deviations below the mean for age- and gender-specific norms, which corresponds to the shortest 2.3% of individuals (Pedicelli, Peschiaroli, Violi, & Cianfarani, 2009). In previous reports, it has been suggested that the frequency of short stature and the median height standard deviation score in 45,X/47,XXX do not differ significantly from those in other females with TS (Blair et al., 2001; Lim et al., 2017; Sybert, 2002). However, the literature review showed that the prevalence of short stature was 64.3%, that is, much lower than that in pure 45,X monosomy cases (over 95%). We speculated that this may relate to the presence of 47,XXX cell lines, because triple-X syndrome often presents with taller stature. In addition, the occurrences of cardiovascular and renal anomalies were both 8.7% (2/23). Women with 45,X/47,XXX mosaicism are more likely to retain residual ovarian function. The occurrences of spontaneous puberty and menarche were 88.9% and 77.1% in this review, much higher than those observed in 45,X monosomy cases. Women with 45,X monosomy rarely become pregnant. Tarani et al. (1998) reviewed the

TABLE 1 Previously reported cases and series with 45,X/47,XXX mosaicism

First Author/year	Age at presentation	Prepubertal state	Spontaneous puberty	Spontaneous menarche	Age of spontaneous menarche	Times of spontaneous pregnancies	Age at pregnancy	Outcome of pregnancies	Age when menses became irregular	Age at menopause
Everest/2015	10	Yes								
Lim/2017	10	Yes								
Hishimura-Yonemaru/2017	12		Yes	NA	NA				NA	NA
Eblen/2003	19		No	PA	PA	1	19	Healthy		
Venkateshwari/2012	24		No	PA	PA					
Saikia/2017	15		No	PA	PA					
Improda/2012	7.8		Yes	Yes	12.8[a]	NA			NA	NA
Kristesashvili/2012	15		Yes	Yes	13	NA			NA	NA
Martin/2018	15		Yes	Yes	15	NA			NA	NA
Akbas/2009	17		Yes	Yes	17	NA			NA	NA
Kivinen/1980	20		Yes	Yes	13	1	19	Twin pregnancy, premature rupture of membranes at the 35th week and premature delivery, healthy children	17	>20
Mavridi/2018	21		Yes	Yes	NA	1	21	Healthy	NA	NA
Maciejewska-Jeske/2015	21		Yes	Yes	13	NA			17	23
Terao/1996	25		Yes	Yes	NA	1	20	Healthy	NA	NA
Sahinturk/2015	26		Yes	Yes	13	6[b]	NA	1,3–6: Spontaneous abortions in the first trimester/2: Healthy	NA	>26
Alves/2012	29		Yes	Yes	14	2	25/28	Healthy/healthy	29	>29
Wang/2015	30		Yes	Yes	13	0			23	29

(Continues)

TABLE 1 (Continued)

First Author/year	Age at presentation	Prepubertal state	Spontaneous puberty	Spontaneous menarche	Age of spontaneous menarche	Times of spontaneous pregnancies	Age at pregnancy	Outcome of pregnancies	Age when menses became irregular	Age at menopause
Bouchlariotou/2011	33		Yes	Yes	12	3	NA/33/34	Healthy/fetal death due to severe intrauterine growth restriction/healthy	NA	>34
Tauchmanovà/2001	33		Yes	Yes	11.5	0			28	31
Acharya/2003	40		Yes	Yes	12	1	40	Termination of pregnancy for the fetus had Down's syndrome, hydrops, single umbilical artery, bilateral clubfoot	NA	>40
Liu/2013	39		Yes	Yes	NA	2	NA	Embryonic diapause/embryonic diapause	NA	NA
Lunding/2015			Yes	Yes	13	NA			NA	<32[c]
Hadnott/2011			Yes	Yes	13	2	21/23	Healthy/healthy	NA	31
			NA	PA	PA	0				
Palmer/1976	NA		NA	PA	PA	NA				
	NA		NA	Yes	NA	NA			NA	NA
Sybert/2002		1	NA	4/7	NA	1/7			NA	NA
Blair/2001	6.1– 20.4 (mean 14.3)	1	5/5	4/4	NA	NA			NA	NA
The present case	30		Yes	Yes	13	0			20	>30
Total			88.9% (24/27)	77.1% (27/35)	13.2 ± 1.3 (Range: 11.5–17)	9 in 13 patients (69.2%; 9/13)	25.7 ± 6.8 (Range: 19–40)	10: Healthy children 1: Fetal death 1: Down's syndrome and artificial termination 2: Embryonic diapause	22.3 ± 4.8 (Range: 17–29)	28.5 ± 3.3 (Range:23–31)

(Continues)

TABLE 1 (Continued)

First Author/year	Karyotype feature	Proportion of 45, X cells (%)	Short stature	Presentations related to TS	Other problems may not related to TS
Everest/2015	45,X[3]/47,XXX[27]	10.0	Yes	Vesicoureteric reflux and kidney dysfunction	
Lim/2017	45,X[32]/47,XXX[8]	80.0	Yes	Slightly webbed, short neck, mild shield chest with wide distance between nipples	
Hishimura-Yonemaru/2017	45,X[7]/47,XXX[93]	7.0	Yes	Limb length discrepancy, scoliosis	
Eblen/2003	45,X[49]/47,XXX[1] (blood); 45,X[14]/ 47,XXX[21](ovarian tissue)	98.0 (blood); 48.5 (ovarian tissue)	Yes	Streak ovaries	
Venkateshwari/2012	45,X[65]/47,XXX[35]	65.0	No	Drooping eyelids and dry eyes, cubitus valgus	
Saikia/2017	NA	NA	Yes	NA	
Improda/2012	45,X[55]/47,XXX[45]	55.0	No	Idiopathic central precocious puberty, scoliosis, subclinical hypothyroidism, moderate global developmental delay, emotional and social immaturity and reading difficulties	
Kristesashvili/2012	NA	NA	Yes	A short and wide neck, a low line of hair, a disproportion of body parts with the shoulder girdle wider than pelvic girdle, cubitus valgus, short fourth metacarpals, oligomenorrhoea since menarche (normal sex hormones)	
Martin/2018	45,X[5]/47,XXX[25]	16.7	No	Mid face hypoplasia, hypothyroidism, a leg length discrepancy	
Akbas/2009	45,X[2]/47,XXX[1]	66.7	Yes	Multiple nevi, short hands, edema on the hands and feet	
Kivinen/1980	45,X[79]/47,XXX[21]	79.0	No	No other clear evidence of TS except short stature	
Mavridi/2018	45,X[52]/47,XXX[48]	52.0	Yes	Duplication of the left renal collecting system	
Maciejewska-Jeske/2015	45,X[131]/47,XXX[9]	93.5	Yes	Neonatal whole body edema (especially of the nape and legs), club feet, cubitus valgus, slightly webbed neck with lowered hair line, renal crossed dystopia, slow weight gain, slow height growth, hemihypotrophy (with the right side of the body being smaller), osteopenia at age 20	Fibroadenoma of left breast
Terao/1996	45,X[86]/47,XXX[14]	86.0	Yes	Repeated seizures, cerebellar cortical atrophy, mental retardation, gait disturbance	
Sahinturk/2015	45,X[35]/47,XXX[65]	35.0	No	Insufficiency of mitral and tricuspid valves, type 1 diabetes mellitus	Endometrium cancer, lymphoma, a family history of recurrent pregnancy loss

(Continues)

TABLE 1 (Continued)

First Author/year	Karyotype feature	Proportion of 45, X cells (%)	Short stature	Presentations related to TS	Other problems may not related to TS
Alves/2012	45,X[28]/47,XXX[2]	93.3	Yes	Cubitus valgus	
Wang/2015	45,X[68]/47,XXX[32]	68.0	Yes	Webbed neck, short limbs, an abnormal upper-to-lower segment ratio, a low posterior hair line with acanthosis nigricans behind the neck	Insulinoma
Bouchlariotou/2011	45,X[88]/47,XXX[12]	88.0	Yes	No other clear evidence of TS except short stature	
Tauchmanovà/2001	45,X[90]/47,XXX[10]	90.0	Yes	Hypertricosis, abnormal upper-to-lower body segment ratio, webbed neck, low posterior hair line, cubitus valgus, short and asymmetrical 4th metacarpi, scoliosis, chronic lymphocytic thyroiditis, learning difficulties	
Acharya/2003	45,X[4]/47,XXX[4]	50.0	No	No clear evidence of TS	
Liu/2013	45,X[36]/47,XXX[14]	72.0	NA	NA	
Lunding/2015	NA	NA	NA	NA	
Hadnott/2011	45,X[49]/47,XXX[1]	98.0	Yes	Hypothyroidism, recurrent otitis, scoliosis	
	45,X[49]/47,XXX[1]	98.0	NA	NA	
Palmer/1976	45,X[37]/47,XXX[10]	78.7	Yes	High-arched palate, short neck, low posterior hairline, nipple abnormalities, webbed neck, deafness, cardiovascular abnormalities	
	45,X[9]/47,XXX[26]	25.7	Yes	Webbed neck	
Sybert/2002	NA	NA	5/11	One had psychiatric diagnosis, other presentations not described	
Blair/2001	NA	NA	4/7	Two had middle ear disease (one had otitis media with effusion, and one had documented hearing loss), other features not described	
The present case	45,X[95]/47,XXX[5]	95.0	Yes	Multiple nevi	
Total			64.3% (27/42)	Cardiovascular anomalies: 8.7% (2/23); renal anomalies: 8.7% (2/23)	

Abbreviations: NA, not available; PA, primary amenorrhea.

[a]This patient had accepted GnRH analog therapy for idiopathic central precocious puberty, and discontinued the therapy at age 12, resulting in recovery of pubertal development which was completed by menarche.

[b]The pregnancy outcomes of this case were not included in the summarizing because this patient had a family history of recurrent pregnancy loss.

[c]The authors did not presented exactly data of menopausal age of the 45,X/47,XXX patient in the case series. They showed median (range) of age at loss of ovarian function in eight miscellaneous TS patients, the 45,X/47,XXX patient included, were 18.28 (12.7–32).

outcome of spontaneous pregnancies in 12 women with 45,X/47,XXX karyotype, and the outcome was normal in 16 (unknown in two) out of 20 pregnancies (80%). Our review showed that 13 cases had fertility requirement, and nine out of 13 cases (69.2%) became spontaneously pregnant for 14 times in total. Ten of 14 pregnancies (71.4%) resulted in healthy liveborn children. However, the publication bias should be considered as researchers may tend to report cases with spontaneously occurring pregnancies because they are special and rare. So the real proportion of fertile individuals may be lower than 69.2%.

Another important problem of TS patients is the high risk of POI, which should be taken into account for young women when planning their family. Ovarian functions decrease with age due to a diminishing number of follicles and menstrual cycle cessation. However, very little is known about the timing and onset of POI in 45,X/47,XXX mosaicism patients with initially normal ovarian function, which makes it difficult to predict their fertility prognosis when consulting. To our knowledge, we conducted the first review analyzing the menopausal age of 45,X/47,XXX mosaicism cases. However, menopausal age was only mentioned for four published cases, with a mean of 28.5 ± 3.3 years. The mean age of the start of irregular menses was 22.3 ± 4.8 years, which may also indicate the beginning of ovarian function decline. From these data, we speculated that patients with 45,X/47,XXX mosaicism may usually present with decreased ovarian reserve around the age of 20 and with menopause at around the age of 30. During the time when they have menstruation, they may be fertile. Therefore, such patients should complete fertility requirement as early as possible. For these patients, a marker should be found to predict the ovarian reserve and menopausal age. Serum AMH levels and AFC are useful markers of the follicle pool and ovarian reserve. Both low AMH and oligofollicular AFC might help to predict age at menopause (Depmann et al., 2016). An age-specific AMH level at the 5th percentile represents women experiencing a relatively early menopause. AFC ≤4 indicates an increased risk of menopause within 7 years (35%) when compared to the risk in women with AFC >4 (13%) (Coelho Neto et al., 2018; Depmann et al., 2016). AMH levels have been evaluated in TS patients and shown to correlate strongly with karyotype (Visser et al., 2013). Lunding et al. (2015) have reported that AMH is a predictor of the imminent POI in women with TS. They found that the best cutoff value for AMH as a marker of POI in TS was 3 pmol/L. Both the sensitivity and specificity were 95%. We suggest that in young mosaic TS women with persistent ovarian function, the ovarian reserve should be monitored by measuring AMH level and AFC. Furthermore, fertility preservation should be considered before follicles begin to disappear. Cryopreservation of both oocytes and ovarian tissue may be feasible.

Foci of endometrial complex hyperplasia were observed in our patient during irregular menstrual period. Endometrial hyperplasia is common in menopausal transition and is associated with elevated estradiol levels without progesterone. Improda et al. (2012) reported a case of precocious puberty in a TS patient with 45,X/47,XXX mosaic karyotype. The occurrence of the two diseases was associated with estrogen and reflected the presence of ovarian function. Therefore, some manifestations related to elevated estrogen level may also occur in patients with TS, especially in those with mosaic karyotypes.

4 | CONCLUSIONS

From the experience of this case of 45,X/47,XXX mosaicism, initially misdiagnosed as 45,X monosomy, we recommend that doctors pay attention to the following points. First, it is important that clinical physicians have a thorough understanding of genetic diseases in order to determine the diagnosis and prescribe the treatment properly. If the putative diagnosis and patient symptoms are inconsistent, further evaluations are needed to avoid misdiagnosing. Second, careful counseling and proper suggestions are needed for patients with 45,X/47,XXX mosaicism. Two thirds of these women may present with short stature. Patients with this karyotype are more likely to have spontaneous puberty, menarche, and pregnancy. However, the risk of POI is also higher, and ovarian failure is usually present at around 30 years of age. Preservation of fertility in patients with TS through cryopreservation of ovarian tissue or other strategy before follicles begin to disappear should be considered.

We believe that the described case and our literature review extend the current knowledge about the clinical symptoms of patients with this genotype. Because 45,X/47,XXX karyotype is rare, collaborative studies involving large TS registries with consistent data enrollment are needed to provide a more evidence-based analysis of the genotype–phenotype associations.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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REFERENCES

Acharya, G., Jonsrud, C., van der Hagen, C., & Maltau, J. M. (2003). Prenatal diagnosis of fetal hydrops associated with Down's syndrome in a 40-year-old woman with a mosaic Turner's karyotype (45, X/47, XXX). *Acta Obstetricia et Gynecologica Scandinavica*, *82*(8), 773–774. https://doi.org/10.1034/j.1600-0412.2003.00071.x

Akbas, E., Mutluhan, H., Savasoglu, K., Soylemez, F., Ozturk, I., & Yazici, G. (2009). Turner syndrome and 45, X/47, XXX mosaicism. *Genetic Counseling*, *20*(2), 141–146.

Alves, C., & Silva, S. F. (2012). Spontaneous procreation in Turner syndrome: Report of two pregnancies in the same patient. *Systems Biology in Reproductive Medicine*, *58*(2), 113–115. https://doi.org/10.3109/19396368.2011.638037

Blair, J., Tolmie, J., Hollman, A. S., & Donaldson, M. D. (2001). Phenotype, ovarian function, and growth in patients with 45, X/47, XXX Turner mosaicism: Implications for prenatal counseling and estrogen therapy at puberty. *The Journal of Pediatrics*, *139*(5), 724–728. https://doi.org/10.1067/mpd.2001.118571

Bouchlariotou, S., Tsikouras, P., Dimitraki, M., Athanasiadis, A., Papoulidis, I., Maroulis, G., … Liberis, V. (2011). Turner's syndrome and pregnancy: Has the 45, X/47, XXX mosaicism a different prognosis? Own clinical experience and literature review. *The Journal of Maternal-fetal & Neonatal Medicine*, *24*(5), 668–672. https://doi.org/10.3109/14767058.2010.520769

Brambila-Tapia, A. J., Rivera, H., Garcia-Castillo, H., Dominguez-Quezada, M. G., & Davalos-Rodriguez, I. P. (2009). 47, XXX/45, X/46, XX mosaicism in a patient with Turner phenotype and spontaneous puberal development. *Fertility and Sterility*, *92*(5), 1747.e1745–1747. https://doi.org/10.1016/j.fertnstert.2009.07.1008

Bryman, I., Sylven, L., Berntorp, K., Innala, E., Bergstrom, I., Hanson, C., … Landin-Wilhelmsen, K. (2011). Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertility and Sterility*, *95*(8), 2507–2510. https://doi.org/10.1016/j.fertnstert.2010.12.039

Coelho Neto, M. A., Ludwin, A., Borrell, A., Benacerraf, B., Dewailly, D., da Silva Costa, F., … Martins, W. P. (2018). Counting ovarian antral follicles by ultrasound: A practical guide. *Ultrasound in Obstetrics & Gynecology*, *51*(1), 10–20. https://doi.org/10.1002/uog.18945

Depmann, M., Broer, S. L., van der Schouw, Y. T., Tehrani, F. R., Eijkemans, M. J., Mol, B. W., & Broekmans, F. J. (2016). Can we predict age at natural menopause using ovarian reserve tests or mother's age at menopause? A systematic literature review. *Menopause*, *23*(2), 224–232. https://doi.org/10.1097/gme.0000000000000509

Eblen, A. C., & Nakajima, S. T. (2003). Spontaneous pregnancy in a woman with 45, X/47, XXX mosaicism in both serum and germ cell lines. A case report. *The Journal of Reproductive Medicine*, *48*(2), 121–123 https://doi.org/0024-7758/03/4802-0121.

Everest, E., Tsilianidis, L. A., Haider, A., Rogers, D. G., Raissouni, N., & Schweiger, B. (2015). 45, X/47, XXX Mosaicism and Short Stature. *Case Reports in Pediatrics*, *2015*, 263253. https://doi.org/10.1155/2015/263253

Gravholt, C. H., Andersen, N. H., Conway, G. S., Dekkers, O. M., Geffner, M. E., Klein, K. O., … Backeljauw, P. F. (2017). Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European Journal of Endocrinology*, *177*(3), G1–g70. https://doi.org/10.1530/eje-17-0430

Hadnott, T. N., Gould, H. N., Gharib, A. M., & Bondy, C. A. (2011). Outcomes of spontaneous and assisted pregnancies in Turner syndrome: The U.S. National Institutes of Health experience. *Fertility and Sterility*, *95*(7), 2251–2256. https://doi.org/10.1016/j.fertnstert.2011.03.085

Hishimura-Yonemaru, N., Okuhara, K., Takahashi, N., Tonoki, H., Iizuka, S., & Tajima, T. (2017). A case of 45, X/47, XXX mosaic Turner syndrome with limb length discrepancy. *Clinical Pediatric Endocrinology*, *26*(4), 259–263. https://doi.org/10.1297/cpe.26.259

Improda, N., Rezzuto, M., Alfano, S., Parenti, G., Vajro, P., Pignata, C., & Salerno, M. (2012). Precocious puberty in Turner Syndrome: Report of a case and review of the literature. *Italian Journal of Pediatrics*, *38*, 54. https://doi.org/10.1186/1824-7288-38-54

Kivinen, S., & Herva, R. (1980). Twin pregnancy in woman with 45, X/47, XXX karyotype. *Obstetrics and Gynecology*, *56*(3), 401–402. 0029-7844/80/090401-02

Kristesashvili, J., Chipashvili, M., Jorbenadze, T., & Greydanus, D. E. (2012). Rare cases of disorders of sex development (DSD) in adolescents with female phenotype. *International Journal of Adolescent Medicine and Health*, *24*(2), 181–190. https://doi.org/10.1515/ijamh.2012.027

Lim, H. H., Kil, H. R., & Koo, S. H. (2017). Incidence, puberty, and fertility in 45, X/47, XXX mosaicism: Report of a patient and a literature review. *American Journal of Medical Genetics Part A*, *173*(7), 1961–1964. https://doi.org/10.1002/ajmg.a.38276

Liu, X. Y., Zhang, H. G., Chen, S., Wang, R. X., Zhang, Z. H., & Liu, R. Z. (2013). 45, X mosaicism in northeast China: A clinical report and review of the literature. *Journal of Assisted Reproduction and Genetics*, *30*(3), 407–412. https://doi.org/10.1007/s10815-012-9927-3

Lunding, S. A., Aksglaede, L., Anderson, R. A., Main, K. M., Juul, A., Hagen, C. P., & Pedersen, A. T. (2015). AMH as predictor of premature ovarian insufficiency: A longitudinal study of 120 Turner syndrome patients. *The Journal of Clinical Endocrinology and Metabolism*, *100*(7), E1030–1038. https://doi.org/10.1210/jc.2015-1621

Maciejewska-Jeske, M., Czyzyk, A., & Meczekalski, B. (2015). The Turner syndrome in patient with 45X/47XXX mosaic karyotype—Case report. *Gynecological Endocrinology*, *31*(7), 526–528. https://doi.org/10.3109/09513590.2015.1018164

Martin, R. J., Smith, G., Hughes, J., & Morrison, P. J. (2018). Incidence, puberty, and fertility in 45, X/47, XXX mosaicism: Report of a patient and a literature review. *American Journal of Medical Genetics Part A*, *176*(4), 1029. https://doi.org/10.1002/ajmg.a.38624

Mavridi, A., Ntali, G., Theodora, M., Stamatelopoulos, K., & Michala, L. (2018). A spontaneous pregnancy in a patient with Turner syndrome with 45, X/47, XXX Mosaicism: A case report and review of the literature. *Journal of Pediatric and Adolescent Gynecology*, *31*(6), 651–654. https://doi.org/10.1016/j.jpag.2018.07.005

Palmer, C. G., & Reichmann, A. (1976). Chromosomal and clinical findings in 110 females with Turner syndrome. *Human Genetics*, *35*(1), 35–49. https://doi.org/10.1007/bf00295617

Pedicelli, S., Peschiaroli, E., Violi, E., & Cianfarani, S. (2009). Controversies in the definition and treatment of idiopathic short stature (ISS). *Journal of Clinical Research in Pediatric Endocrinology*, *1*(3), 105–115. https://doi.org/10.4008/jcrpe.v1i3.53

Sahinturk, S., Ozemri Sag, S., Ture, M., Gorukmez, O., Topak, A., Yakut, T., & Gulten, T. (2015). A fertile patient with 45X/47XXX mosaicism. *Genetic Counseling*, *26*(1), 29–34.

Saikia, U. K., Sarma, D., & Yadav, Y. (2017). Delayed presentation of Turner syndrome: Challenge to optimal management. *Journal of Human Reproductive Sciences*, *10*(4), 297–301. https://doi.org/10.4103/jhrs.JHRS_114_17

Sybert, V. P. (2002). Phenotypic effects of mosaicism for a 47, XXX cell line in Turner syndrome. *Journal of Medical Genetics*, *39*(3), 217–220. https://doi.org/10.1136/jmg.39.3.217

Tarani, L., Lampariello, S., Raguso, G., Colloridi, F., Pucarelli, I., Pasquino, A. M., & Bruni, L. A. (1998). Pregnancy in patients with Turner's syndrome: Six new cases and review of literature. *Gynecological Endocrinology*, *12*(2), 83–87. https://doi.org/10.3109/09513599809024955

Tauchmanova, L., Rossi, R., Pulcrano, M., Tarantino, L., Baldi, C., & Lombardi, G. (2001). Turner's syndrome mosaicism 45X/47XXX: An interesting natural history. *Journal of Endocrinological Investigation*, *24*(10), 811–815. https://doi.org/10.1007/bf03343932

Terao, Y., Hashimoto, K., Nukina, N., Mannen, T., & Shinohara, T. (1996). Cortical dysgenesis in a patient with Turner mosaicism. *Developmental Medicine and Child Neurology*, *38*(5), 455–460.

Venkateshwari, A., Srimanjari, K., Srilekha, A., Begum, A., Sujatha, M., Sunitha, T., … Jyothy, A. (2012). Mosaic triple X syndrome in a female with primary amenorrhea. *Indian Journal of Human Genetics*, *18*(2), 246–249. https://doi.org/10.4103/0971-6866.100790

Visser, J. A., Hokken-Koelega, A. C., Zandwijken, G. R., Limacher, A., Ranke, M. B., & Fluck, C. E. (2013). Anti-Mullerian hormone levels in girls and adolescents with Turner syndrome are related to karyotype, pubertal development and growth hormone treatment. *Human Reproduction*, *28*(7), 1899–1907. https://doi.org/10.1093/humrep/det089

Wang, S., Yang, L., Li, J., & Mu, Y. (2015). Concurrent insulinoma with mosaic Turner syndrome: A case report. *Experimental and Therapeutic Medicine*, *9*(3), 801–804. https://doi.org/10.3892/etm.2015.2167

Zhong, Q., & Layman, L. C. (2012). Genetic considerations in the patient with Turner syndrome–45, X with or without mosaicism. *Fertility and Sterility*, *98*(4), 775–779. https://doi.org/10.1016/j.fertnstert.2012.08.021

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