Early versus late intervention for twin reversed arterial perfusion sequence: an open-label randomized controlled trial

"TRAPIST": TRAP Intervention STudy

version	Date	Highlights of changes
1.0	12-07-2015	
1.1	21-10-2015	Added participating centers: Auckland and UCLH
1.2	1-3-2016	Correction name website www.monochorionictwins.org

		(active March 2016), added Fabio Peralta Brasil
1.3	16-05-2016	Interval late intervention extended to 19 weeks (instead of 18 weeks) to allow 1.3 mm fetoscopic laser at the request of J. Stirnemann

Summary

Description: Clinical trial comparing early versus late intervention in TRAP Sequence

Title: Early versus late intervention for twin reversed arterial perfusion sequence: an open-label randomized controlled trial

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Monitoring Data Committee: Ed Juszczak (Clinical Trialist, University of Oxford, UK), Magnus Westgren (Fetal Medicine Specialist, Karolinska Institute, Sweden), Colin Morley (Pediatrician, University of Cambridge, UK), Keith Reed (parent organisation, TAMBA, London, UK)

Study design: Multi-center open-label randomized controlled trial to assess if early intervention (12.0-14.0 weeks) (study group) improves the outcome of TRAP sequence as compared to late intervention (16.0-19.0 weeks) (control group). We will randomly assign women diagnosed with TRAP sequence diagnosed between 12.0 and 13.6 weeks to an early or late intervention group (1:1), using a web-based application and a computer-generated list with random permuted blocks of sizes 2 or 4 (www.sealedenvelope.com), stratified by gestational age (GA) at inclusion (11.6 -12.6 weeks versus 13.0-13.6 weeks). Analysis will be by intention to treat.

Primary outcome: pump twin neonatal survival and birth at or after 34.0 weeks.

Secondary outcomes: need for re-intervention, maternal morbidity, gestational age at birth, neonatal outcome, 2-year neurodevelopmental outcome,

Study population: Women expecting monochorionic diamniotic twin pregnancies diagnosed with TRAP sequence between 11.6 and 13.6 weeks with a minimum age of 18 years, eligible for early intrauterine treatment and willing to participate in the study after informed consent.

Sample size: To detect a difference of 25% in neonatal survival and birth at or after 34 weeks between the early (75%) and late (50%) intervention groups, 58 women will need to be included in each arm to achieve at least 80% power at a significance level (alpha) of 0.05 using a Pearson's chi-squared test. To account for 2 interim analysis using the O' Brien-Fleming rule and a 5% loss to follow-up rate, 63 instead of 58 women will need to be included in each arm.

Study calendar: Start recruitment: January 1st, 2016. End recruitment: December 31st, 2019. Publication April 2020. End neurodevelopmental follow-up: June 2022. Publication outcome September 2022.

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1. General information

1.1. Title, protocol identifying number and date.

Early versus late intervention for twin reversed arterial perfusion sequence: an open-label randomised controlled trial

Acronym: TRAPIST, TRAP Intervention STudy

ClinicalTrials.gov identifier: NCT02621645

Information for the public and health care providers : www.monochorionictwins.org

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2. Rationale

2.1. Justification of the relevance of the trial.

2.1.1. Background

Twin reversed arterial perfusion sequence (TRAP) is a rare anomaly unique to monochorionic twin pregnancies, with an estimated prevalence of 1 in 35 000 pregnancies but with a mortality of more than 50% for the healthy pump twin[1]. Monochorionic twins are identical and share a single placenta with vascular anastomoses that connect the two fetal circulations. TRAP is a complication of this shared circulation and occurs if one of the twins dies in early pregnancy.

In TRAP, blood flows from a structurally normal pump twin in a reverse direction towards its demised co-twin, which becomes a true parasite without cardiac activity from its own, hence also called the acardiac twin. TRAP is nowadays diagnosed already at the 12 weeks ultrasound scan and is characterized by a monochorionic twin pregnancy with one structurally normal and one grossly abnormal twin (Figure 1).

Figure 1: Ultrasound image at 12 weeks of healthy pump (left) and abnormal acardiac twin (right)

TRAP caries a high risk of death of the pump twin, which can be reduced significantly by an intrauterine intervention to arrest the reverse circulation of the acardiac twin[2, 3]. Ultrasound-guided intrafetal coagulation as well as fetoscopic coagulation of the cord and/or anastomosing vessels have been described to arrest the reverse flow. For intrafetal coagulation, a needle is positioned in the acardiac twin under

ultrasound guidance near its umbilical cord insertion and laser, radiofrequency, monopolar or microwave ablation is used to arrest the reverse flow (Figure 2)[2]. Coagulation of the umbilical cord and/or anastomosing vessel is performed using laser energy under endoscopic guidance[3].

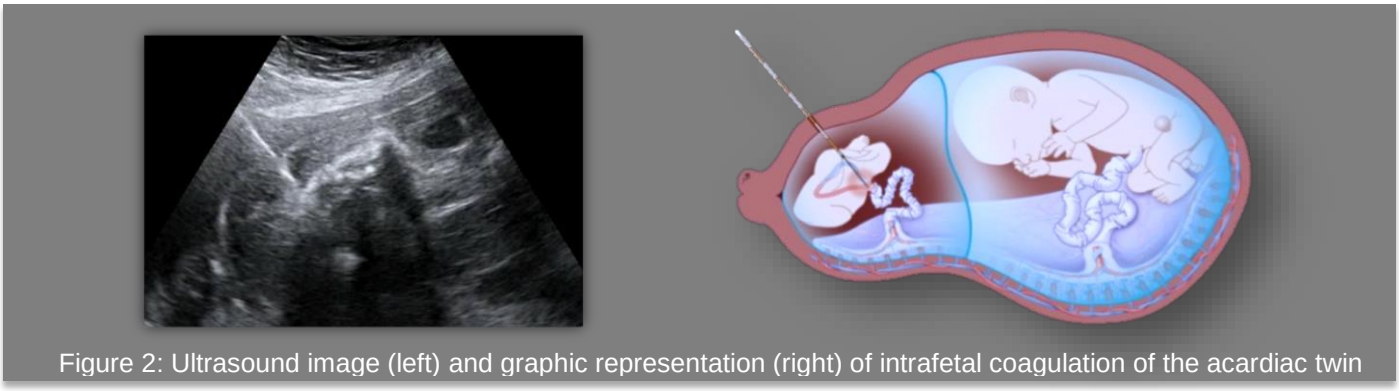


Figure 2: Ultrasound image (left) and graphic representation (right) of intrafetal coagulation of the acardiac twin

Traditionally, these interventions are carried out only after 16 weeks of gestation. Before this time period, the amniotic and chorionic membranes are still separated by the exocoelomic cavity and experience with amniocentesis before 16 weeks suggested that the risk of membrane rupture and miscarriage is substantially increased if performed before obliteration of the exocoelomic cavity[4-6]. Also, TRAP was usually only first diagnosed at the time of the 20 weeks anomaly scan. However, most cases are now diagnosed already by 12 weeks as a consequence of the widespread introduction of this early scan in the screening for chromosomal anomalies[7].

If the pump twin survives to 16 weeks and is treated thereafter, approximately 80% will survive[8]. However, a major disadvantage of delaying the intervention until after 16 weeks' gestation is the high mortality of the pump twin (up to 33%) between the diagnosis at 12 weeks and the planned intervention at 16 weeks[9]. These early demises are entirely unpredictable[9]. As such, the survival rate for TRAP diagnosed at 12 weeks and treated after 16 weeks is estimated to only about 50%[8 9]. Also, a recent meta-analysis demonstrated an inverse relationship between gestational age at treatment and gestational age at birth, suggesting that an earlier intervention may decrease the risk of very preterm birth. An intervention at 12-14 weeks may thus prevent the early deaths and reduce the risk of very preterm birth, but might also increase the risk the miscarriage because of premature rupture of the membranes.

2.1.2. Preliminary data

The promotor is the first author of the above-mentioned study that demonstrated the high loss rate of pump twins between the diagnosis at 12 weeks and the planned intervention after 16 weeks, which raised the current question of whether an earlier intervention might improve outcome[9]. Several case series reported by other investigators participating in this trial have shown the feasibility, safety and effectiveness of intrafetal laser coagulation at 12-14 weeks (n=19)[2, 10-12], but a randomized controlled trial (RCT) is necessary to examine whether an early intervention at 12 weeks prevents the death of those who would have died before 16 weeks, without worsening the outcome of those that are now treated after 16 weeks.

All investigators are part of an active research network for studies in monochorionic twin pregnancies. The most important publications of the consortium are the RCT on fetoscopic laser surgery versus amnioreduction for the treatment of twin transfusion syndrome, published in the NEJM in 2004[13] and the RCT on a new laser technique for twin transfusion syndrome, published in the Lancet in 2014[14].

2.2. Description of the study population.

Patients will be invited to participate in the trial if they are referred to the fetal medicine unit between 11.6-13.6 weeks, expecting monochorionic diamniotic twins diagnosed with TRAP sequence, if the normal pump twin is structurally normal, if they are more than 18 years old and opt for an intrauterine intervention that can be safely performed in the 12.0-14.0 weeks window.

2.3. Statement testing will be done according to the protocol, Good Clinical Practice and applicable legal requirements.

The trial will be conducted by the sponsor, participating sites and all investigators in accordance with the protocol, the Declaration of Helsinki, the guidelines on Good Clinical Practice (GCP) and all legal requirements, including applicable national legislation, for the conduct of this trial.

3. Objective

The aim is to investigate if an early intervention (between 12.0 and 14.0 weeks) improves the outcome for the pump twin as compared to a late intervention (16.0-19.0 weeks). The hypothesis is that an earlier intervention will prevent unpredictable early pump twin demise and prolong gestation. The rationale of the combined primary outcome of survival and absence of very preterm birth is that the purpose is not only survival, but survival of healthy infants, which is more likely if birth is after 34.0 weeks.

4. Design

4.1. Specific description of primary and secondary variables.

Primary outcome

✓Neonatal survival and birth at or after 34.0 weeks of the pump twin (proportion)

Secondary outcomes

✓Need for re-intervention, such as repeat intervention or intrauterine transfusion (proportion)

✓Maternal morbidity (proportion)

- Need for transfusion for hemorrhage
- Abruption
- Chorioamnionitis as defined on pathology
- Sepsis
- Bowel perforation
- Other serious maternal morbidity requiring admission to the intensive care unit (ICU)

✓Preterm birth

- Miscarriage
- Time from randomization to birth (weeks)
- Preterm prelabor rupture of membranes (PPROM)(proportion) and time from randomization to PPROM (weeks)
- Preterm birth <28, <32, <37 weeks (proportion)

✓Neonatal outcome

- Birth weight (grams)
- Stillbirth (proportion)
- Neonatal death (proportion)
- Severe neonatal morbidity (proportion) defined as the presence of at least one of the following: chronic lung disease (defined as oxygen dependency at 36 weeks gestational age), patent ductus arteriosus needing medical therapy or surgical closure, necrotising enterocolitis grade 2 or higher, retinopathy of prematurity stage 3 or higher, ischemic limb injury, amniotic band syndrome, or severe cerebral injury. Severe cerebral injury includes at least one of the following: intraventricular hemorrhage grade 3 or higher, cystic periventricular leukomalacia grade 2 or higher, ventricular dilatation greater than the 97th percentile, porencephalic or parenchymal cysts, or other severe cerebral lesions associated with adverse neurological outcome[15]

✓Per protocol analysis and comparison of high volume vs low volume centers of primary outcome and maternal morbidity parameters

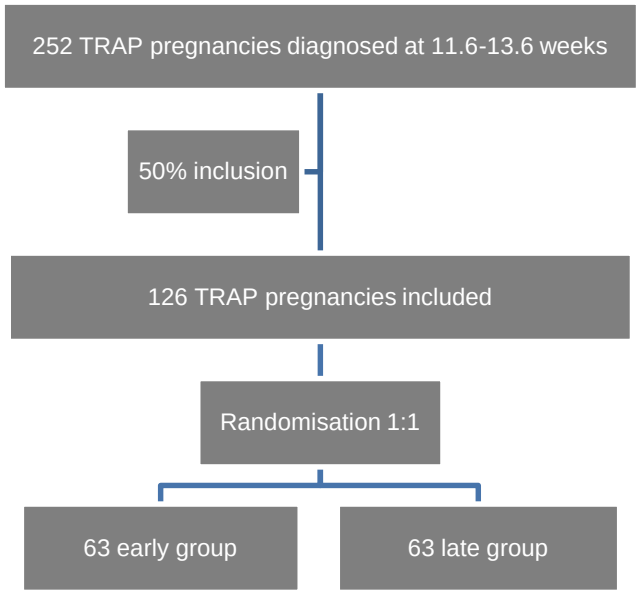
✓2-year neurodevelopmental outcome

- Intact survival rate (proportion) defined as the number of surviving infants with normal development at two years of age corrected for prematurity as assessed by the ASQ® score for infant development. A score of more than 2 SD below the mean score for term-born children will be considered abnormal. Centers that have a follow-up scheme in place, may additionally report the Bayley III score[18].

4.2. Description of the trial design.

We propose to conduct a multi-center open-label randomized controlled trial to assess if early intervention (12.0-14.0 weeks) (study group) improves the outcome of TRAP sequence as compared to late intervention (16.0-19.0 weeks) (control group). We will randomly assign women diagnosed with TRAP sequence diagnosed between 11.6 and 13.6 weeks (1:1) to an early or late intervention group, using a web-based application (www.sealedenvelope.com) with a computer-generated list with random permuted blocks of sizes 2 or 4, stratified by gestational age at inclusion (11.6 -12.6 weeks versus 13.0-13.6 weeks). Analysis will be by intention-to-treat. Outcome will be adjudicated blinded to group allocation.

4.3. Flowchart.



4.4. Description of the intervention.

All interventions will be done under local anaesthesia and/or conscious sedation in sterile conditions by an experienced operator. They must be performed within 1 week after randomisation and at the latest at 14.0 weeks in the early group and 19.0 weeks in the late group. In the early group, only intrafetal coagulation will be used. Intrafetal ablation will be performed under ultrasound guidance using an 18-gauge (1.27 mm) to 20-gauge (0.91 mm) needle with a free-hand technique. The needle is introduced into the pelvis/abdomen of the TRAP mass close to the intra-abdominal portion of the feeding vessel, while avoiding puncture of the placenta and pump twin sac. The procedure is considered successful when there is complete cessation of reverse flow into the TRAP mass on intraoperative color-flow mapping.

In the late intervention/control group either intrafetal coagulation or fetoscopic laser coagulation will be performed of the cord and/or anastomosing vessels, unless the flow has stopped spontaneously or demise of the pump twin has occurred in the meantime. Intrafetal coagulation is done as described above by using a 17-gauge (1.47 mm) to 20-gauge needle. Alternatively, fetoscopic laser coagulation of the cord or anastomosing vessels can be performed through a 17-gauge to 7 Fr trocar and 1 -1.3 mm fetoscope and 400 µm laser fiber. The rationale not to standardize the technique in the late intervention group is that several techniques have been reported for treatment after 16 weeks without any significant differences in outcome[8]. Also, it is usual for the surgeon to adapt the technique to the requirements of each individual case, e.g. for a posterior placenta, he/she may prefer fetoscopic rather than intrafetal coagulation. Not restricting the technique to only 1 option will therefore more truly represent current practice and increase the generalizability of the trial's findings.

Patients will be discharged the same day or 1 day after the procedure. Management and follow-up will be similar for the study and the control or current practice group. A follow-up scan is usually performed 1 week after the intervention to check for fetal well-being and exclude anemia. A detailed ultrasound scan will be arranged in a fetal medicine center at 20 and 30 weeks to assess the heart and brain anatomy. Some centers may offer an MRI scan at around 30 weeks as part of the protocol for monochorionic twin pregnancies that underwent an intrauterine intervention. Antenatal, peripartum and postnatal care of the mother will be similar to that of a singleton pregnancy and at the discretion of the referring physician. Intrauterine intervention for TRAP sequence is not an indication for cesarean or elective preterm birth.

4.5. Expected duration of subject's participation.

The duration of the subject's participation will be 2.5 years from the time of randomization (11.6-13.6 weeks) to the completion of the study (corrected age of 2 years). At the corrected age of two years, parents will be invited to fill out the parent-completed Ages and Stages Questionnaire (ASQ®) to assess neurodevelopmental outcome of their infants.

4.6. Maintenance of the randomization codes.

We will use a web-based application (www.sealedenvelope.be) with a computer-generated list with random block sizes of two to four, stratified by gestational age at inclusion (12.0 -12.6 weeks versus 13.0-13.6 weeks). The investigators will be blinded to the randomization sequence.

4.7. Definition of what is considered to be the end of the study.

The study will end after assessing the neurodevelopmental outcome by the parent-completed Ages and Stages Questionnaire (ASQ®) at 2 years of age corrected for prematurity of the surviving children.

5. Selection and withdrawal of subjects

5.1. Inclusion criteria.

✓TRAP sequence in a monochorionic diamniotic twin pregnancy diagnosed between 11.6 and 13.6 weeks, as determined by the crown-rump length of the pump twin in spontaneous conceptions and by the date of insemination or embryonic age at replacement in pregnancies resulting from subfertility treatment
✓Women aged 18 years or more, who are able to consent
✓Anatomically normal pump twin
✓Provide written informed consent to participate in this RCT, forms being approved by the Ethical Committees

5.2. Exclusion criteria.

✗Contraindication for an intervention due to a severe maternal medical condition or threatening miscarriage
✗Inaccessibility of the acardiac twin due to a retroverted uterus, severe maternal obesity, uterine fibroids, bowel or placental superposition
✗A major anomaly in the pump twin, requiring surgery or leading to infant death or severe handicap
✗Spontaneous arrest of the reverse flow and/or pump twin demise at diagnosis

Patients diagnosed with TRAP sequence will be informed about the nature of the disease, the expected outcome and the possible management options including termination of pregnancy, expectant management and intrauterine intervention. Patients who opt for an intervention and who are eligible for participation will be invited by the fetal medicine specialist at the time of diagnosis. Patients that are not eligible or eligible but not willing to participate will be invited to partake in the TRAP Registry to collect the pregnancy and long-term neurodevelopmental outcome of all first trimester TRAP pregnancies not included in the trial (see separate protocol). Principal investigators can download patient information leaflets and informed consent forms in Dutch, English, German, Italian, Spanish and Hebrew from the study website (www.TRAPISTtrial.eu).

5.3. Withdrawal criteria.

No patient will be withdrawn from the study after randomisation by the investigators. However, every participant can voluntarily withdraw from participation at any time, without any implications for her future care.

6. Efficacy assessment

6.1. Specification of efficacy parameters: Primary and secondary endpoints.

Primary outcome:

✓Neonatal survival and birth at or after 34.0 weeks of the pump twin

Timeframe for assessment: 2 weeks after expected date of birth

Secondary outcomes:

✓Need for re-interventions, such as repeat intervention or intrauterine transfusion

Timeframe for assessment: 2 weeks after expected date of birth

✓Maternal morbidity

- Need for transfusion for hemorrhage
- Abruption
- Chorioamnionitis as defined on pathology
- Sepsis
- Bowel perforation
- Other serious maternal morbidity requiring admission to ICU

Timeframe for assessment: 2 weeks after expected date of birth

✓Preterm birth

- Miscarriage
- Time from randomization to birth
- PPROM and time from randomization to PPROM
- Preterm birth <28, <32, <37 weeks

Timeframe for assessment: 2 weeks after expected date of birth

✓Neonatal outcome

- Birth weight (grams)
- Stillbirth
- Neonatal death
- Severe neonatal morbidity defined as the presence of at least one of the following: chronic lung disease (defined as oxygen dependency at 36 weeks gestational age), patent ductus arteriosus needing medical therapy or surgical closure, necrotising enterocolitis grade 2 or higher, retinopathy of prematurity stage 3 or higher, ischemic limb injury, amniotic band syndrome, or severe cerebral injury.
  Severe cerebral injury includes at least one of the following: intraventricular hemorrhage grade 3 or higher, cystic periventricular leukomalacia grade 2 or higher, ventricular dilatation greater than the 97th percentile, porencephalic or parenchymal cysts, or other severe cerebral lesions associated with adverse neurological outcome[15]

Timeframe for assessment: 42 days (28 days neonatal period+2 weeks postdates) after expected date of birth

✓Per protocol analysis and comparison of high volume vs low volume centers of primary outcome and maternal morbidity parameters
Timeframe for assessment: 2 weeks after expected date of birth

✓2-year neurodevelopmental outcome

- Intact survival rate defined as the number of surviving infants with normal development at two years corrected for prematurity as assessed by the ASQ® score for infant development. A score of more than 2 SD below the mean score for term-born children will be considered abnormal. Centers that have a follow-up scheme in place, may additionally report the Bayley III score.

Timeframe for assessment: 2 years after expected date of birth

6.2. Methods and timing to assess, record and analyse the efficacy parameters.

	Intervention	Routine visits after intervention	Monthly visits as part of routine follow-up	Birth	Postnatal follow-up	Corrected age of 2 years
Survival and birth at or after 34 weeks	✓	✓	✓	✓		
Need for re-intervention	✓	✓	✓			
PPROM and time from randomization to PPROM	✓	✓	✓			
Miscarriage, time from randomization to birth, birth weight, stillbirth				✓		
Neonatal death				✓	✓	
Neonatal complications				✓	✓	

Per protocol analysis	✓	✓	✓	✓		
ASQ® score						✓
Maternal morbidity	✓	✓	✓	✓		

7. Assessment of Safety

7.1. Procedures to record and report adverse events.

All adverse events occurring in women (PPROM, miscarriage, preterm labour), fetuses (intrauterine demise) and neonates (neonatal death and morbidity) must be recorded and are an integral part of the study outcome.

7.2. Definitions.

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation participants undergoing intervention, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the study procedure, whether or not considered related to the procedure.

Serious Adverse Event (SAE): A serious adverse event in the mother is any untoward medical occurrence that results in death or is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity.

7.3. Procedures for immediate notification of serious or unexpected adverse events.

All SAEs that are life-threatening or result in death of the mother must be reported to the promotor within 24 hours. She will perform an initial check of the report, request any additional information, and she will notify it to the steering committee and DSMC. Occurrence of a life-threatening SAE or SAE that results in death of the mother should lead to a meeting of the DSMC who can decide to discontinue the study. All SAE information will be recorded.

8. Statistics

8.1. Description of statistical methods.

The primary analysis will compare the proportion of pump twins who survive the neonatal period and are born at or after 34.0 weeks between the early and late intervention group. The secondary analysis will compare the need for re-intervention, maternal morbidity, time to birth, PPROM and time to PPROM, neonatal and long-term neurodevelopmental outcome between the early and late intervention group. Analysis will be intention to treat.

The following statistical analysis plan is proposed:

Primary outcome	Statistical methods
Neonatal survival and birth at or after 34.0 weeks	Pearson's chi-squared test [RR, (95%CIs)]

Secondary outcomes	Statistical methods
Need for additional interventions	Pearson's chi-squared test [RR, (95%CIs)]
Maternal Morbidity	Pearson's chi-squared test [RR, (95%CIs)]
Time from randomization to birth	Log-rank test [HR, (95%CIs)]
PPROM	Pearson's chi-squared test [RR, (95%CIs)]
Time from randomization to PPROM	Log-rank test [HR, (95%CIs)]
Preterm birth <28, <32, <37 weeks	Pearson's chi-squared test [RR, (95%CIs)]
Gestational age at birth	2-sample student's t-test [mean ± SD]

Birthweight	2-sample student's t-test [mean ± SD]
Stillbirth	Pearson's chi-squared test [RR, (95%CIs)]
Neonatal death	Pearson's chi-squared test [RR, (95%CIs)]
Severe neonatal morbidity	Pearson's chi-squared test [RR, (95%CIs)]
Per protocol analysis	Pearson's chi-squared test [RR, (95%CIs)]
Abnormal ASQ® score	Pearson's chi-squared test [RR, (95%CIs)]

Multivariate logistic regression will be done to adjust for the GA age strata used as a balancing factor at randomization[19]. Because this is a small trial, multivariate logistic and Cox regression may also be used to adjust for any imbalances between the 2 groups at baseline. Possible confounders are maternal age, BMI, parity, mode of conception, socio-economic class, previous history of preterm birth, smoking, and chronic maternal disease.

An interim analysis by the data safety and monitoring committee (DSMC) will be performed at 33% (n= 40) and 66% (n=80) of enrolment. The O' Brien-Fleming rule will be used to stop the trial early for efficacy. More specifically, if 34 weeks after recruitment and end of the neonatal period of the 40th patient, there is a difference between the 2 groups in the proportion of pump twins that survive and are born at or after 34.0 weeks that reaches a significance of P<0.0005, then the trial will be stopped early. Similarly, if 34 weeks after inclusion of the 80th patient, there is a difference in the primary outcome between the 2 groups that reaches a significance level of P<0.014, then the trial will be stopped early (O'Brien-Fleming stopping rule for efficacy). If the conditional power is less than 10% at one of the 2 interim analyses, the trial will be stopped early for futility. In other words, if the probability of achieving a statistical significant result is less than 1 in 10, the trial will be discontinued for futility.

8.2. Expected number of subjects to be included.

To detect a difference of 25% in neonatal survival and birth at or after to 34.0 weeks between the early (75%) and late (50%) intervention groups, 58 women will need to be included in each arm to achieve at least 80% power at a significance level (alpha) of 0.05 using a Pearson's chi-squared test.

Since we intend to perform 2 interim analyses, the P-value must be set at 0.045 according to the O' Brien-Fleming stopping-rule for efficacy to correct for multiple comparison. Therefore, to detect a difference of 25% in neonatal survival and birth at or after 34.0 weeks between the early (75%) and late (50%) intervention groups, 60 instead of 58 women will need to be included in each arm to achieve at least 80% power at a significance level (alpha) of 0.045 using a Pearson's chi-squared test.

In view of the short follow-up time (28 days after the expected date of birth), we expect the loss-to-follow up rate to be maximum 5% (n=6). To account for this potential 5% loss-to-follow-up rate, the sample size must be increased to 126 patients (120/0.95).

8.3. Criteria for completion of the trial.

The trial will be completed as soon as 63 patients are included in each arm, or earlier if requested by the DMSC. Completion of the trial will be announced on the study website (www.TRAPISTtrial.eu).

8.4. Potential pitfalls.

TRAP is a rare condition (1 in 35000 pregnancies), so recruitment may be slow. However, if we collaborate with other major fetal medicine centers in Europe, Canada and Israel, this would mean that each year about 100 cases are evaluated. Taken into account that only half will be eligible or willing to participate, it is expected that 3 years of study recruitment will be necessary.

Estimated differences are based on small case series and may be over-optimistic, survival rate may be higher in the late intervention group or lower in the early intervention group and the study may be underpowered to show smaller but still clinically meaningful differences. As such a 10% difference in the primary outcome (60% versus 50%) would still be clinically important, but would require the inclusion of 388 women in each arm, which is not feasible in view of the rarity of TAPS. Nevertheless, even if the study fails to show a significant difference, it will provide information on the 2-year neurodevelopmental outcome of the children, which so far has never been documented for this condition.

8.4. Selection of subjects to be included in each analysis.

The analysis will include all the subjects that have been randomized. All the analyses will be performed by intention-to-treat.

9. Direct Access to Data Source

During the course of the trial, only the members of the DSMC will have direct access to the electronic Case Report Forms (CRF) (www.sealedenvelope.com) in order to perform the interim analyses, monitor data acquisition and quality, and safeguard the patient's safety. At the end of the trial, the DSMC will blind the database for the outcome adjudication (removal of group identifier, gestational age of treatment and method of treatment).

10. Quality and Control Assurance

Steering committee: The steering committee will be composed by promotor of the study L.Lewi and J.Deprest (both feto-maternal –medicine specialists) and Ben Van Calster (statistician) from the University Hospitals, Leuven in Belgium, by D. Oepkes (feto-maternal medicine specialist) and E. Lopriore (paediatrician) from the Leiden, Medical centre, the Netherlands and by A. Khalil from St George's Hospital, London, UK. In order to ensure the quality of the data, they will provide instructions and provide support to principle investigators involved in the trial on how to enter the data in the purpose-designed electronic CRF-forms (www.sealedenvelop.com). The promotor of the study will sign the study protocol and the investigator's commitment; she will apply for the reference Ethics Committee and the Director's approval and she will review the final report of the study. The members of the steering committee will recruit patients at their local sites and register the data in the electronic CRFs.

Principal investigators: The principal investigators will recruit patients at their local study sites and register all data in the electronic CRFs.

DMCS: There will be an independent DSMC composed of Ed Juszczak (Clinical Trialist, University of Oxford, UK), Magnus Westgren (Fetal Medicine Specialist, Karolinska Institute, Sweden), Colin Morley (Pediatrician, University of Cambridge, UK). The DSMC will perform regular monitoring according to ICH GCP and the DAMOCLES recommendations. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitors will verify that the clinical trial is conducted in compliance with the protocol, GCP and the local regulatory requirements. The DSMC has the authority to stop the trial early for evidence-based reasons such as efficacy and futility (stopping rules defined in 8.1), patient's safety or based on new information that makes the trial unnecessary or unethical. Also, the DSMC may stop the trial early for reasons of performance if accrual is too slow, if the quality of the data is poor or in the event of fraud or misconduct. The DSMC also has to ensure that the study can reach valid conclusions. Therefore, the DSMC is empowered to modify the sample size or study design. Serious adverse events (SAEs) are to be reported to the DSMC as defined above, who will judge on the consequences.

Serious Breaches: A serious breach is defined as a breach of GCP or the trial protocol which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial. All serious breaches will be notified to the steering committee, the DSMC and the Ethical Committee from the University Hospitals Leuven, Belgium.

11. Risk, benefit and ethical issues

Risks of untreated TRAP sequence: Untreated TRAP carries a risk of up to 33% of demise between the first and early second trimester[9]. If the fetus survives to the second trimester, then the risk of demise is up to 50%[1]. So, the actual mortality of untreated TRAP may be as high as 80%. The cause of death is either high output cardiac failure, miscarriage or severe preterm birth due to polyhydramnios. As such, mean gestational age at birth is around 30 weeks. Additionally, there is concern about long-term neurodevelopmental outcome, not only because of the high risk of preterm birth of a sick neonate but also because very deoxygenated blood returns from the acardiac twin toward the pump twin, which results in a decreased total oxygen delivery. No data are available on short and long-term neurodevelopmental outcome[16]. Some experts recommend treatment only of the estimated weight of the acardiac mass is ≥50% than that of the pump twin. However, this weight cut-off is based on a postnatal pathology study of 49 cases[1]. Also, it has been evaluated in a small number of cases at mid-pregnancy only and therefore its predictive value in the first and early second trimester is unknown. As such, early demise can occur even if the acardiac/pump weight ratio is less than 0.5. Also, if an intervention is needed because of cardiac failure later on in pregnancy, the intervention is technically more challenging. Finally, a rescue intervention may also come too late to prevent antenatal brain damage, as was suggested in a cohort study in which 3 out of 4 TRAP cases that were treated after 23 weeks had signs of antenatal brain injury [17].

Risks of TRAP sequence treated at 16.0-19.0 weeks (control group-standard treatment): Because early demise is largely unpredictable, most experts now offer prophylactic treatment from 16 weeks onward in the early second trimester. However, the downside of such an approach is the 33% death rate between the first and early second trimester[9]. Nevertheless, if the pump twin survives to the early second trimester, the survival after an intrauterine intervention is around 80%[2]. So, the actual mortality of cases treated in the early second

trimester may be as high as 50%. Intrafetal interventions for TRAP are established to be safe for the mother, and so far no serious adverse maternal events have been reported. However, the main complication of any intrauterine intervention is PPROM, which may occur in up to 40% of cases. As such, mean gestational age at birth is reported to be around 36 weeks with 20% delivering prior to 34 weeks. Long-term outcome is still poorly documented. In the above-mentioned cohort, none of the 15 cases treated prior to 23 weeks sustained any developmental impairment[17].

Risks of TRAP sequence treated at 12.0-14.0 weeks (study group): Intervention in the first trimester may prevent the 33% of early demises, but may also increase the risk of miscarriage, because amnion and chorion are still separated at that time in gestation. Whereas such early intervention may increase the risk of miscarriage, it may actually decrease the risk of very preterm birth, as suggested by a recent meta-analysis. As such, the mean gestational age at birth of 9 cases treated in the first trimester was 39 weeks[8]. Several case series have established the feasibility, safety and effectiveness of intrafetal laser coagulation at 12.0-14.0 weeks (n=19)[2,10-12] We therefore hypothesize that an intervention at 12.0-14.0 weeks will increase the survival rate as well as decrease the very preterm birth rate. Nevertheless, a RCT is necessary to examine whether a prophylactic intervention at 12.0-14.0 weeks prevents the death of those who would have died before 16 weeks, without worsening the outcome of those that are currently treated after 16 weeks.

Minimizing potential risk: All procedures will be performed by fetal medicine specialists with extensive experience with intrafetal coagulation procedures as well as fetoscopy. All principle investigators work in major university centers with multidisciplinary teams familiar with intrauterine surgery. To prevent maternal infectious complications, procedures will be performed under prophylactic intravenous antibiotics. Also, preoperative tocolytics will be administered to prevent procedure-related miscarriage.

The promotor will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations. The protocol, informed consent form, participant information sheet and any applicable documents will be submitted to the Ethics Committees (ECs) of the participating centres for written approval. All substantial amendments to the original approved documents will be also sent for review to the ECs for written approval. The study will not begin until the approval of the EC and Director's consent.

12. Data Management and Registry File

Patient's participation in the study will be annotated into the medical records. All data will be collected in a dedicated web-based database that will be accessed by the participating centres with a username and password. The randomization will be web-based (www.sealedenvelope.com). If the patient fulfils the inclusion criteria, the computer generated list will randomise her to an early or late intervention group.It will be ensured that the participants' anonymity is maintained throughout the study. Only a participant ID number on the CRF in the electronic database will identify the participants. All documents will be stored securely and only accessible by authorized personnel. The study will comply with the Data Protection Legislation.

13. Costs, reimbursement and insurance

This is an academic non-sponsored multi-centre study that is initiated by the steering committee and does not provide funding for either of the 2 study arms. The study will not carry any additional costs to the patients next to what they incur when they are referred for TRAP treatment. Patients will not be paid or reimbursed for participation in the study. All Belgian patients participating in the trial are insured during their enrolment by the sponsor in accordance with Article 29 of the Belgian law related to experiments on humans, 7th May 2004.

Insurance details:

VanBreda
risks and benefits
Plantin Moretuslei 297
2140 Antwerpen
Belgium
www.vanbreda.be
Contract Number: 299.053.700

Sites participating in the study will at least be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty owed to them by the sites concerned, without prejudice to any other liability in accordance with national legislation. Individual sites participating in the study have to arrange their own insurance or indemnity in respect of these liabilities.

14. Publication policy

The promoter takes the commitment of publishing the results of the study. The steering committee together with a statistician (Ben Van Calster) will write the manuscripts. The first manuscript will deal with the primary outcome and most secondary outcomes, whereas the second manuscript will report on the secondary outcome of 2-year neurodevelopmental delay and intact survival. The steering committee and all principle investigators who contributed by randomizing patients will be co-authors of both manuscripts as part of the TRAPIST-consortium. All investigators must commit that none of the data collected in this trial will be reported separately prior to the publication of the study. Results will be presented to a relevant fetal medicine forum or media only after acceptance of publication. After publication, a summary of the results will be published on the study website (www.TRAPISTtrial.eu)

15. Miscellaneous

The sponsor, participating sites and all investigators involved in the study shall treat all information and data related to the study as confidential and with the proper respect for the privacy of each participant. The parties shall equally warrant to not disclose such information to third parties or disclose such publicly, but shall use such information solely for the purpose of this study. All data shall be coded or de-identified prior to transfer of such data to sponsor.

Parties have expressly agreed that any and all data collected and prepared in the context of the study shall be the property of the sponsor, provided that the participating sites shall remain the owner of their source data and may utilize such data as it deems appropriate without the approval of sponsor.

The participating sites and their proper investigators warrant that they shall not perform the study without having obtained the proper, written informed consent from each participant, in accordance with applicable legislation and as approved by the appropriate ethics committee/review board.

16. References

[1]MOORE TR, GALE S, BENIRSCHKE K. (1990) Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning. *Am J Obstet Gynecol*.163. p.907-912.

[2]PAGANI G1, D'ANTONIO F, KHALIL A, PAPAGEORGHIOU A, BHIDE A, THILAGANATHAN B. (2013) Intrafetal laser treatment for twin reversed arterial perfusion sequence: cohort study and meta-analysis. *Ultrasound Obstet Gynecol*. 42. p.6-14.

HECHER K, LEWI L, GRATACOS E, HUBER A, VILLE Y, DEPREST J. (2006) Twin reversed arterial perfusion: fetoscopic laser coagulation of placental anastomoses or the umbilical cord. *Ultrasound Obstet Gynecol.* 28. p. 688-691.

[4]NICOLAIDES KH, BRIZOT M, PATEL F, SNIJDERS R. (1994) Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation. *Lancet*. 344. p.435–439.

[5]SUNDBERG K, BANG J, SMIDT- JENSEN S, BROCKS V, LUNDSTEEN C, PARNER J, KEIDING N, PHILIP J. (1997) Randomised study of risk of fetal loss related to early amniocentesis versus chorionic villus sampling. *Lancet*. 350. p.697–703.

[6]CEMAT GROUP. (1998) Randomised trial to assess safety and fetal outcome of early and mid-trimester amniocentesis. *Lancet*. 351. p.242–247.

[7]SNIJDERS RJ, NOBLE P, SEBIRE N, SOUKA A, NICOLAIDES KH. (1998) UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet*. 352. p.343-346.

[8]CHAVEEVA P, POON LC, SOTIRIADIS A, KOSINSKI P, NICOLAIDES KH. (2014) Optimal method and timing of intrauterine intervention in twin reversed arterial perfusion sequence: case study and meta-analysis. *Fetal Diagn Ther*. 35. p.267-279.

[9]LEWI L, VALENCIA C, GONZALEZ E, DEPREST J, NICOLAIDES KH. (2010) The outcome of twin reversed arterial perfusion sequence diagnosed in the first trimester. *Am J Obstet Gynecol*. 203. p.213.e1-4.

[10]O'DONOGHUE K, BARIGYE O, PASQUINI L, CHAPPELL L, WIMALASUNDERA RC, FISK NM. (2008) Interstitial laser therapy for fetal reduction in monochorionic multiple pregnancy: loss rate and association with aplasia cutis congenita. *Prenat Diagn*. 28. p.535-543.

[11]SCHEIER M, MOLINA FS. (2012) Outcome of twin reversed arterial perfusion sequence following treatment with interstitial laser: a retrospective study. *Fetal Diagn Ther*. 31. p.35-41.

[12]BERG C, HOLST D, MALLMANN MR, GOTTSCHALK I, GEMBRUCH U, GEIPEL A. (2014) Early vs late intervention in twin reversed arterial perfusion sequence. *Ultrasound Obstet Gynecol*. 43. p.60-64.
[13]SENAT MV, DEPREST J, BOULVAIN M, PAUPE A, WINER N, VILLE Y. (2004) Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med*. 351. p.136-144.

[14]SLAGHEKKE F, LOPRIORE E, LEWI L, MIDDELDORP JM, VAN ZWET EW, WEINGERTNER AS, KLUMPER FJ, DEKONINCK P, DEVLIEGER R, KILBY MD, RUSTICO MA, DEPREST J, FAVRE R, OEPKES D. (2014) Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomised controlled trial. *Lancet*. 383. p. 2144-2151.

[15]LOPRIORE E, SUETERS M, MIDDELDORP JM, OEPKES D, VANDENBUSSCHE FP, WALTHER FJ. (2005) Neonatal outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser occlusion of vascular anastomoses. *J Pediatr* .147. p. 597–602.

[16]JELIN E, HIROSE S, RAND L, CURRAN P, FELDSTEIN V, GUEVARA-GALLARDO S, JELIN A, GONZALES K, GOLDSTEIN R, LEE H. (2010) Perinatal outcome of conservative management versus fetal intervention for twin reversed arterial perfusion sequence with a small acardiac twin. *Fetal Diagn Ther.* 27.p.138-141.

[17]LEWI L, GRATACOS E, ORTIBUS E, VAN SCHOUBROECK D, CARRERAS E, HIGUERAS T, PERAPOCH J, DEPREST J. (2006) Pregnancy and infant outcome of 80 consecutive cord coagulations in complicated monochorionic multiple pregnancies.*Am J Obstet Gynecol*. 194.p.782-789.

[18]KERSTJENS JM, NIJHUIS A, HULZEBOS CV et al. (accepted for publication).The Ages and Stages Questionnaire and neurodevelopmental impairment in two-year-old preterm-born children. *PLOSone.*

[19]KAHAN BC, MORRIS TP. (2012) Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ*. 345. e5840.

[20] DAMOCLES STUDY GROUP, NHS Health Technology Assessment Programme .(2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet.* 365(9460). p.711-22.

Tasks	Time	Feb-June 2015	Jul-Dec 2015	Jan 16-Dec 2019	Jan – April 2020	Jul 18-Jun 2022	Jul-Sep 2022
Protocol & database development Investigator meeting	5 Mo	✓					
ERB approval, liaising with recruiting centers and training	6 Mo		✓				
Recruitment, randomization & data collection	36 Mo			✓			
Data analysis, paper preparation & publication primary outcome	4 Mo				✓		
ASQ-exam-2 year follow-up of surviving infants	48 Mo					✓	
Data analysis, paper preparation & publication primary outcome	4 Mo						✓

17. Annex

Annex 1: Timeline

<u>Annex 2:</u> Patient information leaflet on the "TRAPISTtrial" for Participants in UZ Leuven

A study comparing an early versus late intervention for twin reversed arterial perfusion sequence

Dear parent(s),

Following the conversation that you had with one of the investigators, please find here the written information about the research study for which we have requested your participation.

Introduction

Your twins have been diagnosed with twin reversed atrial perfusion (TRAP) sequence and you have been offered treatment for this condition. As you heard from your doctor, TRAP may have serious consequences for your pregnancy. TRAP is a very rare condition occurring in 1 in a 100 monochorionic twin

pregnancies or 1 in 35 000 pregnancies. Monochorionic twins are identical and share a single placenta with vascular anastomoses that connect the two fetal circulations. TRAP is a complication of this shared circulation and occurs if one of the twins dies in early pregnancy.

In TRAP, blood flows from the healthy twin in a reverse direction towards its demised co-twin. The demised twin has no longer any heart activity from its own and that is why it is also called the acardiac twin. The healthy twin pumps blood towards the acardiac twin, hence the name pump twin. Thanks to the reverse blood flow, the acardiac twin continues to grow. However, the reverse flow strains the heart of the pump twin, which may lead to heart failure and increased urine output. Subsequently, heart failure may cause the demise of the pump twin and the increased urine production may lead to too much fluid and trigger preterm birth.
Without treatment, about 80% of pump twins will die either because of heart failure or very preterm birth. As such, untreated TRAP twins are born on average at 30 weeks (2.5 months too early). The consequences of TRAP for the long-term development of the children are unknown. An intrauterine intervention to arrest the reverse flow improves the prognosis for the pump twin. Although TRAP sequence is nowadays diagnosed at the time of the first trimester scan, as it was in your situation, such interventions are performed only after 16 weeks because the membranes surrounding the twins are not fused yet prior to 16 weeks.

There are 2 types of interventions. Your physician may choose to use a fine needle that produces heat to arrest the reverse follow. The needle is positioned near to the acardiac's blood vessels using ultrasound guidance (see Figure). Alternatively, your physician may opt to burn the cord or communicating vessels of the acardiac twin using a miniature 1 mm endoscope. After such intervention, the chances of survival for the pump twin are 80% and the pregnancy can be prolonged on average to 36 weeks. The survival rate is not a 100% because the pump twin may die or the intervention may cause rupture of the membranes and thereby lead to miscarriage or very preterm birth. There is limited information on the long-term development of these children, but the outcome seems very good if the child is not born too early.

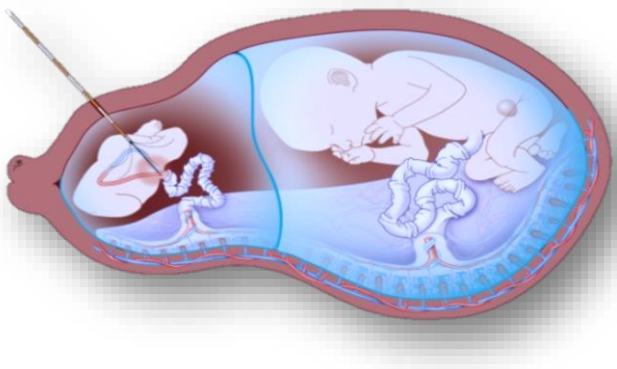


Figure illustrating the needle intervention to arrest the reverse flow

Since TRAP is now diagnosed in the first trimester, it appears that about 1 in 3 to 1 in 4 pump twins dies between the diagnosis in the first trimester and the planned intervention after 16 weeks. On the other hand, in another 1 in 4 cases, the flow towards the acardiac stops spontaneously, such that the planned intervention is no longer necessary at 16 weeks. At the time of the first trimester ultrasound scan; it is not possible to identify those pregnancies that will result in subsequent demise of the pump twin, spontaneous resolution or persistent flow. An intervention in the first trimester may prevent these early demises, but it may also increase the risk of miscarriage due to rupture of the membranes because these are not fused yet at the time of diagnosis. Also, for the 1 in 4 pregnancies in which the flow will have stopped spontaneously by 16 weeks, an intervention in the first trimester is unnecessary. Small reports have shown that interventions can be done safely in the first trimester, but a large study is necessary to demonstrate that an intervention in the first trimester results in better outcomes than waiting until after 16 weeks. We therefore request your participation in an international research project that is coordinated by the University Hospitals Leuven in Belgium (the sponsor) and that involves several other fetal medicine centers around the world in order to include 126 patients.

Aim of the study

The purpose of the study, for which your participation is requested, is to examine the outcome of the pump twin comparing an intervention prior to 14 weeks (early intervention) to the standard intervention after 16 weeks (late intervention). We will compare the survival rate, the risk of an early birth, the problems after birth and the development of the child when he/she is 2 years old.

Study design

If you agree to participate in this study, then fate will determine if you receive either an early or rather a late intervention. Therefore, there will be 1 chance out of 2 you either receive the early or the late intervention.

Course of the study

The treatment before and after the surgery will be the same in both groups. Also, there is no difference in the duration of hospitalization or in the frequency of follow-up visits. When your child reaches the age of 2 years, you will be asked to fill out a questionnaire about the development of your child.

Extra burden for the participants

There are no additional costs related to participation in this study (no extra blood samples or hospital visits). As mentioned above, we will ask you to fill out a questionnaire when your child is 2 years old to examine his/her development.

Possible risks of participating in this study

Recent small studies have shown that an intervention can be done safely in the first trimester. However, an early intervention may increase the risk of miscarriage due to early membrane rupture or may involve other risks, which are currently unforeseeable. Whether these risks outweigh a possible better outcome is unknown.

Voluntary participation

Your collaboration to this study is voluntary. In case you decide to participate in the study, you have the right to withdraw your permission at any time. There is no need to give any reason for this. Whether you participate or not will not have any consequences for the relationship with your physician. If you decide not to participate or if you withdraw your participation, you will be treated with the standard intervention after 16 weeks.

Confidentiality of the data

Your participation in the study means that you agree to the investigator collecting data about you and to these data being used for research purposes and in connection with scientific and medical publications. You are entitled to ask the investigator what data are being collected about you and what is their use is in connection with the study. You have the right to inspect these data and correct them if they are incorrect.

The investigator has a duty of confidentiality vis-à-vis the data collected, and you are assured that all data will be handled confidentially and that unauthorized persons will have no insight in your data. The investigator will never to reveal your name in the context of a publication or conference but also he/she will encode (your identity will be replaced by an ID code in the study) your data before sending them to the manager of the database of collected data (UZ Leuven). The investigator and his/her team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records. The personal data transmitted will not contain any combination of elements that might allow you to be identified. The results of this study may be used in a scientific publication, but the data cannot be related to you personally. If you want, we can communicate the results of this study to you. We will inform

your referring obstetrician and general practitioner of your participation in the study and if your child is transferred to another unit, we will inform the pediatrician.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point of your withdrawal, will be retained. To verify the quality of the study, it is possible that your medical records will be examined by persons subject to professional secrecy and designated by the ethics committee, the coordinating center of the University Hospital Leuven or by an independent audit body. In any event, this examination of your medical records may only take place under the responsibility of the investigator and under the supervision of one of the collaborators designated by him/her.

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities. The gathering and processing of your personal data shall be done in accordance with rights the Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and the Law of 22 August 2002 on patient rights.

Insurance

Any participation in a clinical study involves risk, however small it is. Even if there is no fault, the sponsor accepts responsibility for any damage caused to the participant (or in the event of death, her dependents). In accordance to the conditions on responsibilities and insurance, as specified in the Belgian law on human experimentation (the law of May 7, 2004), the University Hospitals Leuven has contracted an insurance to cover any possible damage that is directly or indirectly related to your participation in the study.

You are therefore asked to report any new health problem to the investigator. He/she will be able to inform you about possible treatments. If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of the disease or the known side-effects of the intervention), he/she will start a declaration procedure to the insurance company. The latter will appoint an expert-if it considers it necessary-to assess whether a link exists between your new health problems and the study.

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer's registered offices.

Responsible researchers at the University Hospitals Leuven

The Ethical Committee of the University Hospitals Leuven has approved this study. If you still have questions concerning this study, you can always contact your physician or one of the investigators that are mentioned below. In case you decide to take part in this research we kindly ask you to sign the informed consent on the next page. With the signature you are not obliged to anything (your signature is not 'binding'), but it only indicates that you have received and understood this information.

Dr. Isabel Couck
016/342294
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Prof. Dr. Liesbeth Lewi
016/342862
Liesbeth.Lewi@uzleuven.be

<u>Annex 3:</u> Patient information leaflet on the "TRAPISTtrial" for patients in participating centers
A study comparing an early versus late intervention for twin reversed arterial perfusion sequence

Dear parent(s),

Following the conversation that you had with one of the investigators, please find here the written information about the research study for which we have requested your participation.

Introduction

Your twins have been diagnosed with twin reversed atrial perfusion (TRAP) sequence and you have been offered treatment for this condition. As you heard from your doctor, TRAP may have serious consequences for your pregnancy. TRAP is a very rare condition occurring in 1 in a 100 monochorionic twin pregnancies or 1 in 35 000 pregnancies. Monochorionic twins are identical and share a single placenta with

vascular anastomoses that connect the two fetal circulations. TRAP is a complication of this shared circulation and occurs if one of the twins dies in early pregnancy.

In TRAP, blood flows from the healthy twin in a reverse direction towards its demised co-twin. The demised twin has no longer any heart activity from its own and that is why it is also called the acardiac twin. The healthy twin pumps blood towards the acardiac twin, hence the name pump twin. Thanks to the reverse blood flow, the acardiac twin continues to grow. However, the reverse flow strains the heart of the pump twin, which may lead to heart failure and increased urine output. Subsequently, heart failure may cause the demise of the pump twin and the increased urine production may lead to too much fluid and trigger preterm birth.

Without treatment, about 80% of pump twins will die either because of heart failure or very preterm birth. As such, untreated TRAP twins are born on average at 30 weeks (2.5 months too early). The consequences of TRAP for the long-term development of the children are unknown. An intrauterine intervention to arrest the reverse flow improves the prognosis for the pump twin. Although TRAP sequence is nowadays diagnosed at the time of the first trimester scan, as it was in your situation, such interventions are performed only after 16 weeks because the membranes surrounding the twins are not fused yet prior to 16 weeks.

There are 2 types of interventions. Your physician may choose to use a fine needle that produces heat to arrest the reverse follow. The needle is positioned near to the acardiac's blood vessels using ultrasound guidance (see Figure). Alternatively, your physician may opt to burn the cord or communicating vessels of the acardiac twin using a miniature 1 mm endoscope. After such intervention, the chances of survival for the pump twin are 80% and the pregnancy can be prolonged on average to 36 weeks. The survival rate is not a 100%, because the pump twin may die or the intervention may cause rupture of the membranes and thereby lead to miscarriage or very preterm birth. There is limited information on the long-term development of these children, but the outcome seems very good if the child is not born too early.

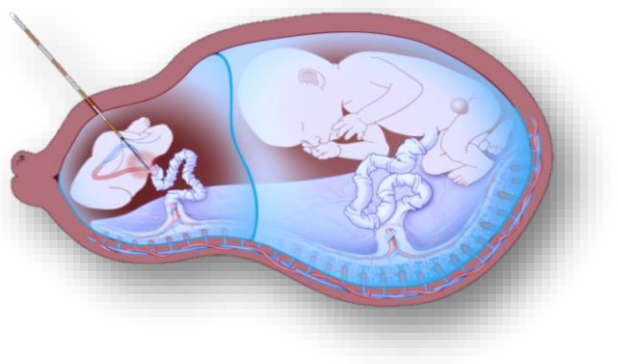

Figure illustrating the needle intervention to arrest the reverse flow

Since TRAP is now diagnosed in the first trimester, it appears that about 1 in 3 to 1 in 4 pump twins dies between the diagnosis in the first trimester and the planned intervention after 16 weeks. On the other hand, in another 1 in 4 cases, the flow towards the acardiac stops spontaneously, such that the planned intervention is no longer necessary at 16 weeks. At the time of the first trimester ultrasound scan; it is not possible to identify those pregnancies that will result in subsequent demise of the pump twin, spontaneous resolution or persistent flow. An intervention in the first trimester may prevent these early demises, but it may also increase the risk of miscarriage due to rupture of the membranes because these are not fused yet at the time of diagnosis. Also, for the 1 in 4 pregnancies in which the flow will have stopped spontaneously by 16 weeks, an intervention in the first trimester is unnecessary. Small reports have shown that interventions can be done safely in the first trimester, but a large study is necessary to demonstrate that an intervention in the first trimester results in better outcomes than waiting until after 16 weeks. We therefore request your participation in an international research project that is coordinated by the University Hospitals Leuven in Belgium (the sponsor) and that involves several other fetal medicine centers around the world in order to include 126 patients.

Aim of the study

The purpose of the study, for which your participation is requested, is to examine the outcome of the pump twin comparing an intervention prior to 14 weeks (early intervention) to the standard intervention after 16 weeks (late intervention). We will compare the survival rate, the risk of an early birth, the problems after birth and the development of the child when he/she is 2 years old.

Study design

If you agree to participate in this study, then fate will determine if you receive either an early or rather a late intervention. Therefore, there will be 1 chance out of 2 you either receive the early or the late intervention.

Course of the study

The treatment before and after the surgery will be the same in both groups. Also, there is no difference in the duration of hospitalization or in the frequency of follow-up visits. When your child reaches the age of 2 years, you will be asked to fill out a questionnaire about the development of your child.

Extra burden for the participants

There are no additional costs related to participation in this study (no extra blood samples or hospital visits). As mentioned above, we will ask you to fill out a questionnaire when your child is 2 years old to examine his/her development.

Possible risks of participating in this study

Recent small studies have shown that an intervention can be done safely in the first trimester. However, an early intervention may increase the risk of miscarriage due to early membrane rupture or may involve other risks, which are currently unforeseeable. Whether these risks outweigh a possible better outcome is unknown.

Voluntary participation

Your collaboration to this study is voluntary. In case you decide to participate in the study, you have the right to withdraw your permission at any time. There is no need to give any reason for this. Whether you participate or not will not have any consequences for the relationship with your physician. If you decide not to participate or if you withdraw your participation, you will be treated with the standard intervention after 16 weeks.

Confidentiality of the data

Your participation in the study means that you agree to the investigator collecting data about you and to these data being used for research purposes and in connection with scientific and medical publications. You are entitled to ask the investigator what data are being collected about you and what is their use is in connection with the study. You have the right to inspect these data and correct them if they are incorrect.

The investigator has a duty of confidentiality vis-à-vis the data collected, and you are assured that all data will be handled confidentially and that unauthorized persons will have no insight in your data. The investigator will never to reveal your name in the context of a publication or conference but also he/she will encode (your identity will be replaced by an ID code in the study) your data before sending them to the manager of the database of collected data (UZ Leuven). The investigator and his/her team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records. The personal data transmitted will not contain any combination of elements that might allow you to be identified. The results of this study may be used in a scientific publication, but the data cannot be related to you personally. If you want, we can communicate the results of this study to you. We will inform your referring obstetrician and general practitioner of your participation in the study and if your child is transferred to another unit, we will inform the pediatrician.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point of your withdrawal, will be retained. To verify the quality of the study, it is possible that your medical records will be examined by persons subject to professional secrecy and designated by the ethics committee, the coordinating center of the University Hospital Leuven or an independent audit body. In any event, this examination of your medical records may only take place under

the responsibility of the investigator and under the supervision of one of the collaborators designated by him/her.

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities.

Insurance

This needs to be specified in accordance with local legislation

Responsible researchers at the participating center

The Ethical Committee of the "participating center" has approved this study. If you still have questions concerning this study, you can always contact your physician or one of the investigators that are mentioned below. In case you decide to take part in this research we kindly ask you to sign the informed consent on the next page. With the signature you are not obliged to anything (your signature is not 'binding'), but it only indicates that you have received and understood this information.

Contact details of PI (s)

Annex 4: Patient's informed consent form

Informed Consent for participation in the research study: Early versus late intervention for twin reversed arterial perfusion sequence-TRAPIST: an open-label randomized controlled trial

I have been informed satisfactorily concerning the study. I have read the written information carefully. I have had the opportunity to ask questions concerning the study. My questions have been answered satisfactorily. I have been able to think about the participation properly. I have the right to withdraw my consent at any time without giving any reason.

Surname and initials: ……

Date of birth: ……

Signature: .....Date:……..

For the physician:

Signatory states that abovementioned individual has been informed both orally and in writing about the above-mentioned study. He/she declares that a premature stopping of the participation by above-mentioned person will absolutely not influence the care to which she is entitled.

Surname and initials: ……

Signature: .....Date:…….....

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