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Navigating fertility dilemmas across the lifespan in girls with Turner syndrome—a scoping review

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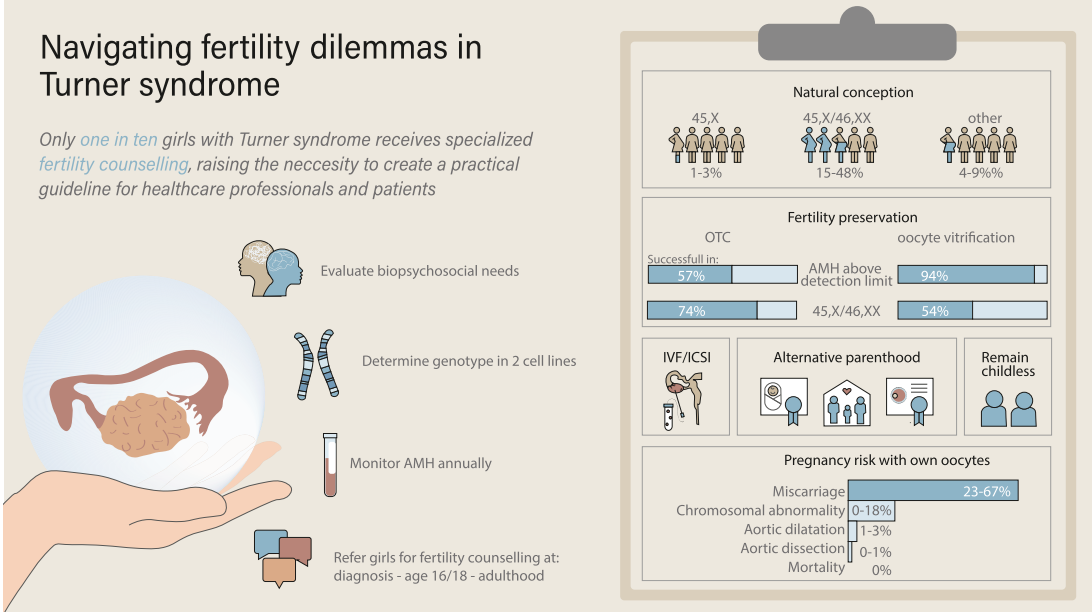
GRAPHICAL ABSTRACT



To guide girls with Turner syndrome with their fertility dilemmas, we recommended that their fertility potential is assessed and that they receive counselling on every available option of family planning at an early age. AMH, anti-Müllerian hormone; OTC, ovarian tissue cryopreservation; TS, Turner syndrome

ABSTRACT

BACKGROUND: Girls with Turner syndrome (TS) lack a partial or complete sex chromosome, which causes an accelerated decline of their ovarian reserve. Girls have to deal with several dilemmas related to their fertility, while only a limited number of them are referred to a fertility specialist and counselled about options of family planning on time.

OBJECTIVE AND RATIONALE: This scoping review provides an update of the literature on fertility in girls with TS throughout their lifespan and aims to propose a clinical practice guideline on fertility in TS.

SEARCH METHODS: Databases of PubMed, Embase, and Web of science were searched using the following key terms: Turner syndrome, fertility, puberty, pregnancy, sex-hormones, karyotype, fertility preservation, assisted reproductive techniques, and counselling, alongside relevant subject headings and synonymous terms. English language articles published since 2007 were critically reviewed. Pregnancies after using donated oocytes and data about girls with TS with Y-chromosomal content were excluded.

OUTCOMES: This search identified 1269 studies of which 120 were extracted for the review. The prevalence of natural conception ranged from 15% to 48% in women with 45,X/46,XX, 1% to 3% in women with 45,X, and 4% to 9% in women with other TS karyotypes. When assessing a girl's fertility potential, it was crucial to determine the karyotype in two cell lines, because hidden mosaicism may exist. In addition to karyotype, assessment of anti-Müllerian hormone (AMH) played a significant role in estimating ovarian function. Girls with AMH above the detection limit were most likely to experience spontaneous thelarche, menarche, and ongoing ovarian function during the reproductive lifespan. Fertility preservation became more routine practice: vitrification of oocytes was reported in 58 girls with TS and a median of five oocytes were preserved per stimulation. Ovarian tissue cryopreservation has demonstrated the presence of follicles in approximately 30% of girls with TS, mostly in girls with mosaic-TS, spontaneous puberty, and AMH above the detection limit. Although girls and their parents appreciated receiving counselling on fertility in TS, only one in ten girls with TS received specialized counselling. Unfamiliarity with fertility preservation techniques or uncertainties regarding the eligibility of a girl for fertility preservation constituted barriers for healthcare professionals when discussing fertility with girls with TS.

WIDER IMPLICATIONS: There currently is a high demand for fertility preservation techniques in girls with TS. A reliable prognostic model to determine which girls with TS might benefit from fertility preservation is lacking. Only a minority of these girls received comprehensive fertility counselling on the full spectrum of fertility, including uncertainties of fertility preservation, pregnancy risks, and alternatives, such as adoption. Fertility preservation could be a viable option for girls with TS. However, the question remains whether enough oocytes can be obtained for a realistic prospect of a live birth. It is important that girls and parents are empowered with the necessary information to make a well-informed decision.

Keywords: Turner syndrome / puberty / fertility / fertility preservation / pregnancy / assisted reproduction / counselling

Introduction

The majority of girls and women with Turner syndrome (TS) face a challenging journey regarding their fertility, with infertility often becoming a certainty (Sutton *et al.*, 2005). The partial or complete absence of one sex chromosome results in an accelerated loss of ovarian reserve at an early age. Consequently, women with TS have to make difficult decisions about family planning and are confronted with insecurities about their fertility and ability to conceive (Schleedoorn *et al.*, 2020; Falsey *et al.*, 2022; Fearon, 2023a). In addition, women with TS are at higher

risk of pregnancy complications (Bernard *et al.*, 2016; Calanchini *et al.*, 2020).

Over the past decades, there has been an increasing request from parents of girls with TS to discuss fertility and fertility preservation options. Accordingly, this led to a growing research interest in fertility preservation in TS, including oocyte vitrification and ovarian tissue cryopreservation (OTC), and the emergence of new data (Brouillet *et al.*, 2023; Nadesapillai *et al.*, 2023b). However, there are still research gaps that remain, since it is extremely difficult to predict which girls will be diagnosed with premature ovarian insufficiency (POI) at a very young age, and which girls will conceive naturally in the future. This poses a significant challenge for medical professionals in providing fertility counselling, especially since there is no consensus on how to address this topic and on how to determine which girls with TS should or should not receive fertility preservation. As a result, only a minority of girls with TS are referred for counselling about options for family planning (Morgan *et al.*, 2019).

This comprehensive scoping review provides an update of recent literature on clinical practice. This review aims to equip healthcare professionals with an overview of original research to enable a well-informed counselling process about fertility in TS. We cover five key topics: understanding fertility potential; chance of natural conception; understanding fertility potential; fertility preservation (vitrification of oocytes and OTC); assisted reproduction with own oocytes; and counselling on fertility.

Methods

This scoping review includes studies regarding women diagnosed with TS and includes topics related to puberty, fertility, fertility preservation, assisted reproduction with own oocytes, pregnancy risks, and counselling. Studies published in English between 1 January 2007 and 1 September 2023 were included.

Protocol

A scoping review was used to establish all types of available evidence including medical, social, cultural and ethical aspects, and to identify any research gaps (Munn *et al.*, 2018). To present the literature in a comprehensive manner, a systematic approach was employed to assess and organize the literature into tables. Quantitative studies, qualitative studies, as well as expert opinions were included. The PRISMA extension for scoping reviews checklist (PRISMA-ScR; Tricco *et al.*, 2018) was used to develop the protocol. The protocol, including eligibility criteria and study selection, was predefined. The protocol can be provided upon request.

Search strategy

The electronic databases of PubMed, Embase, and Web of Science were searched for eligible publications. An experienced librarian supported during the search process. The final search was performed on 1 September 2023. The full electronic search is available in Supplementary Data File S1.

Screening and selection

Publications derived from the electronic databases were transferred to EndNote version 20.3, Clarivate, Philadelphia, PA. After the removal of duplicates, publications were exported to Covidence systematic review software, Veritas Health Innovation, Melbourne Australia. All studies were independently screened for title and abstract by two authors (S.v.d.C. and J.v.d. V., K.F. or S.N.). Conflicts were discussed with a third author. The same process was repeated for full-text assessment (S.v.d.C. and K.F.). Reviews and conference abstracts were excluded for data extraction. Data about individuals with Y-chromosomal material or a small deletion (distal to Xq24) were excluded. Reviews were retained for reference screening. The PRISMA-ScR flow chart visualizes the study selection process (Fig. 1).

Data analysis

Studies included for data extraction were exported to a predefined data-charting form in Excel. The data-charting form was designed by the first author (S.v.d.C.), with input from the other authors, and tested within the research team. Predetermined themes were assigned by the research team (headings in results section) and divided into subthemes (subheadings in results section) based on the available literature.

After analysis of the literature, women with TS were stratified into three groups according to their genotype: monosomy 45,X, mosaicism 45,X/46,XX or 'other' karyotype. The group 'other' karyotypes included women with structural aberration of the X-chromosome or women with mosaicism with 47,XXX. Karyotypes were determined in lymphocytes unless otherwise described.

To satisfy reproducibility, the following definitions were used: natural conception—pregnant without the help of assisted reproduction techniques (only studies that give clear statements of natural conception were included); spontaneous thelarche—girls with TS who experienced the onset of breast development of at least Tanner stage B2 (Marshall and Tanner, 1969) without induction with oestrogens; spontaneous menarche—girls with TS who experienced vaginal bleeding without oestrogen induction; and POI—girls or women with hypergonadotropic hypogonadism and/or with symptoms of ovarian insufficiency (e.g. no or stunted puberty, flushes or irregular menstrual cycle) before the age of 40 years.

Results

Figure 1 provides a schematic representation of the review process: 1269 articles were screened, of which 120 were eligible for data extraction.

Understanding fertility potential

The advancements in understanding folliculogenesis in women with TS has led to significant progress in comprehending the reproductive capacities. Likewise, various clinical parameters, including karyotype, pubertal development, and hormone levels, play a crucial role in estimating the fertility potential and ovarian reserve at different ages.

Folliculogenesis

The accelerated decline in the number of oocytes in women with TS becomes evident as early as foetal development, as indicated by an increased number of oocytes showing signs of apoptosis. Furthermore, a significantly reduced number of oogonia in the ovaries of girls with TS was observed (Modi *et al.*, 2003; Reynaud *et al.*, 2004). Research conducted over the past two decades suggested several mechanisms to explain this phenomenon. One hypothesis suggests that the inability of oocytes to undergo meiotic pairing during the prophase stage can be attributed to the absence of a sex chromosome (Burgoyne and Baker, 1985). Another hypothesis suggests that the lack of gap or tight junctions, which are crucial for interaction between oocytes and granulosa cells, impairs the formation of primordial follicles (Rogers *et al.*, 1992). Additionally, it has been hypothesized that a reduced number of

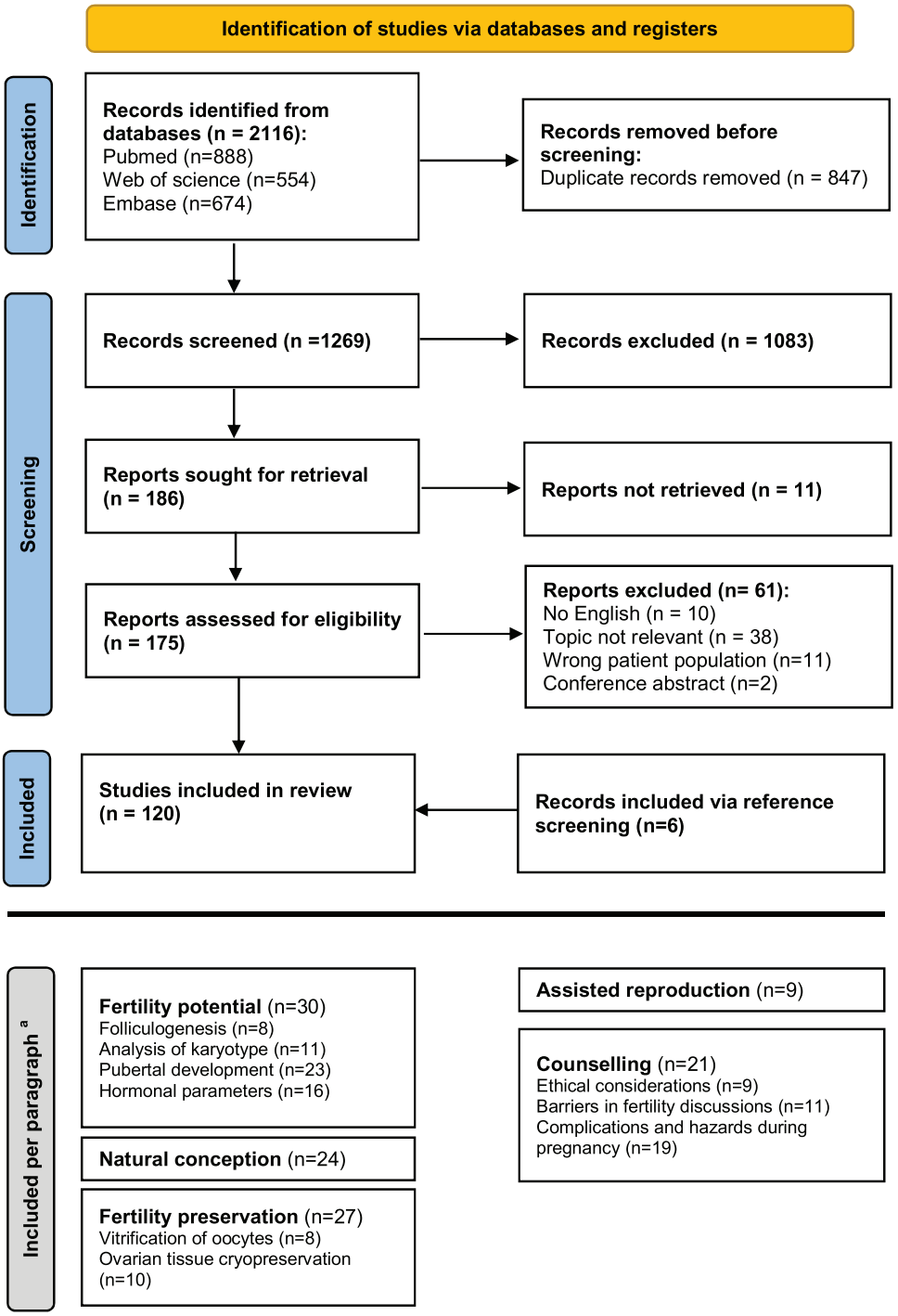


Figure 1. PRISMA flowchart for scoping reviews. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj.n71. [a]Some studies are included in multiple paragraphs.

oogonial mitoses may contribute to the lower follicle numbers compared to women without TS (Gosden, 1995). Recent research has provided more information on folliculogenesis in women with TS, including follicle density, morphology, and chromosomal content.

Reduced follicle density was observed in the ovaries of foetuses with TS with gestational age of 12–42 weeks. In 22/24 45,X-foetuses and 2/5 45,X/46,XX foetuses, no follicles were found, while numerous follicles were found in all control ovaries (Lundgaard Riis *et al.*, 2021). After birth, the follicle density was also significantly lower in ovaries of prepubertal girls with TS (131–2121 follicles/mm^3) and peri- and post-pubertal girls with TS (50–872 follicles/mm^3) compared to age-matched controls (respectively, 2946–7401 and 1553–2045 follicles/mm^3) (Peek *et al.*, 2023). Other studies confirmed the reduced follicle density in the ovarian cortex of women with TS (Borgström *et al.*, 2009; Peek *et al.*, 2019, 2023; Schleedoorn *et al.*, 2022; Nadesapillai *et al.*, 2023b). In contrast, Mamsen *et al.* (2019) observed that 7/9 girls with TS with follicles in the ovarian cortex had a follicle density within 95% CI of age-matched controls, although the CI was

broad and not specified. To note, when assessing histology sections, it is important to consider that follicles are not evenly distributed in the ovary. Since only a very small ovarian cortex fragment is often used to determine the number of follicles, this might cause misinterpretation of the total ovarian reserve (Lambalk *et al.*, 2004).

In addition to the reduced numbers of follicles, an abnormal morphology is often observed. Abnormal morphology affected 31% of follicles of girls with TS, which was significantly higher compared to individuals without TS with 12% abnormal follicles (Peek *et al.*, 2023). The abnormal morphology of follicles included an incomplete or distorted layer of granulosa cells (Mamsen *et al.*, 2019; Nadesapillai *et al.*, 2023b), partially missing connection to the basal lamina (Mamsen *et al.*, 2019), a less clear structure of follicles, and darker and smaller oocytes (Lundgaard Riis *et al.*, 2021). Abnormal morphology of follicles was observed more frequently in girls with a structural aberration of the X-chromosome compared to girls with TS without a structural aberration (Schleedoorn *et al.*, 2022; Nadesapillai *et al.*, 2023b).

The chromosomal content of primordial follicles of 17 girls with mosaic-TS contained a normal X-chromosomal content in 95% of oocytes (143/150), while in granulosa and stromal cells high levels of aneuploidy were observed, respectively 20–100% and 3–95% (Peek *et al.* 2019, 2023). Similar observations were described in a case report of a girl with 45,X karyotype and a hidden mosaicism in the ovarian cells (Nadesapillai *et al.*, 2021b). In line with these studies, Balen *et al.* (2010) published a case report showing that all retrieved oocytes had a normal karyotype. Nevertheless, it is imperative to acknowledge that these oocytes have undergone a process of selection by ovarian hyperstimulation, which might lead to a higher probability of a normal karyotype.

Considering the abnormal morphology and aneuploidy of granulosa and stromal cells, the developmental potential of small follicles could be impaired. The capacity of primordial follicles in girls with TS to complete folliculogenesis was explored by grafting ovarian cortex tissue of girls with mosaic-TS in immunocompromised mice (Peek *et al.*, 2023). This study established that primordial follicles of cryopreserved-thawed ovarian cortex tissue of girls with mosaic-TS were indeed capable of developing into antral follicles. Interestingly, with the expansion of the granulosa cell layer during folliculogenesis, the percentage of aneuploid granulosa cells decreased considerably during folliculogenesis, resulting in a higher proportion of 46,XX granulosa cells in secondary and antral follicles.

Analysis of karyotype

The diagnosis TS is routinely confirmed by karyotyping of 20 lymphocytes. However, Graff *et al.* (2020) compared the conventional karyotyping in 20 lymphocytes with FISH on 200 buccal cells. The results showed a hidden mosaicism in 8/40 women with 45,X-TS (20%). Similar results were found in other studies where different karyotypes or ratios in karyotype were identified in the analysis of multiple cell lines (Brambila-Tapia *et al.*, 2009; Freriks *et al.*, 2013; Castronovo *et al.*, 2014; Ros *et al.*, 2014; Peek *et al.*, 2019, 2023; Schleedoorn *et al.*, 2022; Nadesapillai *et al.*, 2023b).

These studies indicate that genotyping of two cell lines provides a more accurate risk assessment of POI (Nadesapillai *et al.*, 2021a). However, despite the analysis of the genotype in lymphocytes and buccal cells, the genotype in ovarian cells can still be different (Nadesapillai *et al.*, 2021b).

Pubertal development

Girls with a 45,X/46,XX karyotype had the highest prevalence of spontaneous thelarche (69%), while spontaneous thelarche was reported in only 18% of girls with a monosomy 45,X and in 42% of girls with 'other' karyotypes (Table 1). According to a descriptive study by Hankus *et al.* (2018) involving 110 girls with TS, girls with 45,X were two times less likely to experience spontaneous thelarche compared to girls with a non-45,X karyotype. The median age of onset of spontaneous thelarche varied between 9 and 14 years (Tanaka *et al.*, 2015; Hamza *et al.*, 2018; Hankus *et al.*, 2018; Wu and Li, 2019; Ruszała *et al.*, 2020; Witkowska-Krawczak *et al.*, 2023).

Spontaneous menarche occurred in 52% of girls with mosaicism 45,X/46,XX, compared to 8% in girls with monosomy 45,X and 15% in girls with 'other' karyotypes (Table 1). Girls with 45,X were three times less likely to experience spontaneous menarche compared to girls with non-45,X karyotypes (Hankus *et al.*, 2018). Despite initial expectations of a correlation between karyotype and the occurrence of menarche, subsequent investigations by Castronovo *et al.* (2014) and Aso *et al.* (2010) did not reveal statistically significant results. The median age of spontaneous menarche varied between 11 and 14.6 years (Aso *et al.*, 2010; Homer *et al.*, 2010; Carpini *et al.*, 2012; NegreiRos *et al.*, 2014; Lunding *et al.*, 2015; Tanaka *et al.*, 2015; Bucerzan *et al.*, 2017; Hamza *et al.*, 2018; Hankus *et al.*, 2018; Wu and Li, 2019; Komura *et al.*, 2021; Witkowska-Krawczak *et al.*, 2023).

POI was reported in 7–8% of girls with 45,X/46,XX, in 100% of girls with 45,X and in 47–67% of girls with TS with 'other' karyotypes aged younger than 21 years (Lunding *et al.*, 2015; Fitz *et al.*, 2021). The majority of studies reported that 77–100% of girls with monosomy 45,X required induction of puberty (Aso *et al.*, 2010; Hagen *et al.*, 2010b; Carpini *et al.*, 2012; NegreiRos *et al.*, 2014; Lunding *et al.*, 2015; Wu and Li, 2019; Ruszała *et al.*, 2020). A single retrospective study by Fitz *et al.* (2021) found a considerable variety in the time from the diagnosis of TS until POI (mean 4.9 years ±SD 4.5 years). POI emerged at a median age of 15 years in girls with 45,X/46,XX. This was significantly younger in girls with 45,X, in which hypergonadotropic levels were seen at a median age of 10 years. Hence, an inverse correlation was observed between the ratio of aneuploidy and the age at POI. Specifically, there is an observed decrease of 0.09 year in the age of onset of POI for every 1% increase in the presence of 45,X-cells. Moreover, Mercer *et al.* (2013) described a small cohort of 20 girls with Xq deletion and mild phenotype of TS. They found a higher incidence of POI, at an earlier age, in girls with a larger deletion of the X-chromosome compared to girls with smaller deletions.

Hormonal parameters

Several hormonal parameters have been identified as useful markers of ovarian function in girls with TS. Among these, FSH, LH, and anti-Müllerian hormone (AMH) are the most used. These hormones can provide valuable information during different stages of development, from mini puberty in infancy to puberty and thereafter.

Mini puberty is the activation of the hypothalamic–pituitary–gonadal axis during the neonatal period. This results in a temporary increase of gonadotrophins and sex steroid levels, and mainly occurs in the first 3–6 months of life (Ljubicic *et al.*, 2022). This time frame might provide a fundamental 6-month diagnostic window of the ovarian potential in girls with TS to enable early fertility counselling (Carpini *et al.*, 2018). The study of Johannsen *et al.* (2018) compared the levels of FSH and LH during mini puberty of four girls with TS (aged 2–5 months) to 1840 girls

Table 1. Overview of studies reporting on spontaneous thelarche and menarche in girls with Turner syndrome.

Study type	Authors	Spontaneous thelarche n(%)				Spontaneous menarche n(%)				Karotype analysis[a]	Remarks
		Total	45, X	45,X/46,XX	Other	Total	45, X	45, X/46, XX	Other		
Retrospective cohort	Lau *et al.* (2009)	6/28 (21%)	1/13 (8%)	5/9 (56%)	0/6 (0%)	4/28 (14%)	0/13 (0%)	4/9 (44%)	0/6 (0%)	NR	
	Hagen *et al.* (2010b)	15/44 (34%)	1/18 (5%)	8/9 (89%)	6/17 (35%)	NR	NR	NR	NR	≥10	
	Carpini *et al.* (2012)	16/32 (50%)	0/12 (0%)	10/10 (100%)	6/10 (60%)	6/32 (19%)	NR	NR	NR	50	
	Castronovo *et al.* (2014)	NR	NR	NR	NR	6/40 (15%)	2/31 (6%)	4/5 (80%)	0/4 (0%)	≥30	
	Negreiros *et al.* (2014)	52/116 (45%)	12/54 (22%)	31/50 (62%)	9/12 (75%)	19/52 (37%)	3/12 (25%)	16/31 (52%)	0/9 (0%)	NR	
	Lunding *et al.* (2015)	35/117 (30%)	3/48 (6%)	15/23 (65%)	17/46 (37%)	29/117 (32%)	2/48 (5%)	15/23(65%)	12/46 (26%)	≥10	
	Tanaka *et al.* (2015)	77/212 (36%)	13/64 (20%)	17/28 (61%)	47/120 (39%)	31/212 (15%)	4/64 (6%)	13/28 (46%)	14/120 (12%)	NR	Mosaic included other numerical TS karyotypes.
	Bucerzan *et al.* (2017)	13/30 (43%)	NR	NR	NR	NR	NR	NR	NR	NR	
	Maggio *et al.* (2018)	3/19 (16%)	NR/7	NR/1	NR/11	3/19 (16%)	NR	NR	NR	NR	
	Hankus *et al.* (2018)	53/110 (48%)	19/61 (31%)	9/11 (81%)	25/38 (66%)	22/110 (20%)	6/61 (10%)	NR	NR	≥10	
	Ruszała *et al.* (2020)	16/35 (46%)	2/12 (16%)	NR	NR	NR	NR	NR	NR	NR	Subgroup non-45, X included 45, X/46, XX, and 'other'.
	Wang *et al.* (2023)	16/66 (24%)	6/28 (21%)	7/12 (58%)	3/26 (12%)	NR	NR	NR	NR	≥10	
	Witkowska-Krawczak *et al.* (2023)	19/34 (56%)	2/11 (18%)	NR	NR	16/31 (52%)	2/11 (18%)	NR	NR	≥20	Subgroup non-45, X included 45, X/46, XX, and 'other'.
Case control	Visser *et al.* (2013)	22/41 (54%)	NR	NR	NR	8/47 (17%)	NR	NR	NR	≥30	
	Hamza *et al.* (2018)	7/21 (33%)	NR	NR	NR	5/21 (23%)	NR	NR	NR	NR	
Observational	Borgström *et al.* (2009)	19/49 (39%)	3/22 (14%)	5/6 (83%)	11/21 (52%)	13/49 (26%)	2/22 (9%)	4/6 (67%)	7/21 (23%)	15–105	
	Nadesapillai *et al.* (2023b)	25/52 (48%)	1/14 (7%)	15/20 (75%)	9/18 (50%)	8/52 (15%)	0/14 (0%)	8/20 (40%)	0/18 (0%)	30	Additional genotyping on 100 buccal cells with FISH analysis.
Total (%)		394/1006 (39%)	63/357 (18%)	122/178 (69%)	133/314 (42%)	170/810 (21%)	21/276 (8%)	64/122 (52%)	33/224 (15%)		

[a] Number of lymphocytes used for conventional blood karyotyping.
NR, not reported; TS, Turner syndrome.

without TS and found that FSH and LH concentrations of all four girls with TS were above the female reference range. AMH levels of seven girls with TS before the age of 5 years are described (Hagen *et al.*, 2010a; Johannsen *et al.*, 2018). Six girls had AMH below the detection limit (45,X n = 2, miscellaneous karyotype n = 4) and one girl with 45,X/46,XX had AMH within the reference range of girls without TS. Information about their pubertal development is not presented.

During mid-childhood (5–10 years old), the FSH concentration of 70 girls with TS remained within the reference range, even in girls who turned out to need puberty induction at a later stage. In these girls, the elevation of FSH did not become manifest until the expected age of pubertal development (Hagen *et al.*, 2010b). Although FSH seems to have little predictive value during mid-childhood, two studies did measure difference in FSH in a different pubertal development. Aso *et al.* (2010) performed a descriptive study and demonstrated that if FSH remained below 10 IU/l until the age of 12 years, a menarche could be expected. In addition, according to the findings of Hankus *et al.* (2018), the probability of experiencing spontaneous menarche when FSH levels exceeded 6.7 IU/l at the age of 6–10 years, was observed to be reduced. In most girls, FSH remained low during childhood, and in these cases AMH appears to be the most reliable indicator for ovarian reserve (Hagen *et al.*, 2010a; Purushothaman *et al.*, 2010; Kallio *et al.*, 2012; Visser *et al.*, 2013; Lunding *et al.*, 2015; Wang *et al.*, 2023). Lunding *et al.* (2015) reported on pubertal development and AMH levels before pubertal onset in a longitudinal observational cohort study that included 15 girls with TS. In 4/5 girls with spontaneous thelarche, AMH was above the detection limit (>0.28 ng/ml). However, AMH was also detectable in 3/10 girls who needed induction of puberty (range 0.28–0.56 ng/ml). In the study of Hagen *et al.* (2010a) all girls with AMH <0.56 ng/ml did not develop spontaneous thelarche. Moreover, AMH-levels were correlated with karyotype, as described by Wang *et al.* (2023), who found significant higher levels of AMH in young girls with 45,X/46,XX aged 4–7 years, compared to girls with 45,X and 'other' karyotypes (median values respectively 1.13 ng/ml vs 0.02 and 0.04 ng/ml).

At pubertal age, AMH above the detection limit was associated with spontaneous thelarche (Visser *et al.*, 2013; Lunding *et al.*, 2015; Hamza *et al.*, 2018; Ruszała *et al.*, 2020; Wang *et al.*, 2023). In the cross-sectional study of Hamza *et al.* (2018), higher AMH levels were found in seven girls with TS ≥12 years of age with spontaneous thelarche compared to 43 girls with TS with induced puberty (2.12 ± 0.76 ng/ml vs 1.01 ± 0.53 ng/ml) and found that the odds of spontaneous thelarche was 18.4 and the odds of spontaneous menarche was 37.5 if AMH was above the detection limit. Similar results were described by Visser *et al.* (2013), who reported that the odds of spontaneous thelarche was 19.3 if girls with TS ≥12 years had AMH above the detection limit. However, AMH below the detection limit does not necessarily rule out spontaneous thelarche, as described in some cases (Ruszała *et al.*, 2020). This is substantiated by Visser *et al.* (2013) who described spontaneous thelarche in 38% of girls with TS with AMH below the detection limit, although low AMH (<0.42 ng/ml, Lunding *et al.*, 2015; <0.7 ng/ml, Hagen *et al.*, 2010a) was associated with POI and had a positive predictive value of 95% that POI would occur. The moment when POI might occur could not be predicted using AMH data in the study of Hagen *et al.* (2010a).

In addition to AMH, inhibin B is also described as a marker to predict ovarian reserve (Hagen *et al.*, 2010b; Messina *et al.*, 2015; Ruszała *et al.*, 2020). Hagen *et al.* (2010b) reported that spontaneous puberty did not occur in 19/20 girls with TS with repeating inhibin B levels below the detection limit during childhood. In addition, spontaneous thelarche did occur in 9/10 girls with TS (2–16 years) with at least one inhibin B measurement above the detection limit. Levels of inhibin B decreased to below the detection limit in the year before POI, as presented in a case series of four girls with TS (Lunding *et al.*, 2015). The conclusions drawn from these two studies underscore a strong correlation between inhibin B and ovarian function.

Summary

In contrast to FSH, LH or the genotype, which primarily represent probabilities, AMH stands out as a marker for assessing ovarian reserve owing to its direct reflection of the growing pool of follicles. Genotyping of two cell lines can enhance the predictability of ovarian decline.

Research gap: there is a demand for a longitudinal interpretation of ovarian reserve, especially in the prepubertal age group, as the level of AMH has a wide variation between girls and is subject to high inter-test variability.

Natural conception

Studies have reported a low prevalence of natural conception in women with TS (Table 2). Two retrospective cohort studies, Bernard *et al.* (2016) and Calanchini *et al.* (2020), found natural conception rates of 5.6% and 13%, respectively, with a mean age of 23–28 years. The prevalence was considerably lower in women with 45,X karyotype (1% and 3.2%) compared to women with 45,X/46,XX karyotype (15% and 48%) and women with other-TS karyotypes (4% and 9%). Although these results indicate the predictive value of karyotype for natural conception, the level of mosaicism appeared not to be predictive for the time to pregnancy, number of pregnancies, live birth or rate of miscarriage (Mortensen *et al.*, 2010; Doğer *et al.*, 2015; Bernard *et al.*, 2016; Calanchini *et al.*, 2020).

Besides the predictive value of karyotype, a TS diagnosis at an older age or spontaneous menarche could indicate higher chances of natural conception. Bernard *et al.* (2016) described that women who were diagnosed with TS at an older age (median 20 vs 10 years) were more likely to conceive naturally, probably owing to a milder phenotype. Moreover, 93–100% of women with TS and natural conception experienced spontaneous menarche (Bernard *et al.*, 2016; Calanchini *et al.*, 2020). Pregnancy risks in women with TS are significantly increased compared to women without TS (Hagman *et al.*, 2011; Bernard *et al.*, 2016; Calanchini *et al.*, 2020).

Summary

When counselling young girls on their chance for natural conception, the reported incidence rates of natural conception could be too optimistic. These rates are based on retrospective studies in which women with TS with a mild phenotype were also included and some even were diagnosed after a pregnancy.

Research gap: a prospective study on the incidence of natural conception in the general population of women with TS.

Fertility preservation

Current options for fertility preservation are vitrification of oocytes and OTC. The process of vitrification of oocytes involves ovarian hyperstimulation, frequent ultrasounds, and follicle aspiration, which is typically performed vaginally. The use of vitrified oocytes is widely applied and has a live birth rate of approximately 50% in women without TS aged ≤35 years (Cobo *et al.*, 2016). Vitrification of oocytes is often offered to women with sufficient ovarian reserve (Oktay and Bedoschi, 2014;

Table 2. Overview of studies reporting on natural conception in women with Turner syndrome.

Study type	Authors	N	Natural conception n (%)	Age at pregnancy (years)[a]	Pregnancies per karyotype n(%)	Pregnancies n (%)	Live birth n (%)	Pregnancy complications (% of pregnancies)						Karyotype analysis[b]	Remarks
								MR	LBW	CA	PE	AD	Mor		
Retrospective nulli vs primi	Bernard *et al.* (2016)	480	27 (5.6%)	27.5 (18–38)	45, X 2/181 (1%) 45, X/46, XX 19/130 (15%) Other 6/169 (4%)	52	30	16/52 (31%)	NR	2/11 (18%)	2/30 (7%)	0/52 (0%)	0/52 (0%)	NR	
	Calanchini *et al.* (2020)	141	18 (13%)	23.5 (15–31)	45, X 2/62 (3%) 45, X/46, XX 11/23 (48%) Other 5/56 (9%)	NR	37	NR (48%)	1/14 (7%)	1/5 (20%)	2/18 (11%)	0	NR	NR	Karyotype was known in 141 women.
Retrospective cohort of pregnancies in TS	Bryman *et al.* (2011)	482	23 (4.8%)	27 (16–42)	45, X 1 45, X/46, XX 25 Other 1	82	37 (45%)	37/82 (45%)	NR	4/37 (11%)	NR	1/82 (1%)	NR	10–30	Results include 4 women with ART.
	Hagman *et al.* (2011)	909	115 (12.7%)	30 (18–41)	45, X 10 45, X/46, XX 50 Other 52 Unknown 3	124	208	NR	NR	NR	1/124 (1%)	1/124 (1%)	0/124 (0%)	<'94 10–25 ≥'95 ≥ 30	
	Hadnott *et al.* (2011)	276	5 (1.8%)	25.6 ± 2.1	45, X 2 45, X/46, XX – Other 3	7	7	NR	0	0	0	0	0	50	
	Doğer *et al.* (2015)	22	11	23 (18–32)	45, X – 45, X/46, XX 17 Other 5	52	17 (33%)	35/52 (67%)	NR	1/3 (33%)	NR	NR	NR	100	Results include 5 women with ART.
	Cadoret *et al.* (2018)	NR	NR	28.7 ± 6.8	45, X – 45, X/46, XX 16 Other 6	22	22	5/22 (23%)	NR	0/22 (0%)	NR	NR	NR	NR	Only ongoing pregnancies are included.
	Obata *et al.* (2020)	NR	5	NR	45, X – 45, X/46, XX 2 Other 3	NR	NR	NR	NR	NR	NR	NR	0	NR	Patient characteristics were not specified for mode of conception
	Cauldwell *et al.* (2022a)	NR	NR	NR	45, X 9 45, X/46, XX 53 Other 11	73	NR	NR	NR	NR	NR	0	NR	NR	Patient characteristics were not specified for mode of conception
Case report	El-Shawarby and Steer (2007)		1	36	45, X	1	NR	NR	NR	NR	NR	NR	NR	NR	Twin pregnancy.
	Mortensen *et al.* (2010)		2	28 30	45, X[199]/47, XXX[1] 45, X[200]	2 2	2 2	NR	0	0	0	0	0	NR	Genotyping with FISH on 200 lymphocytes
	Alves and Silva (2012)		1	25/28	45, X[28]/47, XXX[2]	2	2	No complications						30	
	Mavridi *et al.* (2018)		1	21	45, X[52%]/47, XXX[48%]	1	1	No complications						NR	
	Strypstein *et al.* (2022)		1	29	45, X[14%]/46, XX[86%]	1	1	No complications						NR	Genotyping with FISH on lymphocytes.

Nulli versus primigravida: women with TS who were never pregnant versus women with TS with natural pregnancy.
[a] Mean±SD or Median (range).
[b] Number of lymphocytes used for conventional blood karyotyping.
AD, aortic dissection; CA, congenital abnormalities; LBW, low birthweight; MR, miscarriage rate; Mor, mortality; N, number of cases; NR, not reported; PE, pre-eclampsia; TS, Turner syndrome.

Talaulikar *et al.*, 2019; Vergier *et al.*, 2019). Girls have to be physically and mentally mature enough to undergo this process. OTC involves a laparoscopic resection of (part of) the ovary. OTC can be conducted at any age and prior to the onset of puberty. This technique has shown a live birth rate of 41% after transplantation of the cryopreserved-thawed ovarian tissue in women without TS (Dolmans *et al.*, 2021).

Vitrification of oocytes

In total, 58 cases of women with TS and vitrification of oocytes are described in 14 retrospective studies and case reports (Table 3). Overall, the first cycle of ovarian hyperstimulation resulted in a median of five vitrified oocytes after follicle aspiration (range 0–21). The majority of women who vitrified at least one oocyte had a 45,X/46,XX karyotype (51%), a median age of 21 years and had experienced a spontaneous onset of thelarche (98%) and menarche (96%). In 94% of cases with at least one vitrified oocyte, an AMH above the detection limit and a FSH below 10 IU/l was observed. With the exception of a single case (Azem *et al.*, 2020), all women with TS undergoing oocyte vitrification exhibited occurrences of spontaneous thelarche and menarche.

Many retrospective cohort studies reported to have a small cohort, though all tried to determine predictive parameters for successful vitrification of oocytes. A correlation between AMH level or antral follicle count (AFC) with the number of vitrified oocytes could not be established (Talaulikar *et al.*, 2019; Martel *et al.*, 2022; Brouillet *et al.*, 2023). Brouillet *et al.* (2023) found a negative correlation with basal FSH levels and oocyte yield ($r = -0.6$) and a positive correlation with the percentage of 46,XX-cells and oocyte yield ($r = 0.77$). This could not be confirmed by other studies (Vergier *et al.*, 2019; Martel *et al.*, 2022). However, some studies suggested that exceptions might exist and that individual variations might play a role. This was demonstrated in reports in which oocytes could be vitrified in cases with AMH levels below the detection limit (Martel *et al.*, 2022; Ulrich *et al.*, 2022), or basal FSH level above 20 IU/l (Brouillet *et al.*, 2023).

Since in most cases of women with TS it is difficult to vitrify a sufficient number of mature oocytes, the study of Oktay and Bedoschi (2014) applied 24-h IVM to increase the number of mature oocytes in three cases of girls with TS (aged 13, 13, and 14 years). This resulted in 6/25 immature oocytes being vitrified as mature oocytes.

Literature on the success rates of oocyte vitrification in women with TS is still scarce. There is merely one case report that described a live birth after the use of vitrified oocytes in a woman with a 45,X[14%]/46,XX[86%]-karyotype in lymphocytes. At the age of 24 years, 29 oocytes were vitrified after two stimulation cycles. All vitrified oocytes were fertilized with ICSI, resulting in 11 embryos. She delivered a healthy girl after the second embryo transfer. The case report described a live birth rate of 3% per vitrified oocyte (Strypstein *et al.*, 2022).

Ovarian tissue cryopreservation

Current knowledge of OTC in TS is limited to six cohort studies and five case reports, involving a total of 195 girls with TS aged between 3 and 22 years (Table 4). Borgström *et al.* (2009) performed a laparoscopy on 57 girls with TS. In 10/57 no ovarian biopsy was obtained because streak ovaries were seen during laparoscopy. In 15/57 (26%) girls with TS, follicles were detected in the ovarian biopsies. Nadesapillai *et al.* (2023b) performed a unilateral ovariectomy in 93 girls with TS. In 30/93 (32%) girls with TS, follicles were found in an ovarian cortex fragment. Both prospective cohort studies did not exclude girls based on karyotype, hormone levels or age, since no reliable predictive parameters for finding follicles were available at that time. Mamsen *et al.* (2019) retrospectively evaluated histological sections of girls with TS who underwent OTC. In 9/15 (60%) girls follicles were found. Zajicek *et al.* (2023) described follicles in 6/9 (67%) girls with TS, however they preselected girls based on at least one positive parameter: detectable AMH, normal FSH or antral follicles seen on transabdominal ultrasound. Rodriguez-Wallberg *et al.* (2023) performed ovarian biopsies in 10 girls with TS, but the tissue was not analysed for presence of follicles.

The follicle density varied considerably in girls with TS between 1 and 1200 follicles/mm^3 (Table 4) and was about 50% higher in prepubertal girls than in pubertal girls with TS (Peek *et al.*, 2023). Moreover, Nadesapillai *et al.* (2023b) calculated the total number of follicles in an ovary and found a higher number of follicles in girls with TS and a 46,XX cell line (mean 5407 follicles) compared to girls with TS without a 46,XX cell line (mean 2276 follicles).

Three parameters that might predict the presence of follicles in the ovarian cortex of girls with TS who opt for OTC were described: karyotype, spontaneous pubertal development, and AMH above the detection level. Girls with a 45,X/46,XX genotype had the highest prevalence of finding follicles: respectively 86% (Borgström *et al.*, 2009), 67% (Nadesapillai *et al.*, 2023b), and 100% (Mamsen *et al.*, 2019). The variation in reported outcomes regarding finding follicles is most likely a result of a difference in inclusion criteria. Girls with a 45,X had the lowest chance of follicles. Only in 5/58 (8.6%) girls with 45,X were follicles detected (Table 4). In addition to karyotype, in 58–64% of girls with spontaneous thelarche, follicles were seen in the ovarian cortex after OTC. Studies described a positive predictive value of 0.59–0.62 for the presence of follicles if a girl experienced spontaneous thelarche (Borgström *et al.*, 2009; Nadesapillai *et al.*, 2023b). Moreover, for girls with TS who had AMH above the detection limit (respectively >0.28 ng/ml, >0.1 ng/ml or >0.16 ng/ml), the chance of finding follicles was significantly higher. Girls with AMH above the detection limit had a positive predictive value of 0.64–0.88 for the presence of follicles (Borgström *et al.*, 2009; Nadesapillai *et al.*, 2023b; Zajicek *et al.*, 2023). However, follicles were also present in 5/46 (11%) girls with TS and hormone replacement therapy, in 5/50 (10%) girls without spontaneous onset of thelarche and in 1/37 (2.7%) girls with TS and AMH below the detection limit. The number of follicles was often lower in these specific cases (0.7–1000 follicles) (Borgström *et al.*, 2009; Mamsen *et al.*, 2019; Nadesapillai *et al.*, 2023b). So far, no correlation has been found between age and follicle density in the ovarian cortex tissue (Mamsen *et al.*, 2019; Nadesapillai *et al.*, 2023b).

OTC is still considered an experimental procedure in girls with TS, owing to the lack of reported data on live birth after auto transplantation of ovarian tissue (OTT) (Schleedoorn *et al.*, 2020; Mumford *et al.*, 2023). Three cases of OTT in girls with TS have been documented, and in two cases no recovery of ovarian function was observed (Rodriguez-Wallberg *et al.*, 2023) while in a recently published case report a clinical pregnancy was observed (Dunlop *et al.*, 2023). This first pregnancy occurred in a woman with 45,X/46,ring (X) who had preserved ovarian tissue at the age of 15 years while having regular menstrual cycles. At the age of 23 years, she had been trying to get pregnant for 2 years and experienced irregular menstrual cycles. After OTT, she experienced resumption of regular menstrual bleeding. Approximately 8 months after OTT, a viable intrauterine pregnancy with a gestational age of 6 weeks was observed. This resulted in a miscarriage a few days later. A considerable number of girls with TS who underwent OTC are still very young and have not returned for

Table 3. Overview of studies reporting on oocyte vitrification in girls with Turner syndrome.

Study type	Author	N	Procedure	Age (years)	Karyotype in % (number of cells analysed)	Spontaneous thelarche	Spontaneous menarche	AMH (ng/ml)	FSH (IU/l)	AFC	oocytes retrieved	MII-oocytes[a] vitrified	Remarks
Retrospective cohort	Oktay and Bedoschi (2014); Oktay *et al.* (2010)	3	Antagonist	13	45, X[90]/47, XXX[10] (30)	Yes	Yes	1.59	5.7	6	19	9	+1 MII-oocyte[b] vitrified after IVM
				14	45, X[45]/46, XX[55] (20)	Yes	Yes	0.9	5.3	12	11	8	
								1.7			7	4	
				13	45, X[20]/46, XX[80] (20)	Yes	Yes	0.76	5.6	6	16	7	+5 MII-oocyte[b] vitrified after IVM
	Talaulikar *et al.* (2019)	7	Antagonist	22	45, X[100] (NR)	Yes	Yes	0.49	6.9	7	9	6	
				18	45, X[83]/46, XX[17] (NR)	Yes	Yes	0.43	3.2	9	13	8	
				18	45, X[61]/46, XX[39] (NR)	Yes	Yes	0.98	7.4	11	9	6	
				25	45, X/46, XX/47, XXX (NR)	Yes	Yes	1.33	2.9	12	10	10	
				21	45, X[63]/46, XX[37] (NR)	Yes	Yes	0.49	6.2	5	4	4	
				22	45, X[50]/46, XX[50] (NR)	Yes	Yes	2.98	8.4	14	6	6	
				26	45, X[88]/46, XX[12] (NR)	Yes	Yes	1.69	7.5	11	12	10	In two stimulation cycles
	Vergier *et al.* (2019)	3	Antagonist	28	46, XX del(Xp) (NR)	Yes	Yes	0.50	10	6	3	2	
											3	2	
											7	5	
				25	45, X0 [100] (100)	Yes	Yes	8.81	6.5	18	20	17	
				18	46, X[83]/45, X[9]/46, XderX[8] (NR)	Yes	Yes	13.30	5.9	PCOS	25	20	
	Martel *et al.* (2022)	13	Antagonist	13	Mosaic	NR	Yes	2.99	5.2	NR	14	12	
				14	Turner syndrome	NR	No	<0.16	0.4	NR	4	2	
				14	Mosaic	NR	Yes	2.08	4.5	NR	21	16	
				14	**Turner syndrome**	**Yes**	**Yes**	**0.03**	**20.6**	**NR**	**0**	**–**	**Three attempts**
				15	**Turner syndrome**	**NR**	**NR**	**NR**	**3.9**	**NR**	**0**	**–**	**Two attempts**
				15	Turner syndrome	NR	NR	NR	0.2	NR	15	15	
				15	**Mosaic**	**NR**	**Yes**	**<0.003**	**1.8**	**NR**	**0**	**–**	
				16	Mosaic	Yes	Yes	1.63	0.5	NR	18	16	In two stimulation cycles
				17	**Mosaic**	**NR**	**Yes**	**NR**	**1.1**	**NR**	**3**	**0**	**Two attempts**
				18	**Mosaic**	**NR**	**NR**	**NR**	**<0.1**	**NR**	**0**	**–**	**Two attempts**
				21	Mosaic	NR	Yes	2.6	6.5	NR	22	12	
				21	**Turner syndrome**	**NR**	**Yes**	**<0.03**	**9.3**	**NR**	**2**	**0**	**Two attempts**
				21	Mosaic	Yes	Yes	5.34	5.4	NR	19	14	
	Brouillet *et al.* (2023)	14	Antagonist	**15**	**45, X[40]/47, XXX[60] (NR)**	**Yes**	**Yes**	**0.06**	**11**	**NR**	**0**	**–**	
				16	45, X[5]/46, X, del(X)[95] (NR)	Yes	Yes	0.4	8.9	2	1	1	
											1	0	
				16	45, X[6]/46, XX[94] (NR)	No	NR	1.29	4.6	8	11	10	
											13	10	
				17	45, X[18]/46, XX[82] (NR)	Yes	Yes	1.16	3.4	6	11	11	
				17	45, X[36]/46, XX[64] (NR)	Yes	Yes	0.85	6.4	20	5	5	
				18	45, X[50]/46, XX[50] (NR)	Yes	Yes	0.89	7.4	9	5	5	
											5	4	
				18	**45, X[89]/47, XXX[11] (NR)**	**Yes**	**Yes**	**0.54**	**7.6**	**3**	**0**	**–**	
				22	45, X[83]/47, XXX[17] (NR)	Yes	Yes	0.6	6.3	4	3	3	
											10	10	
											7	4	
				22	45, X[90]/47, XXX[10] (NR)	Yes	Yes	0.26	20.2	9	1	1	
											3	2	

(continued)

Table 3. (continued)

Study type	Author	N	Procedure	Age (years)	Karyotype in % (number of cells analysed)	Spontaneous thelarche	Spontaneous menarche	AMH (ng/ml)	FSH (IU/l)	AFC	oocytes retrieved	MII-oocytes[a] vitrified	Remarks
				22	45, X[39]/47, XXX[61] (NR)	Yes	Yes	0.58	10.3	8	2	2	
				24	45, X[95]/46, XX[1]/47, XXX[4] (NR)	Yes	Yes	2.3	NR	12	8	4	
				24	45, X[30]/46, XX[70] (NR)	Yes	Yes	NR	NR	8	5	4	
											6	6	
				30	45, X[30]/46, XX[70] (NR)	Yes	Yes	3.7	5.9	40	9	9	
				35	45, X[32]/46, XX[68] (NR)	Yes	Yes	1.97	7.2	15	1	1	
											3	3	
											16	12	
	Rodriguez-Wallberg *et al.* (2023)	10	NR	14–22		10/10	10/10	1.1 ± 1.0 (0.3–3.2)				5.1 ± 5.4 (0–19) per cycle	7.4 ± 7.0 (0–19) oocytes preserved per girl. 5 girls underwent repeated treatments
Case report	Kavoussi *et al.* (2008)	1	Antagonist	28	Mosaic	NR	NR	NR	4.3	40	15	13	
	Lau *et al.* (2009)	1	Agonist	16	45, X[98]/47, XXX[2] (NR)	Yes	Yes	NR	6.3	6	2	2	
	Balen *et al.* (2010)	1	Antagonist	28	45, X[93]/46, XX[7] (30)	Yes	Yes	6.13	3.3	NR	12	9	Oocytes used for FISH analysis
											10	7	
											30	NA	Embryo preservation, resulting in 13 embryos
	El-Shawarby *et al.* (2010)	1	Flare-up agonist	22	45, X[86]/47, XXX[11]/46, XX[3] (NR)	Yes	Yes	1.19	4.6	7	8	8	
	Ito *et al.* (2020)	1	Antagonist Duostim	23	45, X [13]/46, XX [87] (30)	Yes	Yes	3.43	10.6	3	10	9	
											9	8	
	Azem *et al.* (2020)	1	Antagonist	7	45, X[71]/47, XXX[29] (52)	Prepubertal	Prepubertal	**1.13**	**5.2**	**5**	**0**[b]	**–**	
										3	6[b]	6[b]	
	Strypstein *et al.* (2022)	1	Antagonist	24	45, X[14]/46, XX[86] (NR)	Yes	Yes	6.4	3.4	37	11	8	
											27	21	
	Ulrich *et al.* (2022)	1	Antagonist	14	Mosaic	NR	NR	<0.1	6	14	11	11	In four stimulation cycles, of which the first was cancelled due to poor response.

Stimulation cycles without oocytes preserved are shown in bold.

[a] Meta-phase II oocytes.

[b] First cycle GnRH-agonist trigger and no oocytes retrieved, second cycle hCG trigger and six oocytes retrieved, which shows the inactivity of the hypothalamus–pituitary–ovarian axis in a prepubertal girl.

AFC, antral follicle count; AMH, anti-Müllerian hormone; N, number of cases; NR, not reported; TS, Turner syndrome.

Table 4. Overview of studies reporting on ovarian tissue cryopreservation in girls with Turner syndrome.

Study type	Author	N	Procedure	Age (years)	Girls with follicles n/cohort (%)	Karyotype		Prepubertal	No spontaneous thelarche	Spontaneous thelarche	Spontaneous menarche[b]	AMH (ng/ml)	FSH (IU/l)	Follicles/mm^3
Prospective cohort study	Borgström *et al.* (2009)	57[a]	Laparoscopic ovarian cortex biopsy. 25–50% of one ovary was biopsied.	8–19	15/57 (26%)	45,X	3 (11%)	0/6 (0%)	1/19 (5%)	2/3 (67%)	1/2 (50%)	0.18–0.39	5.5–36.3	9–290
						N = 28	**25 (89%)**	**6/6 (100%)**	**18/19 (95%)**	**1/3 (33%)**	**1/2 (50%)**	**0.08–0.40**	**3.3–123**	–
						45,X/46,XX	6 (86%)	1/1 (100%)	1/1 (100%)	4/5 (80%)	3/4 (75%)	0.32–1.40	1.6–8.9	60–1.200
						N = 7	**1 (14%)**	**0/1 (0%)**	**0/1 (0%)**	**1/5 (20%)**	**1/4 (25%)**	**NR**	**NR**	–
						Other	6 (27%)	0/1 (0%)	2/11 (18%)	4/10 (40%)	4/7 (57%)	0.11–1.72	1–93.4	1–22
						N = 22	**16 (73%)**	**1/1 (100%)**	**9/11 (82%)**	**6/10 (60%)**	**3/7 (43%)**	**0.09–0.83**	**7.8–112.4**	–
	Nadesapillai *et al.* (2023b)	93	Laparoscopic unilateral ovariectomy	3–19	30/93 (32%)	45,X	1 (4%)	0/14	1/13 (8%)	0/1 (0%)	0	0.37	5.2	3
						N = 28	**27 (96%)**	**14/14 (100%)**	**12/13 (92%)**	**1/1 (100%)**	**0**	**<0.10**	**5.0–58.8**	
						45,X/46,XX	22 (67%)	9/13 (%)	1/5 (20%)	12/15 (80%)	7/8 (%)	0.8–3.0	2.2–7.8	0.2–247
						N = 33	**11 (33%)**	**4/13 (%)**	**4/5 (80%)**	**3/15 (20%)**	**1/8 (%)**	**0–0.3**	**5.6–60.0**	
						Other	7 (22%)	3/14 (%)	0/9 (0%)	4/9 (33%)	0	0.1–1.0	2.6–8.1	0.4–7
						N = 32	**25 (78%)**	**11/14 (%)**	**9/9 (100%)**	**5/9 (67%)**	**0**	**<0.10**	**2.9–40.0**	
	Rodriguez-Wallberg *et al.* (2023)	10	Laparoscopic ovarian cortex biopsy	1–17	Not analysed	NR		3/10	NR	NR	NR	NR	NR	NR
Retrospective cohort study	Jensen *et al.* (2017)	6	Laparoscopic unilateral ovariectomy	6–17	NR	Non-Mosaic	4	NR	NR	NR	NR	NR	NR	NR
						Mosaic	2							
	Mamsen *et al.* (2019)	15	Laparoscopic ovarian cortex biopsy	5–22	9/15 (60%)	45,X	1 (50%)	1/2 (50%)	NR	NR	–	0.73	NR	106
						N = 2	**1 (50%)**	**1/2 (50%)**	-	**NR**	–	**NR**	**13**	–
						45,X/46,XX	4 (100%)	1/1 (100%)	NR	NR	3/3 (100%)	0.06–20.2	<0.1–5.1	3–519
						N = 4	–	–	-	-	–	–	–	–
						Other	4 (44%)	0/3	NR	NR	4/5 (80%)	0.30–1.62	0.4–5.5	1–20
						N = 9	**5 (78%)**	**3/3 (100%)**	NR	NR	**1/5 (20%)**	**<0.04–3.2**	**4.2–82.9**	–
	Zajicek *et al.* (2023)	9	Laparoscopic unilateral or partial ovariectomy	2–18	7/9 (78%)	45,X	1							
							NR							
						45,X/46,XX	5	NR	NR	NR	NR	NR	NR	NR
							NR							
						Other	NR							
							1							
Case report	Huang *et al.* (2008)	1	Laparoscopic ovarian wedge resection	16	1/1	45,X[20]/46,XX[80]				yes	yes	NR	9.8	NR
	Balen *et al.* (2010)	1	Laparoscopic bilateral ovarian punch biopsies	17	1/1	45,X[93]/46,XX[7]				yes	yes	NR	NR	NR
	Joshi *et al.* (2021)	1	Laparoscopic unilateral ovariectomy	5	0/1	NR		yes				NR	NR	–
	Cheng *et al.* (2022)	1	Laparoscopic unilateral ovariectomy	3	1/1	45,X[19]/46,XX[81] Umbilical cord		yes				1.06	4.27	440
	Dunlop *et al.* (2023)	1	Laparoscopic bilateral ovarian cortex biopsies	15	1/1	45,X/46,X,ring(X)				yes	yes	0.04	1.9	3

Percentages are based on the number of girls who have a certain patient characteristic (e.g. prepubertal in combination with 45,X karyotype) and who have follicles or not. Girls without follicles in the ovarian cortex are shown in bold.

[a] In 10/57 girls no biopsy was performed, because streak ovaria were seen during laparoscopy.

[b] Girls with spontaneous menarche are also included in group with spontaneous thelarche.

AFC, antral follicle count; AMH, anti-Müllerian hormone; N, number of cases; NR, not reported.

OTT. Therefore, research efforts have been mainly directed towards obtaining more insights into the potential effectiveness of OTC for girls with TS, the quality of follicles in the ovarian cortex tissue and the potential markers to identify girls who could benefit from OTC.

Recently, Peek *et al.* (2023) performed a study in which ovarian tissue of girls with TS and age-matched controls was xenografted into immunodeficient mice. After retrieval of the grafted ovarian tissue, three significant observations were made. First, the follicle density decreased in tissue from both prepubertal and pubertal girls with TS and age-matched controls after xenografting. However, the follicle density was significantly higher in prepubertal girls compared to pubertal girls, before and after xenografting. Second, the proportion of growing follicles increased from 2–4% to 28–54%, while the proportion of morphologically abnormal follicles in girls with TS decreased from 30–31% to 6–8%, which is comparable to age-matched controls. Third, granulosa cells of unilaminar follicles from girls with TS were mostly aneuploid, but a considerable decrease in the percentage of aneuploid granulosa cells in secondary and antral follicles was observed after retrieval of the grafted ovarian tissue.

Summary

Vitrification of oocytes is a viable option for adolescents with TS. While the correlation between AMH and successful oocytes vitrification has been challenging to establish owing to small sample sizes in the published literature, combining available data suggests a strong correlation. However, sufficient AMH is needed for a realistic prospect of live birth, as multiple stimulation cycles might be needed. Although spontaneous menstrual bleeding and normal basal FSH reflect intact ovarian function, they do not directly indicate a sufficient ovarian reserve for oocyte vitrification.

Similarly, the presence of follicles in cryopreserved ovarian tissue correlates with AMH levels above the detection limit. Yet, for a realistic chance of live birth following OTT, sufficient AMH, as a correlate of sufficient ovarian reserve, is essential for adequate follicle survival. A 46,XX cell line and spontaneous thelarche increase the likelihood of the presence of follicles in the ovarian cortex. Follicle presence could not be related to age, yet prepubertal girls, with a higher follicle count than pubertal girls, are more likely to benefit from OTC although their follicle number remains significantly lower than that of girls without TS. Small follicles are able to develop into antral follicles after OTT; however, no live births have been reported so far in women with TS.

Research gap: the results of live birth after vitrification of oocytes or OTT.

Assisted reproduction techniques with own oocytes

There are few retrospective studies on ART using oocytes from women with TS. The predominant ART methods used were ICSI and IVF. Women with TS who underwent ovarian hyperstimulation followed by follicle aspiration and IVF or ICSI were aged between 25 and 39 years and had a 45,X/46,XX mosaic karyotype in 78% of all cases. Four women had 45,X monosomy (2%). The number of retrieved mature oocytes per stimulation cycle varied between 0 and 10 oocytes. Studies showed a large variation in clinical pregnancy rate (6–73%) and live birth rate (2.4–63%) per embryo transfer (Table 5).

In addition to ICSI or IVF, four out of 10 studies incorporated preimplantation genetic testing (PGT). Numerous investigations have used PGT to enhance reproductive outcomes, by selecting euploid embryos for transfer, with the aim of optimizing live birth rates, while minimizing the incidence of miscarriages and congenital abnormalities (Giles *et al.*, 2020; Gungor *et al.*, 2021; Liao *et al.*, 2021; Acet *et al.*, 2022). PGT was performed at different phases of embryogenesis: biopsy of polar body (Manno *et al.*, 2009), Day 3 (Giles *et al.*, 2020) or Day 5 (Liao *et al.*, 2021). The study by Liao *et al.* (2021) revealed a higher incidence of sex chromosome aneuploidy in the embryos of women with TS versus women without TS (7% vs 1.6%). Moreover, Acet *et al.* (2022) studied whether the level of mosaicism of women with TS contributed to the aneuploidy of embryos, and compared embryos of 10 women with high grade mosaicism (≥10% 45,X) with 26 women with low grade mosaicism (<10% 45,X). To note, a TS diagnosis can only be confirmed when a minimum of 10% of cells are aneuploid, or in combination with clinical signs of TS (Gravholt *et al.*, 2017). Acet *et al.* (2022) reported a significant higher rate of euploid embryos in women with high-grade mosaic-TS compared to women with low-grade mosaic-TS (39% vs 25%). However, pregnancy rates were not different. Furthermore, the study by Gungor *et al.* (2021) presented a cohort of 53 women with TS and ICSI-PGT versus 46 women with TS and ICSI-non-PGT and found significantly more pregnancies (36% vs 26%) and fewer miscarriages (11% vs 15%) per women after ICSI-PGT, respectively. Similar results after ICSI-PGT were found by Giles *et al.* (2020) and Liao *et al.* (2021), who reported clinical pregnancy rates of 42–72% and miscarriage rates of 14–31%. These studies differ from other studies that described clinical pregnancy rates of 6–31% and miscarriage rate of 60% in ICSI procedures without PGT in women with TS (Doğer *et al.*, 2015; Acet *et al.*, 2022). The study of Liao *et al.* (2021) concluded that when an euploid embryo, following PGT, was transferred to 72 women with TS, the pregnancy and miscarriage rates were comparable to those without TS. Ten newborns, of which a minimum of seven were born after ICSI-PGT, underwent screening for congenital abnormalities, and both studies reported healthy newborns (Giles *et al.*, 2020; Gungor *et al.*, 2021).

Summary

Research on ART is limited in women with TS. The published studies frequently combined IVF and ICSI with PGT and are biased by including women with a very late diagnosis of TS and mild phenotype. PGT could be of added value to reduce the time to pregnancy and number of miscarriages. However, PGT is only an option for women with a large number of embryos, which are needed to select euploid embryos, limiting this option to a small proportion of women.

Research gap: controlled studies on the value of PGT in women with TS undergoing IVF or ICSI with follow-up on pregnancies and the occurrences of chromosomal abnormalities.

Counselling

Infertility is the most frequently cited concern of girls with TS within each age group and their parents (Sutton *et al.*, 2005). Fertility counselling of girls with TS has been an important research topic over the last years (Table 6). Girls with TS and their parents who had fertility counselling expressed a high degree of appreciation, because counselling was a relevant addition to their overall healthcare experience (Joshi *et al.*, 2021; van der Coelen *et al.*, 2022; Fearon, 2023b; Granero-Molina *et al.*, 2023). Only a minority of girls with TS had received fertility counselling.

Table 5. Overview of studies reporting on ART with own oocytes in women with Turner syndrome.

Study type	Authors	N	Procedure	Age (years)[a]	Karyotype		Karyotype analysis[b]	AMH[a] (ng/ml)	FSH[a] (IU/l)	AFC[a]	Stimulation cycles	MII-oocytes[a]	Embryos	CPR (%)	LBR (%)	MR (%)	CA	Remarks
Retrospective cohort	Doğer *et al.* (2015)	10	ICSI	NR	NR		100	NR	NR	NR	35	NR	NR	5/82 (6.1%)	2/82 (2.4%)	3/5 (60%)	NR	
	Giles *et al.* (2020)	56	IVF-PGT	38.2 (37.3 –39.0)	Mosaic	56	NR	NR	NR	NR	65	9.1 (7.8 –10.4)	256	13/31 (42%)	7/31 (22.5%)	4/13 (31%)	0	
	Gungor *et al.* (2021)	98	ICSI (-PGT)	33.2 ± 4.2	45,X/46,XX Other	55 43	100	NR	7.3 ± 1.0	8.1 ± 3.3	98	NR	NR	12/NR 17/NR	9/NR 9/NR	5/12 (29%) 8/17 (47%)	0	Additional genotyping with FISH.
	Liao *et al.* (2021)	67	ICSI-PGT	35.4 ± 5.8	45,X 45,X/46,XX Other	4 51 12	60–100	3.2 ± 3.4	NR	13.5 ± 9.5	100	NR	213	22/30 (73%)	19/30 (63%)	3/22 (14%)	NR	
	Acet *et al.* (2022)	36	ICSI	36.2 ± 1.9 35.5 ± 0.9	45,X[≥10%]/46,XX 45,X[<10%]/46,XX	10 26	NR	NR NR	6.7 ± 1.2 5.7 ± 0.7	10.2 ± 1.4 10.9 ± 1.0	36	6.8 ± 0.4 9.4 ± 1.6	5.2 ± 0.4 6.4 ± 1.3	NR NR	11/36 (30%) (31%)	NR NR	NR	Genotyping with FISH on 400 cells.
Case report	Moore *et al.* (2008)	1	ICSI/IVF	28	45,X[5]/46,XX[25]		30	NR	7.3	NR	4	9 (total 36)	18 (50%)	0/7	0/7	–	–	TS-diagnosis after 3 cycles
	Manno *et al.* (2009)	1	ICSI-PGT	33	45,X[390]/47,XXX[10]		NR	0.53	8–10	NR	2	2–3 (total 5)	0–3	1/1	2/1	–	NR	Genotyping with FISH on 400 cells.
	Murakami *et al.* (2014)	1	OI	38	45,X[14]/46,XX[16]		30	NR	3.5	NR	9	–	–	2	1	1	0	Mole pregnancy
	Brouillet *et al.* (2023)	1	ICSI	29	45,X[87]/46,XX[13]		NR	1.78	7.6	11	2	3–7 (total 10)	6	1/3	0/3	1/1	–	

[a] Mean±SD or Median (range).
[b] Number of lymphocytes used for conventional blood karyotyping.
AFC, antral follicle count; AMH, anti-Müllerian hormone; CA, congenital abnormality of live birth; CPR, clinical pregnancy rate per embryo transfer; LBR, live birth rate per embryo transfer; MII, metaphase II oocyte; MR, miscarriage rate per clinical pregnancy; N, number of cases; NR, not reported; OI, ovulation induction; PGT, pre-implantation genetic testing; TS, Turner syndrome.

Table 6. Overview of studies reporting on fertility counselling in women with Turner syndrome.

Study type	Authors	Research aim (A) and methods (M)	Main results from women with TS (Wom), parents (Par), and healthcare professionals (HP)	
Delphi study	Schleedoorn *et al.* (2020)	**A:** To explore the expert opinion on OTC in TS. **M:** Three round Delphi study with 25 healthcare professionals, 10 ethicists and 7 women with TS, 13 parents of girls with TS	**Wom & Par & HP**	• OTC should be explored for women with TS in a research setting. • Infertility in women with TS can result in psychological distress. • Women with TS should have equal access to fertility preservation, like other patient populations. • Women with TS should not only be counselled about OTC but also other options of family planning. • The presence of the girl with TS during fertility counselling is recommended. • Women with TS opting for OTC should be discussed within a multidisciplinary team.
Focus group	van der Coelen *et al.* (2022)	**A:** To explore the experiences with fertility counselling for women with TS. **M:** Three focus group interviews with 13 parents of girls with TS and 12 healthcare professionals. Questionnaire to 60 girls with TS and their parents who had counselling for OTC.	**Wom**	• Fertility counselling was appreciated. • Counselling about OTC gave hope to future offspring.
			Par	• The option of OTC was difficult to decline because for many girls this might be the only option to have a biological child. • Parents were afraid of decision regret. • The decision was complicated by the unknown success of livebirth after the use of cryopreserved ovarian tissue.
			HP	• Families had high expectations of OTC, therefore it was difficult to provide informed consent. • Provision of multiple counselling moments is recommended to obtain informed consent. • It was difficult to offer an invasive procedure with unknown chances of success.
Interview study	Johnson *et al.* (2017)	**A:** To evaluate the beliefs and feelings about future fertility and healthcare requirements for making decisions related to fertility. **M:** Semi-structured interviews with 19 parents of children with differences in sex development, of which 3 with TS.	**Par**	• Fertility of their child was a major concern for parents. • Deciding when to inform their children about infertility was challenging. • There is a need for reliable medical information and research to inform their children. • Fertility preservation was important to give their child the choice to have biological children. • Parents were reluctant to decide on fertility matters for their child and had worries about false hope. • There were concerns regarding the costs of fertility preservation.
	Nadesapillai *et al.* (2023a)	**A:** To gain insight in the reasons to decide for or against OTC **M:** Semi-structured interviews with 8 girls with TS and 20 parents who had counselling for OTC.	**Wom & Par**	• OTC provided hope for future offspring and clarity about fertility. • The decision was complicated by the uncertain success of OTC. • The long-term health consequences of OTC were unknown. • Families felt time pressure to decide about OTC because of the accelerated decline of the ovarian reserve. • Families decided to opt for OTC to anticipate decision regret. • Girls with TS wanted to contribute to research.
	Fearon (2023b)	**A:** To explore considerations on OTC in girls and women with TS **M:** semi-structured interviews with 19 women with TS and 11 mothers of girls with TS	**Wom & Par**	• Women with TS endorsed the advancements in technology for family planning, and they would have opted for this option if it was feasible for them. • Benefits of OTC in TS: the potential to experience normal conception, the chance for a biological child, the improved psychological well-being through family planning options, and avoidance of emotional and social complexities linked to intrafamilial donation. • Concerns of OTC in TS: the emotional impact of OTC, the young age of girls with TS to understand the procedure and its implications, the pressure later in life to use the ovarian tissue, the unknown consequences of removing one ovary. • Families should receive comprehensive and age-specific information to decide about OTC

(continued)

Table 6. (continued)

Study type	Authors	Research aim (A) and methods (M)	Main results from women with TS (Wom), parents (Par), and healthcare professionals (HP)	
Survey study	Granero-Molina *et al.* (2023)	**A:** To Explore the sexuality experiences of women diagnosed with TS **M:** Semi-structured interviews with 18 women with TS (aged 22–51 years)	**Wom**	• There is a lack of training for healthcare professionals regarding sexuality and reproductive queries in women with TS. • A multidisciplinary team is needed to guide girls with TS from childhood to adulthood in their reproductive concerns. • Healthcare professionals are not aware of the guideline of pregnancy in women with TS.
	King *et al.* (2016)	**A:** To explore barriers in discussing infertility with girls with TS. **M:** Questionnaires were provided via social media to 215 caretakers of girls with TS.	**Par**	• 50% discussed infertility with their daughter, mostly when the daughter was around 6–10 years old. • The psychosocial maturity of the girl with TS was of importance in the timing of discussing infertility. • Barriers in discussing infertility: lack of understanding the diagnosis of TS, fear of negative emotions and feelings of guilt. • There is a lack of resources to support the fertility discussion.
	van Hagen *et al.* (2017)	**A:** To explore concerns about the cardiovascular health and pregnancy in women with TS **M:** Questionnaire to 104 women with TS	**Wom**	• About 50% had concerns about the influence of pregnancy on their cardiovascular health. Especially in women with cardiac abnormalities compared to those without cardiac abnormalities (75% vs 21%). • 12% were not aware of their current fertility status. • Preconception cardiac screening was done in 71% of women with TS who attempted pregnancy.
	Joshi *et al.* (2021)	**A:** To report the paediatric fertility preservation project **M:** Survey to patients between 0 and 17 years who were at risk of loss of ovarian function. Including 1 girl with TS and 37 other patients	**Par**	• All parents were grateful to have had counselling about fertility preservation. • All parents received sufficient information to decide about fertility preservation. • Difficulties in deciding on fertility preservation: concerns about the risks of the fertility preservation procedure (35%), costs (15%), chances of success (12%), and discussing infertility with their child (9%).
	Falsey *et al.* (2022)	**A:** To explore interest of women with TS in options of family planning **M:** Questionnaires provided via patient organization and social media to 226 women with TS >18 years	**Wom**	• 42% of women with TS did not know their specific TS karyotype. • 69% desired to become a parent, with adoption being the most pursued option (64% of desired parents). • Considerations in family planning options: age (68%), risks of pregnancy (62%), time required to become a parent (61%), desire to become pregnant (59%) risks for the newborn (55%), desire to have a biological child (53%) • 34% had concerns about their health when becoming pregnant • 36% discussed their fertility strategy with a healthcare professional. This did not result in a different fertility strategy, but women with TS expressed more concerns about the pregnancy risks when they had discussed it.
	Theroux *et al.* (2022)	**A:** To explore strategies for fertility counselling **M:** Questionnaires to 119 paediatric endocrinologists	**HP**	• 70% of paediatric endocrinologists discussed impacts on fertility potential in paediatric care. • 56% usually referred girls with TS with menarche to a fertility specialist and 19% usually referred girls with TS without menarche. • 67% discussed one or more pregnancy risks. • Barriers in discussing fertility preservation: giving false hope, absence of interest of the girl with TS or family, inexperience with fertility preservation techniques, logistical barriers (insurance, access). • 92% liked to receive extra training in fertility counselling.

(continued)

Table 6. (continued)

Study type	Authors	Research aim (A) and methods (M)	Main results from women with TS (Wom), parents (Par), and healthcare professionals (HP)	
Retrospective cohort	Morgan *et al.* (2019)	**A:** to explore counselling about fertility and fertility preservation for girls with TS at paediatric centres **M:** 469 patient files of girls with TS were screened for fertility counselling	**HP**	• 67% had fertility counselling, and in 27% of cases, the girl with TS was present during the counselling. • 10% of girls with TS were referred to discuss fertility preservation. Girls with TS with menarche were most likely to be referred (41%, OR 9.27). • 62% did not receive counselling about pregnancy risks. Menarche and multidisciplinary care were positively associated with counselling about pregnancy.
	Obata *et al.* (2020)	**A:** To explore the counselling on pregnancy in women with TS **M:** Questionnaire to perinatal centres who had experienced cases of pregnancy in women with TS. 20 pregnant women with TS were included.	**HP**	• Preconceptionally counselling was provided to 25% of pregnant women with TS. • 25% of pregnant women with TS underwent an MRI before they were pregnant. • 65% of pregnant women with TS underwent an echocardiography before they were pregnant.
	Calanchini *et al.* (2020)	**A:** To explore the issues in counselling on pregnancy options and risks for women with TS **M:** Files from 25 pregnant women with TS were screened	**HP**	• Pre-pregnancy cardiac evaluation was performed 48% of pregnant women with TS, including MRI in 17% of cases.

OR, odds ratio; OTC, ovarian tissue cryopreservation; TS, Turner syndrome.

Ethical considerations in fertility counselling in Turner syndrome

The ethical considerations in fertility counselling for TS can be assigned according to the four pillars of medical ethics: beneficence, autonomy, justice, and non-maleficence.

The beneficence for healthcare professionals in discussing (future) fertility involves exploring different options of family planning for girls with TS (van der Coelen et al., 2022). These options are not only limited to fertility preservation, but also include awaiting natural chances of pregnancy, oocyte donation, adoption, surrogacy, foster care, and remaining childless. In addition to healthcare professionals, girls with TS and their parents too are willing to contribute to research into options of fertility preservation in order to gain more knowledge for all women with TS (van der Coelen et al., 2022; Fearon, 2023b; Nadesapillai et al., 2023a).

Autonomy is valued by involving girls with TS as much as possible during counselling. Ideally, girls with TS are involved in counselling regardless of age and counselling is adjusted accordingly (Schleedoorn et al., 2020). However, the decision whether or not to opt for OTC is sometimes offered at a very young age, and consequently the decision is often made by parents. In this regard, anticipated decision regret plays a major role (Fearon, 2023b). An interview study by Nadesapillai et al. (2023a) and focus group interviews by van der Coelen et al. (2022) with a total of 43 parents who had to make the decision about OTC with their daughter with TS, revealed that parents felt that they had to seize all opportunities for a biological child for their daughter. First, to ensure the girl's autonomy in making future decisions regarding the usage of frozen ovarian tissue. Second, to alleviate the potential burden of blame of the daughter towards her parents for not seizing the option of OTC. However, parents were also concerned that if ovarian tissue was cryopreserved, their daughter might feel compelled to use the ovarian tissue later in life because her parents had made the decision for her earlier (van der Coelen et al., 2022; Fearon, 2023b; Nadesapillai et al., 2023a).

Justice is given by discussing all options of family planning. Fearon (2023b) conducted semi-structured interviews with 19 adult women with TS and 11 mothers of girls with TS. They established that women with TS appreciated the opportunity to choose between several options, such as waiting for natural conception, fertility preservation, oocyte donation, adoption, surrogacy or otherwise, as is the case for women without TS. This element of justice was confirmed in an ethical Delphi study by Schleedoorn et al. (2020) who reached consensus between 25 healthcare professionals, 10 ethicists, seven women with TS and 13 parents, on whether or not to offer OTC to girls with TS.

The non-maleficence principle weighs heavily for many healthcare professionals and parents. Discussing all options of family planning, even those that may not be applicable to a specific case, might result in significant emotional distress for the girl with TS (Theroux et al., 2022; van der Coelen et al., 2022). In addition, some options, such as OTC, oocyte vitrification, oocyte donation, and ART, are invasive procedures with possible complications and could harm girls with TS. Moreover, these procedures could create false hope, because these techniques have low live birth rates or have not resulted in a live birth yet (OTC) (Taggar and Engmann, 2021; van der Coelen et al., 2022; Fearon, 2023b; Nadesapillai et al., 2023a). Another aspect of non-maleficence to take into account is that a pregnancy in a woman with TS often comes with increased pregnancy risks, and there are other options of family planning available that do not come with these risks, such as adoption, surrogacy or foster care (Paulson, 2019; Schleedoorn et al., 2020; Falsey et al., 2022).

Barriers in fertility discussions

According to the clinical guideline for girls with TS, it is crucial to initiate discussions regarding the shortened reproductive lifespan and to consider fertility preservation counselling at an early age (Gravholt et al., 2017). However, a retrospective study by Morgan et al. (2019) found that only 10% of girls with TS were referred to a fertility specialist and that the parents as well as the girl with TS were present during consultation for 27% of the time. Likewise, a survey study among 226 women with TS reported that 36% had discussed fertility with a healthcare professional (Falsey et al., 2022). Women with TS with spontaneous menarche were most likely to be referred to a fertility specialist (referral in 56–59% of cases) (Morgan et al., 2019; Theroux et al., 2022). These results demonstrated that many women with TS did not receive fertility counselling, indicating that barriers to discussing fertility do indeed exist. Paediatricians recognized that both the unfamiliarity with fertility preservation techniques and a lack of interest from families prevented them from discussing fertility with girls with TS and/or their parents (Theroux et al., 2022). In addition, healthcare professionals were less likely to provide fertility counselling if fertility preservation seemed not feasible, had less access to fertility preservation care or did not have appropriate insurance (Morgan et al., 2019; Theroux et al., 2022; van der Coelen et al., 2022). Although awareness regarding this topic has increased, 92% of healthcare professionals still expressed interest in receiving extra training in fertility counselling. Moreover, appropriate tools and resources for facilitating effective fertility counselling services were highly recommended (Lin et al., 2016; Morgan et al., 2019; Theroux et al., 2022).

Similar to healthcare professionals, parents would also like to have tools to discuss fertility with their daughter, because they too encounter difficulties in determining the appropriate timing and approach to discuss infertility (King et al., 2016; Johnson et al., 2017; Fearon, 2023a). A survey study, which included 215 caretakers of girls with TS, reported that around 50% of the parents had discussed fertility with their daughter (King et al., 2016). When they discussed fertility, they mostly weaved it into normal conversations when their daughter was around 6–10 years old. The other half of respondents had not discussed fertility yet and were dealing with barriers, such as fear of negative emotions, feelings of guilt or a lack of proper resources, that allowed them to have this kind of conversation (King et al., 2016; Johnson et al., 2017). Similar concerns while discussing fertility with their daughter were reported by an interview study with 19 women with TS (aged 21–60 years) and 11 mothers of girls with TS (Fearon, 2023b). Psychosocial maturity was the most important prerequisite for discussing fertility, as was parental confidence with the topic (King et al., 2016; Joshi et al., 2021).

Complications and hazards during pregnancy

The elevated risk profile of pregnant women with TS is widely documented (Tables 2 and 5). Hence, one in two women with TS were afraid for the impact of a pregnancy on their health, which was more apparent in women with TS with cardiac abnormalities (van Hagen et al., 2017; Falsey et al., 2022; Granero-Molina et al., 2023). Studies stressed the importance of pre-conceptional counselling. However, only 25–71% of women with TS had pre-conceptional counselling (van Hagen et al., 2017; Morgan et al., 2019; Obata et al., 2020), and 48–65% had had imaging of the aorta (Calanchini et al., 2020; Obata et al., 2020).

During counselling about a future pregnancy, various risks are discussed, including maternal and foetal complications associated with pregnancy in women with TS. Maternal risks include miscarriages, pre-eclampsia, and the potential dilatation of the aortic diameter, which could lead to aortic dissection and mortality. Additionally, foetal risks, such as small for gestational age and congenital abnormalities, are also addressed. Among these risks, miscarriage stands out as the most prevalent, with reported rates ranging between 23% and 67% (Table 2), compared to 10% in women without TS aged 25–29 years (Magnus *et al.*, 2019). Homer *et al.* (2010) found a correlation between higher number of 45,X-cells in women with mosaic-TS and the increased prevalence of miscarriage ($P = 0.026$). Pre-eclampsia occurred in 6–11% of the reported natural conceptions (Hagman *et al.*, 2011; Bernard *et al.*, 2016; Calanchini *et al.*, 2020), compared to 4.6% of women without TS (Abalos *et al.*, 2013). Kooijman *et al.* (2021) compared the aortic diameter increase in 27 pregnant women with TS with age- and karyotype-matched nulligravida women with TS and did not find a significant difference in aortic diameter in the period before, during or after the pregnancy. Aortic dissection was documented in 0.9–1.2% of pregnancies (2/382 pregnancies), and they both survived (Bryman *et al.*, 2011; Hagman *et al.*, 2011). All other studies reported no aortic dissection. The study of Hagman *et al.* (2013) reported aortic aneurysm in 1.6% of pregnant women with TS. These two cases were known to have a congenital abnormality of the aorta (aortic coarctation/unspecified septal defect). Reassuringly, all studies reported an absence of mortality caused by cardiovascular events during or post-pregnancy (Mortensen *et al.*, 2010; Hagman *et al.*, 2011, 2013; Hadnott *et al.*, 2011; Bernard *et al.*, 2016; Obata *et al.*, 2020; Ramage *et al.*, 2020; Campens *et al.*, 2021; Grewal *et al.*, 2021). Regarding foetal complications, Ramage *et al.* (2020) compared pregnancies of women with TS to women without TS and found a higher risk for small for gestational age (odds ratio 4.5) and birth before 37 weeks (odds ratio 2.9). In addition, there is an increased likelihood of chromosomal abnormalities in offspring born to women with TS, with prevalence rates between 0% and 18% (Bernard *et al.*, 2016). Chromosomal analysis was performed in 15 newborns, revealing a TS diagnosis in two girls. In addition, one girl was diagnosed with TS in adulthood because of multiple miscarriages. All three girls had a structural abnormality of the X-chromosome, and so did their mother (Bernard *et al.*, 2016; Calanchini *et al.*, 2020).

Summary

In recent years, there has been an increased focus on fertility counselling in girls with TS and their families. Key considerations include granting the girl's autonomy in family planning by involving her early in conversations and emphasizing the pregnancy risks. On the other hand, fertility counselling could result in unrealistic hope of biological offspring. This research highlighted the barriers for counselling, such as the fear for negative emotions, the unfamiliarity with the options, and how to discuss fertility while adhering to the ethical principles. As a result, only a minority receives adequate fertility counselling.

Research gap: studies focussing on the implementation of fertility counselling in girls with TS and their families is needed.

Discussion

Summary

This review provides a comprehensive appraisal of the existing literature on fertility in women with TS. Throughout life, women with TS face various fertility dilemmas, since only 5–13% are able to conceive naturally. The prevalence of natural conception is highest in women with mosaic 45,X/46,XX (Bernard *et al.*, 2016; Calanchini *et al.*, 2020). Recently, it has been established that the percentage of 45,X-cells in the ovary generally differs from lymphocytes or buccal cells that are normally used for characterization of the genotype (Peek *et al.*, 2019). This could explain pregnancies in women with 45,X in lymphocytes. While AMH levels indicate ovarian reserve and FSH levels in pubertal girls serve as valuable predictors, longitudinal measurements are essential for accurate prediction of the ovarian function. This is crucial, as spontaneous pubertal development and the presence of a small number of follicles are also observed when the AMH level is below the detection limit (Hankus *et al.*, 2018).

The decline of the ovarian reserve over time is difficult to predict, therefore girls with TS and their parents ask for fertility preservation options. Currently, two fertility preservation techniques are available for girls with TS. The first is vitrification of oocytes: an established technique in women with TS. So far, one live birth has been reported using vitrified oocytes in a woman with TS (Strypstein *et al.*, 2022). Second is OTC, which is considered an experimental technique in girls with TS. The few cases describing OTT in women with TS have not resulted in live birth yet (Dunlop *et al.*, 2023; Rodriguez-Wallberg *et al.*, 2023). However, a xenotransplantation study showed that, although a major decline in follicle density after OTT was observed, small follicles from girls with TS (45,X/46,XX) are capable of continuing folliculogenesis (Peek *et al.*, 2023).

A subset of women who retain ovarian functionality and have a desire to conceive opt for ART, such as IVF or ICSI. The ovarian response to ovarian hyperstimulation in ART in these women with ovarian functionality was comparable to women without TS. The clinical pregnancy rate after IVF or ICSI varied between 6% and 73% and live birth rate between 2% and 63% per embryo transfer (Doğer *et al.*, 2015; Liao *et al.*, 2021).

Fertility counselling in TS is complicated and there is a strong need for a practical guideline. This guideline should give guidance on how to provide counselling and how to embed counselling in daily practice, with clear indications of when to refer girls and on how to decide who is responsible for referral.

Practical guideline: fertility in Turner syndrome

The following practical guideline (Fig. 2) was established based on the results section and clinical opinion from the various experts included in this review.

Provision of fertility counselling

We advocate a centralized provision of fertility counselling by a dedicated multidisciplinary team, consisting of gynaecologists, paediatricians, (paediatric) cardiologists, psychologists, and medical ethicists. Each expert in this team has a designated role as this would ensure optimized quality and consistency of the counselling process (King *et al.*, 2016; Morgan *et al.*, 2019; Schleedoorn *et al.*, 2019, 2020; Calanchini *et al.*, 2020; Joshi *et al.*, 2021; Granero-Molina *et al.*, 2023). The counselling should include information about options of family planning and cardiac comorbidities and complications associated with pregnancy (Morgan *et al.*, 2019; Schleedoorn *et al.*, 2020). Psychosocial support should be available and actively offered to girls with TS and their parents, especially during the counselling process.

The timing of referral is determined and guided by the preferences and needs of both the girl and her parents. Referral to discuss options of family planning should be considered at time of diagnosis, at pubertal age, at age 16–18 years, and continue during adulthood. It is imperative to address fertility-related

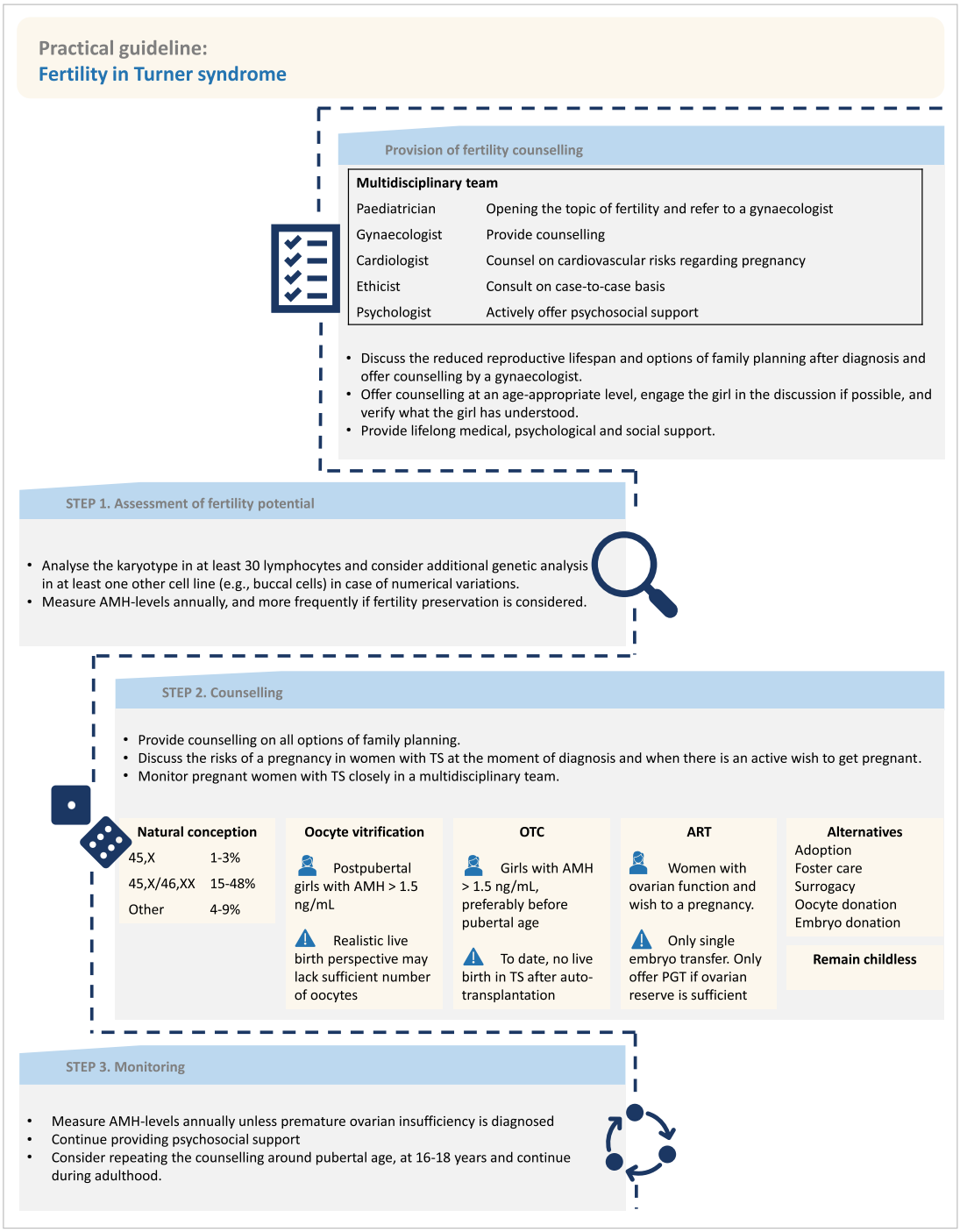


Figure 2. Practical guideline for fertility in girls with Turner syndrome. AMH, anti-Müllerian hormone; OTC, ovarian tissue cryopreservation; PGT, pre-implantation genetic testing; TS, Turner syndrome.

information at an age-appropriate level and, if possible, to engage the girl in the discussion. Furthermore, it is crucial to verify if the girl has understood what was explained to her by asking her questions regarding the subject (Mascarenhas *et al.*, 2019; Azem *et al.*, 2020; Schleedoorn *et al.*, 2020; van der Coelen *et al.*, 2022). In case of intellectual disability and/or psychiatric comorbidity, multidisciplinary consultation should be considered before counselling (Gravholt *et al.*, 2017; Björlin Avdic *et al.*, 2021). The key points are to:

- discuss the reduced reproductive lifespan and options of family planning after diagnosis and offer counselling by a gynaecologist.
- consider repeating the counselling around pubertal age and the age of 16–18 years.
- offer counselling at an age-appropriate level, engage the girl in the discussion if possible, and verify what the girl has understood.
- provide lifelong medical, psychological, and social support.

Step 1: assessment of fertility potential

Two factors are considered important in establishing the fertility potential of a girl with TS. First, we recommend establishing the karyotype in at least 30 lymphocytes (Gravholt *et al.*, 2017; Berisha *et al.*, 2020). Consider confirming the genotype in a second cell line, preferably buccal cells, in girls with a numerical TS-genotype (e.g. 45,X, 45,X/46,XX or 45,X/47,XXX) to determine the presence of multiple cell lines, and thus estimate the fertility potential more precisely (Graff *et al.*, 2020; Nadesapillai *et al.*, 2023b). Second, we recommend to determine the level of AMH at diagnosis and to evaluate this annually in order to estimate the ovarian reserve (Blakemore *et al.*, 2019). Consider measuring AMH levels more frequently if fertility preservation is considered. With longitudinal parameters, the course of the ovarian function can be monitored more precisely and discussed with the girl and her parents in a timely manner. From the age of 10 years, FSH could be a useful additional marker to AMH in determining a girl's fertility potential. Increased FSH levels (twice above the upper limit of normal) and/or repeated AMH below the detection limit is indicative of POI (Aso *et al.*, 2010; Hagen *et al.*, 2010b; Hankus *et al.*, 2018; Nadesapillai *et al.*, 2023b). Once POI is diagnosed, repeated measurement of AMH or FSH is no longer useful. The key points are to:

- analyse the karyotype in at least 30 lymphocytes and consider additional genetic analysis in at least one other cell line (e.g. buccal cells) in case of numerical variations.
- measure AMH levels annually, and more frequently if fertility preservation is considered.

Step 2: counselling

If full assessment of karyotype and hormonal markers is completed, the girl and her parents should be offered counselling on all options of family planning, including the individualized feasibility (Oktay and Bedoschi, 2014; Gravholt *et al.*, 2017; Blakemore *et al.*, 2019; Calanchini *et al.*, 2020; Schleedoorn *et al.*, 2020). Moreover, it should be mentioned that a pregnancy may be discouraged in the future if there are contra-indications for a pregnancy (Mascarenhas *et al.*, 2019; Nawroth *et al.*, 2020; Rodriguez-Wallberg *et al.*, 2020; Schleedoorn *et al.*, 2020). The key point is:

- provide counselling on all options of family planning and pregnancy risks.

The following information should be integrated into counselling and discussed on an individual basis.

Natural conception

The prevalence of natural conception is highest (15–48%) in women with mosaic 45,X/46,XX and lowest (1–3%) in women with monosomy 45,X. In women with a structural abnormality of the X-chromosome ('other') the prevalence is between 4% and 9% (Bernard *et al.*, 2016; Calanchini *et al.*, 2020). Nevertheless, it should be discussed that fertility declines with age and it is not apparent at prepubertal or pubertal age whether or not women possess the ovarian capacity to conceive naturally. Girls with spontaneous menarche and cyclic bleeding should be informed about the necessity of contraceptives, and in case of considering conception the need for cardiac assessment.

Oocyte vitrification

A viable option for post-pubertal girls with TS who are physically and mentally mature enough to undergo the intensive procedures of ovarian hyperstimulation and subsequent oocyte aspiration (Gravholt *et al.*, 2017). Since 2007, this procedure has been described in 58 cases with TS and has resulted in one live birth in this population. Based on expert opinion, we recommend that oocyte vitrification should only be offered to girls with sufficient levels of AMH in repeated measures, e.g. >1.5 ng/ml, and who experienced spontaneous thelarche and menarche. In cases with lower AMH levels, deviation from standard practices may be justified, subject to informed shared decision making. The question remains how many preserved oocytes will be needed for a realistic prospect of a live birth. In women without TS ≤35 years, the use of 15 vitrified oocytes resulted in a live birth rate of 70% (4.7% per oocyte) and increased to 95% if 25 vitrified oocytes were utilized (3.8% per oocyte) (Cobo *et al.*, 2018). The case report of a live birth in a woman with TS after oocyte vitrification showed a live birth of 3% per vitrified oocyte. So far, no reliable mathematical model for live birth rates after oocyte vitrification in women with TS exists. However, in girls with TS a median of five oocytes (range 0–21) per cycle was vitrified. Given the 23–67% risk of miscarriages for women with TS (Bernard *et al.*, 2016; Borini and Coticchio, 2019; Calanchini *et al.*, 2020), a lower live birth rate than 3% per oocyte could be expected and approximately 35–50 vitrified oocytes might be necessary if a similar likelihood of 95% live birth is being pursued. This high number of retrieved oocytes is not realistic for girls with TS owing to their compromised ovarian reserve. This stresses the importance of realistic counselling to prevent false hope. It should be discussed that several stimulation cycles with oocyte retrieval are necessary to obtain enough oocytes. Therefore, it is crucial to carefully evaluate the medical-ethical justification and the girl's preferences before proceeding with each subsequent cycle.

The key points are to:

- offer oocyte vitrification to post-pubertal girls with spontaneous thelarche and menarche and AMH above 1.5 ng/ml (repeated measures) who are mature enough to undergo the procedure.
- mention that for a realistic perspective on live birth a relatively high number of oocytes are needed, with multiple stimulation cycles, which might not be feasible considering the reduced ovarian reserve.

Ovarian tissue cryopreservation

This option for fertility preservation that may also be offered before puberty, since no reproductive maturity is required. Follicles were found in the ovaries of one out of three girls with TS, mostly in girls with 46,XX-cell line, and AMH above the detection limit (Borgström *et al.*, 2009; Peek *et al.*, 2019, 2023; Nadesapillai *et al.*, 2023b). A higher follicle density was found in prepubertal girls compared to pubertal girls (Peek *et al.*, 2023). Nonetheless, in girls with TS, higher rates of morphologically abnormal follicles and a reduced number of follicles were found (Mamsen *et al.*, 2019; Peek *et al.*, 2023). Despite the unfavourable characteristics, the small follicles of girls with 45,X/46,XX were capable of developing to secondary and antral stages after xenotransplantation (Peek *et al.*, 2023). The success of restoration of ovarian function after OTT in girls with TS is limited by a reduced number of follicles, a reduced rate of morphologically normal follicles, and the known loss of 50–90% of oocytes after OTT caused by hypoxia (te Velde and Pearson, 2002; Dolmans *et al.*, 2021). Therefore, based on expert opinion, we suggest discussing OTC as an option for girls with AMH above 1.5 ng/ml (repeated measures), preferably before puberty given their higher number of follicles, and offering it only within a research setting (Peek *et al.*, 2023). Unilateral

ovariectomy in women without TS has a low complication risk and shortened the reproductive lifespan by only 1–3 years (Bjelland et al., 2014; Rosendahl et al., 2017; Grynberg et al., 2023). Unfortunately, the impact of unilateral ovariectomy on ovarian function in girls with TS is unknown (Jensen et al., 2017). Moreover, no live births have been reported after OTT in women with TS (Dunlop et al., 2023; Rodriguez-Wallberg et al., 2023). The key points are to:

- discuss OTC as an option for girls with AMH above 1.5 ng/ml (repeated measures), preferably before puberty, and offer it only within a research setting. Do not exclude girls from OTC based on karyotype only.
- mention that OTC is considered experimental in girls with TS, that a significant loss of follicles is expected after OTT related to the procedure, and that so far no live birth has been reported.

ART

Three items are considered important in ART for women with TS. First, a sufficient oocyte yield is unlikely for most women with TS since the reported cases of women with TS who underwent ART were mostly diagnosed during or after IVF/ICSI and therefore likely to have an oocyte yield comparable to women without TS. Second, we recommend opting for single embryo transfer to prevent complications associated with multiple pregnancy (Söderström-Anttila et al., 2019; Abir et al., 2020; Rodriguez-Wallberg et al., 2020). Third, the added value of PGT in ART may be limited in case of poor ovarian response (Gungor et al., 2021; Liao et al., 2021). High numbers of oocytes are needed to select euploid embryos for transfer. Therefore, we recommend offering PGT only to women with sufficient ovarian reserve, or if the women so desire. The key points are to:

- consider ART for women with sufficient ovarian reserve when they express an active wish to become pregnant.
- select single embryo transfer.
- only offer PGT to women with sufficient ovarian reserve or at the express wish of a woman with TS.

Alternatives

Options of family planning with children of non-genetic origin include adoption, foster care, surrogacy, and donation of oocytes or embryos. A common encountered option is intra-familial donation of oocytes by a sister, niece or mother of the women with TS. This way, the child would be genetically related to the women with TS. However, it is important to note that intra-familial donation could lead to emotional, ethical, and social complexities (Fearon, 2023a). When discussing family planning, it is imperative not to overlook the valid option of leading a childless life. The key point is to:

- discuss alternative options of future parenthood and the option to remain childless.

Preconception counselling

Considering the increased health risks of a pregnancy in women with TS, it is strongly recommended to provide preconception counselling (Bondy et al., 2009; Lin et al., 2016; Gravholt et al., 2017; van Hagen et al., 2017; Blakemore et al., 2019; Söderström-Anttila et al., 2019; Abir et al., 2020; Andersen and Gravholt, 2022; Bamba et al., 2022; Brown, 2022). During counselling, several issues should be addressed, including cardiac screening and risks of miscarriage (23–67%), pre-eclampsia (6–7%), small for gestational age (0–7%), and cardiovascular complications such as dissection of the aorta (0–1%) (Doğer et al., 2015; Bernard et al., 2016; Cadoret et al., 2018; Calanchini et al., 2020). None of the studies included in this review described mortality after cardiovascular complications related to a pregnancy. This may be attributed to the enhanced medical care for pregnant women with TS (Cadoret et al., 2018; Andersen and Gravholt, 2022). We recommend close monitoring of pregnant women with TS by a multidisciplinary team consisting of gynaecologists and cardiologists, with frequent perinatal and postnatal controls (Bondy et al., 2009; Gravholt et al., 2017; Mavridi et al., 2018; Abir et al., 2020; Martín et al., 2021; Andersen and Gravholt, 2022; Brown, 2022; Cauldwell et al., 2022a,b). The key points are to:

- discuss the risks of a pregnancy in women with TS at the moment of diagnosis and when there is an active wish to get pregnant.
- monitor pregnant women with TS closely in a multidisciplinary team.

Step 3: monitoring

We recommend monitoring AMH levels on an annual basis, or at a frequency determined after careful consideration in consultation with the girl or woman with TS (Oktay and Bedoschi, 2019). In cases where AMH consistently is below the detection limit and/or POI is diagnosed, we recommend discontinuing further AMH evaluation. In addition, it is important to maintain psychosocial support and offer information on family planning options if requested.

Society's impact

Society has a major impact on women with TS when it comes to fertility. Fertility is generally regarded as a goal pursued by all individuals, and the decision to remain childless may necessitate justification within one's social environment (Fearon, 2023a; Radkowska-Walkowicz and Maciejewska-Mroczek, 2023). This society's pressure to have children could even be more pronounced in certain ethnic or religious contexts. In addition, women do not always qualify for options such as adoption because they are often wrongly assumed to have a shorter life expectancy or reduced social capabilities (Wasserman and Asch, 2012; Söderström-Anttila et al., 2019; Radkowska-Walkowicz and Maciejewska-Mroczek, 2023). Also, financial capabilities and insurance coverage can play a role in the choice options of family planning (Mascarenhas et al., 2019; Theroux et al., 2022) and this leads to inequity in accessibility to care. However, we advocate offering fertility counselling to all girls with TS to the best of a clinician's knowledge. A conscious decision about family planning is likely to enhance a woman's ability to cope with infertility and contribute to her overall satisfaction with her decisions.

Strengths and limitations

In this scoping review, articles were systematically screened and selected using the PRISMA checklist (Tricco et al., 2018) and multiple databases were searched. Whereas other reviews primarily focus on fertility preservation, this review focusses on all facets of fertility. Fertility in TS is examined with a broad scope and a wide time range of more than 15 years, which resulted in a comprehensive presentation of original research. In this way, we have provided tools for a practical guideline for fertility counselling for healthcare professionals. The findings could be limited by the karyotype descriptions of several studies, since the karyotype was either not clear or conducted with a limited number of

cells, leading to potential misinterpretation of a girl's fertility potential. In addition, the karyotype group labelled as 'other' consisted of a heterogeneous group. Consequently, formulating precise statements concerning the girls in the 'other' group remained challenging. Furthermore, statements and recommendations were sometimes based on a single study because of the limited available literature on several aspects. Moreover, the studies were generally based on small numbers of girls with TS with heterogenous characteristics, thereby impeding the extrapolation of findings.

Future perspectives

Prediction models are necessary to transcend the fertility counselling and identify appropriate candidates for fertility preservation. To achieve this, international collaboration is necessary to pursue large longitudinal cohorts of girls with TS, with and without fertility preservation. These cohorts should have well-defined karyotypes and long-term follow-up of fertility outcome. In the future, IVM of primordial follicles to mature oocytes may provide a solution for cryopreserved ovarian tissue containing low numbers of follicles. However, the development of this technique remains pending. Furthermore, research should be conducted on gene expression in ovarian cells to further understand the pathophysiology of POI in girls with TS. This might provide valuable insights into the potential consequences of aneuploid ovarian cells on folliculogenesis. Finally, comprehensive qualitative research is essential to develop a shared-decision tool for appropriate fertility counselling for girls with TS and their parents.

Conclusion

This review provides insight into the current knowledge of fertility in girls with TS and creates awareness of the importance of repeated discussions about the options of family planning. These options include fertility preservation techniques, as well as alternative options or the conscious decision to remain childless. With this review, we aimed to reduce the barrier for referral to an expert team for fertility counselling and offered a guideline for counselling. The topic of fertility necessitates thorough discussion tailored to the individual needs of girls with TS and their parents. In addition, it requires reconsideration on multiple occasions to enhance decision satisfaction.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

Data from screening and full-text review are available from authors upon reasonable request.

Authors' roles

All authors participated in the design of the review article. Literature search was performed by S.v.d.C. Screening and selection of articles were performed by S.v.d.C., J.v.d.V., K.F., and S.N. The first draft of the manuscript was written by S.v.d.C. with assistance of K.F., R.P., and J.v.d.V. All authors critically revised and confirmed the manuscript. Ten of the included studies in this review originate from our research group. K.F. and J.v.d.V. are involved in the revision group of the international guidelines for management of TS (2023).

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Conflict of interest

The authors have no conflicts of interest related to this review.

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