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Pregnancies in women with Turner Syndrome: A retrospective multicentre UK study

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Running Title "Pregnancies in women with Turner Syndrome"

Abstract

Objective

To determine the characteristics and outcomes of pregnancy in women with Turner Syndrome

Design

Retrospective 20-year cohort study (2000-2020)

Setting

16 tertiary referral maternity units in the UK

Population or Sample

81 women with Turner syndrome who became pregnant

Methods

Retrospective chart analysis

Main Outcome Measures

Mode of conception, pregnancy outcomes

Results

We obtained data on 127 pregnancies in 81 women with a Turner phenotype. All non-spontaneous pregnancies (54/127 (42.5%)) were by egg donation. Only 9/31 (29%) of pregnancies in women with karyotype 45,X were spontaneous, compared with 53/66 (80.3%) with mosaic karyotype 45,X/46,XX ($p < 0.0001$). Women with mosaic 45,X/46,XX were younger at first pregnancy by 5.5-8.5 years compared to other TS-karyotype groups ($p < 0.001$), and more likely to have a spontaneous menarche (75.8% vs 50% or less, $p = 0.008$). There were 17 miscarriages, 3 terminations of pregnancy, 2 stillbirths and 105 livebirths. Two women had aortic dissection (2.5%); both were 45,X karyotype, with bicuspid aortic valves and ovum donation pregnancies, one died. Another woman had an aortic root replacement within six months of delivery. 10/106 (9.4%) births with gestational age data were preterm and 22/96 (22.9%) with singleton birthweight/gestational age data weighed $< 10^{\text{th}}$ centile. The caesarean section rate was 72/107 (67.3%). In only 73/127 (57.4%) of pregnancies was there documentation of cardiovascular imaging within 24 months prior to conceiving.

Conclusions

Pregnancy in women with TS is associated with major maternal cardiovascular risks and deserve thorough cardiovascular assessment and counselling prior to assisted or spontaneous pregnancy managed by a specialist team.

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Tweetable Abstract: Pregnancy in women with TS is associated with an increased risk of aortic dissection

Word Count 3100

Short Title: Turner Syndrome and Pregnancy Outcome

Introduction

Turner Syndrome (TS) is the commonest sex chromosome abnormality in women, affecting about 1 in 2000 live-born girls (1, 2). It results from the total/partial absence or complex rearrangement of an X chromosome in all (or a proportion of) the cells of an affected female. Diagnosis is made through chromosomal analysis. TS is characterised by short stature and gonadal dysgenesis in combination with a range of other typical phenotypic characteristics. Subfertility is common. Women with a mosaic karyotype 45,X/46,XX typically show a less severe phenotype. Congenital cardiac abnormalities occur in about 50% of women with TS and include aortic coarctation, bicuspid aortic valve (3, 4) and partial anomalous pulmonary venous drainage. Aortic dilatation and dissection risk is increased 100-fold in women with TS(5), particularly if there is a bicuspid aortic valve, coarctation of the aorta, and/or hypertension. Pregnancy further increases this risk (2). Hypertension affects about half of the adult population with TS (6) and hypertensive women are at increased risk of aortic dissection (4.5% in one report (7)). Stockholm et al reported increased mortality (standardised mortality ratio 2.86 compared with the general population (6)), mainly because of cardiovascular complications.

Only about a third of women with TS will have signs of spontaneous puberty, and the majority of women with TS experience premature ovarian failure at a young age (8). This limits the possibility of spontaneous pregnancy (9-12). As assisted reproductive technologies have become increasingly available, over the last 10 years there have been a number of cohort studies reporting pregnancies through oocyte donation in women with TS (12-15). However, concerns have been expressed regarding the high rate of maternal complications in women with TS (10-13).

The aim of our multicentre retrospective study was to assess maternal, obstetric and neonatal outcomes in a large cohort of women with TS and highlight areas where optimisation of care may improve outcomes in the future.

Methods

UK centres that have a combined obstetric cardiac clinic were contacted via email in June 2020 to participate in a retrospective study of pregnancies, miscarriages and abortions in women with TS. In total twenty centres were contacted, and 16 centres agreed to participate

and were able to identify pregnancies between January 2000-December 2020. Karyotypes were divided into four groups; (a) 45,X (b) mosaicism with a second or third cell-line with more than one X chromosome (45,X/46,XX; 45,X/46,XX/47,XXX), (c) other TS karyotypes, or (d) unknown. Demographics of the mothers, and details of the pregnancy outcomes were collected by chart review by the local investigators and were collated by the lead investigator i.e. no identifiable data were shared. Maternal cardiovascular data were similarly recorded including imaging, maternal congenital cardiac abnormalities, and aortic size index (aortic diameter/body surface area (ASI)). Cardiovascular events were defined as any documented episodes of aortic dissection, hypertension or ischaemic heart disease in pregnancy or up to 6 weeks postpartum or requirement for cardiac surgery in pregnancy or up to a year postpartum.

The study was approved by the research governance office at Imperial College Healthcare Trust on 25th June 2020- Ref 1419990

Data were analysed using SPSS V.26 for Windows. Categorical data are presented as frequencies (numbers) and percentages. Data are presented as medians with the inter-quartile range (IQR). Analysis of variance was done using Pearson ChiSquare, and Fisher's exact test for two by two analysis. Correlations were calculated using Pearson's product moment correlation if variables were continuous and Spearman's rank-order correlation if either of the variables was ordinal. Differences between continuous variables were assessed with the Mann Whitney U test if they were not normally distributed. All tests were two tailed and $p < 0.05$ was considered statistically significant.

Patient Involvement

There was no direct patient or public involvement in this study.

Results

Eighty-four women with a diagnosis of TS who had undergone at least one pregnancy were identified in 16 centres. The number of pregnancies reported per centre ranged from one to 42, and total pregnancies numbered 130. There were no clinical data about pregnancies for three women, so these were excluded from the analysis, leaving for study 127 pregnancies in

81 women. There was recorded evidence that the pregnancies had been planned in 89/103 (86.4%). Considering all pregnancies, 73/127 (57.5%) of pregnancies were following spontaneous conception. However, only 9/31 (29%) of pregnancies in the 45,X group were spontaneous conceptions compared with 53/66 (80.3%) in the mosaic group with a second or third cell line with more than one X ($p < 0.0001$ by Fisher's exact test). The rates of spontaneous pregnancies were 11/24 (45.8%) and 0/6 (0%) in the 'other' and 'unknown' groups, respectively. All 'non-spontaneous' pregnancies were conceived by donor egg In Vitro Fertilisation (IVF). There were five sets of twins (all dichorionic diamniotic), all conceived by IVF with donor eggs (two in the 45,X group and one in each of the other three groups). The median gestation at delivery of twins was 36 weeks (IQR 4, min 34, max 38) compared with 39 weeks (IQR 1, min 25, max 42) in all other pregnancies. Because of the lack of normative standards, twins have been excluded from the analysis of birthweight.

Overall, there were three terminations of pregnancy, 17 miscarriages and 107 potentially viable births, of which 52 were in nulliparous women and 55 were in women with one or more previous pregnancies. There were two recorded stillbirths of a potentially viable infant, resulting in a total of 105 live births for further analysis. The two stillbirths were both from spontaneous conceptions, one at 25 weeks (associated with early onset pre-eclampsia, birthweight not recorded) and one at 28 weeks complicated by early onset fetal growth restriction (birthweight 840g). Results were analysed as births to nulliparous women (so each woman can contribute only one baby, her first viable infant), and then by subsequent births.

Maternal demographics at the first recorded pregnancy are shown in Table 1, classified according to genetic diagnosis; 45,X (24 cases), mosaic 45,X with 46,XX (38 cases), other (13 cases); a list of the 'other' diagnoses is shown in supplementary Table 3, and unknown (6 cases, clinical diagnosis with no karyotype available as detailed reports on their TS karyotypes were not available). Women with mosaic TS (45,X/46,XX) were younger at the time of first conception when compared to the other groups by 5.5-8.5 years ($p < 0.001$, Wilcoxon rank sum test), and significantly more likely to have a spontaneous menarche (75.8% vs 50.0% $p = 0.008$ Pearson Chi-Square). 9/23 (39.1%) pregnancies in women with 45,X were in parous women, compared with 36/61 (59.0%) in women with mosaic 45,X/46,XX ($p = 0.142$ Fisher's exact test).

With respect to the outcome of the pregnancies (tables 2 & 3), the outstanding feature is the very high caesarean section rates in all diagnostic groups, which overall was 72/107 (67.3%) - 38/52 (73.1%) in nullipara and 34/55 (61.8%) in parous women. The elective CS rates were 22/52 (42.3%) in nullipara and 25/55 (45.5%) in parous women. Rates of vaginal delivery were significantly higher in the women who conceived spontaneously 30/62 (48.4%) compared with ovum donation 5/45 (11.1%) ($p < 0.001$).

Birthweight data were excluded from analysis in 5 (twins) and missing in 5 cases and gestational age was missing in 1. In the remainder, there was a high rate of small for gestational age (SGA) babies, with 22 of 96 (22.9%) weighing $< 10^{\text{th}}$ centile at birth. The rate was 3/20 (15.0%) in the 45,X group, 13/57 (22.8%) in the mosaic with 46,XX group, 4/14 (28.6%) in the 'other' group and 2/5 (40.0%) in the 'unknown' group. These rates are not significantly different. The overall rate of preterm birth was 10/106, 9.4%. (1/23 (4.3%) in 45,X, 5/61 (8.2%) in mosaics, and 1/16 (6.3%) in 'other'. Unexpectedly, it was 3/6 (50%) in the 'unknown' group (significantly different from the other groups, $p = 0.006$ by Fisher's exact test). There were no significant differences in rates of preterm birth or birth weight between spontaneous pregnancies and those conceived by egg donation IVF.

Only in 73/127 (57.4%) of pregnancies was there documentation of cardiovascular imaging (echocardiogram and/or cardiac Magnetic Resonance Imaging (MRI)) recorded within the 24 months prior to conception. Excluding women who had miscarriages or terminations, cardiovascular imaging was recorded as having been performed during 88/107 of pregnancies (82.2%). With regards to underlying cardiac lesions, 11/81 (13.6%) women were known to have a bicuspid aortic valve and 5/81 (6.2%) women had aortic coarctation; in four cases this had been surgically repaired. A further three women had preconceptual aortic root replacement and they encountered no significant problems in pregnancy. There were three major adverse cardiac events. One woman, 45,X karyotype, aortic sinus index (ASI) 15 mm/m² and bicuspid aortic valve, with an egg donation pregnancy, suffered a type A dissection (dissection of the ascending aorta) at 18 weeks' gestation. The baby was stillborn but the mother survived. A further patient, also 45,X karyotype who conceived her pregnancy by egg donation IVF, had much of her pregnancy care overseas and only came to the UK in the late third trimester. She had a bicuspid aortic valve with aortic size index (ASI) measuring 16 mm/m² at 37 weeks gestation with a singleton pregnancy, developed

gestational hypertension, and died from a type A dissection two days after an emergency CS. A third patient, with a spontaneous conception, mosaic with 46,XX with a dilated aorta (ASI 25 mm/m²), bicuspid valve and repaired aortic coarctation, agreed to undergo termination at 15 weeks after a discussion about the risks of pregnancy. Preconception care was outside a specialised centre; she went on to have an elective aortic root replacement within six months.

11 of 107 (10.3%) pregnancies were complicated by gestational hypertension and 20 of 107 (9.3%) with pre-eclampsia, with no significant differences between diagnostic groups. The rate of pre-eclampsia was slightly higher in nullipara (6/52, 11.5%) than in parous women (4/55, 7.3%) but the difference was not statistically significant ($p=0.519$). It was also higher in women with egg donation IVF (5/45, 11.1%) compared to women with spontaneous conception (5/62, 8.1%), but again the difference was not statistically significant ($p=0.739$ Fisher's exact test).

The overall rate of gestational diabetes was 8/107 (7.5%). It was 1/23 (4.3%) in the 45, X group and 1/61 (1.6%) in the mosaic with 46,XX group. The rates were significantly higher in the 'other' group (4/17, 23.5%) and the unknown group (2/6, 33%) ($p=0.001$ by Pearson Chi-Square).

Estimated blood loss was available in 74 cases. The overall rate of minor postpartum haemorrhage (PPH, ≥ 500 ml) was 37/74 (50.0%) and major PPH ($\geq 1,000$ ml) 6/74 (8.1%), with no significant differences by karyotype group. The incidence of major PPH was entirely in the operative delivery group; 1 of 8 (12.5%) in cases with instrumental delivery and 5 of 53 (9.4%) with caesarean section.

Discussion

Main findings

Pregnancy complications – maternal cardiac. Data from our contemporary UK cohort of women with TS illustrate that pregnancy in TS should be considered high risk. The rate of aortic dissection in our study was 2.5% in women undergoing pregnancy (1.57% of

pregnancies) (two cases, with one maternal death) and another woman required aortic root replacement within six months of a documented pregnancy.

Chevalier et al in 2011(14) reported two maternal deaths due to aortic dissection in a multicentre French study of 93 pregnancies in women who had IVF oocyte donation. However, our findings differ from a recent smaller (68 women) contemporary cohort by Grewal et al, which did not show any cardiac events in pregnancy (16). In 2018 the American Heart Association published their recommendations for the care of women with TS (including cardiovascular risks in pregnancy) in a document entitled 'Cardiovascular Health in Turner Syndrome' (15). Their advice is in keeping with that of the European Society of Cardiology which suggests that women with TS who have normal aortic diameters should be considered to be modified WHO (mWHO) Class 2, defined as having only a small increased risk of maternal mortality, but that pregnancy should be avoided in women with previous aortic dissection, or with an ascending aorta (indexed to body surface area (ASI)) of greater than 25 mm/m², or an ASI 20-25 mm/m² pre-pregnancy with associated risk factors for dissection such as bicuspid aortic valve or hypertension (17). Our findings suggest that this conclusion in relation to women with normal aortic diameters should be tempered with caution. In our cases where aortic dissection occurred in pregnancy, both had ASI reported <20 mm/m² pre-pregnancy. Our data are more in keeping with the rate of severe cardiac complications reported by Hagman et al (14) in their series of 106 TS women who delivered after oocyte donation who reported that 3.3% of women developed life threatening complications, most commonly cardiovascular.

Other maternal, fetal and neonatal complications. In keeping with other studies, the overall median centile birthweight (N=95) of 28 (IQR 10-59) in our study was lower than in the average population (50, IQR 25-75 by definition) and 22/96 (22.9%) babies were SGA defined as <10th centile (there was no significant difference between the karyotype groups). However, rates of gestational hypertension and pre-eclampsia were relatively low (10.3% and 9.3%) compared with other studies. The rates of gestational hypertension appear to be similar to those commonly reported for the general population (up to 10%), (18) but given the elevated risk of aortic dissection in TS it remains imperative that hypertension is treated appropriately as highlighted in the recent International Guidelines (2). The overall rate of

preterm birth in our cohort was relatively low at 10/106 (9.4%) and much less than other contemporary studies in TS (16). The background rate of preterm birth in the UK is approximately 8% (24). We hypothesise that the low rate of preterm birth in our study is due to low rates of gestational hypertension and pre-eclampsia, so that most pregnancies progressed to term. A French cohort study from 2011(19) reported that only 40% of 93 pregnancies in TS following egg donation were uncomplicated - 17.1% had gestational hypertension and 20.7% pre-eclampsia; 27.5% of babies were small for gestational age (<10th centile) at birth; and 38.3% of babies were born at fewer than 36 weeks of gestational age. More encouragingly, a follow-up study of 170 pregnancies (spontaneous and egg donation) following the introduction of guidelines for pregnancy in TS demonstrated an improvement in outcome, with no serious maternal complications, but 19% still had gestational hypertension and 8% pre-eclampsia, and 15% of babies were born before 35 weeks of gestational age(20). Grewal et al (12) also reported high rates of babies born small for gestational age (18% <10th centile); preterm delivery (<37 weeks gestation) occurred in 8%. . Similarly, a Canadian study also showed greater rates of preterm birth and small for gestational age in this cohort of women (21)Andre et al (8) reported rates of gestational hypertension of 28% and pre-eclampsia of 10.3% in 39 pregnancies, with gestational diabetes in 7.7%. Whilst rates of PPH of a litre or more were modest at 8.1%, it should be acknowledged that women with TS will generally have smaller circulating blood volumes because of their smaller stature and so will be more sensitive to this degree of blood loss.

The overall rate of gestational diabetes mellitus (GDM) in our study was 7.5%, which is not significantly different from the normal range of incidence in the UK (8-24%) (22). Rates of reported GDM in other studies of TS and pregnancy have varied between 5-9% (11, 14). Our data reinforce the importance of screening for gestational diabetes in women with TS (23).

Mode of delivery. The overall rate of caesarean delivery was very high in our cohort (67.3%), as reported in other studies (10), particularly where the pregnancy was conceived through egg donation (88.9%)(14). Rates of caesarean delivery were lower, 51.6%, in pregnancies that were conceived spontaneously. Indications for caesarean section were not recorded in all cases. Anecdotally, women and obstetricians may be nervous about vaginal delivery when there is a cardiovascular risk for the mother and where the birthweight

centile is often lower than the average for the population. However, the recent international guidelines suggest that it is reasonable to aim for vaginal delivery in women with TS and ascending ASI $<20\text{mm/m}^2$, although the strength of evidence is weak (2). It is noteworthy that the only significant difference in obstetric complications when assessing pregnancies conceived spontaneously and those through egg donation was mode of delivery.

Given the potential complications listed above, it is vitally important that women with TS have access to preconceptional care with aortic imaging performed prior to a planned pregnancy(24, 25). Our data show that only 54% women had had cardiac imaging within two years of conception. In line with other authors we recommend that when pregnancy is being planned or if a women presents pregnant, imaging should be undertaken if the usual routine scheduled imaging has not occurred in the last 2 years time(24). It is hoped that the recently published guidelines will lead to an improvement in pre-conceptual assessment, as was shown to a certain extent in the follow-up French study (20). Women with TS planning pregnancy should be cared for by a multidisciplinary team including cardiologist and maternal medicine obstetrician who are familiar in managing such cases.

Strengths and Limitations

A strength of our study is the aggregation of data from 16 units across the UK, resulting in a relatively large cohort of study patients compared to other series. However, it is retrospective and there were some missing data, particularly on aspects such as preconception care, where recording may be spread across a number of disciplines and clinicians. When there were missing data on aspects such as imaging, we assumed that this meant it had not been performed, which may not always have been the case. We only collected data from women managed within specialist centres, which may account for the relatively low rates of preterm birth. The pregnancies occurred over 20 years and international guidance for management of TS in pregnancy has only been published within the last five years.

Interpretation

Our multicentre study demonstrates relatively favourable obstetric outcomes for women with TS undergoing pregnancy. However, caution is justified in relation to cardiovascular risk, and in particular the risk of aortic dissection. Women with TS must have contemporary aortic imaging to assist clinicians with counselling to inform risk and try to mitigate vascular complications, although dissection as with other aortopathies in pregnancy is relatively unpredictable(26). Dissection can occur in women with TS with no cardiac disease and normal aortic diameters and pregnancy per se should therefore be considered as an independent risk factor for aortic dissection.

Conclusion

All women with TS should undergo detailed and thorough multidisciplinary evaluation prior to pregnancy and be given full information about the risks to both mother and baby, followed by a discussion of the management options. Pregnancy and delivery in all women with TS should be considered to be high risk and managed within expert specialist centres familiar with their needs and ideally where there is readily available access to both cardiology and cardiothoracic services should these be required.

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Nil

Author Roles:

MC and HT conceived and coordinated the study. PS analysed the data. MC wrote the first and HT and PS edited the manuscript. All other authors carried out data collection and approved the final manuscript.

Ethical Approval

This study was approved by Imperial College NHS Healthcare Trust on the 20th June 2020- Institutional Reference Number 1419991

Disclosure of Interest

LM is supported by NIHR Oxford Biomedical Research Centre and is an employee of, and holds shares in, Sensyne Health plc

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