

Turner syndrome and spontaneous pregnancy

Síndrome de Turner e gravidez espontânea

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ABSTRACT

The objective of this study is to describe patients with Turner syndrome (TS) who had spontaneous pregnancy and, when possible, to present the frequency of this outcome in this genetic condition. This is a literature review conducted in MedLine/PubMed, using the following English descriptors: Turner syndrome and spontaneous pregnancy. The following filters have been activated: articles with a publication date from the last 10 years that present the descriptors in the title/abstract. Twenty-nine articles were identified using the electronic search. After applying the inclusion and exclusion criteria, the number of articles selected was seven. However, two more articles were included after consulting the reference lists of these seven studies, totaling nine scientific articles. The frequency of spontaneous pregnancy ranged from 1.26% to 5.6%. Sixty-two TS patients who spontaneously became pregnant and 153 pregnancies were reported. There was a predominance of karyotype 45,X/46,XX (42 patients). Three patients were diagnosed with TS in adulthood and two of them after pregnancy. The minimum age at pregnancy was 21 years and the maximum 32. In the gestational outcome, an expressive number of children born, and abortions were observed, the latter with values of 54.9% and 34.6%. The present study described patients with TS and spontaneous pregnancy with mosaic (more frequent) and pure karyotype. It is believed that this value may be underestimated, since few studies have investigated primarily spontaneous pregnancy in this genetic condition, and many TS patients may not have been diagnosed because of the wide phenotypic variability associated with this chromosomal abnormality.

Key words: Turner syndrome; pregnancy; fertility; pregnancy outcome; karyotype.

INTRODUCTION

Turner syndrome (TS) is characterized by the partial or total absence of an X chromosome and affects approximately one for every 2,500 female births. Cardinal features include short stature, gonadal dysgenesis, and infertility⁽¹⁾.

The diagnosis of this genetic condition is performed by karyotype tests study, and about 40%-60% of patients with TS exhibit monosomy for the X-chromosome (45,X), followed by mosaicism of a 45,X cell line with, at least, another cell line; the others have structural abnormalities of the X-chromosome⁽²⁻⁵⁾. The presence of the Y-chromosome is associated with a high risk of developing gonadoblastoma, and molecular analysis to detect Y-chromosome sequences is indicated regardless of the karyotype of the TS patient⁽⁶⁾.

A previous study showed impaired fertility in TS⁽⁴⁾. In this regard, for most patients, infertility is unavoidable. In order

to achieve maternity, such patients may resort to adoption or assisted reproduction techniques (ART), such as heterologous *in vitro* fertilization (IVF) (oocyte donation), the most common option, or homologous/autologous (use of the TS patient's own gametes)^(7, 8). A study with 276 adult patients with TS showed that 87.7% of them had no children and 12.3% had children. From this latter value, 9.1% chose adoption; 1.4% achieved spontaneous pregnancy; 1.4% has chosen ART and 0.4% referred spontaneous pregnancy and ART⁽⁹⁾.

Based on these data, a minority of TS patients can conceive spontaneously, without the need to use the aforementioned options. In the literature, there is only one review study, published in 2015, on spontaneous pregnancy in TS⁽¹⁰⁾. In Brazil, there is still no statistical data on the prevalence of pregnancy in TS patients⁽¹¹⁾. Therefore, the purpose of this study is to increase knowledge about this topic, which is incipient, thus calling for further research.

OBJECTIVE

The objective of this study is to describe patients with TS who had spontaneous pregnancy and, when possible, to present the frequency of this outcome in this genetic condition.

MATERIAL AND METHODS

This is a literature review performed in the MedLine/PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) in August 2018, using the descriptors “Turner syndrome and spontaneous pregnancy”. The following filters were activated: articles with publication date in the last 10 years that present the descriptors in the title/abstract.

Twenty-nine articles were identified in the electronic search. The inclusion criteria were: research articles, original or case reports; published in English or Portuguese; available free of charge in full version and closely related to the research topic. After the application of these criteria, 22 articles were excluded for the following reasons: revision ($n = 8$), revision and French language ($n = 3$), not related to the subject in question ($n = 10$) and no availability of the full version for free ($n = 1$). This selection was based on the reading of the title and/or abstract. Thus, after

applying the inclusion and exclusion criteria, the number of articles selected were seven. However, a further two articles^(11, 12) were included after consulting the reference lists of these seven studies, totaling nine scientific articles.

RESULTS

Table 1 presents the characterization of the nine studies included in this literature review regarding the type of study and number of patients with TS investigated, objective, TS patients and spontaneous pregnancy and frequency. TS information regarding the karyotype of patients and age at diagnosis, as well as pregnancy (age, number and outcome) are presented in **Table 2**.

DISCUSSION

The present study aims to describe TS patients who had spontaneous pregnancies and, when possible, to determine their frequency. There is only one review on this topic in the literature, conducted in 2015, which presented results of studies published in the period from 1960 to 2014⁽¹⁰⁾. Only three studies^(4, 13, 14) are common between both reviews. One of the studies included in this literature review also carried out a review of the literature⁽¹⁵⁾.

TABLE 1 – Characterization of the nine studies included in the literature review regarding the type of study and number of TS patients investigated, objective, number of TS patients and spontaneous pregnancy and frequency

Studies	Type of study and number of TS patients investigated	Objective of the study	TS patients and spontaneous pregnancy	Frequency
Mortensen <i>et al.</i> (2010) ⁽¹³⁾	Case report	To report two cases of spontaneous pregnancy in TS	Two	-
Bryman <i>et al.</i> (2011) ⁽¹⁶⁾	Original article/research 482 TS patients	To report the pregnancy rate and outcomes of Swedish Turner centers, in relation to the karyotype, as well as maternal and child morbidity	23	4.8% (23/482) 40.3% (23/57)
Hadnott <i>et al.</i> (2011) ⁽⁹⁾	Original article/research 276 adult TS patients	To evaluate the fetal and maternal outcomes of pregnancies in women with TS	Five (one spontaneous pregnancy after assisted reproduction)	1.8% (5/276)
Alves & Silva (2012) ⁽¹⁴⁾	Case report	To report two spontaneous and successful pregnancies in a TS patient	One	-
Alves <i>et al.</i> (2013) ⁽⁴⁾	Original article/research 79 patients (20 – group 1 and 59 – group 2)	To evaluate the clinical, karyotype, gonadal function and ultrasound characteristics of the uterus and ovaries of women with TS	One	1.26% (1/79) 1.69% (1/59)
Bernard <i>et al.</i> (2016) ⁽⁵⁾	Original article/research 480 TS patients	To evaluate the prevalence and outcome of spontaneous pregnancies in a large cohort of French women with TS	27	5.6% (27/480)
Vieira <i>et al.</i> (2017) ⁽¹¹⁾	Case report	To report the outcome of a spontaneous pregnancy in TS patients and present a review on the management of this unusual association	One	-
Mavridi <i>et al.</i> (2018) ⁽¹⁵⁾	Case report and literature review	To report a spontaneous pregnancy in a TS patient	One	-
Mačkić-Durović <i>et al.</i> (2018) ⁽¹²⁾	Case report	To report a unique mosaic TS case	One	-

TS: Turner syndrome.

TABLE 2 – Characterization of the studies regarding the karyotype of TS patients and spontaneous pregnancy, age at diagnosis and at pregnancy, number of pregnancies and outcome

Studies	Maternal karyotype of ST patients with spontaneous pregnancy	Age (years) at TS diagnosis	Age (years) in spontaneous pregnancy	Number of spontaneous pregnancies	Outcome of pregnancy
Mortensen <i>et al.</i> (2010) ⁽¹³⁾	45,X	10	28 (1 st pregnancy)	Two	Two healthy boys
	45,X	7	23 (1 st pregnancy)	Two	One girl and one boy with normal karyotype
Bryman <i>et al.</i> (2011) ⁽¹⁶⁾	45,X/46,XX (<i>n</i> = 22)	Not informed	Not informed	82	37 children born
	45,X/46,XY (<i>n</i> = 1)				37 spontaneous abortions
Hadnott <i>et al.</i> (2011) ⁽⁹⁾	45,X/46,X,del(X)(p22.1)	14	31 (ART) and 32	Two	Seven births, one child with cerebral palsy
	45,X	18 months	24	One	
	45,X	16	25 and 28	Two	
	45,X/47,XXX	10	21 and 23	Two	
	45,X	At birth	25	One	
Alves & Silva (2012) ⁽¹⁴⁾	45,X/47,XXX	28	25 and 28	Two	One girl and one boy with normal karyotype
Alves <i>et al.</i> (2013) ⁽⁴⁾	45,X	33	31	One	One fetal death <i>in utero</i> in the thirtieth week
Bernard <i>et al.</i> (2016) ⁽⁵⁾	45,X (<i>n</i> = 2)	20*	27.5* (1 st pregnancy)	52	30 children born
	45,X/46,XX (<i>n</i> = 19)				(13 boys and 17 girls)
	45,X/46,XY (<i>n</i> = 1)				16 spontaneous abortions
	Isochromosome X (<i>n</i> = 1)				Two legal abortions
	Mosaic ring chromosome (<i>n</i> = 2)				Three medical interruptions
	Others (<i>n</i> = 2)	One intrauterine fetal death			
Vieira <i>et al.</i> (2017) ⁽¹¹⁾	45,X/46,XX	8	28	One	One neonatal death
Mavridi <i>et al.</i> (2018) ⁽¹⁵⁾	45,X/47,XXX	5	21	One	One girl with normal karyotype
Mačkić-Đurović <i>et al.</i> (2018) ⁽¹²⁾	45,X/47,XX,+21/46,XX	30	Not informed	Two	Two children with Down syndrome

TS: Turner syndrome; ART: assisted reproductive technology; *median.

It presented results from four extensive studies on spontaneous pregnancies in TS^(5, 9, 16, 17). These studies analyzed 1,648 women with TS, 86 reached spontaneous conception (5.2%), 128 babies were born and most patients (76.7%) presented karyotype 45,X/46,XX. In the present literature review, which included three extensive studies^(5, 9, 16), the overall frequency of spontaneous pregnancy was 4.5%.

The frequency of spontaneous pregnancy ranged from 1.26% to 5.6% (Table 1). Pregnancy occurred in 57 (12%) of the 482 Swedish patients with TS, and spontaneous pregnancy occurred in 23 of the 57 women with TS (40%), especially those with mosaic karyotype (45,X/46,XX)⁽¹⁶⁾. The frequency of spontaneous pregnancy in TS may be undervalued, since many women with this chromosomal anomaly and with preserved fertility may not have been diagnosed⁽⁴⁾. In addition, we must consider that phenotypic variability in TS is large, from patients with exuberant body dysmorphic disorder to those almost indistinguishable from the general population^(18, 19). Therefore, those with no evident dysmorphism are difficult to diagnose and many of them may have spontaneous pregnancies, and the cytogenetic diagnosis may be not performed or possibly delayed or randomly. The studies

included in this review described a total of 62 TS patients with spontaneous pregnancy, with a total of 153 pregnancies (Tables 1 and 2).

In the present review, four studies described patients with pure karyotype (45,X) who conceived spontaneously^(4, 5, 9, 13). Our data disagree with those previously published that reported that there was no report of a woman with TS karyotype 45,X and spontaneous pregnancy⁽¹⁷⁾. A case report described a patient 45,X with three pregnancies, her first daughter exhibiting normal karyotype; her second pregnancy ended in spontaneous abortion and the third pregnancy resulted in the birth of a girl with karyotype 45,X⁽²⁰⁾.

Seven studies described spontaneous pregnancy in mosaic karyotype^(5, 9, 11, 12, 14-16). According to the literature, spontaneous pregnancy is usually more frequent in patients with mosaic TS^(17, 21).

Three studies reported TS patients with karyotype 45,X/47,XXX^(9, 14, 15) with a predominance of healthy children. One of these patients underwent amniocentesis at 16 weeks of gestation, which revealed a fetus with 46,XX karyotype. This procedure was adopted due to the greater risk of aneuploidy

among the descendants of TS women⁽¹⁵⁾. Two other successful pregnancies also occurred in a 33-year-old female with mosaic TS (45,X/47,XXX) who conceived spontaneously and exhibited short stature as the sole manifestation of the syndrome⁽²²⁾. On the other hand, a previous study described a 26-year-old TS patient with this same karyotype and five miscarriages. The patient exhibited type 1 Diabetes *mellitus*, endometrial cancer and, in her family history, her mother presented recurrent loss of pregnancy. Their first, third, fourth, fifth and sixth pregnancies resulted in miscarriages in the first trimester. Her second pregnancy resulted in the birth of a healthy daughter with a karyotype 46,XX⁽²³⁾. Another recent case report described a 10-year-old girl with TS with mosaic karyotype (45,X/47,XXX) who exhibited mild phenotype of short stature and spontaneous puberty⁽²⁴⁾. In this case, patient follow-up is recommended to verify the occurrence of pregnancy. Karyotype 45,X/47,XXX is rare, and only 1.5% of TS patients exhibit this chromosomal constitution⁽²⁴⁾.

In the present study, there was a predominance of karyotype 45,X/46,XX (42 patients) among the 62 who had spontaneous pregnancy (Table 2). From the 22 mosaic TS patients investigated, 17 of them were 45,X/46,XX, and 16 from the 22 conceived, of which, 11 spontaneously and five by IVF⁽²¹⁾. The karyotype 45,X/46,XX was also the most prevalent, since it was found in 25 from the 31 TS patients who presented spontaneous pregnancy⁽¹⁷⁾.

Regarding the age of TS diagnosis, only one occurred at birth and eight patients were diagnosed between the ages of 18 months and 16 years. According to the literature, from the 138 TS cases aged from 0 to 18 years, 14 (10.1%) were diagnosed between 0 and 1 year; 67 (48.6%) between 1 and 12 years (mostly between 7 and 12 years); and 57 (41.3%) between the ages of 12 and 18 years⁽¹⁸⁾.

An interesting finding was the TS diagnosis in adulthood, in three studies^(4,12,14). Interestingly, two patients had the TS diagnosis after pregnancy^(4,14). A study with 178 patients with TS showed that 76.4% of the girls were diagnosed in childhood/adolescence due to their short stature, and only 12.4% in adult life⁽³⁾. This study also showed that the mean age at diagnosis was 12.6 years, which is lower in those with karyotype 45,X⁽³⁾. The patient with TS and triple mosaicism (45,X/47,XX,+21/46,XX) was only submitted to karyotyping after their second pregnancy. Her first child died at birth, and after cytogenetic analysis, it was established that she had Down syndrome. In the second pregnancy, the patient was submitted to amniocentesis and the result also showed that the child had Down syndrome⁽¹²⁾. These ascertain that the TS diagnosis in this patient was at random. Due to her history, the patient decided to undergo preimplantation genetic diagnosis in the future⁽¹²⁾.

The minimum age in spontaneous pregnancy of TS patients was 21 years and the maximum was 32 years. A relatively recent study evaluated the reproductive and obstetric outcomes of natural conception and IVF in 22 mosaic TS patients and showed that the median age at the first spontaneous pregnancy was 23 years and at diagnosis, 34.5⁽²¹⁾.

Our results also showed that repeated pregnancy was common in most studies^(5,9,12-14,16). Considering that spontaneous pregnancy in TS is a rare condition, repeated pregnancy should be even more uncommon⁽¹⁴⁾.

In the gestational outcome, an expressive number of children born and abortions were observed, the latter with values of 54.9%⁽¹⁶⁾ and 34.6%⁽⁵⁾. A previous review of the literature showed that from the 160 pregnancies that occurred in 74 women with TS, 29% ended in spontaneous abortion, 7% led to the stillbirth outcome, 20% gave birth to malformed babies (TS, Down syndrome, etc.) and only in 38% of the cases healthy children were born⁽²⁵⁾. Another study reported a total of 52 pregnancies, of which 17 (32.7%) resulted in liveborn and 35 (67.3%), in abortion⁽²¹⁾. According to Bernard *et al.* (2016)⁽⁵⁾, from the 30 children born, the karyotyping test was performed only in 11 of the 17 girls, two of whom were diagnosed with TS [(45,X/46,X,r(X) and 47,X,der(X)t(X;Y)x2/46,X,der(X)t(X;Y)]. One of the studies mentioned as a limitation the non-accomplishment of the karyotyping tests in the descendants of TS women⁽¹⁶⁾. Problems arising from birth occurred in five of the 68 children (37 of them conceived by spontaneous pregnancy), that is, 7%. It is worth mentioning that 80% of them (4/5) were born from spontaneous pregnancies⁽¹⁶⁾. There was a report of the birth of a child with cerebral palsy, but there were no children with chromosomal alterations⁽⁹⁾.

An even higher frequency of spontaneous pregnancy (7.6% – 31/410) was described by Birkebaek *et al.* (2002)⁽¹⁷⁾ and two women became pregnant after IVF. In this study, there was a predominance of mosaic karyotype ($n = 27$) among the 33 pregnant women with TS and the birth of 64 children (32 girls and 32 boys) in 61 pregnancies⁽¹⁷⁾. Karyotyping test was performed in 25 of the 64 children and six of them exhibited chromosomal alterations⁽¹⁷⁾.

There are few studies published in the literature on spontaneous pregnancy in TS^(5,9,16), which evidences the need for further research in this area, in order to clarify the actual frequency of spontaneous conception in this genetic condition.

It is recommended that during the pregnancy of a TS patient, a multidisciplinary team composed of specialists in the field of maternal-fetal medicine, cardiology and endocrinology should closely monitor these pregnant women due to risks, such as

worsening of cardiovascular diseases during pregnancy and specific complications. The team should provide those patients who wish to keep going to the end of pregnancy to perform a thorough risk assessment and genetic counseling prior to conception, in addition to rigorous neonatal follow-up⁽¹¹⁾.

CONCLUSION

The present study described patients with TS and spontaneous pregnancy with pure and mosaic (more frequent) karyotype. The frequency ranged from 1.26% to 5.6%. It is believed that this value may be underestimated, since few studies have primarily investigated spontaneous pregnancy in this genetic condition

and many TS patients may not have been diagnosed because of the wide phenotypic variation associated with this chromosomal abnormality.

FINANCING

This study received no funding.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

RESUMO

O objetivo deste estudo é descrever pacientes com síndrome de Turner (ST) que tiveram gravidez espontânea e, quando possível, apresentar a frequência desse defeito nessa condição genética. Trata-se de uma revisão bibliográfica realizada no MedLine/PubMed, utilizando os descritores, em inglês: Turner syndrome and spontaneous pregnancy. Os seguintes filtros foram ativados: artigos com data de publicação dos últimos 10 anos que apresentassem os descritores no título/abstract. Foram identificados na busca eletrônica, 29 artigos. Após aplicação dos critérios de inclusão e exclusão, o número de artigos selecionados foi sete. No entanto, mais dois artigos foram incluídos após a consulta das referências bibliográficas dos sete estudos, totalizando nove artigos científicos. A frequência de gravidez espontânea variou de 1,26% a 5,6%. Foram relatadas 62 pacientes com ST que engravidaram espontaneamente e 153 gravidezes. Houve predomínio do cariótipo 45,X/46,XX (42 pacientes). Três pacientes foram diagnosticadas com ST na idade adulta e duas delas após a gestação. A idade mínima na gestação foi 21 anos e a máxima, 32. No desfecho gestacional, foi observado um número expressivo de crianças nascidas e abortos, este último com valores de 54,9% e 34,6%. O presente estudo descreveu pacientes com ST e gravidez espontânea com cariótipo mosaico – mais frequente –, e puro. Acredita-se que esse valor possa estar subestimado, uma vez que há poucos estudos que investigaram primariamente a gravidez espontânea nessa condição genética, e muitas pacientes com ST podem não ter sido diagnosticadas devido à ampla variabilidade fenotípica associada a essa anomalia cromossômica.

Unitermos: síndrome de Turner; gravidez; fertilidade; resultado da gravidez; cariótipo.

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