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TITLE: Subsequent fertility, pregnancy and gynecologic outcomes after fetoscopic laser therapy for twin-twin transfusion syndrome compared to normal monochorionic twin gestations

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IMPLICATIONS AND CONTRIBUTIONS

Fetoscopic laser coagulation is the current first line treatment for twin-to-twin transfusion syndrome, yet long term maternal outcomes are poorly documented. We compared reproductive, obstetric, gynecologic and psychological outcomes in women who previously underwent laser to those of women with uncomplicated monochorionic (MC) twins. No adverse medium-term reproductive nor gynecologic adverse events were self-reported, however psychological or emotional problems are more frequent than in women with uncomplicated MC twins. This mainly affects women who lost one or more fetuses in the index pregnancy. This should prompt our attention beyond the limits of the index gestation with active identification and support of this vulnerable population.

CONDENSATION

Patients who underwent fetoscopic laser coagulation for twin-to-twin transfusion syndrome do not report adverse medium-term reproductive nor gynecologic adverse events, yet more psychological problems.

SHORT TITLE

Reproductive outcomes after fetoscopic laser therapy

ABSTRACT

BACKGROUND: An improved survival and quality of life for neonatal survivors after fetoscopic laser therapy (FLC) for twin-twin transfusion syndrome (TTTS) has been reported. However, little is known about the medium-term maternal effects after FLC with respect to reproductive and gynecologic outcomes.

OBJECTIVE: To document reproductive, obstetric, gynecologic and psychological outcomes in women who underwent FLC for TTTS.

STUDY DESIGN: Monocentric controlled study on consecutive women who underwent FLC for TTTS between 2007 and 2013 at the University Hospitals Leuven (cases; n=198). Controls were women followed for an uncomplicated monochorionic diamniotic (MCDA) twin pregnancy and with uneventful course during the same time period (controls; n=211). All patients received a questionnaire enquiring on their fertility, later pregnancies and gynecologic outcomes.

RESULTS: The response rate was 50.4% (cases: n=95; controls: n=109). Most baseline characteristics were similar across both groups. Women in the FLC group attempted more frequently a new pregnancy (34% (31/92) versus 21% (22/107) in controls; $p<0.05$) and became more often pregnant (100% (31/31) versus 82% (18/22); $p<0.05$). We observed a shorter inter-pregnancy interval in cases than controls (median interval: 12 (IQR 5-27) versus 24 (IQR 15-30) months; $p<0.05$). This was also observed in cases who lost one or more fetuses or babies in the index pregnancy (median interval: 9 (IQR 3.5-25.5) months; $p<0.05$). The complication rate during subsequent pregnancies (26% (8/31); versus 11% (2/19); $p=0.194$) and at delivery (17% (5/30) versus 11% (2/19); $p=0.554$) were comparable. More women who underwent FLC reported relevant psychological symptoms (44% (40/92) versus

21% (23/107); $p < 0.05$). When only women were considered in whom there was a double surviving twin pair, there were no differences in psychological symptoms compared to controls (16% (15/55) versus 21% (23/107); $p = 0.411$). Gynecologic problems were equally frequent in both groups (20% (18/92) versus 31% (33/107); $p = 0.069$).

CONCLUSION: No adverse medium-term maternal effects with respect to fertility, obstetric and gynecologic outcomes were observed after FLC. However, these women reported more psychological or emotional problems than women with MCDA without FLC.

KEYWORDS

fetoscopic laser coagulation / fertility / gynecologic outcome / pregnancy outcome / psychological outcome / twin-twin transfusion syndrome

INTRODUCTION

Monochorionic diamniotic (MCDA) twins comprise 20-30% of spontaneous and 4-5% of iatrogenic twin gestations. In those, the risk for perinatal complications is much greater than in dichorionic twins and singletons pregnancies.^{1,2} This is due to the presence of vascular anastomoses connecting the fetal circulations which are responsible for a range of pregnancy complications, including twin-twin transfusion syndrome (TTTS). About 10% of MCDA twin pregnancies are affected by TTTS, a serious complication characterized by unbalanced fetofetal transfusion over the chorionic plate anastomoses.^{1,3-5} Because TTTS typically occurs in the pre-viable period, its prognosis is dismal without treatment. Polyhydramnios-related miscarriage or the preterm birth of two sick neonates is common, as well as intrauterine demise of one or both twins.^{4,5} Fetoscopic laser coagulation (FLC) of chorionic plate anastomoses combined with amnioreduction has been shown to be the best first line treatment for this condition.^{3,6}

Though a lot of research has shown improved survival and quality of life for survivors after fetoscopic laser surgery, there are to our knowledge no studies on their mother's later reproductive, obstetrical and gynecologic outcomes. Given the likelihood of a less than perfect fetal or neonatal outcome, or the simple fact of increased stress by intensive follow up with many uncertainties, the psychological impact on individual families may be significant. Herein, we aimed to investigate such effects in women with monochorionic twins who earlier had FLC as compared to women with uncomplicated monochorionic twins.

MATERIALS AND METHODS

This was a single centre study conducted at the Fetal Medicine Unit of the University Hospitals Leuven. We searched our database for patients who underwent fetoscopic laser coagulation (FLC) for twin-twin transfusion syndrome (TTTS) between 2007 to 2013 (cases). As controls, we selected patients with MCDA pregnancies who, following the diagnosis of monochorionicity in the first trimester, were managed at our unit during the same time span. Furthermore, we selected those pregnancies who were not complicated by TTTS, intra-uterine growth restriction (IUGR), twin-anemia polycythemia syndrome (TAPS) or discordant anomaly and without fetal or neonatal loss.¹ The medical records were searched for maternal age, parity prior to the index pregnancy and loss of either or both twins during the index pregnancy or neonatal period.

Patients were sent an invitation to participate, with comprehensive information and a questionnaire (Appendix 1 and 2). Consenting patients were left the choice to either fill out this survey online, using LimeSurvey (version 2.00+ Build 130708, The LimeSurvey Project Team, Hamburg, Germany) or using a hard copy to be returned in a prepaid envelope. The survey was based on a questionnaire used in a previous study on patients undergoing fetoscopic surgery for severe congenital diaphragmatic hernia.⁷ That questionnaire was in turn based on earlier used surveys on patients undergoing open maternal fetal surgery.⁸ The survey consisted of 19 multiple choice questions (MCQ), 5 questions with a standardized format reply (SFR), and 11 open questions (OQ). The first segment of the survey (3 MCQ, 2 SFR, 1 OQ) covered the desire to further conceive after the index pregnancy and the time interval until conception. There was also possibility to indicate whether there was a relationship between the problem in the index pregnancy (monochorionicity *per se*, or any of its complications) and the decision (not) to conceive again. The second segment (11 MCQ,

4 OQ) queried the outcomes of later pregnancies (number of fetuses, gestational age at birth, delivery method, weight at birth, occurrence of congenital anomalies) as well as obstetric complications during pregnancy or labor with a specific enquiry to complications which could relate to the uterine scar, and fertility problems (pre-existent or new problems, need for assisted reproduction technology). In the third segment (1 MCQ, 1 OQ), patients were requested to report on psychological problems they experienced after the index pregnancy and on the possible relationship with that pregnancy. The fourth segment (4 MCQ, 3 SFR, 4 OQ) asked for gynecologic problems after the index pregnancy (abnormal menstruations, lower abdominal pain, others). Patients also had the option to provide contact information of their treating physician when consenting for additional information being asked to their physician. The questionnaire finished by an open question (1 OQ) in which the patients could add any other problems that they thought might have occurred after the index pregnancy, yet not covered by the previous questions. The questionnaire was available in Dutch, French and English; translations were done by native speakers. This study was approved by the Ethics Committee on clinical studies of the UZ Leuven (S59805).

The answers of the surveys were pooled in a Microsoft Excel database (Microsoft Corp, Redmond, WA, USA) by the primary author and analysed using SPSS (v.24; IBM Software, Inc., Armonk, NY, USA). All data are reported as number, percentage, median and interquartile range (IQR). Categorical variables were analysed by the Pearson chi-square test, subgroups were analysed by the Mann-Whitney U test; the numerical variables were analysed by the Mann-Whitney U test. Patients with missing data were excluded from analysis and detailed in tables. A p-value of <0.05 was considered significant.

RESULTS

We identified a total of 409 patients, 198 cases and 211 controls, in our database. Table 1 displays the demographic variables for cases versus controls. Per definition, controls experienced no fetal or neonatal loss. The interval between the index delivery and survey was significantly longer (+6 months) in controls than for a median interval of 74 months in cases. There was also a difference in geographical background. Cases were less likely to be further managed at our unit (69% (134/198) following FLC since they were referred back, whereas controls were by definition patients managed locally throughout their pregnancy (100% (211/211); $p < 0.05$).

Four patients were not invited because of insufficient contact information (two cases and one control) or unrelated maternal death (one control) (Figure 1). Therefore 405 women were eventually contacted between January 2017 and June 2017, initially by e-mail, in case of bounce back or missing contact, through a letter, and in the absence of a reply, by telephone. Ten women refused to participate in the study (6 cases and 4 controls) and were included in the non-responders. We received 95 surveys from cases and 109 controls by six months after the start of the study (response rate 50.4%).

Table 1 displays demographic variables of respondents versus non-respondents. There were no significant differences except that there were more responders managed locally (in the University Hospitals Leuven), irrespective of their group assignment. Also the interval between the index delivery and survey was comparable. The response rate in women treated for TTTS was comparable to that of women with uncomplicated MCDA pregnancies (48% (95/196) versus 52% (109/209); $p = 0.459$).

Three surveys of cases and two of controls were eventually discarded because of incomplete answers or obvious inconsistencies in their answers (2% (5/204)). This left answers from 199 women. Table 2 displays their reproductive outcomes. Following the index pregnancy, cases were more likely to attempt a new pregnancy than controls (34% (31/92) versus 21% (22/107), respectively; $p<0.05$). There was no difference in parity at baseline in these patients. Women who were known to have lost one or two fetuses or babies following laser coagulation, attempted more frequently a new pregnancy compared to those who did not experience fetal or neonatal loss (79% (26/33) versus 7% (4/55), respectively; $p<0.05$). There were no de novo infertility problems: of those attempting to conceive, more women in the FLC group became pregnant (100% (31/31) versus 82% (18/22) in controls; $p<0.05$). Twelve participants became pregnant by assisted reproductive technology (ART); however, they required ART before. Women having undergone FLC attempted a new pregnancy earlier than controls (median interval 12 (IQR 5-27) versus 24 (IQR 15-30) months; $p<0.05$). This difference was also observed when only comparing cases who lost one or two fetuses or babies in the index pregnancy to controls (median interval 9 (IQR 3.5-25.5) months; $p<0.05$).

Table 3 displays details on these 67 subsequent pregnancies (44 cases and 23 controls). In the first gestation after the index pregnancy, there was no difference in first trimester losses (13% (4/31) in cases versus 16% (3/19) in controls; $p=0.777$). One control patient had an unplanned pregnancy ending in an induced abortion in the first trimester for social reasons. There were no second or third trimester losses observed in either groups. Forty-two women delivered beyond viability. There was no difference in weight at birth of the first baby after the index pregnancy (median 3.47 (IQR 3.12-3.65) versus 3.65 (IQR 3.29-3.80) kilograms; $p=0.331$). Fourteen women reported at least one complication during subsequent pregnancies or during delivery of those pregnancies, as detailed in Table 4.

One hundred and forty-six women did not wish to conceive again (66% (61/92) in cases versus 79% (85/107) in controls; $p<0.05$). In both groups, there were as many women who indicated that this decision was related to events in the index pregnancy (15% (9/61) versus 6% (5/85); $p=0.074$). They reported as reasons fear for new pregnancy complications (5/9 cases and 0/5 controls), psychological distress persisting since the index pregnancy (4/9 and 2/5), care for the baby or babies (1/9 and 2/5) or because of completion of the family (2/5 controls). Those women from both groups who chose not to conceive again were of the same age (median 37.4 years in cases versus 37.9 years in controls; $p=0.802$). One of these women mentioned that this was due to her age; she was in the laser group (12.5% (1/8) versus 0% in controls (0/5); $p=0.724$). There were no cases or controls who indicated that the need for IVF impacted their decision.

Fifty-one women report gynaecological problems after the index pregnancy, as detailed in Table 4. Women from both groups did report similar rates of problems (20% (18/92) in cases versus 31% (33/107) in controls; $p=0.069$). Psychological and emotional problems are detailed in Table 4. They were more commonly reported by women undergoing laser (44% (40/92)) than by controls (21% (23/107); $p<0.05$). Problems most commonly reported were anxiety concerning the health of the index baby/babies or fear for repetition and feelings of guilt. Nineteen cases (20%) reported grieving the loss of a child. Other problems were a depressed mood and a variety of other feelings difficult to grasp in a single common denominator (details in Appendix 3). When only women were considered in whom there was a double surviving twin pair, there were no differences in psychological and emotional problems (16% (15/55) versus 21% (23/107); $p=0.411$).

COMMENT

We did not identify significant differences in subsequent fertility, pregnancy and gynecologic outcomes between patients who had FLC and patients with uncomplicated MCDA pregnancies. However, following laser surgery, psychological or emotional problems were more common. This coincided with the loss of either one or both twins in the index pregnancy. Grieving the loss of a child, anxiety and feelings of guilt seem to play an important role, whereas a depressed mood was evenly reported in both groups.

Apart from the potential immediate complications of fetoscopic surgery during the index pregnancy, there is the theoretical concern for an impact on later reproductive life. In this study, almost twice as many women from the FLC group attempted another pregnancy and reassuringly all were successful in achieving this. Their desire to conceive again we tie to the loss of one or both babies due to TTTS: the vast majority of women (79% (26/33)) who lost one or more babies attempted another pregnancy, as compared to only 7% of women who did take home two babies ($p<0.05$). Those women who had a laser, and who experienced a loss, attempted to conceive even earlier than those who had a successful pregnancy outcome (9 vs. 12 months). Conversely, the majority of those who did not wish to conceive again, did not indicate this decision was related to events in the index pregnancy.

The primary concern of open maternal-fetal surgery is uterine dehiscence (14%) and rupture (14%).⁸ This should be less after fetoscopic surgery, which essentially uses a 2.3 to 5 mm access to the uterus.^{9,10} In this study using self-reported outcomes, no uterine ruptures were mentioned by our patients. One woman in each group indicated there was some problem with a uterine scar. In the control group that problem was in retrospect related to a caesarean section scar. One woman who underwent laser surgery indicated that the

“fetoscopic scar led to adhesions and constipation”. However, this was an interpretation, and there was no indication in the medical records for this complaint to be a dehiscence or threatening rupture.

One out of four participants reported gynecologic problems of any kind, yet without a different likelihood in groups. This is somewhat higher than in our previous study in singletons undergoing fetoscopic surgery, though patients in both studies were of comparable age (37 years).⁷ One explanation might be that caesarean deliveries are more often performed in twin pregnancies than in pregnancies with CDH (which are usually singleton pregnancies). Women who previously had a caesarean delivery report more frequently abdominal pain and abnormal bleeding.^{11,12}

Four out of ten women who underwent laser reported subsequent psychologic and emotional problems. This number is comparable to what we observed in women who gave birth to a baby with CDH.⁷ The most logical reason for that seems to us a problematic outcome in the index pregnancy. We are strengthened in this interpretation by the fact that this difference disappeared when comparing cases with two surviving infants to our controls (who per definition experienced no loss). Nevertheless, an uncomplicated monochorionic diamniotic pregnancy seemed to have a psychological impact as well. One in five women indicated such problems. Therefore, it seems that psychological support should be liberally offered to women with monochorionic twins, even in the absence of TTTS. Other studies show that multiple births often have an impact on the mental health of parents, resulting in depression, anxiety and parenting stress.¹³

We acknowledge a number of weaknesses to our study. First, there was a difference in geographical background, yet this is because we perform surgery on patients who come from all over Europe. They may have another cultural background and cope with such problems differently. The majority of respondents are from Belgium, so conclusions on our study population may only apply locally. Second, the response rate was less than desirable, yet is acceptable and more than what we observed in a similar study on mothers with fetuses with CDH (40%).⁷ Third, we did not use condition specific and validated questionnaires. In their absence, we modified a questionnaire that was used before by Wilson et al for women undergoing open fetal surgery, for studying women undergoing endoscopic fetal surgery for CDH.^{7,8} Fourth, it should be noted that complications are self-reported and not validated by a physician. This may lead to inaccuracies of the occurrence, nature and severity of some medical complications. Another limitation is that many of the psychological problems were not categorized, as they appeared to be of variable nature. Given the relevance and high likelihood of a psychological impact, it would be interesting in future studies to use validated instruments for the assessment of the long-term psychological impact. Sixth, though we have a fairly high number of patients, the sample size might still be too low to make conclusions on rare complications or regarding events that do not occur in both groups. With these numbers, statistics become unreliable for very rare complications or for events, such as fetal losses, that are confined to one specific group (women who underwent FLC). Though we observed differences in psychologic impact and interval to next pregnancy in women with loss(es), it is possible that we underestimate its magnitude. Finally, there were ten women who refused to participate (6 cases and 4 controls). That number is not insignificant. If these women would be the ones with severe complications, we may have underestimated the impact of fetoscopic surgery.

Our study also has some strengths. It first provides relevant information on reproductive and gynecologic outcomes following fetoscopic surgery for TTTS, information which is to our knowledge until now almost non-existent. Second, we used an appropriate control group. Therefore we feel confident that fetoscopic surgery for TTTS does not have medium-term adverse gynaecological and reproductive effects. The psychological impact seems to be high due to the burden of the loss of a child. Strong support for these women is advocated.

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332 **TABLES**333 **Table 1: Demographic variables**

<u>Parameter</u>	<u>Cases</u> (n=198)	<u>Controls</u> (n=211)	<u>p-value</u>	<u>Responders</u> (n=204)	<u>Non-responders</u> (n=201)	<u>p-value</u>
Loss of one or more of the fetuses during index pregnancy or neonatal period^a	69 (39%)	0 (0%)	p<0.05	34 (17%)	34 (19%)	p=0.705
Women managed locally throughout pregnancy^b	134 (69%)	211 (100%)	p<0.05	188 (92%)	155 (77%)	p<0.05
Parity during index pregnancy ≥ 1^c	107 (54%)	114 (58%)	p=0.444	106 (53%)	111 (57%)	p=0.433
Median age at delivery of index pregnancy (years)^d	30 (27-33)	30 (28-33)	p=0.656	30 (28-33)	30 (27-33)	p=0.243
Median age at survey (years)	37 (33-40)	37 (35-41)	p=0.204	37 (35-40)	37 (33-41)	p=0.398
Interval between delivery of index pregnancy and survey (months)^d	74 (54-101)	80 (59-103)	p<0.05	77 (53-100)	77 (57-103)	p=0.193

334 - Data are displayed as n(%) or median (IQR)

335 - Missing values: ^aCases 22, Controls 0; Responders 4, Non-Responders 17; ^bCases 3,336 Controls 1; Responders 1, Non-Responders 0; ^cCases 0, Controls 14; Responders 4, Non-337 Responders 6; ^dCases 7, Controls 0; Responders 2, Non-Responders 5

338 **Table 2: Reproductive outcomes in patients who submitted completed questionnaires**

<u>Parameter</u>	<u>Cases</u> (n=92)	<u>Controls</u> (n=107)	<u>p-value</u>
Parity at index pregnancy ≥ 1^a	47 (51%)	57 (55%)	p=0.602
Further attempt to conceive	31 (34%)	22 (21%)	p<0.05
Of those attempting to conceive			
Patients with ≥ 1 subsequent pregnancies	31 (100%)	18 (82%)	p<0.05
Requiring for the first time ART	0 (0%)	0 (0%)	
Interval between delivery of index pregnancy and attempt at new pregnancy (months) ^b	12 (5-27)	24 (15-30.25)	p<0.05
Interval between attempt and delivery subsequent pregnancy (months) ^c	10 (9-14.5)	14 (10-16)	p=0.192
No further attempt to conceive	61 (66%)	85 (79%)	p<0.05
Decision related to the index pregnancy	9 (15%)	5 (6%)	p=0.074

339 - Data are displayed as n(%) or median (IQR)

340 - Missing values or exclusions: ^aCases (0 missing values), Controls (3 missing values); ^bCases341 (2 missing values), Controls (0 missing values); ^cCases (2 missing values, 4 excluded due to

342 obvious erroneous data), controls (4 did not conceive again thus were excluded);

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344 **Table 3: Subsequent pregnancy outcomes**

<u>Parameter</u>	<u>Cases</u> (n= 31)	<u>Controls</u> (n= 19)	<u>p-value</u>
Subsequent pregnancy outcome			
Gestational age at delivery			
Termination of pregnancy <20 weeks	0	1 (5%)	
Miscarriage (loss <20 weeks)	4 (13%)	3 (16%)	p=0.777
Pregnancy loss at 20-24 weeks	0	0	
Delivery at 24-28 weeks	0	0	
Delivery at 38-36 weeks	0	0	
Delivery ≥ 37 weeks	27 (87%)	15 (79%)	p=0.450
Birthweight (in kilograms) ^a	3.47 (3.12-3.65)	3.65 (3.29-3.80)	p=0.331
Delivery mode ^a			p=0.615
Vaginal	20 (74%)	10 (67%)	
Caesarean delivery	7 (26%)	5 (33%)	
Patients with ≥ 1 of the following complications during subsequent pregnancies	8 (26%)	2 (11%)	p=0.194
Exact number of pregnancies with			
Bleeding during pregnancy	2	0	
Placental problems	1	0	
Hypertension	0	0	
Gestational diabetes	3	1	
Others ^b	3	1	

Patients with ≥ 1 of the following complications during the delivery of subsequent pregnancies^c	5 (17%)	2 (11%)	p=0.554
Exact number of pregnancies with			
Problems with uterine scar	1	1	
Preterm labour and/or preterm rupture of the membrane	2	0	
Others ^d	2	1	

345 - Data are displayed as n(%) or median (IQR)

346 - Missing values or exclusions: ^aCases (4 pregnancy losses <20 weeks excluded), controls (3
 347 pregnancy losses <20 weeks and 1 termination of pregnancy excluded); ^cOne case is
 348 excluded due to obvious inconsistency

349 - Others: ^bCases (1 hydramnios, 1 ectopic pregnancy, 1 Braxton-Higgs treated medicinally),
 350 controls (1 hyperemesis gravidarum); ^dCases (1 prolonged labour, 1 internal bleeding),
 351 controls (1 urgent caesarean delivery due to an unexpected breech position)

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Table 4: Self-reported gynecological and psychological outcomes in cases and controls.

<u>Problems</u>	<u>Cases</u> (n=92)	<u>Controls</u> (n=107)	<u>p-value</u>
Patients reporting ≥ 1 gynecological problem(s) after their index pregnancy	18 (20%)	33 (31%)	p=0.069
Abdominal pain	11 (12%)	15 (14%)	p=0.667
Abnormal menstrual bleeding	6 (7%)	15 (14%)	p=0.086
Others ^a	4 (4%)	12 (11%)	p=0.076
Patients reporting ≥ 1 psychological problem(s) after their index pregnancy	40 (44%)	23 (21%)	p<0.05
Depressed mood	7 (8%)	5 (5%)	p=0.386
Anxiety concerning health of the baby, fear for repetition	13 (14%)	6 (6%)	p<0.05
Grieving the loss of a child	19 (20%)	0 (0%)	p<0.05
Feelings of guilt	6 (7%)	0 (0%)	p<0.05
Others ^b	6 (7%)	12 (11%)	p=0.250

- Data are displayed as n(%) or median (IQR)

- Others: ^aCases (1 premenstrual syndrome, 2 post-operative adhesions, 1 ovarian cyst),

controls (1 lasting pain caused by scar of caesarean delivery, 2 retained placental tissue, 3

ovarian cysts, 2 urogenital prolapses, 1 urinary incontinence, 1 mastalgia, 1 hematoma after

caesarean delivery, 1 uterine cysts); ^bSee Appendix 3

FIGURE LEGENDS

363

364 **Figure 1:** Flow chart of included patients

Figure 1

SUPPLEMENTAL DIGITAL CONTENT

Appendix 1: Questionnaire designed for cases

Gynecological outcomes after fetoscopic laser therapy

This questionnaire consists of 35 items. Filling it in will take around 15 minutes.

A. Pregnancy desire

[1] Have you attempted to get pregnant after your pregnancy in which a twin to twin transfusion syndrome was detected?

☐ Yes (Proceed to question 4)

☐ No (Proceed to question 2)

[2] Is there any relationship between the problem in your pregnancy or pregnancy outcome of the twin to twin transfusion syndrome and the fact that you have not attempted a new pregnancy?

☐ Yes (Proceed to question 3)

☐ No (Proceed to question 22)

[3] Are you willing to summarize the reason why you haven't attempted a new pregnancy?

(Proceed to question 22)

[4] How much time was there between the delivery in the pregnancy with twin to twin transfusion syndrome and a new attempt to get pregnant?

Months

[5] Have you been pregnant since your previous pregnancy with a twin to twin transfusion syndrome?

☐ Yes (Proceed to question 6)

☐ No (Proceed to question 22)

[6] How much time was there between the delivery of pregnancy with twin to twin transfusion syndrome and the delivery of the following pregnancy?

Months

B. Later pregnancy outcomes

We would like to investigate whether there were any problems or complications during one of these later pregnancies. We would like you to answer the following questions separately for the first three pregnancies after the pregnancy in which a twin to twin transfusion syndrome was diagnosed.

[7] Was it a singleton, twin or triplet?

	Singleton	Twin	Triplet	Not applicable
First pregnancy after twin to twin	☐	☐	☐	☐

transfusion syndrome				
Second pregnancy after twin to twin transfusion syndrome	☐	☐	☐	☐
Third pregnancy after twin to twin transfusion syndrome	☐	☐	☐	☐

39

40 **[8] What was the estimated gestational age at the moment of delivery? (the normal**41 **gestational age is 40 weeks)**

	Miscarriage or loss prior to 20 weeks of pregnancy	20-24 weeks	24-28 weeks	28-36 weeks	>37 weeks	Not applicable

First pregnancy after twin to twin transfusion syndrome	☐	☐	☐	☐	☐	☐
Second pregnancy after twin to twin transfusion syndrome	☐	☐	☐	☐	☐	☐
Third pregnancy after twin to twin transfusion syndrome	☐	☐	☐	☐	☐	☐

42

43 [9] The delivery was

	Vaginal	Caesarean delivery	Not applicable
First pregnancy after twin to twin transfusionsyndrome	☐	☐	☐
Second pregnancy after twin to twin	☐	☐	☐

transfusionsyndrome			
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐

44

45 [10] What was the birth weight of your child in grammes? Please fill in 0 when not

46 applicable.

	Weight (in grammes)	Weight (in case of twins, in grammes)	Weight (in case of triplets, in grammes)
First pregnancy after twin to twin transfusionsyndrome			
Second pregnancy after twin to twin transfusionsyndrome			
Third pregnancy after twin to twin transfusionsyndrome			

47

48 [11] Was there any congenital anomaly/malformation?

	Yes	No	Not applicable
First pregnancy after	☐	☐	☐

twin to twin transfusionsyndrome			
Second pregnancy after twin to twin transfusionsyndrome	☐	☐	☐
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐

49

50 **[12] If so, what kind of anomaly?**

51

52

53

54 **[13] Were there any problems or complications during your pregnancy after your**

55 **pregnancy with twin to twin transfusion syndrome?**

	There were no problems or complications	Vaginal bleeding during your pregnancy	Placenta problems	High blood pressure/Pre- eclampsia	Gestational diabetes	Others	Not applicable

First pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐
Second pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐

56

57 [14] If you marked “others” in the previous question, please specify:

58

59

60

61

62

63

64 [15] Were there any problems/complications during labor or delivery after your pregnancy

65 with twin to twin transfusion syndrome?

	There were no problems or complications during labor or delivery	The water broke too early (more than 24 hours before labor)	Labor occured too early (before 8 months/37 weeks)	Excessive blood loss during delivery	Problems with the uterine scar of the previous fetoscopic surgery	Others	Not applicable
First pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐
Second pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐	☐	☐

66 [16] If you marked "others" in the previous question, please specify:

67

68

69

70

71 **[17] May we contact your gynecologist to provide us detailed information about these**

72 **problems?**

73 ☐ Yes

74 ☐ No

75 **[18] If so, could you please give us the name and address of your gynecologist?**

76 ☐ Name :

77

78 ☐ Address :

79

80

81 ☐ Telephone number :

82

83 ☐ Email address :

84

85 **[19] Did you get pregnant spontaneously, i.e. without medical help?**

	Yes	No	Not applicable

First pregnancy after twin to twin transfusionsyndrome	☐	☐	☐
Second pregnancy after twin to twin transfusionsyndrome	☐	☐	☐
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐

86

87 **[20] If there were fertility problems, did these exist before the pregnancy in which the**
88 **twin to twin transfusion syndrome was diagnosed?**

89 ☐ Yes

90 ☐ No

91

92 **[21] What type of assisted reproduction techniques did you require?**

	Medication to stimulate ovulation	Artificial insemination (using own sperm)	IVF (In Vitro Fertilization)/ ICSI (Intracytoplasmic sperm injection)	Use of donor sperm and/or female egg	Not applicable

				(oocyte).	
First pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐
Second pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐
Third pregnancy after twin to twin transfusionsyndrome	☐	☐	☐	☐	☐

93

94 **C. Psychological impact**

95 **[22] Have you had any psychological or emotional problems related to the twin to twin**
 96 **transfusion syndrome or the pregnancy outcome?**

97 ☐ Yes98 ☐ No

99

100

[23] Could you please describe them?

D. Gynecological problems

[24] Did you have abnormal menstruations after you delivered the baby/babies of the twin to twin transfusion syndrome?

☐ Yes

☐ No

[25] If so, how many months after you delivered the baby/babies of the twin to twin transfusion syndrome did this problem start?

Months

[26] What was the cause of this bleeding according to your gynecologist or general practitioner?

[27] Did you have a lot of lower abdominal pain after you delivered the baby/babies of the twin to twin transfusion syndrome?

☐ Yes

☐ No

[28] If so, how many months after you delivered the baby/babies of the twin to twin transfusion syndrome did this pain start?

Months

[29] What was the cause of this pain according to your gynecologist or general practitioner?

[30] Did you have any other gynecological problem since you delivered the baby/babies of the twin to twin transfusion syndrome?

☐ Yes

☐ No

[31] If so, how many months after you delivered the baby/babies of the twin to twin transfusion syndrome did these problems start?

Months

[32] Which problem occurred and what was the cause according to your gynecologist or general practitioner?

[33] May we contact your gynecologist to provide us detailed information about these problems?

☐ Yes

☐ No

[34] Could you please give us the name and address of your gynecologist or general practitioner?

▪ Name

▪ Address

▪ Telephone number

▪ Email address

E. Other

[35] If you experienced other medical problems after your surgery for twin to twin transfusion syndrome or if you have any other remarks regarding this questionnaire, please write these in the box below:

A large empty rectangular box with a black border, intended for the respondent to write their remarks. A large, light gray diagonal watermark reading "ACCEPTED MANUSCRIPT" is visible across the page, passing through this box.

Thank you very much for your participation.

Appendix 2: Questionnaire designed for controls

Subsequent fertility, pregnancy and gynecological outcomes in women with monochorionic twins

This questionnaire consists of 35 items. Filling it in will take around 15 minutes.

A. Subsequent pregnancy desire

[1] Have you attempted to get pregnant after your identical twin pregnancy?

☐ Yes (Proceed to question 4)

☐ No (Proceed to question 2)

[2] Is there any relationship between a problem in your previous identical twin pregnancy or its outcome and the fact that you have not attempted a new pregnancy?

☐ Yes (Proceed to question 3)

☐ No (Proceed to question 22)

[3] Are you willing to summarize the reason why you haven't attempted a new pregnancy?

(Proceed to question 22)

[4] How much time was there between the delivery of the identical twins and a new attempt to get pregnant?

192 Months

193

194 **[5] Have you been pregnant since your previous identical twin pregnancy?**

195 ☐ Yes

196 ☐ No

197 **[6] How much time was there between the delivery of the twins and the delivery of the**
 198 **following pregnancy?**

199 Months

200

201 **B. Later pregnancy outcomes**

202 We would like to investigate whether there were any problems or complications during one
 203 of these later pregnancies. We would like you to answer the following questions separately
 204 for the first three pregnancies after the previous identical twin pregnancy was detected.

205 **[7] Was it a singleton, twin or triplet?**

	Singleton	Twin	Triplet	Not applicable
First pregnancy after identical twin pregnancy	☐	☐	☐	☐
Second pregnancy after	☐	☐	☐	☐

identical twin pregnancy				
Third pregnancy after identical twin pregnancy	☐	☐	☐	☐

206

207 **[8] What was the estimated gestational age at the moment of delivery? (the normal**
208 **gestational age is 40 weeks)**

	Miscarriage or loss prior to 20 weeks of pregnancy	20-24 weeks	24-28 weeks	28-36 weeks	>37 weeks	Not applicable
First pregnancy after the identical twins	☐	☐	☐	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐	☐	☐	☐
Third pregnancy after the identical	☐	☐	☐	☐	☐	☐

twins

209

210 [9] The delivery was

	Vaginal	Caesarean delivery	Not applicable
First pregnancy after the identical twins	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐
Third pregnancy after the identical twins	☐	☐	☐

211

212 [10] What was the birth weight of your child in grammes? Please fill in 0 when not

213 applicable.

	Weight (in grammes)	Weight (in case of twins, in grammes)	Weight (in case of triplets, in grammes)
First pregnancy after the			

identical twins			
Second pregnancy after the identical twins			
Third pregnancy after the identical twins			

214

215 **[11] Was there any congenital anomaly/malformation?**

	Yes	No	Not applicable
First pregnancy after the identical twins	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐
Third pregnancy after the identical twins	☐	☐	☐

216 **[12] If so, what kind of anomaly?**

217

218

219

220

221

222 **[13] Were there any problems or complications during your pregnancy after your**

223 **pregnancy with identical twins?**

	There were no problems or complications	Vaginal bleeding during your pregnancy	Placenta problems	High blood pressure/pre-eclampsia	Gestational diabetes	Others	Not applicable
First pregnancy after the identical twins	☐	☐	☐	☐	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐	☐	☐	☐	☐

Third pregnancy after the identical twins	☐	☐	☐	☐	☐	☐	☐

224

225 [14] If you marked “others” in the previous question, please specify:

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236 [15] Were there any problems/complications during labor or delivery after your pregnancy
237 with identical twins?

	There were no problems or complications during labor or delivery	The water broke too early (more than 24 hours before labor)	Labor occurred too early (before 8 months/37 weeks)	Excessive blood loss during delivery	Problems with the uterine scar in case of an earlier caesarean delivery	Other	Not applicable
First pregnancy after the identical twins	☐	☐	☐	☐	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐	☐	☐	☐	☐
Third pregnancy after the	☐	☐	☐	☐	☐	☐	☐

identical twins							

238

239 **[16] If you marked “others” in the previous question, please specify:**

240

241

242

243 **[17] May we contact your gynecologist to provide us detailed information about these**

244 **problems?**

245 ☐ Yes

246 ☐ No

247 **[18] Could you please give us the name and address of your gynecologist?**

248 ☐ Name :

249

250 ☐ Address :

251

252 ☐ Telephone number :

253

254 ☐ Email address :

255

256 **[19] Did you get pregnant spontaneously, i.e. without medical help?**

	Yes	No	Not applicable
First pregnancy after the identical twins	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐
Third pregnancy after the identical twins	☐	☐	☐

257

258 **[20] If there were fertility problems, did these exist before the pregnancy of the identical**259 **twins?**260 ☐ Yes261 ☐ No262 **[21] What type of assisted reproduction techniques did you require?**

	Medication to stimulate ovulation	Artificial insemination (using own sperm)	IVF (In Vitro Fertilization)/ ICSI (Intracytoplasmic sperm injection)	Use of donor sperm and/or female egg (oocyte).	Not applicable
First pregnancy after the identical twins	☐	☐	☐	☐	☐
Second pregnancy after the identical twins	☐	☐	☐	☐	☐
Third pregnancy after the identical twins	☐	☐	☐	☐	☐

263

264 **C. Psychological impact**

265 **[22] Have you had any psychological or emotional problems related to complications**
266 **during the pregnancy of the identical twins or the pregnancy outcome?**

267 ☐ Yes

268 ☐ No

269 **[23] If so, could you please describe them?**

D. Gynecological problems

[24] Did you have abnormal menstruations after you delivered the baby/babies of your identical twin pregnancy?

☐ Yes

☐ No

[25] If so, how many months after you delivered of the baby/babies of your identical twin pregnancy did this problem start?

Months

[26] What was the cause of this bleeding according to your gynecologist or general practitioner?

[27] Did you have a lot of lower abdominal pain after you delivered the baby/babies of your identical twin pregnancy?

☐ Yes

☐ No

[28] If so, how many months after you delivered the baby/babies of your identical twin pregnancy did this pain start?

Months

[29] What was the cause of this pain according to your gynecologist or general practitioner?

[30] Did you have any other gynecological problem since you delivered the baby/babies of your identical twin pregnancy?

☐ Yes

☐ No

[31] How many months after you delivered the baby/babies of your identical twin pregnancy did these problems start?

Months

[32] Which problem occurred and what was the cause according to your gynecologist or general practitioner?

[33] May we contact your gynecologist to provide us detailed information about these problems?

☐ Yes

☐ No

[34] Could you please give us the name and address of your gynecologist or general practitioner?

▪ Name :

▪ Address :

▪ Telephone number :

▪ Email address :

E. Others

[35] If you experienced other medical problems after your identical twin pregnancy or if you have any other remarks regarding this questionnaire, please write these in the box below:

A large empty rectangular box with a black border, intended for the respondent to write any other remarks or medical problems experienced after the identical twin pregnancy. The box is currently empty.

Thank you very much for your participation.

Appendix 3: Other psychological and emotional problems

Cases (6):

- Emotional pregnancy
- Emotional period after operation
- Feelings of emptiness
- Loss of energy
- Not specified
- Care for survivor

Controls (12):

- Hard time taking care for twins (3)
- Emotional period after pregnancy (3)
- Emotional pregnancy, exhausted
- Hard to process that twins were premature
- Burn out, care for twins
- Unplanned pregnancy, divorce
- Missed career opportunity due to care for twins
- Exhausted, nervous