Published in final edited form as:

Fertil Steril. 2011 June ; 95(7): 2251–2256. doi:10.1016/j.fertnstert.2011.03.085.

Outcomes of Spontaneous and Assisted Pregnancies in Turner Syndrome: The NIH Experience

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Abstract

Objective—To assess fetal and maternal outcomes of pregnancies in women with Turner syndrome (TS).

Design—Retrospective case series.

Setting—Clinical research center.

Patients—276 adults with cytogenetically-proven TS participating in an intramural natural history protocol

Interventions—None.

Main Outcome Measures—Menstrual and obstetric histories, 50-cell karyotypes, and cardiovascular evaluation including aortic diameter measurements.

Results—Our cohort included five women with spontaneous pregnancies and five with pregnancies using assisted reproduction (ART). All five women with spontaneous pregnancies had spontaneous puberty, despite 45,X in $\geq 90\%$ of their 50-cell karyotype. Participants had a total of 13 pregnancies and 14 live births. One child had cerebral palsy; the others were chromosomally and developmentally normal. Delivery was by Cesarean section in 4/7 spontaneous and 6/6 ART-related pregnancies. One mother experienced pre-eclampsia in an ART-related twin pregnancy requiring preterm delivery; she has marked but stable aortic dilation years later.

Conclusions—Approximately 2% of our study cohort experienced spontaneous pregnancies despite high grade X monosomy, and a similar number achieved pregnancy via oocyte donation and ART. The potential for life-threatening cardiovascular complications warrants comprehensive screening prior to conception, single embryo transfer, and caution regarding unintentional pregnancies for TS women.

Keywords

fetal outcome; maternal risk; pregnancy; Turner Syndrome

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Disclosure & Conflicts of Interest: None

INTRODUCTION

Turner Syndrome (TS) is the most common cause of hypergonadotropic hypogonadism in girls and young women (1). Turner syndrome is caused by the absence of all or a significant portion of one sex chromosome during embryonic development, and is characterized by short stature and early ovarian failure in most affected individuals (2). Ovaries appear to develop normally in the 45X fetus, but accelerated atresia causes near complete follicle depletion by birth or early childhood (3-4). Sufficient follicles survive to allow for spontaneous menarche in 5-20% of girls with TS, although early menopause ensues (5-7). A registry-based study reported that 7.6% of women with cytogenetically diagnosed TS achieved spontaneous pregnancy, although most had few 45,X cells, and the clinical basis for cytogenetic testing was not available (8). Case reports also frequently concern spontaneous pregnancies in TS women who are mosaic for a normal cell line (9-11). Further, some case reports and small series have suggested an excess of miscarriage, fetal malformations, and chromosomal defects such as trisomy 21 in spontaneous Turner pregnancies (12-14).

Infertile TS patients have increasingly addressed the possibility of child bearing via the use of assisted reproductive technologies (ART) involving oocyte donation and IVF-ET (15). Pregnancy and child bearing in this population may be particularly challenging due to the high prevalence of congenital aortic disease (2) associated with an increased baseline risk of aortic dissection and rupture (16). As the risk of dissection is increased during pregnancy overall (17), the risk for TS women may be further exaggerated during pregnancy, similar to the observed association in Marfan syndrome (18). Karnis *et al.* estimated a catastrophic cardiovascular complication rate of 2% for ART-related pregnancies in U.S. women with TS (17) and the French have also experienced a 2% pregnancy-associated death rate related to aortic dissection in TS following oocyte donation (19).

We undertook a retrospective analysis of feto-maternal outcomes in spontaneous and ART-related pregnancies for women participating in the NICHD natural history study; we document the rate of spontaneous pregnancy according to full TS karyotype and phenotype and assess the risk of miscarriage, fetal malformation, or fetal chromosomal anomaly associated with TS pregnancies. Finally, with this study we aim to investigate whether maternal cardiovascular risk is associated with underlying cardiovascular defects, or use of ART as opposed to spontaneous conception.

MATERIALS AND METHODS

We studied 276 participants in the National Institute of Child Health and Human Development (NICHD) natural history study on TS aged 21 years and older. Participants were recruited through the NIH website: <http://turners.nichd.nih.gov/> between 2001 and 2010. The study was approved by the NICHD institutional review board, and all participants gave written informed consent. Study subjects and controls included phenotypic females aged 21 to 67 years, with a 50-cell peripheral blood leukocyte (PBL) karyotype in which greater than 70% of cells demonstrated loss of all or part of the second sex chromosome.

Self-reported menstrual and obstetric histories were obtained for each subject at the time of presentation to the NIH protocol. Cardiovascular anatomy was evaluated using cardiac magnetic resonance (CMR) imaging. We focused especially on aortic valve structure and aortic diameters (at the level of the sinuses of Valsava (SV), sinotubular junction (STJ), right pulmonary artery (AA), and descending aorta (DA) as described by Ho, *et al.*) (20).

All data were analyzed using STATVIEW5 (SAS Institute Inc., Cary, NC) software. Data are expressed as mean $\pm$ standard error and percentages. Comparisons between groups were

performed using ANOVA analysis of variance. *P* values of 0.05 considered statistically significant.

RESULTS

We screened 290 consecutive adult participants in the Turner study; exclusions were for karyotype criteria (10), missing obstetrical history (2) and failure to undergo CMR (2). Of the 276 individuals in our final sample, 90.6% were self-reported Caucasians, 4.3% were African American, 3.3% were Hispanic, 1.1% were Asian American, and 0.7% were “other”. The average duration since most recent delivery and initial evaluation in the NIH protocol was 10.2 ± 2.9 years (range, 2 – 30 years).

Spontaneous Pregnancies

Of the 276 participants, five had spontaneous conceptions, including one subject who became spontaneously pregnant after a successful ART pregnancy (Figure 1). Four of the five spontaneously fertile patients had a 45,X karyotype in ≥ 49 cells of the 50-cell karyotype. The fifth had 45,X in 90% of her cells, with a distal Xp deletion in the remaining 10% (Table 1). All these women had spontaneous menarche and pubertal development (age 13.4 ± 1.8 years; range, 12 – 16 years). The average age of menopause was 38 ± 5.8 years (range, 31 – 49 years), reported by three of the five women. Apart from preserved ovarian function, these women had major features of TS. Their average adult height was 139.9 ± 7.1 cm (range, 127.8 – 147.0 cm), renal and cardiac anomalies were common, and most had a pediatric history of chronic, recurrent otitis. Additionally, most were affected by hyperlipidemia, thyroid dysfunction, and skeletal abnormalities including osteopenia, cubitus valgus, and scoliosis (Table 1). The age at diagnosis ranged from diagnosis at the time of birth to the age of 16 years.

These five women had seven spontaneous singleton pregnancies resulting in seven live births (Table 1). In each case, the patients continued to have spontaneous menses until pregnancy. There were no obstetric complications or acute maternal cardiovascular events. The average age at delivery was 25.6 ± 2.1 years (range, 21 – 32 years), with Cesarean deliveries accounting for 4/7 of births. There was one case of cerebral palsy among the offspring; however there were no low birth weight or preterm infants, and no children born with chromosomal anomalies (Table 1).

Assisted Pregnancies

Five women utilized oocyte donation and IVF-ET to conceive. The varied karyotypes for each patient are listed in Table 2. Spontaneous menarche was absent in this group, except for one woman who was unsuccessful trying to conceive for three years, despite reportedly normal menarche and menstrual cycles. She had a successful ART pregnancy, followed by a normal spontaneous pregnancy one year later.

There were six ART pregnancies and seven resulting live births, including one twin gestation. The women who carried the twin pregnancy developed preeclampsia and required pre-term delivery. The average age at delivery for the ART group was 29.8 ± 2.4 years (range, 26 – 32 years). Two of six deliveries following assisted reproduction occurred preterm, and all were via Cesarean section (Table 2). Four of the seven of infants from assisted pregnancies were classified as low birth weight (less than 2,500 grams), including one very low birth weight baby (less than 1,500 grams). There were no reported developmental or chromosomal anomalies.

Cardiovascular Outcomes

Most of these pregnancies occurred prior to recent publications on cardiovascular risk for pregnant women with TS (21). Hence, cardiovascular pre-screening was not done and pre-pregnancy aortic diameters are unavailable. Therefore, we compared post-pregnancy aortic diameters in parous women to age- and aortic valve structure-matched nulliparous women. Given the size of our cohort, we would have expected the minimum detectable difference in ascending aortic diameter between parous and nulliparous participants to be 0.8mm, assuming $p < 0.05$ and 80% power. Observed absolute diameters were, in fact, similar in parous and nulliparous groups (Table 3). Body surface area (BSA) indexed aortic diameters were also similar in the two groups (not shown). Aortic diameters were greater in the ART group than in nulliparous and spontaneous pregnancy groups at each of the four distinct aortic loci measured in our study, but these were not statistically significant differences (Table 3). This was due to extreme aortic dilation in the one woman that had a twin gestation complicated by preeclampsia. Her first cardiovascular evaluation was done at the NIH 11 years after pregnancy. At that time, her ascending aorta was dilated to 41 mm with aortic size index of 2.4 cm/m^2 (above the 99th percentile according to Matura *et al.* (22)). Her aortic diameters have remained stable during eight years of follow-up after initial evaluation in our study.

DISCUSSION

This study reviews pregnancy in a cohort of 276 TS women participating in a natural history study defined by stringent karyotype analyses and comprehensive clinical evaluation. This analysis provides essential information on characteristics of women that experience spontaneous pregnancies, and compares fetomaternal outcomes in spontaneous and ART-related pregnancies. The data presented here contribute to a more complete knowledge base that will enhance the ability of care providers to counsel women with TS and help these women make more informed decisions concerning pregnancy.

The frequency of spontaneous pregnancy among women with 'pure, 45,X' TS is not established. There are several case reports of pregnancies among Turner women with 45,X in the peripheral blood karyotype (9, 12, 14, 23-37), some of which report additional X or Y chromosome material detected in blood or other tissues using variable methods with unreported standardized procedures and quality controls. We report spontaneous menarche, pubertal development, and pregnancy in 5/276 women (1.8%) with short stature and other clinical features of TS in which the diagnosis of TS was established by missing all or major parts of one sex chromosome in greater than 70% of their 50-cell PBL karyotype. Interestingly, the proportion of pure, or nearly pure, 45,X individuals was greater in the spontaneous pregnancy group; three of the five fertile women had 100% 45,X cells, one had 98% 45,X cells with 2% 46,XX, and one had 90% 45,X cells with 10% 46,XdelXp.

These women had a total of 7 spontaneous pregnancies, three of which were unexpected and unintentional. Two of these unintended pregnancies were in a participant who had her second unintended pregnancy while taking oral contraceptives for birth control. This woman was diagnosed at birth because of lymphedema, her karyotype was 45,X on 200 leukocyte preparations, and she has extreme short stature, cardiac and renal anomalies, and hearing loss. We cite her case to make two important points. The first is that spontaneous (and unintended) pregnancy is quite possible even in women with apparently pure 45,X and classic TS. These spontaneous pregnancies were associated with spontaneous menarche and pubertal development in our cohort. As such, appropriate education and pregnancy prevention measures must be part of care for girls with TS that demonstrate spontaneous puberty. In particular, given reports of acute, catastrophic events associated with TS pregnancies, counseling for older girls and young women with TS should include potential

for spontaneous pregnancy, use of effective contraceptive methods to avoid unwanted pregnancy, education regarding the risk for life-threatening cardiovascular pregnancy complications, and information on parenting alternatives such as adoption or surrogacy. The second important issue relates to the genetic predisposition to infertility in TS. Examples of spontaneous fertility in 45,X individuals demonstrate the likelihood that there are many genetic loci contributing to oocyte generation and survival, and thus affecting overall fertility. Fertile women with 45,X TS likely have autosomal alleles that enhance fertility by compensating for haplo-insufficiency for unknown X-linked genes involved in ovarian function.

Some early reports suggest an excess of miscarriage, fetal malformations, and chromosomal defects such as trisomy 21 in spontaneous Turner pregnancies (10, 12-14). However, the apparent excess risk for trisomy 21 may be more closely associated with advanced maternal age than X-chromosome deficiency in Turner syndrome according to case reports (13, 38-39). The seven spontaneous pregnancies reported here produced live born, normal appearing infants without chromosomal anomalies. A fertile, 45,X woman may produce oocytes containing either a normal, single X or no sex chromosome, resulting in zygotes that are either eukaryotic or 45,X. In the latter case, the gestation is unlikely to survive (40), but in the rare cases of survival, the resulting zygote would have TS (26-27). On the other hand, if pregnancy occurs in a woman with a structurally abnormal X chromosome, there is a distinct possibility of passing the abnormal chromosome to offspring, which could then have phenotype similar to the mother. Thus, the specific maternal karyotype should be considered when counseling TS women regarding reproduction and potential risks for offspring.

Our series is notable for a high rate of Cesarean delivery. In fact, Cesarean section was performed in 10 of 13 deliveries, including all 6/6 deliveries in the ART pregnancy group. The major reason cited for Cesarean section in our study group was fetopelvic disproportion, which is expected given the small stature and narrow pelvis in most women with TS (2). Considering that many women with TS have a predisposition to aortopathy that may be augmented during pregnancy or labor, the use of Cesarean section for delivery is reasonable.

An increased rate of pregnancy induced hypertensive (PIH) disorders has been reported in gestations following oocyte donation in general, and may be even greater among women with TS (15, 19, 41). There were no cases of PIH in the 7 spontaneous pregnancies reported here. Among the 6 oocyte donation pregnancies, there was one case of pre-eclampsia in a twin gestation. The risk for this complication in TS is highly related to multiple gestations, as noted more than one decade ago by Hovatta *et al.* (5).

Severe cardiovascular outcomes should also be considered in addition to obstetric complications of note in this population. Although there were no aortic dissections or deaths in the subjects presented here, there is an approximately 2% risk of pregnancy-associated death and aortic dissection in TS women in ART pregnancies (17, 19, 21). It is plausible that pregnancy associated hemodynamic and hormonal factors may promote deterioration in the compromised cardiovascular system of women with TS. It remains unknown, however, if apparently healthy Turner women with normal cardiovascular anatomy and function determined by adequate screening— including cardiac magnetic resonance (42)— are at increased risk, as all the well-documented catastrophic complications have occurred in women with underlying aortic pathology (43-48).

Three of the nine women with pregnancies in this series had bicuspid aortic valves (BAV). Two of those women had spontaneous pregnancies and retained normal valve function and normal (BSA-indexed) aortic diameters years later. The third woman with BAV had a twin

ART pregnancy that was complicated by pre-eclampsia, and she has a markedly dilated aorta. Although we do not have pre-pregnancy aortic measurements, we view this as a likely complication of her pregnancy. We evaluated the effects of pregnancy on aortic diameter, but our sample size was underpowered to detect significant differences in aortic size. Larger sample sizes are essential to accommodate investigations of the effects of age, type of pregnancy, and aortic valve structure on the aortas of TS women during and after pregnancy. Another important issue that requires further investigation concerns the potential extra risk of oocyte donation versus spontaneous pregnancy. The 2% risk of aortic dissection is obtained from oocyte donation pregnancies (17, 19), while case reports suggest a lesser risk in spontaneous pregnancies in women with TS (49). It is unknown whether catastrophic events occur in the 50% of patients with normal cardiovascular systems because existing data do not include adequate evaluation of the maternal cardiovascular system.

Further reporting of large cohorts, including detailed descriptions of maternal age, full karyotype, pre- and post-pregnancy cardiovascular status, method of conception, delivery method, and feto-maternal outcomes is necessary to elucidate the relationship between these factors and outcome in TS pregnancies. Studies including this essential data are necessary for the evaluation of risk associated with pregnancy in TS women via large, prospective registry or balanced meta-analysis. However, until such analysis is possible, the potentially fatal downstream effects of preeclampsia, aortic dissection, and other complications that may be increased in TS pregnancies warrant patient education regarding the potential for spontaneous pregnancy, comprehensive cardiovascular screening prior to conception (42), single embryo transfer in ART, and caution regarding unintentional pregnancies TS women overall.

Acknowledgments

Financial Support: HD000628-18 National Institutes of Health, Division of Intramural Research, Bethesda, MD
HHMI-NIH Research Scholar Program, Howard Hughes Medical Institute, Chevy Chase, MD

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Figure 1.

Pregnancies in TS women. 87.7% of participants had no children. 9.1% chose to adopt children, 1.4% had spontaneous pregnancies, 1.4% achieved only assisted pregnancies, and the remaining 0.4% experienced both spontaneous and assisted pregnancy.

Table 1

Phenotype of TS women with spontaneous pregnancies.

Patient	Karyotype [# of cells]	Height (cm)	Associated TS Findings	Age at Diagnosis	Age at Puberty	Age at Pregnancy	Type of Pregnancy	Pregnancy Outcome	Age at Menopause
5	45,X[45]/46,X,del(X)(p22.1)[5]	137.0	RO, HT, HL, Diabetes	14 years	14 years	31 years	ART	CS	49 years
6	45,X[50]	139.5	BAV, HT, HL, Sc	18 months	12 years	24 years	Spontaneous	CS	>26 years
7	45,X[50]	127.8	Osteopenia, HT, RO, HL	16 years	16 years	25 years	Spontaneous	CS	34 years
8	45,X[49]/47,XXX[1]	147.0	RO, Sc, HT	10 years	13 years	21 years	Spontaneous	Healthy	31 years
9	45,X[50]	145.2	BAV, lymphedema, renal dysplasia, RO, HL	birth	12 years	25 years	Spontaneous	Healthy	>27 years

BAV = bicuspid aortic valve; CS = Cesarean section; HL = hearing loss; HT = hypothyroidism; RO = recurrent otitis; Sc = scoliosis.

Table 2

Phenotype of TS women with ART pregnancies.

Patient	Karyotype [# of cells]	Age at Pregnancy	Type of Pregnancy	Pregnancy Outcome
1	45,X[25]/46,X,del(X)(p11.4)[24]/46,XX[1]	26 years	ART	CS
		31 years	ART	CS
2	45,X[49]/47,XXX[1]	29 years	ART	CS, PreX, Twins, PTD, LBW
3	45,X[50]	30 years	ART	CS, PTD, LBW
4	46iXq[50]	32 years	ART	CS, LBW
5	45,X[45]/46,X,del(X)(p22.1)[5]	31 years	ART	CS
		32 years	Spontaneous	CS

CS = Cesarean section; LBW = low birth weight; PTD = preterm delivery; PreX = preeclampsia.

Table 3Pregnancy and Aortic Diameters^a in TS Women.

	Nulliparous ^b (n = 88)	Parous (n = 9)	Spontaneous (n = 4)	ART (n = 5)
SV (mm)	28.5 ± 0.4	28.0 ± 1.3	26.7 ± 0.7	28.7 ± 2.1
STJ (mm)	25.4 ± 0.4	24.7 ± 1.0	23.4 ± 0.8	25.8 ± 1.5
AA (mm)	28.0 ± 0.5	28.3 ± 1.9	25.9 ± 1.0	30.2 ± 3.2
DA (mm)	18.8 ± 0.4	17.7 ± 0.7	17.5 ± 0.5	17.8 ± 1.3
BAV (%)	32	33	50	20

^a Aortic diameters were measured at the sinus of Valsalva (SV), sinotubular junction (STJ), ascending aorta at the level of the right pulmonary artery (AA) and descending aorta (DA) at the same level.

^b Nulliparous women were matched to parous women by age (40.0±1.0 versus 38.4±3.3 years, respectively) and aortic structure (there were no individuals with aortic coarctation).