Twin to twin transfusion syndrome: a collaboration between Poznan University of Medical Sciences and Loma Linda University School of Medicine

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Abstract

We present two cases of twin-to-twin transfusion from two institutions. Laser photocoagulation was used to ablate the bridging aterio-venous shunts in one cases permitting resolution of early evidence of hydrops fetalis, while in the other prompt recognition of fetal cardiac failure after amniotic fluid reduction with cesarean section allowed for neonatal intensive with survival. We discuss the origins of twin-to-twin syndrome and it contemporary treat-ment, and fetal and neonatal complications that can arise in this monochorionic multi-fetal gestations and current medical management.

Key words: Twin to twin transfusion syndrome, fetoscopy, fetal distress, oligiohydraminos, polyhydraminos, NICU care, laser treatment during fetal life

Introduction

Twin-to-twin transfusion syndrome (TTTS) represents a serious complication of monochorionic multiple gestations that is associated with a high risk of fetal or neonatal mortality, especially in preivable gestations and in infants with cardiac, neurologic and developmental disorders in later infancy. The diagnosis has in the past been associated with neonates with an intertwin weight difference of 15-20% and a hemoglobin difference of 15-20% and a haemoglobin difference of > 5 gm/dl [1, 2]. However, TTTS can occur without hemoglobin differences. With advances in prenatal ultrasonography one of the most important findings is differences in amniotic fluid volumes. Because of fetal losses the incidence of monochorionic multi-fetal gestations, the incidence of TTTS is under-diagnosed, but it is estimated to be from 1:40 to 1:60 twin pregnancies and between 9-15 percent of monochorionic twin gestations [3, 4].

The patho-physiology is the inter-twin vascular anas-tomosis and the role of flow imbalances between twins. These anastomosis may be aterio-venous (AV), veno-arterial (VA), aterio-arterial, and veno-venous shunts, but aterio-venous (AV) anastomosis in the most commonly found in TTTS. AV and VA anastomoses consist of “feeder” blood vessels on the surface of the chorionic plate of the placenta that descend into the common cotyledon capillary network where they undergo anastomosis.

Whereas aterioarterial and venovenous anastomoses are exclusive on the surface of the placenta, flow in these latter two types of anastomosis is bidirectional and the net flow is related to opposing hydrostatic pressures of each fetus. Although these vascular connections are found in nearly all monochorionic twins approximately 9-15% have flow patterns from arterio-venous shunting of sufficient pressure differentials to cause TTTS [5].

Early ultrasonographic manifestations in the asym-ptomatic mother, is the evidence of a single monochorionic placenta with polyhdramnios/oligohdraminos sequence that can occur prior to 20 weeks gestation. While prior to 20 weeks the one amniotic fluid “pocket” is < 2 cm while the other is > 8 cm, and after 20 weeks the maximum vertical pocket for polyhydramnios is defined as > 10 cm [3, 4]. When twin anemia-polycythemia is found (representing a large differences in hemoglobin values in the cord blood of more than 5 gm/dl) without oligohydraminos/polyhydraminos sequence, the term Twin anemia-polycythemia sequence is more appropriate and this occurs 3-6% of monochorionic/diamniotic twins, while after laser therapy the incidence is about 2% up to 10% [6]. In addition to amniotic fluid volume differences, fetal echocardiographic findings and peripheral Doppler findings of donor and recipient twins have been graded by Quintero Scoring or the Children’s Hospital of Philadelphia (USA) scoring system to identify the pre-
sence and severity of atrioventricular valvular incompetence, ventricular wall thickening, and ventricular function as assessed by Doppler flow characteristics [7].

We report two cases from our institutions of detection of TTTS diagnosed prenatally. In the initial report, discordant fetal growth and early onset of hydrops fetalis prompted intraamniotic fetoscopic laser ablation of many of the bridging vessels (about 12 anastomosis were identified and lasered), and in the second case male twins with TTTS were recognized on fetal ultrasound and prompt delivery enabled neonatal interventions including volume and blood replacement in the donor twin that was life-saving.

Case Report 1

Monozygotic male twins delivered by emergency cesarean section were delivered at 35 weeks to a 28 year old Gravida 2 para 1 Caucasian mother who had undergone laser photocoagulation of bridging vessels at 20 weeks gestation through a fetoscope because of evidence of twin to twin transfusion and discordant intrauterine growth. The mother’s prenatal laboratory assessments were unremarkable and she was group B streptococcus negative, HIV negative, and negative for syphilis, gonorrhea, and had a negative test for tuberculosis. She was blood group O negative. Electronic fetal heart rate pattern was not reassuring and given an NIH fetal monitoring classification of II, and there was evidence of early hydrops fetalis in Twin A. At the time of fetal bridging vessel laser obliteration there was approximately 12 bridging vessels that had laser vascular obliteration due to twin-to-twin vascular bridging as demonstrated on placental examination (Fig. 1).

In these monozygotic male twins, Twin A weighed 2140 grams and Twin B weighed 1720 grams (approximately 10% weight difference). At 35 weeks twin A was appropriate weight for gestational age, while twin B was symmetrically small for gestational age. Hematocrits in Twin A was 44% and in Twin B was 36% and both infants had respiratory distress consistent with transient tachypnea of the newborn. Twin B had early onset hypoglycemia with the lowest glucose measured at 36 mg/dl that responded to intravenous glucose administration, while twin A remained euglycemic. Both infants required supplemental oxygen for 3 days and Twin A was treated with nasal CPAP for 24 hours while twin B also requiring institution of nasal CPAP at 6 cm H2O for 48 hours. On cranial ultrasound, there was no evidence of intraventricular hemorrhage in either twin. Initially both infants required parenteral nutrition, but by the end of the 7th day after birth both infants were tolerating maternal milk either by nipping or by intermittent naso-gastric tube feedings.

Fig. 1. Placenta of 35 week monozygotic twins who underwent laser photocoagulation at 20-21 weeks using a fetoscope. Approximately 12 laser pulses were used at points along the dividing amniotic membranes of twin A (visualized as areas of local white areas of fibrosis (focal infarction after laser treatment) on the placental surface. These vascular anastomosis were ablated using a Jag laser pulses through a Olympus fetoscope. (Dr. B. Oshiro and Dr. T. A. Merritt, Dept. of Ob/Gyn, and Neonatology Loma Linda University School of Medicine)

Case report 2

Twin male infants were born in Department of Neonatology in Poznan University Hospital, and we observed acute TTTS syndrome. A 32 year old multigravida with a monochorionic-diamniotic twin pregnancy at 31 weeks of gestation was admitted into the Delivery Department because of irregular contractions consistent with preterm labor. From patient’s relation and maternity notes this pregnancy had no complications so far. The diagnosis of monochorionicity was based on detection of T-sign in the first trimester ultrasound examination. The patient was referred to the Department of Perinatology and Gynecology Ultrasound Unit for evaluation. Ultrasound on admission demonstrated discordant growth in the level of 19% (estimated weight of recipient twin was 1960 ± 286 g and donor twin was 1588 ± 232 g). Moreover, we detected signs of stage IV twin-to-twin transfusion syndrome (TTTS) by Quintero staging. The ultrasound examination revealed polyhydramnios in the recipient sac (maximum vertical pocket (MVP) – 14 cm), ascites and pericardial effusion, as well as abnormalities in fetal Doppler measurements: increased resistance in the umbilical artery (PI = 2.14), pulsations in the umbilical vein and reverse flow in the ductus venosus (Fig. 2). Furthermore, echocardiography showed cardiomegaly.
ventricular hypertrophy, impaired contractility of both ventricles, holosystolic tricuspid valve (TV) regurgitation (velocity of 2-3 m/s), monophasic inflow through TV, holosystolic mitral valve (MV) regurgitation (velocity of 3 m/s reaching veins), extension of the proximal parts of the pulmonary veins, biphasic inflow through MV into the left ventricle. The diameter of the pulmonary artery valve was 4.9 mm with peak systolic velocity (PSV) reaching 75 cm/s and the the diameter of the aortic valve was 4 mm with PSV up to 45 cm/s. According to these abnormalities we diagnosed fetal congestive heart failure. This diagnose was based on Cardiovascular Profile Score score (3 points) [8]. The donor twin presented a signs of oligohydramnios (MVP = 1.8 cm) without a detectable urine bladder. The Doppler blood flow velocimetry in the umbilical artery, umbilical vein, middle cerebral artery and ductus venosus was within reference ranges. The fetal echocardiography showed increased peak systolic velocity in the aorta (up to 120 cm/s) with signs of hyperkinetic circulation and tachycardia with fetal heart rate up to 170 beats/min. The ultrasound examination revealed a high risk of the intrauterine fetal death in monochorionic diamniotic twin pregnancy complicated by TTTS stage IV with heart failure of the recipient. A decision of antenatal corticosteroid therapy to enhance fetal lung maturation was made; however, the obstetric decision was also made for immediate cesarean section.

Male twins delivered by emergency cesarean section were delivered at 31 weeks gestational age to a 32 year old gravida 3 Para 2 Caucasian mother. There were no signs of PPROM, nor intrauterine infection was present. Mother was blood group B negative. Twin A weighed 2120 g and twin B weighed 1470 g. Hematocrit in Twin A was 71% and in twin B it was 26%. In twin A the hemoglobin was 15 g/dl and the infant B the hemoglobin was 4.8 g/dl. Apgar scores for twin A were 3 at 1 min, 4 at 3 min, 6 at 5 min and 6 at 10 min.
This newborn required intubation shortly after delivery and synchronized intermittent mandatory ventilation was started. The echocardiography has shown signs of cardiomyopathy and heart failure with persistent fetal circulation. The patient was treated with pressors, diuretics, inhaled nitric oxide, and received two doses of surfactant with no improvement of general condition. Very poor diuresis was observed – oliguria and anuria occurred. A Cardiology Consultation was obtain and on the first day the echocardiogram showed signs of the pulmonary hypertension, tricuspid valve regurgitation stage III, PDA, foramen ovale and enlargement of the left ventricle and signs of hypovolemia. Fresh frozen plasma was ordered and diuretics administered. During the second consultation, cardiologist confirmed severe hypertrophy of the left ventricle and also a hypoplastic aorta’s arch. Infusion of prostaglandin was added.

Due to Twin A’s serious condition a decision on cardiac surgery was postponed until the patient’ was more stable. On the second and the third day infant’s condition was still extremely severe, and was without further improvement after following treatment. At the beginning of the fourth day, bradycardia occurred. This infant died at the beginning of the fourth day of life.

Apgar scores for twin B were 4 at 1 minute, 6 at 3 minutes, 5 at 5 and 10 minutes after birth. He was resuscitated using T-piece NeoPuff using an FiO₂ 21-40% in the delivery room. Shortly after admission to NICU newborn due to severity of distress syndrome required intubation. He received 1 dose of surfactant. SIMV was required and continued for 4 days. Due to increasing hypercapnea and respiratory acidosis, HFOV was initiated and continued for 4 days. Chest radiograph showed right-side tension pneumothorax and a chest tube was placed to remove non-alveolar gas. Mechanical ventilation was stopped at 10 day of life and non-invasive ventilation at 14 day of life. Due to anemia he received red blood transfusion several times (at 1, 3, 5 and 28 day of life). Hyperbilirubinemia of prematurity was documented on day 2 and newborn required treatment of fototherapy for next 3 days. Due to accompanying inflammatory changes in the lungs interpreted as bilateral pneumonia route of antibiotics was stared. Echo examination showed only foramen ovale without any other functional changes. On cranial ultrasound there was no evidence of intraventricular hemorrhage but did demonstrate bilateral hyperechogenic areas suggestive of periventricular leukomalacia. This infant required TPN from the day of life 1. Minimal enteral feedings was introduced at day 8, slowly and gradually increased. Parenteral nutrition was stopped at day 19. Newborn started to nipple at day 27 and just before discharge breastfeeding was achieved. The initial examination of the eye and retinal vasculature was performed after 4 weeks of life and showed no changes consistent with retinopathy of prematurity. Follow-up eye examination was planned after discharge of the infant which occurred on the 36 th day after birth.

**Discussion**

Compared to mothers of dichorionic twins, mothers of monochorionic twin are 6 times more likely to miscarry before 24 weeks, have a higher risk of premature delivery before 32 weeks (9% versus 6%), and more likely will have both twins with intrauterine growth restriction (8% versus 2%). Monochorionic pregnancies have a perinatal mortality rate three times higher and are eight times more likely to have cerebral palsy than dichorionic pregnancies [9]. The prognosis of untreated severe TTTS is very poor, perinatal mortality rates of 70-100 percent are reported, with long term issues such as neurologic, cardiac, and renal impairment occurring in survivors.

For decades in the USA, repeated amnioreduction has been the most common therapy for TTTS. Current recommendations indicate that selective fetoscopy laser photocoagulation was become more widely approved in many centers in both Poland and America. The technique was first described by De Lia and colleagues [10], who first described fetoscopic laser photocoagulation of vessels crossing the intertwin membrane to treat the anatomical cause for the syndrome. Their small data have showed survival of 53% in 26 patients, that was no significantly better than those in previous studies, where serial amnioreduction procedure were performed and the neurological outcome was normal, as evaluated by head ultrasound. Data from United Kingdom, by Ville and colleagues [11] have reported 53% survival with a fetoscopic laser therapy, which was significantly better in comparison with the historical controls at the same center with serial amnioreductions (37%). They have also pointed out the lower rate of other abnormalities detected by ultrasonography compared with historical studies.

A systematic review and meta-analysis [12] describing neurologic outcome in pregnancies complicated by TTTS and treated with laser therapy have reported that the incidence of neurologic complications at birth was 6.1%, and the incidence of any degree of neurologic problems at follow-up at 6 to 48 months of age was 11.1% with no significant differences between donors or recipients. Cerebral palsy was estimated for 39.7% of long-term abnormal neurological outcomes. These risks are
not significantly different from the baseline risks in monochorionic twins without TTTS. It means that almost all the risk of neurologic disabilities in survivors is due to prematurity and prematurity-related complications, rather than direct outcome of TTTS or laser therapy [12-14]. However, in comparison to dichorionic pregnancies, pregnancies complicated by TTTS has a higher risk of cerebral injury [13]. Different studies of TTTS treated with laser treatment have focused on renal and cardiovascular outcomes. There were levels of markers indicating renal function comparable between donor and recipient [15]. This study might indicate that hypovolemia that develops in the donor twin results in vascular remodeling [16] and may be prevented by laser ablation [17]. Laser therapy can also improve flow through the pulmonary valve of the recipient twin, but complications may persist and required further cardiovascular intervention in newborn life [18].

Complications are described associated with laser ablation treatment. These include the most common on of premature rupture of membranes with rates within 1 to 3 weeks following treatment ranging from 7 to 17% [19]. The rest of complications includes fluid leakage into the maternal peritoneal cavity, vaginal bleeding, abruption and chorioamnionitis. The rate of these complications are comparable to those of amnioreduction, with the exception of PPROM, that is more often reported after laser therapy. The other remarkable complication is twin anemia polycythemia sequence (TAPS). In post-laser TAPS, small arteriovenous anastomoses between the recipient and donor allow slow passage of red cells in a reverse manner so that the recipient twin becomes anemic and the donor becomes plethoric [20].

Conclusion

TTTS is one of the most serious complications of monochorionic multifetal gestations and is associated with increased fetal/neonatal mortality and morbidity. The infants who survive are at risk of severe cardiac, neurologic and developmental disorders. Unbalanced placental intertwin vascular anastomosis play a key role in the etiology of TTS. One twin becomes hypovolemic (donor twin) and the other hypervolemic (recipient twin), and the subsequent cardiovascular changes in response to volume changes lead to the TTTS phenotype. Prenatal diagnosis of TTTS is based on ultrasonographic evidence of a single monochorionic placental with polyhydraminos/oligohydramnios sequence. In severe oligohydraminos there may be a so-called “stuck twin” because of lack of space between the fetus and uterine wall. Obstetric intervention using laser photoagulation ablation of bridging arterio-venous shunts on the chorionic surface has been shown to reduce the magnitude of these shunts and reduce or eliminate the unbalanced flow and improved fetal survival.

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References

De Lia J.E., Cruikshank D.P., Keye W.R. Jr. (1990) Feto-
soscopic neodymium: YAG laser occlusion of placental ves-
sels in severe twin-twin transfusion syndrome. Obstet.
Gynecol. 75: 1046-53.

Ville Y., Hyett J., Hecher K. et al. (1998) Preliminary ex-
perience with endoscopic laser surgery for severe twin-

Rossi A.C., Vanderbilt D., Chmait R.H. (2011) Neo-
developmental outcomes after laser therapy for twin-twin trans-
fusion syndrome: a systematic review and meta-

Spruijt M., Steggerda S., Rath M. et al. (2012) Cerebral in-
jury in twin-twin transfusion syndrome treated with feto-


Beck M., Gräf C., Ellenrieder B. et al. (2005) Long-term outcome of kidney function after twin-twin transfusion syndrome treated by intrauterine laser coagulation. Pe-
diatr. Nephrol. 20: 1657.


Gardiner H.M., Taylor M.J., Karatza A. et al. (2003) Twin-
twin transfusion syndrome: the influence of intratertine laser photoagulation on arterial distensibility in child-


Yamamoto M., El Murr L., Robyr R. et al. (2005) Incidence and impact of perioperative complications in 175 fetosco-
py-guided laser coagulations of chronic plate anasto-


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