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Sildenafil Citrate in Management of Intrauterine Growth Restriction: A Case Study

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Abstract

Background: In IUGR the fetus fails to achieve its normal growth potential. For achieving optimal fetal growth, an adequate blood flow in uteroplacental vascular bed is essential. Abnormal vasculature adaptations that result in aberrant blood flow have been implicated as a possible cause of IUGR. Sildenafil is a PDE-5 inhibitor. Because of its vasodilator action, it might offer an alternative in the treatment of IUGR by improvement in Doppler velocimetric indices.

Case presentation: In this study a case of pregnancy complicated with IUGR was examined and sildenafil was orally administered to her.

Conclusion: Sildenafil citrate being a vasodilator offers a novel and excellent option in the management of pregnancies complicated with IUGR by improving fetoplacental circulation as evident by improved umbilical artery Doppler indices and improved fetal weight.

Keywords: IUGR; Umbilical Artery Doppler; Sildenafil Citrate

Abbreviatations: IUGR: Intrauterine Growth Restriction; ACOG: American College of Obstetrics and Gynecology; RCOG: Royal College of Obstetrics And Gynecology; SKIMS: Sher-I-Kashmir Institute Of Medical Sciences; RI: Resistive Index; PI: Pulsatility Index; ALP: Alkaline Phosphatase; LFT: Liver Function Test

Introduction

Intrauterine growth restriction (IUGR) is defined as a fetus at or below the 10th percentile in weight for its gestational age as adopted by the American College of Obstetrics and Gynecology (ACOG) and the Royal College of Obstetrics and Gynecology (RCOG). Early-onset IUGR is often associated with high perinatal morbidity and mortality [1]. As placental size, uteroplacental blood flow, and expression of angiogenic and vasoactive factors are altered in pregnancies complicated by IUGR, it has been suggested that therapeutic agents that target placental blood flow might be used in management of such pregnancies [2]. Currently, there is no standard pharmaco-therapy for the management of IUGR, however, few studies conducted so far have suggested the effectiveness of sildenafil in this pregnancy related complication. Sildenafil is a selective PDE-5 inhibitor. It increases uterine blood flow by its vasodilatory action. In this case-study, sildenafil citrate therapy was able to decrease umbilical artery Doppler indices and resulted in favorable neonatal outcome.

Case Presentation

A 29-year-old G3A2 hypothyroid 18week pregnant female attended the OPD of Obstetrics and Gynecology Department, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Medical College and Hospital, for antenatal check up in the month of May 2018. First trimester of pregnancy was normal in course. Patient was asked for a biweekly antenatal follow up. At 20 weeks ultrasonography was performed which was normal without any evidence of fetal anomaly. Repeat USG along with color Doppler was performed at 26 weeks which showed fetal weight of 620 grams. Color Doppler showed raised umbilical artery systolic/diastolic (s/d) ratio of 4.3, resistive index (RI) 0.80 and pulsatility index (PI) 1.88. The Doppler and USG findings were suggestive of placental insufficiency and IUGR. Patient was advised bed rest and sildenafil citrate at 20mg twice a day was prescribed to her. Moreover, the liver function test (LFT) of patient showed raised alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, for which ursodeoxycholic acid 150mg twice a day was prescribed. The patient and her husband were counselled regarding risks and bleak prognosis of the pregnancy.

USG and Doppler were performed weekly to access the fetal parameters. After 4 weeks of starting sildenafil therapy, i.e. at 30 weeks, Doppler showed improved umbilical artery diastolic flow,

s/d ratio of 3.6 RI: 0.74 and PI: 1.71. The fetal weight at 30 weeks was around 1100 grams. After 30 weeks the dose sildenafil was increased to 20mg thrice a day. Repeat USG and Doppler were performed at 32 weeks, which showed further improvement with umbilical artery s/d ratio of 3.1, RI 0.66 and PI: 1.51. The fetal weight at 32weeks was around 1450 grams.

The treatment with sildenafil was continued up to 34th week. Doppler performed at 34th week showed further gradual improvement in uteroplacental perfusion with s/d ratio of 2.9, RI: 0.64 and PI: 1.21. Cesarean was performed at 35th week and normal male child of 2.1kg was delivered. The maternal and neonatal courses were uneventful. The infant was examined by pediatrician and found to be normal.

Discussion

Fetal growth restriction results from the factors which alter uteroplacental perfusion and therefore alter the nutrient delivery to the fetus [3,4]. IUGR has a multifactorial etiology and it is hard to define a specific cause. The onset of IUGR is due to the factors of maternal, fetal and placental origin and an increase in oxidative stress [5]. Maternal factors such as severe maternal malnutrition, underweight at the beginning of gestation and low weight gain during the gestation are the causative factors of IUGR [6]. Chronic maternal stress compromises normal regulation of hormonal activity during gestation, because it increases β-endorphin, glucocorticoids, catecholamines and CRH (corticotrophin-releasing hormone) levels. An excess of the aforementioned hormones, in addition to an increase in cortisol levels, breaks through the placenta and can reduce fetal weight at birth. Catecholamines can also induce vasoconstriction of blood vessels causing placental hypoxia in the fetus [7,8]. In animal models it has been observed that hypoxia induces a decrease of serum vitamin E levels and an increase in thromboxane production [9]. These metabolic alterations are responsible for an abnormal placental development and the decrease in steroid production. All these changes could lead to a feto-placental vascular resistance and an increase of oxidative stress, which could be responsible for the appearance of IUGR [10,11].

The placenta, as a key organ for fetal growth, has a major role in amino acid transport, the most important nutrient for fetal life. During pregnancy, there is an active transport across the placenta from the maternal to the fetal circulation. In IUGR pregnancies, the concentrations of most essential amino acids (valine, leucine and isoleucine) are decreased in fetal tissues but are significantly higher in maternal tissues leading to pregnancy maladaptation [12]. Several studies in animals have shown a significantly reduced uptake of oxygen, glucose and essential amino acids in IUGR pregnancies [13-15]. Also, in vitro study in humans has shown a reduced uptake of leucine and lysine, suggesting a reduced activity of cationic amino acid transporters [12]. Together, this data suggests that the amino acid transport has a key role to play in the fetal development. The deficiency of these amino acid transporters results in IUGR pregnancies [16]. Sildenafil Citrate is a selective PDE-5 inhibitor. It acts by preventing the degradation of the second messenger cyclic guanosine 3′, 5′-monophosphate by the enzyme PDE-5. This results in increased nitric oxide production and consequent vascular smooth muscle relaxation and an increase in vasodilation [17]. It increases uterine blood flow by improving endothelial function of myometrial vessels [18]. Additionally, sildenafil potentiates estrogen induced vasodilation [19]. Various studies have shown that sildenafil improves uteroplacental blood flow which in turn improves fetal weight by increased availability of oxygen and nutrients to fetus [20,21]. In this case study administration of sildenafil improved the umbilical artery indices and fetal weight. A normal baby was delivered with uneventful neonatal follow up.

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