



## Turner Syndrome and Infertility: A Review of Literature

Emine Demirel<sup>1\*</sup>, Emre Ekmekci<sup>1</sup>, Zeynep Soyman<sup>2</sup> and Sefa Kelekci<sup>1</sup>

<sup>1</sup>Izmir Katip Celebi University, School of Medicine, Department of Obstetrics and Gynecology, Izmir, Turkey

<sup>2</sup>Istanbul Education and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey

**\*Corresponding author:** Emine Demirel, M.D., Izmir Katip Celebi University, Faculty of Medicine, Department of Obstetrics and Gynecology, Izmir, Turkey, Tel: +90 232 243 43 43, Fax: +90 232 243 15 30, E-mail: er\_em.dr@hotmail.com

### Abstract

Fertility of women with Turner Syndrome is now being more interested due to the new improvements in assisted reproductive techniques. Turner Syndrome is characterized by the premature atresia of ovarian follicles. Atresia starts at intrauterine period and continues till all ovarian follicles go to atresia. The time of this period changes from patient to patient. Also Turner Syndrome is related with higher risks in pregnancy. These include higher incidence of spontaneous abortion, fetal anomaly, maternal morbidity and mortality in pregnancy. Patient with Turner Syndrome should be evaluated carefully, because these patients are at risk for cardiovascular disease that can be dangerous in pregnancy. In this review, we researched the literature about fertility in Turner Syndrome and options about solutions for fertility problems in Turner Syndrome.

### Keywords

Infertility, Pregnancy, Turner Syndrome

### Introduction

Turner syndrome (TS) is characterized by a complete or partial absence of one X chromosome. It is associated with various developmental, endocrine, cardiovascular, psychosocial and reproductive disturbances. 45,X chromosomal constitution is the most karyotype for non-mosaic Turner syndrome [1]. About half the patients have a mosaic pattern. The most common pattern is 45X0/46XX and 6% of patients have partial structural chromosomal deletions on second X chromosome (46XXq or 46XXp deletions). Also a ring X chromosome complement can be identified in rare cases. The different Turner karyotypes (monosomy, mosaicism and structural deletion) are determined by analysing the frequencies of different cell lines using conventional karyotyping on lymphocytes. Thus, the syndrome might be attributable to a limited amount of genetic material in these abnormal chromosomes [2].

Turner Syndrome is the most common sex chromosomal disorder among women, affecting one in 2000 live-born girls [3]. Patients have a short stature and most of them are primary amenorrheic at puberty. There is a failure to enter puberty due to the accelerated atresia of ovarian follicles and causing gonadal insufficiency and infertility [4]. But the atresia rate of follicles is not same at one to other. So, in some cases spontaneous puberty may occur and ovulatory cycles can start and these may have a potential for fertility, although premature ovarian failure is likely to occur in early adult life [5].

### Fertility in Turner Syndrome

It is reported that 16% normally develop spontaneous puberty [6]. In a study with 276 women with TS, 10 women had 13 different pregnancies spontaneous or by the help of assisted reproductive techniques. Five women had a spontaneous pregnancy and the other five women needed assisted reproductive techniques [7]. Most fertile women with TS have the karyotype 45,X0/46,XX, but few with the karyotype 45,X0 have been reported [8]. In a Danish study on 410 patients diagnosed TS, thirty-three women, one with 45X0, 27 with mosaicism and five with structural abnormalities of the second X had given birth to 64 children in 61 pregnancies. Two women had become pregnant by means of in vitro fertilization, including a woman with 45,X by egg donation. Thus, 31 women (7.6%) had at least one spontaneous pregnancy [9]. Mosaicism is the major factor for much of the variability in phenotype in TS patients, including the degree of ovarian dysfunction [10]. Rigorous analysis for mosaicism can be performed with karyotype of an adequate number of peripheral blood leucocytes (e.g. 100 cells), analysis of cells from more than one tissue type or via fluorescence in situ hybridization (FISH) with X and Y probes [11].

There is increasing interest in fertility and use of assisted reproductive technologies for women with Turner syndrome (TS). With the advances in assisted reproductive technologies, new options are available for TS patients. Current parenting options include adoption, surrogacy, and spontaneous and assisted reproduction [12]. Current evidence suggests that 45,X0 germ cells are not capable to complete whole meiosis and are being eliminated during the development of germ cells. The detected ovarian follicles seem to be originated from a small amount of 46, XX karyotyped germ cells. So, the functional ovarian tissue in Turner Syndrome is a result of partial mosaicism in ovarian tissue [12,13]. Reproductive techniques seem to be only effective only for mosaic and structural chromosomal deletion cases not effective for pure monosomies. But this should be kept in mind that absence of mosaicism in peripheral blood does not preclude the absence of mosaicism in ovarian tissue. A significant proportion of 45,X conceptions are thought to result from postzygotic loss of the second sex chromosome, implying that mosaicism is frequently present, even when not detectable in blood. This explains the spontaneous pregnancies in pure monosomic TS patients [14].

Up to one third of TS patients with structural abnormalities in X chromosome tend to have spontaneous puberty. Although

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the incidence of spontaneous thelarche is relatively common, a small percentage will have spontaneous menarche. Spontaneous pregnancies can be seen more common at these patients (2-5%). But, at the pregnancies of these patients if male embryos that inherit the structurally abnormal X chromosome they will be nonviable. Also, female offspring are at risk of a more severe phenotype if X-inactivation does not favour the intact X [12,15].

## Pregnancy at Turner Syndrome

Patients with Turner Syndrome when have a pregnancy there is an increased risk of miscarriage, stillbirths and malformed babies. Possible explanations for these can be the chromosomal abnormalities in the fetuses, mostly Down and Turner syndrome, which have been noted in both the aborted fetuses and the live-born children of these patients at a higher rate than in the general population (4 versus 0.4% for trisomy 21 and 15 versus 0.5% for Turner syndrome) [16,17]. Prenatal diagnostic tests should be offered to all pregnant TS women and the pregnancies should be regarded as high risk [12].

Furthermore, there may be other multiple factors for poor prognosis in pregnancy. Autoimmune disorders are common in Turner syndrome patients; some of the miscarriages might have an autoimmune origin [18]. New evidence from oocyte donation programs has additionally shown that 21-hydroxylase deficiency and diminished endometrial receptivity might be another cause of the miscarriages [19]. Presence of mosaicism does not seem to reduce the malformation rate for the fetus [20]. Also TS patients tend to have uterine anomalies more common. The uterus may be structurally abnormal (e.g. bicornuate), small due to delayed oestrogen replacement at puberty, or endometrial receptivity may be poor due to long-term hypoeastrogenism, which should be avoided [17]. Uterine size was associated with history of spontaneous puberty, and duration and type of hormone replacement oestradiol-based regimens were better than oral contraceptive-based regimens [21].

22-50% of the offspring of TS women have intrauterine growth restriction, low birth weight and prematurity.

These may be due to primary factors associated with the TS mother, or iatrogenic factors such as late-onset maternal oestrogen therapy and resultant small uterine size [22,23].

Also pregnancy may be dangerous for the mother. Because TS patients have a lot of co-occurred diseases such as cardiovascular disease and autoimmune diseases. They have increased risk for pregnancy related complications. Hypothyroidism, obesity, diabetes, hypertension and preeclampsia, which occur in approximately 40% of patients with TS compared with 6-12% of the general population [23,24]. Also TS patients have an increased risk for aortopathy and aortic cystic medial necrosis. Aortic dissection risk increases with multiple pregnancies [25]. Because of this multiple embryo transfer is strongly contraindicated in women with TS [26]. TS patients should have a detailed cardiac examination before pregnancy. Cardiac pregnancy contraindication criteria for pregnancy have been suggested by consensus in French and US groups: History of aortic surgery or aortic dissection, coarctation of the aorta, Aortic size index  $>2.5$  cm/m<sup>2</sup> or maximal aortic diameter 3.5 cm, uncontrolled hypertension despite treatment, portal hypertension with esophageal varicose veins and presence of other major cardiac anomalies [27].

## Treatment Options for Fertility

TS patients should have hormonal therapy from childhood to adulthood for better reproductive results. Sexual development and normal height and body weight is important for better reproductive results [17]. Growth hormone should be started at 2-5 ages and should be continued till the expected body weight and height [28]. Estrogen is important for sexual development but estrogen should not be used alone due to the biphasic effect of it on bone epiphyseal growth plates [18]. In girls receiving GH, oestrogen should not be given when the bone age is  $<11$  or 12 years or until near final height has been achieved, that is, when only one more year of GH therapy is required [18]. After initiation of breast development and uterine growth, the

dose should be increased to maintenance levels of  $0.9\pm1.25$  mg of conjugated estrogen or 2 mg of micronized oestradiol per day, with the addition of cyclic therapy with progestins to induce cyclic vaginal breakthrough bleeding [29]. But current recommendations to start low-dose estrogen or especially transdermal estradiol therapy at 12 year of age allows for normalized development of secondary sexual characteristics, as well as uterine and bone mineral development [30-32]. Recent investigations suggest that the use of transdermal estradiol appears to be linked to a lower risk of thrombosis when compared with oral estrogens [31].

HRT should be administered over the long term for women with TS because of its benefits on cardiovascular disease and osteoporosis [18]. Many invasive reproductive techniques are not successful for the treatment of infertility in Turner Syndrome and newer technologies such as ovarian cryopreservation are presently considered. The options for assisted reproductive techniques are: Heterologous in vitro fertilization (oocyte donation) and homologous in vitro fertilization (patient's own gametes) [12]. For women with TS who experience ovarian failure oocyte donation is an option for pregnancy. However initial success rates are similar to normal population after transfer, success reduces with the advancing pregnancy. A review of 23 women with TS following ovum donation in Belgium reported a miscarriage rate of 44% and take home baby rate of 18% per transfer [22].

Women with TS sometimes are diagnosed with poor success rates at ovarian hyperstimulation and poor ovarian response. Types of homologous IVF include oocyte collection for immediate IVF and embryo transfer, or various methods of fertility preservation (cryopreservation of individual mature oocytes, cryopreservation of ovarian tissue containing immature primordial follicles or cryopreservation of embryos) for possible future use in an individual with actual or expected decline in ovarian function [33].

Because of accelerated atresia of ovarian follicles before puberty or reproductive ages fertility preservation techniques are now being used as good alternative for TS patients. So, preserved oocytes can be used in future for homologous invitro fertilization or surrogacy. The primary purpose of ovarian cryopreservation is to keep and save the primordial follicles in the ovarian cortex before all ovarian follicles have gone to atresia. Clinical pregnancy rates for this technique are similar to those attained from fresh oocytes, and over one thousand live births have been reported in the non-TS population [34]. But the success rate for TS patients is unclear. There are case reports on oocyte and ovarian tissue preservation for TS patients [35]. The appropriate age at which fertility preservation should be performed for patients with TS remains unclear. Ovarian stimulation is required before oocyte preservation because mature oocytes should be preserved [36].

Hreinsson et al. first described ovarian cryopreservation in adolescents at 2002 [37]. Ovarian tissue cryopreservation seems not to be effective as oocyte preservation due to the problems at invitro maturation of primordial follicles. Because, cryopreservation of ovarian tissue would be only preserve primordial and primary follicles. And pre-ovulatory antral follicles, which contain immature oocytes at the germinal vesicle stage, do not usually survive the cryopreservation procedure of ovarian tissue. Procedure can be performed laparoscopically [38]. Whole ovarian tissue cryopreservation is an alternative. It may have a higher success rate [39]. Preserved ovarian tissue can be transplanted onto the orthotopic site that is the ovarian fossa or on to a heterotopic area. Another alternative to preservation is heterologous ovarian tissue transplantation. Mhatre and Mhatre (2006) reported the first mother-to-daughter transplantation of ovarian tissue in a 15-year-old patient with TS [40]. Recommended criteria for ovarian tissue preservation include: spontaneous puberty, FSH  $<40$  IU/l, ages 14 or above and normal cardiac status. Also monosomy is a negative predictor [41].

## Conclusion

Spontaneous pregnancies are rare in women with TS and are mostly in those with mosaic karyotypes. Women with TS evaluated

carefully throughout life, especially before puberty. Selected patients should be informed about treatment options for fertility and risk of pregnancy. They should be counselled about cryopreservation techniques.

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