Fertility preservation in Turner syndrome

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Premature ovarian insufficiency is a relatively rare condition that can appear early in life. In a non-negligible number of cases the ovarian dysfunction results from genetic diseases. Turner syndrome (TS), the most common sex chromosome abnormality in females, is associated with an inevitable premature exhaustion of the follicular stockpile. The possible or probable infertility is a major concern for TS patients and their parents, and physicians are often asked about possible options to preserve fertility. Unfortunately, there are no recommendations on fertility preservation in this group. The severely reduced follicle pool even during prepubertal life represents the major limit for fertility preservation and is the root of numerous questions regarding the competence of gametes or ovarian tissue cry-banked. In addition, patients suffering from TS show higher than usual rates of spontaneous abortion, fetal anomaly, and maternal morbidity and mortality, which should be considered at the time of fertility preservation and before reutilization of the cryopreserved gametes. Apart from fulfillment of the desire of becoming genetic parents, TS patients may be potential candidates for egg donation, gestational surrogacy, and adoption. The present review discusses the different options for preserving female fertility in TS and the ethical questions raised by these approaches. (Fertil Steril® 2016;105:13–9. ©2016 by American Society for Reproductive Medicine.)

Key Words: Fertility preservation, Turner syndrome, oocyte vitrification, ovarian tissue cryopreservation

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Primary ovarian insufficiency (POI) is a remarkably heterogeneous gonadic disorder, with a wide spectrum of etiologies, including iatrogenic treatments, infectious, inflammatory, cytogenetic and genetic diseases. Although most of POI remains unexplained, an increasing number of genetic abnormalities have been recently identified to be at risk of follicular depletion and infertility (1, 2).

Contrary to men, women are endowed with a fixed and non-replenishable supply of germ cells. The maximum number of germ cells occurs at fetal mid-gestation when a total of 6–7 million are present. Thereafter, the number of germ cells irretrievably declines and no further de novo gametogenesis occurs. At birth, the number of germ cells is estimated to be approximately 1–2 million. At the onset of puberty, the germ cell number is typically reduced to approximately 300,000. Thereafter, during the reproductive years, a number of oocytes begin to develop with only one or a few becoming dominant while the others undergoing a process of atresia (3). The absolute number of oocytes continues to decline with age irrespective of whether the woman has ovulatory cycles. At approximately the age of 37–38 years, there is often an accelerated rate of follicular loss, which occurs when the number of follicles reaches about 25,000 (4). At the time of menopause, fewer than 1000 follicles remain.

Monosomy of the X chromosome due to partial or complete loss of one X chromosome in a 46,XX fetus or of loss of a Y chromosome in a 46,XY fetus, know as Turner syndrome (TS), affects 1 in 2500 newborn females (5). TS has been recognized as the most established genetic cause of POI, usually occurring prior to puberty (5).

Several lines of evidence indicate accelerated germ cell apoptosis may be the main mechanism of follicular depletion in TS (6). However, the

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coexistence of a mosaic peripheral blood karyotype, with at least one non-45,X cell line coexisting with the 45,X cells is not a rare condition. In particular, mosaicism may explain the phenotypic variability, and the depth of ovarian dysfunction (7). The likelihood of functional ovarian tissue in women with TS therefore relies on the presence of 46,XX germ cells in the ovaries. Hence, spontaneous puberty, menarche, and fertility, are more likely to be retained in women with 45,X/46,XX mosaicism rather than complete monosomy 45,X (8–11). It is worth noting that a completely nonmosaic 45,X karyotype in peripheral blood leucocytes does not preclude the coexistence of 45,X/46,XX mosaicism in the ovary.

Over the past decades, advances in cryopreservation techniques have raised hopes of fertility preservation in women at risk of POI, as a result of gonadotoxic treatments or due to the natural history of the disease itself. It is established that a subset of girls with genetic abnormalities reducing their ovarian reserve, possesses a small residual of ovarian follicles at birth or early childhood. Therefore the identification of these girls as early in life as is possible represents a major issue, for discussing the different fertility preservation options.

In this article we address the different options for preserving female fertility in TS and the ethical questions raised by these approaches.

FERTILITY PRESERVATION OPTIONS

Most adult women with TS already have established ovarian failure with high serum follicle-stimulating hormone (FSH) levels at the time they wish to start a family. Although this does not indicate absolute absence of viable follicles (12), ovarian stimulation for homologous in vitro fertilization is often unrealistic and patients are usually guided towards egg donation. As a consequence, considering fertility preservation during adolescence and perhaps childhood may represent a better option, even though data is lacking. Approaches to fertility preservation in TS vary greatly, depending on the pubertal status, the remaining ovarian function and the degree of psychological maturity.

Since the number of primordial follicles endowed within the ovaries is higher in younger girls, the diagnosis of the disease as early as possible is a key point. However, the dramatic lack of reliable markers of the follicular ovarian status before puberty still represent a major limit for defining the best timing for fertility-sparing methods in young patients suffering from TS. Indeed, before puberty, serum FSH and estradiol levels are low due to the physiologic state of hypogonadotropic hypogonadism and therefore not correlated with the ovarian reserve. Over the past decades, antimüllerian hormone (AMH) has become the most reliable hormonal marker of the follicular stockpile in adults (13). However, the paucity of available data on AMH during childhood accounts for the need to interpret its values in this population with caution (14). Visser et al. (15) recently studied serum AMH levels in girls and adolescents with TS and reported detectable values of this peptide in 21.9% of patients, the results correlating with karyotypes. In addition, AMH was detected in 77% of girls with 45,X/46,XX karyotypes, but in only 10% of those with 45,X karyotypes. As a result, AMH may be a promising marker of ovarian function in TS patients (16).

Furthermore, the ultrasonographic antral follicle count, which is probably the best marker of the follicular ovarian status when performed transvaginally, is most often infeasible in young virgin patients. Therefore, the strategy for fertility preservation is currently based on transabdominal follicle counting, AMH concentrations, and serum FSH levels in post-pubertal girls.

Oocyte Cryopreservation following Ovarian Stimulation

The first birth attributable to use of frozen and thawed oocytes in humans was reported almost 30 years ago (17). Considered experimental for several decades, the emergence of vitrification freezing protocols has markedly improved oocyte survival, fertilization, and pregnancy rates (18). Most studies have shown significantly improved post thaw survival rates with vitrification (90–95%) in comparison with slow-freezing, while fertilization and pregnancy rates obtained with vitrified/warmed oocytes are similar to those reported with fresh oocytes (18–20). In addition, no increase in chromosomal abnormalities or birth defects has been noted in children born from cryopreserved oocytes (18, 21). As a result, oocyte cryopreservation is now considered an established procedure in adults and post-pubertal girls (22–24).

Ovarian stimulation requires exogenous FSH administration for 10 to 15 days, followed by transvaginal ultrasound-guided retrieval of mature oocytes directly available for cryopreservation (24–26). Given the relative immaturity of the function of hypothalamus-pituitary-ovarian axis in adolescents, luteinizing hormone supplementation is proposed on the day of gonadotropin-releasing hormone antagonist administration, in order to achieve adequate steroidogenesis.

Even in young post-pubertal TS patients, a limitation may be the very low number of FSH-sensitive follicles endowed within the ovaries and/or the high values of baseline FSH. In clinical practice, a trial of ovarian stimulation is often worth performing when baseline FSH is below 20 UI/L. High doses of recombinant FSH are usually required, ranging from 225 to 450 IU/day. However, the success rates of oocyte cryopreservation in young TS patients have not been demonstrated. It is conceivable that not all oocytes will be suitable for fertilization or will develop with a normal karyotype. This point might be added to a possible suboptimal competence of oocytes recovered in young patients. Indeed, although the maximum rates of embryo aneuploidy is increasing with age, women below 25 years show relatively high values, questioning the competence of oocytes recovered in very young patients (27). However, technologies such as preimplantation genetic screening may enable embryos originating from the stored oocytes to be screened for numerical chromosomal abnormalities. In addition, similar genetic analysis can be performed by polar body biopsy in oocytes (28). Thus, it is anticipated that at least a fraction of oocytes frozen from these patients should lead to successful pregnancies.

In adolescent girls, high doses of estrogen can accelerate and stop prematurely the growth (29). Especially in TS