Fertility in patients with Turner syndrome

Turner syndrome (TS) is characterized by a complete or partial absence of one X chromosome (1). The most frequent chromosome constitution is 45X0, although approximately half of patients have a mosaic chromosome complement, the most common being 45X0/46XX (15%) and 46XXq or 46XXp deletions (6%). The chromosome constitution is important because patients with deletions on Xp have short stature and congenital malformations, whereas those with a deletion on Xq only have gonadal dysfunction. There are also rare cases of female TS patients with 46XY 45X0/46XY karyotypes. TS accounts for 15% of miscarriages and occurs in 3% of all females conceived (1/1500–2500 female births).

The typical clinical features of TS are short stature, square appearance, webbed neck, characteristic unusual facies, low posterior hairline, broad chest with widely spaced nipples, and a "shield" chest. Poor development of lymphatic channels may also cause ear deformities. Patients have an elevated rate of cardiovascular and renal anomalies, which can cause cardiovascular disorders. Autoimmune disorders such as primary hypothyroidism are common (10%–30% of patients). Abnormal mesenteric bleeding is also typical from different diseases (e.g., Crohn's disease, ulcerative colitis) and other metabolic disorders such as glucose intolerance with mild insulin resistance and obesity. Because of these medical problems, patients with TS have a shorter lifespan than the general population.

Most women with TS (95%-98%) are infertile due to gonadal dysgenesis caused by oocyte loss from week 18 of pregnancy onwards or concentrated during the first few postnatal months and years. In most 45X0 patients, it results in streak ovaries. However, at puberty, a minority, mostly those with mosaic karyotypes, have ovaries with a relatively low number of follicles, which enable spontaneous puberty: breast budding and pubic and axillary hair (5%–25% of patients) and menstrual cycles (2%–5%). However, natural pregnancies and live births are rare.

In their current report, Calanchini et al. (2) studied fertility issues and pregnancy outcomes in 156 patients (median age 32 years; 23 with a mosaic karyotyoe) in a single adult TS clinic focusing on their fertility choices. This is probably the first single-center multidisciplinary study of fertility in women with TS. The spontaneous pregnancy rate was 13.5% with a live-birth rate of 11.5% (72% female infants with normal karyotypes), mostly in patients with a mosaic karyotype. This pregnancy rate was similar to that reported in Denmark in 410 (15.6%) patients (3). It is noteworthy that in the current study (2), four of the women were diagnosed with TS after their first pregnancy, and one only after her daughter had miscarriages and was confirmed as a TS patient. The miscarriage rate was 47.6%. Oocyte cryopreservation was considered in four women with regular menstrual cycles, but oocyte retrieval was conducted in only one non-mosaic patient. Only 14 patients attempted pregnancy with oocyte donation, resulting in 50% live births. It is noteworthy that women who requested oocyte donations were older than those who conceived spontaneously. Pregnancies via oocyte donation are often not financially affordable to these women (2). Pregnancy-related cardiovascular changes were assessed in only 12 women (increased aortic diameters at sinuses). The study did not show an excess in morbidity or mortality during pregnancy. The authors also claim that they had the largest case series of spontaneous pregnancies with a triple X cell line and reported natural pregnancies with live births in two women with blood X0 monosomy, possibly because of ovarian mosaicism. TS patients conceiving by oocyte donation as well as spontaneously require multidisciplinary clinical follow-up, as these women have small stature, might have additional cardiovascular and other morbidities, and should be monitored during pregnancy. Therefore, if oocyte donation is considered, it is recommended to transfer only one embryo in order to avoid multi-fetal gestations (1, 2). Most reports regarding oocyte donation have shown that the pregnancy rate of women with TS is similar to that in other women who required egg donation (1). Some studies have reported higher miscarriages with egg donations, which might be due to uterine-endometrial factors.

Oocyte freezing can be considered in mosaic TS patients with regular menstrual cycles (2), although results of this procedure have not yet been reported in TS patients. The authors recommended not to attempt oocyte cryopreservation before the age of 12 years (2). Although germinal vesicle-stage oocytes can be retrieved and can undergo in vitro maturation and cryopreservation (4), this approach has been reported only in one case report of a 16-year old mosaic TS patient.

Ovarian tissue cryopreservation is one of the methods used to preserve fertility in cancer patients, with the intention of transplantation after survival at adulthood (1, 4, 5). It can be considered mostly for mosaic patients at early ages and can be combined with retrieval of immature oocytes; however, this method was not used in the current study (2). To evaluate the feasibility of ovarian retrieval for cryopreservation, the first test should be pelvic ultrasound, as streak ovaries might be too small to be adequately visualized (1). If the ovaries are visualized, plasma gonadotropin levels can be evaluated, and if exaggerated levels of plasma gonadotropins, especially follicle-stimulating hormone have been demonstrated, such ovaries should not be cryopreserved. If ovarian biopsies are not cryopreserved before puberty, levels of gonadotropins can be assessed when indications of puberty occur. In some adolescent patients, administration of gonadotropin-releasing hormone can be attempted to stimulate the hypophyseal–pituitary axis, as an additional test to confirm ovarian function and gonadal integrity. Nevertheless, in most patients, a single determination of plasma follicle-stimulating hormone and luteinizing hormone is enough to determine gonadal failure (1, 5). In addition, antimüllerian hormone can be evaluated from the plasma (2, 5). In some cases, pre-cryopreservation retrieval of ovarian biopsy samples by laparoscopy might be considered for follicular evaluation by histology (1). Because of the invasiveness of this diagnostic procedure, this operation should be considered only rarely, if other tests have failed to produce clear-cut answers.

However, to the best of our knowledge, there are no reports of ovarian implantation in TS patients.

Parents of girls with a diagnosis of TS and young women with this disorder should be counseled regarding the high possibility of gonadal failure and infertility. They should be made aware that if pregnancy does occur, it will probably be at high risk for miscarriage as well as fetal and possible chromosomal abnormalities in the offspring (1), although the latter was not identified by Calanchini et al. (2). If oocyte donation is considered, it is recommended to transfer only one embryo in order to avoid multiple pregnancies. In some cases, surrogacy can be considered. As unplanned pregnancies have been reported (1, 2), it is advisable to counsel this population regarding birth control. Spontaneous pregnancies are rare in women with TS and occur mostly in those with mosaicism. Women who wish to attempt natural conception should not postpone it, as fertility is likely to diminish rapidly with time. Pregnancies with oocyte donation as well as spontaneous pregnancies are usually high risk because of these individuals' various health problems and require multidisciplinary clinical follow-up because of their small stature and their associated morbidities (e.g., cardiovascular problems) (1, 2). The miscarriage rate is also high, and patients need to be monitored carefully during pregnancy.

The future perhaps holds further hopes for pregnancies in women with TS (1, 5). As some girls with TS, mostly those with mosaic karyotypes, have follicles in their ovaries, their ovarian function should be tested; thereafter, ovarian tissue might be retrieved by laparoscopy even before puberty and cryopreserved for possible replantation. Another possibility is oocyte cryopreservation from young girls who demonstrate signs of puberty, with future oocyte fertilization and embryo transfer.

In cases in which ovarian cryopreservation may be considered, the clinician must explain to the parents and patients the uncertainty of the actual follicular content in the cryopreserved ovaries, and possibly of their insufficient number to survive cryopreservation and transplantation. The clinician should also emphasize that pregnancies from ovarian tissue implantation will carry the same risks as natural pregnancies in women with TS: chromosomal abnormalities, congenital malformations, and a high risk of miscarriage and stillbirths. Therefore, in all pregnancies from autologous oocytes, genetic counseling and prenatal diagnosis should be recommended.

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REFERENCES

1. Abir R, Fisch B, Nahum R, Orvieto R, Nitke S, Ben Rafael Z. Turner's syndrome and fertility: current status and possible putative prospects. Hum Reprod Update 2001;7:603–10.
2. Calanchini M, Aye CYL, Orchard E, Baker K, Fabbri A, Mackillop K, et al. Fertility issues and pregnancy outcomes in Turner syndrome. Fertil Steril 2020;114:144–55.
3. Birkebaek NH, Crüger D, Hansen J, Nielsen J, Bruun-Petersen G. Fertility and pregnancy outcome in Danish women with Turner syndrome. Clin Genet 2002;61:35–9.
4. Huang JY, Tulandi T, Holzer H, Lau NM, Macdonald S, Tan SL, et al. Cryopreservation of ovarian tissue and in vitro matured oocytes in a female with mosaic Turner syndrome: case report. Hum Reprod 2008;23:336–9.
5. Borgstrom B, Hreinsson J, Rasmussen C, Sheikhi M, Fried G, Keros V, et al. Fertility preservation in girls with Turner syndrome: prognostic signs of the presence of ovarian follicles. J Clin Endocrinol Metab 2009;94:74–80.