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Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study

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STUDY QUESTION: What are the obstetric and neonatal outcomes of deliveries after oocyte donation (OD) in women with Turner syndrome (TS)?

SUMMARY ANSWER: Pregnancies among women with TS carry a substantial risk, particularly for hypertensive disorders. Potentially life-threatening complications occurred in 3.3% of pregnancies. The neonatal outcomes were generally reassuring, with similar rates of preterm birth and low birthweight (LBW) as after conventional IVF and better than previously reported in deliveries after OD in women with TS.

WHAT IS KNOWN ALREADY: OD pregnancies in women with TS are known to be high-risk pregnancies.

STUDY DESIGN, SIZE, DURATION: This retrospective cohort study included 106 women with TS who delivered after OD ($n = 122$ deliveries, $n = 131$ newborns) in three Nordic countries (Finland, Denmark, Sweden) between 1992 and 2011.

PARTICIPANTS, SETTING AND METHODS: Women with TS who delivered after OD in three Nordic countries were identified ($n = 110$). Four women declined to participate or were lost to follow-up, thus 106 women were included in the study. The medical data from fertility clinics, antenatal clinics and the hospitals where the women had been treated and/or delivered were scrutinized.

MAIN RESULTS AND THE ROLE OF CHANCE: In this cohort, the karyotype was 45,X in 44% of the women with TS. Ten women (9.4%) had a known cardiac defect before pregnancy. Single embryo transfer was performed in 70.3% of the cases and the multiple birth rate was 7.4%. In total, 35.0% of the pregnancies were associated with a hypertensive disorder including pre-eclampsia in 20.5%. Potentially life-threatening complications occurred in four pregnancies (3.3%), including one woman with aortic dissection, one with mild regurgitation of the tricuspid and mitral valve, one with a mechanical heart valve who developed HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) and one who underwent a post-partum hysterectomy due to severe haemorrhaging. Neonatal outcomes were reassuring, with a preterm birth rate of 8.0% and LBW rate of 8.8% in singletons. Major birth defects were found in 3.8% of the children. The perinatal mortality was 2.3% (3/131), including a set of extremely preterm twins.

LIMITATIONS, REASONS FOR CAUTION: Although this study was performed over a period of almost 20 years in three different countries, with a low drop-out rate and little missing data, much larger series are needed to assess rare events. This study also lacks an appropriate control group.

WIDER IMPLICATIONS OF THE FINDINGS: This study suggests that cardiovascular evaluation before and during pregnancy may contribute to favourable obstetric outcomes in many cases. Maternal outcomes were in agreement with the literature while neonatal outcomes were generally better than previously reported. The outcomes were consistent across the three countries, supporting generalizability to similar populations.

STUDY FUNDING/COMPETING INTEREST(S): No conflict of interest was reported. The study was supported by grants from the Gothenburg Medical Society, the Medical Care Executive Board of the Region Västra Götaland, grants from the ALF agreement at the Sahlgrenska University Hospital, the Hjalmar Svensson foundation, NFOG Nordic Fund, the Finnish Society of Paediatric and Adolescent Gynecology and *Liv och hälsa* Foundation in Finland. The Nordic Expert group's research work was unconditionally supported by MSD Finland, Norway and Denmark.

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Key words: Turner syndrome / oocyte donation / outcome / perinatal

Introduction

Turner syndrome (TS) is caused by X chromosome abnormalities, most commonly by the 45,X karyotype. The syndrome is associated with reduced adult height, hypergonadotropic ovarian failure and infertility or subfertility. Spontaneous pregnancies occur in only 2–7% of women with TS (Tarani *et al.*, 1998; Birkebaek *et al.*, 2002; Bryman *et al.*, 2011) and pregnancies in women with 45,X monosomy are hardly ever seen.

Oocyte donation (OD) has, since the first delivery in 1984 (Lutjen *et al.*, 1985), been an option for treatment in infertility in women with TS. Pregnancy rates after embryo transfer with donated oocytes in women with TS are the same or similar to those observed in other groups of oocyte recipients (Press *et al.*, 1995; Yaron *et al.*, 1996; Foudila *et al.*, 1999).

However, pregnancies achieved with donated oocytes are associated with a high incidence of first trimester bleeding and a 2- to 3-fold higher risk of gestational hypertension and pre-eclampsia when compared with conventional IVF (Serhal and Craft, 1989; Abdalla *et al.*, 1998; Söderstrom-Anttila *et al.*, 1998; Yaron *et al.*, 1998; Klein and Sauer, 2002; Sheffer-Mimouni *et al.*, 2002; Wiggins and Main 2005; van der Hoorn *et al.*, 2010; Stoop *et al.*, 2012). The incidences of intrauterine growth restriction, preterm birth (PTB) and birth defects have mostly been comparable with conventional IVF (van der Hoorn *et al.*, 2010), although impaired fetal growth in OD pregnancies when compared with conventional IVF has been noted (Gibbons *et al.*, 2011).

Studies on obstetric and perinatal outcome in Turner OD pregnancies are few, but an exceptionally high risk of complications, especially hypertensive disorders and pre-eclampsia, has been reported. The frequency of gestational hypertension and pre-eclampsia has varied between 36 and 63% (Foudila *et al.*, 1999; Bodri *et al.*, 2006; Alvaro Mercadal *et al.*, 2011; Chevalier *et al.*, 2011). High rates of PTB and small for gestational age (SGA) have also been reported (Bodri *et al.*, 2006; Chevalier *et al.*, 2011).

Concern has been raised regarding serious pregnancy risks for the mother, including death due to obstetric complications, in combination with pre-existing maternal cardiovascular abnormalities (Chevalier *et al.*, 2011; Karnis, 2012). Women with TS have a 25–50% incidence of congenital cardiovascular malformations, the most common being aortic coarctation and a bicuspid valve (Ho *et al.*, 2004; Sachdev *et al.*, 2008; Mortensen *et al.*, 2012). They also have a pre-disposition for dilatation of the aortic root, in some cases leading to aortic dissection (Carlson and Silberbach, 2007; Mortensen *et al.*, 2012). Aortic dilatation and dissection are associated with an intimal medial thickness of the aortic wall, causing it to weaken. Estrogen deficiency might contribute to this intimal thickening (Ostberg *et al.*, 2005; Mortensen *et al.*, 2012). In 2003, Karnis *et al.* (2003) reported that the risk of death from rupture of aortic dissection during pregnancy may be 2% or higher. The authors also found that only ~50% of women with TS in the USA had a cardiac examination before fertility treatment. Consequently, the American Society for Reproductive Medicine has introduced specific recommendations for screening and management of women with TS before and during pregnancy (ASRM, 2012). To our knowledge, nine cases of aortic dissection have been reported in pregnant women with TS after OD and of these, only two women survived (Carlson and Silberbach, 2007; Chevalier *et al.*, 2011). The total number of TS women treated with OD is unknown.

In the Nordic countries, women with TS have been treated with OD since 1992 when OD was started in Finland and Denmark. The first Finnish experience of OD treatment in 18 women with TS produced 11 deliveries but showed a high rate of spontaneous abortion (40%), and gestational hypertension and pre-eclampsia were present in 36% of the pregnancies (Foudila *et al.*, 1999). In Denmark, treatment with donated oocytes has been registered in the IVF Register since 1994 and in Sweden OD has been allowed since 2003, while in Norway OD is still prohibited by law.

The aim of this retrospective Nordic cohort study was to analyse obstetric and neonatal outcomes after OD in women with TS, who gave birth between January 1992 and January 2011.

Additional aims were to assess the prevalence of cardiac examinations before and during pregnancy, and the incidence of maternal mortality as well as the causes of deaths during pregnancy and up to 3 months post-partum.

Materials and Methods

The study included women with TS who gave birth after treatment with OD in Finland, Denmark and Sweden between 1992 and 2011. Data regarding general health, as well as obstetric and neonatal outcomes of the women and their newborns were collected.

In Finland, all fertility clinics performing OD treatment were contacted and asked to identify women with TS who had delivered after OD

treatment. Written informed consent from these women was obtained. Data regarding karyotype, follow-up of basic health and pregnancy outcomes were collected from medical records of paediatric, gynaecological and obstetric hospitals. Data on OD treatments and embryo transfers were obtained from the fertility clinics. Information about Finnish donors and hormone replacement therapy (HRT) in women with TS has been reported in detail in a previous publication (Foudila *et al.*, 1999). Briefly, the recipients used estradiol valerate 4–8 mg daily for ~2 weeks before embryo transfer. Micronized vaginally administered progesterone (Lugesteron; Leiras, Turku, Finland) was started on the day of the donor's oocyte retrieval. If this resulted in pregnancy, the HRT was gradually diminished and stopped at 12 weeks of gestation. Although it was possible to use a known oocyte donor, e.g. a sister or friend, in Finland from 1992 to 2007, most oocyte donors were anonymous to the recipient couple. Since September 2007, it has been mandatory that all unknown donors in Finland must be registered with identifying information in a national donor register, which makes it possible for the children born from these pregnancies to obtain information about the donor after they turned 18 years.

In Denmark, all women with a delivery after OD were identified by cross-linking the Danish IVF Registry and the Medical Birth Register (MBR) using the Central Personal Registry (CPR) number. The CPR numbers of the women were cross-linked with the Cytogenetic Central Register to identify women with TS and to identify the exact karyotype. Thereafter the diagnoses of the women with TS were obtained from the National Discharge Registry. The CPR numbers of the children and perinatal data were extracted from the MBR. By contacting the women with TS and after written informed consent, supplementary data were collected from the medical records from the fertility clinics (seven public and five private clinics performed OD) and other relevant hospitals. Until January 2007, only anonymous OD from IVF treated women younger than 36 years was allowed (oocyte sharing), but since then the Danish legislation has permitted anonymous OD from healthy women. In Denmark OD is carried out at private and public clinics, although most OD has been performed at public fertility clinics. The donors receive no payment and throughout the whole study period the oocyte supply was far below demand in Denmark. Consequently, no matching between donor and recipient was possible. The recipients were treated with high doses of estrogen, normally 6 mg from cycle day 2 for at least 10 days. On the day of hCG injection to the donor, the recipient started treatment with vaginally administered progesterone. If pregnancy was obtained, the hormone therapy continued until gestational weeks 8–10.

In Sweden, all fertility clinics performing OD (all were public clinics) were contacted and asked to identify all women with TS treated with OD resulting in a delivery. Written informed consent was obtained from the women. Data regarding general health, cardiac examination, pregnancy, delivery and neonatal outcomes were collected from the medical records from fertility clinics, antenatal clinics and the hospitals where the women had been treated and/or delivered. Oocyte donors in Sweden are matched with recipients for height, weight, eye and hair colour if possible. HRT is given to TS recipients, with a high dose of estrogen for at least 10 days. Progesterone is added 2 days before embryo transfer. Luteal support is given until 12 gestational weeks, in a decreasing schedule. In Sweden, all donors are open-identity donors and the child has the option of receiving identifying information at a mature age.

The following maternal characteristics were recorded: karyotype, age at diagnosis, pre-existing diseases including congenital cardiac disease, pre-pregnancy and pregnancy cardiac examination, age at delivery, height, body mass index (BMI) and smoking habits at the first antenatal visit, previous deliveries, pregnancy and delivery outcomes and mode of delivery.

Karyotypes were subgrouped into 45,X monosomy, 45,X/46,XX mosaics or other TS karyotype. Other TS karyotypes included: 45,X/46X,i(X) and 46,X,i(X), 45,X/46XY 45,X/46,XY/47,XXX, 45,X/47,XXX, 45,X/46,XX/47,XXX/48,XXXX, 45,X/46der(X) (including ring chromosomes, deletions, inversions and translocations). In most cases of mosaicism, no information about the percentages of mosaic cell lines was available. Gestational hypertension was defined as a blood pressure ≥140/90 mm Hg after 20 weeks of gestation in at least two readings ≥4 h apart. Pre-eclampsia was defined as sustained increase in blood pressure to ≥140/90 mm Hg after 20 weeks of gestation combined with proteinuria of at least 1+ or more on a semi-quantitative dipstick; hypertension and proteinuria were to be apparent on two different occasions of at least 4 h apart.

Neonatal outcomes included data on median gestational age (determined according to the day of embryo transfer, which varied from Day 16–19), PTB (<37 weeks), very preterm birth (<32 weeks), extreme PTB (<28 weeks), mean birthweight, low birthweight (LBW) (<2500 g), very LBW (<1500 g), extreme LBW (<1000 g), SGA defined as < −2 standard deviations (SDs) below the Swedish growth standard (Maršál *et al.*, 1996), large for gestational age defined as > +2 SDs above the Swedish growth standard, low Apgar score (<7 at 5 min), admissions to neonatal intensive care units (NICU), birth defects (any Q codes according to the international classification of diseases (ICD) 9 or 10) and perinatal mortality (stillbirths and live born infants with death within the first week of life). In Finland, all stillbirths after 22 completed gestational weeks were included. In Denmark, all stillbirths after 28 completed gestational weeks were included until 2004 and thereafter all stillbirths after 22 completed gestational weeks were included. In Sweden, all stillbirths after 28 completed gestational weeks were included until 1 July 2008 and thereafter all stillbirths after 22 completed gestational weeks were included.

Obstetric outcomes in 11 women with TS from Finland and in 11 women with TS from Sweden included in this study have been reported previously (Foudila *et al.*, 1999; Hagman *et al.*, 2011). All women with TS from Denmark are also included in the study by Malchau *et al.* (2013).

Statistical methods

Data were analysed using a statistical software package (SPSS, PASW Statistics 18). Descriptive data are presented for continuous variables as median and range or mean and SDs and for categorical data as numbers and percentages. Comparison between continuous variables was performed with the Mann–Whitney *U*-test. Data are presented for all women and deliveries, for each country, for singletons and twins separately and for each karyotype. Selected outcomes in women with 45,X monosomy were compared with outcomes in women with a mosaic or other TS karyotype.

Ethical approval

The study received approvals from the Ethics Committee of Gynecology and Obstetrics, Paediatrics and Psychiatry, Hospital district of Helsinki and Uusimaa, Finland and from the Regional Ethics Committee in Sweden, at the University of Gothenburg (Dnr 693-10).

According to the Danish legislation, studies based on register data and questionnaires do not require approval from an ethics committee. The study was approved by the Danish Data Protection Agency (CVR-no11-88-37-29) and the National Board of Health.

Results

In all, 110 women with TS who gave birth between 1992 and January 2011 were identified. In Finland, all 10 clinics performing OD were

contacted, 6 clinics participated, 3 clinics had not treated women with TS and 1 clinic who had treated 2 patients resulting in 2 live births did not participate. In Denmark, only one woman of all those identified with a delivery after OD declined to participate. In Sweden, all seven IVF clinics performing OD responded. One woman with TS in Sweden declined to participate. Therefore, data on 106 women with 122 deliveries and 131 newborns were available for analysis.

Maternal background

Maternal background characteristics are presented in Tables I and II. Of the women with TS, 44.0% (44/100) had a 45,X karyotype, 16.0% (16/100) had a 45,X/46,XX mosaicism and 40% (40/100) had other TS karyotypes. None of the women had low-grade mosaicism (<6%), although the degree of mosaicism was not known for all women. The median height of the women was 154 (138–170) cm.

Table I Background characteristics[a] in women with TS who delivered after OD in the Nordic countries 1992–2011.

	Finland (1992–2011)	Denmark (1994–2011)	Sweden (2003–2011)	All
Women with TS, *n*	39	35	32	106
Karyotype				
Monosomy, *n* (%)	17/35 (48.6)	13/35 (37.1)	14/30 (46.7)	44/100 (44.0)
45,X/46,XX mosaic, *n* (%)	6/35 (17.1)	7/35 (20.0)	3/30 (10.0)	16/100 (16.0)
Other TS karyotypes[b], *n* (%)	12/35 (34.3)	15/35 (42.9)	13/30 (43.3)	40/100 (40.0)
Age at diagnosis, median (range)	14.0 (0–37)	14.0 (0–42)	12.0 (0–22)	13.0 (0–42)
Unknown, *n*	3	1	9	13
Height, cm, median (range)	153 (140–170)	152 (138–169)	156 (140–164)	154 (138–170)
Unknown, *n*	0	1	0	1
BMI, median (range)	24 (20–42)	24 (18–32)	25 (19–33)	24 (18–42)
Unknown, *n*	1	1	0	2
Smoking, yes, *n* (%)[c]	6/37 (16.2)	7/31 (22.6)	1/32 (3.1)	14/100 (14.0)
Chronic hypertension[d], *n* (%)	2/39 (5.1)	1/35 (2.9)	1/32 (3.1)	4/106 (3.8)
Diabetes mellitus[d], *n* (%)	1/39 (2.6)	2/35 (5.7)	1/32 (3.1)	4/106 (3.8)
Thyroid disease[d], *n* (%)	3/39 (7.7)	6/35 (17.1)	14/32 (43.8)	23[e]/106 (21.7)
Renal disease[d], *n* (%)	1/39 (2.6)	0/35 (0.0)	5/32 (15.6)	6[f]/106 (1.9)
Hepatic disease[d], *n* (%)	1/39 (2.6)	0/35 (0.0)	1/32 (3.1)	2[g]/106 (1.9)
Congenital heart defects[d], *n* (%)	4[h]/39 (10.3)	4[i]/35 (11.4)	2[j]/32 (6.3)	10/106 (9.4)
Cardiovascular examination before pregnancy[k], *n* (%)	28/48 (58.3)	14/36 (38.9)	31/31 (100)	73/115 (63.5)
Cardiovascular examination <2 years before pregnancy[k], *n* (%)	23/48 (47.9)	11/36 (30.6)	22/31 (71.0)	56/115 (48.7)
Cardiovascular examination with ECG/MRI during pregnancy[k], *n* (%)	9/43 (20.9)	9/36 (25.0)	17/26 (65.4)	35/122 (28.7)
Age of mother at first OD delivery, median (range)	31.0 (22–42)	33.0 (23–46)	31.5 (23–40)	32.0 (22–46)
Unknown, *n*	0	0	0	0
Nulliparity at first OD delivery, *n* (%)	39/39 (100)	34/35 (97.1)	32/32 (100)	105/106 (99.1)
Women with 1 OD delivery, *n* (%)	28/39 (71.8)	33/35 (94.3)	29/32 (90.6)	90/106 (84.9)
Women with 2 OD deliveries, *n* (%)	11/39 (28.2)	2/35 (5.7)	3/32 (9.4)	16/106 (15.1)

BMI, body mass index; ECG, echocardiography; MRI, magnetic resonance imaging.
[a]There are missing data on some outcomes.
[b]Other = 45,X/46X,i(X) 46X,i(X) 45,X/46,XY 45,X/46,XY/47,XXX 45,X/47,XXX 45,X/46,XX/47,XXX/48,XXXX 45,X/46der(X) (including ring chromosomes, deletions, inversions and translocations).
[c]At first antenatal appointment at first OD delivery.
[d]A woman can have more than one disease.
[e]Hypothyroidism ($n = 21$), hyperthyroidism ($n = 2$).
[f]Bilateral double renal pelvis ($n = 1$), nephrotic syndrome ($n = 1$), renal transplant due to haemolytic uraemic syndrome ($n = 1$) and unilateral congenital renal atresia ($n = 1$).
[g]Elevated liver enzymes.
[h]Bicuspid aortic valve ($n = 1$), aortic coarctation ($n = 1$), small ventricular septal defect ($n = 1$) and aortic regurgitation ($n = 1$).
[i]Aortic coarctation ($n = 1$), aortic and tricuspid regurgitation ($n = 1$), aortic stenosis ($n = 1$) and hereditary cardiac valve disease ($n = 1$).
[j]Aortic stenosis with mechanical heart valve ($n = 1$) and small ventricular septal defect ($n = 1$).
[k]Per delivery.

Table II Embryo transfer strategy[a] in women with TS who delivered after OD in the Nordic countries 1992–2011.

	Finland (1992–2011)	Denmark (1994–2011)	Sweden (2003–2011)	All
Number of women, *n*	39	35	32	106
Fresh embryo transfer, *n* (%)	31/50 (62.0)	32/35 (91.4)	22/34 (64.7)	85/119 (71.4)
SET in fresh embryo transfers, *n* (%)	24/31(77.4)	15/31 (48.4)	21/22 (95.5)	60/84 (71.4)
Frozen thawed embryo transfers, *n* (%)	19/50 (38.0)	3/35 (8.6)	12/34 (35.3)	34/119 (28.6)
SET in frozen thawed embryo transfers *n* (%)	9/19 (47.4)	2/3 (66.7)	12/12 (100)	23/34 (67.6)
Mean number of embryos transferred (SD) (fresh and frozen cycles)	1.34 (0.48) $n = 50$	1.47 (0.51) $n = 36$	1.03 (0.17) $n = 35$	1.29 (0.46) $n = 121$
Deliveries, *n*	50	37	35	122
Multiple pregnancies, *n* (%)	3[b]/50 (6.0)	10[c]/37 (27.0)	0 (0)	13/122 (10.7)
Multiple births, *n* (%)	2/50 (4.0)	7/37 (18.9)	0 (0)	9/122 (7.4)

SET, single embryo transfer; SD, standard deviation.
[a]There are missing data on some embryo transfers.
[b]Vanishing twin ($n = 1$).
[c]Vanishing twin ($n = 1$), fetal reduction ($n = 2$).

All but one woman were nulliparous at their first OD delivery. Median maternal age at first delivery was 32.0 (22–46) years, median BMI was 24 (18–42) and of the women, 9.6%, (10/104) were obese with a BMI ≥30. Four women suffered from chronic hypertension, 23 from thyroid disease (21 from hypothyroidism, 2 from hyperthyroidism), 4 from diabetes mellitus, 6 from renal diseases and 2 women had elevated liver enzymes (Table I).

Cardiovascular evaluation before pregnancy

Ten women (9.4%) had a known cardiac defect before pregnancy (Table I) and in four women the defect had been surgically corrected [aortic coarctation ($n = 2$), aortic stenosis ($n = 2$)]. Pre-pregnancy cardiovascular examination by a cardiologist was performed in 73 cases (63.5%) before pregnancy and in 56 cases (48.7%) <2 years before OD treatment (Table I). Except for the women with known cardiac defects, all pre-pregnancy cardiac examinations were normal.

Embryo transfer strategy

Embryo transfer strategies are presented in Table II. Single embryo transfer was performed in 71.4% of fresh and 67.6% of frozen embryo transfers. The mean number of embryos transferred was 1.3.

Cardiovascular evaluation during pregnancy

During pregnancy cardiovascular evaluation with echocardiography (ECG) or magnetic resonance imaging (MRI) was performed in a total of 35 pregnancies (28.7%), in 5 of 10 with a known cardiac defect (Table I). In one woman with a previously normal cardiovascular examination, mild left ventricular dilatation with regurgitation was found in gestational week 21. Another woman had an emergency computed tomography (CT) which was considered normal but appeared to have been misdiagnosed later when an aortic dissection was diagnosed after delivery. All other women with normal cardiovascular examinations before pregnancy also had normal cardiovascular evaluations during pregnancy.

Obstetric outcomes

Of 122 deliveries, 113 were singleton and 9 were twin deliveries. The multiple birth rate was 7.4%. 'Vanishing twin' of one twin occurred in two of the twin pregnancies and two fetal reductions (from twins to singletons) were performed.

Data regarding obstetric outcomes were available for 117 of the pregnancies and are presented for the different countries and for singletons and twins in Table III. Data regarding obstetric outcomes in relation to different karyotypes are presented in Table IV. Of all pregnancies, 35.0% of the pregnancies (41/117) were associated with a hypertensive disorder including pre-eclampsia in 20.5% (24/117). The pre-eclampsia was classified as severe in 4.3% (5/117). Among those 16 women who delivered their second child, 3 developed pre-eclampsia (18.8%). In singleton pregnancies, hypertensive disorders occurred in 30.4% (14/46), in 28.6% (4/14) and in 39.0% (16/41) of women with a 45, X karyotype, mosaic and other TS karyotype, respectively. Induction of labour was performed in 29.5% (36/121). Indications for induction of labour were pre-eclampsia, post-date pregnancy or preterm rupture of the membranes. Induction of labour was followed by emergency Caesarean section (CS) in 72.2% (26/36), the most common indication being slow, if any, progress in labour.

CS was performed in 82.0% (100/122) of all deliveries and in 34.4% (42/122) this was an emergency CS. The most common indications for elective CS were cephalo-pelvic disproportion or breech presentation.

Of the 22 vaginal deliveries, 13 were in women with a 45,X karyotype. Women with TS and vaginal deliveries were taller when compared with women who delivered by Caesarean sections (median 159.5 cm, range 148–168 cm versus 152 cm, range 138–170 cm, $P = 0.001$).

Placental complications occurred in five women [placenta previa ($n = 2$), placenta accreta ($n = 2$) and placental abruption ($n = 1$)]. Eight women had heavy post-partum haemorrhaging (>1000 ml), seven were given blood transfusions and one underwent a hysterectomy (twin pregnancy) due to placenta accreta and severe bleeding. One woman with severe bleeding was treated with high-dose

Table III Obstetric complications[a,b] and mode of delivery in women with TS and OD in the Nordic countries 1992–2011.

	Finland (1992–2011), singleton pregnancies	Denmark (1994–2011), singleton pregnancies	Sweden (2003–2011), singleton pregnancies	All singleton pregnancies	All twin pregnancies	All pregnancies
Number of deliveries	48	30	35	113	9	122
Gestational hypertension[c], *n* (%)	9/45 (20.0)	2/29 (6.9)	5/35 (14.3)	16/109 (14.7)	1/8 (12.5)	17/117 (14.5)
Pre-eclampsia *n* (%)	9/45 (20.0)	5/29 (17.2)	7/35 (20.0)	21/109 (19.3)	3/8 (75.0)	24/117 (20.5)
Diabetes[d], *n* (%)	5/45 (11.1)	4/29 (13.8)	2/35 (5.7)	11/109 (10.1)	0/8 (0.0)	11/117 (9.4)
Intrahepatic cholestasis, *n* (%)	3/45 (6.7)	2/29 (6.9)	1/35 (2.9)	6/109 (5.5)	2/8 (25)	8/117 (6.8)
Cardiovascular complications, *n* (%)	1/45[e] (2.2)	0/29 (0.0)	1/35[f] (2.9)	2/109 (1.8)	0/8 (0.0)	2/117 (1.7)
Placental complications, *n* (%)	2[g]/45 (4.4)	1[h]/29 (3.4)	1[i]/35 (2.9)	4/109 (3.7)	1[j]/9 (11.1)	5/118 (4.2)
CS, *n* (%)	42/48 (87.5)	22/30 (73.3)	30/35 (85.7)	94/113 (83.2)	6/9 (66.7)	100/122 (82.0)
Emergency CS, *n* (%)	17/48 (35.4)	9/30 (30.0)	15/35 (42.9)	41/113 (36.3)	1/9 (11.1)	42/122 (34.4)
Induction of labour, *n* (%)	9/48 (18.8)	8/29 (27.6)	18/35 (52.9)	35/112 (30.9)	1/9 (11.1)	36/121 (29.5)
Assisted vaginal delivery, *n* (%)	1/48 (2.2)	0/30 (0.0)	4/35 (11.4)	5/113 (4.4)	0/9 (0.0)	5/122 (4.1)
Spontaneous vaginal delivery, *n* (%)	6/48 (13.0)	7/30 (23.3)	1/35 (2.9)	14/113 (12.4)	3/9 (33.3)	17/122 (13.9)

[a]There are missing data on some outcomes.
[b]A woman can have more than one complication.
[c]Includes women with chronic hypertension.
[d]Includes women with pre-existing diabetes mellitus.
[e]Mild left ventricular dilatation with regurgitation.
[f]Aortic dissection.
[g]Placenta accreta ($n = 1$) and placental abruption ($n = 1$).
[h]Placenta previa ($n = 1$).
[i]Placental abruption ($n = 1$).
[j]Placenta accreta ($n = 1$), hysterectomy perfomed due to severe bleeding.

anticoagulation therapy due to a mechanical heart valve. At the beginning of OD treatment, she had a BMI of 31 and hypothyroidism. She developed severe pre-eclampsia with HELLP syndrome (haemolysis, elevated liver enzymes, low-platelets) and was delivered by CS in gestational week 29. The OD treatment in 2006 was her eighth attempt to achieve a pregnancy. Both mother and child recovered.

One 28-year-old woman with a TS mosaicism had an aortic dissection in 2009. She had had several OD treatments before she became pregnant. She had a BMI of 28 and substituted hypothyroidism, but was otherwise healthy with a normal cardiovascular examination before pregnancy. She developed severe pre-eclampsia in gestational week 38 and a CT scan was performed a few days before delivery owing to chest pain, but without confirming an aortic dissection. The diagnosis of aortic dissection was made 20 days after delivery, when she presented with acute symptoms of severe chest pain and dyspnoea. A new CT showed aortic dissection. The first CT was re-evaluated and it was confirmed that the aortic dissection could have been diagnosed at the first CT scan. She was treated conservatively and surgical correction was successfully performed 1.5 years later.

One 42-year-old woman with a TS mosaicism was diagnosed with heart regurgitation and left ventricular dilatation in gestational week 21 in 2008. She had hypothyroidism and chronic hypertension treated with antihypertensive drugs before pregnancy. Cardiovascular examination before pregnancy was normal. No further complications occurred and she was delivered by elective CS at 39 weeks of gestation owing to hypertension and breech presentation. Her diagnoses were mild regurgitation of the tricuspid and mitral valve. She left hospital 4 days after delivery in good condition with a healthy male child.

No thromboembolic complications were reported during pregnancy, delivery or before discharge from the maternity ward.

The median follow-up time was 4 years (4 months to 19 years) after the last delivery. One woman died 9 years after delivery; the cause of death is unknown.

Neonatal outcomes

Neonatal outcomes are presented in Table V. In total, 131 children were born, 113 singletons and 9 sets of twins. The perinatal mortality was 2.3% (3/131). One unexplained stillbirth occurred in gestational

Table IV Obstetric complications[a,b] and mode of delivery in singleton deliveries according to karyotype in women with TS and OD in the Nordic countries 1992–2011.

	Women with monosomy, X0 (*n* = 42)	Women with Turner 45,X/46,XX mosaic (*n* = 14)	Women with other Turner karyotypes[c] (*n* = 36)	All women with TS and known karyotype (*n* = 92)
Number of deliveries	50	14	42	106
Gestational hypertension[d], *n* (%)	7/46 (15.2)	3/14 (21.4)	3/41 (7.3)	13//101 (12.9)
Pre-eclampsia, *n* (%)	7/46 (15.2)	1/14 (7.1)	13/41 (31.7)	21/101 (20.8)
Diabetes[e], *n* (%)	3/47 (6.4)	1/14 (7.1)	6/41 (14.6)	10/102 (9.8)
Intrahepatic cholestasis, *n* (%)	2/47 (4.3)	1/14 (7.1)	3/40 (7.5)	6/101 (5.9)
Cardiovascular complications, *n* (%)	0/47 (0)	2/14 (14.3)	0/41 (0)	2/102 (2.0)
Placental complications, *n* (%)	4/47[f] (8.5)	0/14 (0)	1/41[g] (2.4)	5/102 (4.9)
CS, *n* (%)	40/50 (80.0)	10/14 (71.4)	36/41 (87.8)	86/105 (81.9)
Emergency CS, *n* (%)	14/50 (28.0)	5/14 (35.7)	17/41 (41.5)	36/105 (34.3)
Induction of labour, *n* (%)	12/50 (24.0)	7/14 (50.0)	14/41 (34.1)	33/105 (31.4)
Assisted vaginal delivery, *n* (%)	2/50 (4.0)	1/14 (7.1)	2/41 (4.9)	5/105 (4.8)
Spontaneous vaginal delivery, *n* (%)	8/50 (16.0)	3/14 (21.4)	3/41 (7.3)	15/105 (14.3)

[a]There are missing data on some outcomes.
[b]A woman can have more than one complication.
[c]Includes45,X/46X,i(X) and 46,X,i(X), 45,X/46XY 45X/46XY/47XXX, 45,X/47,XXX, 45,X/46XX/47XXX/48XXXX, 45,X/46der(X) (including ring chromosomes, deletions, inversions and translocations).
[d]Includes women with chronic hypertension.
[e]Includes women with pre-existing diabetes mellitus.
[f]Placenta previa (*n* = 2), placenta accreta (*n* = 1) and placental abruption (*n* = 1).
[g]Placental accreta (*n* = 1).

week 42 in a boy with a normal karyotype and a birthweight of 3600 g. One twin pair were born SGA in gestational week 25 and died during the first week of life because of immaturity.

Preterm birth (<37 weeks) occurred in 8.0% (9/113) of singletons and in 66.7% (6/9) of twin pregnancies. LBW (<2500 g) occurred in 8.8% (10/113) of singletons and 72.2% (13/18) of twins. Of all the infants, 15.0% (17/113) of the singletons and 33.3% (6/18) of the twins were born SGA.

The rate of children with any birth defect was 6.1% (8/131) (Table V). Five children (3.8%) had major birth defects [atrial septal defect and polydactyly (*n* = 1), transposition of the great arteries (*n* = 1), malformation of the eye lid (*n* = 1), anal atresia (*n* = 1), retentio testis (*n* = 1) and three children had minor defects: hip luxation (*n* = 2), tongue cord tendon (*n* = 1)].

Singletons of primiparous women with 45,X monosomy were compared with those of primiparous women with a mosaic or other TS karyotypes. There were no differences in median gestational age [273 (254–291) and 273 (204–297) days, respectively, $P = 0.63$], median birthweight [3087 g (1500–3945) and 3175 g (1020–4690), respectively, $P = 0.81$] or median percentage of birth deviation [−11.7 (−46.8 to 35.4) and −11.2 (−47.5 to 21.5) respectively, $P = 1.0$].

Discussion

The main finding in this large Nordic collaborative study is that the pregnancies among women with TS carry a substantial risk, particularly for hypertensive disorders. OD pregnancies in women with TS are associated with a high risk of cardiovascular complications. There was no maternal mortality, but potentially life-threatening complications occurred in four pregnancies (3.3%). We found one woman with aortic dissection, one woman with a mechanical heart valve who developed HELLP syndrome in 29 weeks of gestation, one woman who underwent a postpartum hysterectomy owing to severe haemorrhaging and one woman who developed heart failure albeit mild.

The neonatal outcomes were generally reassuring, when compared with IVF and OD pregnancies in general (Källén *et al.*, 2005a,b; Sazonova *et al.*, 2011; Malchau *et al.*, 2013) and better than previously reported in women with TS, despite a similar twin rate (Bodri *et al.*, 2006; Alvaro Mercadal *et al.*, 2011; Chevalier *et al.*, 2011). The reason for this difference is not clear but may be an effect of patient selection or other confounders, such as the low incidence of pre-existing hypertension in this TS population. OD for women with TS is an established treatment in the Nordic countries, introduced in Finland and Denmark in 1992. Accompanying risks in Turner

Table V Neonatal outcomes in children born after OD in women with TS in the Nordic countries 1992–2011.

	Finland (1992–2011), singletons (*n* = 48)	Denmark (1994–2011), singletons (*n* = 30)	Sweden (2003–2011), singletons (*n* = 35)	All singletons (*n* = 113)	All twin pregnancies (*n* = 9), all twins (*n* = 18)	All pregnancies (*n* = 122), all children (*n* = 131)
Live births, *n*	48/48	29/30	35/35	112/113	18/18	130/131
Stillbirths, *n* (%)	0/48 (0.0)	1/30 (3.3)	0/35 (0.0)	1/113 (0.9)	0/18 (0.0)	1/131 (0.8)
Perinatal mortality, *n* (%)	0/48 (0.0)	1/30 (3.3)	0/35 (0.0)	1/113 (0.9)	2/18 (11.1)	3/131 (2.3)
Gestational age, days, median (range)	274 (222–297), *n* = 48	269 (243–295), *n* = 30	279 (204–292), *n* = 35	274 (204–297), *n* = 113	246 (175–268), *n* = 9	273 (175–297), *n* = 122
<37 weeks, *n* (%)	3/48 (6.3)	3/30 (10.0)	3/35 (8.6)	9/113 (8.0)	6/9 (66.7)	15/122 (12.3)
<32 weeks, *n* (%)	0/48 (0.0)	0/30 (0.0)	1/35 (2.9)	1/113 (0.9)	2/9 (22.2)	3/122 (2.5)
<28 weeks, *n* (%)	0/48 (0.0)	0/30 (0.0)	0/35 (0.0)	0/113 (0.0)	1/9 (11.1)	1/122 (0.8)
Birthweight, g, median (range)	3110 (1020–4200), *n* = 48	3103 (1925–4690), *n* = 30	3250 (1102–4170), *n* = 35	3150 (1020–4690), *n* = 113	2208 (379–2880), *n* = 18	3042 (379–4690), *n* = 131
<2500 g, *n* (%)	3/48 (6.3)	4/30 (13.3)	3/35 (8.6)	10/113 (8.8)	13/18 (72.2)	23/131 (17.6)
<1500 g, *n* (%)	1/48 (2.1)	0/30 (0.0)	1/35 (2.9)	2/113 (1.8)	2/18 (11.1)	4/131 (3.1)
<1000 g, *n* (%)	0/48 (0.0)	0/30 (0.0)	0/35 (0.0)	0/113 (0.0)	2/18 (11.1)	2/131 (1.5)
% Weight deviation[a], median (range)	−11.6 (−47.5–12.9), *n* = 48	−11.4 (−34.6–35.4), *n* = 30	−8.8 (−34.1–24.9), *n* = 35	−10.9 (−47.5–35.4), *n* = 113	−16.0 (−53.2 to 0.46), *n* = 18	− 11.7 (−53.2 to 35.4), *n* = 131
SGA (< −2 SD)[a], *n* (%)	8/48 (16.7)	4/30 (13.3)	5/35 (14.3)	17/113 (15.0)	6/18 (33.3)	23/131 (17.6)
LGA (> +2 SD)[a], *n* (%)	0/48 (0)	1/30 (3.3)	1/35 (2.9)	2/113 (1.8)	0/18 (0.0)	2/131 (1.5)
Boys/girls (% boys of all children) unknown	17/31 (35.4)	17/12 (58.6) *n* = 1	16/19 (45.7)	50/62 (44.6) *n* = 1	7/11 (38.9)	57/73 (44.6) *n* = 1
Admission to NICU >1 days[b], *n* (%)	5/41 (12.2)	7/29[c] (24.1)	7/32 (21.9)	19/102 (18.6)	10/16 (62.5)	29/118 (24.6)
Apgar score <7 at 5 min[b], *n* (%)	2/37 (5.4)	1/26[c] (3.8)	2/34 (5.9)	5/99 (5.1)	0/18 (0.0)	5/117 (4.3)
Number of children with any serious birth defect, *n* (%)	2[d]/48 (4.2)	1[e]/30 (3.3)	2[f]/35 (5.7)	5/113 (4.4)	0/18 (0.0)	5/131 (3.8)

SD, standard deviation; SGA, small for gestational age; LGA, large for gestational age; NICU, neonatal intensive care unit.
[a]According to the Marsal reference curve (Marsal *et al.*, 1996).
[b]There are missing data on some children.
[c]1 stillbirth excluded.
[d]Anal atresia (*n* = 1), retentio testis (*n* = 1), in addition two minor birth defects (hip luxation (*n* = 1) and tongue cord tendon (*n* = 1).
[e]Lid eye defect (*n* = 1) and no minor birth defects.
[f]Atrialseptal defect and polydactyli (*n* = 1), transposition of the great vessels (*n* = 1), in addition one minor birth defect (hip luxation (*n* = 1).

pregnancies have been noted especially since 2003, when Karnis et al. reported an estimated maternal mortality rate of 2%, for reasons of aortic dissection or rupture in pregnant women with TS after OD treatment (Karnis et al., 2003). To date there have not been many reports of women with TS and pregnancy and the few that exist show higher maternal and neonatal risks than observed in the present study (Bodri et al., 2006; Alvaro Mercadal et al., 2011; Chevalier et al., 2011).

Congenital structural anomalies of the cardiovascular system occur in ~50% of women with TS (Matura et al., 2007; Mortensen et al., 2012), the most common being aortic coarctation and a bicuspid aortic valve. In general, women with TS have a high lifetime expected risk of aortic complications with a median age at dissection of 31 years as reported in a review of 85 cases (Carlson and Silberbach, 2007). Risk factors other than pregnancy include aortic coarctation, bicuspid aortic valve and hypertension (Lin et al., 1998; Sybert, 1998; Carlson and Silberbach, 2007; Bondy, 2008; Sachdev et al., 2008; Mortensen et al., 2012). In 11% of women with TS and aortic dissection, no known risk factors were identified (Carlson and Silberbach, 2007). Several international and national guidelines have been written in recent years recommending pre-pregnancy evaluation and careful monitoring during pregnancy in women with TS (ASRM, 2008; Cabanes et al., 2010; ASRM, 2012). According to American and French guidelines, all women with TS should be evaluated with ECG and MRI before pregnancy and any risk factor or significant abnormality found on imaging should be regarded as a relative or absolute contraindication for pregnancy.

Before the report of Karnis et al. in 2003, few women with TS had a cardiovascular examination before or during pregnancy. In the present Nordic cohort, no woman with TS had a pre-pregnancy cardiac evaluation done before 2000. This explains why the proportions of women with cardiac examinations were only 58% in Finland and 39% in Denmark when compared with 100% in Sweden, where OD treatment started much later, in 2003. Among these women having had cardiovascular examinations, 10 had a cardiovascular defect, including 2 cases of aortic coarctation and 1 case of bicuspid aortic valve. No aortic dissection occurred among these pregnancies; but there was one severe haemorrhage peri-partum.

The only woman with aortic dissection in our study had a normal pre-pregnancy cardiac screening. This case illustrates the difficulties of recognizing which woman with TS may develop aortic dissection and rupture and the difficulty of diagnosing a dissection. The risk of dissection in this woman was highly increased during pregnancy by severe pre-eclampsia.

Boissonnas et al. re-evaluated 18 women with TS requesting OD, who had undergone pre-pregnancy cardiac evaluations before treatment (Boissonnas et al., 2009). All women were considered to be cardiovascular healthy. When a cardiologist familiar with TS re-evaluated these women, seven were diagnosed with a cardiac abnormality and therefore denied OD.

Follow-up of women with TS should preferably be organized at specialized Turner centres, increasing the chance of correct cardiovascular evaluation both before and during pregnancy. In Finland, only some adult women with TS are followed up at university hospitals, while most are monitored by their gynaecologists. In Sweden, most women with TS are examined every fifth year at Turner centres located at the university hospitals and annually at the local health clinics. In Denmark, there are also centres for TS women at the university hospitals, still many women with TS are followed by gynaecologists in the primary sector. In the Nordic countries, as elsewhere, it is difficult to refuse women with TS OD. Each IVF doctor is responsible for his or her TS patient's preconceptional counselling about the associated medical risks in pregnancy for women with TS (Wasserman and Asch, 2012).

Almost 22% of the women with TS in this study suffered from hypothyroidism. Most of them were Swedish women, in whom the figure was 43.8%. The incidence was much higher than the comparable incidence of 25% in a Swedish non-pregnant TS population (El-Mansoury et al., 2005) and might be explained by the careful pre-pregnancy screening of women with TS pregnant after OD conception in Sweden. In the Finnish women with TS, the rate was 7.7% and in the Danish women, it was 17.1%. The criteria for diagnosing hypothyroidism are the same in these three different Nordic countries, leaving this difference between the countries unexplained. It is most probably a coincidence.

The incidences of renal disease, chronic hypertension, diabetes mellitus and hepatic disease were also elevated when compared with the general population, but lower than in previous reports about morbidity in women with TS (Gravholt et al., 1998; Sybert, 1998; Gravholt, 2005; El-Mansoury et al., 2008). Renal disorders are common in TS, and occur in 30–40% of the women, which is nine times higher than in the general population (Gravholt et al., 1998). In the present study, this was illustrated by two women with unilateral renal atresia, one woman with a renal transplant, one woman with a double renal pelvis and one woman with a nephrotic syndrome. Four of these five women had a 45,X karyotype.

The risk of pre-eclampsia is reported to be raised in both spontaneously conceived and OD TS pregnancies (Foudila et al., 1999; Bodri et al., 2006; Chevalier et al., 2011; Hadnott et al., 2011). It has also been shown repeatedly that the frequency of pregnancy-induced hypertension and pre-eclampsia is 16–40% in oocyte recipients in general (Serhal and Craft, 1989; Blanchette, 1993; Abdalla et al., 1998; Sheffer-Mimouni et al., 2002). The reason for the increased occurrence of hypertension in OD pregnancies is not clear. Possible explanations are a high rate of primiparity and a higher rate of placental pathology owing to immunological factors (Gundogan et al., 2010). In the present study of women with TS the incidence of hypertensive disorders and pre-eclampsia was 35%, which is very similar to that reported in a French study of 82 deliveries (38%) (Chevalier et al., 2011). Hypertensive disorders before pregnancy was seen in only four women, but during pregnancy the incidence was increased. This might indicate underreporting of hypertensive disorders before pregnancy in this TS population.

OD pregnancies in general have been associated with a high risk of post-partum haemorrhaging (Abdalla et al., 1998). The reason for this tendency is unclear, but placental implantation abnormalities have been discussed (van der Hoorn et al., 2010). In this study, placental complications occurred in 4.2% and post-partum haemorrhaging was seen in 7% of the women, which is comparable or lower than previously reported in OD pregnancies, but still significant.

The neonatal outcomes in singletons were reassuring, with a median birthweight of 3150 g. At many fertility clinics matching of external characteristics such as height between the oocyte donor and the recipient is a rule, and this may also be reflected in the size of

the babies. The median gestational age of 39 weeks for singletons could be explained by the high incidence of elective CS. Despite a high incidence of hypertensive disorders, the rates of PTB and LBW were lower than previously reported (Bodri *et al.*, 2006; Chevalier *et al.*, 2011). In this study, PTB occurred in 12.3% in all deliveries when compared with more than 38.3% in the report by Chevalier. In singletons, in our study, PTB occurred in 8.0% and LBW in 8.8%. In comparison, the rates of PTB and LBW in singletons were 7.8 and 5.3% in a recent large register study on IVF with own gametes from Sweden (Sazonova *et al.*, 2011) and in a Danish study on outcome after OD, PTB and LBW rate were 14.3 and 10.7%, respectively (Malchau *et al.*, 2013) thus rather similar to the rates in the present study.

Chevalier also reported an incidence of 27.5% SGA (Chevalier *et al.*, 2011) and Bodri reported intrauterine growth retardation in four of the nine fetuses (Bodri *et al.*, 2006) when compared with a lower frequency of 17.6% in this study. The previous study from Sweden on obstetric outcomes after both OD and spontaneous pregnancies in 115 women with Turner karyotype showed no difference in SGA in Turner pregnancies when compared with a reference group of 56 000 women from the Swedish MBR (Hagman *et al.*, 2011).

The incidence of major birth defects was 3.8%, which is comparable with the incidence of conventional IVF (Källén *et al.*, 2005a). No chromosomal anomalies in the neonates were recorded. There was no statistical difference in neonatal outcomes in women with 45,X karyotype when compared with all other women with TS.

The strength of this study is that it is a nationwide study performed in three different Nordic countries and it is to our knowledge the largest study on deliveries after OD in women with TS. The study period was 20 years and all identified Turner oocyte recipients except four were included. Despite some differences in maternal characteristics and in embryo transfer strategy, outcomes were similar in the different countries. Few data were missing, especially for neonatal outcomes.

The limitations of the study are that we do not have complete Nordic data from women who were declined OD due to maternal morbidity, thus selection of healthy women might have occurred, particularly in the later years, when new guidelines concerning cardiac complications became known. In our study, we had a low rate of cardiac and renal defects when compared with other studies (Landin-Wilhelmsen *et al.*, 2001; Freriks *et al.*, 2011). Differences in the incidence of malformations between studies may also depend on how well the women are investigated.

A further limitation is that we do not have information about spontaneous pregnancies and OD treatments outside the Nordic countries in women with TS.

Furthermore, data on unsuccessful cycles for the complete Nordic cohort of women with TS were unfortunately not available. However, live birth per embryo transfer for women with TS was for the largest clinic in Finland (1999–2008) 33.3%, in Denmark (1995–2011) 30.5% and in one of the largest clinics in Sweden, (2003–2011) 33.3%. In the majority of cycles in Finland and Sweden, SET was performed. In Denmark, SET was performed in around 50%. The rate of live birth per embryo transfer is comparable to other Nordic results after OD in general [Finland 25.2% (2010), Sweden 33.5% (2009), Denmark 24.2% (2007–2009)], but in contrast to the report from Bodri, showing an extremely low birth rate after SET in women with TS (Bodri *et al.*, 2009).

Other limitations are that for rare events much larger series are needed and the study lacks an appropriate control group.

Finally, owing to the retrospective study design and the way of identifying the women with TS (by IVF clinics and by registries), we cannot exclude that some cases may have been missed.

In conclusion, this is a large collaborative study from three Nordic countries of obstetric and neonatal outcomes in 106 women with TS and their 131 newborns. The study confirms that OD conceptions in women with TS are high-risk pregnancies with an increased risk of pregnancy-induced hypertension and pre-eclampsia together with a high-frequency of CS as noted in previous studies. However, most of the infants were singletons and they had better neonatal outcomes than found in previous reports.

Single embryo transfer should be used to avoid the added risks of a twin pregnancy, and this is particularly important in women with TS. Centralized pretreatment cardiovascular assessments are recommended. In women with cardiovascular abnormalities or other severe health problems, refusal of OD treatment and other alternatives must be considered. The risk of aortic dissection is difficult to predict and these pregnancies should be frequently monitored with special emphasis on keeping the blood pressure levels within the normal range. We recommend that ECG or MRI be performed one to three times during the pregnancy. Symptoms in pregnant women with TS should always be taken seriously and examinations should be done to identify cardiovascular morbidity and to prevent severe events. The recommendations are summarized in Table VI.

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Table VI Recommendations before OD and follow-up during pregnancy in women with Turner syndrome.

Centralized cardiovascular assessment before pregnancy
OD should be avoided, if cardiovascular or other severe health problems occur
Tests for thyroid, renal and liver abnormalities and for diabetes
Single embryo transfer is recommended
Pregnancies must be careful monitored
Blood pressure <140/90
ECG/MRI is recommended two to three times during pregnancy
Symptoms must be taken seriously
Pregnancies are of high risk
Aortic dissection is difficult to predict

Authors' roles

All authors designed the study. A.H., V.S.A., A.L. and A.P. collected data and created the summary database. A.H. and V.S.A. performed the literature search. A.H., V.S.A., U.B.W., A.L. performed analysed the data and wrote the manuscript. All authors have revised the article and have given final approval of the submitted version.

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Conflict of interest

None declared.

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