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Spontaneous Pregnancy in Mosaic Turner syndrome: Case Report and Recent Insights for Genetic and Reproductive Counselling

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Abstract

Introduction: Pregnancy in mosaic Turner Syndrome (TS) occurs relatively rarely. Phenotypes of mosaic TS and fertility outcomes may vary according to the degree of mosaicism.

Objective: Our study aimed to report the occurrence of spontaneous pregnancy in a case of mosaic TS and report recent recommendations in the matter of genetic counselling in that entity.

Results: A 31-year-old patient was referred for cytogenetic testing after three an embryonic pregnancies. She was measured at 155 cm and weighed 57 kg. Her menarche occurred at the age of 14 and her menstrual cycles were regular. She presented high-level anti-thyroperoxydase antibodies (600 IU/ml) and normal cardiologic evaluation (echocardiography and electrocardiogram). The karyotype revealed a mosaic turner syndrome, mos 45, X /46, XX. She presented after that evaluation with a spontaneous pregnancy with a negative blood screening for fetal aneuploidy at 14 weeks of pregnancy. Genetic counselling was performed and included options for future fertility, such as IVF, oocyte cryopreservation and Preimplantation Genetic Diagnosis (PGD). A healthy male infant was born at 39 weeks of gestation after caesarean surgery and precautious cardiac monitoring was performed during pregnancy.

Conclusion: Recurrent miscarriages and subtle short stature were the specific features of our clinical case. Genetic and fertility counselling were crucial for an adapted follow-up during the pregnancy and the establishment of strategies concerning future conceptions.

Introduction

TS (Turner Syndrome) prevalence has been reported with an incidence of 1 in 2500 live births and is one of the most common chromosomal abnormalities worldwide [1,2]. The classic form of Turner syndrome is associated with a 45,X karyotype, accounting for approximately half of all cases. Twenty-five (25%) have a partial deletion of one X chromosome and 20% carry varying degrees of mosaicism, most commonly a 45,X/46,XX karyotype [3]. A majority of women with Turner syndrome develop accelerated follicular atresia that predisposes them to primary amenorrhea, premature ovarian failure, and infertility later on in their lives. Mosaic cases have milder phenotypic features compared to pure 45, X cases and may show normal pubertal development and regular menstruation. In that case, the diagnosis is often established later than in the pure form of Turner syndrome, while timely fertility counselling and exploration of fertility preservation options are crucial [4]. Furthermore, TS patients' pregnancy is associated with high risks of maternal mortality due to cardiovascular and metabolic complications, spontaneous abortion, and karyotype abnormalities of the fetus. Cases of pregnancy in mosaic TS are rare, and most of the knowledge concerning reproductive and obstetric outcomes relies on case reports and case series [5]. Appropriate management of that cases include adapted genetic and fertility counselling. The greater number of reported cases in that feature and the new benefits from the practice of assisted reproductive technologies has brought new insight on genetic and fertility counselling for that patient. Our study aimed to present a case of spontaneous pregnancy after three consecutive miscarriages in a mosaic TS and report the recent recommendations emitted in the literature concerning genetic counselling in that entity.

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Case Presentation

A 31-year-old patient was referred to our cytogenetic and reproductive laboratory with a history of recurrent miscarriages characterized by three an embryonic pregnancy (blighted ovum), diagnosed around 5 to 7 weeks of pregnancy. Our patient was measured at 155 cm and 55 kg, respectively. Her menarche has occurred at the age of 14 years, and her menstruation has been claimed to be in a regular cycle (with a cycle of 26–28 days). Blood pressure was normal, ranging between 100/70 mmHg and 120/80 mmHg. The level of antibodies was elevated (600 IU/mL) compared to normal ranges in the laboratory, but our patient remains euthyroid. She just presented with a low level of vitamin D that was corrected, and she also benefits from a folic acid prescription. Blood screening tests (cytomegalovirus, rubella, Toxoplasma gondii antibodies, total blood cell count, blood biochemistry, and haemoglobin electrophoresis), glucose tolerance tests, urinalysis, and general urine culture were all normal. An ultrasound of the abdomen and pelvis revealed normal anatomy for the uterus and ovaries. Echocardiography showed a normal aorta and aortic valve. Ophthalmologic examination and audiography were normal. Her karyotype revealed a mosaicism: TS, mos 45, X [6], 46, XX. [7].

Two months after this exploration and prescription, in the context of amenorrhea, the ultrasound detected 7 weeks of gestation with an apparently healthy embryo. Nuchal translucency was measured at 1.2mm during the ultrasound performed at 13 weeks of pregnancy. The karyotype of her partner was normal, 46, XY. Our patient benefits from a blood screening for fetal

aneuploidy at 14 weeks of pregnancy. The couple was informed about general fertility outcomes concerning mos TS and options concerning IVF as oocyte cry conservation and Preimpletation Genetic Diagnosis (PGD) for future fertility projects. Special attention was paid on cardiovascular health during pregnancy. Blood pressure was normal, so was the echocardiography and the electrocardiogram that were offered during the first trimester of the pregnancy and the third one, before the caesarean section. A healthy male infant was born at 39 weeks of gestation after caesarean surgery.

Discussion

Frequencies, fertility outcomes and prognostic

Only 5.2% of women with Turner syndrome achieve spontaneous conception, and most patients (76.7%) present with a 45,X/46,XX karyotype [2]. Live birth and abortion were found to be 32.6 and 67.3% in a cohort of mosaic Turner's syndrome evaluated by a review of the literature and a cross-sectional study of 22 cases, respectively [5]. Only a few patients conceived in the first two years consecutive to their marriage. Pregnancy in TS occurs relatively rarely, being observed in only 4.8–7.6% of affected women [8].

Correlation phenotype genotype correlation

Mos TS can present a normal phenotype with a shorter height, and this short stature seems to be the main clinical manifestation in the mosaic form [3,9], as was the case for our patient. According to Kruk K [8], Turner syndrome mosaicism presents itself uncommonly to primary care providers, who often fail to recognize its subtle signs. Mosaics are diagnosed later than 45,X cases (generally, 8 years later) and the standard Karyotype can miss low-level X monosomy [10]. On the other hand, abnormal chromosomal findings can be absent in blood and be present in some other tissue [11,12]. More than half of individuals who are diagnosed with TS have detectable mosaicism in their peripheral blood karyotypes. The impact of mosaicism on TS-related cardiovascular, endocrine, autoimmune, and reproductive phenotypes is incompletely understood [13]. Cardiac complications such as coarctation or dissection of the aorta, myocardial infarction, hypertension and eclampsia are frequently reported in the pure form 45,X. In the case of, 45,X/46,XX mosaic forms, cardiovascular complications are rarely reported [14].

Mosaicism seems to mitigate the TS phenotype and the cardiovascular risk factor profile [15]. The is chromosome Xq karyotype has a higher association with diabetes mellitus [16]. Pathological features like hypo gonadotropic hypogonadism are more likely to be reported in the pure form than in the mosaic form [17].

Genetic counselling

It is usually explained to patients that TS is a rare disease that appears randomly. Knowledge about molecular processes is improving in the field of genetics. Some genes on the X chromosome that escape inactivation have been implicated, and recently, it has also been demonstrated that epigenetics could explain the variability in the presentation of the disease [18].

Tuke MA, et al. [14], suggest that the clinical management of women with 45,X/46,XX mosaicism should be minimal, particularly those identified incidentally. Indeed, women with a mosaic 45,X/46,XX were less short and had no reported cardiovascular complications. The presence of mosaic TS *vs.* an 45,X karyotype may carry fewer risks for associated morbidity, including reproductive health. However, women with mosaic TS continue to demonstrate higher than background rates of hypertension, hypothyroidism, bicuspid aortic valve and short stature [19].

Inheritance

Turner syndrome can be inherited from mother to daughter, even though there is an increase in the incidence of spontaneous abortion in these patients [10]. The prediction model for inheritance is very difficult to establish because of tissue mosaicism, particularly in mosaicism TS [11]. The author explains that compared to the general population, there is an increased risk for the offspring's in terms of TS (15% *vs.* 0.5%) and for T21 21 (4% *vs.* 0.4%), justifying T21 screening despite the fact that there is a limitation to screening tests for the common chromosomal abnormalities in TS.

Fertility counselling

Fertily counselling concern oocyte preservation, ART procedure and practice of PGD.

Oocyte preservation

In, 2023, Lundgaard Riis M, et al. [20], provided recent insights about the timing of accelerated fetal germ cell loss in a human study. Indeed, knowledge about the biological mechanism of POI (Premature Ovarian failure) in girls with TS is clinically useful for fertility preservation strategies. That is the reason why early fertility counselling at the onset of spontaneous puberty is strongly recommended [18,21].

TS adolescents should be referred during transition to adulthood for FP counselling to avoid referral delay and limit time-related diminished ovarian reserve [22]. Fertility prognostic seems better for mosaic 45, X/46, XX. Classic turner syndrome phenotype, including short stature and primary amenorrhea. In contrast, women with mosaic 45, X/46, XX were less short and had a normal reproductive lifespan and birth rate. Mosaic TS with spontaneous menarche have the highest likelihood of conceiving without ART even if there are improved chances for future pregnancy with fertility preservation [21].

ART

In Vitro Fertilization (IVF) is the most commonly used method for patients with TS [3]. Even with a good ovarian response, IVF outcomes can be very poor, marked by oocyte immaturity Moore [22]. The first live birth achieved using cryopreserved oocytes with mosaic TS was reported in 2022 [23]. With IVF, the fertility prognosis for mosaic TS has evolved and according to Acet F, et al. review [11], the pregnancy rates in the low-grade and high-grade mosaic Turner syndrome patients' cycles were recorded to be between 30.8% and 30% respectively.

There would be a probable correlation between a high number of retrieved oocytes and a successful ovarian response to stimulation, which may be due to cryptic ovarian mosaicism [24]. Some authors, like Ito A, et al. [25], demonstrated all the interest of duostim in fertility preservation for women with TS.

PGD

Better outcomes in pregnancy were reported after preimplantation cytogenetic analysis of the embryos [25]. According to Borini A and Coticchio G [26] and Giles J, et al. [27], PGTA is considered a valid treatment option as an alternative to oocyte donation, especially if associated with strategies of embryo accumulation. We still don't clearly know how the degree of mosaicism can affect the results and that is the reason why Borini A and Coticchio G [26] suggests that future investigations should require a more precise karyotypic definition of the study population.

Conclusion

Spontaneous pregnancy in mos is very rare but possible. Recurrent miscarriages and a subtile short stature were the specific features of our clinical case. Our patient could achieve a normal pregnancy without major complications. Nevertheless, the early diagnosis of that genetic condition was strategic for an adapted follow-up during pregnancy, including cardiovascular monitoring to prevent complications. In our case, counselling was offered to the patient with all the possible upcoming options for fertility, i.e. oocyte preservation and preimplantation genetic diagnosis, through Assisted Reproductive Techniques (ART) procedures.

Ethical Considerations

Ethical principles were considered in this article, and the participants were informed about the purpose of the research and the confidentiality of their information.

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Conflict of Interest

The authors declared no conflict of interest.

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