CEOG Clinical and Experimental Obstetrics & Gynecology

Treatment using tadalafil for dichorionic diamniotic twin pregnancy with fetal growth restriction

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Summary

Fetal growth restriction (FGR) is the most important cause of perinatal morbidity and mortality in developed countries. Clinicians are often forced to end the pregnancy due to fetal indications, inflicting iatrogenic prematurity on a fetus with associated high risk of adverse neonatal outcomes. Here, the authors report a case of dichorionic diamniotic (DD) twin pregnancy with FGR whose pregnancy was successfully prolonged using tadalafil, a phosphodiesterase 5 inhibitor. A 22-year-old primigravid woman presented at 25 5/7 weeks of gestation with DD twin pregnancy with FGR. Tadalafil administration was begun at this time. Her pregnancy was prolonged by 90 days after initiation of tadalafil. Tadalafil may be a novel treatment to prolong the period of pregnancy in cases of DD twin pregnancy with FGR and threatened premature labor.

Key words: Dichorionic diamniotic twin pregnancy; Fetal growth restriction; Tadalafil; Threatened premature labor.

Introduction

Fetal growth restriction (FGR) is the most important cause of perinatal morbidity and mortality in developed countries [1]. Clinicians are often forced to end the pregnancy due to fetal indications, inflicting iatrogenic prematurity on a fetus with associated high risk of adverse neonatal outcomes [2].

There are few reports regarding use of sildenafil citrate, a phosphodiesterase (PDE) 5 inhibitor, for treatment of FGR [3-5]. PDE5 is an intracellular second messenger that degrades cyclic guanosine monophosphate (cGMP), which is responsible for regulating intracellular calcium efflux and vascular smooth muscle relaxation [6]. A previous study in rats reported that sildenafil citrate reversed the effects of FGR by improving uteroplacental and fetal perfusion [3]. In addition, there is currently one ongoing randomized, controlled trial using sildenafil citrate for treatment of FGR [5]. PDE5 inhibitors inhibit PDE5 enzymatic activity, thereby sustaining increased concentrations of intracellular cGMP, resulting in vasodilation and increased blood flow [5, 6]. PDE5 inhibitors have been reported to increase uterine arterial and fetoplacental perfusion [6], and seem to be safe and effective for treatment of FGR [7, 8].

Here, the authors report a case of dichorionic diamniotic (DD) twin pregnancy with FGR whose pregnancy was successfully prolonged using the PDE5 inhibitor tadalafil.

Case Report

A 22-year-old primigravid woman presented at 23 5/7 weeks of gestation with DD twin pregnancy and FGR, as defined by

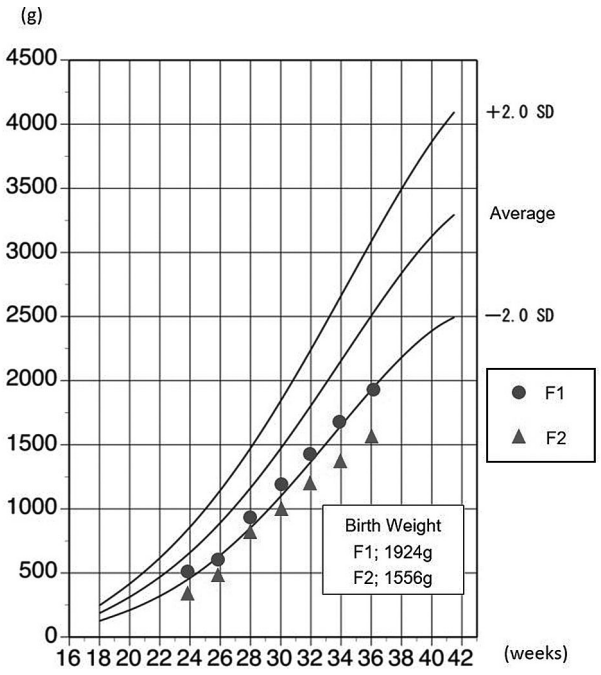

Figure 1. — Course of estimated fetal body weight (EFBW) measured by using ultrasonography. Fetal growth increased after two weeks of tadalafil administration compared with two weeks before administration (F1: 6.0 g/day *vs.* 17.0 g/day; F2: 4.1 g/day *vs.* 18.2 g/day).

Revised manuscript accepted for publication July 19, 2017

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLV, n. 4, 2018
doi: 10.12891/ceog4340.2018

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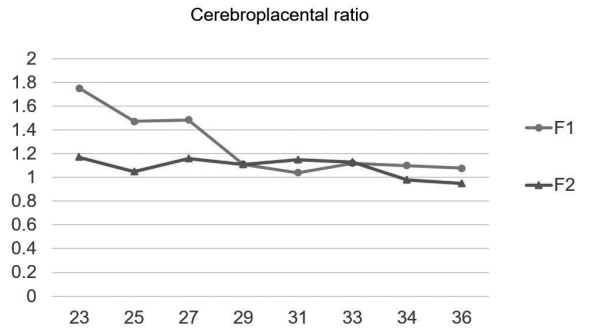

Figure 2. — Course of cerebroplacental ratio. Cerebroplacental ratio of both fetuses increased after two weeks of tadalafil administration.

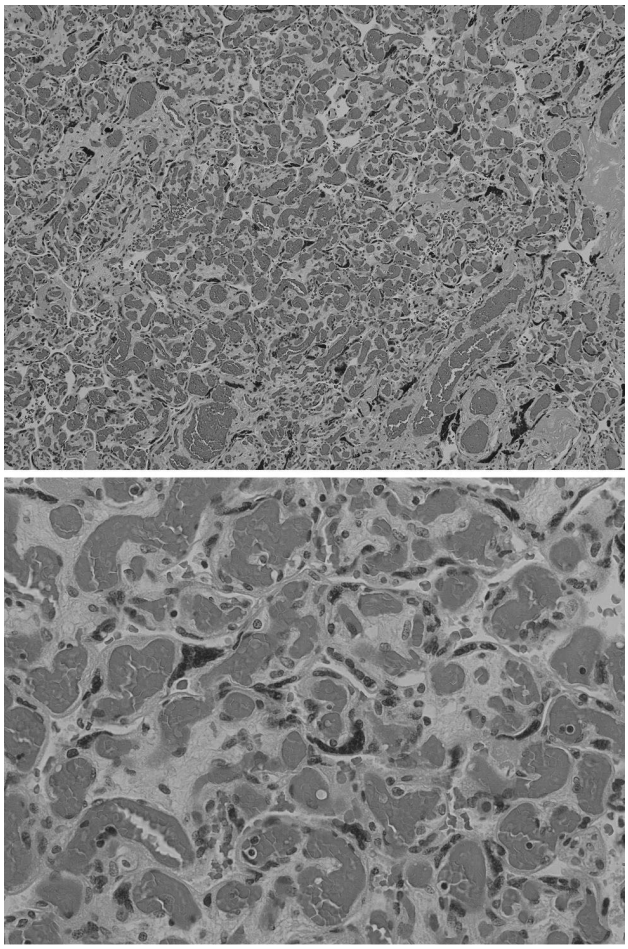

Figure 3. — Pathologic findings of the placenta using hematoxylin and eosin staining. Capillary blood vessels in the stroma of the villi show dilation due to congestion.

American College of Obstetricians and Gynecologists guidelines [9, 10]. Her height was 146 cm, weight was 38.5 kg, and body mass index (BMI) was 18.0 kg/m^2. She received regular antenatal care and estimated fetal body weight (EFBW) was within normal range through 21 5/7 weeks of gestation. Her fetuses (F1, F2) were diagnosed with FGR at 23 5/7 weeks of gestation at a regular antenatal care appointment. At 25 5/7 weeks of gestation, she was admitted to the present tertiary perinatal care center and administration of tadalafil (20 mg/day) was begun. At this time, in utero growth showed normal cerebroplacental ratio (F1: 1.47; F2: 1.05), maximum vertical pocket (F1: 4.24 cm; F2: 3.85 cm), and fetal heart rate patterns. Regular fetal assessments, including measurements of fetal growth, Doppler imaging, and cardiotocography, were performed.

Fetal growth was increased after two weeks of tadalafil administration compared with two weeks before administration (F1: 6.0 g/day *vs.* 17.0 g/day; F2: 4.1 g/day *vs.* 18.2 g/day) (Figure 1). Subsequently, F1 grew along the lines of –2.0 SDs, while F2 showed mild deceleration of growth from 30 weeks of gestation (Figure 2). In utero growth was maintained during treatment, with cerebroplacental ratio >1, normal amniotic fluid indices, and normal fetal heart rate patterns in both fetuses. Course of cerebroplacental ratio is shown Figure 2. Cerebroplacental ratio of both fetuses was increased after two weeks of tadalafil administration. After that, cerebroplacental ratio of both fetuses showed a decrease, and was <1 in F2 at 36 weeks of gestation.

Although the patient had low BMI and multiple pregnancy as two risk factors for threatened premature labor (TPL) [11], no short cervix was observed and no tocolysis was required during treatment. She delivered by cesarian section at 36 4/7 weeks of gestation and was briefly admitted to the neonatal unit, but had no major complications. Indications for cesarian section were labor onset and abnormal fetal position (F1: vertex; F2: breech). Both neonates were female, F1 weighed 1924 grams, and F2 weighed 1556 grams. Overall, her pregnancy was prolonged by 90 days after initiation of tadalafil. Umbilical cord insertion of both fetuses was velamentous. Cause of FGR in both fetus was velamentous insertion as suggested. Pathologic examination of the placenta using hematoxylin and eosin (HE) staining showed that capillary blood vessels in the stroma of the villi were dilated due to congestion (Figure 3). Maternal at delivery, and cord blood of F1 and F2 blood concentrations were 56.96 ng/mL, 32.76 ng/mL, and 69.16 ng/mL, respectively. No significant maternal or fetal adverse events were observed during treatment.

Discussion

Currently, there is no effective treatment for FGR and no validated criteria for termination of pregnancy due to FGR. In this case, the authors demonstrated the ability to prolong the period of pregnancy by 90 days in a case of DD twin pregnancy with FGR using tadalafil. In particular, fetal growth increased after two weeks of tadalafil administration compared with two weeks before administration. This increase in gestation time vastly improved the neonatal outcomes. In addition, although this case had low BMI and multiple pregnancy as two risk factors for TPL, her pregnancy was maintained for 36 weeks of gestation without tocolysis.

FGR results from decreased placental blood flow manifested by placental ischemia, umbilical factors, etc [1, 2]. Tadalafil causes dilation of blood vessels due to degrading cGMP [6], and as such, has the potential to improve decreased placental blood flow. Dastjerdi *et al.*, in a previous rat study, reported that PDE5 inhibitor increased fetopla-

cental perfusion due to vasodilation [6]. In the present case, hematoxylin and eosin staining of the placenta showed that capillary blood vessels in the stroma of the villi were similarly dilated. Fetal growth increased after two weeks of tadalafil administration, but began to decrease from 30 weeks of gestation. In another case using tadalafil for treatment of FGR, maternal blood concentration of tadalafil at delivery was low compared with the present report [8]. In twin pregnancy, a dose of tadalafil of 20 mg/day may be sufficient to show a beneficial effect on fetal growth from 30 weeks of gestation, at 40% to 45% above normal circulation volume.

High doses of sildenafil citrate have been shown to inhibit myometrial contractions [12]. However, it has been suggested that the effect on uterine smooth muscle may not be mediated by a conventional dose of sildenafil citrate [12]. Although PDE5 enzymes are widely distributed in blood vessels, tadalafil is particularly selective of PDE5 enzymes found in reproductive organs [13]. Therefore, compared with sildenafil citrate, tadalafil may provide a better therapeutic benefit to TPL.

In conclusion, the authors presented a case showing temporary improvement of fetal growth following administration of tadalafil. Most importantly, tadalafil sufficiently enabled pregnancy prolongation, which improved the neonatal outcomes in DD twin pregnancy with FGR.

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