Early Human Development 91 (2015) 751–754

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Donor catch-up growth after laser surgery for twin–twin transfusion syndrome☆,☆☆,★,★★

Ramen H. Chmait [a,*], Andrew H. Chon [b], Sheree M. Schrager [c], Eftichia V. Kontopoulos [d], Rubén A. Quintero [d], Douglas L. Vanderbilt [e]

[a] Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Keck School of Medicine, University of Southern California, United States
[b] Department of Obstetrics and Gynecology, Kaiser Permanente Los Angeles, CA, United States
[c] Division of Hospital Medicine, Children's Hospital Los Angeles, United States
[d] Jackson Fetal Therapy Institute, Jackson Memorial Hospital, Miami, FL, United States
[e] Department of Pediatrics, Division of General Pediatrics, Keck School of Medicine, University of Southern California, United States

ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 3 July 2015
Accepted 21 August 2015

Editor: C.R. Rosenfeld

Keywords:
Catch-up growth
Growth restriction
Laser surgery
Twin–twin transfusion syndrome

ABSTRACT

Objective: To assess fetal growth after laser surgery for TTTS at the time of prenatal diagnosis, birth, and at 2 years of age.
Design/methods: Growth data were collected from surviving children treated between 2007 and 2010 as part of a study to assess neurodevelopment at 24 months (±6 weeks) corrected age. Fetal weights were obtained via ultrasound using Hadlock's formula at the time of preoperative assessment for laser surgery. Birth weights were recorded by the staff at the delivering institutions. Weights at 2 years corrected age were recorded at the time of neurodevelopmental testing. Weights were converted into percentiles according to standard growth curves. Growth restriction was defined as <10th percentile for given age. Multilevel latent growth curve models in Mplus (twins nested in families) examined weight change over time as a function of donor status, and repeated measures ANOVA was utilized to assess in donor–recipient weight discordance over time for twin pairs.
Results: 99 of 206 children (56 of 130 families) were studied. There were no differences between enrolled and non-enrolled patients in donor/recipient status and survival rates, fetal demise, intrauterine growth restriction, Quintero stage, and gestational age of surgery or delivery. 48.5% were donors. The median fetal, birth, and 2-year weights for all twins were 288 g, 1.9 kg, and 11.8 kg, respectively, and the overall prevalence of growth restriction was 28%, 22%, and 3%, respectively. Growth restriction rates at prenatal diagnosis were 56% in donors vs. 2% in recipients (OR = 64.3, $p < 0.001$); at birth, 35% vs. 10% (OR = 5.0, $p < 0.01$); and at 2 years, 6% vs. 0%. Donors showed significant gains in weight percentile (B = 13.1, $p < 0.001$) and a significant decrease in growth restriction rates over time (B = −1.6, $p < 0.001$). Weight discordance between donor and recipient pairs also significantly decreased over time (linear $F(1,42) = 54.34$, $p < 0.001$).
Conclusions: After laser surgery for TTTS, donor twins exhibit significant catch-up growth by two years of age.

1. Introduction

Multiple gestations are at increased risk for abnormal fetal growth resulting in poor perinatal outcomes [1–6]. Children born small for gestational age have an increased risk of suboptimal growth [7,8], glucose intolerance [9], neurologic morbidity [10], and cardiovascular disease [9,11,12]. Monochorionic twins in particular are at increased risk for intrauterine growth restriction (IUGR) [2,13–15] and weight discordance between twins [16–21]. Two factors that are specific to monochorionic twins and contribute to the relatively high rate of poor growth are unequal placental share and the presence of vascular communications [21–24].

Twin–twin transfusion syndrome (TTTS) arises in monochorionic twins due to unequal exchange of blood through placental vascular communications, resulting in volume and nutritional depletion in the

☆ This study was conducted in Los Angeles, CA.
☆☆ Previously presented: Portions of this manuscript were presented in Abstract #750982 *** Poster Session ***Pediatric Academic Societies Annual Meeting 2014, Vancouver, British Columbia from May 3, 2014 – May 6, 2014.***
★ Financial support: The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Award Number KL2RR031991 and UL1TR000130. The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH.
★★ CondensationThe donor twin demonstrates significant and progressive catch-up growth after laser therapy for twin–twin transfusion syndrome.
* Corresponding author at: Keck School of Medicine, University of Southern California, 1300 North Vermont Avenue, Suite 710, Los Angeles, CA 90027, United States. Tel.: +1 323 361 6074; fax: +1 323 361 6099.
E-mail address: chmait@usc.edu (R.H. Chmait).

http://dx.doi.org/10.1016/j.earlhumdev.2015.08.006
0378-3782/

donor twin, and volume overload and heart failure in the recipient twin. Treatment of TTTS with selective laser photocoagulation of the communicating vessels (SLPCV) has been shown to improve perinatal outcomes [25–28]. However, fetal growth after laser therapy for TTTS has not been extensively studied. One study demonstrated that the mean twin discordance decreased from 28% before laser therapy to 18% at birth [29]. Another study showed improvement of donor twin IUGR following laser therapy for TTTS that was associated with a mean 8.2% reduction of twin weight discordance by birth [30]. We are aware of only one study to date that has assessed pre- and postnatal growth of twins with TTTS treated by laser surgery [31]. In that study, Maschke et al. noted that laser therapy was associated with a significant reduction of in utero growth acceleration in recipients, resulting in decreased twin weight discordance at birth, and significant catch-up growth was observed in the donor twins during childhood [31].

The aim of our study was to assess fetal and early childhood growth after laser therapy for TTTS.

2. Material and methods

Patients treated for TTTS at Los Angeles Fetal Therapy (Keck School of Medicine, University of Southern California) between 2007 and 2010 were eligible for study recruitment. Growth data were collected from surviving children as part of a study to assess neurodevelopment at 24 months (±6 weeks) corrected age [32]. TTTS was diagnosed at initial assessment if the monochorionic diamniotic multiple gestation had a maximum vertical pocket of fluid ≥8 cm in the recipient's sac and ≤2 cm in the donor's sac. The patients were staged prospectively according to the Quintero staging system [33]. Cases were treated exclusively by SLPCV with or without sequential technique, as described in detail previously [34]. The estimated fetal weight (EFW) of each fetus was obtained sonographically using Hadlock's formula at the time of preoperative assessment for laser surgery, and prospectively inputted into the database [35]. Fetuses noted to measure less than the 10th percentile according to Hadlock's standard for a given gestational age were designated as having IUGR. Information that was gathered at our center and prospectively recorded in a database for each case included: maternal demographics, findings of consultative ultrasound including Quintero staging, maximum vertical pocket, cervical length and fetal Doppler values, and gestational age both at the date of diagnosis and of laser surgery.

After delivery, the patients and delivering institutions were contacted to obtain birth weights, gestational age at delivery, and perinatal survival. The birth weights were extracted from the medical records or obtained from the mother, and the measurements were inputted into the database retrospectively. The children were then recruited to participate in a neurodevelopmental assessment study at 24 months (±6 weeks) corrected age. Chronological age correction was performed for all children born before 37 weeks' gestation; the corrected age was defined as 24 months (±6 weeks) from the estimated date of confinement. The children were weighed in the outpatient assessment clinic at Children's Hospital Los Angeles during the neurodevelopmental assessment examination. Thus the weights obtained at 2-year corrected age were acquired prospectively. Weights were converted into percentiles according to standard singleton growth curves [36]. Growth restriction at birth and at the 2-year corrected age assessment was defined as less than the 10th percentile in weight for the given chronological age. Finally, discordance among twin pairs at all study points was calculated as follows: the difference of weight (recipient twin weight minus donor twin weight) divided by the recipient twin weight.

Weight change over time was modeled using multilevel latent growth curve models in Mplus software (version 7.2; Muthén & Muthén, Los Angeles, CA), with twins nested in families and donor status included as an individual (twin) level variable [32]. The robust maximum likelihood estimator (MLR), which is robust to violations of normality, was used in all multilevel analyses given the relatively flat distributions observed in the weight percentile outcomes. This multilevel approach was utilized in this analysis because this methodology extends the general linear regression model by accounting for the genetic and environmental experience that is shared by twins of the same family (the shared or pregnancy level) and the experiences that are unique to each child (the individual or child level). The latent growth curve model further extends this approach. Rather than using regression to predict weight outcomes at each time point directly, we presuppose an underlying ("latent") intercept and slope that characterize growth in this outcome over time, and then use the multilevel regression model to test predictors of the latent intercept and slope. Descriptive statistics and repeated measures analysis of variance (ANOVA) to examine weight discordance over time among twin pairs were conducted using IBM SPSS Statistics software (version 21; SPSS Inc., Chicago, IL).

This study was approved by the Institutional Review Boards of the Health Sciences Campus of the University of Southern California and Children's Hospital Los Angeles.

3. Results

During the study period, 130 consecutive TTTS cases were treated with SLPCV between 16 and 26 weeks' gestation. Of these, 57 families comprising 100 eligible children were enrolled in the study. Fourteen co-twins from these families did not survive the prenatal or neonatal period and therefore could not be assessed at the 2-year follow-up; reliable measurements could not be attained for one additional survivor at the follow-up appointment, resulting in a final analytic sample of N = 99 children from 56 families. Neurocognitive assessments of the surviving children were previously reported [32]. There were no differences between enrolled and non-enrolled patients in donor/recipient status and survival rates, fetal demise, IUGR, Quintero stage, and gestational age at surgery or delivery.

Table 1 summarizes the demographics of the study cases. Of the eligible children, 48.5% were donors. The overall median fetal, birth and 2-year weights were 288 g, 1.9 kg, and 11.8 kg, respectively. The overall prevalence of growth restriction at prenatal diagnosis, birth, and 2-year follow-up was 28%, 22%, and 3%, respectively. Growth restriction rates at prenatal diagnosis were 56% in donors vs. 2% in recipients (OR = 64.3, $p < 0.001$); at birth, 35% vs. 10% (OR = 5.0, $p < 0.01$);

Table 1
Child demographics and weight measures (N = 99).

Child demographics	N (%)
Donor (vs. recipient) status	48 (48.5%)
Male sex	51 (51%)
Race	
White	43 (43%)
Hispanic	37 (37%)
Asian	11 (11%)
Black	5 (5%)
Other/decline to state	3 (3%)
Donor weight outcomes	**Median (IQR) or N (%)**
Fetal measures	
Estimated weight (g)	288 (213–457)
Weight percentile	31 (7–59)
IUGR	28 (28%)
Birth measures	
Weight (kg)	1.9 (1.3–2.2)
Weight percentile	25 (10–50)
IUGR	22 (22%)
Two-year measures	
Weight (kg)	11.8 (11.0–13.2)
Weight percentile	50 (25–75)
GR	3 (3%)

Note: IUGR = intrauterine growth restriction; GR = growth restriction.