Received: 14 January 2024 | Revised: 29 April 2024 | Accepted: 12 May 2024

DOI: 10.1111/cen.15078

ORIGINAL ARTICLE

Reproduction

WILEY

Fertility and pregnancy outcomes in women with Turner syndrome: A single centre experience

Elizabeth Burt | Melanie C. Davies | Ephia Yasmin | Antoinette Cameron-Pimblett | Vikram Talaulikar | Clementina La Rosa | Sophie A. Clarke | Gerard S. Conway

Reproductive Medicine Unit, Institute for Women's Health, University College London Hospitals, London, UK

Correspondence
Elizabeth Burt, Reproductive Medicine Unit, Institute for Women's Health, University College London Hospitals, 235 Euston Rd, London NW1 2BU, UK.
Email: elizabeth.burt1@nhs.net

Abstract

Objective: Many women with Turner syndrome (TS) will consider fertility options and pregnancy. We wished to examine the fertility and pregnancy outcomes in women with TS undergoing oocyte donation (OD) treatment or spontaneous pregnancy in a large single-centre cohort. General population reference data or data from those with idiopathic premature ovarian insufficiency were used as comparators.

Design: A retrospective single-centre cross-sectional study.

Patients and Measurements: Seventy-four women with TS underwent OD treatment with a total of 105 pregnancies, and 31 women with TS had 71 spontaneous conceptions. Fertility outcomes included clinical pregnancy and live birth rate. Pregnancy outcomes included miscarriage rate, prevalence of hypertension, gestational diabetes, lower segment caesarean section (LSCS), small for gestational age (SGA), prematurity and vertical transmission of TS.

Results: In those with TS, OD pregnancies were associated with increased rates of LSCS and SGA compared to spontaneous pregnancies; LSCS (OR: 4.19, 95% CI: 1.6–10.8, $p = .003$) and SGA (OR: 2.92, 95% CI: 1.02–8.38, $p = .04$). There were no recorded cardiac events but 5 (17.2%) cases of vertical transmissions of TS in daughters were identified. OD in those with TS was associated with a lower live birth rate per cycle started (OR: 0.53, 95% CI: 0.34–0.84, $p = .008$) and a higher rate of miscarriage compared to women with POI (40% vs. 26.2%, $p = .04$).

Conclusions: We show that pregnancy in women with TS, whether OD or spontaneously conceived, carries obstetric risks, and therefore, women with TS, considering pregnancy, should receive comprehensive pre-pregnancy counselling and optimal obstetric care.

KEYWORDS

oocyte donation, premature ovarian insufficiency, spontaneous pregnancy, Turner syndrome, uterus

1 | INTRODUCTION

Turner syndrome (TS), with partial or complete loss of the X chromosome, renders the ovarian germ cell pool vulnerable to hastened atresia.[1] Accelerated oocyte apoptosis and impaired folliculogenesis occur during the prenatal and early postnatal period, and the karyotype can be predictive for the degree of ovarian preservation and function.[2] Those with monosomy are most susceptible to complete oocyte depletion. However, a proportion of women with TS will retain some ovarian activity, with spontaneous menarche occurring in 5%–20% of women and spontaneous pregnancy reported in 2%–8%.[3,4] For those with ovarian insufficiency, oocyte donation (OD) IVF is a treatment option for conception.

Pregnancy in women with TS carries excess risks above the general population, irrespective of mode of conception, with increased miscarriage rates and maternal sequelae especially aortic dissection.[5–8] Furthermore, OD pregnancies in women without TS are associated with elevated risk of hypertensive disorders of pregnancy, preterm birth, low birth weight and increased rates of lower segment caesarean section (LSCS).[9–11] Women with TS who retain ovarian function and have a spontaneous pregnancy, still have increased obstetric risks including miscarriage[5,12–14] and also risk passing on chromosomal anomalies to their offspring.[12,14,15] The latter, however, is poorly quantified in the literature making accurate clinical counselling a challenge.

In this study, we set out to examine reproductive outcomes in women with TS from a large single-centre cohort. In particular, we sought to compare the maternal outcomes in our cohort who received regular health surveillance and cardiology review with previously reported literature. In addition, we were able to compare OD pregnancy outcomes in TS with those in women with other causes of premature ovarian insufficiency (POI) attending our centre. Previous literature has used comparative data from OD pregnancies with indications including increased maternal age and women with naturally declining ovarian reserve. Women with idiopathic POI provide a better comparison group, and there have been no direct comparisons of fertility and OD pregnancy outcomes between those with TS and POI.

2 | MATERIALS AND METHODS

2.1 | Participants

In this retrospective single-centre cross-sectional study, participants were recruited from the dedicated TS clinics of the Reproductive Medicine Unit at University College London Hospital (UCLH). These clinics have attendance from throughout the UK. However, fertility treatment and antenatal services usually took place at a hospital local to the participant's home. The inclusion criteria for recruitment were age above 16 years, a diagnosis of TS with OD or spontaneous pregnancy. TS was diagnosed clinically and confirmed with karyotype analysis.

2.2 | Clinical data

We sought to identify all women who had tried to conceive or who had been pregnant by individual interviews and detailed note review.

The TS karyotype was recorded and, for the purposes of analysis for outcomes, was categorised into 45,X or other. Age at each cycle of OD or at each pregnancy was collected in addition to their current age. Height, weight and BMI (kg/m^2) measurements were recorded before the first fertility treatment or first pregnancy. The presence of treated hypothyroidism before fertility treatment or pregnancy was recorded (excluding those who had subclinical hypothyroidism treated at the time of fertility treatment). Menstrual cycle history included a record of primary or secondary amenorrhoea or regular menstrual cycles. The presence of hypertension (HTN) or diabetes before fertility or pregnancy was also recorded.

The TS clinical care guidelines, published in 2017, provide guidance on pre-pregnancy care and echocardiogram assessment based on aortic size index (ASI) and cardiac pathology.[16] This level of care was already in place at UCLH before formalisation of the recommendations, having been developed over the preceding 20 years. Regular echocardiogram assessment for women with TS every 2–5 years is standard routine health surveillance at UCLH with additional pre-pregnancy assessment. Furthermore, a detailed plan for recommended antenatal monitoring, including cardiology surveillance, is provided once pregnancy is confirmed, as most women will receive antenatal care in their local area.

Cardiac status in TS included the presence of cardiac pathology (bicuspid aortic valve or coarctation and repair of the aorta). Echocardiogram assessment, ASI and cardiology assessment before fertility treatment or pregnancy were recorded.

2.3 | Fertility treatment

Fertility treatment occurred between the years of 1986–2023. Given the changes in practice over time, moving towards elective single embryo transfer (eSET), and the fact that multiple fertility centres with varying protocols contributed to this data, variables predicting outcome were restricted to the recipient characteristics. The age of the donor, endometrial preparation protocol and thickness, number and stage of embryos, the use of fresh or vitrified embryos and sperm source were not included in the analysis.

The primary outcomes analysed were pregnancy rate and live birth rate per cycle started, with the delivery of multiple pregnancy counted as one live birth event, which is consistent with the reporting of Human Fertilisation Embryo Authority (HFEA). Treatment cycles were categorised into first cycles and subsequent cycles.

2.4 | Pregnancy data

Pregnancies were recorded between 1979 and 2023. Pregnancy history included mode of conception, either spontaneous conception or with OD. Miscarriage was defined as a pregnancy loss before 23 weeks and 6 days gestation, not including termination of pregnancy or ectopic pregnancy. Live birth was defined as the delivery of a live baby (or babies) after 24 + 0 weeks gestation. Intrauterine death (IUD) was defined as foetal demise after 24 weeks of gestation. Termination of pregnancy and the reason, if known, was recorded.

Gravidity was the number of pregnancies, and parity was defined as the number of pregnancies that developed past 24 weeks gestation. For outcomes, pregnancy was categorised into the first pregnancy and subsequent pregnancies/deliveries.

Pregnancy complications were recorded for those that developed past 24 weeks and resulted in live birth or IUD. All pregnancies, including multiple pregnancies were recorded, however given the known increased incidence of adverse maternal and neonatal outcomes associated with multiple pregnancy, only singleton pregnancies were included in the analysis of pregnancy complications.[17,18] Hypertensive disorders of pregnancy consisted of either pregnancy-induced HTN and/or preeclampsia and excluded those who had preexisting HTN. The development of gestational diabetes mellitus (GDM) was recorded and excluded those with preexisting diabetes mellitus. Mode of delivery was categorised into vaginal delivery including both spontaneous and instrumental delivery and LSCS, both elective and emergency.

Neonatal outcomes for each singleton pregnancy resulting in live birth after 24 weeks gestation included gestational age (weeks) at the time of delivery, with preterm birth being defined as delivery less than 37 + 0 weeks' gestation.[19] Birthweight percentile was calculated[20] and small for gestational age was defined as a birthweight less than the 10th percentile. Information regarding the health of offspring was included and the presence of chromosomal anomalies was recorded.

2.5 | Comparison to normative data

Outcome data for TS spontaneous pregnancies were compared to normative general population data. The rate of miscarriage in the general population is 15.3%.[21] Normative data for singleton spontaneous pregnancies was adapted from Storgaard et al.[9] The percentages used in this meta-analysis of each original paper for spontaneous singleton pregnancies were used, and a mean was calculated.

2.6 | Comparison group with POI

Participants were identified from the dedicated POI clinics of the Reproductive Medicine Unit at UCLH. For the purposes of this study, POI was defined as hypergonadotrophic hypogonadism with karyotype 46XX. Subjects were excluded if POI had resulted from oncology treatment. Clinical data, fertility treatment and pregnancy data were recorded as above. For those with POI, only OD pregnancies after the diagnosis were included for analysis, although prior pregnancies were recorded for the purpose of defining gravidity and parity.

2.7 | Statistical analysis

Statistical analysis was completed using SPSS version 27 for Mac. The Shapiro–Wilk test was used to test the normality of continuous variables. Height, weight, BMI, age at time of first fertility treatment, number of fertility cycles, age at pregnancy, gravidity, parity, gestational age and birth weight percentiles were not normally distributed. Birth weight was normally distributed. Therefore, for uniformity, variables were described in frequencies and percentages or median, 5th and 95th percentile and nonparametric tests were used for analysis. χ^2 analysis was used to examine the differences in categorical variables and to compare TS spontaneous pregnancy outcomes to normative general population data.

For binary fertility and pregnancy outcomes, regression analysis with forward selection (likelihood ratio) was used. Adjustment was made for age and cycle number for fertility outcomes. For early pregnancy outcomes adjustment was made for age and gravidity. For maternal and neonatal outcomes, adjustment was made for age and parity, given the association between some adverse pregnancy outcomes and advanced maternal age and parity.[10,22,23] Results were presented as odds ratio (OR) and 95% CI. Statistical significance was defined as a p value less than .05.

3 | RESULTS

3.1 | Participants with TS

Seventy-four women underwent OD treatment, and 31 women had spontaneous conception. Three women had both OD treatment and spontaneous pregnancies. The clinical characteristics of each group are shown in Table 1.

Karyotype analysis was recorded in 93 (91.1%) women with TS. Of those undergoing OD treatment, 28 had monosomy X, 17 isochromosome X, 9 mosaic 45,X/46,XX, 6 mosaic 45,X/46,XY, 6 mosaic 45,X/46,XrX and 1 partial X deletion. Sixteen (21.6%) women had a cardiac pathology: 14 bicuspid aortic valves and two previous surgery for aortic coarctation. Eight (10.8%) women had preexisting HTN and 5 (6.8%) preexisting diabetes. Twenty-three (31.1%) women had been treated for hypothyroidism. Sixty (81.1%) had primary amenorrhoea, 13 (17.6%) had secondary amenorrhoea and 1 (1.4%) had a regular cycle.

Karyotypes in those with TS and spontaneous conception were 14 with mosaic 45,X/46,XX, 6 complex anomalies, 4 partial X deletion, 2 mosaic 45,X/46,XY, 2 mosaic 45,X/46,XrX, 1

TABLE 1 Participant characteristics in women with TS undergoing either OD treatment or with spontaneous pregnancy.

	Turner syndrome		
	TS OD treatment	TS spontaneous	*p* Value
Number of women	74	31	
Height (m)	1.50 (1.39–1.59)	1.50 (1.42–1.71)	.53
BMI (kg/m^2)	25.6 (20.0–36.6)	24.5 (20.3–37.5)	.46
Monosomy X	28/67 (41.8%)	1/30 (3.3%)	<.001
Cardiac pathology	16/74 (21.6%)	4/31 (12.9%)	.23
Hypothyroidism	23/74 31.1%	4/31 (12.9%)	.05
Primary amenorrhoea	60/74 (81.1%)	2/31 (6.5%)	<.001

Note: Results are displayed as either median and 5th–95th percentile or percentage. Note three women had both an OD treatment and a spontaneous pregnancy. *p* Values were displayed for the subgroup analysis between the two groups.

Abbreviations: OD, oocyte donation; TS, Turner syndrome.

isochromosome X and 1 monosomy X. Four (12.9%) had a cardiac pathology: 2 bicuspid aortic valve, 1 previous surgery for aortic coarctation and 1 valvular surgery. No women had existing HTN or diabetes. Four (12.9%) women had treated hypothyroidism. Two (6.5%) had primary amenorrhoea, 3 (9.7%) had secondary amenorrhoea, and 26 (83.9%) had a regular menstrual cycle.

Ninety-one (89.2%) women had an echocardiogram before pregnancy and 49 (48%) had a dedicated pre-pregnancy cardiology consultation. ASI results were available for 81 women (79.4%) as 8 women had an echocardiogram examination in their local hospital and two women had a cardiology assessment with echocardiogram and the aortic measurements were described as normal, but no ASI was reported.

ASI was greater than 2 cm/m^2 in 16/81 (19.7%) and 12 of these women had a specialist cardiology review also. No woman had an ASI > 2.5 cm/m^2.

3.2 | Pregnancy outcomes in TS spontaneous pregnancy

Thirty-one women with TS had 71 spontaneous conceptions. Pregnancy outcome data can be seen in Table 2. Forty- three pregnancies (60.6%) resulted in live birth and 45 children were born; 41 singletons and 2 sets of twins. Twenty-three pregnancies (32.4%) resulted in miscarriage. Five TOPs were recorded in 4 women, the reason being social in 3 women and non-disclosed in the fourth.

There was no case of aortic dissection. In singleton pregnancies, the incidence of HTN pathology and GDM was 12.5% and 15%, respectively. The mode of delivery was LSCS in 51.2% (13 elective and 8 emergency). The rate of preterm delivery was 2/38 5.3% and SGA was 6/38 15.8%.

There were 29 female (64.4%) and 16 male babies (35.6%) born to women with TS and spontaneous pregnancy, giving a M:F ratio of 0.55. which is significantly different than the expected 24:21 based on the ratio of 1.06 in the general population ($p = .01$).[24]

There were 5 cases (17.2%) of daughters born with TS. The associated maternal karyotypes were 2 with 46,X,t(X;Y)(p22.3;q11), 1 with 46X,del(X) (Xq21.3), 1 with 46,X,r(X) and 1 with 46X,del(X) (p21.1). In the first 3 cases, the daughter's karyotype was the same as the mother's and in the latter cases the daughter's karyotype was unknown. Two cases of vertical transmission occurred over three generations within the same family.

3.3 | TS spontaneous pregnancies vs population reference data

The incidence of miscarriage in women with TS and spontaneous pregnancy was higher than the miscarriage rate in all recognised pregnancies in the general population of 15.3%[21] ($p \leq .001$). Compared to population data of spontaneous singleton pregnancy, TS spontaneous singleton pregnancies were associated with an increased rate of HTN pathology (12.5% vs. 2.9%, $p \leq .001$), GDM (15% vs. 3.7%, $p \leq .001$), LSCS (51.2% vs. 16.9%, $p \leq .001$) and SGA (15.8% vs. 2.7%, $p \leq .001$). There was no significant difference in the rate of preterm delivery.

3.4 | OD fertility treatment in TS

Information regarding participants undergoing OD and outcomes can be seen in Table 3. Seventy-four women with TS underwent OD. Three women had a spontaneous pregnancy before embarking on fertility treatment.

Information was collected for 196 cycles of fertility treatment in women with TS. Four cycles did not result in embryo transfer and were abandoned. The median number of cycles per patient was 2 (5th–95th percentile 1–7). The clinical pregnancy rate and live birth rate per cycle started were 53.6% and 31.1%, respectively.

3.5 | Pregnancy outcomes in TS after OD

Information regarding pregnancy outcomes can be seen in Table 2. Sixty-five women with TS had a total of 105 pregnancies after OD. Sixty-one pregnancies (58.1%) resulted in live birth and 70 children were born; 53 singletons, 7 sets of twins and 1 set of triplets. Forty-two (40%) pregnancies ended in miscarriage and 2 (1.9%) resulted in ectopic pregnancy.

There was no case of aortic dissection during pregnancy in those with TS and OD pregnancy. In those with TS and OD singleton pregnancies, excluding those with preexisting HTN or diabetes, the incidence of HTN pathology was 8/48 (16.7%) and GDM 4/51 (7.8%). Caesarean section was the mode of delivery in 44/53 (83%)

TABLE 2 Pregnancy outcomes in women with TS undergoing either OD or spontaneous pregnancy compared to women with POI and OD pregnancy and general population data.

	TS OD	TS spontaneous	TS OD versus TS spontaneous	POI OD	TS OD versus POI OD	Normative data spontaneous singleton pregnancy
Women (*n*)	65	31		50		
Pregnancies (*n*)	105	71		84		
Number of children born	70	45		73		
Live birth rate	61/105 (58.1%)	43/71 (60.6%)	0.74	62/84 (73.8%)	0.02	
Miscarriage rate	42/105 (40%)	23/71 (32.4%)[a]	0.30	22/84 (26.2%)	0.04	15.3%
Termination of pregnancy	0	5/71 (7%)		0		
Intrauterine death	0	0		0		
Singletons	53/61 (86.9%)	41/43 (95.3%)		51/62 (82.3%)		
Twins (sets)	7/61 (11.5%)	2/43 (4.7%)		11 (17.7%)		
Triplets (sets)	1/61 (1.6%)	0		0		
Age at pregnancy	34 (26–43.4)	27 (18–39)	<0.001	34.5 (27–43.5)	0.14	
HTN pathology	8/48 (16.7%)	5/40 (12.5%)[b]	0.56	10/48 (20.8%)	0.60	2.9%
GDM	4/51 (7.8%)	6/40 (15%)[b]	0.27	8/48 (16.7%)	0.17	3.7%
LSCS	44/53 (83%)	21/39 (51.2%)[b]	0.005	28/49 (57.1%)	0.004	16.9%
Preterm birth	9/51 (17.6%)	2/38 (5.3%)	0.07	4/47 (8.5%)	0.18	4.7%
SGA	17/48 (35.4%)	6/38 (15.8%)[b]	0.04	13/47 (27.7%)	0.41	2.7%

Note: Results are displayed as either median and 5th–95th percentile or percentage. *p* Values displayed for the subgroup analysis of modes of conception in those with TS, between diagnostic groups or compared to general population data.

Abbreviations: GDM, gestational diabetes mellitus; HTN, hypertension; LSCS, lower segment caesarean section; OD, oocyte donation; SGA, small for gestational age; TS, Turner syndrome.

[a]Significantly different than general population data (all pregnancies).

[b]Significantly different from general population data (spontaneous singleton pregnancies).

(emergency LSCS in 17/44 38.6% and elective LSCS in 27/44 61.4%). The incidence of preterm birth and SGA was 17.6% and 35.4%, respectively.

3.6 | Comparison of the mode of conception in TS

Women with TS who had a spontaneous pregnancy were younger than those undergoing OD pregnancy. There was no difference in height or BMI between the two conception modes; however, those undergoing OD were more likely to have 45,X, and primary amenorrhoea compared to those with spontaneous pregnancies.

Compared to TS spontaneous pregnancies, the rate of LSCS was significantly higher in those with OD pregnancy (83% vs. 51.2%, $p = .005$) as was the rate of SGA (35.4% vs. 15.8%, $p = .04$). There was no difference in the rate of live birth, miscarriage, HTN, GDM or preterm delivery. Regression analysis adjusting for age at pregnancy and parity showed the raised rates of both LSCS (OR: 4.19, 95% CI: 1.61–10.8, $p = .003$) and SGA (OR: 2.92, 95% CI: 1.02–8.38, $p = .04$) remain significant with no other parameter reaching significance.

3.7 | Comparison of fertility and OD pregnancy outcomes between TS and POI

Fifty-three women with POI underwent OD (Table 3). Four had a spontaneous pregnancy before embarking on fertility treatment. There was no difference in the age of the first treatment cycle between TS and POI. Women with TS were significantly shorter and had a higher BMI compared to those with POI. Women with TS were significantly more likely to have primary amenorrhoea than those

TABLE 3 Fertility treatment outcomes in women with Turner syndrome or premature ovarian insufficiency undergoing oocyte donation treatment.

	Oocyte donation subgroup		
	TS	POI	*p* Value
Total number of women	74	53	
Height (m)	1.50 (1.39–1.59)	1.65 (1.51–1.77)	<.001
BMI (kg/m^2)	25.6 (20.0–36.6)	22.7 (18.9–34.9)	.008
Hypothyroidism	23/74 (31.1%)	11/53 (20.8%)	.19
Primary amenorrhoea	60/74 (81.1%)	11/53 (20.8%)	<.001
Number of cycles	196	136	
Number of women with prior pregnancy	3	4	
Number of cycles per woman	2 (1–7)	2 (1–5)	.63
Age at first treatment (years)	33 (25–43.5)	33 (25.7–43.3)	.78
Abandoned cycles	4/196 (2%)	5/136 (3.7%)	.36
The pregnancy rate per cycle started	105/196 (53.6%)	84/136 (61.8%)	.13
The live birth rate per cycle started	61/196 (31.1%)	62/136 (45.6%)	.007

Note: Results are displayed as either median and 5th–95th percentile or percentage. *p* Values displayed for the subgroup analysis across the different diagnostic groups.

Abbreviation: TS, Turner syndrome.

with POI. In those with POI, Fragile X premutation was identified in four women. The prevalence of treated hypothyroidism was not different between TS and POI. No women with POI had preexisting HTN or diabetes.

Information was collected for 136 treatment cycles in women with POI. Five cycles did not result in embryo transfer and were abandoned. The median number of cycles per patient was 2 (5th–95th percentile 1–5).

Whilst the pregnancy rate per cycle started was not different between those with POI or TS, the live birth rate per cycle started was lower in those with TS than POI (TS 31.1% vs. POI 45.6%, $p = .007$). Regression analysis demonstrated that when adjusted for age and cycle number, TS was associated with a lower live birth rate per cycle started (OR: 0.53, 95% CI: 0.34–0.84, $p = .008$) with no other parameter reaching significance.

In the POI group, 50 women had 84 OD pregnancies, and 73 children were born. The pregnancy outcomes can be seen in Table 2. In the OD group, those with TS, compared to POI, had lower live birth and increased miscarriage rate (live birth 58.1% vs. 73.8%, $p = .02$ and miscarriage 40% vs. 26.2%, $p = .04$) which both remained significant with regression analysis adjusting for age and gravidity; OR for live birth of 0.49 (95% CI: 0.26–0.91, $p = .02$) and an OR for miscarriage of 1.87 (95% CI: 1.00–3.50, $p = .04$) with no other factor reaching significance. The rate of LSCS was greater in those with TS pregnancy (83% vs. 57.1%, $p = .004$) and when adjusted for parity and age at pregnancy, the OR was 4.26 (95% CI: 1.63–11.1, $p = .003$). No difference between the diagnostic groups was identified in the rate of HTN pathology, GDM, preterm birth or SGA.

4 | DISCUSSION

In this paper, we set out to examine fertility and pregnancy outcomes in women with TS from a large single-centre cohort. We show that overall pregnancy in women with TS, whether OD or spontaneously conceived, carries obstetric risks above the general population. Reassuringly there were no recorded cardiac events in this cohort. In spontaneous pregnancies, five cases of vertical transmissions were identified. Women with TS who had OD had a higher rate of miscarriage compared to women with POI using OD.

Whilst TS OD pregnancy is associated with increased rates of LSCS delivery and SGA compared to TS spontaneous pregnancy, the risk for other outcomes with OD was not different from those in spontaneous pregnancies suggesting that there is not an excessive summative risk of TS with OD.

Cardiac health is a particular focus in women with TS considering a pregnancy. Interestingly, no cardiac event including aortic dissection occurred during the antenatal or post-partum period, which are events reported in the literature.[5–8] The 2017 published TS clinical care guidelines outline that an echocardiogram should be completed within 2 years before conception with calculation of the ascending ASI. If the ASI > 2.5 cm/m^2 or between 2.0 and 2.5 cm/m^2 with compounding cardiac pathology such as bicuspid aortic valve, coarctation of the aorta, HTN, elongation of the transverse aorta or history of aortic dissection then pregnancy should be avoided. During pregnancy, as aortic dissection has occurred in women with normal pre-pregnancy cardiac status,[6] an echocardiogram should occur at least once at approximately 20 weeks of gestation in the absence of

any identified risk factors or every 4–8 weeks during pregnancy and up to 6 months postpartum if other risks present.[16]

The more favourable cardiovascular outcomes detailed in this paper may reflect the early adoption of pre-pregnancy cardiovascular surveillance guidelines at UCLH. Cardiology assessment dates back to pregnancies in 2001 and an echocardiogram in 1999. In this TS cohort of women seeking fertility, the prevalence of cardiac pathology was lower than the cited rate in the overall TS population of 25%–50%[14,25] suggesting that a degree of case selection had taken place.

HTN during pregnancy is more prevalent in this TS cohort (both OD and spontaneous pregnancy) compared to spontaneous conception population data, however our paper did not find a difference in HTN between the modes of conception in TS, which is in contrast to previous papers suggesting a summative risk of OD and TS.[6,7,26,27] Other more recent papers have found comparable levels between the conception groups.[8,14] Reassuringly, whilst women with TS undergoing pregnancy still pose a higher cardiovascular risk, the rate of HTN pathology in those with TS and spontaneous pregnancy (12.5%) and those undergoing OD (16.7%) in our study was on the lower side of the other quoted rates in the literature 11%–20% in those with spontaneous conception[12,14] and 15%–62.5% for OD.[6,7,13,27–29] Furthermore, there was not a significant difference in the rate of HTN pathology between TS and POI OD pregnancies, which is in contrast to other papers.[26,27] There may be many variables affecting the prevalence of HTN, including local treatment thresholds and decision making by the local team.

Vertical transmission of TS is a known risk in women with spontaneous conception. This has been poorly documented in past literature and as systematic screening has not been undertaken the real incidence remains unknown.[12,14,15,30,31] In the study by Birkebaek et al., chromosomal analysis was completed for 25 of the 64 (38.4%) children born following spontaneous conception in those with TS. Five girls (5/32 15.6%) were found to have chromosomal aberrations consistent with TS.[32] Tarani et al. reported 13 spontaneous pregnancies in six women with TS, and out of eight live births, two daughters had TS.[31] Bernard et al. reported the outcomes from 56 spontaneous pregnancies in women with TS, and in those 30 children born, TS was detected in two daughters (6.6%) and trisomy 21 and 13 in others.[12] In the series by Calanchini, TS was diagnosed in one female in adulthood and she was found to have the same karyotype as her mother.[14]

We demonstrated a higher rate of vertical transmission than that previously highlighted in the literature partly because of one family passing on mosaic an X;Y translocation over three generations. This karyotype has been shown to be prone to transmission previously.[33] As a consequence of our findings, we recommend that preconception consultation should include a discussion regarding the option of prenatal or antenatal genetic counselling.

In those with TS undergoing OD, we found a pregnancy rate per cycle of 53.6% which is comparable to other papers of women with TS which vary between 33% and 57%.[27,29] Encouragingly, the live birth per cycle started in our cohort of 31.1% in those with TS is comparable to or higher than other reports of 3.2%, 17.9% and 27% and 33%.[6,14,27,32] We found that the pregnancy rate per cycle was similar between TS and POI, as has been reported by other groups comparing pregnancy rates to oocyte recipients for other indications.[32,34,35] We demonstrated a lower live birth rate per cycle started in women with TS undergoing OD compared to POI. This was not accounted for by abandoned cycles. One explanation may be deficient uterine and endometrial integrity in those with TS affecting optimal embryo implantation.

Miscarriage in TS is raised regardless of the mode of conception.[5,6,13,27,31,32,36] We identified a higher miscarriage rate in those with TS compared to both POI and general population data. In women with TS and OD pregnancies, the rates of miscarriage in the literature vary from 25% to 44% compared to our rate of 40%.[5,13,14,27,29] The higher miscarriage rate witnessed for both TS and POI with OD may be coupled with the higher prevalence of thyroid pathology and autoimmunity associated with these diagnoses.[16,37] Despite the occurrence of hypothyroidism being similar in those with TS and POI, there was still an elevated miscarriage rate and lower live birth rate in those with TS OD, suggesting that mechanisms other than thyroid dysfunction may be implicated, perhaps uterine factors. The earlier loss of ovarian activity in those with TS, compared to POI, leads to a higher proportion with primary amenorrhoea necessitating pubertal induction treatment. Despite seemingly sufficient exogenous oestrogen therapy, uterine size is often reduced compared to women with normal puberty.[38] However, the increased risk was also seen in those with secondary amenorrhoea and those with spontaneous conception, suggesting other compounding inherent factors affecting uterine function such as poor endometrial thickness, deficient uterine vascularity, collagen deficiency, lack of X-linked genes regulating endometrial receptivity or poor epithelial integrity with lack of tight junctions.[34,35,39,40]

The miscarriage rate in women with TS experiencing spontaneous pregnancy in this study was 32.4%, which falls in the ranges previously reported between 22.8% and 67.3%.[5,13,14,31] In our paper, we found a comparable rate of miscarriage in those with TS undergoing OD or spontaneous pregnancies which challenges the hypothesis previously suggested that oocytes from women the TS carry an increased risk of aneuploidy.[5,31]

The rate of LSCS was higher in women with TS irrespective of mode of conception and when compared with either population reference data or our POI cohort, consistent with previous reports.[6,11–13,34,39] The increased rate of LSCS in women has been linked to multiple factors, including short stature and feto-pelvic disproportion,[12,24] avoidance of exacerbation of underlying cardiovascular disease, expedited delivery due to maternal/foetal indications or patient preference. Whilst many women with TS will have an LSCS, and LSCS may be the preferred mode of delivery for some patients and obstetricians, it should not be overlooked that LSCS also poses risks and is itself associated with haemodynamic changes.[16] Therefore, LSCS should not be the default, and vaginal delivery should not be excluded. Notably, 29% of women with TS achieved a vaginal delivery, so a trial of labour may be possible depending on the multidisciplinary team review.

Pregnancies in women with TS have been shown to be associated with increased rates of prematurity and low birth weight.[6,7,9,12,13,27–29] This may be placentally driven[9] or alternatively, the HTN disorders may cause intrauterine growth restriction and, in turn, precipitate premature delivery. Concurring with this, we demonstrate higher rates of SGA in TS OD pregnancies compared to TS spontaneous conceptions and general population reference data. Premature delivery, however, was not found to be different between TS spontaneous and TS OD pregnancies, which is in contrast with some earlier studies,[7,27] but not others,[6,8] possibly reflecting differences in active management of complications minimising the need for expedited delivery and iatrogenic prematurity.

eSET should be standard best fertility practice and in those with TS planning OD treatment eSET should be particularly advocated to minimise the additional maternal and perinatal morbidity and mortality associated with multiple pregnancy.[17,18] The better maternofoetal outcomes in our paper maybe because we limited analysis to singleton pregnancies, however the multiple pregnancy rate in our TS OD cohort is low at 13.1%. Given our data covers several years predating the HFEA 'One at a Time' campaign in 2007, our rate of multiple pregnancies is encouraging, suggesting that patient education and adherence to policy is being met. Historically, eSET was less common, the paper by Chevalier et al. reported a double and triple embryo transfer of 40% and 18%, respectively[7] and multiple pregnancies may have contributed to increased adverse outcomes in earlier papers.

We demonstrated a predominance of female offspring following spontaneous conception in women with TS. This is to be expected as a 45,Y0 karyotype would not result in a viable pregnancy. Other authors have also commented on this finding with calculated M:F ratios between 0.37 and 0.84.[12,14,24]

We are aware of several limitations of our study. Information was gathered mainly by patient recall which may have led to some inaccuracies, however the reliability of self-reported pregnancy outcomes has been investigated by other groups, with reassuring results.[41] We were not able to obtain the karyotype of two of the daughters born with TS as the mothers were lost to follow-up. Locating all the antenatal cardiac data is challenging as antenatal care took place in other centres local to the patient's home. Furthermore, all karyotypes were not available as the paediatric data was not accessible in some cases.

In conclusion, women with TS considering pregnancy should receive comprehensive education regarding pregnancy and understand that overall pregnancy may pose a higher risk than those without TS. Pre-pregnancy counselling for those with TS who have the possibility of spontaneous pregnancy needs to address the possibility of vertical transmission. Overall our results on the risk of pregnancy are reassuring, and it is possible that improved cardiovascular screening and obstetric management are already showing the benefits of guidelines for adult care of women with TS.[16]

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Participants gave informed consent to take part in the study as part of the Turner Syndrome Life Project and The Reproductive Development Life Course Project (LO/2174 and 16/LO/0682 Chelsea Research Ethics Committee).

ORCID

Elizabeth Burt http://orcid.org/0000-0003-3801-0151
Gerard S. Conway http://orcid.org/0000-0002-3346-5029

REFERENCES

1. Modi DN, Sane S, Bhartiya D. Accelerated germ cell apoptosis in sex chromosome aneuploid fetal human gonads. *Mol Hum Reprod*. 2003;9(4):219-225.
2. Castronovo C, Rossetti R, Rusconi D, et al. Gene dosage as a relevant mechanism contributing to the determination of ovarian function in Turner syndrome. *Hum Reprod*. 2014;29(2):368-379.
3. Pasqualini-Adamo J. [Turner's syndrome and pregnancy]. *Rev Fr Gynecol Obstet*. 1988;83(11):717-721.
4. Dabrowski E, Jensen R, Johnson EK, Habiby RL, Brickman WJ, Finlayson C. Turner syndrome systematic review: spontaneous thelarche and menarche stratified by karyotype. *Hormone Res Paediatr*. 2019;92(3):143-149.
5. Bryman I, Sylvén L, Berntorp K, et al. Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertil Steril*. 2011;95(8):2507-2510.
6. Hagman A, Loft A, Wennerholm UB, et al. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod*. 2013;28(6):1598-1609.
7. Chevalier N, Letur H, Lelannou D, et al. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *The J Clin Endocrinol Metabolism*. 2011;96(2):E260-E267.
8. Cauldwell M, Steer P, Adamson D, et al. Pregnancies in women with Turner syndrome: a retrospective multicentre UK study. *BJOG: An Int J Obstetr Gynaecol*. 2022;129(5):796-803.
9. Storgaard M, Loft A, Bergh C, et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. *BJOG: An Int J Obstetr Gynaecol*. 2017;124(4):561-572.
10. Elenis E, Svanberg AS, Lampic C, Skalkidou A, Åkerud H, Sydsjö G. Adverse obstetric outcomes in pregnancies resulting from oocyte donation: a retrospective cohort case study in Sweden. *BMC Preg Childbirth*. 2015;15:247.
11. van der Hoorn MLP, Lashley EELO, Bianchi DW, Claas FHJ, Schonkeren CMC, Scherjon SA. Clinical and immunologic aspects of egg donation pregnancies: a systematic review. *Hum Reprod Update*. 2010;16(6):704-712.
12. Bernard V, Donadille B, Zenaty D, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Hum Reprod*. 2016;31(4):782-788.
13. Cadoret F, Parinaud J, Bettiol C, et al. Pregnancy outcome in Turner syndrome: a French multi-center study after the 2009 guidelines. *Eur J Obstet Gynecol Reprod Biol*. 2018;229:20-25.

14. Calanchini M, Aye CYL, Orchard E, et al. Fertility issues and pregnancy outcomes in Turner syndrome. *Fertil Steril*. 2020;114(1):144-154.
15. Birkebaek N, Crüger D, Hansen J, Nielsen J, Bruun-Petersen G. Fertility and pregnancy outcome in Danish women with Turner syndrome. *Clin Genet*. 2002;61(1):35-39.
16. Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome. *Eur J Endocrinol*. 2017;177(3):G1-G70
17. Kilby MD, Bricker L, on behalf of the Royal College of Obstetricians and Gynaecologists. Management of monochorionic twin pregnancy. *BJOG*. 2016;124(1):e1-e45.
18. Twin and triplet pregnancy. National Institute for Health and Care Excellence: Guidelines. 2009.
19. Preterm labour and birth. National Institute for Health and Care Excellence: Guidelines. 2009.
20. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol*. 2018;52(1):44-51.
21. Quenby S, Gallos ID, Dhillon-Smith RK, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397(10285):1658-1667.
22. Chauhan SP, Rice MM, Grobman WA, et al. Neonatal and maternal composite adverse outcomes among low-risk nulliparous women compared with multiparous women at 39-41 weeks of gestation. *Obstetr Gynecol*. 2020;136(3):450-457.
23. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. *PLoS One*. 2013;8(2):e56583.
24. Hagman A, Källén K, Barrenäs ML, et al. Obstetric outcomes in women with Turner karyotype. *The J Clin Endocrinol Metabolism*. 2011;96(11):3475-3482.
25. Donadille B, Christin-Maitre S. Heart and Turner syndrome. *Ann Endocrinol*. 2021;82(3-4):135-140.
26. Karnis M. Catastrophic consequences of assisted reproduction: the case of Turner syndrome. *Semin Reprod Med*. 2012;30(2):116-122.
27. Bodri D, Vernaeve V, Figueras F, Vidal R, Guillén JJ, Coll O. Oocyte donation in patients with Turner's syndrome: a successful technique but with an accompanying high risk of hypertensive disorders during pregnancy. *Hum Reprod*. 2006;21(3):829-832.
28. Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the US National Institutes of Health experience. *Fertil Steril*. 2011;95(7):2251-2256.
29. Mercadal BA, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner's syndrome and partial X monosomy. *Hum Reprod*. 2011;26(8):2061-2068.
30. Blumenthal AL, Allanson JE. Turner syndrome in a mother and daughter: r(X) and fertility. *Clin Genet*. 1997;52(3):187-191.
31. Tarani L, Lampariello S, Raguso G, et al. Pregnancy in patients with Turner's syndrome: six new cases and review of literature. *Gynecol Endocrinol*. 1998;12(2):83-87.
32. Bodri D, Guillén JJ, Schwenn K, Casadesus S, Vidal R, Coll O. Poor outcome in oocyte donation after elective transfer of a single cleavage-stage embryo in Turner syndrome patients. *Fertil Steril*. 2009;91(4 suppl):1489-1492.
33. Portnoï MF, Chantot-Bastaraud S, Christin-Maitre S, et al. Familial Turner syndrome with an X;Y translocation mosaicism: implications for genetic counseling. *Eur J Med Genet*. 2012;55(11):635-640.
34. Yaron Y, Ochshorn Y, Amit A, Yovel I, Kogosowski A, Lessing JB. Patients with Turner's syndrome may have an inherent endometrial abnormality affecting receptivity in oocyte donation. *Fertil Steril*. 1996;65(6):1249-1252.
35. Foudila T, Soderstrom-Anttila V, Hovatta O. Turner's syndrome and pregnancies after oocyte donation. *Hum Reprod*. 1999;14(2):532-535.
36. Andre H, Pimentel C, Veau S, et al. Pregnancies and obstetrical prognosis after oocyte donation in Turner syndrome: a multicentric study. *Eur J Obstet Gynecol Reprod Biol*. 2019;238:73-77.
37. Webber L, Davies M, Anderson R, et al. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI. ESHRE guideline: management of women with premature ovarian insufficiency. *Hum Reprod*. 2016;31(5):926-937.
38. Burt E, Davies MC, Yasmin E, et al. Reduced uterine volume after induction of puberty in women with hypogonadism. *Clin Endocrinol*. 2019;91(6):798-804.
39. Khastgir G, Abdalla H, Thomas A, Korea L, Latarche L, Studd J. Oocyte donation in Turner's syndrome: an analysis of the factors affecting the outcome. *Hum Reprod*. 1997;12(2):279-285.
40. Rogers PAW, Murphy CR, Leeton J, Hosie MJ, Beaton L. Turner's syndrome patients lack tight junctions between uterine epithelial cells. *Hum Reprod*. 1992;7(6):883-885.
41. Farland LV, Prescott J, Sasamoto N, et al. Endometriosis and risk of adverse pregnancy outcomes. *Obstetr Gynecol*. 2019;134(3):527-536.

How to cite this article: Burt E, Davies MC, Yasmin E, et al. Fertility and pregnancy outcomes in women with Turner syndrome: a single centre experience. *Clin Endocrinol (Oxf)*. 2024;101:51-59. doi:10.1111/cen.15078