

Sildenafil Citrate – A Potent Solution To Fetal Growth Reduction/ Oligohydramnios

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Abstract- Fetal growth restriction (FGR), is a condition where an unborn baby (fetus), is smaller than what is expected for the number weeks of pregnancy (gestational year). This is usually described as a weight that is less than the 10th per centile. It is a baby whose estimated weight is less than the 10th percentile. An AFI that shows a fluid level less than 5 cm (or the 5th percentile) or a lack of fluid pockets 2-3 cm in depth at 32-36-week gestation would indicate oligohydramnios. It vasodilates myometrial arteries, and increases the amniotic fluid quantity. To provide a comprehensive description of sildenafil Citrate's use in iugr or oligohydramnios, we reviewed the numerous literature sources.

Index Terms- phosphodiesterase5 inhibitor, cyclic guanosine monophosphate, transdermal, cerebroplacental ratio, pre- eclampsia, nitic oxide.

I. INTRODUCTION

Fetal growth restriction, also known as intrauterine growth limitation ([IUGR]), is a term used to describe a fetus who has not reached its potential for growth due to environmental or genetic factors. IUGR can occur due to impaired gas exchange or if the nutrients provided to the fetus do not allow it to thrive normally in utero. This can happen due to any maternal condition that causes a decrease in oxygen-carrying ability (e.g. This can be caused by any maternal disease that reduces oxygen-carrying capacity (e.g., hemoglobinopathy, smoking, cyanotic heart diseases, or hemoglobinopathy) or disorders in the oxygen delivery network secondary to maternal cardiovascular diseases [1].

When there is no rupture of the membranes, oligohydramnios occurs. This is defined by the amniotic fluid index (AFI) being less than 5 cm or the AFI falling below the 5th percentile. The condition affects 3-5% of pregnancies and is caused by ruptured membranes, placental insufficiency, congenital abnormalities, post-term pregnancy, prostaglandin synthase inhibitors, twin-to-twin transfusions, or idiopathic causes.¹

Fetal growth restriction can affect up to 8% in all pregnancies. This includes those with early-onset and late-onset fetal growth restrictions with higher perinatal mortality. Our country has a high burden of IUGR. [2] IUGR is responsible for more than half of all stillbirths. Perinatal mortality accounts for 10%. [2,3] The survival rates of severely-growth-restricted fetuses that are very far from term (28 WEEKS FROM GESTATION) is poor.

II. PATHOPHYSIOLOGY OF IUGR / OLIGOHYDRAMNIOS AND THEIR OUTCOMES-

Perinatal deaths caused by IUGR account for the second highest rate of death after prematurity. It is associated with an increased risk of perinatal complications such as hypoxemia and low Apgar scores. There are also possible adverse effects on neonatal outcomes [3,4].

To determine if a fetus is at risk, an estimated fetal weight of at least 10th percentile must be used. This cannot be used as a cutoff for uteroplacental dysfunction. It is possible that a certain number of fetuses below the 10th per centile are constitutionally small. In terms of follow-up growth, the most popular and easiest method to measure the distance between the pubic bone and the mother's fundus is also a good option. This distance is usually measured in centimeters after the 20th week.

Growth-restricted fetuses increase the risk of intrauterine fatality (IUFD) and may even lead to sequels in childhood. [3].

This is a common problem in pregnancy and can lead to reduced fetal growth. Often, the etiology for IUGR is not known. However, it is possible to identify fetal (infections, malformations and chromosomal aberrations), placental (chorioangioma), infarctions, circumvallated or confined placentas, confined placental mosaicism, obliterative vasculopathy, etc.), In addition to maternal factors, external factors and genetic predetermination of fetal growth affect fetal outcomes, including chronic hypertension, pregestational diabetes, cardiovascular disease, substance abuse, and autoimmune conditions [6-8].

Hemodynamic modifications include maternal uterine, fetal umbilical and middle cerebral arteries, as well as precordial veins to treat cardiac effects of placental dysfunction [9-10]. Circulatory adaptation is characterized by an increase in umbilical artery blood flow resistance and a decrease in middle cerebral artery blood flow resistance [11].

Although the pathophysiology behind oligohydramnios remains elusive, it has been recognized as a sign that chronic suboptimal placental function is present when there is no rupture of membranes.²

III. EFFECT OF SILDENAFIL CITRATE IN IUGR/ OLIGOHYDRAMNIOS-

Despite the serious risks of IUGR-affected pregnancies there is no treatment. Clinicians have no other options but to deliver the baby early, which can lead to increased morbidity or mortality [11-12].

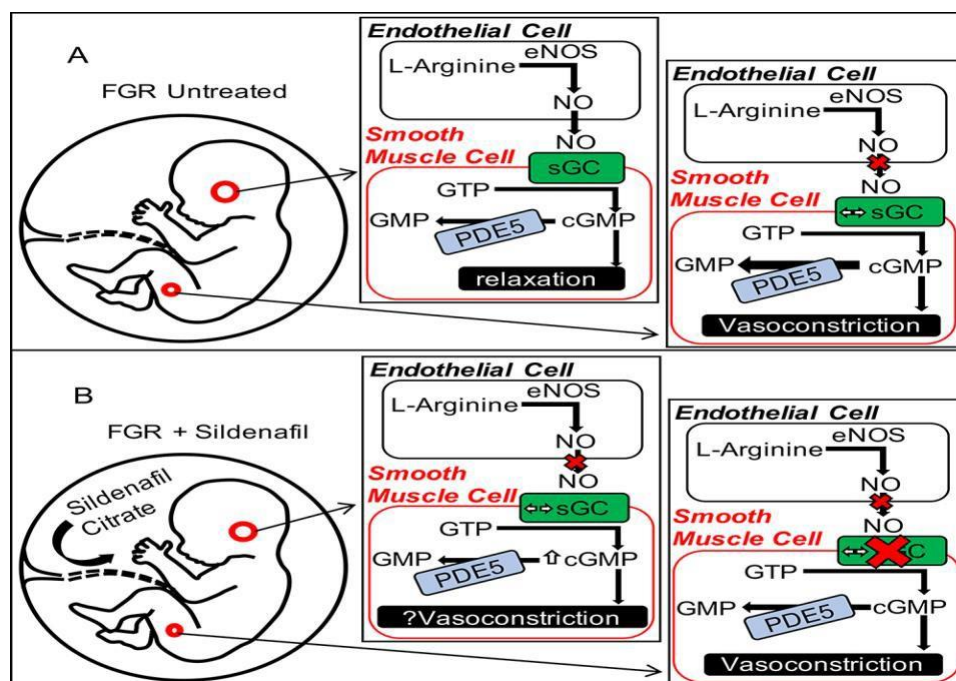
There are no drugs currently being developed for obstetrical conditions. This has led to the evaluation of drugs that are currently in clinical practice for other conditions, which will be evaluated on a re-purpose basis to assess their potential therapeutic value in the treatment of IUGR. [10, 11].

Normal pregnancy sees the release of nitric dioxide (NO), which is a powerful vasodilator. Pregnancies with pre-Eclampsia, IUGR or other complications may have a decreased release of NO.

Nitric oxide (NO), is made from L-arginine by nitric oxygen synthases. The NO increase in cyclic Guanosine Monophosphate (cGmp) causes relaxation of the blood vessels smooth muscle [4].

Potential therapeutic agents for IUGR include drugs that increase the NO effect.

Sildenafil citrate acts as a phosphodiesterase5 inhibitor, slowing down the breakdown of cyclic Guanosine Monophosphate (cGMP), and increasing nitric oxide-dependent vasodilatation. [fig1] Sildenafil is used to treat pulmonary hypertension during pregnancy. It is also being considered for treatment of intra-uterine development retardation (IUGR) and premature labour [5,6]. Sildenafil has been suggested as a possible therapeutic strategy for maintaining placental function during pre-eclampsia [5,6].



[fig1. Effect of sildenafil citrate on fgr, image courtesy: American heart association journals]

Recent research has shown that sildenafil citrate increases vasodilation in myometrial small arteries. It is also associated with fetal growth, which could be a therapeutic option for IUGR [6,7].

Sildenafil citrate can increase the amniotic fluid volume of pregnancies that are complicated by oligohydramnios.

IV. DISCUSSION

There seems to be an incessant discussion and review about sildenafil citrate use in IUGR/oligohydramnios. They supported its use and saw positive results. A few of them found no effect on birth weight or gestational age at delivery.

Von Dadelszen et al. In an open-label pilot trial, [7] examined the potential of sildenafil to increase fetal growth. Ten women who had pregnancies with severe early-onset FGR and where the chances of intact fetal survival were less than half of the expected, accepted 25-mg sildenafil TDS. The outcomes were compared to those of sildenafil-naive pregnancies that occurred contemporaneously (n=17). The AC showed a higher post-treatment fetal growth velocity (n=17) [9/10 (treated) and 7/17 (control); odds ratio was 12.9; 95% CI, 1.3,126]. It is not clear if higher termination rates and permissive stillbirths in sildenafil-naive patients are due to poorer management or a worse prognosis.

E. Ferreira et al. [8,9]. A retrospective and descriptive series of all pregnant women in hospital who were treated with sildenafil for severe IUGR. The study included 19 pregnant women in hospital who had received sildenafil to treat severe IUGR. Sildenafil was administered in an average of 25 weeks plus 3 days (median: 25, [20+1], 30+6]), at an average dose of 20 mg daily, from conception to delivery. The average fetal weight before sildenafil was 558g [237], 1208]. It increased to 807g at delivery (median 820, [320 and 1360]), and then gained 249g (median 123, [-46 732]). His study did not include a control arm. [10].

Trapani et al. Trapani et al. They compared maternal arterial blood pressure, Z-scores for the pulsatility indicator (PI) of UtA and UA, and fetal MCA, before and after applying a transdermal GTN patches (average dose, 0.4mg/h), oral Sildenafil citrate 50mg, or placebo.

After sildenafil citrate (20.4%) and GTN (21.0%), there was a marked decrease in UtA PI. GTN (19.1%), and sildenafil citrate (18.2%) both showed significant UA-PI reductions. When sildenafil and GTN groups were compared, there was no difference in UtA and UA-PI. In the placebo group, there were no changes in Doppler velocity and in any other group was no significant increase in MCA-PI. Pre-eclampsia patients with high maternal arterial blood pressure will see their maternal arterial blood pressure drop with both sildenafil citrate and GTN administration. In both groups, no effect was observed on birthweight.

Dastjerdi et al. A randomized, double-blinded, placebo-controlled trial was also conducted. It involved 41 pregnant women who had intrauterine growth retardation between 24-37 weeks gestation. They were evaluated for the effects of Sildenafil citrate in uteroplacental circulatory as determined by Doppler ultrasound of the umbilical arteries and the middle cerebral arteries. The Sildenafil-treated fetuses showed a significant drop in the systolic/diastolic ratios, pulsatility indicator for the umbilical and an increase in the middle cerebral artery pulseatility index (MCAPI). The researchers concluded that sildenafil citrate could improve fetoplacental flow in pregnancies with intrauterine growth restriction. It could be used as a therapeutic strategy to increase uteroplacental bloodflow in pregnancies that are affected by fetal growth restriction (FGR). This is in line with our research.

Amr El-Shalakany and colleagues. Tab sildenafil 25mg tds increased fetal birthweight, increased mean gestational time at delivery, and decreased NICU admissions. El-Sayed et. In a randomized controlled trial, 54 patients with FGR or abnormal Doppler indexes at 24 weeks were randomly assigned 1:1 to either an intervention (receive sildenafil citrate 50 mg) or control (receive placebo). There was significant pregnancy prolongation, increased GA at birth, and improved neonatal weight (p=. 0001) and less admission to neonatal intensive medical unit.

Also, Lin et al. Lin et al. [12] reported a decrease of uterine artery pulsatility, and resolution of uterine artery itching after sildenafil citrate administration to a case IUGR at 26 weeks gestation. They also found an increase in EFW, despite no maternal or neonatal adverse outcomes.

Despite some negative studies, sildenafil citrate has proven promising in vitro and in animal studies for the treatment of pre-eclampsia and IUGR.

Wareing et al. Wareing et al. The vessels were constricted (with U46619) or U46619), and then relaxed (with bradykinin), before and after being incubated with sildenafil citrate, a phosphodiesterase-5 inhibitor. The researchers concluded that sildenafil citrate

improved the endothelial function and myometrial vessels of women with intrauterine growth restriction. Sildenafil citrate could be a therapeutic option to increase uteroplacental bloodflow in FGR pregnancies.

Oral sildenafil 20 mg tablets twice daily for six weeks increased Doppler indexes in umbilical arterial and cerebroplacental ratios, but it had no effect whatsoever on gestational weight or gestational age at delivery.

V. CONCLUSION-

Sildenafil citrate treatment could offer a new hope for better perinatal outcomes in pregnancies that are complicated by IUGR or impaired placental circulation. However, further studies with large samples size are needed to confirm its effectiveness.

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