Influence of Pregnancy on Aortic Diameter in Women With the Turner Syndrome

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Women with Turner syndrome (TS) have high prevalence of cardiovascular anomalies. Literature suggests pregnancy is associated with a higher dissection risk, presumably preceded by aortic dilatation. Whether the aortic diameter truly changes during pregnancy in TS is not well investigated. This study aims to evaluate ascending aortic diameter change during pregnancy and reports on cardiac events during and directly after pregnancy. This tertiary hospital retrospective study investigated all TS women pregnancies (2009 to 2018). Outcome parameters included aortic diameter growth and aortic complications, specifically dissection. Thirty-five pregnancies in 30 TS women, 57% assisted by oocyte donation. Mean age at delivery 32 ± 5 years. In 27 pregnancies of 22 women imaging was available. From over 350 childless TS women a comparison group of 27 was individually matched. The median ascending aortic diameter growth between pre- and postpregnancy imaging was 1.0 mm (IQR −1.0; 2.0), no significant change (p = 0.077). Whether the patient had a bicuspid aortic valve (p = 0.571), monosomy X or mosaic karyotype (p = 0.071) or spontaneous pregnancy or resulting from oocyte donation (p = 0.686) had no significant influence on diameter change. Aortic growth between pregnancy and matched childless group (0.23 vs 0.32 mm/year, p = 0.788) was not significant over 3.3 ± 2 versus 4.4 ± 1 years. During pregnancy or the first 6 months after delivery no aortic complications were observed. In conclusion, this study suggests pregnancy in TS women does not induce faster ascending aortic diameter increase. Also not in presence of a bicuspid aortic valve, monosomy X karyotype, and oocyte donation. No aortic complications occurred. Based on current study pregnancy in TS women seems safe. **(Am J Cardiol 2021;140:122−127)**

Turner syndrome (TS) is a rare disorder, occurring in 1 in 2.500 newborn female infants.[1] It is caused by a total or partial loss of one X chromosome. Turner karyotypes include monosomy X (45,X) and mosaic karyotype.[2] Congenital cardiovascular anomalies are present in up to 50% of the TS population, including aortic dilatation (23%) and bicuspid aortic valve (BAV; 22% to 39%).[3−7] They contribute to a standardized mortality ratio 3 times higher than in the general female population.[8] Although rare, aortic dissection is the most feared complication in TS women, and pregnancy entails a period of additional risk. Pregnancy is a challenge due to premature ovarian failure. Only a small minority is able to conceive spontaneously. However, pregnancy became possible for a growing group since oocyte donation availability.[9,10] Current guidelines advise against pregnancy when the ascending aortic size index (ASI) is 20 to 25 mm/m^2 with associated risk factors for aortic dissection or >25 mm/m^2.[11] Up to 90% of aortic dissections occur in patients having predisposing risk factors (e.g., aortic coarctation, BAV and hypertension).[12,13] Whether the ascending aortic diameter truly changes (possible higher dissection risk) more than expected during pregnancy is not well-investigated in TS women. Therefore, this study aims to evaluate the ascending aortic diameter change during pregnancy and reports on cardiac events during or in the first 6 months after pregnancy.

Method

A retrospective analysis was performed in a tertiary hospital (Radboud university medical center, Nijmegen, the Netherlands), where to date the outpatient clinic comprises >300 karyotypically proven TS women. All spontaneous pregnancies or pregnancies resulting from oocyte donation were included of patients with TS who delivered between January 2009 and December 2018. For the analysis of the ascending aortic diameter change, women were included if aortic imaging was performed before, during and after pregnancy.

From over 350 childless TS woman a comparison group was individually matched to the 27 pregnant TS women included for analysis of ascending aortic diameter change. In order of importance, the match was formed on the basis of age during imaging, BAV, hypertension, karyotype, height, and weight. The study was part of a larger study for

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which Institutional Ethical Board (CMO Arnhem-Nijmegen) gave approval.

In all TS women, measurement of the ascending aortic diameter was conducted following American Society of Echocardiography guidelines of echocardiography and cardiac-MRI (CMR).[14] Therefore we echocardiographically measured at end-diastole from the leading edge of the anterior root wall to the leading edge of the posterior aortic root wall, 3cm above the aortic valve. All echocardiographic aortic measurements were performed by an experienced sonographer and experienced cardiologist. The CMR measurements were performed by an experienced radiologist. Preferably CMR was used to measure aortic diameters pre- (T0) and postpregnancy (Tpost) and echocardiography was used during pregnancy (first, second, and third trimester, T1, T2, T3). Literature suggests that echocardiography and CMR are comparable when measured correctly following the guidelines.[15] Therefore, when T0 or Tpost CMR was not performed, echocardiography measurement was used in aortic diameter analysis. When Tpost imaging was not available, the T3 diameter was used.

Medical records were reviewed for karyotype, height, weight before pregnancy, presence of Congenital cardiovascular anomalies such as a BAV, aortic coarctation, hypertension and/or aortic dilatation (before pregnancy), mode of pregnancy (spontaneous or resulting from oocyte donation), age at delivery, and mode of delivery. Aortic dilatation was defined as an ASI $\geq$20 mm/m^2. Ascending aortic diameter measurements of the prepregnancy period, during the first, second and third trimester, and postpregnancy period were recorded. Other outcome parameters scored were aortic diameter change, aortic height index (AHI), and cardiac complications during pregnancy or the first 6 months after delivery, specifically aortic dissection. An aortic growth of $\geq$3 mm was considered significant. Pregnancy induced hypertension was defined as a blood pressure >140/90 mm Hg after 20 weeks gestation, pre-eclampsia as blood pressure >140/90 mm Hg and proteinuria after 20 weeks gestation. We choose to use the AHI instead of the ASI, since weight can fluctuate during pregnancy and height is reliably constant. The AHI of the ascending aorta was calculated for all subjects. AHI (mm/m) was defined as $\textit{Aortic diameter}\ \frac{(mm)}{Height}\ (m)$.

The statistical analyses were performed using the IBM Statistical Package for Social Sciences version 22.0 (SPSS 22). Continuous data were calculated as mean $\pm$SD or, or if the distribution was skewed or the Shapiro-Wilk test showed abnormal distribution, as median and range or interquartile range (IQR). For categorical data frequencies and percentages were reported. The paired *t*test was used for comparison of aortic diameters before, during and after pregnancy, the unpaired *t*test for comparison of numerical data of the subgroups. Pearson's Chi-square test was used for the comparison of categorical data. A p-value of <0.05 was considered statistically significant for all analyses.

Results

In total 35 pregnancies in 30 TS women were registered (Table 1). Mean age at delivery was 32.3 $\pm$ 4.6 years. One patient, not included in the analysis of ascending aortic diameter change, had an aortic coarctation and no women had hypertension before pregnancy. Pregnancy was assisted by oocyte donation in 57% of women. Five women were pregnant twice. No significant differences were found whether or not we include the second pregnancy of these 5 women in the aortic diameter change analyzes, therefore we included all double pregnancies. Eight pregnancies were lacking imaging data; no imaging (n = 1), only Tpost echocardiography or CMR (n = 6), only T2 echocardiography and Tpost CMR (n = 1). No significant differences were found when comparing baseline characteristics between these 8 pregnancies and the 27 with sufficient imaging. Therefore those 8 pregnancies were excluded and the remaining 27 pregnancies in 22 TS women were included for the analysis of ascending aortic diameter change. This study includes TS woman with predominantly a normal aortic diameter. At baseline, dilatation of the ascending aorta (ASI $\geq$20 mm/m^2) was present in 3 (11%) women before their pregnancy. No women had an ASI above 25 mm/m^2. Table 2 shows the matched 27 childless TS women on baseline.

The performed pre- and postpregnancy imaging for cardiovascular evaluation differed per pregnancy, as shown in the supplement tables. In 4 cases no Tpost imaging was performed, thus T3 imaging was used. The time between latest preaortic imaging and first aorta imaging during pregnancy was 1.2 $\pm$ 0.9 years and the time between T3 and first imaging post-partum was 1.1 $\pm$ 0.8 years.

The mean ascending aortic diameter before, during and after pregnancy and the change are shown in Table 3. The mean ascending aortic diameter at T0 imaging was 27.3 $\pm$ 3.8 mm with an AHI of 17.2 $\pm$ 2. 5 mm/m and at first Tpost imaging was 28.0 $\pm$ 4.2 mm with an AHI of 17.7 $\pm$ 2.7 mm/m. The median ascending aortic diameter growth between T0 and Tpost imaging was 1.0 mm (IQR $-$1.0;2.0) over a mean time period of 3.3 years $\pm$ 2 years, with no significant change (p = 0.077). No statistically significant difference was found in change in ascending aortic diameter in T3 versus postpartum echocardiography (p = 0.829), T3 echocardiography versus postpartum CMR (p = 0.706), and postpartum echocardiography versus postpartum CMR (p = 0.706). The measurements during pregnancy between T1 and T2 (p = 0.879), T2 and T3 (p = 0.170), and T3 and Tpost echocardiography (p = 0.291) were also not significantly different. No significant differences were found in baseline characteristics (weight (p = 0.328), height (p = 0.304), body mass index (p = 0.159), and body surface area (BSA; p = 0.584)) between the pregnancies with ($\geq$3 mm) and without significant aortic growth. The ascending aortic diameter change was not significantly different between patients with or without BAV (p = 0.571). Whether the patient had a monosomy X or mosaic karyotype (p = 0.071), a spontaneous pregnancy or resulting from oocyte donation (p = 0.686) or a vaginal delivery or by caesarean section (p = 0.476) also had no significant association with ascending aortic diameter growth in this study population.

From the childless TS group, 27 women were individually matched with the 27 pregnant women. The total median aortic growth was 1.0 mm (IQR $-$1.0; 2.0) in the pregnant group over a mean time period of 3.3 $\pm$ 2 years versus

Table 1.
Baseline characteristics pregnant Turner syndrome (TS) women

	Pregnant women; Mean (±SD), median (range) or n (%)	Pregnancies with significant aortic growth (≥3 mm)	Pregnancies without significant aortic growth (≤2 mm)	p Value (significant vs nonsignificant change)
Pregnancies/deliveries				
Total pregnant TS women	30			
Total deliveries	35			
Pregnancies included for aortic growth analysis/ pregnant woman	27 (77%)/22 (73%)	5	22	
Patient demographics				
Mean age at delivery (years)	32.3 ± 4.6	31.8 ± 5.4	31.2 ± 4.6	0.801
Mean height (cm)	158.9 ± 6.2	160.6 ± 5.8	157.6 ± 5.7	0.304
Median weight pre pregnancy (kg)	61.0 (45-96)	57.0 (50-64)	60.5 (45-94)	0.328
Median BMI (kg/m^2)	23.0 (18-38)	21.9 (21-24)	23.9 (18-37)	0.159
Mean BSA (m^2)	1.6 ± 0.2	1.6 ± 0.1	1.6 ± 0.2	0.584
Cardiovascular anomalies				
Bicuspid aortic valve	7/30 (23%)	1	8	0.484
Aortic coarctation	1/30 (3%)	0	0	-
Hypertension (prepregnancy)	0/30 (0%)	0	0	-
Karyotype				0.071
45 × 0	3/30 (10%)	1	2	
Mosaicism	26/30 (87%)	3	20	
Unknown	1/30 (3%)	1	0	
Mode of pregnancy				0.686
Spontaneous	14/35 (40%)	2	11	
Oocyte donation	20/35 (57%)	3	11	
Unknown	1/35 (3%)	0	0	
Mode of delivery				0.476
Vaginal	11/35 (31%)	2	14	
Caesarean section	21/35 (60%)	3	7	
Unknown	3/35 (9%)	0	1	

BMI = body mass index; BSA = body size index; cm = centimeters; kg = kilograms; m = meters; mm =millimeters; n = number; SD = standard deviation; TS = Turner syndrome.

Table 2.
Characteristics pregnant versus childless women

Characteristics	Pregnant women; (N = 27)Mean (±SD), median (range) or n (%)	Childless women; (N = 27)Mean (±SD), median (range) or n (%)	p Value
Patient demographics			
Mean age T0 or first imaging (years)	30.6 ± 4.7	28.2 ± 4.8	0.068
Mean height (cm)	158.2 ± 5.7	157.8 ± 5.4	0.912
Median weight T0 or first imaging (kg)	60.0 (45-94)	57.0 (42-95)	0.407
Median BMI (kg/m^2)	23.0 (18-36)	22.9 (18-45)	0.211
Mean BSA (m^2)	1.6 ± 0.2	1.6 ± 0.5	0.385
Cardiovascular anomalies			
Bicuspid aortic valve	9/27 (33%)	6/27 (22%)	0.362
Hypertension (prepregnancy)	0/27	0/27	
Karyotype			0.245
45 × 0	3/27 (11%)	7/27 (26%)	
Mosaicism	23/27 (85%)	20/27 (74%)	
Unknown	1/27	0/27	

BMI = body mass index; BSA = body size index; cm = centimeters; kg = kilograms; m = meters; n = number; SD = standard deviation; T0 = prepregnancy.

1.0 mm (IQR 0.0; 2.0) in the childless group over a mean time period of 4.4 ± 1 years, which was not significantly different (p = 0.435). The median aortic growth per year (mm/year) also showed no significant difference (p = 0.788) between the pregnant group with a median of 0.23 mm (IQR −0.17;0.69) and 0.32 mm (IQR 0.00;0.47) in the childless group (Figure 1).

No life-threatening complications, specifically no aortic dissections, or death occurred during pregnancy or the first 6 months after delivery. During pregnancy 1 patient

Table 3.
Aortic diameter change before, during and after pregnancy

Imaging modality	T0 (CMR n = 25, echo n = 26)	T1 (echo n = 20)	T2 (echo n = 23)	T3 (echo n = 24)	Tpost (CMR n = 15 echo n = 16)	Change	pValue
CMR or echo*	27.3 ± 3.8	27.4 ± 3.7	27.4 ± 3.7	28.3 ± 3.5	28.0 ± 4.2	0.7 ± 1.9	0.077
CMR†	27.0 ± 3.9				28.1 ± 4.2	1.1 ± 1.8	0.042
Echo‡	27.8 ± 4.5	27.4 ± 3.7	27.4 ± 3.7	28.3 ± 3.5	28.7 ± 4.0	0.9 ± 2.6	0.187

CMR = cardiac magnetic resonance imaging; Echo = echocardiography; T0 = prepregnancy; T1, T2, T3 = first, second and third trimester; Tpost = postpregnancy.

* Latest prepregnancy imaging whether this was MRI or echocardiography. Imaging modality during pregnancy was echocardiography. Postpregnancy imaging preferably using CMR and when not available postpartum echocardiography or echocardiography on T3.

† Imaging modality compared between 14 cases who underwent pre- and postpregnancy CMR imaging.

‡ Imaging modality compared between 15 cases who underwent pre- and postpregnancy echocardiography imaging.

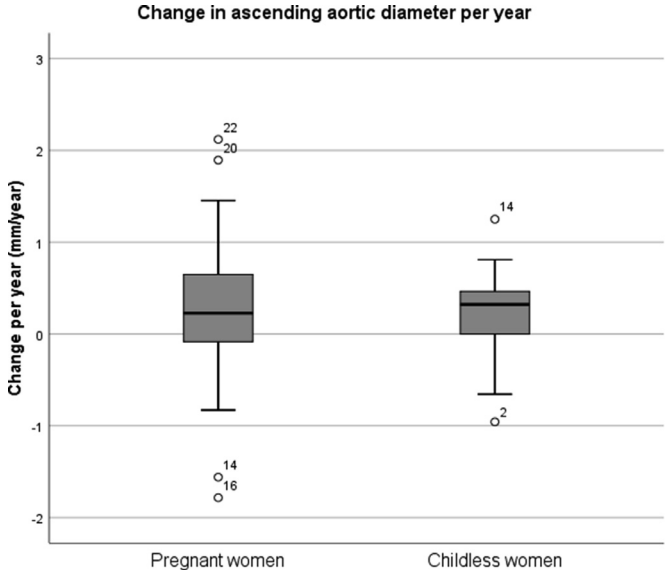

Figure 1. Title: Change in ascending aortic diameter per year. Results: The median aortic change per year (mm/year) showed no significant difference (p = 0.788) between the pregnant group with a median of 0.23 mm (IQR −0.17; 0.69) and 0.32 mm (IQR 0.00; 0.47) in the childless group. Mm = millimeters.

developed pregnancy induced hypertension at full-term and 3 patients developed pre-eclampsia. In the patients with pre-eclampsia labor was induced at 37 weeks of pregnancy. One of them was pregnant with a dichorionic diamniotic twin. One case of pre-eclampsia occurred in a woman pregnant after oocyte donation, the other 2 in spontaneously pregnant women. These 4 pregnancy-related complications did not occur in the 5 women with multiple gestations. The 4 women did not have advanced maternal age compared with the other women in the study population. One other patient had a complicated caesarean section due to postpartum hemorrhage.

Discussion

Present study is, to the best of our knowledge, the first that reports aortic diameter changes during pregnancy of TS women and compared an individually matched nonpregnant TS group. In this cohort of pregnant TS women, no significant aortic diameter increase was observed during the prepregnancy, pregnancy, and postpregnancy period. Furthermore, also compared with a matched group of childless TS women, no significant differences were observed in aortic diameter change. No aortic cardiac complications were observed.

The fact we did not observe a significant aortic diameter change in the course of the pregnancy could be explained by the small sample size, observer variability or that there is no significant change in aortic diameter. For this reason, we compared the pregnant TS group with a matched control group and this also showed no significant difference between these groups. We predominantly measured the pre- and postpregnancy diameters with CMR, but in some patients we only had an echocardiogram, which in theory could have caused an intermodality variation. However, recently a study by Bons et al showed that the difference between CMR and echocardiography is very small.[15]

In this small cohort of pregnant TS women, we observed no aortic complications. The low incidence of aortic dissection or rupture in general and still very low incidence in TS women, could explain the absence of aortic complications. A selection bias could cause an absence of aortic complication, because relative young, healthy TS women got pregnant and only 10% of the women had a 45 × 0 karyotype.

Karyotype 45 × 0 is seen as a predictor of aortic complications. BAV was present in 23%, which has also been described as a risk factor.[16,17] In 57% oocyte, donation was used to become pregnant which has been associated with aortic complication.[18] However, in our study we found no impact of these "risk factors," although the prevalence was low and no hard conclusions can be made.

Studies published to date report variable rates of aortic dissection and death. Karnis et al suggested that TS women undergoing assisted reproductive technology (ART), such as oocyte donation, may have a 2% risk of death from aortic dissection. Of 258 donor-egg programs 52% responded, reporting 94 live births with no dissections or deaths. The authors assumed that the TS pregnancy rate was comparable in nonresponding clinics, so they estimated 200 total ART pregnancies. During the same period 4 case reports were published of death from aortic dissection in Turner ART pregnancies, thus they estimated a 2% risk of aortic dissection (4/200 = 2%).[9] Chevalier et al analyzed 93 ART pregnancies of which 2 patients (2%) died due to aortic dissection or rupture.[19] Over the past years several other studies reported a 0%,[18,20,21] 0.005% (1/202)[22] or 0.009% (1/106)[23] aortic dissection rate in pregnant TS women and no maternal deaths. The mortality rate is <1% when combining results from published studies. Although aortic growth is concerning, aortic dissection can occur in the setting of a normal aortic growth rate.[24] The American Society for Reproductive Medicine and the American Heart Association previously introduced recommendations for screening and management of TS women before and during pregnancy, including treatment of hypertension, prepregnancy screening, and periodic echocardiography or CMR during pregnancy, as we have conducted in our study population.[25,26] When these advises would be implemented by other hospitals the risk of aortic dissection may be further reduced in the future.

The absolute aortic diameter should be corrected for small body size in small people like TS women.[27] Aortic size index (ASI, aortic size/BSA) has been proposed to predict risk for aortic dissection in TS women.[17,28–30] However one of the pitfalls is that the ASI becomes lower in obese patients and relatively larger in slim patients. Therefore some women will be labeled as having a normal diameter. Tanweer et al and Zafar et al found that the AHI is equal or slightly superior to the ASI in the estimation of adverse aortic outcomes, such as dissection, rupture and death.[31,32] In the present study we choose to correct using only the height (AHI), because most of the time during pregnancy there is a significant weight gain, which would cause a higher BSA and therefore a smaller corrected aortic diameter.

This study has limitations inherent to the retrospective study design. The sample size is small since TS is a relatively uncommon disorder and not every TS women becomes pregnant. Larger series are needed to assess rare events. We studied subjects in our tertiary hospital, therefore patient selection bias cannot be excluded. A strength is the fact that we monitored and documented ascending aortic diameter change during pregnancy and compared them to a individually matched nonpregnant TS group. Previous studies mainly described hypertensive disorders and the risk of aortic dissection, but not the actual change in diameter during pregnancy.

Conclusion

This study suggests that pregnancy in TS women does not induce a faster ascending aortic diameter increase and therefore possibly have no significant increased risk of aortic dissection. Also in the presence of a bav, monosomy X karyotype and oocyte donation no faster aortic diameter increase was observed. No aortic complications occurred. Based on the present study pregnancy in TS women seems safe. We propose to use the AHI instead of the ASI, in pregnant women since these women have a fast change in weight during pregnancy and because it has been shown that it predicts outcome equal to body surface area.

Author Contributions

Silje S Kooijman: Data curation, investigation, formal analysis, writing − original draft, visualization; Antonie L Duijnhouwer: Conceptualization, supervision, writing − review & editing; Roland R J van Kimmenade: writing − review & editing; Arie P J van Dijk: writing − review & editing; Esther Hink: writing − review & editing; Menko-Jan de Boer: writing − review & editing; Janneke Timmermans: writing − review & editing; Jolien W Roos-Hesselink: writing − review & editing

Disclosures

The authors have no conflicts of interest to disclose. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.047.

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