Case Report

Comprehensive medical treatment of women with Turner syndrome may improve pregnancy outcomes: A case report

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Abstract. A 35-year-old primiparous woman was diagnosed with Turner syndrome at the age of 12 yr due to short stature. Her karyotype showed a mosaic pattern [45, X(19)/46, XX(11)]. She had been followed up by the pediatric service. GH was not prescribed because, although she was of relatively short stature, her growth trajectory was reasonable. She was started on estrogen replacement therapy at 15 yr of age and switched to Kaufmann therapy after 1 yr. After transitioning her care to the gynecology service at 20 yr of age, she was screened for complications and Kaufmann therapy was continued. No abnormalities were detected in the pre-pregnancy screening. She conceived by *in vitro* fertilization and embryo transplantation with oocyte donation. No severe complications occurred during gestation, and she gave birth to a female neonate vaginally at 41 wk and 6 d of gestation. The neonate's birthweight was 3166 g, and her Apgar scores were 8 and 9 at 1 and 5 min, respectively. No severe complications occurred during the postpartum period. Comprehensive medical treatment and appropriate transition from pediatric to adult services may improve the pregnancy outcomes of women with Turner syndrome.

Key words: Turner syndrome, pregnancy, transition, GH, estrogen

Introduction

The rate of spontaneous pregnancy among women with Turner syndrome (TS) is about 2–5%

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(1), with a higher rate of spontaneous abortion than that of the general population (2). The advancement of reproductive medicine in recent years has resulted in an increased number of successful pregnancies and deliveries among women with TS. The pregnancy rate of patients receiving donated oocytes is the same among women with and without TS (3). On the other hand, complications during the perinatal period are more common in women with TS than in the general population (4, 5), and more than 80% of pregnant women with TS who received donated oocytes delivered their babies by cesarean section (CS) (4). Recently, the importance of

Fig. 1. Schematic showing the course of clinical practice and transition from pediatric to adult services.

transition and continuing medical care from childhood and adolescence to adulthood has been highlighted in the management of women with TS (6). Transition, defined as an uninterrupted, coordinated, developmentally appropriate, psychosocially sound, and comprehensive process that is needed for children with special health care needs, includes the transfer from pediatric to adult services (7). However, this has not yet been implemented in the current medical system (8), which may explain the poor pregnancy outcomes of women with TS.

Here we report the case of a woman who was diagnosed with TS in childhood, received appropriate comprehensive medical treatment, and was able to deliver vaginally without severe complications.

Case

Our case is that of a 35-yr-old primiparous woman. Her height was 151 cm, non-pregnant body weight was 48 kg, and body mass index was 21.1 kg/m². She was diagnosed with TS at the age of 12 yr due to her short stature, and her karyotype showed a mosaic pattern [45, X(19)/46, XX(11)]. She had been followed up by the pediatric service. GH was not prescribed because, although she was of relatively short stature, her growth trajectory was reasonable. She was started on estrogen replacement therapy (ERT) at the age

of 15 yr and switched to Kaufmann therapy a year later. Her first menstruation was induced by the hormone therapy. At 20 yr of age, she was transferred to the gynecology service, where she was screened for complications, and the Kaufmann therapy was continued (Fig. 1). During follow-up, bone mineral density (BMD) of the lumbar vertebrae (L2–4) was found to be 0.709 g/cm² (%YAM 71%) and osteopenia was detected, so vitamin D was orally administered. There were no other complications related to the TS, such as hearing defects, occult blood in the urine, ptosis, or neurocognitive or psychosocial issues. At 29 yr of age, she married and wished to start fertility treatment. At that time, her blood pressure was 107/67 mmHg, which was within the normal range. Her uterus length was 6.6 cm, which was an average length for an adult female. Echocardiography and thoracoabdominal magnetic resonance imaging (MRI) were performed for cardiovascular disease screening before pregnancy; the findings were unremarkable. No abnormalities were found on endocrine function tests, including thyroid function and glucose tolerance. Based on the unremarkable pre-pregnancy screening, she was offered a trial ovulation induction, but this failed. At the age of 28 yr, her anti-Müllerian hormone (AMH) value was 0.55 ng/mL. The mean and 10th percentile of AMH at 28 yr of age in the general population were 3.94 and 1.23 ng/mL,

respectively; thus, her AMH level was extremely low (9, 10). Consequently, she was diagnosed with premature ovarian failure and offered donated oocytes in an attempt to induce conception.

At 33 yr of age, she conceived by *in vitro* fertilization and embryo transplantation with oocyte donation but had a miscarriage. She conceived in the same way again at 35 yr of age. She presented to the outpatient clinic of our perinatal center at 6 wk and 4 d of gestation and continued her prenatal care in our center. After the first visit to our department, we recommended that she check her blood pressure at home and continue until delivery. Her blood pressure remained within the normal range. She was screened for impaired glucose tolerance with a 75-g oral glucose tolerance test at 12 wk of gestation and a 50-g glucose challenge test at 25 wk of gestation; the findings were normal. No abnormality was observed on maternal echocardiography at 21 wk and 33 wk of gestation. Fetal growth was good with no restrictions. Because there are many reports of CS due to cephalopelvic disproportion (CPD) in women with TS, pelvimetry using the Guthmann-Martius method was performed at 36 wk of gestation, but this did not reveal a narrow pelvis. A trial vaginal delivery was chosen given the absence of indications for CS. At 41 wk and 6 d of gestation, spontaneous labor ensued. Despite a fully dilated uterine cervix, delivery did not progress from station +2. Thus, a pair of forceps was used to deliver the neonate vaginally. The female neonate had a birthweight of 3166 g and Apgar scores of 8 and 9 at 1 and 5 min, respectively. The maternal BMD of the lumbar vertebrae (L2–4) was 0.675 g/cm² (%YAM 66%) on postpartum day 5; therefore, oral vitamin K was administered. There were no significant problems; thus, she continued breastfeeding during the hospitalization and after discharge. No other complications were observed during the postpartum period and she was discharged with her neonate.

Discussion

Here we reported the case of a woman with TS who received appropriate comprehensive medical care and was able to deliver her neonate vaginally. Our findings suggested that comprehensive medical care and appropriate evaluation of complications improve the pregnancy outcomes of women with TS.

TS has an incidence of 1 in 2000 live born girls, and it manifests with various pathologies due to complete or partial deletion of, or mosaic, X chromosomes, including short stature, ovarian dysfunction, hypertension, and impaired glucose tolerance (11). Many of the women with TS are diagnosed in childhood due to their short stature. Afterward, under ideal care, they receive GH if needed and start ERT at the appropriate timing. Various complications, including those related to gynecology and endocrinology, should be checked by adult services (6, 12). The importance of the transition from pediatric to adult services, as well as the importance of checking for complications, has recently been pointed out (12). Our patient was diagnosed with TS at the age of 12 yr due to her short stature and received appropriate medical intervention, including initiating ERT at the appropriate timing under the pediatric service. Transfer to the adult service was smooth and the comprehensive medical care was continued. One report suggests that starting ERT at the appropriate timing leads to the acquisition of bone mass and adequate uterine volume for pregnancy (13). In our case, because ERT was started at the appropriate timing, her uterus length before starting infertility treatment was 6.6 cm, comparable to the 6–8 cm observed in the general population (14). Thus, an adequate uterine volume for pregnancy was achieved and she was a candidate for infertility treatment. This clinical course suggests that appropriate ERT may prevent fetal growth restrictions and preterm birth.

Perinatal complications of women with TS are diverse. In a report of perinatal complications

in women with TS conceiving by oocyte donation, 20.5% of 122 pregnant patients had preeclampsia; fatal complications including aortic dissection occurred in 4 cases (4). One of the fatal complications during pregnancy in women with TS is aortic dissection/rupture, with a mortality rate of 2% (5). Therefore, in women with TS who are considering pregnancy, screening for cardiovascular disease using echocardiography and thoracoabdominal MRI before pregnancy is crucial. In our case, these tests were performed before pregnancy and their findings were unremarkable. Women with TS are at high risk of developing hypertension, impaired glucose tolerance, and thyroid disease (11); hence, they are more prone to hypertensive disorders of pregnancy, preeclampsia, and gestational diabetes mellitus (15) and should be evaluated for these complications appropriately. Our patient received a 75-g oral glucose tolerance test at 12 wk of gestation and a 50-g glucose challenge test at 25 wk of gestation as screening for impaired glucose tolerance, and both were unremarkable. We advised her to check her blood pressure at home during the pregnancy; the values remained within the normal range. As a screening for cardiovascular diseases, echocardiography was conducted at 21 and 33 wk of gestation, and no abnormalities were found.

Some reports suggest that women with TS have a higher proportion of CS than the general population. Hagman *et al.* reported that, among 122 pregnancies by oocyte donation, 100 (82.0%) delivered by CS (4). Similarly, Bernald *et al.* reported that, among 30 spontaneous pregnancies, 14 patients (46.7%) delivered by CS (2). The major reasons for CS were CPD and breech presentation. Although the proportion of CS in developed countries has been increasing in recent years, it remains higher in women with TS than in the general population. In our case, the patient was not extremely short at pregnancy (height, 151 cm). In addition, pelvimetry was performed by the Guthmann-Martius method at 36 wk of gestation with no suggestion of a

narrow pelvis. These findings suggest that the administration of hormonal therapy at an appropriate time contributes to improving pelvic morphology and decreases CPD and breech presentation in women with TS.

Women with TS are at a high risk of developing osteoporosis (12), and their bone metabolism during the perinatal period must be considered. In the postpartum lactation period, bone resorption is enhanced, decreasing bone mass (16). It is necessary for women with TS to undergo a BMD evaluation during the postpartum lactation period, and appropriate treatment or stopping breastfeeding should be considered if needed. In our case, we evaluated the BMD and performed the appropriate intervention in the course of transition, and we were able to maintain her BMD levels in the mild osteopenia range. BMD evaluated on postpartum day 5 was low (0.675 g/cm^2 , %YAM 66%). Vitamin K was administered orally. There was no subsequent deterioration in BMD, and breastfeeding was continued. In the recent clinical practice guideline for women with TS, the need to assess bone metabolism in childhood was described (17). In our case, information about bone metabolism was insufficient and osteopenia was detected before pregnancy. If there were a better transition with respect to bone metabolism between childhood and adolescence, there would be greater improvement in the bone metabolism of women with TS.

Due to advancements, such as oocyte donation, in reproductive medicine, pregnancies and deliveries in patients with TS are expected to increase. Nevertheless, women with TS are at a higher risk of pregnancy-related complications, and appropriate assessment and management of these complications are crucial. Improvements in pregnancy outcomes can be expected as a result of appropriate comprehensive medical treatment from childhood to adulthood. Thus, a smooth multi-disciplinary approach, including transition from pediatric to adult services, is mandatory.

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