

Case report

Maternal sirolimus therapy and fetal growth restriction

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Abstract

Fetal growth restriction associated with continued maternal sirolimus therapy in pregnancy has not been reported. We hereby present a case of maternal sirolimus therapy resulting in fetal growth restriction and propose a multi-hit model. This hypothetical model is based on inhibition of mTOR signaling pathway and epigenetic modulation. This case report adds to the paucity of literature on continued monotherapeutic maternal sirolimus in pregnancy and its adverse fetal effects.

Keywords: *sirolimus; fetal growth restriction; mTOR*

Introduction

Fetal growth restriction (FGR) is defined as a pathological in utero process whereby the fetus fails to achieve its expected growth potential [1]. Fetal growth is determined by the genetic potential and the supply of nutrients and oxygen [1, 2]. For clinical purposes, causes of FGR are broadly classified as either maternal, fetal and placental. Maternal causes include chronic medical conditions, pre-eclampsia, malnutrition and substance abuse. Fetal causes are chromosomal abnormalities, in utero infections and multiple gestation. The most common cause is the placental insufficiency from a variety of intrinsic or environmental conditions [1]. Roos et al. first described the possible role of mechanistic Target of Rapamycin (mTOR) pathway in regulating fetal growth [3].

Central to fetal growth disorder lies on the molecular mechanism of the mTOR signaling pathway in the placenta and fetal organs [2, 4]. This nutrient sensing pathway is crucial for placental transfer of essential nutrients involved in growth and development of the fetus in utero. Inhibition of the mTOR signaling in placenta and fetal organs is known to result in suboptimal growth. Various sensory inputs such as nutrition, oxygen, endocrine and growth factors modify the signal generated at mTOR pathway and alter the fetal growth trajectory [1, 2, 4].

Case report

A 29-year-old, G2P2 mother was diagnosed with blue rubber bleb nevus syndrome more than five years ago and has had two pregnancies while being treated with sirolimus. These children were small for gestational age at birth and are the focus of this case report. Upon diagnosis of this rare disorder, the patient was treated with oral sirolimus 2mg twice daily. Her cutaneous lesions resolved significantly at 6 months

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follow up. She had a flare up of the lesions when she discontinued treatment before preconception. Her family history is unremarkable. She conceived naturally at one year of sirolimus therapy through a non-consanguineous marriage. Both the partners are of average built and denied tobacco, alcohol or substance use. In view of the previous flare up history following preconception planning, she was advised to continue sirolimus by the treating physician. Prenatal care for the first pregnancy included an ultrasound for determination of gestational age and routine monitoring of possible side effects of sirolimus. Regular blood investigation revealed normal complete blood count, liver and renal functions, sugar and lipid profile. Routine antenatal checkup done at the rural health care center by the Health Assistant were uneventful. Records maintained in the prenatal care book showed normal blood pressure, maternal weight gain, height of fundus corresponding to gestational age and normal hemoglobin level. Fetal ultrasound done at 36 weeks of gestation at the district hospital by a sonographer technician revealed a single live fetus with adequate amniotic fluid and expected fetal weight corresponding to 34 weeks. In view of maternal medical condition, sirolimus therapy and suspected fetal growth restriction, the mother was referred to the tertiary hospital. No gross anomalies were noted on limited anomaly examination and umbilical artery doppler study was within the normal range for the gestational age. At 40 weeks, she delivered a normal live male newborn weighing 2200 grams (<10th percentile on the customized fetal growth chart) with Apgar score of 9 and 10 at 1 and 10 minutes respectively. The baby had poor suckling and presumed physiological jaundice which were managed with intravenous fluid and phototherapy. Neonatal bilirubin and hemoglobin levels were not recorded. At two years of life, the milestones recorded in the child health card were appropriate for the age. The second pregnancy was likewise conceived naturally while the mother was on sirolimus therapy. Early in this pregnancy she was informed of the risks of miscarriage, poor growth and birth defects. Antenatal check up

at the rural health center was unremarkable. Although, referred to the maternal fetal medicine specialist at the national referral hospital, the couple could not make it due to Covid movement restrictions. A live, normal male newborn weighing 2400 grams (<10th percentile on the customized fetal growth chart) was delivered at 39 weeks with Apgar score of 9 and 10 respectively at 1 and 10 minutes respectively. The postnatal period was uneventful. The mother was advised to continue sirolimus following the delivery.

Discussions

Blue rubber bleb nevus syndrome (BRBNS) is predominantly sporadic and rare multiple venous malformations in the skin and internal organs [5]. It is caused by somatic mutations in the TEK gene encoding TIE2 proteins [5]. The few case reports on obstetric outcome in BRBNS has shown optimal neonatal outcome unless the uterine wall or placenta is involved. A case report by Terata et al. described placenta previa in the setting of BRBNS leading to preterm delivery by emergency cesarean section [6]. Our case did not develop placenta previa that could predispose to preterm delivery or fetal growth restriction.

Although small scale studies suggest safety of sirolimus on pregnancy, there is no mention of growth restriction in the fetus [7, 8]. Moreover, the study by Sifontis et al. is limited by polypharmacy and organ transplant conditions [8]. The largest series on sirolimus treatment is maintained with Transplant Pregnancy Registry International 2017 [9]. In this series of 37 pregnant women on sirolimus for different organ transplants, four reported birth defects such as Tetralogy of Fallot, vermian hypoplasia of cerebellum, facial malformations and multiple orofacial defects although the last two cases also had mycophenolate as additional treatment. Regarding pregnancy outcome, 30% of the pregnancies ended in miscarriages although sirolimus cannot be truly indicted due to polypharmacy with mycophenolate in 19 of the pregnancies. The effect on birth weight has not been mentioned in this series. Shen et al. has described three



pregnancies while on sirolimus for lymphangiomyomatosis [10]. However, treatment was discontinued in all cases before the first trimester. None of the fetuses had FGR or congenital malformations. Apart from this series, maternal sirolimus therapy and pregnancy outcome have been reported in few case reports. A case report by Pluym et al. has described FGR in maternal sirolimus therapy for fetal cardiac rhabdomyoma. However, it was unclear whether left ventricular outflow obstruction or the sirolimus therapy was the factor to which FGR could be attributed [11]. Park et al. did not find FGR in their case report and Barnes et al. did not report the birth weight in their case report [12, 13]. In both the cases, maternal sirolimus therapy was started only in the second trimester. Chu et al. also described maternal sirolimus therapy and favorable pregnancy outcome but the treatment was discontinued at 27 weeks of gestation [14]. However, Malatesta et al. described a case of continued maternal sirolimus therapy and a term live baby weighing 2850 grams without any malformation [15].

Sirolimus originally known as rapamycin is used as an anticancer, an immunosuppressant and an antiproliferative agent in various disease conditions. Currently, the FDA mentions sirolimus as category C drug. Although rapidly absorbed, sirolimus has low oral bioavailability due to individual differences in liver and small intestine metabolism with cytochrome P450 3A enzymes. Sirolimus has a wide volume of distribution and is extensively bound to protein giving an elimination half-life of 62 hours [16]. Its wide range of molecular activities are mediated through the inhibition of mTOR pathways via specific intracellular cytoplasmic or nuclear receptor protein complex. Activation of mTOR signaling pathway via mTORC1 and mTORC2 cascades in downstream anabolic actions such as protein and lipid synthesis, regulation of cell cycle through genetic transcription and post-translational modifications [17, 18]. The mTOR1 pathway is involved in cellular growth and proliferation whereas mTOR2 is mainly involved in cellular maturation and survival [4].

At the placental level, mTOR signaling is related to placental transfer of glucose, amino

acids and fatty acids necessary for fetal growth [2, 3, 7]. In placenta and fetal liver, mTOR inhibition due to hypoxia and enhanced amino acid response (AAR) signaling due to amino acid depletion is associated with increased synthesis of insulin-like growth factor binding protein (IGFBP) and its phosphorylation leading to reduced fetal insulin-like growth factor-1 (IGF-1) [2]. Reduced maternal and fetal IGF-1 level leads to diminished cellular hyperplasia and hypertrophy in the fetus [2]. Consequent to placental mTOR inhibition, low amino acid and glucose level in the fetus are known to inhibit mTOR signaling in fetal endocrine pancreas leading to reduced β -cell proliferation and maturation [19]. Subsequently anabolic action of insulin and IGF-1 is diminished causing a growth-restricted fetus. This is an indirect action of mTOR inhibition on fetal endocrine pancreas.

The mechanism of placental transfer of sirolimus is not known. From case reports of maternal sirolimus therapy for fetal conditions, it is obvious that placental transfer takes place [11-13]. Unlike adults, most of the fetuses are susceptible to low serum concentration of sirolimus. Human placentas have little to no cytochrome P450 subenzyme expression or its activity. Even if there is cytochrome P450 3A enzyme in the placenta, it may be resistant to inducing xenobiotics, including sirolimus [18, 20]. Most of the fetuses lack cytochrome P450 3A isoforms in the liver [20, 21]. Based on the enzymology, it is reasonable to infer higher cord blood concentration than maternal level of sirolimus [11, 13, 21].

The direct action of sirolimus on human pancreatic β -cells has been reviewed by Dai et al. [22]. Through mTOR inhibition, transcription, post-translational modification and release of insulin and insulin-like growth factor (IGF) is dysregulated, albeit reversible, on withdrawal of the drug. Sirolimus is also known to increase peripheral insulin resistance via inhibition of insulin receptor substrate (IRS) in adipose tissues [7, 17]. Based on mTOR inhibition of downstream pathways on anabolic effects at the placenta, fetal liver and endocrine pancreas, it is reasonable to explain the growth restriction in our case (Figure 1) [16, 23].



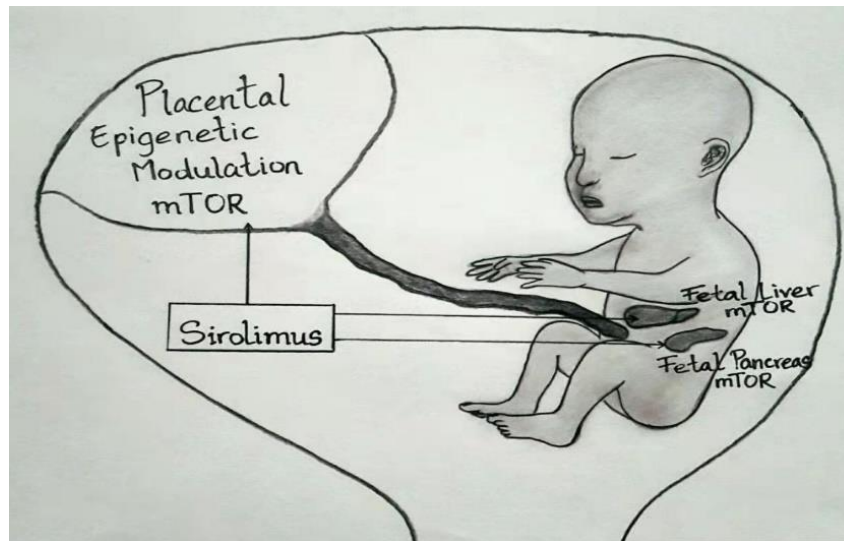


Fig. 1. Maternal sirolimus induced multi hit model and foetal growth restriction

From epigenetic point of view, placental epigenetic changes are known to cause fetal growth restriction [18, 24]. Placental genome methylation is driven by various modulators in relation to fetal growth. DNA methylation changes in placenta can result in altered gene expression leading to diminished levels of growth factors, receptors, enzymes, transport proteins and so on. For example, hypomethylation of H19 and IGF genes resulted in reduced nutrient transporters across the placenta [24]. No direct evidence of sirolimus induced epigenetic changes has been proven in human placenta although experimental animal models clearly demonstrated the changes [25].

The mother in our case did not develop diabetes, hepatic or renal impairment while on long term sirolimus therapy indicating low bioavailability after oral administration from cytochrome P450 enzymatic clearance. These maternal adverse effects would have altered our interpretation on maternal sirolimus and fetal growth restriction. The mother also did not have gastrointestinal vascular lesions on endoscopic examination which, otherwise, could contribute to maternal malabsorption and FGR. Our argument is solely based on mTOR signaling, possible epigenetic changes and fetal growth thereby missing the other placental nutrient signaling pathways such as AMP-activated protein kinase, AKT and

insulin/IGF-1 pathways [4, 26]. Perhaps, the fetal growth restriction in this case was not severe owing to compensatory signaling adjustment of non mTOR pathways. Retrospectively, in view of normal sonographic fetal profile in the 3rd trimester, umbilical Doppler, birth weight and mild neonatal morbidity, a diagnosis of late onset FGR was made in both cases [27]. Simply, we may view this case scenario as a relative nutrient depletion in a setting of normal placental vasculature and circulation.

There are limitations in this case study. This mother had delivered no children who had not been exposed to sirolimus prenatally. Such children might have served as comparison to help exclude other potential factors contributing to FGR in this mother. The Health Assistant at the rural health center failed to appreciate the smaller fundal height, and thus, missed the late onset fetal growth restriction during the first pregnancy. Goto et al. in their meta-analysis reported unreliability of fundal height measurement as primary screening tool to predict fetal growth restriction with sensitivity and specificity of 72% and 73% respectively [28]. Even with use of sonographic parameters, the likelihood of suboptimal fetal growth detection is only 25% on average and the scenario would less accurate in hands of technician sonographer [29]. Our case is also limited by lack of

biochemical markers, absence of serum trough level measurement and the therapeutic range of sirolimus. The mother was advised to breast feed the baby on condition that sirolimus is a FDA category C drug in pregnancy and lactation.

Conclusion

Maternal sirolimus therapy in pregnancy per se could not be associated with fetal teratogenicity. However, its use may lead to fetal growth restriction through possible

placental epigenetic modulation and inhibition of mTOR signaling pathway.

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Competing interests

The authors declare that they have no competing interests.

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