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Case Report

Effects of tadalafil on the uterine artery of fetal growth restriction

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Summary

Fetal growth restriction (FGR) is the most important cause of perinatal morbidity and mortality during the perinatal period. However, there is no established standard regarding the appropriate delivery time or treatment methods for fetuses with FGR. Reduced uterine arterial blood flow has been reported with FGR; however, if this is improved, then FGR may also be improved. Phosphodiesterase 5 inhibitors have vasodilating actions. When administered to the mother, they may improve FGR by improving fetal placental blood flow through improvements in uterine arterial blood flow.

Key words: Uterine artery bold flow; Fetal growth restriction; PDE5 inhibitor; Tadalafil; Fetus.

Introduction

Fetal growth restriction (FGR) is the most important cause of perinatal morbidity and mortality in developed countries [1]. However, there is no consensus regarding FGR management. Therefore, it is important to evaluate fetal well-being and how long the pregnancy can be extended to allow organ maturity. However, there are situations when the fetus should be delivered despite immaturity. For these premature infants with FGR, the postnatal risk is high; however, the mortality and morbidity associated with chronic lung disease, necrotizing enterocolitis, and sepsis are higher for premature infants without FGR than those for premature infants with FGR [2]. Premature birth increases the mortality rate associated with immaturity, but delaying the delivery time increases the risk of intrauterine fetal death due to continuing the pregnancy in an inappropriate uterine environment. For early-onset FGR diagnosed prior to 32 weeks of gestation, the current treatment is induced labor, thereby causing a dilemma for obstetricians [3]. Although several randomized control trials have examined the possible promotion of fetal growth using interventions in mothers, beneficial effects on fetal development have not been reported [4-6]; therefore, there is no fetal treatment for FGR [7].

One report suggested decreased blood flow in the uterine artery with FGR [8]. Therefore, it is possible that improving the uterine arterial blood flow may become an established treatment method for FGR. One way to improve the uterine arterial blood flow may be by improving the placental blood flow with vasodilation using a phosphodiesterase 5 (PDE5) inhibitor. PDE5 inhibitors act on cyclic guanosine monophosphate (cGMP) to relax vascular smooth muscle and increase blood flow. Doppler evaluation of the uterine artery blood flow using ultrasonic tomography to evaluate the placental blood flow is available. This is the only clinical method of evaluating placental perfusion in vivo. Blood flow to the pregnant uterus flows into the intervillous space after flowing into the helical artery via the uterine artery and its branch vessels. When FGR is caused by abnormal formation of the spiral artery, these measurements will be abnormal. Color Doppler imaging makes it possible to clearly distinguish the uterine artery because of its improved reproducibility of blood flow; therefore, it is believed that the uterine artery blood flow can be sufficiently evaluated by ultrasonic tomography [9]. The authors report changes in the uterine artery blood flow after using PDE5 inhibitors for FGR.

Case Report

A 26-year-old woman (gravida 1, para 1) presented at 30 3/7 weeks of gestation with FGR. Her height was 153 cm, weight was 47 kg (pre-pregnancy body weight was 43 kg), and body mass index was 18.3. Her previous pregnancy was delivered via cesarean because of non-reassuring fetal status. There was no obvious cause of FGR. After achieving a spontaneous pregnancy, the patient had no abnormality during the course of her prenatal examinations. The estimated fetal weight was 1215 g (standard deviation [SD] −2.0). FGR was diagnosed because the SD was lower than -1.5 on the fetal growth curve, prepared according to the standardized ultrasonic fetal measurements (Japanese standard) recommended by the Ultrasonic Society of Japan [12]. There were no maternal infections that could have caused FGR, and fetal malformations were not observed. No abnormality was found in the placenta or umbilical cord. Oral administration of tadalafil 20 mg/day was started at 32 0/7 weeks of gestation to improve the placental blood flow. The authors measured the uterine arterial blood flow before beginning oral administration every week and plotted the median values of the uterine arterial blood flow rates according to blood flow changes that occurred over the course of

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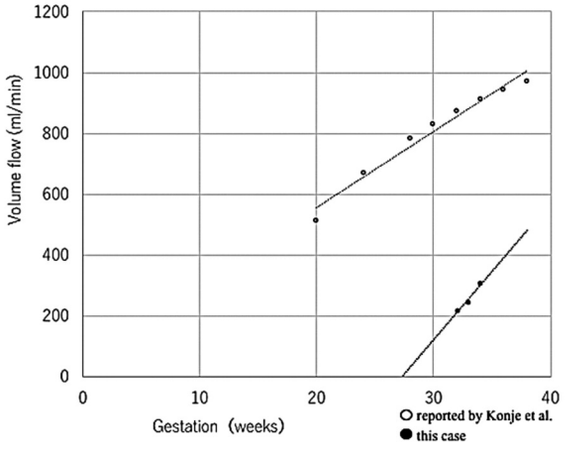

Figure 1. — Changes in uterine arterial blood flow after oral administration of tadalafil are shown.
Upper graph: Standard changes in uterine arterial blood flow that occurred with each gestational week, as reported by Konje *et al.*
Lower graph: The changes in uterine arterial blood flow of this case.

gestation. Although the uterine arterial blood flow before commencement of oral administration decreased considerably compared to the standard, the rate of increase in uterine arterial blood flow after oral administration of tadalafil was higher than the median change in uterine arterial blood flow reported by Konje *et al.* [11] (Figure1). After oral administration, side effects were not observed in the mother or fetus. Labor began at 34 5/7 weeks of gestation. An emergency cesarean delivery was performed because of her history. She delivered a baby boy with a birth weight of 1,890 grams. After birth, he was managed in the neonatal intensive care unit. Umbilical arterial blood gas analysis results were as follows: pH, 7.244, pCO_2, 50.2 mmHg, pO_2, 36.5 mmHg, and base excess (BE), -6.4 mmol/L. The placenta was 16×15 cm and the placental weight was 350 grams. No apparent infarction or chorioamnionitis was observed during pathological tissue examination.

Before measurements were performed, the mother rested for more than 20 minutes in the semi-recumbent position. It was confirmed that there were no abnormalities in the measured uterine artery waveform. The appropriate waveform is defined by the absence of the following: an increased systolic/diastolic (A/B) ratio (> 2.6), with or without a notch on the uterine artery blood flow velocity waveform or a normal AB (< 2.6) ratio with either a unilateral notch or a bilateral notch on the uterine artery blood flow velocity waveform. The method of visualization of the uterine artery conformed to that of Bower *et al.* [10]: by placing the transducer in the lower lateral quadrant of the uterus and angling it medially, the authors identified crossover of the external iliac artery and placed the range gate over the entire diameter of the uterine artery 1 cm distal to that site. The Doppler waveform was measured during three to six heartbeat cycles, and the median of three measurements was used as the measured value. Using a computer, the left and right uterine arterial blood flow rates were measured as the blood flow velocity and the time-averaged flow velocity (TAV) mean and inner diameter of the uterine artery. Standard changes in uterine arterial blood flow that occurred with each gestational week, as reported by Konje *et al.* [11], were used to evaluate the uterine artery.

The uterine artery Doppler mode was selected when measuring the uterine arteries with a specialized machine. This ensured that settings were as standardized as possible. Pulse repetition frequency was adjusted for each examination to ensure the best fit of the waveforms.

The following preset variables were used: harmonic setting; mid, power; 100%, gain; -3, C7 M5 P3 E3, SRI II; 2, frequency; low, quality; normal, pulse Doppler wall motion filter; 60 Hz, and sample size; 2 mm. The angle correction was measured within 60 degrees.

Discussion

For singleton pregnancies involving FGR without obvious cause, the present authors started oral administration of tadalafil to improve the placental blood flow at 32 0/7 weeks of gestation. Thereafter, a marked increase in uterine arterial blood flow was observed as compared to the standard increase in uterine arterial blood flow that accompanied the increase in the number of gestation weeks. Tadalafil acts on cGMP by inhibiting PDE5 and expanding blood vessels. The authors believe that tadalafil can increase uterine blood flow and fetal growth by improving placental blood flow. This is because the increase in uteroplacental blood flow during pregnancy is due to angiogenesis and vasodilation and contributes to proper fetal growth.

The production and local release of nitric oxide, which stimulates cGMP production, lead to vasodilation in the placenta [13]. Sildenafil, a selective PDE5 inhibitor, has been used to treat pulmonary hypertension in pregnant women and has been shown to improve arterial endothelial function in the uterine muscle of pregnant women with preeclampsia and FGR pregnancies [14]. It has also been suggested to improve perfusion of the placenta and fetus when used to treat pregnancy-related hypertension. The authors administered tadalafil, which has a higher selectivity for PDE5 than sildenafil, especially in the reproductive system, and a longer half-life in cases of FGR [15]. In this case, as the blood flow increased in the uterine artery, estimated body weight also increased. This increase was remarkable compared with the body weight status before tadalafil administration (12.0 g/day: 19 weeks 5 days to 30 weeks 3 days and 223-1,125 grams; 29.0 g/day: 32 weeks 0 days to 34 weeks 5 days and 1,338-1,890 grams).

The weight of the fetus with FGR is closely associated with the long-term prognosis of pregnancy, and the authors believe that increased uterine arterial blood flow may contribute to fetal weight gain. However, it is unknown whether only increased blood flow in the uterine artery contributes to fetal weight gain. In addition, this case showed strong susceptibility to tadalafil and improved uterine arterial blood flow. Therefore, long-term measurements of uterine arterial blood flow may clarify whether the effects of increased uterine arterial blood flow are transient. More cases are needed to evaluate uterine arterial blood flow changes using similar measurement methods.

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