Fertility and Pregnancy in Turner Syndrome

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Abstract

Turner syndrome (TS) occurs in one in 2500 live female births and is one of the most common chromosomal abnormalities in women. Pregnancies in women with TS, conceived with either autologous or donated oocytes, are considered high risk because of the associated miscarriages and life-threatening cardiovascular complications (aortic dissection, severe hypertension). Therefore, it is imperative to conduct a full preconception evaluation and counselling that includes cardiac assessment with Holter blood pressure monitoring, echocardiography, and thoracic MRI. Abnormal findings, such an aortic dilatation, mandate close monitoring throughout the pregnancy and the immediate postpartum period and could possibly contraindicate pregnancy. When in vitro fertilization using donated oocytes is performed in these women, only a single embryo should be transferred. Women with a Turner mosaic karyotype appear to have a lower risk of obstetrical and cardiovascular complications but should nevertheless undergo the full preconception evaluation. In this article, we offer guidelines on the management of women with TS in the preconception period, during pregnancy, and postpartum.

Résumé

Le syndrome de Turner (ST), dont la fréquence est d'une naissance féminine vivante sur 2 500, constitue l'une des anomalies chromosomiques les plus répandues chez la femme. La grossesse conçue par ovocyte autologue ou donné est considérée comme présentant un risque élevé pour les femmes atteintes du ST, en raison des fausses couches et des complications cardiovasculaires menaçant le pronostic vital (dissection aortique, hypertension grave) qui sont associées à cette pathologie. Par conséquent, il est impératif d'accomplir une évaluation préconception complète et de procéder à des consultations prévoyant une évaluation cardiologique par surveillance Holter, par échocardiographie et par IRM du thorax. Des résultats anormaux, dont la dilatation aortique, exigent une surveillance étroite tout au long de la grossesse et de la période postpartum immédiate. Ils pourraient également constituer une contre-indication de grossesse. Lorsqu'on réalise une fécondation in vitro d'ovocytes donnés chez ces femmes, un seul embryon devrait être transféré. Bien que le risque de complications obstétricales et cardiovasculaires semble être plus faible chez les femmes présentant un caryotype du syndrome de Turner en mosaïque, celles-ci devraient néanmoins faire l'objet d'une évaluation exhaustive avant de concevoir. Dans le présent article, nous proposons des lignes directrices quant à la prise en charge des femmes atteintes du ST durant la période préconceptionnelle, la grossesse et la période postpartum.

Key Words: Turner syndrome, pregnancy, aortic dissection, oocyte donation
Mots-clés: Syndrome de Turner, grossesse, aortic dissection, don d'ovocyte

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INTRODUCTION

Turner syndrome occurs in one in 2500 live female births and is one of the most common chromosomal abnormalities in women.[1] It is characterized by ovarian dysgenesis and a varying number of extragonadal abnormalities.[2] The syndrome is caused by partial or complete loss of one of the X chromosomes, leading to a haploinsufficiency of genes implicated in the development and maintenance of ovarian reserve. The result is accelerated follicular atresia, primary amenorrhea, absence of pubertal changes, and infertility. In some cases, puberty occurs and women experience menstrual cycles, but they ultimately develop premature ovarian failure, leaving them with a limited time period during which they can become pregnant.[3]

The development of assisted reproduction technologies, especially oocyte vitrification, has allowed many women with TS to achieve pregnancy, either by oocyte donation or by fertility preservation at a young age. However, these pregnancies are accompanied by increased maternal mortality and morbidity from aortic dissection, hypertensive disorders, and other medical conditions,[2–4] and these women should be counselled and closely monitored from preconception to postpartum.

In 2010, a group of French experts published recommendations on the management of women with TS before and during pregnancy, based on a review of the literature available at the time.[4] The access of women with TS to ART has dramatically increased since then, and recent data have emerged on pregnancy outcomes in these patients. Two large studies assessing maternal-fetal complications in women with TS after oocyte donation have recently been published.[5,6] The first, a French multicentre study including all ART centres affiliated with the French Study Group for Oocyte Donation, reviewed maternal-fetal outcomes in 93 women,[5] and the second, a Nordic cohort study published in 2013, reviewed outcomes in 106 women with TS who delivered after oocyte donation between 1992 and 2011.[6]

The purpose of this review was to include data from these recent publications and to update the guidelines offered to clinicians involved in the management of women with TS in the preconception period, during pregnancy, and postpartum.

METHODS

We performed a literature search using PubMed, Medline, and Embase to identify relevant articles published between 1950 and 2015. Our search was limited to articles in English and French, and we included abstracts only when enough data were available. Further relevant articles were searched by examination of the reference lists of all included studies, reviews, and other previously identified articles.

The search was conducted using the MeSH terms "Turner syndrome," "pregnancy," "delivery," "aortic dissection," "fertility preservation," and "oocyte donation."

We included any type of study that reported original data regarding maternal or neonatal outcomes or any type of recommendations about fertility and pregnancy in women with TS.

ABBREVIATIONS

ART	assisted reproduction technologies
FP	fertility preservation
IVF-DO	in vitro fertilization cycles with donor oocytes
OTC	ovarian tissue cryopreservation
POF	premature ovarian failure
TS	Turner syndrome

Preconception Care

When treating women with TS, clinicians are faced with challenges in multiple areas; these include genetic, endocrine, cardiovascular, developmental, psychological, and reproductive concerns. Therefore, a multidisciplinary approach from the early years of childhood is essential for optimal care. Indeed, hormone therapy should begin at an early age to compensate for the associated hypogonadism, allowing for induction of puberty, promotion of secondary sex characteristics, development of the uterus, and prevention of bone demineralization and subsequent osteoporosis.

Women with TS who are considering pregnancy should be referred to a reproductive endocrinologist for counselling on the available options. In vitro fertilization with donor oocytes can be offered in cases with confirmed POF; pregnancy rates are comparable to the rates achieved in women who undergo IVF-DO cycles for other indications. Moreover, when women with a late diagnosis of TS are seen because of infertility and are scheduled for IVF with autologous or donated oocytes, their evaluation should include a thorough examination of the uterus because the lack of hormone therapy might lead to inadequate development of the uterine cavity. In such cases, estrogen-based hormone therapy is indicated for several months, even years, to allow for optimal growth of the myometrium, endometrium, and uterine vessels.[7,8]

Many reports have shown that pregnancies achieved via IVF-DO are accompanied by a high rate of maternal mortality and morbidity, mainly because of cardiovascular complications.[9–15] The TS-associated cardiovascular disorders that can complicate pregnancy include congenital heart disease, systemic hypertension, aortic dissection, and myocardial ischemia. Indeed, it has been reported that 23% to 50% of women with TS have congenital heart disease, the most frequent types being bicuspid aortic valve, coarctation of the aorta, and aortic dilatation.[16] The risk of aortic dissection is significantly increased during pregnancy, first because of the estrogen-mediated increase in cardiac output and second because of the gestational hypertension and preeclampsia usually associated with pregnancies achieved with oocyte donation.[5,6] Chevalier et al. reported two cases of fatal aortic dissections among 93 pregnancies following IVF-DO in women with TS.[5] Moreover, according to recent cohort studies, the risk of preeclampsia in women with TS is approximately 21%[5,6] and is mainly

increased in patients with renal disorders, such as renal malposition, horseshoe kidney, ureteral duplication, and hydronephrosis, which are observed in 25% to 43% of patients.[17] On the other hand, even though women with TS have a higher risk of metabolic disorders than the general population, their risk of gestational diabetes does not seem to be increased compared with other IVF-DO pregnancies[7] and is estimated to be approximately 4% to 9%.[5,6] Finally, cholestasis of pregnancy complicates 1% to 7% of pregnancies in women with TS.[5,6]

Physicians counselling and monitoring women with TS should be aware of all pregnancy-associated complications and the possible increased risk of fetal chromosomal abnormalities (Table 1) and should follow proper guidelines for preconception, antenatal, and postpartum care.

The preconception evaluation (Table 2) includes renal, liver, and thyroid function testing (the last of these to rule out hypothyroidism, which is found in 22% of adult women with TS[6]); evaluation of glucose tolerance; and measurement of 25-hydroxyvitamin D levels. An abdominopelvic ultrasound is required to rule out renal malformations and hepatic disorders (in cases of abnormal liver function testing), and recent bone mineral densitometry results (within 3 to 5 years) should be available. A cardiology consultation, with echocardiography and cardiac MRI, and a maternal-fetal medicine consultation are also required before pregnancy.

Patients should be counselled that 40% of pregnancies following IVF-DO in TS women are completed without complication.[5]

Table 1. Risk during pregnancy in women with TS

Fetal risks	Maternal risks
Miscarriage: 29%[3] Perinatal fetal death: 2%[6] Small for gestational age (≤10th percentile): 18% to 28%[5,6] Prematurity (<37 weeks): 12%[6] Genetic risks in pregnancies with autologous oocytes: X chromosome anomalies (X monosomy, structural anomalies)	Thyroid dysfunction: 22%[6] Gestational diabetes: 4% to 9%[5,6] Gestational hypertension: 15% to 17%[5,6] Preeclampsia: 21%[5,6] Caesarean section: 82%[5,6] Worsening of congenital heart disease: 1%[6] Heart failure: 1%[5] Aortic dissection: 1% to 2%[5,6] Maternal death: 2%[5] (most due to aortic dissection or rupture or risk increased with bicuspid aortic valve, coarctation of the aorta, aortic root dilatation, hypertension, obesity, and multiple pregnancies)

Table 2. Preconception evaluation in women with TS

Clinical and laboratory testing	Imaging
• Body mass index • Screening for hypertension and treatment if indicated • Pap testing • Thyroid function tests (serum TSH, T_4), antithyroid antibodies • Fasting blood sugar, HbA1c, 75 g oral glucose tolerance test • Assay of 25-hydroxyvitamin D blood level • Liver function tests (ALT, AST, γGT, alkaline phosphatase) • Renal function tests (plasma creatinine, urinary protein/creatinine ratio) • Echocardiography, consultation with a congenital heart disease specialist • Maternal-fetal medicine consultation • Nutrition counselling • Measurement of transglutaminase antibodies (2 to 5 years)	• Renal ultrasound • Hepatic ultrasound (if liver function tests are abnormal) • Pelvic ultrasound • Echocardiogram and cardiac MRI (calculation of aortic size index) • Bone mineral densitometry (3 to 5 years)

TSH: thyroid stimulating hormone; HbA1c, glycated hemoglobin; ALT: alanine transaminase; AST: aspartate transaminase; γGT: glutamyl transferase.

However, despite the available guidelines, many women with TS are not adequately counselled preconceptionally. Indeed, a survey in the United States, published in 2003, found that 50% of women with TS who became pregnant following IVF-DO did not have an adequate preconception cardiovascular assessment.[18]

In 2010, the Collège National des Gynécologues et Obstétriciens Français published the first national guidelines for the management of women with TS before and during pregnancy.[4] According to these guidelines, pregnancy is formally contraindicated in patients with a history of aortic surgery or dissection, when the diameter of the ascending aorta indexed for body surface area (aortic size index) exceeds 2.5 cm/m^2 and in cases of coarctation of the aorta or resistant hypertension (Table 3). An isolated bicuspid aortic valve is not a contraindication for pregnancy but is considered a risk factor.[4,19]

The American Society for Reproductive Medicine issued its guidelines in 2012.[19] It considers TS to be a relative contraindication to pregnancy and encourages women with TS to seek alternative ways to start a family, such as surrogacy or adoption. Women with TS considering pregnancy should have preconception cardiology and maternal-fetal medicine consultations. Finally, a cardiac MRI with

Table 3. Contraindications to pregnancy in women with TS

Absolute contraindications	Relative contraindications
History of aortic surgery History of aortic dissection Aortic dilatation with ASI > 2 cm/m^2 (ASRM), > 2.5 cm/m^2 (CNGOF) Coarctation of the aorta Resistant hypertension	Turner syndrome (ASRM) Suboptimally controlled diabetes Suboptimal uterine development Bicuspid aortic valve Aortic dilatation Portal hypertension with esophageal varices

ASI: aortic size index; ASRM: American Society for Reproductive Medicine; CNGOF: Collège National des Gynécologues et Obstétriciens Français.

abnormal findings and/or an aortic size index > 2 cm/m^2 are absolute contraindications to pregnancy (see Table 3).[20]

FERTILITY PRESERVATION IN WOMEN WITH TURNER SYNDROME

Women with TS have a short reproductive lifespan because of the high risk of POF. Indeed, the pool of ovarian follicles is already exhausted by adolescence in 60% of patients, and only 30% will experience spontaneous pubertal development.[21] It is worth noting that pubertal development is correlated with karyotype and occurs in 40% of women with a mosaic TS compared with 9% of women with monosomy X.[22,23] Subsequently, fertility is impaired, even in women who go through puberty and have menstrual cycles, and only 2% to 8% manage to conceive spontaneously.[24,25] Most of these pregnancies occur in women with mosaicism (87% to 92% of cases).[24,25]

Therefore, many women with TS will seek counselling for FP at a young age, before follicular depletion occurs because they are not yet ready to start a family (because of young age, absence of a partner, and social and economic factors). There are many FP techniques currently available for women with TS. Controlled ovarian stimulation followed by vitrification of mature oocytes is currently the preferred method for FP, with multiple reports confirming its feasibility.[26–28]

Ovarian tissue cryopreservation is another available option for FP and is the only method applicable in pre-pubertal girls.[29] This method requires the removal of fragments of ovarian cortex, most frequently via a laparoscopic approach, with freezing of the fragments for later transplantation. The fragments of ovarian cortex contain hundreds to thousands of follicles and oocytes, depending on the patient's age and ovarian reserve. Preliminary data confirm the feasibility of OTC in women with TS.[30,31] Indeed, Hreinsson et al. first confirmed the presence of follicles in the ovarian cortex in eight of nine adolescents with TS who underwent OTC for FP.[30] In a series of 57 OTC procedures in girls with TS, they found follicles in the retrieved tissue in 15 cases (26%); six of seven girls with mosaicism (86%) had follicles.[31]

Given the low chances of spontaneous pregnancies in women with TS, even in those with mosaicism, FP with oocyte vitrification and/or ovarian tissue freezing should be discussed at a relatively young age, preferably immediately after pubertal development (13 to 15 years of age), while the ovaries are still functional. Successful FP in women with mosaic TS using one or both of these methods has been described, but no pregnancies have been reported to date.[32]

Obstetrical and Postpartum Care

Pregnancies in women with TS are considered to be high risk. A study of 115 pregnancies in women with TS from the Swedish national registry found the risk of aortic dissection to be 1% during pregnancy,[33] whereas a study in the United States of 101 pregnancies in women with TS achieved with IVF-DO found the maternal risk of death from aortic dissection to be 2%.[34] Patients should be counselled and closely monitored during pregnancy for the increased risk of maternal cardiovascular and metabolic complications, fetal chromosomal abnormalities in cases of spontaneous pregnancies or following IVF with autologous oocytes, and maternal and fetal complications associated with IVF-DO (see Table 1).[20]

Pregnancy in women with TS requires close monitoring by a multidisciplinary team that should include a maternal-fetal medicine specialist, a cardiologist, and an endocrinologist and should be carried out in a tertiary care centre if possible. At any time during pregnancy, the involvement of physicians from other fields, such as hepatology, nephrology, medical genetics, and obstetric medicine, could be required (Table 4).

At our institution, all pregnant women with TS have a monthly prenatal visit and at least one cardiology consultation in each trimester of pregnancy.

During the first trimester, blood pressure, weight, and urinary protein are checked at each prenatal visit. Liver function tests (alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, alkaline phosphatase), assay of serum TSH, and a 75 g oral glucose tolerance test are performed, followed by a mandatory consultation with an endocrinologist. The frequency of follow-up with the endocrinologist depends on the findings

Table 4. Monitoring during pregnancy in women with TS

Multidisciplinary follow-up
Complete prenatal diagnosis in pregnancy with autologous oocytes, upon request in pregnancy with IVF-DO
Blood pressure monitoring at each visit
Cardiology consultation and echocardiography in each trimester
Increased monitoring during third trimester (possible thoracic MRI)
Screening test for proteinuria: urinary protein/creatinine ratio
Blood glucose monitoring—early screening for gestational diabetes: • 75 g oral glucose tolerance test at 10 to 12 weeks' gestation • If normal, repeat at 24 to 28 weeks' gestation • If diabetes or glucose intolerance in pre-pregnancy: capillary glucose measurements before and one hour after eating
Nutrition counselling with monitoring of gestational weight gain
Thyroid function tests before 9 weeks' gestation
Liver function tests during first trimester, with repeat and monitoring if abnormal
Route of delivery assessed by multidisciplinary team (increased risk of Caesarean section because of fetal-pelvic disproportion)
Close cardiovascular monitoring peripartum (risk of aortic dissection)

and comorbidities. An echocardiogram is always performed at between 12 and 14 weeks' gestation.

During the second trimester, blood pressure, weight, and urinary protein are also checked at each monthly visit, and another 75 g oral glucose tolerance test and echocardiogram are performed at approximately 24 weeks' gestation. Liver function tests are repeated only in cases of pruritus and/or icterus, and a hepatic ultrasound is performed if liver function testing is abnormal.

During the third trimester, blood pressure, weight, and urinary protein are checked weekly, and echocardiography is performed monthly until delivery. Liver function tests are only performed in symptomatic patients, followed by a hepatic ultrasound when required. It should be noted that patients with renal malformations undergo monthly renal function tests throughout pregnancy.

Pregnant women with TS have a markedly increased rate of Caesarean section, with rates as high as 80% reported in the literature, mainly because of fetal-pelvic disproportion.[5,6] The timing of the Caesarean section after 34 weeks' gestation is determined by the mother's cardiovascular status. Vaginal delivery with close monitoring of blood pressure can be attempted if fetal-pelvic disproportion is ruled out and there are no other contraindications; assisted delivery with vacuum extractor or forceps is recommended.[4] Women with TS who have successful vaginal deliveries tend to be taller than those who deliver by Caesarean section.[6]

According to the Nordic cohort study (a retrospective review of 131 newborns from 122 deliveries following IVF-DO in women with TS), the neonatal outcomes were generally reassuring, with a preterm birth rate of 12.3% before 37 weeks' gestation and only 2.5% before 32 weeks' gestation.[6] Median birth weight was 3042 g (range 379 to 4690) and the small for gestational age (< -2 standard deviation) rate was 17.6%.[6] Finally, 24.6% of newborns required admission to NICU for more than one day.[6] The French cohort study reported a preterm birth rate of 38% before 38 weeks' gestation and 10% before 31 weeks' gestation. Median birth weight was 2599 g (range 680 to 4200), and the small for gestational age rate was 27.5%.[5]

Children born from autologous oocytes should be carefully examined immediately after birth to rule out congenital defects.

We could not find any published guidelines regarding the follow-up and monitoring of TS women in the postpartum period. At our centre, patients undergo another full cardiovascular assessment and standard obstetrical and endocrinological follow-up. We offer contraception for women with TS who have regular menstrual cycles and estrogen-progestin hormone therapy in women with POF.

Breastfeeding mothers are prescribed vitamin D for bone health (1000 IU per day) and a progesterone-only pill or an intrauterine device for contraception.[35] Combined oral contraception is only started when breastfeeding has been completed. Non-breastfeeding mothers are prescribed a combined oral contraceptive agent six weeks after delivery, during which time vitamin D (1000 IU per day) is given for bone health.

Finally, the regular follow-up with cardiovascular, endocrine, metabolic, and hepatic evaluations is maintained on a yearly basis, and bone densitometry is performed every five years.[36]

CONCLUSION

Pregnancies in women with TS, conceived with either autologous or donated oocytes, are considered high risk because of many potential maternal and fetal complications.

Every TS woman with a desire for pregnancy should be informed of the following concerns:

1. the increased risk of miscarriage;
2. the increased risk of fetal chromosomal abnormalities in pregnancies achieved with autologous oocytes;
3. the high risk of maternal morbidity and mortality secondary to cardiovascular and metabolic complications;
4. the obligation to transfer only one embryo in cases of IVF-DO, to minimize the risk of multiple gestation;

5. the increased risk of Caesarean section because of the medical complications and the narrow pelvic outlet associated with TS;
6. the need for close follow-up by a multidisciplinary team, preferably in a tertiary care centre; and
7. the risk of obstetrical and neonatal complications (intrauterine growth restriction, prematurity, preeclampsia).

Women with mosaic TS appear to have a lower risk of cardiovascular and obstetrical complications, even though data on the subject are limited. Therefore, these women should also have a full preconception workup to evaluate the risk and to guide their follow-up.

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