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

patients in whom the final height is one of the major issues, the question arises of a deleterious effect of hyperestrogenia concomitant to ovarian stimulation. The question of the possible detrimental effect of a sporadic increase in serum estradiol levels has been subject to debate for many years, in particular in adult women with hormone sensitive tumors such as breast cancer. Although the expected impact of a 5- to 10-fold increased estradiolemia during a mean of 5 days (30), is poor, robust data are still lacking. However, specific protocols, combining letrozole and exogenous gonadotropins administration, have recently been proposed for allowing the yield of numerous mature oocytes while maintaining serum estradiol levels at normal ranges (31, 32). Thus, it is conceivable that in a near future, the indications of such a protocol might be extended to young TS patients, candidate for fertility preservation, in whom an increased hyperestradiolemia should be avoided.

Oocyte cryopreservation after controlled ovarian hyperstimulation probably represents the best option for preserving fertility in post-menarchal girls, typically 13 years of age or older. Evaluation for physical and psychosocial suitability for the procedure represents a major step prior to being included in an oocyte freezing program.

Cryopreservation of Oocytes Recovered during Natural or Modified Natural Cycle

Oocyte retrieval and freezing can be performed during unstimulated (natural) cycles in patients diagnosed with diminished ovarian reserve, but typically no more than a single oocyte is available for freezing (33). Because pregnancy rates after oocyte cryopreservation increase in parallel with the number of gametes in storage, this strategy, used for fertility preservation, involves the repetition of cycles. Although this approach remains unrealistic in cancer patients requiring rapid gonadotoxic treatments, it may be considered in postpubertal women with genetic diseases of POI, with persistent menstrual cycles, unable to respond to exogenous FSH administration, in whom removal of an ovary for cryopreservation does not represent a relevant indication due to the dramatically reduce supply of primordial follicles.

It has been suggested in recent years that natural-cycle in vitro fertilization (IVF) may be a promising alternative for treating infertility of poor responders (34, 35). The biological advantages of natural-cycle IVF may provide a single oocyte of better quality and thus allow the transfer of a healthier embryo into a more receptive endometrial environment (36). However, it is now well established that the overall pregnancy rates achieved with modified natural-cycle IVF in patients $>$ 35 years are low, probably as a result of the poor oocyte quality. Since candidates for fertility preservation in case of TS are relatively young, it is conceivable that collecting many oocytes through recurrent natural cycles might be interesting in terms of oocyte competence. Apart from the transvaginal puncture, the main limit for this strategy may be the high number of cycle required for obtaining an "interesting" number of frozen oocytes, which may slow down the fertility preservation process.

In Vitro Maturation of Oocytes

Retrieval of immature oocytes from unstimulated small antral follicles followed by in vitro maturation (IVM) in which oocytes are cultured from the germinal vesicle to the metaphase II stage and then cryopreserved, has more recently emerged in the field of female fertility preservation. Cumulo-oocyte-complexes may be recovered transvaginally or from ovarian tissue harvested for cryopreservation, even in prepubertal patients (37).

The number of germinal vesicle stage oocytes recovered is strongly correlated with the number of antral follicles visible into the ovaries. As a result, IVM alone may not be suitable in young patients with genetic diseases at high risk of POI, due to their early reduction of ovarian reserve. However, IVM creates another opportunity for oocyte cryopreservation without ovarian stimulation, especially in those girls undergoing ovarian tissue harvesting for cryopreservation. Yet, the pregnancy potential of in vitro matured oocytes from harvested ovarian tissue remain poorly established even though 2 live births have recently been reported in cancer patients (38, 39).

Embryo Cryopreservation

Embryo cryopreservation is a well-established technique and has been used in fertility centers worldwide for the past 30 years in infertile patients. Indeed, comparable live birth rates have been reported with the use of fresh or cryopreserved embryos (15). Protocols and methods of egg retrieval are identical for oocyte and embryo freeze cycles. However, an immediate access to sperm from a partner or a sperm donor is mandatory, thus limiting applicability of embryo cryopreservation as an relevant option for fertility preservation in girls and un-partnered young women.

Ovarian Tissue Cryopreservation

Even though ovarian tissue cryopreservation is still considered experimental in adults (25), it is the only strategy that allows preservation of fertility and endocrine ovarian function, and therefore, is the technique of choice for prepubertal girls at high risk of POI. Indeed, primordial follicles can be found in ovarian tissue harvested for cryopreservation from both mosaic and non-mosaic TS girls up to 17 years of age (40). A Swedish study of 57 girls with TS identified predictive factors for the presence of healthy follicles within the ovarian tissue (41); spontaneous pubertal development, mosaic peripheral blood karyotype, normal serum FSH and AMH levels. However, it is important to notice that the reliability of these criteria may be questioned since some patients failed to show any follicles within their ovarian tissue (42, 43). On the contrary, missing these criteria does not prevent the possibility of natural pregnancy (44, 45). If the option of ovarian tissue cryopreservation is chosen, it may be interesting to consider its association with ex vivo IVM from cumulo-oocyte-complexes recovered in the laboratory, even though poor yield is expected.

Ovarian tissue cryopreservation, which implies the intentional reduction of a part of the follicular stockpile, requires the surgical removal of ovarian cortex fragments, most

frequently via a laparoscopic approach. The ovarian tissue can further be grafted back orthotopically to the pelvis or heterotopically to alternative sites (subcutaneous tissue of the abdominal wall, forearm, or chest wall) (46, 47).

However, the function of frozen-thawed ovarian tissue after grafting remains suboptimal. Indeed, hypoxia and hyperactivation of follicular growth (48–51) account for the substantial loss of primordial follicles and reduction of oocyte quality after transplantation (52). Since primordial follicles are the most resistant to ischemic damage after grafting (53), the chance of restoring fertility is related to the number and quality of follicles endowed within the transplanted cortical tissue (54). Therefore, in candidates for ovarian tissue cryopreservation, the quantity of ovarian tissue removed should be influenced by the expected probability of POI (55). Although biopsies might have been sufficient to cryopreserve a large number of ovarian follicles in young girls, coagulation is sometimes necessary for hemostasis, possibly resulting in ovarian damages. Moreover, as ovaries are often small in TS patients, with a poor density of follicles, damage to the remaining cortex after coagulation may have a dramatic impact. Therefore, it is recommended to remove as much tissue as possible, typically an entire ovary.

To date, around 60 live births have been reported after autotransplantation of ovarian tissue. All these pregnancies resulted from use of ovarian tissue that was harvested from and subsequently transferred back to adult women choosing ovarian tissue cryopreservation performed in the setting of medical diagnoses such as cancer or other medical conditions (56). Evidence indicates that prepubertal ovarian tissue recovered before puberty has specific histologic characteristics and is remarkably different from adult ovary (57). However, it may keep its potential for restoring an endocrine function following thawing and transplantation (58). In addition, the competence of ovarian tissue in term of gametic production has recently been demonstrated with the first live birth obtained after transplantation of ovarian tissue recovered from a premenarchal girl (59). Yet, data on efficiency of this approach in girls or women with TS are lacking.

In summary, ovarian tissue cryopreservation can be offered to girls with TS who are found to have adequate ovarian reserve but who cannot wait until sufficient maturity to undergo oocyte cryopreservation. The promise of this technology for girls with TS is at present hypothetical, given that no girl with TS who has undertaken this approach thus far has returned for autotransplantation of the previously cryopreserved ovarian tissue. The probability of success of this approach is unknown and this option remains experimental at the current time. In candidates for ovarian tissue cryopreservation, it is probably interesting to attempt to recover ex vivo some immature eggs for IVM and further cryopreservation of metaphase II oocytes (60).

ETHICAL CONCERNS

Fertility preservation in TS raises numerous ethical considerations. The primary objective remains to improve the psychosocial wellbeing and to promote autonomy of patients, by giving them the best possible opportunity to have their own biological children (61, 62). However, it is important to be aware that, at present, the techniques of fertility preservation are associated with low success rates and therefore may produce false hope and later psychosocial harm. In particular, the promise of all available approaches of fertility preservation for girls with TS is still hypothetical. As a consequence, it is possible that the invasive nature of each technique may not outweigh by expected benefits.

An important part of ethical questions are related to the possibility to offer fertility preservation techniques during childhood/adolescence. In particular, young patients may be not sufficiently mature on a psychological standpoint and competent to make their own decision, requiring an institutional review board-approved consent from the parents. Information should be provided on the remarkable lack of data regarding the efficiency of fertility preservation in girls or women with TS. Otherwise, the potential non-use of gametes or ovarian tissue cryopreserved in relation with possible contraindication to pregnancy should be evoked.

In virgin adolescents, transvaginal procedure for oocyte retrieval may be difficult to accept by the patient and/or her parents. If egg collection may be feasible by laparoscopy, we think that, due to its invasive characteristic, it should not be recommended in absence of medical reason. However, medical decision of accepting fertility preservation with transvaginal procedure collides with individual feelings and the burden of the cultural weight. Therefore, questions regarding the concept of virginity may be subject to discussion with a psychologist to help patients to make their decision.

PREGNANCY IN TURNER SYNDROME

Regardless of whether conception is natural or medically assisted, increased rates of spontaneous abortion and fetal abnormality have been reported, as well as intrauterine growth restriction, low birth weight and prematurity (6, 63). The high risk of miscarriage may be attributable to fetal genetic abnormalities or to a detrimental uterine environment (64–66). Otherwise, women who have X monosomy or structural anomalies of the X chromosome may produce gametes with the sex chromosome anomaly, resulting in an affected zygote and ensuing spontaneous abortion or offspring with TS. For this reason, cycling mosaic TS women may consider prenatal testing or even in vitro fertilization with pre-implantation genetic testing to avoid aneuploidy prior to embryo transfer.

On a maternal standpoint, the possible complications include thyroid dysfunction, obesity, diabetes, obstructive nephropathy, hypertension, and preeclampsia (67–70). Low birth weight, intrauterine growth restriction, preterm labor, and preterm delivery are also more likely in pregnancies in women with TS (70, 71). However, the most important concerns remain the risk of heart failure, aortic dissection, and sudden death (72–74). Overall, maternal mortality in TS women has been reported to be as high as 1–2%, which is 100–200 times greater than in the general population (75–77). Pre-conception cardiac evaluation to include

measurement of the aortic size index is strongly recommended for any woman with TS seeking pregnancy. Pregnancy and post-partum should be carefully handled by a multidisciplinary team.

EGG DONATION

Oocyte donation was until recently the only reproductive option for carrying a pregnancy in women with TS who experience ovarian failure. Despite some success reported using anonymous, maternal or sibling-to-sibling oocytes, the clinical pregnancy rates in TS are two-fold lower in comparison with unscathed recipients (12, 65,68–70, 78, 79). A review of 23 women with TS following egg donation reported a miscarriage rate of 44% and take home baby rate of 18% per transfer (69). Reduced uterine receptivity from prolonged hypoestrogenism and relatively hypoplastic uteri have been suggested as plausible mechanisms (64, 65, 80).

GESTATION SURROGACY AND ADOPTION

Gestational surrogacy (GS) has now become an accepted option for couples experiencing fertility problems. Women with certain medical conditions, which make pregnancy life-threatening but for whom the long term prospects for health are good, can be considered as potential candidates for surrogacy. Given the known potential cardiac and medical complications of TS, GS is both a reasonable and advisable alternative to autologous or heterologous in vitro fertilization in countries that legally allow it. Therefore, the American Society of Reproductive Medicine recommends that all patients with TS should be counseled about GS and adoption as alternatives to pregnancy (81). Two distinct types of surrogates could be considered; the surrogate gestational mother (host uterus or gestational carrier) provides the gestational but not the genetic component for reproduction and the surrogate mother who will provide both the genetic and gestational component for reproduction (true surrogacy).

Adoption is a also a viable option for TS women who desire to be parents, without taking any of the maternal or fetal risks associated with the gravid stage.

CONCLUSION

Fertility preservation in young patients with TS represents a major issue. However, due to the precocious alterations of the ovarian function, the strategy aiming at preserving the reproductive potential of these girls is highly complex. The present challenge is to identify these women as early in life as is possible, so as to allow them to benefit from a variety of existing fertility preservation options. In addition, patients and their family should be aware that fertility preservation in these situations remains at a pioneering and experimental level, with a remarkable lake of data on the real competence of the frozen gametes. Discussion regarding the possible genetic transmission and the potential risk of contraindication to pregnancy is needed as well as information on alternative options to fulfill the desire for parenting.

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