Fertility in Turner Syndrome

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Abstract
There is increasing interest in fertility and use of assisted reproductive technologies for women with Turner syndrome (TS). Current parenting options include adoption, surrogacy, and spontaneous and assisted reproduction. For women with TS, specific risks of pregnancy include higher than usual rates of spontaneous abortion, foetal anomaly, maternal morbidity and mortality. Heterologous fertility assistance using oocytes from related or unrelated donors is an established technique for women with TS. Homologous fertility preservation includes cryopreservation of the patient’s own gametes prior to the progressive ovarian atresia known to occur: preserving either mature oocytes or ovarian tissue containing primordial follicles. Mature oocyte cryopreservation requires ovarian stimulation and can be performed only in post-pubertal individuals, when few women with TS have viable oocytes. Ovarian tissue cryopreservation, however, can be performed in younger girls prior to ovarian atresia – over 30 pregnancies have resulted using this technique, however none in women with TS. We recommend consideration of homologous fertility preservation techniques in children only within specialised centres, with informed consent using protocols approved by a research or clinical ethics board. It is essential that further research is performed in order to improve maternal and foetal outcomes for women with TS.

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Introduction

Advances in reproductive medicine increasingly offer the possibility of childbearing to women who have declining ovarian function. These new techniques are being considered for young women who have Turner syndrome (TS), in whom accelerated oocyte atresia usually leads to ovarian failure before childbearing age. While patients’ expectations rise with technical advances, there are associated issues regarding safety, and ethical use in a younger TS population. In adult women with TS, pregnancy is associated with increased risk of maternal mortality, foetal loss, foetal congenital abnormality and abnormal karyotype (1-3). Success rates are low for many invasive reproductive techniques, and newer technologies such as ovarian cryopreservation are presently considered experimental.

Specialists involved in the care of individuals with TS face a range of important considerations. Adult reproductive endocrinologists involved in fertility assistance, have relatively recently begun to appreciate the mortality risk to the TS mother that pregnancy may entail (2, 4). Assisted reproduction techniques possible in children prior to the decline of ovarian reserve, such as ovarian tissue cryopreservation, require paediatric surgery. Ethical challenges relating to consent and beneficence thus arise for the paediatric endocrinologist and gynaecologist. During any pregnancy that eventuates, obstetricians and cardiologists must be prepared for life-threatening complications.

These concerns must be balanced against the fact that TS women report infertility to be one of the greatest challenges they face (5). Young women and their parents are often intensely interested in future fertility options. While women with TS enjoy a good quality of life, infertility is significantly associated with poor self esteem and psychosocial adjustment, and demands discussion with empathy and sensitivity (6). A review of 276 women with TS in the US found that 9.1% chose to adopt children and 3.2% had spontaneous or assisted pregnancies, however 87.7% of this cohort had no children (7).
This clinical practice update will discuss fertility in TS, pregnancy risks, the reproductive technologies in current use, and associated ethical issues. It will not cover parenting choices such as adoption and surrogacy, but recommends that these need to be considered in view of the pregnancy risks and fertility outcomes in TS [Table 1].

**Fertility in Turner syndrome**

Turner syndrome (TS) affects 1 in 2000 liveborn females, and is associated with partial or complete loss of one X chromosome in a 46,XX fetus or of loss of a Y chromosome in a 46,XY fetus, resulting in monosomy of the X chromosome (8-10). It is characterized by ovarian failure, which occurs prior to puberty in most cases. Approximately 30% of women with TS have a mosaic peripheral blood karyotype, where 45,X is present only in some cells (11). Women with 45,X mosaicism have a 45,X cell line which co-exists with at least one non-45,X cell line, e.g. 45,X/46,XX, 45,X/47,XXX, 45,X/46,XX/47,XXX, 45,X/46,X,i(Xq), 45,X/46,XY. Mosaicism is thought to account for much of the variability in phenotype, including the degree of ovarian dysfunction (12). Rigorous analysis for mosaicism can be performed with karyotype of an adequate number of peripheral blood leucocytes (eg. 100 cells), analysis of cells from more than one tissue type, or via fluorescence in situ hybridization (FISH) with X and Y probes (11, 13).

Women with TS and a mosaic karyotype containing a Y chromosome, e.g. 45,X/46,XY, usually have complete gonadal dysgenesis and streak gonads. In these gonads, which are unlikely to have potential for fertility or significant hormone production, the risk of germ cell malignancy is 10-15% due to presence of Y chromosomal material (14, 15). Risk-reducing gonadectomy should be considered in this group after diagnosis (14).

Spontaneous puberty occurs in 15-30% of girls with TS, and 2-5% experience menarche (16). Approximately 2-5% of women with TS are able to conceive (7, 17). It has therefore been recommended that counselling for young TS women who undergo spontaneous pubertal development should include
potential for spontaneous unintended pregnancy, contraception, and education regarding complications in pregnancy (7).

Current evidence suggests that 45,X germ cells are unable to complete meiosis and are eliminated during germ cell development (18, 19). When ovarian follicles are observed, they originate from small numbers of 46,XX germ cells and not from 45,X cells (18, 20). The likelihood of functional ovarian tissue in women with TS therefore relies on the presence of 46,XX germ cells in the ovaries. As expected, fertility is more likely to be retained in women with 45,X/46,XX mosaicism rather than complete monosomy 45,X (7, 17, 21). Even in the presence of initially functioning ovarian tissue, development of premature ovarian failure remains common, and the risk of chromosomal abnormality in the offspring of women with mosaic TS appears to be increased compared to the general population (22, 23).

It is worth noting that a completely non-mosaic 45,X karyotype in peripheral blood leucocytes does not preclude the co-existence of 45,X/46,XX mosaicism in the ovary. A significant proportion of 45,X conceptions are thought to result from post-zygotic loss of the second sex chromosome, implying that mosaicism is frequently present, even when not detectable in blood (12). Such phenomena may explain a report describing multiple spontaneous pregnancies in two women with 45,X TS (24). In one of the women, both karyotype and FISH analysis confirmed classical monosomy X in peripheral blood. The other woman had monosomy 45,X in 199 of 200 metaphases, with 47,XXX found in one.

Approximately 40% of women with TS have a structural abnormality of the second X chromosome, resulting in partial X monosomy (11), such as deletion Xp, ring X, and isochromosome Xq. For these categories, mosaicism with 45,X or 46,XX cell lines is common. Some structural abnormalities of the X chromosome, for example, loss of the distal part of Xp, are compatible with spontaneous menarche and fertility, and there are examples of mother-daughter transmission (25). Risk to offspring is increased:
male embryos that inherit the structurally abnormal X will usually be non-viable, and female offspring are at risk of a more severe phenotype if X-inactivation does not favour the intact X.

Risks for the foetus

Regardless of whether conception in women with TS is spontaneous or assisted, increased rates of spontaneous abortion and foetal abnormality have been described. In a review of 160 pregnancies in 74 women with TS, 29% resulted in miscarriage, 20% were associated with foetal anomalies such as TS and Down syndrome, and 7% resulted in perinatal foetal death (3). In a Danish study, 6 (24%) of 25 offspring of TS women had an abnormal karyotype (19).

Spontaneous abortion may be due to abnormalities in foetal chromosomes or to an abnormal uterine environment. 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 hypo-oestrogenism, which should be avoided (26-28). In 86 women with TS, 31% were found to have an immature uterus and 20% had not taken regular oestrogen. 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 (28).

Approximately 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 (3, 29, 30).

Anomalies of the X chromosome can be inherited. Women who have X monosomy or structural anomalies of the X chromosome may produce oocytes with the sex chromosome anomaly, resulting in an affected zygote and ensuing spontaneous abortion or offspring with TS.

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In view of the risk for foetal anomalies, antenatal diagnostic testing should be offered to all pregnant TS women and the pregnancies should be regarded as high risk.

**Risks for the mother**

Pregnant women with TS require tertiary medical and obstetric care due to increased risk for pregnancy-related complications. These include thyroid dysfunction, obesity, diabetes, hypertension and pre-eclampsia, which occur in approximately 40% of patients with TS compared to 6-12% of the general population (2, 29-31). Severe complications such as deterioration of congenital heart disease, heart failure, aortic dissection and sudden death are well described. (32-34). Importantly, women with TS are at increased risk of development of aortic cystic medial necrosis independent of congenital heart disease; 10% of patients with aortic dilatation, dissection, or rupture have no prior cardiac risk factors (35, 36). Women with TS are at significant risk for aortopathy and also for short stature – it is thus important to assess aortic size corrected for body surface area (aortic size index), although dissection can still occur at smaller aortic sizes in the absence of valve and arch abnormalities (36, 37).

In an unbiased study of 115 women from a national TS cytogenetic registry in Sweden, the risk of aortic dissection was found to be 1%, and in a review of 101 TS pregnancies from oocyte donation programs in the United States, the risk of maternal death due to aortic dissection was estimated to be at least 2% (4, 38). The risk of aortic dissection is associated with factors such as congenital cardiovascular malformation (particularly bicuspid aortic valve, coarctation of the aorta and aortic root dilatation), history of foetal lymphoedema, hypertension, obesity and multiple pregnancy (39, 40). Multiple embryo transfer is strongly contraindicated in women with TS (30, 41). A review of pregnancies in 93 women demonstrated inadequacies of care, with only 37.6% pre-screened with echocardiography or MRI: 37.8% experienced hypertensive illness and 2 died from aortic rupture (2). Prematurity occurred in 38.3%, more commonly in those who were hypertensive; inta-uterine growth restriction occurred in 27.5%, and there was one foetal demise associated with pre-eclampsia. Only 40% had an entirely normal pregnancy.

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Women with known cardiovascular malformations should therefore consider avoiding pregnancy entirely; cardiac exclusion criteria for pregnancy have been suggested by consensus in French and US groups (1, 32, 40, 42) [Table 2]. Termination of pregnancies due to factors associated with maternal TS risk has been reported (17).

Involvement of a cardiologist for pre-pregnancy risk assessment and frequent review during pregnancy is recognized as essential. Initial evaluation should include echocardiogram and MRI of cardiac anatomy and aortic dimensions, although it is unclear whether this screening will eliminate any risk. Some TS women who had aortic dissection showed a preceding increase in ascending aortic diameter and had a high aortic size index (normalized diameter to surface area) (36). However the presence of normal aortic dimensions does not exclude the risk of sudden aortic dissection (37).

While vaginal delivery may be possible, elective or emergency caesarean section may be required to minimize cardiac risk, to manage foeto-pelvic disproportion due to maternal short stature and narrow pelvis, or to expedite delivery in management of preeclampsia (7, 30, 43).

**Assisted reproduction**

Assisted reproduction techniques have offered women with TS the opportunity for childbearing, with varying rates of complications and success [Table 3, and reviewed in (44)]. In a Swedish cohort of 482 women with TS, 12% achieved pregnancy, of which 40% were spontaneous, 60% with assisted reproduction and of these 53% used oocyte donation (17). In 276 women in the US, 1.4% achieved pregnancy with assisted reproduction, all with oocyte donation (7).

**Heterologous in vitro fertilization (oocyte donation)**

Oocyte donation from either related or non-related women was until recently the only reproductive option for women with TS who experience ovarian failure, with this technique showing some success. While
initial pregnancy rates (determined by human chorionic gonadotropin level) may be comparable to the rest of the population utilizing in vitro fertilization (IVF) technologies, successful clinical pregnancy rates (visualization of a gestation sac) are lower than for women who undergo oocyte donation for other reasons: 17-40% versus 73% (27, 29-31, 45, 46). 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 (30). In a Swedish cohort of 30 women following oocyte donation, 26% of clinical pregnancies ended in miscarriage, much lower than the miscarriage rate of 45% using the patient’s own gametes (17). Donated oocytes can also be cryopreserved for future use using the methods which will be described for homologous IVF.

Heterologous ovarian tissue transplantation is a method which has not yet been reported in women with TS, however has shown success in providing fertility to approximately 30 women worldwide (44).

*Homologous in vitro fertilization (patient’s own gametes)*

Patients with TS are often counselled against homologous IVF due to poor success rates and risk of chromosomal aberrations in the offspring (3). Most adult women with TS already have established ovarian failure with a high serum follicle stimulating hormone (FSH) level at the time they wish to start a family, although this does not indicate absolute absence of viable follicles (47).

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. While immediate IVF and embryo transfer has been used successfully in TS, harvesting of oocytes or ovarian tissue for storage in girls and women with TS remains experimental, despite an increasing body of literature (17, 48).
Fertility preservation

Oocyte preservation

Oocyte preservation involves a process of mature oocyte collection, incubation in cryoprotectant and vitrification - a rapid freezing technique to minimize ice formation. The ovulated oocyte is large and somewhat vulnerable to damage during cryopreservation and thawing, however this procedure is now offered in many fertility clinics for adult cancer patients. 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 (49, 50). Oocyte preservation requires ovarian stimulation and ultrasound monitoring for 2 weeks beforehand to increase yield, with oocyte retrieval performed transvaginally under ultrasound guidance (51). Some degree of psychological and physical maturity is therefore required, with retrieval performed under general anaesthetic in the youngest reported patient, at age 14 years (51). This technique also offers the possibility of preserving oocytes with a view to surrogacy, if pregnancy is avoided due to associated risks.

Cryopreservation of mature oocytes with the aid of ovarian stimulation has previously seldom been considered a viable option in TS, as women requesting assisted fertility often have ovarian failure by the time of consultation. In adolescents with TS ovarian function may still be present, however the majority of ovarian follicles found are immature primordial follicles, which require stimulated maturation prior to collection for storage.

There have been isolated case reports of mature oocyte preservation after gonadotropin stimulation in adolescents and young women with mosaic TS and positive indicators of ovarian reserve (18, 52, 53). Pregnancies have not been reported in this population.

Ovarian tissue cryopreservation

There have been recent proposals that cryopreservation of ovarian cortical tissue could be offered to younger girls with TS, in order to preserve any viable primordial follicles for possible use in future

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fertility treatment (47, 53). Of note in the wider population, ovarian tissue cryopreservation has a poorer success rate than oocyte preservation, due to difficulties associated with in vitro maturation of primordial follicles for oocyte retrieval (54). However, whole ovarian tissue transplantation has been shown to be robust, with a high success rate (44). Various methods have been described for tissue cryopreservation, including laparoscopic collection of ovarian cortical tissue containing immature oocytes and immediate vitrification, followed by thawing at the required time for fertilization, and autotransplantation of the ovarian tissue with in situ oocyte maturation (55, 56). The tissue may be transplanted onto an orthoptic site (the ovarian fossa or pre-existing ovary) or onto a heterotopic site (such as abdominal wall). The aim of reimplantation onto an orthoptic site is reactivation of ovarian maturation and function within the graft followed by spontaneous conception (44, 57). With heterotopic grafts, pregnancies may be achieved through hormonal stimulation, follicle aspiration and IVF (58). High rates of oocyte loss associated with freezing, thawing, maturation and graft ischemia have been minimised with vitrification of ovarian tissue and microsurgery (59, 60). Another technique described employs in-vitro maturation of oocytes prior to freezing (61).

Precedent for use of this method in children has been established, with cryopreservation offered for a separate group of girls - those with cancer about to undergo gonadotoxic treatment (62). However, even in this group the procedure is recommended only in specialised centres, using institutionally approved protocols and stringent consent. At the time of writing, over 30 live births have been reported using cryopreservation of ovarian tissue in adult women, none from tissue taken from adolescents or younger girls, and none from 45,X individuals (63, 64). Orthoptic transplantation appears to have higher success contributing to the live births reported, and there is a question whether some of these livebirths have arisen from unresected ovarian tissue which remained in situ, rather than the autotransplanted cryopreserved tissue (65, 66). Spontaneous pregnancy has been observed after heterotopic transplantation of ovarian tissue in the subcutaneous anterior abdominal wall, suggesting that autotransplantation of cryopreserved ovarian tissue may restore function in residual, normally placed ovarian tissue (44, 67-69).

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Given the existence of the technical ability to perform cryopreservation but the lack of successful pregnancy outcomes for women with TS, the clinical question that arises is when, and from whom, should ovarian tissue be surgically removed for freezing and long-term tissue storage? Critical aims would be to ensure that children without follicles are not unnecessarily exposed to surgery, that any window of opportunity for oocyte preservation prior to complete follicle loss is utilized, and that the amount of damage to the ovary is minimized during the harvest, in particular minimizing the risk of converting a functioning to a non-functioning ovary.

A large longitudinal study of 104 girls with TS using serial ultrasound found that in the minority of those with visible, non-streak ovaries, there was apparent ovarian growth and follicular development from birth until puberty (70). This occurred in small dysgenetic ovaries as well as in ovaries of normal appearance. The authors suggested that the greatest period of follicle loss in females both with and without TS may be during the foetal and neonatal period, but that those with TS start with a reduced number (71).

A report of ovarian tissue sampling and storage in 57 girls with TS in Sweden has provided some data to aid identification of candidates for cryopreservation (47). Seven individuals had mosaic TS with complete X chromosomes (45,X/46,XX or 45,X/47,XXX) and 22 had structural anomalies including isochromosomes and ring chromosomes, with karyotypes including Y chromosome segments included in the structural anomaly group. Factors predictive of presence of healthy follicles included mosaic peripheral blood karyotype, normal range serum FSH, and normal range serum anti-Mullerian hormone (AMH, expressed in growing follicles), together with a history of spontaneous pubertal development. Negative predictive factors included monosomy or structurally anomalous karyotype, high serum FSH, low serum AMH, and no evidence of spontaneous puberty. There was no difference between groups aged above and below 12 years regarding number of follicles. The authors suggested that girls with TS should be counselled about fertility options at age 13 or 14, and that the discussion should include cryopreservation of ovarian tissue in those with mosaic karyotype and spontaneous puberty in the absence
of any elevation in FSH or reduction in AMH. It was noted, however, that if laparoscopic harvest of ovarian tissue was performed in this entire group of children, not all specimens would contain follicles [Table 4] (72).

These proposed indicators of the presence of follicles were the basis of an analysis in a series of 28 TS girls, of whom 4 (14%) were identified as candidates for fertility preservation (53). Of note in this Canadian study, serum FSH concentration increased with age, and girls with levels below 40 IU/L were younger than those with levels above 40 IU/L (11.5 ± 2.4 years versus 14.3 ± 2.0 years, respectively). In those with a mosaic karyotype, elevation of serum FSH > 40 IU/L occurred at approximate age 16 years. Serum inhibin A has also been proposed as an indicator of ovarian reserve in girls with TS (73, 74).

Although these authors suggest using selection criteria of mosaic karyotype, normal range serum FSH and AMH to reduce the chance of any girls who may have had follicles to harvest being missed, there are case reports of women with TS who have conceived despite failing to fulfil these criteria (47). Recent work in the general population has demonstrated that although AMH may be indicative of quantitative ovarian reserve, it does not predict the chance of a live birth, as similar live birth rates per mature follicle produced occur irrespective of AMH quartile (75).

Further research is required in order to ascertain if harvesting ovarian tissue prior to puberty would increase the chance of preserving viable oocytes. Currently no evidence exists for this proposal, although a benefit cannot be excluded. Of note, it is also theoretically possible that ovarian harvest for cryopreservation may actually decrease the chance of a pregnancy occurring, e.g. if nests of 46,XX cells are removed and subsequently lost in the process of cryopreservation and autografting.

The chromosome complement of retrieved oocytes may be affected in a similar way to spontaneous TS pregnancies, carrying the same risk for chromosomal problems in the offspring, thus genetic counselling and pre-implantation/prenatal diagnosis are warranted.
Embryo cryopreservation

Cryopreservation of embryos has not been thought suitable in children and young women as it requires sperm for fertilization. It is an established form of fertility preservation in the general population. The majority of good quality embryos survive cryopreservation and thawing, and perinatal outcomes are normal (76). This technique requires retrieval of mature oocytes through superovulation, and immediate fertilization.

Ethical considerations

The primary ethical question raised by these techniques is whether to offer intervention for fertility preservation during childhood/adolescence, and if so, which intervention, and at what stage.

Homologous IVF techniques such as ovarian tissue cryopreservation and oocyte preservation may improve the psychosocial well-being of women with TS, by increasing the chance of having a child with their own genetic complement. Offering these interventions in adolescence promotes autonomy by increasing the range of future options (56, 77). Considerations against, include concern that techniques associated with low success rates may produce false hope and later psychosocial harm; concern that risks associated with invasive retrieval of tissue are not outweighed by benefits that can reasonably be expected; concern that the offer of intervention may not actually promote autonomy, where the child with TS is not competent to make her own decision and her future choices are not represented by her parents; and concern that the young person may not comprehend maternal and foetal risks associated with any pregnancy which may ensue. In the case of ovarian tissue cryopreservation, there is a further risk of reduction in fertility by removing potentially viable tissue. Physicians must first do no harm.

If assisted reproduction is offered to young patients who have TS, consideration is required to whether this should be offered to all, or only to those where the probability of success lies above a minimum level. If there is virtually no chance of viable ovarian tissue existing based on clinical and biochemical grounds,
then it would be unethical to offer intervention to preserve this tissue, which would be futile and could cause harm.

There are potential legal issues for parents and clinicians regarding the decision to remove and preserve gonadal tissue (with the inherent surgical risk and potential risk of reduction in viable gonadal tissue), on behalf of a child who is unable to consent, rendering a parent or clinician negligent. Reasons for each decision should be articulated and documented. Where tissue is removed from a minor with parental consent, the legalities of who ‘owns’ the tissue need to be clarified.

**Conclusion**

The availability of reproductive technologies promises potential for fertility preservation in young women with TS, however we await reports addressing whether preserved gametes can lead to the much wanted safe and successful pregnancies. In the interim, some of these technologies raise new dilemmas for paediatric clinicians. In the majority of girls with TS, there is a narrow window of opportunity to discuss interventions such as cryopreservation of ovarian tissue or oocytes. Families may view this with a degree of urgency. However, ovarian tissue cryopreservation itself remains experimental, no pregnancies have been reported in women with TS, and the risks of pregnancy to the TS mother are great.

While the medical community has made significant gains in reproductive technology, it is clear that greater effort is required to assist counselling of both young women with TS and their families regarding future fertility options. Focus should be on improved coordination between health disciplines, efforts to keep abreast of current reproductive technologies, transparent communication regarding expectations and potential risks of pregnancy, and stringent transition of care to practitioners familiar with the risks involved.

Until evidence of any benefit from earlier intervention exists, we agree with the recommendation that invasive techniques be considered at the age where a child with TS has some understanding of the underlying indication (47). At this stage, invasive fertility preservation treatment should be considered.
only in specialised centres with approved institutional protocols. This could occur via the institutional clinical research or clinical ethics boards, in order to enable a thorough review of the risks and expected outcomes in each case.

We look forward to further research into outcomes of assisted reproduction in women with TS, particularly for autologous cryopreserved gametes. Of equal importance, we call for further evaluation of the cardiac risks of pregnancy in women with TS, stringent auditing and publication of all pregnancy outcomes, and strategies to address associated morbidity and mortality. Physicians may then be better placed to provide assistance to achieve the much-wanted pregnancies without causing harm.

TABLE 1. Parenting options for women with Turner Syndrome.

<table>
<thead>
<tr>
<th>Parenting Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adoption</td>
<td>Parenting of a child who cannot be cared for by their biological parents.</td>
</tr>
<tr>
<td>Surrogacy</td>
<td>Planned pregnancy which is carried by another female on behalf of the woman with TS. Gametes used can be donated or the patient’s own.</td>
</tr>
<tr>
<td>Heterologous IVF</td>
<td>Use of donated gametes to create an embryo for implantation in a pregnancy carried by the woman with TS.</td>
</tr>
<tr>
<td>Homologous IVF</td>
<td>Use of the patient’s own gametes to create an embryo for implantation in a pregnancy carried by the woman with TS.</td>
</tr>
</tbody>
</table>

TABLE 2. Recommended contraindications to pregnancy in women with Turner Syndrome.

- History of aortic surgery or aortic dissection
- Coarctation of the aorta
- Aortic size index >2.5 cm/m² or maximal aortic diameter 3.5cm
- Uncontrolled hypertension despite treatment
- Portal hypertension with oesophageal varicose veins
- Other major cardiac anomaly
<table>
<thead>
<tr>
<th>Technique</th>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterologous IVF</td>
<td>Ovum donation and IVF-embryo transfer</td>
<td>Receipt of oocytes from a healthy donor, followed by IVF and fresh or frozen-thawed embryo transfer.</td>
<td>Rate of pregnancy loss and karyotypic abnormalities in offspring reduced. No need for invasive procedures in the child.</td>
<td>The TS mother is not the biological mother. Established in adult women with TS. Pregnancy rate 17-40% per embryo transfer.</td>
</tr>
<tr>
<td></td>
<td>Ooocyte donation and cryopreservation</td>
<td>If ovum donation from a relative is performed for a child, the oocytes are cryopreserved until the appropriate time for IVF and embryo transfer.</td>
<td>As above. Maintenance of familial genetic lineage.</td>
<td>Donor must have good ovarian function. Parentage confusion in resultant offspring. Risk of donor coercion.</td>
</tr>
<tr>
<td>Homologous IVF</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>IVF and embryo transfer</td>
<td>Ovarian stimulation, collection of oocytes, then IVF and embryo transfer (fresh or frozen thawed embryos).</td>
<td>Requires maturation of ovarian follicles. Requires sperm from partner or donor. Not appropriate in children.</td>
<td>An established IVF procedure for the general adult population. Most healthy embryos survive the process. A small number of pregnancies have been reported in women with TS.</td>
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<tr>
<td>Oocyte cryopreservation</td>
<td>Ovarian stimulation, collection of mature oocytes transvaginally and vitrification or slow freezing of oocytes.</td>
<td>Does not require sperm. Does not require surgery. Requires maturation of ovarian follicles. Requires some physical and psychological maturity. May require a general anaesthetic for oocyte retrieval in adolescents. Not appropriate in prepubertal children.</td>
<td>Over 1000 births have been reported in the general adult population Case reports exist of oocyte collection in young adolescents and women with TS, no pregnancies reported.</td>
<td></td>
</tr>
</tbody>
</table>
Ovarian tissue cryopreservation involves laparoscopic collection of ovarian tissue containing immature ovarian follicles, which is then cryopreserved. Some reports of in vitro maturation of follicles prior to vitrification.

Ovarian stimulation is not required preoperatively. No lower age limit.


Approximately twenty reported births in adult women. Experimental, but established precedent in children undergoing cancer treatment. No pregnancies in TS.

TABLE 4. Recommended criteria for consideration of ovarian cryopreservation in children and adolescents with Turner Syndrome

- Age 14 years and above
- Spontaneous pubertal commencement
- FSH <40 IU/L
- AMH measurable
- Normal cardiac status
- Informed consent obtained from child and family: including counselling regarding mortality risk, foetal risk, and absence of current success using this technology
- Institutional clinical or research ethics approval, including criteria for follow-up

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