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Sildenafil administration in early onset intrauterine growth restriction

Abstract

Early onset growth restriction has traditionally had a poor perinatal outcome in the past. Recently sildenafil citrate has emerged as a potential management option in the treatment of this condition as it is postulated that its vasodilatory effect improves uterine blood flow and hence outcome at delivery.

Keywords: sildenafil citrate, vasodilatory effect, primigravida, dexamethasone

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Introduction

Two cases of severe early oset intrauterine growth restriction who presented to us within days of each other were treated with sildenafil and the outcome of the pregnancies was followed up. The first case was a 39year old primigravida who was diagnosed with asymmetrical growth restriction at 22^{+4} weeks into the pregnancy which was classified as Stage 3fetal growth restriction according to the Fetal Medicine Barcelona Growth Calculator. The second case studied was a much younger 23year old primip who was also disagnosed with Stage 3fetal growth restriction. Both patients were started on 25mg sildenafil three times a day. In the first case there was improvement in velocimetric profile whilst in the second there was minimal improvement.

Early onset intrauterine growth restriction carries a poor prognosis for the foetus, especially with early deterioration of Doppler indices. In such instances, sildenafil can be useful since it acts as a vasodilator and increases uteroplacental flow to promote foetal growth.

Case 1

A 39year old nulliparous lady was being followed up routinely for her pregnancy with no problems in the first trimester. She had her first antenatal visit at 8weeks gestation and was started on folic acid and vitamin D supplements and 400mg cyclogest twice a week due to her age. A 12^{+}week dating scan showed a CRL of 72mm which was equivalent to 13^{+3} weeks gestation and showed that the pregnancy was low risk for trisomies.

At 22^{+4}weeks gestation she was noted to have asymmetrical IUGR, with a normal head circumference, a 3week lag in the abdominal circumference and a raised uterine artery Doppler pulsatitility index – left uterine artery PI was 2.96 and the right uterine artery PI was 1.47. An anomaly scan done at the same time was normal showing a normal spine, a three vessel cord, normal abdominal organ and brain development and normal cardiac development and rhythm. She was also noted to have two fibroids, one 5cm in diameter and another 2cm in diameter, with the larger being covered by the placenta.

At this point of the pregnancy she was admitted to hospital for further investigations: an infectious screen resulted negative, whilst other blood investigations including a complete blood count, a renal profile and a liver profile were all within the normal range. Blood pressure monitoring was normal, excluding pre-eclampsia, and she was discharged home on 25mg sildenafil three times a day.

She has readmitted after 7weeks, at 29^{+4} with stage 3 foetal growth restriction. Basic blood investigations and blood pressure monitoring were normal again and she was given two doses of dexamethasone to aid foetal lung maturation. A middle cerebral artery Doppler which was done was normal and a Doppler of the uterine arteries which was repeated showed that it was improving – on the left it was 1.86 and on the right it was 0.93. When Doppler was repeated after two days, PI values of the uterine artery Doppler were 1.6 on the left showing further improvement (Table 1).

Table 1 Umbilical artery pulsatility indices for case 1

Gestation	Umbilical artery pulsatility index	Weight (grams)
2^{2+4}	1.75	330
24	N/A	414
28	1.43	649
2^{9+4}	1.99	767
2^{9+6}	1.66	N/A

She was planned to deliver by elective C-section at 30^{+3} after both the patient and her partner were consented regards the risks of perinatal morbidity and mortality at such a gestational age, however, he needed urgent operative delivery after foetal distress was noted on routine cardiotocography went down to 45 beats per minute and lasted for 90seconds. The foetal weight at birth was 840grams and the Apgars were 4: 8: 8 at 1, 5 and 10minutes respectively. The baby was transferred to the neonatal intensive care unit where he was intubated and surfactant was administered. On general examination he was noted to have hypospadias. He was stable by day 5 and had a normal brain ultrasound. He continued to make progress and reached a kilo after around 2weeks of life. At around day 28 he developed abdominal distension and sepsis and it was decided to perform a laparotomy which revealed necrotising enterocolitis, a known complication of

prematurity. An ileostomy and a mucus fistula were performed and the baby improved once again. However, his condition deteriorated once again on day 34 and a second laparotomy revealed severe necrotising enterocolitis again. After resecting the affected bowel only 17cm remained and after long discussions with parents it was decided to withdraw care on day 41 of life in view of the anticipated poor quality of life of the baby.

Case 2

A 23year old nulliparous lady was diagnosed with stage 3 foetal growth retardation at 23+weeks of gestation. She had a dating scan at 9+3 weeks 'which confirmed viability and confirmed that dates were correct. At 13weeks gestation she had a scan which excluded major trisomies and was started on aspirin. At 16weeks gestation she developed a raised blood pressure which persisted. She was admitted at 23+3 weeks for further investigation of the foetal growth restriction and was started on 20mg sildenafil three times a day orally. An infectious screen and basic blood investigations were all normal. A scan on admission showed a three-week lag in growth and severe symmetrical IUGR. There were no obvious structural abnormalities and an anomaly scan was normal. Doppler of the uterine artery pulsatility indices were 1.58 on the left and 1.61 on the right. The placenta was also noted to be abnormal with half of it filled with blood lakes and uterine artery notching, increasing the risk of pre-eclampsia and IUGR. Uterine artery Doppler was followed up regularly on an outpatient basis and after administration of sildenafil growth was noted to improve and uterine artery Doppler getting progressively worse as seen in Table 2.

Table 2 Growth, umbilical artery and uterine artery Doppler pulsatility indices for case 2

Gestational weeks	Umbilical artery pulsatility index	Left uterine artery pulsatility index	Weight (grams)
23+3	1.76	1.58	294
23+5	1.62	1.9	N/A
24	1.66	1.78	N/A
24+3	N/A	2	393
29+3	1.63	1.63	806
29+6	1.62	1.62	N/A

She was readmitted at 29+4weeks gestation and was given dexamethasone for foetal lung maturation. An elective C-section in view of the worsening PI values was done at 30+1 weeks, after the patient and her partner were consented regards the need for delivery by C-section and the risks of infant mortality and morbidity at such a gestational age.

Foetal birth weight was 760 grams and Apgars were 7:8 at 1 and 5minutes respectively. The baby was transferred to the neonatal intensive care unit where he was noted to be suffering from hypoglycaemia, a symmetric severe growth restriction, hyperbilirubinemia and respiratory distress. He was also noted to have ambiguous genital with a phallic length of 1cm and bilateral ovoid structures high in the groin. On further investigation, he was diagnosed with partial androgen insensitivity. He was also diagnosed with an atrial septal defect and a patent ductus arteriosus when an ECHO was done. He was discharged from hospital after several weeks to be followed up at the outpatient department.

Discussion

Intrauterine growth retardation (IUGR) happens when there is pathological growth restriction of the foetus and is estimated to occur in about 10-15% of all pregnancies,[1] with early-onset IUGR complicating about 0.2% of pregnancies.[2] The commonest reason for this is placental-vascular insufficiency and this is in turn associated with several other sequelae, including stillbirth, preterm birth and functional complications once the infant is born like respiratory distress and necrotizing enterocolitis.[2–4]

Uteroplacental insufficiency is one of the major causes for IUGR since it leads to limitation in oxygen and nutrient availability to the foetus and thus leads to impaired growth. It is characterised by failure of the trophoblast to invade the spiral arteries in the myometrium and thus the vessels do not dilate and are more likely to occlude or infarct.[5] Maternal co-morbidities like diabetes, renal disease, autoimmune disease and acquired thrombophilias will exacerbate the state of placental vessels.[3,6] Foetal abnormalities and infections were also found to be associated with IUGR.[7,8]

IUGR can easily be interchanged with small for gestational age (SGA), however, these are two different entities, with the former being a more serious condition with a worse prognosis. In SGA there is a constitutionally small foetus with a good perinatal outcome, whilst in IUGR there is an element of placental insufficiency and is associated with a poor perinatal outcome.[9,10] IUGR can also be split into early and late: in both cases presented above, IUGR was early and this is associated with a higher morbidity and mortality since the placental disease would be worse with higher uterine artery Dopplers.[11] Deterioration in such cases is gradual: initially there would be raised uterine artery Dopplers followed by raised umbilical artery Dopplers and a decrease in the middle cerebral artery Doppler as the foetus enters the compensated hypoxia phase. If the placental insufficiency does not improve, the foetus will decompensate leading to a raised ductus venosus Doppler and abnormalities in the cardiotocograph, and could eventually lead to death.[12,13] Thus, it is very important to monitor the foetus via regular ultrasound to detect any important changes.

At our unit, foetal growth restriction (FGR) is graded using the Fetal Medicine Barcelona Growth Calculator which grades FGR from stage I to IV, with stage I representing mild placental resistance and stage IV representing a high suspicion of acidosis with high risk of death. Both cases were admitted to hospital in stage III FGR which essentially means that there was a low suspicion of acidosis but with severe hemodynamic adaptation.

Sildenafil is a vasodilator that traditionally has been used to treat erectile dysfunction and pulmonary arterial hypertension. However, recent research has shown that it can also be used in the management of early onset IUGR, although to date the data available is still limited. It acts via its vasodilatory effects to increase utero-placental blood flow and thus aid with foetal growth. It achieves this via the action of nitric oxide synthases which use the amino acid L-arginine to produce nitric oxide. This in turn diffuses into the smooth muscle of vessels leading to relaxation of the muscle via the action of cGMP and an increase in blood flow and oxygen and nutrient flow towards the foetus. Sildenafil, a phosphodiesterase-5-inhibitor, blocks the enzymes that break down cGMP, thus prolonging the relaxatory effects on muscle.[14,15]

In fact, a meta-analysis which included two trials showed that

administration of drugs like sildenafil lead to an improvement of the umbilical and middle cerebral artery Doppler velocimetries, reflecting the improved blood flow towards the foetus.[16] A small randomised control study of 41 patients showed improvement in the parameters reflecting fetoplacental perfusion after administration of sildenafil.[17] In another study, patients who had early onset IUGR defined as an abdominal circumference below the 5th percentile and were either less than 25weeks pregnant or had an estimated foetal weight of less than 600g were given 25mg sildenafil three times a day until birth. Treatment resulted in an increase in the abdominal circumference and when compared to those who did not receive sildenafil and infants were more likely to survive.[17] However, the study was underpowered and a larger scale randomised control study is needed to confirm these findings.

There are also several case reports which report success on treating IUGR with sildenafil. In 2014 a patient with abnormal umbilical artery flow and IUGR was treated with 50mg sildenafil three times a day due to the uteroplacental insufficiency. There was an improvement in Doppler for three weeks until delivery was expedited due to reversed end-diastolic flow. However, the baby survived and was discharged from intensive are after 80days.[18] Another review reports improvement in Doppler after administration of 25mg sildenafil twice a day vaginally with treatment being stopped at 36weeks gestation and a healthy child was delivered.[19–21]

In both of our cases, IUGR was due to utero-placental insufficiency since other causes were excluded, although, in the second case there was also an element of pre-eclampsia which is commonly associated with IUGR and can worsen the prognosis. Interestingly, in the first case where there was improvement in the Doppler readings, and emergency C-section was done for foetal distress and the infant died shortly after birth due to complications arising as a result of his prematurity. In the second case, although there was next to no improvement in the Doppler readings, the infant survived and was eventually taken home. Interestingly, we also noted that both infants, which were male, suffered from genital abnormalities

Conclusion

In conclusion, when intrauterine growth restriction presents very early the outcome for the baby is rarely good. Very often monitoring of the fetus shows early deterioration of Doppler indices which could eventually lead to intra uterine demise. The aim of management is to get the fetus to viability and deliver in a good condition before this happens. This is where Sildenafil seems to be a useful tool. It acts via its vasodilatory effect to increase uteroplacental blood flow and thus promote fetal growth. In both cases presented the growth restriction was due to placental insufficiency since other causes were excluded. In the second case there was an element of hypertension which might have worsened the prognosis. Interestingly the use of Sildenafil in the first case was associated with improvement in Dopplers while in the second case although there was next to no amelioaration of Doppler flow the infant survived and is doing well so far. Also of interest is the fact that both babies had abnormalities of genitalia with hypospadias and ambigious genitalia being diagnosed at birth.

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Conflict of interest

The authors do not have any conflict of interest in the writing of this article.

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