Next steps towards improved care for twin anemia polycythemia sequence

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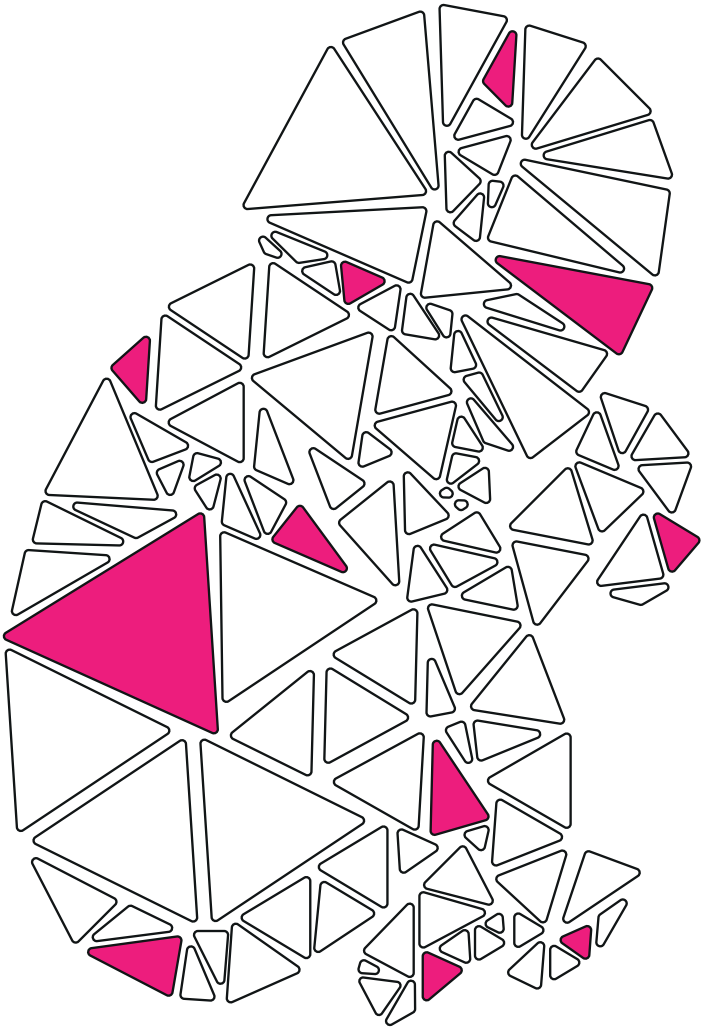

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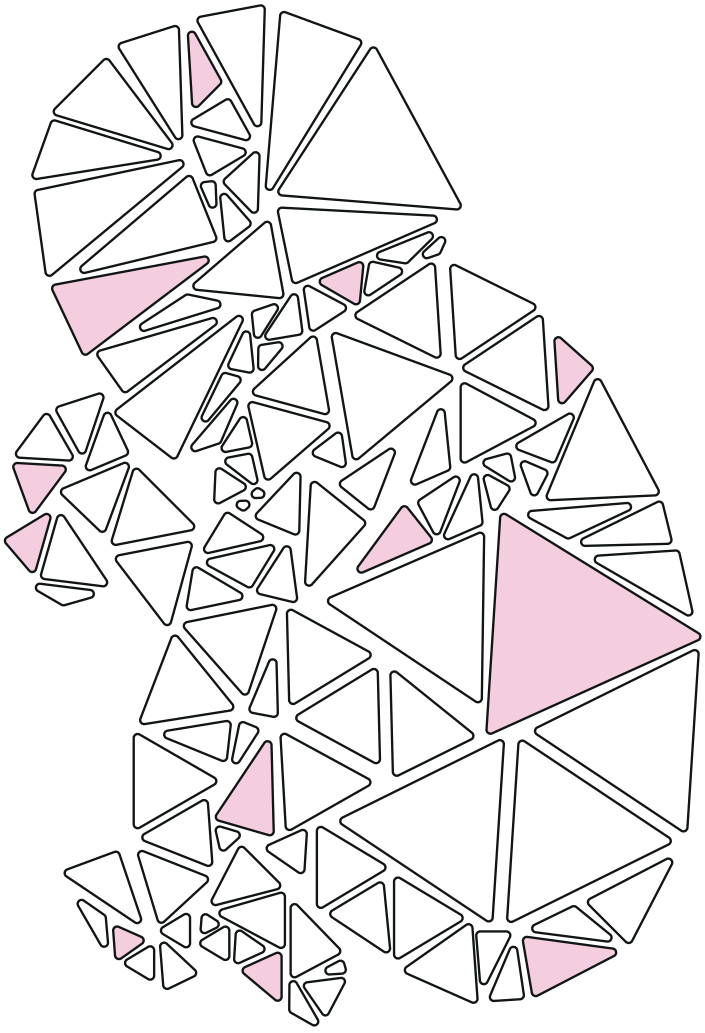
Chapter 6

The TAPS Trial: fetoscopic laser surgery for twin anemia polycythemia sequence - an open-label international multicenter randomized controlled trial (protocol)



Abstract

Background

Twin anemia polycythemia sequence (TAPS) can arise from chronic unbalanced feto-fetal blood flow through miniscule vascular placental anastomoses in monochorionic twins, leading to anemia in the TAPS donor and polycythemia in the TAPS recipient. TAPS is associated with severe short- and long-term outcomes. Management options for TAPS include expectant management, preterm delivery, intra-uterine transfusion in the donor with or without a partial exchange transfusion in the recipient, fetoscopic laser surgery of the placental anastomoses and selective feticide. The best treatment option for TAPS is unknown. We propose to conduct a multi-center open-label randomized controlled trial to assess if fetoscopic laser surgery improves the outcome of TAPS compared to standard care.

Methods

We will randomly assign 44 monochorionic twin pregnancies with TAPS ≥ stage 2, diagnosed between 20+0 and 27+6 weeks of gestation, to the fetoscopic laser surgery group or the standard treatment group (IUT/PET, expectant management, preterm delivery), using a web-based application with a computer-generated list with random permuted blocks, stratified by gestational age at inclusion (20+0-23+6 weeks vs. 24+0-27+6 weeks) and TAPS type (spontaneous vs. post-laser TAPS). Primary outcome will be gestational age at birth; secondary outcomes include a composite of perinatal mortality and severe neonatal morbidity, haematological complications, procedure-related complications and long-term neurodevelopmental outcome at the corrected age of 2 years. Analysis will be intention-to-treat.

Discussion

As TAPS is associated with adverse short- and long-term outcome, investigation of the optimal antenatal management is of utmost importance. This study seeks to gather evidence on the potential beneficial role of laser surgery in the outcome of twins diagnosed with TAPS.

Trial Registration:

NL6879, available at https://www.trialregister.nl/trial/6879

Background

Monochorionic twins share a single placenta and are connected to each other through inter-twin vascular anastomoses, which allow the blood to transfer bidirectionally between the two fetuses. Unbalanced net inter-twin blood transfusion may lead to various complications, including twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS). TTTS was first described in the 19th century and results from an imbalanced inter-twin blood flow causing hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient twin, the so-called twin oligohydramnios-polyhydramnios sequence (TOPS). TAPS is a newly described form of chronic and slow inter-twin blood transfusion through minuscule placental anastomoses leading to anemia in the TAPS donor and polycythemia in the TAPS recipient, without sings of TOPS.[1] TAPS may occur spontaneously in 3-5% of monochorionic twin pregnancies (spontaneous TAPS) or may develop in 2-16% of TTTS cases after incomplete laser surgery of the placental equator resulting in a few small residual anastomoses (post-laser TAPS).[2-6]

TAPS can be diagnosed either antenatally or postnatally. Antenatal diagnosis is based on discrepant Doppler ultrasound measurements of the middle cerebral artery - the peak systolic velocity (MCA-PSV), showing an increased MCA-PSV in the donor twin suggestive of fetal anemia, and decreased velocities in the MCA-PSV in the recipient, suggestive of polycythemia. An inter-twin MCA-PSV differences > 0.5 MoM is indicative for the diagnosis of TAPS.[7] Postnatal diagnosis is based on a large inter-twin hemoglobin difference (> 8 g/dL), and at least one of the following: reticulocyte count ratio > 1.7 (reticulocyte count of donor/ reticulocyte count of recipient) or minuscule placental anastomoses (diameter < 1 mm), detected through color dye injection of the placenta after birth.[8, 9] Since TAPS is a heterogeneous disease, a classification system for both antenatally and postnatally diagnosed TAPS is proposed to help discriminate between different forms of TAPS (Table 1 & 2).

Table 1. Antenatal TAPS classification

Antenatal Stage	Findings at Doppler ultrasound examination
Stage 1	MCA-PSV donor > 1.5 MoM and MCA-PSV recipient < 1.0 MoM, without other signs of fetal compromise
Stage 2	MCA-PSV donor > 1.7 and MCA-PSV recipient < 0.8 MoM, without other signs of fetal compromise
Stage 3	As stage 1 or 2, with cardiac compromise of the donor, defined as critically abnormal flow[a]
Stage 4	Hydrops of donor
Stage 5	Intrauterine demise of one or both fetuses preceded by TAPS

[a] Critically abnormal Doppler is defined as absent or reversed end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein, increased pulsatility index or reversed flow in the ductus venosus

Table 2. Postnatal TAPS classification

Postnatal stage	Inter-twin Hb difference, g/dL
Stage 1	> 8.0
Stage 2	> 11.0
Stage 3	> 14.0
Stage 4	> 17.0
Stage 5	> 20.0

Neonatal outcome in TAPS may vary from isolated large inter-twin hemoglobin differences to severe cerebral injury and neonatal death.[10-12] Due to polycythemia-hyperviscosity syndrome, TAPS recipients are at risk of developing thrombocytopenia and ischemic limb injury.[8, 13] TAPS donors have increased chances to develop hypoalbuminemia, hypoproteinemia, leukopenia and short-term renal dysfunction.[14-16] Long-term outcome studies show that severe neurodevelopmental impairment occurs in 9% of TAPS survivors.[17, 18] TAPS donors had an increased risk for adverse outcome and showed high rates of cognitive delay and hearing problems.

Antenatal management options for TAPS include expectant management, fetoscopic laser coagulation of the vascular equator of the placenta, intra-uterine blood transfusion (IUT) in the donor with or without a partial exchange transfusion (PET) in the recipient, induced preterm delivery and selective feticide. However, the best management option for TAPS is not clear. Fetoscopic laser coagulation of the anastomoses at the vascular equator of the placenta is

the only causative treatment. Although laser surgery is proven to be effective in decreasing perinatal mortality and morbidity in TTTS,[19] data on the beneficial effect of laser therapy in TAPS are scarce. Importantly, laser surgery in TAPS may be technically more challenging than in TTTS, due to the absence of TOPS, preventing optimal visualization of the vascular equator. An alternative treatment option is performing an IUT in the anemic donor. However, IUT is only a symptomatic treatment and therefore reintervention up to 2-4 times (depending on the gestational age at diagnosis, severity of the disease and occurrence of complications) might be necessary. Moreover, a potential side effect of IUT is worsening of polycythemia in the recipient. To reduce the risk of increasing polycythemia a combination procedure of IUT in the donor and PET in the recipient can be of additional value. However, despite its temporary character, IUT (with PET) may be easier to perform and technically more feasible than laser therapy.

There are only a few studies on outcome of laser therapy for TAPS pregnancies.[20-24] In a small multicenter retrospective study where laser treatment is compared to IUT or expectant management, laser therapy appeared to improve the perinatal outcome by prolonging the pregnancy and reducing the incidence of respiratory distress syndrome.[25] Sananes et al. found the same result in a single center prospective cohort study, comparing in-utero therapy (laser surgery and IUT) to expectant management in TAPS twins.[26] A recent analysis of our own data, performed in October 2018 for the purpose of this trial proposal, shows that laser therapy might have a beneficial effect on gestational age at birth, severe neonatal morbidities and long-term neurodevelopmental outcome when compared to IUT(+ PET) or expectant management (Table 3) However, in all the above-mentioned studies analyses, study groups were small (N= 6 – 15) and due to the retrospective character of these analyses, data might have been subject to selection bias.

We therefore propose to conduct a randomized controlled trial to evaluate the possible beneficial effect of fetoscopic laser surgery and to determine the most optimal management option for TAPS.

Table 3. The outcome of TAPS twins ≥ stage 2, gestational age at diagnosis < 28w, based on the analysis of our own data (2003-2018) in October 2018.

	Expectant (N=16)	**IUT (+PET) (N=16)**	**Laser (N=15)**
GA at birth	31.0 (27.8-24.6)	28.2 (25.8-31.7)	32.3 (30.1-35.7)
Fetal demise	3/32 (9)	6/32 (19)	5/30 (17)
Neonatal mortality	5/32 (16)	2/32 (6)	0/30 (0)
Perinatal survival	24/32 (75)	24/32 (75)	25/30 (83)
Severe neonatal morbidity	12/28 (43)	10/16 (39)	2/25 (8)
NDI	10/19 (53)	6/19 (32)	2/18 (11)
Severe NDI	4/19 (21)	1/21 (5)	1/18 (6)

Data are presented as median (IQR) or n/N (%)
IUT = intrauterine transfusion, PET = partial exchange transfusion, GA = gestational age, NDI = neurodevelopmental impairment

Methods

Aim

The primary aim of this trial is to investigate whether laser surgery will prolong pregnancy in TAPS twins. Prolonging pregnancy is known to be of paramount importance for neonatal and long-term neurodevelopmental outcome. Low gestational age at birth is independently associated with increased risk for severe neonatal morbidity.[27, 28] In addition, we will study perinatal mortality, neonatal morbidity, hematological complications, procedure-related complications and long-term neurodevelopmental outcome in this population.

Design

The design of this study will be a multicenter open-label randomized controlled trial. We will randomly assign monochorionic twin pregnancies diagnosed with TAPS ≥ stage 2 between 20+0-27+6 weeks of gestation to the fetoscopic laser surgery group or the control group, using a web-based application (*Castor*) with a computer-generated list with random permuted blocks, stratified by gestational age at inclusion (20+0 – 23+6 weeks vs. 24+0-27+6 weeks) and TAPS type (spontaneous vs. post-laser TAPS). Analysis will be performed according to the intention-to-treat principle. The outcome adjudication will be performed blinded to group allocation.

Participants

Our study population will consist of patients diagnosed with a monochorionic twin pregnancy complicated with TAPS. In order to be eligible to participate in this study, the patient must meet all of the following criteria (1) having monochorionic twin pregnancy complicated by either spontaneous or post-laser TAPS, stage ≥ 2, diagnosed between 20+0 - 27+6 weeks of gestation (2) being 18 years or more (3) be able to give written informed consent. Women were not eligible when one of the following criteria was applicable (1) TAPS stage 1 (2) TAPS stage ≥ 2, diagnosed within 1 week after laser surgery for TTTS (3) TAPS diagnosed in a triplet or higher order multiple pregnancy (4) TAPS who already underwent an intrauterine treatment (except for laser surgery for TTTS in post-laser TAPS cases) (5) TAPS with co-existent congenital anomalies (including severe cerebral injury) in one or both twins.

Procedure

Eligible women will be randomly allocated to the experimental group or the control group. Women allocated to the experimental group will receive laser therapy within 72 hours after randomization. Women allocated to the control group will be treated with standard care. Standard care includes IUT (with or without PET), preterm delivery or expectant management, depending on the judgement of the fetal surgeon and the preference of the patient. In both groups, antenatal, peripartum and postnatal care of the mother will be similar to that of uncomplicated monochorionic twin pregnancies. After birth, a full blood count (including reticulocyte count) is performed as part of the standard postnatal care for TAPS twins. In addition, all participants will be asked for permission to inject the placenta with color dye. During neonatal period, no additional follow-up examinations other than the regular care for premature neonates will be performed. At the corrected age of 2 years (corrected age is defined as chronological age in months – #months premature), all TAPS survivors of both groups will undergo a neurological examination and an assessment of cognitive and motor development (BSID-III) and parents will fill in a screening list for developmental delay (ASQ) and a checklist for child behavior (CBCL). An overview of the design of the study, including a timeframe for assessment for each outcome, is depicted in Figure 1.

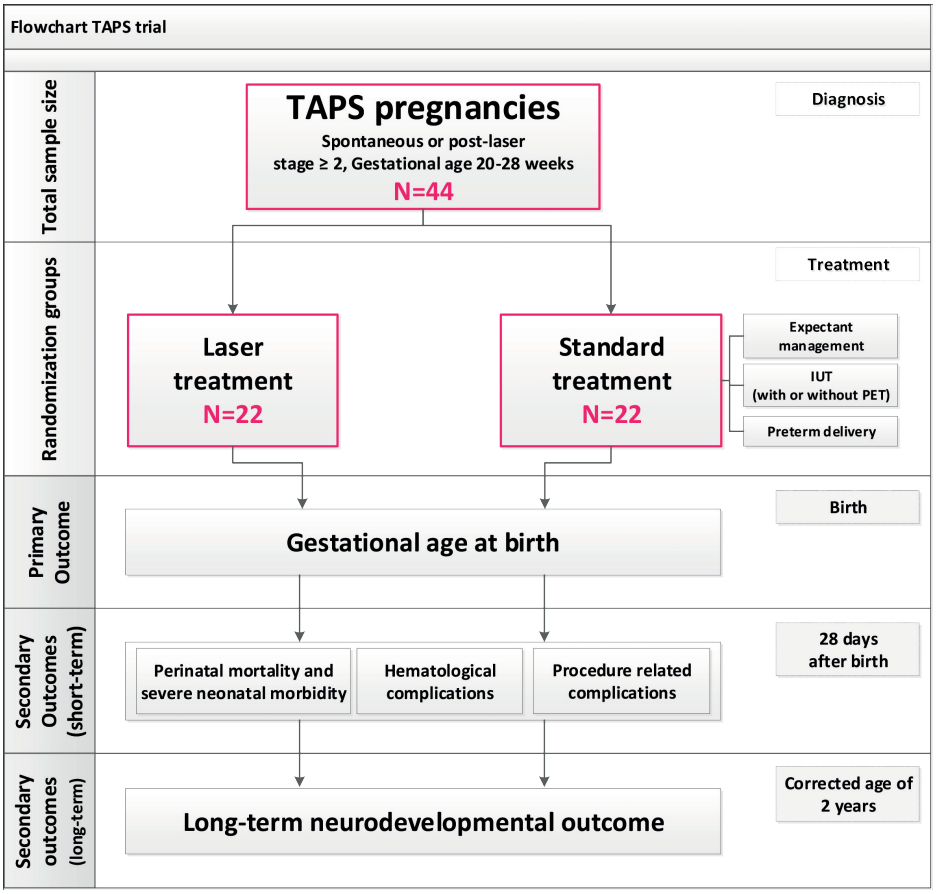


Figure 1. Overview of the design of the TAPS Trial, including a time frame for assessment for each outcome parameter. TAPS; twin anemia polycythemia sequence; IUT, intrauterine transfusion; PET, partial exchange transfusion; GA, gestational

Experimental treatment

In the experimental group, laser surgery must be performed within 72 hours after randomization. Fetoscopic laser surgery will be done under local or regional anesthesia by experienced fetal surgeons. Each surgeon has performed at least 60 previous laser procedures and is competent to undertake the Solomon technique. First, by continuous ultrasound visualization, a cannula will be introduced into the amniotic cavity of the recipient twin either by the Seldinger technique or by sharp trocar insertion. Depending on the gestational age, a 1.3 mm or 2.0 mm fetoscope (Karl Storz, Tuttlingen, Germany) and 7-10 Fr cannula will be used. After identifying the vascular anastomoses, a 400 µm or 600 µm laser fiber connected to a diode or Nd:YAG laser device

(Dornier MedTech, Westling Germany) will be introduced trough the opening sheath. All visible anastomoses will be coagulated using one to three bursts of a few seconds each with a power setting of 20-50 W, depending on the vessel diameter. After coagulation of all the visible anastomoses, the Solomon technique will be performed: to connect the white areas that resulted from coagulation of the anastomoses, a thin line of tissue at the placental surface will be coagulated from one edge of the placenta to the other at a power setting of 20-50 W. Follow-up will consist of close monitoring with ultrasound including Doppler measurements of the MCA-PSV at least biweekly.

Standard treatment

In the control group the choices of treatment include expectant management, IUT (with or without PET) or preterm delivery, depending on the judgment of the fetal surgeon with regard to the gestational age and stage of TAPS. Treatment with laser surgery will not be performed in the control group; this procedure will solely be performed in the experimental group.

- *Expectant management:* Expectant management will consist of close monitoring with ultrasound including Doppler measurements of MCA-PSV, at least every week. Since no (intrauterine) intervention is performed to mitigate or resolve the symptoms of TAPS, twins managed expectantly might deteriorate during the course of pregnancy. Depending on the judgement of the caretaker regarding the condition of the fetuses, ultrasound evaluation can be performed more frequent and admission to the hospital for fetal monitoring with cardiotocography (CTG) can take place. In case of progression, the caretaker can decide to perform IUT (with or without PET) or preterm delivery.

- *IUT (with PET):* Treatment with IUT can be performed either intravascularly into the umbilical cord, intrahepatic in umbilical vein or indirectly via the peritoneal cavity. The choice of transfusion site is left up to the caretaker, and will be based on the position of the fetus. Since IUT is not a definitive treatment and is only a temporary solution, the donor may become anemic and the recipient even more polycythemic, and the MCA-PSV levels may return to their pre-transfusion levels. Therefore, repeated IUT may be required. In case of polycythemia in the recipient, a combination of IUT in the donor with PET in the recipient may be envisaged. With PET, 5-10 ml of

the recipient's blood will be removed slowly and will be replaced with saline, repeatedly. A follow-up scan will be performed the same day or following day and one week after intervention to check for the condition of the fetuses. Further follow-up during the course of the pregnancy will be the same as in the pregnancies managed expectantly and will consist of close monitoring with ultrasound including Doppler measurements of the MCA-PSV at least every week.

- *Preterm delivery:* Generally, all monochorionic twin pregnancies receive induction of labor or cesarean section at 36 weeks of gestation. However, the caretaker might opt for a preterm delivery in some cases.
    - Criteria for performing a preterm delivery (for both the experimental and control group) are: signs of fetal distress (suboptimal or abnormal CTG in one or both fetuses, worsening of the condition of one or both fetuses without the option of (re)intervention with IUT (+PET)), intrauterine infection or iatrogenic monoamnionicity.

Outcome variables

The primary outcome will be gestational age at birth (in completed weeks and additional days). The secondary outcomes will include a composite outcome of perinatal mortality or severe neonatal morbidity, hematological complications, procedure-related complications, and long-term neurodevelopmental outcome at the corrected age of 2 years. Perinatal mortality will be defined as fetal demise or neonatal death within 28 days after birth. Severe neonatal morbidity is based on the presence of at least one of the following: respiratory distress syndrome requiring mechanical ventilation or surfactant, proven early onset neonatal sepsis (positive blood cultures within 72 hours post-partum), retinopathy of prematurity (ICROP stage 3 or higher[29]), necrotizing enterocolitis (stage 2 or higher[30]), patent ductus arteriosus requiring medical therapy or surgical closure, and/or severe cerebral injury. Severe cerebral injury was diagnosed if one of the following was identified on cerebral imaging: intra-ventricular hemorrhage (grade 3 or higher[31]), cystic periventricular dilatation (> 97th percentile[32]), porencephalic or parenchymal cysts, or other severe cerebral lesions associated with adverse neurological outcome. Hematological complications were defined as: anemia in the donor requiring a blood transfusion within 24 hours after birth, polycythemia in the recipient requiring

a partial exchange transfusion within 24 hours after birth, necrotic skin injury, limb ischemia, thrombocytopenia (platelet count < 150/microL), severe hypoalbuminemia (albumin levels < 20 g/dL), severe hypoproteinemia (protein levels < 40 g/L). The definition of procedure-related complications was based on one of the following: amniotic band syndrome, iatrogenic monoamnionicity, preterm premature rupture of the membranes, placental abruption, clinical chorioamnionitis, histological chorioamnionitis and/or funisitis. Long-term neurodevelopmental outcome at the corrected age of 2 years was assessed with the following instruments: Bayley Scales of Infant and Toddler Development version 3 (BSID-III)[33], and/or Ages and Stages Questionnaire (ASQ-3)[34], Child Behavior Checklist (CBCL 1.5-5y).[35] Neurodevelopmental impairment (NDI) was defined as: cerebral palsy (gross motor function classification system (CMFCS) grade 1[36]), cognitive or motor delay (score < 85 according to BSID-II(33)), impaired functioning in communication/fine and gross motor/problem solving personal and social functioning (score > 1SD below the mean according to the ASQ-3[34]), severe visual loss (blind or partially sighted), severe hearing loss (needing hearing aids). Severe NDI is classified as: cerebral palsy (GMFCS > grade 1[36]), severe cognitive or motor delay (score < 70 according to the BSID-III[33]), severely impaired functioning in communication/fine and gross motor/problem solving/personal and social functioning (as assessed with the ASQ-3[34]), bilateral blindness (visual acuity of less than 3/60 in the better eye[37]), bilateral deafness (severe or profound hearing loss in both ears[38]). Behavioral problems were defined as a T-score ≥ 64 for one of the following broad band scales: total problem score, internalizing problems (anxious/depressed, withdrawn, somatic complaints), externalizing problems (rule-breaking, aggressive behavior) as assessed with the CBCL 1.5-5y.[35]

Data collection of non-randomized patients

In order to demonstrate a representative sample of included patients, coded data of non-randomized patients will be collected. Data will include maternal, fetal and neonatal baseline characteristics as well as outcome parameters: gestational age at birth, perinatal mortality and severe neonatal morbidity, hematological complications and procedure related complications. The collected data for the non-randomized patients will include the same parameters as used for the randomized patients. Data will be stored in the Castor database.

Sample-size calculation

Based on the analysis of 95 TAPS twins stored in in our database between 2003-2017, we expect a prolongation of pregnancy of 3 weeks for the group treated with laser therapy (mean gestational age at birth: 32 weeks) compared to the group treated with standard care (mean gestational age at birth: 29 weeks). Based on these expected values, group sample sizes of 22 achieve 80% power to detect a difference of 3 weeks between the null hypothesis that both groups means are 29 weeks of gestational age, and the alternative hypothesis that the mean gestational age of the laser group is 32 weeks, with estimated group standard deviations of 3.1 and 3.5 and with a significance level (alpha) of 0.05 using a two-sided Mann-Whitney U test. With the expected number of TAPS pregnancies referred to at least 5 participating centers, this would mean an inclusion period of 2.5-3 years.

Statistical analyses

Continuous data will be reported as median (interquartile range) and will be compared between groups using the Mann-Whitney U test. Proportions will be reported as n/N (%) and compared between groups using the χ^2 test or the Fisher's exact test where appropriate. Differences with a p-value of less than 0.05 will be regarded as statistically significant. To account for the fact that observations between co-twins are not independent, outcome for management groups will be compared using the Generalized Estimated Equation (GEE) module.

Discussion

According to previous literature, TAPS is associated with high rates of perinatal mortality and short- and long-term morbidity, mainly in TAPS donors.[12, 17, 18] A strong risk factor for adverse outcome is gestational age at birth. In order to improve the outcome for TAPS twins, it is of paramount importance to determine the most optimal management strategy for this condition. Fetoscopic laser surgery is the only treatment that is aimed at treating the cause of TAPS and prolonging pregnancy. In the TAPS Trial, a multicenter open-label randomized controlled trial, we will investigate the possible beneficial effect of laser treatment on gestational age at birth, perinatal mortality and neonatal morbidity, and long-term outcome.

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