Oocyte cryopreservation in mosaic Turner syndrome with polycystic ovaries

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Objective: To report a case of a patient with Turner syndrome (TS) mosaicism and polycystic ovarian syndrome (PCOS), who underwent successful ovarian stimulation, oocyte retrieval, and cryopreservation.
Design: Case report.
Subject(s): A female patient with mosaic TS (45,X [24%]/46,XX [76%]) and a paternally inherited balanced reciprocal translocation t(2:6) diagnosed with PCOS.
Intervention(s): Controlled ovarian stimulation, oocyte retrieval, and cryopreservation.
Main outcome measure(s): Successful oocyte retrieval and cryopreservation.
Result(s): We report an interesting case of a patient with TS mosaicism 45,X [24%]/46,XX [76%] and a paternally inherited t(2:6) balanced reciprocal translocation, who was diagnosed with PCOS on the basis of oligomenorrhea and ultrasound polycystic ovary morphology (antral follicle count of 17 and >20, left and right ovaries, respectively), underwent 2 cycles of ovarian stimulation, oocyte retrieval, and cryopreservation, resulting in 19 cryopreserved oocytes.
Conclusion(s): Our case highlights the importance of early counseling regarding fertility options in patients with mosaic TS and the need for careful monitoring of ovarian reserve during this process, which could be done by measuring the anti-müllerian hormone or antral follicle count. It also underscores the possibility of women with mosaic TS being affected by PCOS. (Fertil Steril Rep® 2023;4: 380–3. ©2023 by American Society for Reproductive Medicine.)
Key Words: Cryopreservation, fertility preservation, oocyte retrieval, polycystic ovarian syndrome, Turner syndrome

Turner syndrome (TS) is a chromosomal abnormality affecting women, whereby one of the X chromosomes is either partially or entirely missing in at least one cell line. TS affects 25–50 per 100,000 women with a decreasing incidence of 45,X karyotype and increasing incidence of other karyotypes including mosaic karyotypes (e.g., 45,X/46,XX, 45,X/46,X,r(X), 45,X/46,Xi(Xq)). Mosaicism in TS originates from mitotic events during postzygotic development and refers to the presence of different karyotypes within one individual, with the most common one being 45,X/46,XX, where some cell lines have only 1 X chromosome and others have 2 X chromosomes. Patients with TS can present with short stature, premature ovarian insufficiency (POI) with consequent infertility, congenital cardiac disease, lymphoedema, endocrine, renal, thyroid, neurodevelopmental, and gastrointestinal problems. However, the mosaic distribution in mosaic TS contributes to the variable and often subtle phenotypic features in affected individuals, making diagnosis harder and frequently delayed. Even though the precise genotype–phenotype correlation is not fully understood, it seems that patients with mosaic TS have better reproductive function, normal levels of gonadotropins or sex hormones, and follicles compared with those with 45,X TS (1, 2).

During gestation, the gonads initially appear to develop normally in TS, until week 18 of gestation, when accelerated oocyte loss occurs. The severity of ovarian dysgenesis is greater in the 45,X karyotype than in mosaic karyotypes. The presence of a higher proportion of 46,XX cells might also contribute to better ovarian function and fertility potential compared with individuals with X monosomy (45,X) in all cells. Spontaneous menarche occurs in a minority of patients with TS, mostly those with mosaic karyotype. However, those patients with TS with initially functioning ovaries often undergo POI, with 90% demonstrating gonadal failure when presenting at 31 years old (1). Unsurprisingly, infertility is common in TS with natural pregnancies being reported in a small number of patients with TS, at higher rates in cases

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of mosaicism (1). Depending on the remaining ovarian function, natural pregnancies and pregnancies after in vitro fertilization (IVF) with or without oocyte donation have been described in patients with TS. Oocyte retrieval and cryopreservation allows those with remaining ovarian reserve to preserve their own eggs, with the first case of a live birth after oocyte cryopreservation (OC) in patient with TS reported in 2022 (3).

Controlled ovarian stimulation precedes oocyte retrieval and comprises 3 steps: exogenous gonadotrophins administration to stimulate multi-follicular development; gonadotropin-releasing hormone (GnRH) agonist or antagonist treatment to suppress pituitary function and prevent premature ovulation; human chorionic gonadotropin (hCG) or GnRH agonist administration which mimics the luteinizing hormone surge to trigger final oocyte maturation. Mature oocytes are retrieved using ultrasound-guided transvaginal aspiration 34–36 hours after the final step (4).

Polycystic ovarian syndrome is a common endocrine condition affecting women of reproductive age, and its occurrence in patients with TS has been infrequently documented (5–7). A diagnosis of polycystic ovarian syndrome (PCOS) is made using the Rotterdam criteria (2003) which were recently endorsed by the European Society of Human Reproduction and Embryology guidelines (2018), whereby a diagnosis is made when an individual has 2 of 3 of the following criteria: clinical and/or biochemical evidence of hyperandrogenism, oligomenorrhea, and polycystic ovarian morphology on ultrasound in patients >8 years post menarche (≥12 follicles measuring 2–9 mm and/or an ovarian volume ≥10 mL for either ovary).

CASE REPORT

The female patient was conceived via IVF and diagnosed antenatally via amniocentesis with mosaic TS (45,X [24%]/46,XX [76%]) and a paternally inherited balanced reciprocal translocation between the long arm of chromosome 2 and the long arm of chromosome 6. This was later confirmed postpartum. The postnatal and childhood periods were uneventful, and the patient underwent normal pubertal development with menarche occurring at the age of 12 years.

She was first referred to Addenbrooke's hospital aged 17 years for annual check-ups because of her karyotype and at this stage had no phenotypical characteristics of TS and had an anti-müllerian hormone (AMH) of 68 pmol/L. At the age of 19 years, she had 31–40-day menstrual cycles and all endocrinology observations remained normal with a body mass index of 23, luteinizing hormone of 3.6 IU/L, follicle-stimulating hormone (FSH) of 6.3 IU/L, 25-Hydroxyvitamin D of 76 ng/mL, thyroid-stimulating hormone of 1.70 mu/L, and normal liver function tests. She also attended cardiology and audiology clinics and had a normal echocardiogram and no sensorineural abnormalities, respectively. She received genetic counseling.

She was counseled regarding the likelihood of POI and the poor pregnancy outcomes of patients with TS. She was keen to consider oocyte retrieval and cryopreservation.

At the age of 20 years, she attended the IVF clinic where she had a transvaginal ultrasound scan and her AMH was rechecked (52 pmol/L). Ultrasound scan demonstrated a normal uterus with polycystic ovaries and an antral follicle count (AFC) of 17 on the left ovary (total size of 28 × 19 × 19 mm) and >20 on the right ovary (total size of 29 × 22 × 18 mm). Her height was measured at 167.7 cm, body mass index was 24.4 and a blood pressure of 120/60. She also had oligomenorrhea (35–40-day menstrual cycles), which together with polycystic ultrasound morphology allowed her to be diagnosed with PCOS, as she was 8 years postmenarche at this time. She was commenced on metformin 500 mg once daily.

Stimulation was performed with a low dose of 100 IU of recombinant FSH because of her age and high AMH. On day 5 she started GnRH antagonist (orgalutran 0.25 mg). The patient underwent regular transvaginal ultrasound scanning, and on day 12 of her cycle, several follicles >14 mm were noted. Estradiol level was 8,019 nmol/L on the day of the hCG trigger. The patient's oocytes were collected transvaginally on day 14. Eighteen follicles >14 mm were visualized and 14 oocytes at metaphase II were retrieved and cryopreserved using rapid vitrification.

A year later, at age 21 years, the patient underwent her second oocyte retrieval, again with 100 IU of recombinant FSH in combination with a GnRH antagonist (cetrotide 0.25 mg), again beginning the latter on day 5. The patient underwent her second oocyte retrieval on day 17 of her cycle. Estradiol level was 3,244 nmol/L on the day of the hCG trigger. Six follicles >14 mm were visualized and 6 oocytes at metaphase II were collected and cryopreserved.

Overall, 19 oocytes have been collected and cryopreserved. At the point of writing none of the oocytes have been fertilized and no subsequent embryo implanted.

Patient Consent

The patient has consented to having her personal information included.

DISCUSSION

Oocyte cryopreservation has become an established fertility preservation technique in adults, particularly in patients with cancer (8). Recently, its use in patients with TS has also increased (3, 9–12). Our case report documents successful oocyte retrieval and cryopreservation in a patient with mosaic TS and PCOS. It highlights the potential of OC as an option for fertility preservation in women with mosaic TS and PCOS, who may face infertility risks.

Patients with TS are at high risk of experiencing POI because of accelerated depletion of their ovarian primordial follicle reserve. This can be a significant concern for these patients and their families. OC has been reported as a method of fertility preservation in both adult and postpubertal children with TS (3, 9–12). In our patient, the number of retrieved mature oocytes was higher than usually described in women with mosaic TS (12). Interpretation of ovarian reserve markers in patients with TS is challenging. The rate of oocyte depletion in patients with TS is highly variable,

and as of now, a definitive correlation between TS mosaicism and ovarian reserve biomarkers, such as AFC or AMH, has not been established (3). Positive predictive factors for follicle quantity include spontaneous puberty, mosaic blood karyotype, age from 12- to 16-year-old, normal baseline FSH (<11 UI/L) and AMH levels (>2 μg/L or 14.3 pmol/L) (12). It has been proposed that serial assessments of AMH be conducted, and OC be considered when AMH levels plateau but before their decline ensues (3, 9).

The decrease in oocyte yield observed between the 2 cycles, from 14 to 5 in a year, has already been documented by Oktay and Bedoschi (11) (8 for the initial cycle and 4 for the subsequent cycle). This decline could be attributed to the depletion of ovarian reserves. These findings highlight the importance of timely fertility preservation options in patients with TS and the need for careful monitoring of ovarian reserve during this process, which could be done by measuring the AMH of AFC.

Until recently, little has been known about TS oocyte quality, however, recent developments in the field are encouraging, as evidenced by reports of the first successful live birth achieved using cryopreserved oocytes from a woman with mosaic TS (3). It highlights the prospective viability of fertility preservation through this avenue for individuals with TS. The number of retrieved oocytes needed to obtain a live birth is yet to be determined in patients with TS; however, non-TS studies subset it to be at least 15 (13).

Furthermore, the increased risk of chromosomal abnormalities in the offspring of patients with TS should be considered, and preimplantation genetic testing for aneuploidy (PGT-A) could be recommended. However, the exact role of PGT-A in reducing pregnancy loss remains unclear (14). In addition, potential limitations of PGT-A in detecting mosaic embryos include sampling bias which may lead to a false-negative result, the extent of mosaicism, where PGT-A might not accurately represent the chromosomal status of an embryo, and the detection threshold which is currently estimated between 4% and 22% (15).

These constraints underscore the potential necessity for supplementary diagnostic tools, such as prenatal diagnostic testing, particularly in instances with relevant family history. This notably includes cases involving balanced translocations where the efficacy of PGT-A in detecting complex abnormalities might be compromised, especially if the balanced translocation involves multiple breakpoints. In light of these considerations, preimplantation genetic testing for structural rearrangements emerges as a potential avenue. Preimplantation genetic testing for structural rearrangements is a targeted test conducted when known chromosomal anomalies are identified in parental genomes, as observed in our patient's case, and tests for unbalanced chromosomal configurations within at-risk regions (15).

Preconception genetic counseling is of paramount importance in the comprehensive management of patients with TS, particularly when addressing fertility preservation and conception. It should encompass a thorough discussion of the potential pregnancy risks associated with TS comorbidities, an exploration of potential genetic risks and the inherent limitations of diagnosis. A pivotal aspect of this process involves setting realistic expectations taking into account the individual's medical history, age, genetic profile, extent of mosaicism, and reproductive goals. Recognizing the inherent complexity of mosaic TS, where the percentage of 45,X cells can vary significantly and consequently result in diverse karyotypes and phenotypes, there's an emerging recognition of the necessity for personalized counseling which could provide the most accurate and relevant guidance.

Polycystic ovarian syndrome is a complex endocrine disorder that is influenced by both genetic and environmental factors, but its exact cause remains unknown. Previous studies have suggested that X-linked genes may play a role in PCOS development by causing abnormal follicular apparatus formation (5, 16). The coexistence of PCOS and TS is rare because of ovarian dysgenesis or early insufficiency. However, a few instances have been reported in the literature, and they have shed light on the potential relationship between these 2 conditions (5–7, 12, 17). A case of a patient with mosaic TS (46,XX 83%; 45,X 9%; 46XderX 8%) with PCOS undergoing OC has been reported before, with a similar number of mature oocytes vitrified (MII, n = 20) (12).

Because of the scarcity of reported cases of patients with TS with coexisting PCOS, there is limited information on the reproductive profile of these patients. Thus, further research is necessary to comprehensively understand the relationship between these 2 conditions and to guide clinical management and fertility preservation strategies.

CONCLUSIONS

Oocyte cryopreservation, as demonstrated in this case, may be a feasible and realistic option for fertility preservation in patients with TS mosaicism and PCOS. Further studies are needed to determine the best timing for OC in this patient population, as well as to evaluate their safety and efficacy. It is important to assess ovarian reserve in patients with mosaic TS, which could be done by measuring AMH or AFC, to help decision making around advising fertility preservation.

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