How can we make pregnancy safe for women with Turner syndrome?

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i. Title

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Abstract

Pregnancy is a crucial issue in patients with Turner syndrome (TS). Although natural pregnancies have been reported in 4-7% of TS patients, most women will need assisted reproductive technologies (ART) with oocyte donation. The main issue is the maternal mortality rate that is higher than in the general population. It is related to cardiovascular anomalies and particularly aortic dissection.

Turner syndrome, per se, is not a contraindication for pregnancy, but a multidisciplinary screening is mandatory before initiating a pregnancy. It includes repeated aortic diameters evaluation, blood pressure measurement and biological testing evaluating thyroid and liver functions, as well as blood glucose level. In order to make the pregnancy safe, contraindications of pregnancy should be respected and identification of high-risk patients for cardiovascular events should be performed. Hypertension and pre-eclampsia prevention may benefit from beta-blockers and aspirin, respectively.

Collaborations between endocrinologists, cardiologists and obstetricians are mandatory during pregnancy and even in the post-partum period. Counseling the patients about the risks of pregnancy, screening them and spreading the international guidelines to physicians taking care of patients with TS are the three pillars of a safe pregnancy.

Keywords

Turner syndrome; Fertility; Pregnancy; Aortic dissection; Mortality

vi. Main text

Introduction

Turner syndrome (TS) affects about 1 in 2,500 newborn girls. It is a chromosomal disorder that affects phenotypic females who have one intact X chromosome and complete or partial absence of the second sex chromosome in association with some clinical conditions. The most common abnormalities are growth failure (95-100% of cases), hypertension (50%), elevated hepatic enzymes (50-80%) and primary ovarian insufficiency (POI) (95%) (Gravholt et al., 2017).

For the majority of women with TS, *in vitro* fertilization (IVF) with oocyte donation represents, since the 1980s (Lutjen et al., 1984), the only way to be pregnant. Those pregnancies are however associated with many maternal, fetal and obstetrical complications (Bodri et al., 2006; Alvaro Mercadal et al., 2011; Chevalier et al., 2011; Hagman et al., 2013; Gravholt et al., 2017).

Since 2007, several recommendations and guidelines have been proposed for the management of patients with TS before and during pregnancy (Bondy et al., 2007; Cabanes et al., 2010; Gravholt et al., 2017). It is now established that pregnancies of TS women should be carefully monitored by a multidisciplinary team including maternal-fetal medicine specialists with expertise in managing patients with TS (Gravholt et al., 2017). This paper will focus on the main pregnancy risks that have to be taken into account to make pregnancies safer in TS. The most important are cardiovascular complications, including aortic dilatation and dissection, gestational hypertension and preeclampsia. Furthermore, on the maternal side, if cardiovascular complications are most dangerous, liver diseases, diabetes and thyroid dysfunction may further complicate the pregnancy in patients with TS.

1. Different types of pregnancies in TS patients

Primary ovarian insufficiency is a classic feature of TS. Haploinsufficiency of X pseudo-autosomal genes leads to an acceleration of follicular atresia (Modi, 2003) and, in most cases, to gonadal failure with primary amenorrhea. However, in 5–20% of girls with TS, follicles are still

present and allow for spontaneous menarche (Pasquino et al., 1997; Hovatta, 1999; Hreinsson et al., 2002). Ovarian status is highly associated with the TS karyotype. In the Turner syndrome life course project, primary amenorrhea was observed in 88.5%; 41.7%; 78.3% and 81.4% of patients with 45,X; 45,X/46,XX mosaicism; Xq isochromosome and 45,X/46,XY mosaicism, respectively (Cameron-Pimblett et al., 2017). In a longitudinal study of 120 Turner syndrome patients in Denmark, the majority of women with 45,X/46,XX mosaic karyotype had ongoing ovarian function in early adulthood (Lunding et al., 2015). According to the remaining ovarian function, three types of pregnancies have been described in TS patients: natural pregnancies, pregnancies after *in vitro* fertilization (IVF) without oocyte donation, and those obtained after IVF with oocyte donation.

Few studies have reported natural pregnancies in women with TS (Birkebaek et al., 2002; Bryman et al., 2011; Hadnott et al., 2011; Bernard et al., 2016). The first study, from Denmark (Birkebaek et al., 2002) was based on a national cytogenetic central register. It included 412 women with TS and the rate of natural pregnancies was 7.6%. The second study from Sweden (Bryman et al., 2011), included 482 TS patients and evaluated both natural pregnancies and pregnancies issued from ART. The prevalence of natural pregnancies was 4.8%. Another study including 276 TS women from the United States (Hadnott et al., 2011) found a lower prevalence of natural pregnancies, reaching only 1.8%. Our group performed a study including 480 French adult patients with TS and reported a natural pregnancy rated of 5.6% (Bernard et al., 2016). Eighteen patients (3.8%) had at least one live born child. The two predictive factors which correlated with occurrence of a natural pregnancy were spontaneous menarche and mosaic karyotype (Bernard et al., 2016). However, 2 patients with a full 45,X karyotype had natural pregnancies. This is probably due to the fact that their ovarian karyotypes were different from the lymphocytes' karyotype. These four studies illustrate the fact that natural pregnancies in women with TS are not as rare as previously thought.

Few data are available concerning pregnancies in women with TS issued from IVF without oocyte donation. Ovarian stimulation is not often performed as those patients usually have a decreased ovarian reserve, with low AMH levels and low antral follicle count (Lunding et al., 2015). However, several cases of ovarian stimulation have been described in patients with Turner syndrome in order to

preserve their fertility(Balen et al., 2010; Oktay et al., 2014). Recently, Talaulikar et al. reported ovarian stimulation in 7 TS patients. The mean oocyte retrieval rate was 9 ± 3.16 oocytes. However, no pregnancy has been reported so far after using cryopreserved oocytes in TS patients (Talaulikar et al., 2018).

Most pregnancies in TS patients are obtained after IVF with oocyte donation as POI concerns 95% of TS patients. The clinical pregnancy rates using this technique in TS women vary between 16 and 40% (Gravholt et al., 2017). Those results are consistent with pregnancy rates in women without TS, undergoing oocyte donation. However, the rate of miscarriage is elevated. Pregnancy losses are most often due to the presence of a hypoplastic or bicornuate uterus and a thinner endometrial lining than that typically seen in pregnant women without Turner syndrome (Khastgir et al., 1997). Another explanation could be a high prevalence of autoimmunity disorders in these patients (Abir et al.,2001). The rate of complication for pregnancies obtained after oocyte donation is high. For instance, in a French study performed in 82 patients with TS, only 40.2% completed their pregnancy without complications (Chevalier et al., 2011).

2. Cardiovascular risk in patients with TS outside of pregnancy

Several studies have shown an increased cardiovascular risk in patients with Turner syndrome, even outside of pregnancy. One of the largest study from UK including 3439 TS patients reported a standardized mortality rate (SMR) of 3.0 (95%CI: 2.7-3.4). It was higher in patients with aortic aneurysm (SMR: 23.6) or aortic valve disease (SMR: 17.9). Circulatory diseases accounted for nearly half (41%) of excess mortality (Schoemaker et al., 2008). Stockholm et al. observed 69 deaths among the 781 TS patients from the Danish cytogenetic register. Their calculated SMR was 2.86 (95% CI 2.2-3.5). It was higher in patients with congenital malformations (SMR: 24.09) (Stochholm et al., 2006) and congenital heart diseases are frequent in women with TS, as they occur in nearly half of patients with TS (Gravholt et al., 2017). The prevalence of bicuspid aortic valves is 15-30% and therefore 30-60 times more frequent than among the general female population. The prevalence of aortic coarctation is 7-18% (Gravholt et al., 2017). Congenital heart disease are known congenital risk

factors for aortic dilatation and dissection (Mortensen et al., 2009). Furthermore, hypertension is an acquired risk factor for aortic dilatation. It is also very prevalent, as high blood pressure has been reported in 60% of TS patients in some studies from northern Europe (De Groote, 2015).

3. Physiology of the cardiovascular system during normal pregnancies

Pregnancy physiology is associated with increases in maternal volemia, heart rate, blood pressure, stroke volume and cardiac output. Gravidic variations in female sex hormone levels play a critical role in pregnancy-induced cardiac adaptation: progesterone surges appear to initiate a ventricular hypertrophic signaling and estradiol in late pregnancy seems to initiate a post-partum cardiac remodeling (Chung et al., 2014). Those hormonal modifications may induce vascular structure modifications potentially resulting in aortic media injury. Furthermore, wall tension and intimal shear forces increase during the first and second trimesters, being maximal during the last trimester.

During delivery in a normal pregnancy, a 30-50% increase in cardiac output and large hemodynamic changes may occur. Indeed, each contraction forces an additional 300-500 ml of venous blood back into the central venous system (Coulon, 2015). Furthermore, during the second stage of labor, blood pressure and heart rate increase due to the pushing efforts and the Valsalva maneuvers. After placental delivery, 500 ml of blood is diverted from the utero-placental bed back into the maternal circulation, which in turn increases central venous pressures, ventricular preload and cardiac output (Coulon, 2015). Arterial microdissections during labor of a vaginal delivery may be associated with dramatic late postpartum aortic acute events.

In the general population, cardiovascular diseases complicate 1-3% of all pregnancies. It represents the second commonest cause of maternal mortality (Chang et al., 2003). However, aortic dissection in the general population remains a very rare event. In the maternal mortality report in the UK, covering maternal deaths between 2003 and 2005, aortic dissection accounted for seven out of 53 cardiac deaths (McClure et al., 2011). In the latest version, arterial aneurysms induced 10 deaths during pregnancy. However, ruptured splenic artery aneurysms were involved. No case of thoracic aortic dissection was

reported (Knight M et al., 2018). In a study from Netherlands, nearly half of maternal cardiovascular deaths were related to an aortic dissection (Huisman et al., 2013). Half of the acute aortic dissection in women under the age of 40 occurs during pregnancy or peripartum period (Williams et al., 1988).

4. What are the cardiovascular complications in pregnant patients with TS?

Several studies have reported cardiovascular risk in TS women during natural pregnancies or during pregnancies obtained after oocyte donation. Significant morbidities have been reported, such as pregnancy-associated hypertensive disorders (PAHD), including preeclampsia, as well as hemolysis elevated liver enzyme and low platelets (HELLP) syndrome (Gravholt et al., 2017). The overall rate of PAHD is around 30-50% of pregnancies with TS. Furthermore, several case reports of aortic dissection have been described during pregnancy in TS patients (**Table I**) (Garvey et al., 1998; Karnis et al., 2003; Ohl et al., 2008; Boissonnas et al., 2009; Chevalier et al., 2011; Carlson et al., 2012). Unfortunately, exhaustive registries of pregnancies in patients with TS are not available. Therefore, the prevalence of cardiovascular events in pregnant patients with TS is difficult to evaluate.

4.1 Cardiovascular complications in pregnancies obtained after oocyte donation

Half of the existing donor-egg programs in the United States were surveyed in 1997. They included 146 Turner patients and 101 pregnancies were observed (Karnis et al., 2003). One patient died from an aortic rupture while awaiting oocyte donation. No deaths were reported during pregnancy. The National Institute of Health reported the outcomes of ART pregnancies in TS patients (Karnis et al., 2003; Hadnott et al., 2011; Practice Committee of American Society For Reproductive Medicine, 2012). Out of the four deaths in (Karnis et al., 2003), one patient had a twin pregnancy, a marked aortic dilatation and she presented with pre-eclampsia.

In Sweden, Hagman et al studied a country-based registry, including 124 pregnant women out of 502 women with TS, between 1973 and 2010. Cardiovascular events occurred during pregnancy or within one year after the delivery (HR 5.78; 95%CI 1.94-17.24). Aortic aneurysm occurred in 11/502

(2.2%) women and in 3 women during pregnancy. Only 63% had cardiovascular examination before pregnancy. Hypertension was observed in 35% of pregnancies and pre-eclampsia occurred in 20.5%. Life-threatening complications occurred in 3.3% of pregnancies. However, no death was observed (Hagman et al, 2011; Hagman et al., 2013).

A French nationwide multicenter study published in 2011 (Chevalier et al., 2011), included all TS patients with pregnancies obtained after oocyte donation. Two out of the 93 patients (2.2%) died of aortic dissection. Both deaths occurred after delivery by cesarean section at 38 wk gestation: the first in the early post-aortoplasty period (Boissonnas et al., 2009), the second died one week after delivery (Ohl, 2008). The rate of pregnancy-associated hypertensive disorders reached 37.8% of those pregnancies. Severe pre-eclampsia occurred in 54.8% of those cases and HELLP syndrome occurred in one patient. Prematurity was observed in 38.3% (p 0.01) and one fetal demise was linked to eclampsia (Chevalier et al., 2011).

4.2 Cardiovascular complications in natural pregnancies of women with TS

Few studies have evaluated the outcome of natural pregnancies in TS patients. So far, 2 cases of aortic dissection have been reported in the literature during the third trimester of natural pregnancies (Hagman et al., 2011). Two other cases have been reported, respectively 2 and 17 years after the pregnancy (Carlson et al., 2012). The relationship between the pregnancy and the aortic dissection in those cases is not demonstrated. In a cohort including 480 women, pregnancy-induced maternal hypertensive disorders occurred only in four cases (13.3% of the 30 achieved pregnancies), including two cases of mild pre-eclampsia (6.7%) (Bernard et al., 2016). One of the patients with pre-eclampsia had an aortic bicuspid valve. Neither aortic dissection nor cardiac complication was observed in any of the pregnant women during pregnancy or post-partum. Hadnott et al also reported 7 achieved natural pregnancy in TS patients without maternal cardiovascular complication (Hadnott et al., 2011). Therefore, natural pregnancies seem to be less complicated than pregnancies obtained after oocyte donation in TS women. One hypothesis may rely on the younger age of patients with TS and natural

pregnancies over the mean age of pregnancies obtained after oocyte donation. Another hypothesis is that patients achieving natural pregnancies have a less severe phenotype of the syndrome than those requiring oocyte donations, especially the cardiovascular phenotype. Indeed, one major predictive factor of NP is the karyotype with mosaicism, which is associated with a less severe phenotype than X monosomy. Moreover, it is known that oocyte donation is an independent risk factor for pregnancy complications (Younis et al., 2015). Another potential explanation relies on the impact of high estrogen levels on the arterial wall. However, during oocyte donation, patients on hormonal replacement therapy have a lower estradiol serum level than during ovarian stimulation with gonadotropins.

5. How to make pregnancies safe in TS patients?

5.1 Identify high risk patients of cardiovascular events

Published international guidelines recommend aortic diameter measurements at each anatomic specific levels of the aortic root, perpendicular to vessel wall, from inner edge to inner edge, at the following levels: aortic annulus, Valsalva sinuses, sino-tubular junction, tubular ascending aorta, aortic cross and descending aorta (Kawel-Boehm et al., 2015). Before the report of Karnis et al. in 2003, few women with TS had a cardiovascular examination before or during pregnancy. In the two largest studies, cardiovascular evaluation had not been optimal as screening before pregnancy with transthoracic echography (TTE) or cardiac magnetic resonance (CMR) had been performed in 38 and 49% of cases, respectively from 93 and 106 women (Karnis et al., 2003; Chevalier et al., 2011). The lack of appropriate screening prior to pregnancy could be the main cause of aortic dissection. The current recommendation is to perform cardiac and aortic imaging (TTE, CMR) within 2 years before planned pregnancy with oocyte donation (Gravholt et al., 2017).

It is usually recommended to index the aortic diameter to the body surface area (BSA), which defines an aortic size index (ASI). In one of the two French patients who died secondary to dissection (Ohl, 2008), the initial diameter before pregnancy had not been indexed to BSA and therefore the

cardiovascular risk had been initially underestimated. Furthermore, Boissonnas et al. studied 18 women with TS requesting oocyte donation. All pre-pregnancy cardiac evaluations had been considered as reassuring (Boissonnas et al., 2009). However, when a cardiologist familiar with TS re-evaluated these women, seven were diagnosed with a cardiac abnormality and therefore denied oocyte donation. Because BSA takes into account the patient's weight, a value of ASI may be distorted before or during pregnancy, especially in obese patients. In such cases, absolute values of aortic diameter may be useful. An ASI level higher than 25 mm/m2 has been associated with a risk of dissection in adult patients (Matura et al., 2007). However, the individual prediction of dissection remains very difficult.

Regarding karyotype, patients carrying a complete 45,X monosomy should be monitored closely, as congenital cardiovascular malformations are more frequent. A 45,X karyotype was present in 80% (39/49) of the published cases of dissection (Carlson et al., 2007). However, patients with mosaic karyotypes are not exempted of dissection, as illustrated in the US registry (Carlson et al., 2012).

Among the risk factors of aortic dilatation, hypertension is an acquired risk factor that should be searched for in order to prevent aortic dilatation, which precludes aortic dissection. Therefore, blood pressure should be evaluated at least each month during pregnancy and its level should be maintained below 135/85 mmHg. In the general population, risk factors of pre-eclampsia and gestational hypertensive disorders are: a previous history of pre-eclampsia, nulliparity, older age, obesity, diabetes, renal insufficiency, antiphospholipid syndrome, and previous history of miscarriage (Abalos et al., 2001). Higher risk of hypertensive disorder with oocyte donation in TS women may be related to an abnormal placenta (Gravholt et al., 2017) and therefore antiplatelet aggregation may be beneficial. The use of low-dose aspirin (75-81 mg) may be considered in pregnant women with TS (Gravholt et al., 2017). Aspirin therapy is recommended for women at increased risk for preeclampsia which would include women with TS. These patients may have poor placental vascular invasion, but that has not been proven. There is no data so far showing that aspirin will reduce the rate of cardiovascular events in any population, as the mechanism of action is likely at the placental level and will not impact maternal systemic vasculature.

Since the risk of dissection is suspected to be 5 times higher during a multiple gestation (Mortensen et al., 2012), it is crucial that women receiving ART by oocyte donation have a single embryo transfer.

A recent French study has assessed pregnancy outcome in TS since 2009. This timing has been chosen as national French guidelines have been published in 2010 (Cabanes et al., 2010). Fourteen oocyte donation centers recruited 103 patients with TS (Cadoret et al., 2018). One hundred and seventy clinical pregnancies were followed, including 35 natural pregnancies and 130 obtained after oocyte donation. No maternal death occurred. Two stillbirths and one intra-uterine fetal death were reported. A pre-conceptional assessment and a gravidic cardiological follow-up were carried out in 74% of cases. Post-partum cardiac ultrasonographies were performed in 45% of pregnancies. Hypertension and pre-eclampsia rates reached 19% and 8% of all pregnancies, respectively. This study reports a higher rate of cardiovascular follow-up than in the previous study published by Chevalier et al. in 2011. Interestingly, the rate of cardiovascular events was much lower. This could be related to the potential benefits of spreading and applying cardiovascular guidelines.

5.2 Respect the contra-indication of a pregnancy in patients with TS

Pregnancy should be avoided in case of an ascending indexed aortic diameter > 25 mm/m2 alone or between 20 to 25 mm/m2 with associated risk factors for dissection, such as a bicuspid aortic valve, an aortic coarctation and an uncontrolled hypertension. In case of an aortic dilatation with an ASI between 20 and 25 mm/m² detected prior to pregnancy, no study to date has answered the question whether elective aortic surgery should be performed before initiating a pregnancy. A history of aortic surgery or aortic dissection is still a contraindication for pregnancy. In such cases, patients should be offered surrogacy and adoption as alternatives for having a family (Practice Committee of American Society For Reproductive Medicine, 2012).

5.3 Close cardiovascular follow-up during pregnancy and the post-partum period

The rhythm of aortic diameter evaluation during pregnancy depends on the initial diameter of the aorta. In all cases, at least one TTE is recommended at 20 weeks of pregnancy. If indexed aortic diameter increases during pregnancy and becomes higher than 20 mm/m², in the presence of known risks factors such as hypertension, aortic bicuspid valve, aortic coarctation, previous dissection, the patients should be regularly monitored. In such cases, TTE should be performed at 4 weeks intervals during pregnancy and during the first month in the post-partum period. Even when dilatation is not detected in the first two trimesters, it should be stressed that dissection presents in the third trimester or postpartum (Lin et al., 2016). CMR without gadolinium injection should be considered in case of deficient visualization of the aorta or when the aortic diameter increases.

When an aortic dilatation is discovered during pregnancy, as angiotensin receptor blockers cannot be prescribed during pregnancy, beta-blockers may be used. However, no study has proven to date, a protective role of this treatment in reducing aortic dilatation during pregnancy. This recommendation is mainly based on studies performed in pregnant patients with Marfan syndrome (Kuperstein et al., 2017).

If a significant progression of aortic dilatation occurs before the fetus is viable, surgical aortoplasty is indicated. If the fetus is viable, cesarean delivery followed by aortic surgery is recommended. During pregnancy, prophylactic surgery may be considered in the case of a dilated aorta > 25 mm/m² with rapid progression > 3 mm (Gravholt et al., 2017). If a pre-existing valve surgery has been performed, risks of thrombosis or bleeding in case of mechanical valve exist (Silberbach et al., 2018). If a bioprosthetic valve is present, the risk of thrombosis or bleeding is lower.

Every physician following a pregnant woman with TS should remember that aortic dissection may occur even without previous dilatation (Practice Committee of American Society For Reproductive Medicine, 2012). As this is a life-threatening medical emergency with high rates of mortality, any patient with acute and severe chest pain should seek prompt medical advice. In the US dissection register (Carlson, 2012), taking care of such women was performed after a delay of 24h, in a large number of cases (68%).

5.4 Optimization of the mode of delivery

In order to make the pregnancy safe, the mode of delivery should be optimized. Pregnant women with aortic dilatation should deliver in a hospital where cardiothoracic surgery is available. Like in the general population, vaginal delivery is initially preferred except in presence of a significant maternofetal disproportion and a significant aortic dilatation. Cesarean section is preferred for women with aortic diameter rapidly increasing or exceeding 25 mm/m2. Between 20-25 mm/m², a vaginal delivery with epidural anesthesia is possible but the patient should be informed that a cesarean section may occur (Gravholt et al., 2017), as a cesarean section allows limitation of blood pressure and cardiac output variations. In the presence of an ASI > 20 mm/m², post-partum monitoring within the hospital is indicated for at least 48 hours (Gravholt et al., 2017). Hence, those high-risk pregnancies should be followed in a specialized tertiary center and choice of delivery route management should be discussed by a multidisciplinary team (Silberbach et al., 2018).

5.5 Biological evaluation of the thyroid, the liver, the kidneys and diabetes

Hypothyroidism due to Hashimoto thyroiditis is the most prevalent autoimmune disorder found in patients with TS (El-Mansoury et al., 2005). It may begin in early childhood, and its prevalence increases with age (Mortensen et al., 2009). The incidence of Graves' disease in young TS patients is around 2-3 % (Bakalov et al. 2012; Aversa et al. 2015). The incidence of thyroid dysfunction is high both during spontaneous pregnancies or those obtained after oocyte donation, in TS patients. Rates of thyroid dysfunction range from 7 to 44 % (Hagman et al. 2013; Bernard et al. 2016). Screening patients with TS for thyroid disease before pregnancy, should prevent complications from uncontrolled overt maternal hypothyroidism, as described in the general population, such as preeclampsia and gestational hypertension, preterm delivery, including very preterm delivery, low birth weight, postpartum hemorrhage, perinatal morbidity and mortality, as well as neuropsychological or cognitive impairment in the child (Männistö et al., 2013).

Liver function should be monitored closely before and during pregnancy, in women with TS. Before pregnancy, hepatic fibrosis should be screened, as cirrhosis with portal hypertension and esophageal variceal bleeding is a contraindication to pregnancy (Cabanes et al., 2010). It is recommended to repeat liver function tests yearly, before oocyte donation. During pregnancy, liver function needs to be monitored. In the French study by Chevalier et al., a patient died of gravidic cholestasis (Ohl, 2008). In mild cases of preeclampsia, there is a mild elevation of serum AST/ALT/Alkaline phosphatase. During HELLP syndrome, serum aminotransferases are more than ten times elevated, and unconjugated hyperbilirubinemia may be present due to hemolysis (Kelly, 2018).

The risk of both type 1 and type 2 diabetes mellitus is highly increased in patients with TS (Bakalov et al., 2008; Schoemaker et al., 2008). Various abnormalities in glucose homeostasis are reported in these patients, including insulin resistance, decreased insulin secretion and impaired glucose tolerance due to both reduced first-phase insulin release and diminished β- pancreatic cell responsiveness (Caprio et al., 1991;Bakalov et al., 2004; Hjerrild et al., 2011). These metabolic abnormalities could be amplified during pregnancy and lead to a high risk of gestational diabetes in women with TS. However, in a clinical study concerning spontaneous pregnancies in women with TS, the prevalence of gestational diabetes was not elevated (3%)(Bernard et al., 2016). Concerning pregnancies of patients with TS after oocyte donation, the rate of gestational diabetes is much higher, around 10% (Hagman et al., 2013). So, women with TS should be screened carefully prior to and during pregnancy to ensure gestational diabetes is rapidly diagnosed and treated.

In order to make a pregnancy safe in a patient with TS, multidisciplinary evaluations are mandatory, including several physicians such as endocrinologists, cardiologists, radiologists and gynecologists. **Table II** reports a check-list of the different evaluations to be performed prior to a pregnancy in a patient with TS. The preconceptional visit is a crucial point in the care of every patient with TS.

Conclusion

Several international and national guidelines have been published in recent years, recommending pre-pregnancy evaluation and careful monitoring during pregnancy and in the post-partum period in women with TS (Cabanes, 2010; Practice Committee of American Society For Reproductive Medicine, 2012; Gravholt et al., 2017). The dissemination of those recommendations should lower the prevalence of complications during pregnancies in patients with TS. However, as the quality of evidence of some of the recommendations from those guidelines have been classified as moderate, low or even very low, studies are still necessary in order to further reduce the risks of pregnancy in patients with TS.

In summary, cardiovascular risks in Turner syndrome during pregnancy are high and therefore cardiovascular pre-pregnancy evaluations as well as follow-up during pregnancy are of utmost importance. A multidisciplinary approach to care of patients with TS seeking a pregnancy, during the pregnancy and during the post-partum period is absolutely necessary.

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viii. Legends

Table I- Summary of published pregnancies with aortic dissection in women with TS

BAV: bicuspid aortic valve; Type A/B: Stanford dissection type (type A: ascending aorta; type B: descending aorta); ART/DO: assisted reproductive technology/oocyte donation.

Table II- Check list of exams to be performed prior to a pregnancy in TS patients

BMI: body mass index [weight(Kg)/height²(m)]; BSA: body surface area (calculated using the Dubois & Dubois formula); ASI: aortic size index (aortic diameter at the level of the tubular ascending aorta/BSA; N<20 mm/m²); CMR: cardiac/cardiovascular magnetic resonance.

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Table II

	Pre-conceptional visit
Clinical examination	weight, height, BMI, BSA Cardiac murmur Ambulatory blood pressure
Thyroid	FT4, TSH, antiTPO antibodies
Diabetes	Fasting glycemia ± HbA1c
Liver	AST, ALT, GGT, PAL ± liver ultrasound
Kidneys	Plasma creatinin
Cardiology	TTE ± CMR including measurement of ASI screening for aortic bicuspid valve/coarctation

Table I

Reference	Age at dissection	Karyotype	Cardiovascular disease	Hypertension/ Pre-eclampsia	Dissection Timing	Pregnancy	Outcome
USA, 1997 (Nagel)							
	-	-	no BAV, no coarctation	Yes/No	1 yr after ART	ART/OD	Deceased
	-	-	no BAV, no coarctation	No/No	3d trimester	-	Deceased
USA, 1998 (Garvey)							
	33	-	coarctation	Yes/No	27 weeks, type A	ART/OD	Deceased
Belgium, 2000 (Weytjens)							
	38	mosaic	no BAV, no coarctation	Yes/Eclampsia	2 weeks postpartum	-	Alive
USA, 2001 (Beauchesne)							
	30	-	BAV/operated coarctation	No	36 weeks, type A	ART/OD	Deceased
Sweden, 2004 (Landin)							
	39	45,X/46,XX/47,XXX	coarctation	Yes/No	3d trimester (7 months)	Natural	Alive
Denmark, 2006 (Gravholt)							
	38	45,X	no BAV, no coarctation	-	1 yr post-partum, type B	ART/OD	Deceased
France, 2008 (Ohl)							
	33	45,X	aortic insufficiency	No	38 weeks, 1 week post-partum	ART/OD	Deceased
France, 2009 (Boissonnas)							
	33	45,X/46,XX/46,XY	BAV	No	37 weeks, type A, 16h post-surgery	ART/OD	Deceased
USA, 2012 (Carlson)							
	27	mosaic	BAV	No	pregnancy before type A	Natural	Alive
	29	-	BAV/left subclav anevrysm	No	3d trimester before type B	ART/OD	Deceased
	48	-	BAV/Aortic stenosis	-	pregnancy after 2 yr	-	Alive
	48	mosaic	BAV	Yes/No	pregnancy 17 yr before type B	Natural	Alive
Scandinavia, 2013 (Hagman)							
	36	45,X/46,XY	-	-	32 weeks	Natural	Alive