Treatment of Growth-Restricted Human Fetuses with Amino Acids and Glucose Supplementation through a Chronic Fetal Intravascular Perinatal Port System

M. Tchirikov\textsuperscript{a} O. Kharkevich\textsuperscript{b} J. Steetskamp\textsuperscript{a} M. Beluga\textsuperscript{b} M. Strohner\textsuperscript{a}

\textsuperscript{a}Clinic of Obstetrics and Gynecology, University Medical Center Mainz, Mainz, Germany; \textsuperscript{b}Republican Research and Practical Center ‘Mother and Child’, Minsk, Belarus

Key Words
Amino acids · Intrauterine growth restriction · Intrauterine treatment · Intravenous infusion · Port implantation

Abstract
Objective: Intrauterine growth restriction (IUGR) carries an increased risk of mortality and morbidity. The accepted procedure to treat IUGR fetuses is premature delivery, which may increase neonatal mortality and morbidity and retards neonatal brain development. Material and Methods: We report here on intravascular supplementation with amino acids and glucose of an IUGR human fetus at 33 weeks of gestation with oligohydramnios and placental insufficiency using the port system (Norfolk Medical Products, Skokie, Ill., USA). The catheter was implanted into the umbilical vein (UV) by cordocentesis, and was then connected to a subcutaneously implanted port system. The treatment course included daily infusions of amino acid solution and 10% glucose into the UV. Results: Daily intravascular fetal nutrition significantly improved both fetal condition and fetal weight gain. No complications were seen. The patient was delivered by cesarean section in the 38th week of gestation. The female newborn weighed 2,130 g and was 47 cm long. Blood sampling from the UV after delivery showed no deviations of amino acids in comparison to standardized curves. In one-year follow-up the child’s development and weight gain was like that of children without IUGR in the anamnesis. Conclusion: This is the first report of the successful use of a subcutaneously implanted intravascular perinatal port system in IUGR human fetuses for long-term administration of nutrients into the UV of a fetus.

Introduction

Intrauterine growth restriction (IUGR) caused by placental insufficiency is one of the most serious prenatal conditions. We used an intravascular supplementation system to supply nutrients to an IUGR fetus in order to achieve improved fetal growth and prolongation of pregnancy.

IUGR is defined for fetuses that have not been able to achieve their genetic potential of growth in utero. The incidence of IUGR is about 3–5% of all pregnancies and its main cause is placental insufficiency [1]. IUGR is a serious prenatal condition which can be seen as one of the major causes of fetal loss (about 40% of all stillbirths are IUGR fetuses) [2]. It is also known that impaired prenatal
growth also causes significantly impaired postnatal development throughout childhood [3]. After diagnosis of IUGR, the prenatal treatment options are limited. IUGR is one of the major causes of premature delivery, which itself causes an increase of perinatal mortality and morbidity in addition to the increased neonatal risk caused by IUGR [4]. As the active placental transport of amino acids and glucose from the mother to the fetus is reduced in IUGR fetuses [5, 6], a logical treatment of placental insufficiency is to find a way to supply amino acids and glucose to the IUGR fetus.

We here report for the first time the successful use of a subcutaneously implanted intravascular perinatal port system in an IUGR human fetus for long-term administration of nutrients into the umbilical vein for the treatment of placental insufficiency and prolongation of pregnancy.

**Materials and Methods**

The procedure was approved by the local ethics committee of the Republican Research and Practical Center ‘Mother and Child’, Minsk, Belarus.

To prove the concept and perfect the technique, subcutaneous ports (BARD System, USA) were successfully used in 24 fetal sheep [7, 8]. The port system (Norfolk Medical Products, Skokie, Ill., USA) for intrauterine fetal nutrition was developed and successfully used in the fetal sheep model at the University of Mainz, Germany. It included a fetal intravascular 1.5 French catheter connected to a subcutaneously placed port system for systemic injection of drugs and fetal blood sampling (fig. 1a). In the currently reported case we were able to adapt these experiences for the treatment of a human IUGR fetus at 33 weeks of gestation with oligohydramnion (amniotic index 5) and increased resistance to flow in the uterine arteries by intravascular nutrient supplementation. To allow permanent nutrient supplementation for the further course of pregnancy, we implanted a port system with permanent access to the fetal umbilical vein. After sonographic localization of the placenta, a small incision into the skin and preparation of a subcutaneous pouch were performed at the side of placental insertion of the cord. The umbilical vein was punctured with a 20 G finder needle under ultrasonic control through the prepared pouch and anterior wall placenta (RAB4-8RS 4D transducer; GE Voluson Expert 730, Milwaukee, Wisc., USA; fig. 1b). After fetal blood sampling, the 1.5 French radio-opaque infusion catheter with a removable 0.006 inch (0.015 cm) stylet was inserted through the needle into the umbilical vein for 9 cm. The amniotic cavity remained intact. The thin stylet was removed, the catheter was shortened and then connected to the vascular access port which was previously flushed with heparinized saline (10 units/ml). The port was fixed in the pouch (Ethicon, Cincinnati, Ohio, USA) and the skin was closed. A 25 G port needle (length 9 mm) was used to enter the port system (fig. 2). Saline solution was injected into the port system under color Doppler ultrasound control to check for the correct position of the catheter in the umbilical vein. The treatment course included daily infusions of amino acid solution (5 ml/h; Vaminolact, Pharmacia, Sweden) with a 10% glucose solution. We decided to limit the volume of the intraumbilical infusion to 10% of the estimated feto-placental blood volume per day [9].

**Fig. 1.** Administration of nutrients into the umbilical vein using a chronic fetal intravascular perinatal port system. a The Port (Norfolk Medical Products, Skokie, Ill., USA). b The introduction of a 1.5 F catheter through the 20 G needle into the umbilical vein, under ultrasound control, for the application of nutrients.
Results

Daily intravascular nutrition significantly improved fetal weight gain (fig. 3). The fetal Doppler parameters remained unaffected until delivery. One week before delivery the infusions were interrupted to avoid fetal infection because an irritation of the skin above the port was seen. At the same time, fetal weight gain also stopped. Delivery took place by caesarean section at 37+0 weeks of gestation and the port system was removed. We did not find any signs of inflammation in the maternal abdomen or on the uterus. The female newborn weighed 2,130 g with a length of 47 cm, head circumference 31 cm, APGAR 8-8-10. Blood sampling from the umbilical vein after delivery showed no deviations in amino acid concentrations compared with the standard values. At the six-month and one-year follow-up examinations the child’s development, especially the weight gain, was comparable to children without IUGR in the anamnesis [10].

Discussion

This is the first report of the successful use of a subcutaneously implanted chronic intravascular perinatal port system in human growth-restricted fetuses for long-term administration of nutrients into the umbilical vein for intrauterine treatment of placental insufficiency and a prolongation of the pregnancy. We were able to demonstrate that the subcutaneous port system could be used in humans for chronic intravenous administration of the drugs to the fetus without complications. The condition sine qua non for the successful intrauterine treatment of placental insufficiency using the chronic fetal intravascular perinatal port system is to avoid damaging the amniotic membrane so that the amniotic cavity remains intact during the implantation of the catheter into the umbilical vein. Thus, the described method could be used only in pregnant women with an anterior or anterior-lateral located placenta. The long-term supplementation of nutrients via a perinatal port system increased the fetal weight gain and prolonged the pregnancy in our case.

The fact that placental insufficiency significantly increases perinatal mortality and morbidity is currently without discussion [2–4]. Infants with IUGR are at increased risk for poorer cognitive outcomes [3], metabolic syndrome (comprising hypertension, diabetes, and cardiovascular disease) [11, 12], precocious puberty, and

Fig. 2. Transcutaneous administration of amino acids and glucose into the umbilical vein using the port system. A 25 G port needle (length 9 mm) was used to enter the port system. The treatment course included daily infusions of amino acid solution (5 ml/h, 25 ml/day; Vaminolact, Pharmacia, Sweden) with a 10% solution of glucose 25 ml/day.

Fig. 3. Fetal weight gain during intraumbilical amino acid and glucose supplementation. The long-term administration of nutrients into the umbilical vein was started at 33+3 weeks of gestation. The arrow indicates interruption of treatment (1). Note the absence of the fetal weight gain without administration of nutrients until the delivery by caesarean section at the 38th week of gestation (2).
short stature compared to gestational age infants. These newborns with IUGR in pregnancy are more frequently referred to an intensive care department, which significantly increases the costs of neonatal treatment. Therefore prolongation of the pregnancy through fetal nutrition via a port system is likely to show an economical benefit.

The IUGR situation affects the fetal programming [11–12]. The metabolic syndrome, increased risk of coronary heart disease, strokes and diabetes mellitus type II have often been found in patients with IUGR in the anamnesis. We suggest that the intra-umbilical venous amino acids and glucose supplementation to the fetus may normalize the fetal programming and avoid the later development of the chronic diseases related to the IUGR.

The only accepted treatment of placental insufficiency in the obstetrical praxis, namely premature delivery, must also be discussed. Premature delivery itself increases perinatal mortality and morbidity [1, 4, 13]. Preterm infants are at risk for poor growth and impaired neurodevelopment. Very early preterm infants show a range of major neurodevelopmental sequelae in 10–15% of cases during infancy, and 30–40% have minor motor, behavioral, and learning disorders at school age. Those children who attend mainstream schools have a high prevalence of minor motor, behavioral, and learning disorders [14, 15]. Cooke [14] reported that cognitive development at eight years of age was associated with intrauterine growth. A birth weight below the 10th percentile was previously associated with poor growth, developmental delay, and language problems at 56 months of age. The prolongation of the pregnancy could improve the later neurodevelopmental ability of IUGR fetuses. Paz et al. [15] demonstrated that term infants with fetal growth restriction are not at increased risk for low intelligence scores at age 17 years. We suggest that the use of intrauterine chronic administration of amino acids and glucose supplementation to the fetus via a port system may normalize the fetal programming and improve the late neurodevelopment of IUGR fetuses.

The risk of this invasive procedure must be discussed. We did not find any complications of the port implantation in the fetal sheep model [7, 8]. However, the sheep situation cannot be simply transferred over for use in humans. We have not found any reports about the port implantations in human fetuses. Van Kamp et al. [16] reported about the complications of intrauterine intravascular transfusion (IUFT) for fetal anemia in humans. The risk of IUFT was 0.9% per cordocentesis and blood transfusion. Thus, the benefit of fetal nutrition to a IUGR fetus via perinatal port and the possible complications of the procedure must be discussed in detail with the parents.

Conclusion

This is the first report of the successful use of a subcutaneously implanted intravascular perinatal port system in an IUGR human fetus for the long term administration of nutrients into the umbilical vein. The intravascular perinatal port system could be used for intrauterine treatment of placental insufficiency of IUGR fetuses and prolongation of pregnancy. The fetal programming of IUGR fetuses could be also normalized by intrauterine nutrition. Prospective international randomized studies have been designed to further test the benefit of this method.

Acknowledgements

We thank Michael Dalton, Norfolk Medical Products (Skokie, Ill., USA) for his technical support. We would like to express our gratitude to Prof. Dr. Steven Johnsen, University of Göttingen, Germany.

References

1 Goldenberg RL, Cliver SP: Small for gestational age and intrauterine growth restriction: definitions and standards. Clin Obstet Gynecol 1997;40:704–714.
2 Mongelli M, Gardosi J: Fetal Growth. Curr Opin Obstet Gynecol 2000;12:111–115.
3 Pryor J, Silva PA, Brooke M. Growth, development and behaviour in adolescents born small-for-gestational age. J Paediatr Child Health 1995;31:403–407.
4 Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.
5 Cetin I, Alvino G: Intrauterine growth retardation: implications for placental metabolism and transport: a review. Placenta 2009;23:S77–S82.
6 Jansson T, Ylven K, Wennegren M, Powell TL: Glucose transport and system A activity in syncytiotrophoblast microvillous and basal plasma membranes in intrauterine growth restriction. Placenta 2002;23:392–399.
7 Tchirikov M, Kertschanska S, Sturenberg HJ, Schröder HJ: Liver blood flow as a possible instrument for fetal growth regulation. Placenta 2002;23:S153–S158.
Amino Acids and Glucose Treatment for Growth-Restricted Fetuses

Tchirikov M: Dilatation of the ductus venosus by stent implantation increases placental blood perfusion in fetal sheep. Am J Obstet Gynecol 2008;198:138e1–138e6.

Ledic L, Moise KJ, Carpenter RJ, Cairo LE: Fetoplacental blood volume estimation in pregnancies with Rh alloimmunization. Fetal Diagn Ther 1990;5:138–145.

Cole TJ, Freeman JV, Preece MA: British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med 1998;17:407–429.

Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS: Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:938–941.

Barker DJ, Osmond C, Forsen TJ, Kajantie E, Eriksson JG: Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005;353:1802–1809.

Thornton IG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M: GRIT study group: infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet 2004;364:513–520.

Cooke RW: Are there critical periods for brain growth in children born preterm? Arch Dis Child Fetal Neonatal Ed 2006;91:F17–F20.

Paz I, Laor A, Gale R, Harlap S, Stevenson DK, Seidman DS: Term infants with fetal growth restriction are not at increased risk for low intelligence scores at age 17 years. J Pediatr 2001;138:87–91.

Van Kamp IL, Klumper FJ, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FP, Kanhai HH: Complication of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. Am J Obstet Gynecol 2005;192:171–177.