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, Theostra, 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 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 × 4.8 × 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 meneses 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; Bouchlriotou 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, (45,208),(988,987)
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             |
| Ebelen/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<sup>a</sup>    | NA                          | NA                               | NA             | NA                     | NA               | NA             |
| Kristesashvili/2012| 15               | Yes               | Yes                | 13                  | NA                          | NA                               | NA             | NA                     | NA               | NA             |
| Martin/2018       | 15                  | Yes               | Yes                | 15                  | NA                          | NA                               | NA             | NA                     | NA               | NA             |
| Akbas/2009        | 17                  | Yes               | Yes                | 17                  | NA                          | NA                               | NA             | 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               | NA             |
| Maciejewska-Jeske/2015 | 21         | Yes               | Yes                | 13                  | NA                          | 17                               | 23             | NA                     | NA               |                |
| Teno/1996         | 25                  | Yes               | Yes                | NA                  | 1                           | 20                               | Healthy        | NA                     | NA               | NA             |
| Sahinturk/2015    | 26                  | Yes               | Yes                | 13                  | 6<sup>b</sup>              | 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                           | 25/28                            | Healthy        | 23                      | 29               |                |

(Continues)
| 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                 | Yes                 | 12                        | 3                             | NA/33/34        | Healthy/fetal death due to severe intrauterine growth restriction/healthy | NA               | >34             |
| Tauchmanová/2001  | 33                  | Yes               | Yes                 | Yes                 | 11.5                      | 0                             | NA             | Termination of pregnancy for the fetus had Down's syndrome, hydrops, single umbilical artery, bilateral clubfoot | 28               | 31              |
| Acharya/2003      | 40                  | Yes               | Yes                 | Yes                 | 12                        | 1                             | 40             | Embryonic diapause/embryonic diapause | NA               | >40             |
| Liu/2013          | 39                  | Yes               | Yes                 | NA                  | 2                         | NA                           | Embryonic diapause                           | NA               | NA          |
| Lunding/2015      | Yes                 | Yes               | Yes                 | Yes                 | 13                        | NA                           | NA             | Healthy/healthy                               | <32c             | NA             |
| Hadnott/2011      | Yes                 | Yes               | Yes                 | Yes                 | 13                        | 2                             | 21/23          | Healthy/healthy                               | 31               |                 |
| Palmer/1976       | NA                  | NA                | PA                  | PA                  | NA                        | NA                           | NA             | NA                                  | NA               | NA             |
| Sybert/2002       | 1                   | NA                | 4/7                 | NA                  | 1/7                       | NA                           | NA             | NA                                  | NA               | NA             |
| Blair/2001        | 6.1–20.4 (mean 14.3)| 1                 | 5/5                 | 4/4                 | NA                        | NA                           | NA             | NA                                  | NA               | NA             |
| The present case  | 30                  | Yes               | Yes                 | Yes                 | 13                        | 0                             | 20             | Healthy children 1: Fetal death 1: Down’s syndrome and artificial termination 2: Embryonic diapause | >30              |                 |

**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, oligomenorrhea 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 |
| Teno/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                                               |                                                     |
| Tauchmanova/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.

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.

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

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.

ACKNOWLEDGEMENTS

The authors are deeply grateful to the patient for agreeing to publish the case. This work was supported by the National Key Research and Development Program (2018YFC1002105).

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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**How to cite this article:** Tang R, Lin L, Guo Z, Hou H, Yu Q. Ovarian reserve evaluation in a woman with 45,X/47,XXX mosaicism: A case report and a review of literature. *Mol Genet Genomic Med.* 2019;7:e732. https://doi.org/10.1002/mgg3.732