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EDITORIAL

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The complexity of fertility preservation for women with Turner syndrome and the potential risks of pregnancy and cardiovascular complications

Turner syndrome is the most common chromosomal abnormality in women, with a prevalence of 1/2500. Most cases are diagnosed in early childhood and adolescence and a minority beyond adult age. In some cases, adult women receive a diagnosis of Turner syndrome during an infertility work-up. Due to the various forms within the wide Turner spectrum, including mosaicisms with only minor phenotypic features, a relative large unknown number of cases should be expected. In Sweden, with a population of 10 million, around 1800 women and girls are expected to present with a Turner genotype. However, only about half of the cases present with clinical features and receive a diagnosis.

As previously reported, for women with Turner syndrome, the most distressing feature of the syndrome is infertility.[1] It is hence of utmost importance to include counseling on reproductive issues when a Turner diagnosis is confirmed. In this issue of *AOGS*, Nawroth et al highlight the complexity of reproductive issues in this specific patient group and discuss recommendations for fertility preservation in women and girls with Turner syndrome.[2]

In Sweden and in the Nordic countries, fertility preservation has been implemented at the reproductive centers of large university hospitals, covering the entire country. The services are also tax-funded and included in the healthcare system, available to the entire population. Women and girls with Turner syndrome have thus benefited from these programs.[3,4] Additionally, the Swedish Turner Academy, established in 1994, provides a National Healthcare Program for Turner syndrome. In the program, girls and women with Turner syndrome are followed up throughout life by the multidisciplinary teams at Turner centers established at all university hospitals.[5] The discussions regarding reproductive options are brought up soon after diagnosis and are also discussed at the time of transition from pediatric to adult healthcare. If any congenital heart or vessel disease (bicuspid aortic valve, coarctatio of the aortae) is present, or operated upon, advice is given to refrain from assisted pregnancy already at this time, if this has not already been discussed with the pediatricians and the parents during early childhood. In all patients who receive a Turner diagnosis, irrespective of age, a thorough cardiac evaluation is performed with echocardiography and/or magnetic resonance imaging. In this way, the cardiovascular status is known before fertility preservation discussions. Cardiac examinations are repeated every 5th year after transition to the adult clinic in order to follow the aortic root diameter. If aorta dilation in relation to body surface area is confirmed, more intensive lowering of blood pressure and consultations with a cardiologist are initiated for possible surgery. The congenital aberrations (bicuspid aortic valve, coarctatio of the aortae) and/or aortic dilation are strongly associated with future aortic dissection, which is a life-threatening catastrophe.[6] In line with international guidelines, medical assistance to become pregnant is not recommended if congenital heart and/or vessel abnormalities, operated or not, or acquired aortic dilation is present in women with Turner syndrome.[5,7] Other options for parenthood should be advised.

If there are no contraindications, fertility counseling and recommendations for fertility preservation are discussed.[5] A previous Swedish study of girls with Turner syndrome aged 8-19 years who underwent laparoscopy for ovarian biopsy and ovarian tissue cryopreservation at Karolinska University Hospital revealed that the probability of identifying ovarian follicles on pieces of biopsies analyzed with histology increased if the following criteria were fulfilled: (a) Turner karyotype showed a mosaicism, (b) girls had spontaneous puberty, a few of them even menarche and (c) FSH and AMH serum concentrations were normal for age.[8] The biopsies were feasible in 47 of 57 girls included in the study and follicles were identified in 15 cases.

We agree with Nawroth et al that cryopreservation of ovarian tissue for girls with Turner syndrome has limitations, in particular if the ovarian reserve is already reduced. Because of this, in the Swedish Turner program we currently recommend that adolescent girls who present with spontaneous start of puberty should be referred for appropriate counseling on fertility preservation and, if possible, performance of fertility preservation with hormone stimulation and oocyte cryopreservation, before it is too late.[9] The vitrification of oocytes is currently a recognized clinical method for fertility preservation, whereas the cryopreservation of ovarian tissue has been largely considered experimental, and the success of later transplantation in patients with limited ovarian reserve, such as girls and women with Turner syndrome, as Nawroth et al noted,[1] is still unknown.

Several reports of pregnancies in women with Turner syndrome in Sweden showed no increased mortality, which seems to be dependent on the careful repeated cardiac evaluations before pregnancy induction/assistance following healthcare guidelines.[10] A register-based study using the genetic laboratory data from all women with a Turner karyotype who gave birth between 1973 and 2010 in Sweden compared with the general population also confirmed those results.[11] Although no mortality was found in that survey, morbidity from circulatory disease was increased before, during and 1 year after delivery, although not thereafter. Most of the pregnancies were spontaneous, also among women with a monosomy. Aortic dissection occurred in 2% of Swedish women with a Turner karyotype during pregnancy, all of whom survived.[11]

The most recent survey of women with Turner syndrome in Sweden, with a follow-up of 23 years according to the national guidelines, reported on 198 women, 9 of whom suffered from aortic dissection, at a mean age of 34 years.[6] The majority of these patients had congenital bicuspid aortic valve or coarctatio aortae. With this in mind, if these cardiac features are confirmed early in life, it is advisable not to encourage fertility preservation during childhood or future pregnancies. Offering hope with false expectations is not ethical, either for the girl or her parents, who probably are those who have the most stress, to become grandparents. Importantly, the majority of women with aortic dissection had a mixed genotype and only a minority had a monosomy.[6] Hence, genotype cannot be used for cardiovascular risk evaluation. It is gratefully acknowledged that Nawroth et al emphasize the importance of taking into account the health of the woman in pregnancy planning.[2] However, the categorical separation of monosomy and mosaicism as predictors of cardiovascular risk is not useful. The dreadful aortic dissection can occur with any karyotype.

Careful blood pressure monitoring and treatment, possibly with a lower target goal than the recommended guidelines for blood pressure treatment in the general population, is essential to lower the pressure on the aortic wall. Annual control of the blood pressure is indicated (and more often if any cardiovascular abnormalities and hypertension are present), as well as checking of thyroid function and blood lipids, as hyperlipidemia and hypothyroidism are more frequent in Turner syndrome than in women in general. If there are no contraindications, and pregnancy is medically assisted, single embryo transfer is strongly recommended in women with Turner syndrome. Careful cardiac, aortic and blood pressure monitoring during pregnancy at the high-risk units for obstetric care is mandatory.

Kenny A. Rodriguez-Wallberg[1]
Kerstin Landin-Wilhelmsen[2]
on behalf of the Swedish Turner Academy

[1]*Karolinska University Hospital, Stockholm, Sweden*
[2]*Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Section for Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden*

Correspondence
Kenny A. Rodriguez-Wallberg
Email: kenny.rodriguez-wallberg@ki.se

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