Turner Syndrome Systematic Review: Spontaneous Thelarche and Menarche Stratified by Karyotype

Elizabeth Dabrowski^a Rachel Jensen^b Emilie K. Johnson^{c, d}
Reema L. Habiby^{a, e} Wendy J. Brickman^{a, e} Courtney Finlayson^{a, e}

^aDivision of Endocrinology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA;

^bNorthwestern University Feinberg School of Medicine, Chicago, IL, USA; ^cDivision of Urology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; ^dDepartment of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ^eDepartment of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Keywords

Turner syndrome · Thelarche · Menarche

Abstract

Background: Girls with Turner syndrome (TS) have a high incidence of primary ovarian insufficiency. Recent data show rates of spontaneous thelarche (ST) of 38% and spontaneous menarche (SM) of 15–16%, with higher rates in those with mosaicism. **Summary:** We systematically reviewed the literature for evidence regarding rates of ST and SM in TS and evaluated rates based on the type of chromosomal mosaicism. We searched MEDLINE via PubMed, Embase, and the Cochrane Database of Controlled Trials. Reference lists were screened. Studies reporting outcomes of ST and SM in girls with TS, diagnosed by genetic analysis, were included. Data was collected regarding study design, cohort type, cohort age, the number of participants with ST and SM, the individual age at diagnosis of ST and SM, the mean age of patients with ST and SM, sample size, the number of participants with secondary amenorrhea, and karyotype. **Key Mes-**

sages: In total 2,699 patients were assessed for ST and 2,890 for SM from 43 articles. Overall the rates of ST were 32% (95% CI 26.4–38.9) and SM 20.8% (95% CI 19.3–22.4). Girls with X monosomy had the lowest rates of ST (i.e., 13%; 95% CI 8.7–19.7) and SM (i.e., 9.1%; 95% CI 7.3–11.3). Girls with 45,X/47,XXX had the highest rates of ST (i.e., 88.1%; 95% CI 62–97.1) and SM (i.e., 66.2%; 95% CI 49.3–79.6). **Conclusions:** Rates of ST and SM differ by karyotype in TS. When counseling patients, the karyotype should strongly influence discussions regarding pubertal development and the future reproductive potential.

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Context

Turner syndrome (TS) is traditionally defined as a chromosomal disorder that affects phenotypic females who have one intact X chromosome and complete or partial absence of the second sex chromosome in association with one or more clinical manifestations [1]. It is the most

common sex chromosome disorder in females, occurring in 1 out of 2,500 live births [2]. Features of TS encompass a wide phenotypic spectrum, of which the most common features are a short stature and premature ovarian insufficiency (POI). Qualitative data shows that POI causing infertility is one of the primary concerns of parents of girls with TS as well as of women with TS [3]. Therefore, understanding the predictors indicative of fertility, including spontaneous thelarche (ST) and spontaneous menarche (SM), is important when counseling patients with TS and their families. Although POI is common, timing is variable; recent data shows rates of ST and SM reaching 38% and 15–16%, respectively [4, 5]. This data also shows that TS patients with mosaicism have greater rates of ST and SM than those with 45,X monosomy [4–6]. Historically TS girls with genetic mosaicism have often been grouped together. However, identification of specific karyotypes that are associated with more or less morbidity may better direct counseling. To our knowledge, no systematic studies have assessed rates of ST and SM among patients with TS who have different types of mosaicism. To address this, a systematic review was performed to establish rates of ST and SM by karyotype to improve puberty- and fertility-based counseling for prepubertal TS patients.

Objective and Methods

Objective

The objectives of this study were to: (1) systematically review rates of ST and SM in patients with TS and (2) evaluate event rates of ST and SM by karyotype.

Methods

Current studies were reviewed in PROSPERO International Prospective Register of Systematic Reviews and, after determining that no overlap existed, our study was registered at <https://www.crd.york.ac.uk/PROSPERO/>. The study was designed based on the Standards for Systematic Reviews [7, 8].

Eligibility Criteria

Studies reporting outcomes of ST and SM in girls with TS, diagnosed by genetic analysis, were eligible for inclusion. ST was defined as breast development prior to exposure to exogenous estrogen and SM as menses prior to exposure to exogenous estrogen. In this review, pubertal failure was defined as a lack of ST by age 13 years and a lack of SM by age 15 years based on commonly accepted normal ranges for ST and SM in females [9, 10]. Not all articles provided the age of pubertal onset or the age of hormone replacement therapy (HRT) administration in individuals; in articles lacking individual pubertal ages, the age ranges were noted and the entire cohort included, including those aged under 13 years for thelarche and under 15 years for menarche. In articles

where individual ages were reported, girls under 13 years of age lacking ST or started on HRT prior to age 13 years and those under 15 years of age lacking SM or started on HRT were excluded from the analysis. Articles with unclear timing of HRT initiation were excluded.

Articles in which data was obtained from patient recall, case reports, and case series were excluded from the evaluation to limit recall and selection bias, respectively. Additionally, articles not published in the English language were excluded from the analysis.

Some articles did not clearly meet the inclusion or exclusion criteria, and in some articles data was incomplete or the data set may have overlapped with another article. In these cases, 3 attempts were made to reach the corresponding authors by electronic mail to confirm data. When the authors could not be reached, the reviewers assessed the article and inclusion or exclusion based on the available data was agreed upon.

The included data was divided into 7 karyotype groups as follows: 45,X; 45,X/46,XX; 45,X/47,XXX; 46, XX with structural abnormalities of the second X; 45,X/46,XX with structural abnormalities of the second X; 45,X with Y-chromosome mosaicism, and other. Rates of ST and SM were evaluated. Patients with Y-chromosome mosaicism comprised about 8–10% of patients with TS and were assessed as their own group. Often, these girls have a gonadectomy prior to ST or SM due to a known risk of germ cell cancer development; patients who underwent gonadectomy prior to age 13 years were excluded from the analysis.

A significant limitation of our paper is that some articles provided all patient karyotypes but reported ST and SM in monosomy versus mosaic patients; they did not provide the type of mosaicism in the pubertal discussion. Unless the authors were reached to clarify the type of mosaicism, these mosaic patients were categorized as “other.”

Search Strategy and Data Sources

In March 2016, the following databases were queried: MEDLINE via PubMed, Embase, and the Cochrane Database of Controlled trials. A research librarian searched databases from the time of the databases' inception to the study search date. The MEDLINE search was conducted first, and then translated to the appropriate syntax for the other databases, using controlled vocabulary when appropriate. MEDLINE search terms included: (“Menarche”[Mesh] OR “Breast/growth and development”[Mesh] OR “Menstrual Cycle”[Mesh] OR “Puberty, Precocious”[Mesh] OR “Sexual Maturation”[Mesh] OR “menarche” OR “thelarche” OR “menstrual cycle” OR “ovarian cycle” OR “endometrial cycle” OR “menstrual cycles” OR “ovarian cycles” OR “endometrial cycles” OR “precocious puberty” OR “premature puberty” OR “sexual precocity” OR “sex precocity”)) AND (“Turner Syndrome”[Mesh] OR “turner syndrome” OR “ullrich-turner syndrome” OR “turner’s syndrome” OR “XO gonadal dysgenesis” OR “monosomy X” OR “bonnieville-ullrich syndrome” OR “bonnieville ullrich syndrome”).

Study Selection

All identified articles were entered into End Note X7 (Thomson Reuters) and screened against inclusion and exclusion criteria. Working in duplicate, 2 independent reviewers reviewed the articles by title and abstract and then independently reviewed the full text of potentially relevant articles. A third reviewer resolved disagreements regarding inclusion of articles or data discrepancies between the 2 reviewers.

Fig. 1. Flowchart of eligible articles.

Data Extraction

The data extracted included journal name, publication year, study type, cohort type, cohort age included in analysis, the individual age of ST and SM when available, the mean cohort age of ST and SM, sample size, the number of participants with secondary amenorrhea, karyotype, and the number of participants with ST and SM.

Statistical Analysis

Event rates of ST and SM in TS in total, and stratified by karyotype, were evaluated. Patients were categorized into 7 groups based on karyotype as listed above.

Summary estimates of event rates for ST and SM were calculated using Comprehensive Meta-Analysis Software (version 2.0). Inherently different study settings and populations were assumed; therefore, a random-effects model was used for all of the analyses.

Results

Search Results

Figure 1 describes the flow of eligible articles. Initially, 861 abstracts were identified (211 were duplicates). The search terms were broad and many resulting articles were not pertinent to our review and excluded based on their title and abstract alone. The full text of 209 articles was reviewed.

Thirty-six of the 209 articles met the inclusion criteria. The most common reasons for article exclusion were: early initiation of estrogen (prior to the pubertal age), a lack of data, or unclear timing on initiation of HRT. The reference lists of the included articles were reviewed in detail and 7 additional articles were added

to the data set [4–6, 11–50]. To have a more complete dataset, attempts were made to contact authors 3 times to clarify data in articles where the karyotype was missing, the cohorts appeared to overlap with another article, or data was ambiguous. When the authors could not be reached, the potential overlap was discussed among the 3 reviewers and a consensus was reached regarding inclusion. Nineteen of the 173 excluded articles met the inclusion criteria but were excluded due to overlapping cohorts.

Study Characteristics

Among the 43 articles meeting the eligibility criteria, the study types included: 20 cohort studies, 9 cross-sectional studies, 4 case-control studies, 3 randomized control trials, and 6 unclassified studies.

In total, 29 studies evaluated ST in patients, assessing a total of 2,699 girls with TS. Thirty-four studies reported the incidence of SM, assessing a total of 2,890 women with TS. Only 4 studies included the age of thelarche; 12 reported the age of menarche and 13 the rate of secondary amenorrhea.

Pooled Event Rate

A total of 32% (95% CI 26.4–38.9) of TS girls experienced ST and 20.8% (95% CI 19.3–22.4) had SM. The average age of ST was 12.32 ± 0.65 years and that of SM was 13.2 ± 0.48 years. The rates of ST and SM by specific karyotype are presented in Tables 1 and 2. Among mosaic TS patients, the rates of ST ranged from 31.1 to 88.1% and those of SM ranged from 13.7 to 66.2%. The lowest

Table 1. Rates of ST

Group	Studies, <i>n</i>	Patients, <i>n</i>	Event rate	Lower limit	Upper limit
45,X	16	679	0.132	0.087	0.197
45,X/46,XX	8	108	0.629	0.532	0.717
45,X/47,XXX	3	23	0.881	0.62	0.971
46,XX with abnormalities of the second X	11	181	0.621	0.484	0.741
45,X/46,XX with abnormalities of second X	12	331	0.306	0.242	0.378
Y-chromosome material	5	8	0.411	0.192	0.673
Other	13	1,369	0.379	0.25	0.529
Total	29	2,699	0.32	0.263	0.383

Table 2. Rates of SM

Group	Studies, <i>n</i>	Patients, <i>n</i>	Event rate	Lower limit	Upper limit
45,XO	23	950	0.091	0.073	0.113
45,XO/46,XX	13	231	0.393	0.269	0.532
45,XO/47,XXX	4	40	0.662	0.493	0.798
46,XX with abnormalities of the second X	16	275	0.355	0.242	0.486
45,XO/46,XX with abnormalities of second X	14	357	0.137	0.103	0.178
Y-chromosome material	5	25	0.191	0.68	0.433
Other	16	1,012	0.33	0.224	0.456
Total	34	2,890	0.208	0.193	0.224

rates of ST and SM in mosaic TS were found in girls with 45,X/46,XX with structural abnormalities of the second X (ST 31.1% and SM 13.7%), whereas those with 45,X/47,XXX had the highest rates (ST 88.1% and SM 66.2%).

Discussion

To our knowledge, this is the only systematic review and data analysis to estimate the percentage of TS girls with ST and SM by specific karyotype. We demonstrate that rates of ST and SM in TS patients vary significantly by karyotype, particularly among different types of mosaicism.

Our analysis revealed that our overall rate of ST, i.e., 32%, corresponds with those currently cited in the literature. However, our overall rate of SM, i.e., 20%, is greater than the 15% currently reported in the literature. Our higher rates of SM are likely due to the use of an older age limit (i.e., 15 years), chosen based on the age range of menarche in typical females. Many prior studies included patients of all ages in the evaluation of ST and SM and thus gave falsely low rates of ST and SM because a portion of the cohort would not be expected to have undergone

pubertal changes at the time of evaluation. When extracting data, if possible, patients under the age of 13 years without thelarche and those under 15 years of age without menarche were excluded from the analysis. These age cutoffs were chosen based on the normal age range of ST and SM in females. Despite efforts to the contrary, patients under 13 years of age were included in the analysis for ST and those under 15 years of age were included in the analysis for SM when data was not specific enough to exclude these individuals. However, when assessing SM in patients older than 15 years (5 articles and 676 subjects), the rates were greater than predicted at 31.1%. Thus, if TS women are precisely evaluated based on the normal timing of puberty in age-matched peers, the rates of SM may be even higher, indicating a greater future fertility potential.

As expected, the rates of ST and SM were higher in all mosaic karyotypes than in girls with 45,X monosomy. Conceptually, it appears that, as the amount of X-chromosome material increases, patients are more likely to have spontaneous pubertal changes [17].

Interestingly, the rates of ST and SM were even greater in those with Y-chromosome material (i.e., 41% for ST

and 19% for SM) than in those with 45,X monosomy (i.e., 9% for ST and 13% for SM). Although the power of this group is limited, as many patients underwent gonadectomy prior to reaching the pubertal age or women with Y-chromosome material were omitted from past studies, this initial data deserves further consideration. There are 3 case reports of TS women with Y-chromosome material becoming spontaneously pregnant and carrying the pregnancy to term [51–53]. Our data further corroborates that women with TS and Y-chromosome material have potential gonadal function as indicated by the presence of ST and SM in some individuals. While current recommendations for girls with TS and Y-chromosome material are to remove the gonads at the time of diagnosis, our data and the reports of spontaneous pregnancy in women with TS with Y-chromosome material indicate that some of these girls and women have ovarian reserve and fertility potential [54, 55]. This complicates the already difficult ethical issues surrounding gonadectomy in minors. Further studies addressing how to weigh the potential of endocrine function versus the risk of germ cell neoplasia are needed.

Establishing normative data regarding ST and SM based on karyotype is particularly important in TS because of the theoretical implications for fertility potential. Currently, infertility is the most significant stressor reported by women with TS [3], and mothers who terminate pregnancies upon learning of a fetal TS diagnosis cite abnormal sexual development and infertility as the primary reasons for termination [56]. Although the rates of spontaneous pregnancy are low in TS women, there have been significant advances in fertility preservation which could allow for oocyte cryopreservation at younger ages, prior to POI [1]. In prior research by Borgström et al. [13], karyotype, ST, and SM predicted the presence of follicles. The presence of follicles raises hope for fertility potential, and while it is yet to be proven it is possible that if the karyotype can predict ST, SM, and the presence of follicles then in the future it may also be used to predict the fertility potential.

Significant strengths of this systematic review are both the diversity of the cohort and the large sample size. The included studies represent an array of different countries, ethnicities, races, and karyotypes, reflective of the TS heterogeneity seen in clinical practice. Furthermore, most articles (31/43; 72%) were published after 2000, reflecting a time period in which genetic testing is more readily available and performed, rather than an older cohort in which, presumably, only the more severe patients were evaluated.

The limitations of this study are as follows: (1) the retrospective analysis limited our ability to obtain further data when the data provided was incomplete for our purposes. For example, articles in which the primary research objective was not pubertal evaluation often provided a list of karyotypes but, when reporting on ST or SM, but only provided the number of monosomy or mosaic patients with spontaneous pubertal changes and did not list ST and SM by karyotype. Although we contacted the study authors for clarification, often the data was too old or the authors could not be reached; thus, these groups of mosaic individuals accounted for the majority of the “other” classification. Additionally, few studies provided the age at which thelarche or menarche occurred, thus, the average age of thelarche or menarche by karyotype could not be accurately determined. (2) We could not control for the inherent bias in research on TS as girls with more severe phenotypes, such as girls presenting with a lack or cessation of puberty, are likely to present for earlier assessment. Even with more readily available genetic testing, some women with TS and POI after ST and SM will not present until later in life and are not included in pediatric studies. (3) The power of the analysis might have been decreased by exclusion of studies. Studies that were not published in full in the English language were excluded from the analysis, potentially decreasing the power of our analysis. However, based on abstracts available in English, only 10 studies not available in English were eligible for full article review. To limit recall bias, studies which included pubertal data based on patient recall were also excluded from the analysis. (4) Studies in this meta-analysis assessed karyotype by peripheral blood, which may not reflect the karyotype of gonadal tissue. Prior studies have shown that, in all surviving females with TS, a mosaic cell line exists, even if it is not identified in a peripheral blood karyotype, supporting postzygotic events rather than germline nondisjunction as the cause of TS [57]. Researchers have speculated that TS girls who progress to ST and SM have 46,XX cell lines that are preferentially expressed in the gonads, explaining function. Thus, our 45,X monosomy group likely has “hidden mosaicism,” which cannot be accounted for as a gonadal karyotype is not routinely obtained. (5) We could not differentiate karyotypes with abnormalities of the second X due to the lack of detail in the cited articles. Patterns within this group may give further insights into event rates for SM and ST.

In summary, this systematic review demonstrates that rates of ST and SM differ by karyotype in girls with TS

and some karyotypes have much higher rates of ST and SM (i.e., up to 88 and 66% respectively) than previously reported, indicating greater gonadal function and potentially increased fertility in some women with TS. Given the wide range of ST and SM by karyotype, karyotype should strongly influence discussions about expected puberty, and possibly about reproductive potential. Larger multicenter studies will allow for increased understanding of different types of mosaicism and other morbidities found in TS.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflict of interests to disclose.

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Author Contributions

Dr. Dabrowski conceptualized and designed this study, carried out the review, coordinated the data analysis, and wrote the initial version of this paper. Ms. Jensen functioned as the second reviewer and reviewed this paper. Dr. Habiby and Dr. Johnson gave input throughout this study and reviewed the data, the findings, and this paper. Dr. Brickman gave input throughout this study, reviewed the data and findings, and critically reviewed this paper. Dr. Finlayson supervised each stage of the research and critically reviewed this paper.

All of the authors approved the final version of this paper as submitted and agree to be accountable for all aspects of this work.

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