

The risk of oocyte donation in patients with Turner syndrome

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Abstract. Women with Turner syndrome generally experience ovarian failure at an early age and very few are fertile. Through oocyte donation, affected women may achieve a pregnancy. These pregnancies, however, appear to be at high risk for fatal aortic dissection or rupture. This article reviews the literature on the obstetric risk of women with Turner syndrome, particularly those pregnancies achieved through oocyte donation. Women with significant risk factors should be counseled against attempting pregnancy. © 2006 Elsevier B.V. All rights reserved.

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Assisted reproductive technologies may put women with Turner syndrome at an unacceptably high risk of death. Specifically, the risk of fatal aortic dissection or rupture appears to be increased in pregnancies achieved through oocyte donation [1]. It is known that Turner syndrome carries with it a risk of aortic dissection or rupture throughout the life span [2]. Risk factors for this potentially fatal event include hypertension, aortic dilatation and the presence of a cardiovascular malformation [2,3]. Significantly, many reported fatalities had no identified risk factors [2]. Twenty-five to fifty percent of those affected with Turner syndrome have associated cardiac anomalies [3–6]. The most common of these are elongated transverse arch, bicuspid aortic valve, aortic coarctation and major venous malformation [2,3,5,6]. The clinical significance of an isolated, elongated transverse arch is not known.

Autopsy findings following fatal aortic dissection or rupture in Turner syndrome commonly reveal cystic medial necrosis, as is seen in Marfan's syndrome [7]. While

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Marfan's syndrome may be used as a clinical model for Turner syndrome, there is insufficient evidence to conclude that the two syndromes follow the same cardiovascular natural history. The New York Heart Association estimates maternal mortality at 5–15% for women with Marfan's syndrome who have a normal aorta and 25–50% for those with aortic involvement [8]. In normal pregnancy, cardiac output is increased 30–50% by mid-gestation [9]. Hemodynamic stress is amplified during the puerperium due to rapid changes in cardiac output [10]. For all women of reproductive age, there is an association between aortic dissection and pregnancy with the risk of dissection or rupture increasing with advancing gestational age [11–13].

Women with Turner syndrome generally experience premature ovarian failure at an early age and very few are fertile. Assisted reproductive technologies now allow these women to attain pregnancy through the use of donated oocytes. However, there is accumulating evidence that pregnancy may not be safe for these women. A current literature search reveals four deaths from aortic dissection in oocyte-donated pregnancies [14–16]. Three of these women died suddenly of aortic dissection, in the third trimester of pregnancy [14,15]. The fourth presented at 24 weeks gestation with epigastric pain and was initially diagnosed with preeclampsia. On further investigation, she was found to have aortic dissection with severe aortic regurgitation. She was treated surgically but died approximately 3 months later following multiple anoxic events [16]. Of the four fatalities, one patient had preexisting essential hypertension and a mildly dilated aortic root, one had no prenatal risk factors identified [14], one had a history of surgical repair of aortic coarctation at age 4 years and a bicuspid aortic valve [15], and the other had essential hypertension prior to pregnancy [16].

In addition to these cases, there are reports of aortic dissection associated with spontaneous pregnancies. One report describes a case of aortic dissection 2 weeks post-partum in a woman with Turner mosaicism (45,X(94%)/46,XX) who conceived spontaneously [17]. Her pregnancy was complicated by eclampsia requiring a cesarean section at 27 weeks gestation. Her past history revealed preterm delivery for eclampsia in a previous spontaneous pregnancy. Another case report describes a woman who suffered a nonfatal aortic dissection in the third trimester of her second spontaneous pregnancy. Coarctation was noted at the time of surgery and repaired at a later date [18].

Few studies have focused on the obstetric risks in women with Turner syndrome who conceived through oocyte donation. One of these studies had the objective of estimating the incidence of aortic rupture, dissection and/or death in pregnancy achieved through oocyte donation, in women with Turner syndrome [1]. Additional objectives of the study were to determine the current state of care for pretreatment screening of women with Turner syndrome planning on undergoing assisted reproduction with donor oocytes, and to evaluate the pregnancy rate and the rate of spontaneous abortion with oocyte donation, in this population.

In this study, all egg donor programs listed in the Center for Disease Control's 1997 National Summary and Fertility Clinic Reports were surveyed and 134 (52%) responded. One hundred and forty-six women with Turner syndrome were treated with oocyte donation. Remarkably, only 72 (49.3%) women had any cardiac screening prior to treatment. Of those screened, 6 patients (8.3%) had cardiovascular malformations identified on echocardiography. Only one of these patients was denied treatment.

No deaths were reported during pregnancy. One patient died from dissecting aortic aneurysm, prior to receiving treatment. One patient experienced renal failure during treatment. The study was conducted following the publication of the aforementioned four cases of sudden death in oocyte-donated pregnancies in this population. All four cases were reported in the U.S. literature, from American clinics; however, the cases were not reported to the investigators. An estimate of maternal mortality of 2% was made through extrapolation.

Another notable conclusion from this study is that cardiac screening is underutilized by 50%. Given the high incidence of cardiac anomalies associated with Turner syndrome and the known increased risk of aortic dissection and rupture in the presence of a cardiovascular malformation, it is alarming that half of the patients treated received no cardiac screening.

The overall live-birth rate found is consistent with that of oocyte-donated pregnancies for other indications at 64%. The low spontaneous abortion rate of 7.1%, questions theories of hypoplastic uterus and endometrial defect that have been proposed to account for high spontaneous abortion rates in other series of oocyte-donated pregnancies in Turner syndrome [19]. In addition, all of the multiple gestations resulted in the live birth of at least one infant, which further argues against the presence of a hypoplastic uterus.

Bodri et al. also examined the rate of obstetrical complications in women with Turner syndrome who conceived through oocyte donation [20]. This retrospective analysis identified 21 patients treated with 30 cycles of oocyte donation between 2001 and 2004. The patients were evaluated by a cardiologist prior to treatment and this evaluation included echocardiography. These evaluations revealed that one woman had mild aortic insufficiency and one had hypertension.

The most striking finding in this study was the high rate of pregnancy-associated hypertensive disorders. The incidence was 67% which is significantly higher than that seen in oocyte donation in general (23–38%) [21] and not explained by advanced maternal age or multiple gestation. Of the nine pregnancies that surpassed the first trimester, six were complicated by hypertensive disorders. One of those six patients presented with preeclampsia and fetal demise at 33 weeks gestation. There were three further cases of preeclampsia including one case of HELLP syndrome (hemolysis, elevated liver enzymes and low platelets). Two additional patients developed pregnancy induced hypertension. No other maternal complications were reported.

All live-born infants in this study, were delivered by cesarean section. The indications for surgery were preeclampsia in two cases and fetopelvic disproportion in the others. Half of the deliveries were preterm and 55% had evidence of intrauterine growth restriction with a birth weight below the 10th percentile.

Women with Turner syndrome are also at risk of pregnancy complications related to the medical conditions commonly associated with the syndrome. The incidence of hypothyroidism in these adults is reported to be as high as 50% [22]. Untreated hypothyroidism in pregnancy increases the risk of spontaneous abortion, intrauterine fetal death, placental abruption and poor perinatal outcome. It also increases the risk of pregnancy induced hypertension which is already more common in women with Turner syndrome. Reports also suggest resultant lower IQ and decreased psychomotor performance in the offspring of women with untreated hypothyroidism in pregnancy

[23]. Ideally, women with Turner syndrome should have their thyroid status determined prior to pregnancy and periodically during pregnancy.

The elevated risk of insulin resistance and diabetes [24,25] in Turner syndrome can also complicate pregnancy. Any glucose intolerance is worsened by obesity, which is also prevalent [25,26]. Women who develop gestational diabetes have an elevated risk of developing pregnancy-related hypertensive disorders, of requiring cesarean section for delivery and of having large-for-gestational-age babies [27]. It is important to carefully screen these women prior to pregnancy and during pregnancy.

There is much debate as to the optimal screening protocol for Turner patients considering pregnancy. Certainly, they require a complete medical evaluation. Investigations should target the conditions known to be associated with Turner syndrome, particularly the cardiovascular system. Cardiac screening should include echocardiography and MRI with or without contrast, to look for cardiovascular malformations and aortic root dilatation [28,29]. The patient should also undergo an ECG due to intrinsic abnormalities in cardiac conduction and repolarization [29]. Blood pressure should be monitored due to the high incidence of hypertension in women with Turner syndrome [30–32].

The American Society for Reproductive Medicine Practice Committee published recommendations on the management of infertility in Turner syndrome [33]. Specifically, the committee recommends that all women planning a pregnancy through oocyte donation require cardiology consultation and screening prior to treatment and that any significant echocardiographic abnormality be considered an absolute contraindication of pregnancy in patients with Turner syndrome. Those with normal findings who attempt pregnancy require frequent formal reevaluation throughout gestation. It must be remembered that a small number of women reported as having no risk factors have suffered a fatal aortic dissection [2].

The committee's recommendations for surveillance during pregnancy include treatment of hypertension and ongoing cardiology assessment with periodic echocardiogram. The recommendations for delivery are that those women with an aortic root diameter of less than four centimetres may attempt vaginal delivery under epidural anaesthesia. Those with baseline or progressive aortic root dilation should have an elective cesarean section under epidural anaesthesia, prior to the onset of labour. These recommendations are likely based on research involving women with Marfan's syndrome [34,35].

Although the advent of oocyte donation has made it possible for many women with premature ovarian failure to achieve a pregnancy, prior to the consideration of oocyte donation patients with Turner syndrome should be counseled about the high risk of cardiac complications, including death, regardless of risk factors. Counseling patients with Turner syndrome about infertility should begin early. It would be prudent to address the potential dangers of pregnancy from the very first discussions of fertility, during the adolescent years.

Women with a significant echocardiographic abnormality, such as bicuspid aortic valve, coarctation of the aorta or aortic dilatation or a history of surgical repair of a cardiac lesion should be counseled against pregnancy due to the high risk of aortic dissection or rupture. Isolated systemic hypertension must be recognized as an independent risk factor for aortic dilation, dissection or rupture. These patients should be counseled extensively as to their increased risk of a fatal cardiac event in pregnancy. Preconception cardiology evaluation

with magnetic resonance imaging and ongoing cardiology evaluation with particular attention to strict control of hypertension in pregnancy is essential. For those that do pursue oocyte donation or in vitro fertilization, elective single embryo transfer is recommended to avoid multiple gestations which further tax the cardiovascular system.

There is a clear need for a data collection mechanism to record and compile outcome data for pregnancies achieved spontaneously or through oocyte donation, in Turner syndrome. Ideally, a national registry would be established and linked directly to international registries for worldwide analysis of pregnancy outcomes. An international collaboration of this nature may provide enough data on this fairly infrequent event to allow for the accurate assessment of maternal morbidity and mortality in women with Turner syndrome and to better guide their care.

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