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Turner's syndrome and fertility: current status and possible putative prospects

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Women with Turner's syndrome should be carefully followed throughout life. Growth hormone therapy should be started at age 2–5 years. Hormone replacement therapy for the development of normal female sexual characteristics should be started at age 12–15 years and continued for the long term to prevent coronary artery disease and osteoporosis. Most women with Turner's syndrome have ovarian dysgenesis; therefore, they are usually infertile, and in very rare cases have spontaneous menses followed by early menopause. Only 2% of the women have natural pregnancies, with high rates of miscarriages, stillbirths and malformed babies. Their pregnancy rate in oocyte donation programmes is 24–47%, but even these pregnancies have a high rate of miscarriage, probably due to uterine factors. A possible future prospect is cryopreservation of ovarian tissue containing immature follicles before the onset of early menopause, but methods of replantation and in-vitro maturation still need to be developed. Should these autologous oocytes indeed be used in the future, affected women would need to undergo genetic counselling before conception, followed by prenatal assessment.

Key words: cryopreservation of ovarian tissue/hormone replacement therapy/natural pregnancies/ oocyte donation/Turner's syndrome

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Introduction: general aspects and characteristics

Turner's syndrome (TS) is characterized by a complete or partial absence of one X chromosome. The most frequent chromosome constitution is 45X (Thompson *et al*., 1991). About half the patients have a mosaic chromosome complement, the most common being 45X/46XX (15%), and 6% of patients have 46XXq or 46XXp deletions. In rare cases, a ring X chromosome complement can be identified. Thus, the syndrome might be attributable to a limited amount of genetic material in these abnormal chromosomes (Turner *et al*., 2000). The cause of the chromosomal abnormality in patients with a 45X karyotype, whether monozomic or mosaic, is usually nondisjunction during meiosis (Rolland and Kirkels, 1981). The maternal X is retained in two-thirds of women, and the paternal X in the remainder (Mathur *et al*., 1991; Lippe, 1996; Saenger, 1996). TS can be transmitted from mother to daughter (Varela *et al*, 1991; Verschragen-Spae *et al*., 1992; Blumenthal and Allanson, 1997), and heredity of the ring chromosome (Blumenthal and Allanson, 1997; Uehara *et al*., 1997) and other mosaic forms have also been reported (Aller *et al*., 1995). The chromosome constitution is important because patients with a deletion on Xp have short stature and congenital malformations, whereas those with a deletion on Xq have only gonadal dysfunction (see next section) (Thompson *et al*., 1991).

Very rarely is a 45X female genotype found in a phenotypic male. The latter probably began life as a 45X/46XY mosaic and the XY line was lost, at least in the tissue studied, or the Y may be unrecognized due to autosome translocation (Thompson *et al*., 1991). There are also a few rare cases of 46XY females in whom a portion of the Y chromosome was deleted (Levilliers *et al*., 1989; Fisher *et al*., 1990). TS patients with either mosaic 45X/46XY karyotypes or with Y marker chromosomes (Y fragments) often have a sex-determining region on the Y chromosome (SRY) (Canto *et al*., 2000). Any patient who has signs of virilization or gonadoblastoma (a germ cell tumour) should be studied for low-level Y-chromosome mosaicism (Saenger, 1996). TS accounts for 15% of spontaneous abortions. It occurs in 3% of all females conceived, or 1 in 1500–2500 female births (Saenger, 1996).

The typical clinical features of TS are short stature (average final height 143 cm), square appearance, webbed neck, character-

istic unusual facies, low posterior hairline, broad chest with widely spaced nipples, and a 'shield' chest. At birth, infants usually have oedema of the dorsum of the foot and, during the neonatal period, swelling of the hands and feet (Turner, 1938; Ford *et al*., 1958; Hook and Warburton, 1983; Saenger, 1993, 1996). Lymphoedema may also be present in fetal life, leading to cystic hygroma, which causes the webbed neck. Poor development of lymphatic channels may also cause deformities of the ears, leading to ear infections later in life. Patients have an elevated rate of renal and cardiovascular anomalies such as coarctation of the aorta and bicuspid aortic valves (50%), which could cause cardiovascular disorders. Autoimmune disorders, such as Hashimoto's thyroiditis, Addison's disease, alopoecia and vitiligo, are also common (Speroff *et al*., 1999a), and primary hypothyroidism, generally associated with antithyroid antibodies, develops in 10–30% of patients (Pai *et al*., 1977; Lippe, 1996; Saenger, 1996; Foudila *et al*., 1999; Hovatta, 1999). Scoliosis develops in about 10%, mostly during adolescence, and it can lead to an additional reduction in height (Saenger, 1996). Abnormal mesenteric bleeding is common, as is Crohn's disease, ulcerative colitis and various other metabolic disorders such as glucose intolerance with mild insulin resistance and obesity (Saenger, 1996; Gravholt *et al*., 1998). As a consequence of these abnormalities, patients with TS have a shorter life span than the general population (Gravholt *et al*., 1998).

Intelligence is usually average or above (Bender *et al*., 1984; Thompson *et al*., 1991; Saenger, 1996), except in rare cases of tiny X-ring chromosomes (Migeon *et al*., 1993; Becker *et al*., 1995; Saenger, 1996), in which the mental retardation might be due, in some cases, to the inability of these abnormal chromosomes to undergo X inactivation (Migeon *et al*., 1993; Becker *et al*., 1995; Turner *et al*., 2000). Moreover, patients often have deficiencies in spatial perception and perceptual or fine motor organization, and their mathematical ability is poor (Thompson *et al*., 1991; Saenger, 1996; Speroff *et al*., 1999a), such that their non-verbal IQ may be significantly lower than their verbal IQ. These neurodevelopmental defects might be attributable to the X-chromosome monosomy or to hormonal anomalies due to the gonadal dysgenesis (see next section) (Saenger, 1996).

Ovarian function and natural pregnancy

Most women with TS (95–98%) are infertile due to gonadal dysgenesis (Singh and Carr, 1966; Weiss, 1971; Lippe, 1996; Hovatta, 1999). It is caused by oocyte loss from week 18 of pregnancy onwards or over the first few postnatal months and years (Singh and Carr, 1966; Weiss, 1971; Tarani *et al*., 1998; Hovatta, 1999). In most 45X patients, the oocyte loss takes place in the early stage of meiotic prophase–pachytene (Tarani *et al*., 1998) and results in a streak ovary composed of white fibrous stromal tissue containing no ova or follicular derivatives (Speroff *et al*., 1999a). However, at puberty a minority, mostly those with mosaic karyotypes, have ovaries with a relatively low number of follicles, so that there is spontaneous pubertal development (Gilboa and Rosenberg, 1975; Novak *et al*., 1995). The actual number of primordial follicles varies among individual patients: Gilboa and Rosenberg identified a few primordial follicles in the ovaries of a 15-year-old monozomic patient, whereas Novak *et al*. identified a normal number in a 29-year-old mosaic patient, despite irregular menses (Gilboa and Rosenberg, 1975; Novak *et al*., 1995). Breast budding and pubic and axillary hair appear in 5–25% of patients and menstrual cycles in 2–5% before the onset of premature menopause (Groll and Cooper, 1976; Lippe, 1996; Saenger, 1996; Hovatta, 1999); however, in rare cases, the gradual loss of germ cells may last up to 40 years (Gilboa and Rosenberg, 1975). In girls who show some signs of puberty, the Xq13-q26 region, which is thought to contain the genes responsible for ovarian function, apparently remains intact (Tarani *et al*., 1998). Ogata and Matsuo postulated that gonadal dysgenesis might depend on chromosome pairing failure during meiotic prophase, causing failure of synaptic formation at the zygotene and oocyte loss (Ogata and Matsuo, 1995). The degree of gonadal dysgenesis depends on the size of the unpaired region of homologue chromosomes. Thus, severe pairing failure causes degeneration of nearly all the oocytes before puberty, primary amenorrhoea and poor secondary sexual development, whereas mild pairing failure leads to the survival of a considerable number of oocytes until puberty, leading to secondary amenorrhoea and secondary impaired sexual development.

Natural pregnancies occur in at least 2% of women with TS (Hovatta, 1999) and to date ~160 spontaneous pregnancies in 74 women have been recorded (Tarani *et al*., 1998). The average age of these women at pregnancy was 23–24 years, and they were usually not >34 years. Most had a mosaic Turner's karyotype containing a 46XX line (Singh *et al*., 1980; Verschragen-Spae *et al*., 1992; Tarani *et al*., 1998), though some had non-mosaic TS (Philip and Sele, 1976; Nielsen *et al*., 1979; Wray *et al*., 1981; Baudier *et al*., 1985; Jacquemyn *et al*., 1989; Swapp *et al*., 1989; Varela *et al*., 1991; Magee *et al*., 1998). An extraordinary case was described by Ayuso *et al*. (1984) of a TS patient with a 45X/46XX/47XXX karyotype who had 14 pregnancies. Eight ended in miscarriage and six went to term; including one of a live-born child with TS. It is noteworthy that natural pregnancies have been described in women with TS who had been amenorrhoeic but received hormone replacement therapy (HRT) (see next section) (Blumenthal and Allanson, 1997; Hovatta, 1999).

Not only are these pregnancies rare, but their rates of miscarriage (29%), stillbirths (7%) and malformed babies (20%) are very high (Dewhurst, 1978; King *et al*., 1978; Nielson *et al*., 1979; Wray *et al*., 1981; Kaneko *et al*., 1990; Tarani *et al*., 1998; Hovatta, 1999). Researchers believe that the miscarriages are due to chromosomal abnormalities in the fetuses, mostly trisomy 21 and TS, which have been noted in both the aborted fetuses and the live-born children of these patients at a much higher rate than in the general population (4 versus 0.4% for trisomy 21 and 15 versus 0.5% for TS) (King *et al*., 1978; Nielsen *et al*., 1979; Swapp *et al*., 1989). The chromosomal abnormalities are probably caused by the transmission of the imbalance in genetic regulation present from mother to offspring (Tarani *et al*., 1998). Recent data from oocyte donation programmes have shown that diminished endometrial receptivity might be another cause of the miscarriages (see section on 'Oocyte donation programmes and pregnancy complications') (Rogers *et al.,* 1992; Yaron *et al*., 1996; Cohen *et al*., 1999). Moreover, since autoimmune disorders are common in patients with TS (Saenger, 1996), some of the miscarriages might have an autoimmune origin, as the presence of autoimmune antibodies is connected to recurrent abortions (Scott, 1985; Ornoy and Abir, 1994).

Hormonal therapy from childhood to adulthood

The aim of hormonal therapy before adulthood in patients with TS is to achieve normal height and induce sexual development (Saenger, 1996). Treatment with growth hormone (GH) stimulates the growth and maturation of the epiphyseal growth plates. Early studies on the use of GH therapy in patients with TS yielded conflicting and inconclusive results (Wilton, 1987). However, a large multicentre study of affected patients showed increased growth velocity in response to GH, administered alone or in combination with androgens, and a significant positive effect of GH on adult height (Rosenfeld *et al*., 1992). Potential candidates for GH therapy are girls with a projected final height below the fifth to tenth percentiles or girls at standard deviations below their genetic target mid-parental height (Lippe, 1996). Treatment with GH should usually be initiated between 2–5 years of age and continued until the bone age exceeds 15 years (Saenger, 1996). GH should be continued until either the final target height is achieved or until near-epiphyseal fusion precludes a significant effect (Lippe, 1996).

When planning the optimal HRT to induce puberty in girls receiving GH, clinicians should consider the biphasic effect of oestrogen on growth, namely stimulatory at low doses and inhibitory at high doses (Saenger, 1996). Furthermore, oestrogen should not be used alone for growth promotion (Lippe, 1996), and when used for feminization induction in conjunction with ongoing GH therapy, further growth augmentation might not occur (Neely and Rosenfeld, 1993; Lippe, 1996). Therefore, the timing of oestrogen administration to induce puberty may have an important impact on growth. In girls receiving GH, oestrogen should not be given when the bone age is <11 or 12 years or until near-final height has been achieved, that is, when only one more year of GH therapy is required (Vanderschueren-Lodeweyckx *et al*., 1990; Lippe, 1996). In more recent studies, Rosenfield *et al*. and Chernausek and Attie noted that the addition of very low oestrogen doses to GH therapy in girls with TS aged 12–15 years had beneficial effects on final height (Rosenfield *et al.*, 1998; Chernausek and Attie, 1999). Poor outcomes were generally due to late initiation of GH therapy and early use of oestrogen therapy.

For optimal promotion of secondary sex characteristics oestrogen therapy should begin at 14–15 years of age (Saenger, 1996). Both Lippe and Saenger recommended starting with low daily doses of oestradiol, for example 0.3–0.625 mg of conjugated oestrogen or 0.5 mg of micronized oestradiol per day for 6–12 months, followed by incremental increases to achieve a gradual process of feminization (Lippe, 1996; Saenger, 1996). This treatment seems to produce better breast development than maintenance doses of HRT (Saenger, 1996). After initiation of breast development and uterine growth, the dose should be increased to maintenance levels of 0.9–1.25 mg of conjugated oestrogen or 2 mg of micronized oestradiol per day, with the addition of cyclic therapy with progestins to induce cyclic vaginal breakthrough bleeding (Saenger, 1993; Lippe, 1996). Adequate oestrogen doses are also essential to complete adolescent bone maturation (Saenger, 1996). Oestrogen replacement therapy may also play a role in improving neurodevelopmental function in TS patients. In a two year, double-blind study, oestrogen-treated girls with TS performed better in various memory and language tasks and showed improved verbal and non-verbal memory compared with a placebo-treated group (Ross *et al*., 2000).

HRT is usually necessary not only for the development of normal female sexual characteristics but also later in life to prevent cardiovascular complications and osteoporosis due to oestrogen loss (Saenger, 1996). Therefore, in women with TS, HRT should be administered over the long term. In sexually active women, especially those in whom female characteristics developed spontaneously, contraceptive pills are needed, and they can serve as adequate HRT (Hovatta, 1999). The oestrogen dose needed to enhance maximum bone mineralization and then prevent bone loss in TS is unknown (Lippe, 1996). However, studies in adult women with TS have shown a positive correlation between bone mineral content and duration of oestrogen treatment (Naeraa *et al*., 1991). Most women require a daily dose of 0.625 mg conjugated oestrogen, or 1 mg micronized oestradiol or a transdermal oestradiol patch of 50 mg twice a week (Saenger, 1996). Progestins can be added either cyclically or continuously. Women with TS also have an increased incidence of fractures, including osteoporotic fractures in adulthood (Gravholt *et al*., 1998). Sylven *et al*. found lower levels of bone mineral density (BMD) and bone mineral content in 47 affected, middle-aged patients (Sylven *et al*., 1995). BMD increased with the use of HRT, but not until after 20 years of treatment. The duration of HRT was the most important factor in maintenance of bone mass (Sylven *et al.*, 1995). In another study of TS, oestrogen replacement therapy was shown to markedly enhance calcium absorption and retention and to reduce the overall rate of whole-body calcium turnover, thereby increasing BMD (Mauras *et al*., 1997). Furthermore, HRT has beneficial effects on blood pressure, an important consideration in light of the finding that over 50% of women with TS have high blood pressure, leading to a higher morbidity and mortality in middle age compared with the normal population (Gravholt *et al*., 1998; Nathwani *et al*., 2000). Elsheikh *at al*. suggested that HRT has favourable effects on central arterial haemodynamics, insulin sensitivity and lipid profile in adult women with TS (Elsheikh *et al*., 2000). However, the optimal duration of oestrogen therapy requires further investigation.

Oocyte donation programmes and pregnancy complications

The successful use of donated oocytes in IVF for the treatment of women with ovarian failure (Lutjen *et al*., 1984) has also brought new hope to TS patients. Several protocols have been proposed for preparing the endometrium for the transfer of embryos derived from donated oocytes. Some consist of stepwise oestrogen administration and lower doses of progesterone (Sauer and Paulson, 1990), and others use a fixed dose of oestrogen (4 mg a day of oestradiol valerate) which is increased if the endometrium lining is thinner than 7 mm on ultrasound scan (Hovatta, 1999). In cases of HRT-induced menstruation, oestradiol is usually administered at a dose of 4–8 mg per day from the second day of the menstruation for at least two weeks. When ultrasonography indicates adequate endometrial development, vaginal micronized progesterone, 900–1200 mg per day, is added 3–5 days before embryo transfer. If pregnancy occurs, the hormone supplementation continues for at least 10 weeks, until

placental steroidogenesis is firmly established (Speroff *et al*., 1999b). Other protocols for endometrial preparation have also been proposed (Younis *et al*., 1996).

Various centres have reported on patients with TS in oocyte donation programmes, in numbers ranging from a few (Rosenwaks, 1986; Devroey *et al*., 1988; Abdalla *et al*., 1989; Cornet *et al*., 1990) to larger groups (Hens *et al*., 1989; Press *et al*., 1995; Yaron *et al*., 1996; Khastgir *et al*., 1997; Foudila *et al*., 1999). The earliest large study described 14 patients with various forms of TS (Hens *et al*., 1989), two of whom became pregnant. This pregnancy rate was not different from that of the non-TS women in the programme, and there were no miscarriages in the TS group. Press *et al.* had similar results with 11 patients with TS (pregnancy rate 24% per cycle and no increase in the number of miscarriages) (Press *et al*., 1995). Khastgir *et al*., who studied 29 women with TS—19 monozomic and 10 mosaics—found no differences in implantation and pregnancy rates between the TS patients and the other women (41.2% pregnancy rate per cycle), or between women with TS of different age groups, or between monozomic and mosaic patients (Khastgir *et al*., 1997). Likewise, Foudila *et al*. described 18 women with TS undergoing oocyte donation who had a similar pregnancy rate to that of the other patients (Foudila *et al*., 1999). Their high pregnancy rate (47% per cycle) might have been attributed to a different HRT regimen, which consisted of continuous oral oestradiol (4–8 mg) combined with 600 mg transvaginal micronized progesterone starting two or three days before embryo transfer, instead of a stepwise oestradiol course and only half the progesterone dosage given in many of the other centres (Davies *et al*., 1990; Pados *et al*., 1992; Sauer *et al*., 1992). Contrary to these findings, Yaron *et al*. noted a lower pregnancy rate than for the other patients in their fertilization programme among 21 patients with TS, seven monozomic and 15 mosaic (Yaron *et al*., 1996). The patients lacking an entire X chromosome did worse than the mosaic patients or those with isochromosomes. Because of the small stature of women with TS and their other health problems which could complicate pregnancy, it is advisable to avoid multiple pregnancies. Therefore, most centres transfer only one or two embryos (Saenger, 1996; Foudila *et al*., 1999; Hovatta, 1999).

Despite these optimistic results, many of the centres reported a higher miscarriage rate in TS patients (40–60%) (Yaron *et al*., 1996; Khastgir *et al*., 1997; Foudila *et al*., 1999). This suggests that miscarriages in TS might be caused by uterine factors (Yaron *et al*., 1996), such as a hypoplastic uterus or low uterine blood flow (Hovatta, 1999). Rogers *et al*. used freeze fracture followed by electron microscopy to study epithelial tight junctions in endometrial biopsies taken from six patients with TS before oocyte donation. Most of the samples did not have tight junctions, and others had reduced and disorganized junctional structures (Rogers *et al*., 1992). Cohen *et al.* described a woman with TS and 21-hydroxylase deficiency who underwent oocyte donation (Cohen *et al*., 1999). A 21-hydroxylase deficiency could cause diminished endometrial receptivity and has been reported in other patients with TS (Larriza *et al*., 1994), but more research is needed before any conclusions can be drawn.

The congenital deformities in patients with TS also place their pregnancies at high risk, whether natural or from donated oocytes (Hovatta, 1999). Cardiovascular complications occur in 10–44% of these women (Birdsall and Kennedy, 1996; Foudila *et al*., 1999; Lippe, 1996), mainly because of congenital coarctation of the aorta and bicuspid aortic valves (Saenger, 1996). Aortic dissection can be a fatal complication during pregnancy (Birdsall and Kennedy, 1996; Nagel and Tesch, 1997). Arterial hypertension without coarctation is also common, although Foudila *et al*. failed to find a significant difference in this complication between women with TS and other women after oocyte donation (Foudila *et al*., 1999); though, women in the general population who require oocyte donations are usually older. In addition, the high rate of glucose intolerance (Saenger, 1996) and disturbances in carbohydrate metabolism associated with TS can complicate pregnancy (Holl *et al*., 1994; Lippe, 1996). Finally, because of their short stature, all women with TS have a small pelvis, which may indicate a Caesarean section as a mode of delivery (Foudila *et al*., 1999; Hovatta, 1999). To avoid some of these complications, women with TS require careful pregnancy screening which must include, in addition to routine check-up, comprehensive cardiovascular examination (including an echocardiogram), glucose challenge test, liver and thyroid function tests and screening for autoimmune disorders (Hashimoto's thyroidism and Addison's disease) to avoid their related pregnancy complications (Scott, 1985; Ornoy and Abir, 1994).

Possible putative fertility preservation

Currently, various hospitals worldwide cryopreserve ovarian biopsy samples containing immature primordial follicles from cancer patients before anti-cancer treatment in order to preserve putative fertility (for a review see Abir *et al*., 1998). A number of methods for the cryopreservation of human ovarian tissue have been suggested (Hovatta *et al*., 1996; Newton *et al*., 1996, 1998; Gook *et al*., 1999), with only a 7% oocyte loss after thawing using optimal protocols (Campbell *et al*., 2000). Since ovaries of some TS patients, mostly those with mosaic karyotypes, contain follicles at various stages of their lives (Singh and Carr, 1966; Weiss, 1971; Gilboa and Rosenberg, 1975; Novak *et al*., 1995), these girls may constitute a new population that could benefit from ovarian cryopreservation followed by transplantation or in-vitro maturation (IVM). Indeed a very recent preliminary report described cryopreservation of ovarian tissue from five TS patients aged 12–19 and histological identification of primordial follicles in the biopsies (Hreinsson *et al*., 2001).

It would probably be worthwhile to retrieve ovarian tissue by laparoscopy for cryopreservation only from patients with mosaic karyotypes, since there is a greater chance that their ovaries contain follicles. The exact age of these patients will probably have to be decided on an individual case basis because of the variation in follicular content among them (Gilboa and Rosenberg, 1975; Novak *et al*., 1995; see also 'Ovarian function and natural pregnancy'). Preferably ovarian biopsies should be cryopreserved even before the first signs of puberty, since most or all of the follicles might already be lost once signs of puberty appear (see also 'Ovarian function and natural pregnancy'). To evaluate the feasibility of ovarian retrieval for cryopreservation, the first test should be a pelvic ultrasound, since streak ovaries in patients with pure gonadal dysgenesis might be too small to be adequately visualized (Lippe, 1996). If the ovaries are visualized, plasma gonadotrophin concentrations can be evaluated, as exaggerated concentrations of plasma gonadotrophins, especially

FSH, have been demonstrated at as early as five days of age (Conte *et al*., 1975; Lippe, 1996) and such ovaries should not be cryopreserved. If ovarian biopsies are not cryopreserved before puberty, concentrations of gonadotrophins can be assessed when some signs of puberty are identified. In some adolescent patients, the administration of gonadotrophin-releasing hormone (GnRH) to stimulate the hypothalamic–pituitary axis, might serve as an additional test to confirm ovarian function and gonadal integrity, as the responses of TS patients are usually exaggerated compared with normal subjects (Illig *et al*., 1975). The results of the GnRH test should be taken with caution, in view of studies showing a failure of GnRH to stimulate abnormal gonadotrophin secretion in two menstruating 45X adolescents with abnormal irregular cycles (Page *et al*., 1990; Lippe, 1996). Nevertheless, in most patients, a single determination of plasma FSH and LH is sufficient to document gonadal failure (Lippe, 1996). In some cases, pre-cryopreservation retrieval of ovarian biopsies by laparoscopy might be considered for follicular evaluation by histology or other more rapid methods (Corvrindt and Smitz, 2000). Because of the invasiveness of this diagnostic procedure as well as the age of the patients, this operation should be considered only rarely, if other tests have failed to produce clear cut answers regarding ovarian function. However, once ovarian biopsies are retrieved for cryopreservation, it might be beneficial for a few samples to be evaluated for follicular content.

Regarding ovarian transplantation, studies on autografts in sheep (Gosden *et al*., 1994; Nugent *et al*., 1997; Salle *et al*., 1998, 1999; Aubard *et al*., 1999; Baird *et al*., 1999; Campbell *et al*., 2000) and transplantation of human tissue into immunodeficient mice have shown losses of 35–50% of primordial follicles due to post-transplantation ischaemia prior to revascularization (Campbell *et al*., 2000). To avoid substantial loss after grafting, which is especially important in TS patients, researchers are seeking improved methods for ovarian graft survival. Nugent *et al*. have already shown that Vitamin E has a protective affect on follicular ischaemia damage after grafting (Nugent *et al*., 1998a). To date, there have only been five reports of transplantation of human ovarian biopsies in women and all of them showed various degrees of follicular development in the transplants (Nugent *et al*., 1998b; Oktay and Karlikaya, 2000; Oktay *et al*., 2000; Oktay, 2001; Radford *et al*., 2001). Unlike in cases of former cancer patients, possible risks of malignancy retransmission through ovarian grafts (Abir *et al*., 1998) do not exist in patients with TS and they might, therefore, be candidates for ovarian transplantation.

Another option for women with TS is IVM of oocytes from primordial follicles in the biopsy sample, followed by IVF (Abir *et al*., 1998; Hovatta, 2000; Picton and Gosden, 2000; Van den Hurk *et al*., 2000). The first approach involves culturing whole slices of ovarian tissue. To date, only a single, malformed, mouse has been produced from a primordial follicle using this strategy (Eppig and O'Brien, 1998), while human primordial follicles developed to secondary stages in a similar culture system as cited in the following reviews (Hovatta, 2000; Picton and Gosden, 2000; Van den Hurk *et al*., 2000) and papers (Hovatta *et al*., 1997, 1999; Wright *et al*., 1999; Louhio *et al*., 2000). Moreover, the low follicular content in ovaries of TS patients could lead to culture of empty ovarian specimens using this culture stategy. The second approach is culturing isolated follicles (Abir *et al*., 1999, 2001; Van den Hurk *et al*., 2000). The method could be useful for women with low numbers of follicles, such as TS patients. In studies conducted in our laboratory, isolated human unilaminar follicles were cultured within supporting collagen gels and developed to secondary stages (Abir *et al*., 1998, 1999, 2001; Van den Hurk *et al*., 2000).

In recent years cryopreservation of mature oocytes followed by intracytoplasmatic sperm injection (ICSI) has proven possible, although its success is limited (Paynter, 2000; Fabbri *et al*., 2001). Thus, eggs could be collected from some menstruating girls with TS after a few hormonal stimulation cycles and cryopreserved for putative fertilization by ICSI (Hovatta, 1999). However, the ethics of having such young girls undergo hormonal stimulation are debatable.

Conclusions

Women with TS should be followed routinely and monitored carefully throughout life. Therapy with GH should be started early, followed by long-term HRT for the development of normal female sexual characteristics as well as the prevention of various health problems. Natural pregnancies are rare in women with TS and mostly occur in those with mosaic karyotypes. Nevertheless, sexually active women with this syndrome need contraceptives, and women who wish to attempt natural pregnancy should not postpone it, as fertility is likely to diminish with time. In oocyte donation programmes, the pregnancy rate of women with TS is usually similar to that of other women and might depend on the specific HRT regimen. However, since women with TS are small, to avoid difficult multiple pregnancies only one to two embryos should be transferred at a time. Patients with TS are usually at high risk during pregnancy because of their various health problems. The miscarriage rate is high and patients need to be monitored carefully during pregnancy.

The future may hold further hopes for pregnancies in women with TS. Since some girls with TS, mostly those with mosaic karyotypes, have follicles in their ovaries, their ovarian function should be tested and thereafter ovarian tissue might be retrieved by laparoscopy even before puberty, and cryopreserved for possible replantation or IVM of the primordial follicles. Another possibility is cryopreservation of mature oocytes collected after hormonal stimulation from young girls who demonstrate some signs of puberty, with future oocyte fertilization by ICSI.

Parents of girls with a diagnosis of TS should be counselled regarding the high possibility of gonadal failure and infertility in their daughters. They should be made aware that if pregnancy does occur, it will probably be at high risk of miscarriage and of fetal and chromosomal abnormalities in the offspring (Lippe, 1996). In cases in which ovarian cryopreservation may be considered, the clinician must explain to the parents the uncertainty of the actual follicular content in the cryopreserved ovaries, and the possibly insufficient number to survive cryopreservation, transplantation or IVM. The clinician should also emphasize that once these new assisted reproduction technologies are developed, they will carry the same risks as natural pregnancies in women with TS: chromosomal abnormalities, congenital malformations, and a high risk of miscarriage and stillbirths. Therefore, in all pregnancies from autologous

oocytes, genetic counselling and prenatal diagnosis should be considered.

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