

## REVIEWS

# Freezing Time and Preserving Hope: Ovarian Tissue Cryopreservation for Girls with Turner Syndrome

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Keywords: Turner Syndrome, Primary Ovarian Insufficiency, Ovarian Tissue Cryopreservation, Oocyte cryopreservation, Hormone Replacement Therapy

<https://doi.org/10.52504/001c.127875>

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## Georgetown Medical Review

Vol. 8, Issue 1, 2024

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Turner syndrome is a chromosomal abnormality that affects 1 in every 2500 live female births. Most patients with Turner syndrome experience primary ovarian insufficiency, often becoming infertile at a young age. Among all of the consequences associated with the illness, infertility is one of the most concerning issues for patients with Turner syndrome. We examine the treatment options that are currently available to aid in preserving patients' fertility until they are ready to have children. Hormone replacement therapy and oocyte cryopreservation are the most standard procedures performed to preserve the fertility of patients with Turner syndrome, but they are not impactful options for patients who are likely to experience primary ovarian insufficiency before puberty. One novel treatment patients could potentially pursue prior to reaching puberty is ovarian tissue cryopreservation. Currently a well-established procedure to preserve fertility in patients with cancer, ovarian tissue cryopreservation has the potential to help patients with Turner syndrome have spontaneous pregnancies safely and successfully, without the adverse effects associated with other fertility preservation techniques. Additional research and funding should be directed towards ovarian tissue cryopreservation in patients with Turner syndrome specifically, so that efficacy, selection criteria, and safety guidelines can be established.

## Introduction

Turner syndrome is one of the most common sex chromosome disorders, occurring in 1 in every 2500 to 3000 live female births.<sup>1</sup> Females are typically born with XX sex chromosomes, but in those with Turner syndrome, their karyotype contains one X chromosome and either a complete or partial absence of the second X chromosome.<sup>2</sup> Approximately 40% to 50% of women with Turner syndrome have a 45,X karyotype, signifying the complete loss of a second X chromosome.<sup>1</sup> About 15% to 20% have mosaic Turner syndrome, meaning they have a combination of cells with the appropriate number of sex chromosomes and others containing monosomy X resulting in a karyotype of 45,X/46,XX.<sup>1,2</sup> A minority of patients with Turner syndrome (5%) have a karyotype that includes a complete or partial Y chromosome.<sup>1</sup> Regardless of karyotype, most instances of Turner syndrome are not inherited; however, the timing of the atypical event leading to Turner syndrome is dependent on the karyotype.<sup>3</sup> With the 45,X karyotype, the

chromosomal abnormality occurs randomly in the parent during the formation of reproductive cells. Conversely, in mosaic Turner syndrome, the abnormality happens randomly during cell division in the early fetal development of the affected individual.<sup>3</sup>

Turner syndrome is typically diagnosed prenatally via genetic tests, such as chorionic villus sampling and amniocentesis, as well as high-resolution ultrasounds and fetal echocardiography that detect physical abnormalities.<sup>4</sup> These techniques only identify the most pronounced phenotypes, leading to missed diagnoses and delayed treatment.<sup>5</sup> If Turner syndrome is suspected postnatally, a karyotype analysis can be performed. To identify low-level mosaicism, buccal cell fluorescence in situ hybridization is used.<sup>6,7</sup>

The most common features of Turner syndrome include webbed necks, low-set ears, a broad chest with widely spaced nipples, short stature, a low hairline on the posterior neck, a high narrow palate, and cubitus valgus.<sup>1</sup>

Girls with the 45,X karyotype are more likely to experience certain congenital malformations, while endocrine disturbances and cardiovascular diseases are more common in women with other Turner syndrome karyotypes. Overall, morbidity and mortality rates are elevated in patients with Turner syndrome regardless of the karyotype presentation.<sup>4</sup> Most importantly, individuals with Turner syndrome often struggle with gonadal insufficiency and infertility.<sup>6</sup> Many patients are born without oocytes and never experience menarche, which necessitates options such as embryo donation, surrogacy, or adoption for family building.<sup>8</sup> However, some patients with Turner syndrome do have viable oocytes, and thus, they have more fertility preservation options. They typically have far fewer than the average female infant due to higher rates of apoptosis within the first 15 to 20 weeks of development.<sup>9</sup> Consequently, by puberty, it is common for patients with Turner syndrome to have already exhausted their oocyte supply. Infertility is often cited as the most traumatic consequence of Turner syndrome, with 50% of women reporting it as a source of depression.<sup>10</sup>

Current treatments for fertility preservation in patients with Turner syndrome include hormone replacement therapy (HRT) and assisted reproductive technologies (ART).<sup>2</sup> Oocyte cryopreservation is the most common ART, but it is highly controversial due to its risks and limitations.<sup>11</sup> The current article presents novel approaches, particularly ovarian tissue cryopreservation (OTC), which also faces controversy due to limited data on its success in patients with Turner syndrome. The biological differences between patients with Turner syndrome and other groups, such as patients with cancer, raise concerns about the efficacy and success of this procedure for those with Turner syndrome, as most data on OTC comes from studies

involving female patients with cancer. However, with further research focused on patients with Turner syndrome, OTC may become a promising fertility option for this group.

## **Current Challenges and Treatments**

### ***Turner Syndrome and Infertility***

About 95% of patients with Turner syndrome experience hypogonadotropic hypogonadism leading to infertility and subsequent premature ovarian failure and primary ovarian insufficiency. Women with Turner syndrome do not produce enough eggs or endogenous hormones to support a pregnancy.<sup>8</sup> While infertility and hypogonadism are universal across Turner syndrome, the degree to which they affect an individual varies depending on the karyotype. The ovaries in a 45,X fetus develop normally until birth; however, at birth or immediately following, follicular atresia ensues.<sup>12</sup> Women with a mosaic karyotype, or those who experience spontaneous puberty without exogenous estrogen supplementation, have follicles in one or both ovaries. In a study conducted by Reynaud et al,<sup>13</sup> researchers examined 10 aborted fetuses with Turner syndrome and compared them with a control group of gestational age-matched fetuses with severe abnormalities that are not known to affect ovarian function. They found a similar number of germ cells in the genital ridge up until 12 weeks, indicating normal primordial germ cell migration in fetuses with Turner syndrome.<sup>13</sup> However, at 18 weeks' gestation, germ cells were barely detected and completely absent by 25 weeks of gestation in fetuses with 45,X. Additionally, primordial and antral follicles were absent in fetuses with 45,X karyotype Turner syndrome, although some were detected in fetuses with Turner syndrome mosaicism. These findings support the presumption that accelerated germ cell death causes germ cell depletion in patients with Turner syndrome. Folliculogenesis is severely impaired in the ovaries of women with Turner syndrome, contributing to a loss of germ cells. Turner syndrome may also be marked by poor oocyte quality, preventing successful fertilization and pregnancy without supplemental therapies.<sup>14</sup>

Most patients with Turner syndrome have a smaller or immaturely formed uterus and present with 30% to 50% lower levels of androgens, but higher levels of follicle-stimulating hormone, luteinizing hormone, and estrogen sulfate than controls.<sup>15</sup> This is an important finding because elevated levels of follicle-stimulating hormone and luteinizing hormone during adolescence are directly linked to reduced ovarian function.<sup>15</sup> Due to these physiologic and hormonal abnormalities, pregnancy among patients with Turner syndrome is rare and poses a severe risk for both mother and baby, with less than 5% of patients experiencing a spontaneous pregnancy. Of these women, pregnancy shows a high risk of birth defects, miscarriage, or stillbirth, with only around 3% of patients giving birth to 1 or more live-born children.<sup>16</sup>

Effective treatment of Turner syndrome requires a comprehensive care plan, relying on the close collaboration of specialists. However, due to the uncommon nature of Turner syndrome and its varied phenotypic presentation, treatment plans seem to highlight the areas of agreement and those of controversy within the clinical community. Despite the frequency of infertility and hypogonadism in patients with Turner syndrome and its impact on quality of life, many of the available treatments, spanning from HRT to oocyte cryopreservation, are intertwined with severe adverse effects.

### ***Estrogen Supplementation***

More than 90% of individuals with Turner syndrome cannot undergo spontaneous puberty and rely on exogenous estrogen for its induction. Currently, HRT with estrogen and progestin supplementation is at the forefront of treatment options.<sup>17</sup> Patients with Turner syndrome usually present with primary amenorrhea or delayed puberty following premature ovarian failure. Around the age of 10 years, serum anti-Müllerian hormone and follicle-stimulating hormone should be measured, as detectable levels are indicative that the patient will undergo spontaneous puberty. If there has been no breast development, elevated gonadotropins, or low anti-Müllerian hormone levels by the age of 12 years, estrogen replacement therapy should begin.<sup>3</sup>

While HRT may mitigate the cardiovascular, hormonal, and metabolic effects of female hypogonadism, the proper dose is not well-established and subsequent benefits and/or accompanying drawbacks remain undefined. At present, most treatment recommendations are based on expert opinion and lack evidential basis.<sup>18</sup> Estrogen replacement therapy should simulate normal pubertal progression and recent advancements in newer HRT regimens, including treatment with conjugated equine estrogens or other synthetics, seem to provide adequate estrogen exposure resulting in a more normal uterine growth.<sup>17</sup> Currently, generalized HRT guidelines established internationally appear sufficient to induce puberty and increase uterine size, validating HRT as an effective therapy against hypogonadism and infertility.<sup>17</sup>

### ***Assisted Reproductive Technologies—Oocyte Cryopreservation and Pregnancy***

Fertility preservation through ART involving newer oocyte cryopreservation and more traditional in vitro fertilization and embryo transfer (IVF-ET) allow women to conceive with their own oocytes.<sup>11</sup> Of the 2, oocyte cryopreservation is considered a more controversial ART because it raises concern about the quality of the eggs yielded from postpubertal ovarian stimulation.

Patients with Turner syndrome who plan on pregnancy are at an elevated risk of complications throughout the gestation period. Complications that cause fetal mortality, such as spontaneous abortion, ectopic pregnancy, or noncardiovascular events, are heightened with the use of both mature and immature cryopreserved oocytes. These risks are further elevated in cases of multiple gestation, so when using ARTs such as IVF or oocyte donation, only a single embryo can be transferred to limit complications.<sup>11</sup> Furthermore, maternal mortality is elevated with ARTs, specifically with oocyte cryopreservation, resulting in increased risk of aortic dissection and rupture due to cardiovascular complications and related hypertensive events. Research from Hadnott et al<sup>11</sup> reported that aortic dissection can occur in as many as 2.0% to 4.8% of pregnancies with Turner syndrome and the incidence of developing preeclampsia exceeds 20%. Additionally, due to cephalopelvic disproportion in women with Turner syndrome, cesarean delivery rates are higher than in the general population, including all potential risks associated with that operation.<sup>2</sup> As such, oocyte cryopreservation treatment, while offering some hope of fertility preservation, seems to elevate the severe medical risks of Turner syndrome pregnancy. To address the psychological burden of this process, extensive counseling is paramount for patients with Turner syndrome who want to conceive with their own oocytes, as well as a full genetic prenatal screening.

Traditionally, women with Turner syndrome–related ovarian failure receive IVF-ET therapy or are encouraged to adopt. While oocyte cryopreservation offers patients with Turner syndrome a chance to reproduce with their remaining oocytes, rapid postnatal loss of oocytes seen in Turner syndrome depletes the pool available for cryopreservation, leading to premature exhaustion of the ovarian reserve by the time patients with Turner syndrome want to conceive.<sup>19</sup> Therefore, identifying the proper time to harvest oocytes for cryopreservation is complicated, and successful preservation is inconsistent.

In a cycle, there are 1 to 2 oocytes present in the metaphase II stage of meiosis that reach full maturity, while the rest degenerate following atresia. In oocyte cryopreservation, the ovaries are stimulated with exogenous gonadotropin to promote ovulation and mature oocytes are collected, vitrified, and cryopreserved.<sup>2</sup> The frozen oocytes may be thawed and fertilized later when the patient decides to reproduce. However, at least 10 oocytes are advised for successful preservation, and given the small number of mature oocytes present in a patient with Turner syndrome at one time, the harvesting process must be repeated multiple times. Not only is the harvesting process extremely tedious, but it is also extremely invasive. Immature oocytes at germinal vesicle or meiosis stage I may also be harvested independent of gonadotropin stimulation from dissected ovarian tissue and then transferred to a cultured

medium that simulates the follicular microenvironment in vivo. The oocytes are cultured to a mature stage so pregnancy may occur through IVF-ET, but with overall little and varied success in patients with Turner syndrome.<sup>2</sup>

## **A Novel Approach to Turner Syndrome Fertility Preservation**

### ***Ovarian Tissue Cryopreservation***

As aforementioned, the use of ARTs, more specifically, the use of oocyte cryopreservation as a method for fertility preservation, offers patients a short time frame to harvest oocytes at the cost of intense hormonal stimulation and repeatedly failed cycles. Furthermore, the previously mentioned approaches to Turner syndrome fertility preservation are offered at the postpubertal state, a limitation that prevents successful intervention at the earliest stage when patients have a high number of oocytes and healthy ovarian tissue. Therefore, it is worth considering a novel, early approach to Turner syndrome fertility preservation that results in the highest possibility for viable implantation and pregnancy.

While oocyte cryopreservation becomes an available treatment option only after puberty, OTC is the primary fertility preservation option for prepubertal girls.<sup>20</sup> Given that women with Turner syndrome are born with not only a reduced number of oocytes, but also impaired primordial follicle formation and increased oocyte apoptosis as compared with healthy women, fertility intervention remains ideal at the earliest stage possible.<sup>14</sup> As such, the novelty of OTC lies in its early intervention, as no sexual maturity is required to freeze ovarian tissue, and the surgical procedure has been performed in patients with Turner syndrome as young as 5 years of age.<sup>21</sup> OTC is also the preferred fertility preservation method for postpubertal women with Turner syndrome who cannot tolerate the hormonal stimulation required of oocyte cryopreservation, or those who cannot delay their therapies any longer.<sup>2</sup>

While oocyte cryopreservation is performed by oocyte retrieval through repeated cycles of ovarian stimulation using exogenous gonadotropin hormone, OTC is a 1-time surgical procedure to obtain the ovarian cortex<sup>2, 22</sup>; using a laparoscopic technique, surgeons obtain as much of the ovarian tissue as possible to maximize the use of the patient's ovarian reserve containing as many follicles as possible. Once obtained, the ovarian cortex is then cryopreserved until the patient is ready for pregnancy. Then, the ovarian cortex is thawed and transplanted into the patient, even if the patient no longer retains her ovary at this point.<sup>2</sup> Methodologically, it is important to note that the widely accepted method of cryopreservation is by controlled-rate freezing of the resected ovarian tissue to later thaw it for pregnancy. However, vitrification also exists as a method of cryopreservation through which the tissue is frozen with extremely rapid cooling, such that ice crystals do not form within the sample.<sup>23</sup> In a study by Keros et al<sup>23</sup> that compared controlled-rate freezing and vitrification, the researchers found that

vitrification resulted in 92% viable oocytes remaining in the tissue, while controlled-rate slow freezing only maintained 49% of the oocytes. This same study established that as compared with slow freezing, vitrification preserved the morphological features of the ovarian tissue such as the ovarian stromal cell structural integrity.<sup>23</sup> As such, vitrification is an evidenced method of increasing ovarian tissue preservation for future transplant success and subsequent pregnancy.

Given that OTC is a well-established procedure indicated for many disease profiles including a myriad of childhood and adult cancers, it is considered a safe procedure with limited postoperative risk. In a study by Babayev et al<sup>20</sup> that evaluated 28 females aged 2.3 to 21.0 years undergoing OTC as indicated by pediatric cancer diagnosis, 42% of the females were able to have ovarian cryopreservation performed concurrently with another procedure.<sup>20</sup> Not only did this study demonstrate the safety of coupling OTC with other surgical procedures if necessary, but it also articulated the safety of OTC treatment across a wide age range, with an emphasis on prepubertal years, with no adverse postoperative outcomes.

### ***The Benefits of Ovarian Tissue Cryopreservation***

To construct an understanding of the use of OTC as a fertility preservation method for women with Turner syndrome, there is value in recognizing that OTC is a well-established technique for female patients with cancer diagnoses. In the study by Babayev et al,<sup>20</sup> 75% of 28 prepubertal females were treated with OTC due to a diagnosed malignancy including a range of leukemias, sarcomas, and lymphomas. The remaining 25% of females were indicated for OTC due to severe combined immunodeficiency syndrome and even diploidy/triploidy (46XX/69XXY). This study not only elucidated the well-established safety and indication of performing OTC in prepubertal females with cancer, but also valued the role of OTC in young girls affected by chromosomal abnormalities. Remarkably, a 2017 meta-analysis by Pacheco and Oktay revealed that of 169 women with OTC treatment as indicated by a cancer diagnosis, 85.2% of women had restored endocrine function, 57.5% (69/120) attained clinical pregnancy, and 37.8% (65/172) gave birth to a live newborn.<sup>24</sup> In essence, this analysis concluded that 1 in 3 women receiving OTC as indicated by disease-induced ovarian insufficiency can become pregnant. Overall, OTC has become an accepted method of early intervention for primary ovarian insufficiency in the context of several health conditions.<sup>19</sup> Offering OTC to women with a genetic cause of ovarian insufficiency and infertility, such as Turner syndrome, is the logical next step.

Not only is OTC a well-established intervention in other disease profiles, but most notably, OTC is the only viable option for fertility preservation in young females with Turner syndrome because it does not rely on sexual maturation.<sup>8</sup> This unique quality of OTC, which ultimately allows women

to preserve their ovarian reserve at its possibly highest function, is a striking opportunity for women with Turner syndrome. A qualitative study was completed in 2022 that examined how parents and their daughters with Turner syndrome determined whether or not to pursue OTC.<sup>25</sup> A total of 90% of respondents felt that counseling regarding future parenthood contributed significantly to the existing care for the girls with Turner syndrome. Both parents and their daughters with Turner syndrome felt that the option to undergo OTC increased their hope regarding the possibility of future offspring and offered greater clarity regarding their ovarian reserve.<sup>25</sup> Their decision to undergo OTC was not impacted by the potential risk of surgical failure, as the likelihood of having genetic offspring without the procedure was already unlikely. Turner syndrome is a difficult disease because many girls become infertile at a young and unpredictable age, often before menarche.<sup>20</sup> As such, opting for OTC before the onset of puberty allows parents to receive information about their child's fertility status and subsequently make well-informed decisions about future fertility treatments. Given that women with Turner syndrome report infertility as the greatest burden of their disease,<sup>8</sup> the overall attitude surrounding OTC-interested families elucidates that this treatment offers a future and a great hope to those girls who want to secure their most optimal chance of maintaining fertility before it is too late.

Interestingly, a recent 2023 murine model study revealed that in animal models, there was evidence that OTC not only preserved ovarian tissue and function for future pregnancy, but also promoted folliculogenesis.<sup>26</sup> In this study by Peek et al,<sup>26</sup> ovarian tissue was retrieved via OTC from girls with Turner syndrome aged 5 to 19 years. After cryopreservation, the ovarian tissue was xenografted into immunodeficient mice for 5 months and the tissue was analyzed for follicle density and morphological changes. The experiment demonstrated that despite the presence of aneuploid granulosa and stromal cells, the xenografted tissue from patients with mosaic Turner syndrome underwent folliculogenesis. Furthermore, secretion of anti-Müllerian hormone, which was initially impaired in the patients with Turner syndrome, was restored in the ovarian tissue after xenografting.<sup>26</sup> This study established evidence of restored endocrine function in cryopreserved ovarian tissue and, most importantly, emphasized the need for prepubertal OTC intervention to restore and maximize folliculogenesis in women with mosaic Turner syndrome. These findings highlight OTC as a potentially instrumental method of preserving and promoting ovarian tissue function for successful future pregnancy in girls with Turner syndrome.

### ***The Limitations of Ovarian Tissue Cryopreservation***

Given the novelty and relatively recent application of OTC in patients with Turner syndrome, there exists a paucity of data regarding the success of pregnancies and births in OTC-treated females with Turner syndrome.

Most of the data on successful OTC-treated pregnancies and births have been derived from female patients with cancer.<sup>20</sup> The ovarian tissue of girls with cancer vs girls with Turner syndrome could be biologically and morphologically different, potentially resulting in varied OTC outcomes between the 2 disease profiles.<sup>4</sup> This discrepancy must be taken into careful consideration when predicting the outcomes of pregnancy and live births due to OTC treatment in women with Turner syndrome.

The evidence supporting OTC treatment for Turner syndrome fertility preservation is met with another shortcoming as described by a 2019 study conducted by Mamsen et al.<sup>21</sup> This study compared a group of 42 young women (aged 1-25 years) undergoing cancer-indicated OTC with a group of 15 girls, adolescents, and young women (aged 5-22 years) undergoing Turner syndrome–indicated OTC to analyze differences in follicle density and morphology. Following the fertility preservation procedure, the experiment identified that compared with the patients receiving cancer-indicated OTC, the women with Turner syndrome had a higher rate of abnormal follicular morphology and lower concentrations of estrogen and testosterone. Overall, follicles were found in only 60% (9/15) of the biopsies before OTC.<sup>21</sup> These findings together caused researchers to conclude that the benefits of OTC were limited to a select group of women with mosaic Turner syndrome that have a greater pool of normal follicles (compared with the average patient with Turner syndrome) before OTC treatment. Ultimately, the risks of OTC are a lack of substantial data to indicate OTC as an optimal Turner syndrome fertility treatment and an overall issue of low pregnancy success in women with Turner syndrome.<sup>4</sup>

Despite risks, OTC can function as a proliferative fertility preservation effort for Turner syndrome with the proper educational initiatives and counseling. Given the current novelty of the treatment, there exists a lack of counseling and educational efforts for young patients with Turner syndrome.<sup>25</sup> In addition to providing adequate counseling on the process and risks and benefits of OTC treatment, psychological therapy and advising are also instrumental for the prepubertal girls with Turner syndrome opting for this treatment. As demonstrated by the 2020 international consensus by Schleedoorn et al,<sup>19</sup> global physicians, surgeons, and experts were in support of OTC treatment, provided that the patients with Turner syndrome chosen were identified using strict selection criteria including optimal ovarian reserve and overall health status. Implementing these criteria alongside counseling efforts will offer support to females with TS seeking OTC treatment and lay the foundation for further OTC research and application in fertility preservation.

## Conclusions

OTC is a newer, less-established approach that avoids some of the downsides of oocyte cryopreservation because it can be performed in prepubertal females and does not require continuous rounds of hormonal stimulation. With ovarian tissue freezing, some or all of the ovary is removed and frozen until the patient is ready to have children. At that time, the ovary is transplanted back into the patient and ovary function is restored. This technique has been successful mainly in patients with cancer trying to preserve their fertility, but the success and adverse effects of this procedure in patients with Turner syndrome are not well-established because there is limited documentation on patients with Turner syndrome who have had OTC and undergone the autotransplant process. In the coming years, more research is required to determine how a patient with Turner syndrome responds to OTC. If success is noted, it will be necessary to establish clear guidelines for which patients with Turner syndrome are good candidates for the procedure due to the variable nature of this syndrome. These practices will provide much-needed insight into this potentially life-changing fertility treatment for patients with Turner syndrome.

Submitted: August 20, 2024 EST. Accepted: November 20, 2024 EST. Published: January 06, 2025 EST.

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