Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial

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OBSTETRICS

Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial

Julien Stirnemann, MD; Femke Slaghekke, MD; Nahla Khalek, MD; Norbert Winer, MD; Anthony Johnson, MD; Liesbeth Lewi, MD; Mona Massoud, MD; Laurence Bussieres, MD; Philippe Aegerter, MD; Kurt Hecher, MD; Marie-Victoire Senat, MD; Yves Ville, MD

BACKGROUND: Selective fetoscopic laser coagulation of the intertwin anastomotic chorionic vessels is the first-line treatment for twin-twin transfusion syndrome. However, in stage 1 twin-twin transfusion syndrome, the risks of intrauterine surgery may be higher than those of the natural progression of the condition.

OBJECTIVE: This study aimed to compare immediate surgery and expectant follow-up in stage 1 twin-twin transfusion syndrome.

STUDY DESIGN: We conducted a multicentric randomized trial, which recruited from 2011 to 2018 with a 6-month postnatal follow-up. The study was conducted in 9 fetal medicine centers in Europe and the Unites States. Asymptomatic women with stage 1 twin-twin transfusion syndrome between 16 and 26 weeks' gestation, a cervix of >15 mm, and access to a surgical center within 48 hours of diagnosis were randomized between expectant management and immediate surgery. In patients allocated to immediate laser treatment, percutaneous laser coagulation of anastomotic vessels was performed within 72 hours. In patients allocated to expectant management, a weekly ultrasound follow-up was planned. Rescue fetoscopic coagulation of anastomoses was offered if the syndrome worsened as seen during a follow-up, either because of progression to a higher Quintero stage or because of the maternal complications of polyhydramnios. The primary outcome was survival at 6 months without severe neurologic morbidity. Severe complications of prematurity and maternal morbidity were secondary outcomes.

RESULTS: The trial was stopped at 117 of 200 planned inclusions for slow accrual rate over 7 years: 58 women were allocated to expectant management and 59 to immediate laser treatment. Intact survival was seen in 84 of 109 (77%) expectant cases and in 89 of 114 (78%) (P=.88) immediate surgery cases, and severe neurologic morbidity occurred in 5 of 109 (4.6%) and 3 of 114 (2.6%) (P=.49) cases in the expectant and immediate surgery groups, respectively. In patients followed expectantly, 24 of 58 (41%) cases remained stable with dual intact survival in 36 of 44 (86%) cases at 6 months. Intact survival was lower following surgery than for the nonprogressive cases, although nonsignificantly (78% and 71% following immediate and rescue surgery, respectively).

CONCLUSION: It is unlikely that early fetal surgery is of benefit for stage 1 twin-twin transfusion syndrome in asymptomatic pregnant women with a long cervix. Although expectant management is reasonable for these cases, 60% of the cases will progress and require rapid transfer to a surgical center.

Key words: anastomoses, fetal death, fetal surgery, fetoscopic surgery, laser ablation, monochorionic twins, multifetal gestation, PPROM, preterm birth, Quintero, Quintero stage 1, randomized trial

Introduction

Twin-twin transfusion syndrome (TTTS) complicates 10% to 15% of monochorionic pregnancies, and it is a major contributor to perinatal mortality and morbidity.[1,2] Its prenatal diagnosis is defined by oligohydramnios in 1 twin and polyuric polyhydramnios in the cotwin and is well standardized.[3] If left untreated, the condition leads to miscarriage, early preterm birth, neurologic damage, or in utero fetal demise of 1 or both twins.[4] Selective fetoscopic laser coagulation of intertwin anastomoses on the chorionic plate was proven to be the best first-line treatment for TTTS compared with amnioreduction through a randomized controlled trial (RCT), which included 142 women.[3,5] However, the benefits of surgery for early stages (ie, Quintero stage 1) of the disease could not be assessed specifically because of the small number of cases included and therefore remains debated because the risks of intrauterine surgery, including preterm premature rupture of membranes (PPROM) in up to 40% of cases, miscarriage or preterm birth, intrauterine fetal death, twin anemia-polycythemia sequence (TAPS), and chorioamnionitis,[6–9] may be worse than those of the natural progression of the disease itself.[10,11] Several observational studies have described the evolution of stage 1 TTTS, a condition defined solely by severe discordance in the amniotic fluid, together with a visible bladder in the donor twin and the absence of Doppler anomalies in either of the twins. The observed evolutions include regression and stability through to worsening of the fetal condition or of the maternal symptoms (preterm labor, pain, or dyspnea). Khalil et al[12] summarized the results of these studies in a meta-analysis of observational, nonrandomized cases, and they showed that overall progression occurred in 27% (range, 10%–50%) of the cases, without separating the progression in Quintero staging and maternal or obstetrical symptoms. In a

Cite this article as: Stirnemann J, Slaghekke F, Khalek N, et al. Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial. Am J Obstet Gynecol 2021;224:528.e1-12.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2020.11.031

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AJOG at a Glance

Why was this study conducted?

This study aimed to determine if stage 1 twin-twin transfusion syndrome (TTTS) should be managed primarily with intrauterine fetoscopic photocoagulation of placental anastomosis or expectantly.

Key findings

In this randomized trial that included 117 pregnancies, there was no difference in the intact survival between surgery and expectant management overall. However, 41% of the cases managed expectantly remained asymptomatic and did not progress to higher stages throughout the pregnancy. In this group, intact perinatal survival was 86%, whereas it was 78% and 71% following immediate or rescue surgery, respectively, although these differences were not statistically significant.

What does this add to what is known?

Expectant management is a safe option in stage 1 TTTS.

large multicentric retrospective analysis of stage 1 TTTS, Emery et al[13] found a 60% rate of progression in the Quintero stage. It therefore seems valid to balance the risk of rapid aggravation with that of severe complications after surgery. We conducted an RCT comparing expectant management and heightened surveillance with intrauterine surgery in stage 1 TTTS.

Materials and Methods

Participants

We conducted the trial at the following 9 maternal-fetal surgery centers: Paris, France (n=68); Leiden, the Netherlands (n=18); Kremlin-Bicêtre, France (n=10); Philadelphia, PA (n=7); Nantes, France (n=6); Houston, TX (n=3); Hamburg, Germany (n=2); Lyon, France (n=2); and Leuven, Belgium (n=1); all 9 centers perform >25 cases of fetoscopic surgery for TTTS per year. This trial was approved by the institutional review board at each center.

TTTS was identified on a ultrasound by the association of polyhydramnios in 1 sac (deepest vertical pocket [DVP] >10 cm when gestational age >20 weeks and >8 cm before 20 weeks' gestation) and oligohydramnios in the other (DVP of <2 cm).[3] We included patients with Quintero stage 1 TTTS defined by a visible bladder in the donor twin and the absence of Doppler anomalies in either twins, which is a positive end-diastolic flow in the umbilical arteries and a positive "A" wave in the ductus venosus.[10] Women with symptoms related to polyhydramnios (contractions, dyspnea, or orthopnea) and/or who had a cervical length measured at ≤15 mm by ultrasound were excluded, as well as cases diagnosed at <16+0/7 weeks' and >26+6/7 weeks' gestation. We also excluded cases with PPROM before enrollment, PPROM before amnioreduction, any fetal malformation, or hydrops.

Eligible patients who declined to participate were also monitored in Paris and Hamburg. These patients were managed as per their request, either by an expectant weekly follow-up or immediate laser surgery as performed in patients randomized in the trial. However, in these cases, the decision for either primary management protocol was based solely on the parental preference.

Randomization and intervention procedures

Following information about the trial, eligible patients who were willing to participate were enrolled in one of the participating centers after they provided written informed consent. Women were randomized 1:1 between expectant management and immediate surgery, without stratification, using a dedicated website maintained by the coordinating center.

The patients allocated to immediate surgery were operated on within 72 hours following randomization. The surgery was performed percutaneously in all cases, using a 1.3-or 2-mm semirigid fetoscope or a 3.3-mm rigid 3-channel fetoscope (Karl Storz SE & Co KG, Tuttlingen, Germany). Maternal anesthesia was obtained by local injection of xylocaine or epidural, possibly with conscious sedation (remifentanil or midazolam). The fetoscope was inserted through an 8−12 Fr trocar placed in the polyhydramniotic cavity under ultrasound control. The placental intertwin anastomoses were coagulated using a Diode or neodymium−yttrium-aluminum-garnet laser (Dornier MedTech GmbH, Wessling, Germany) aimed at the vascular equator. Excess amniotic fluid was removed at the end of the procedure.

The patients allocated to expectant management were followed weekly by ultrasound. Each examination comprised biometric, amniotic fluid, Doppler, and cervical length assessments. In case of progression within Quintero stages, polyhydramnios-related symptoms, or significant cervical shortening, rescue therapy was systematically offered. In cases showing progression at <27+0/7 weeks' gestation, emergency fetoscopic laser surgery was considered as the first-line treatment. In cases showing progression at ≥27+0/7 weeks' gestation, amnioreduction and steroids for lung maturation were the most usual first-line treatment.

Following surgery, follow-ups were by weekly ultrasound investigations up until delivery. Delivery was either spontaneous or decided upon according to the local obstetrical protocols, including elective delivery (cesarean or vaginal) at around 34 weeks' gestation.[14,15]

Outcomes

The primary outcome was defined as infant survival at 6 months postnatal without severe neurologic morbidity. Severe neurologic morbidity was defined as an abnormal neurologic examination at 6 months postnatal (severe neurodevelopmental delay or abnormal motor

examination), intraventricular hemorrhage grade 3 or 4 on postnatal ultrasound and magnetic resonance imaging (MRI), periventricular leukomalacia on postnatal ultrasound and MRI, bilateral blindness, or deafness.

Secondary outcomes included severe extraneurologic complications of prematurity at 6 months (any of the following: necrotizing enterocolitis at ≥stage 2, bronchopulmonary dysplasia, renal failure, or retinopathy of prematurity) and maternal and obstetrical morbidity including miscarriage (spontaneous delivery <24 weeks), PPROM, preterm birth at <28 weeks and <32 weeks, placental abruption, and chorioamnionitis.

Although a 2-year follow-up was planned as part of determining the secondary outcomes, we report on the outcomes at 6 months herein.

Statistical analysis

Previous reports published at the time of designing the trial reported perinatal survival rates of 71% to 77% in stage 1 pregnancies managed expectantly,[16,17] and intact survival of 64% of twins following laser surgery (stages 1 and 2).[3] We aimed to detect a 15% clinically relevant difference (a difference between 60% and 75%) in survival without neurologic damage at 6 months between the groups. With 80% power and a 2-sided α=0.05, 100 pregnancies (ie, 200 fetuses) in each study group would be sufficient to detect such a difference, adjusting for the correlation between twins using an intracluster correlation of 0.3, estimated from the primary trial by Senat et al.[3] No interim analyses were planned. However, given the slow accrual rate after 7 years, the data monitoring committee decided to stop the trial at 117 of 200 inclusions and proceed with analyzing the available data. Conditional power for the trial, defined as the probability that the final study result would be statistically significant in the end, given the data observed thus far, was computed under the following 3 hypotheses for the remaining data: (1) that it would follow the treatment effect postulated by the initial design, (2) that it would follow the effect found at the end of recruitment, and (3) that it would follow the null hypothesis of no difference between the randomization arms.[18]

The treatment effect was reported using risk ratios (RRs). To account for the correlation between pairs of twins, the binary outcomes, defined at the infant level, were analyzed using several models including mixed models and generalized estimating equations (GEEs). All the models provided consistent results. Finally, we reported the confidence intervals (CIs) for the RRs and P values, computed from a Poisson model in the GEE framework.[19] The analyses were performed according to an intention-to-treat principle.

The time interval between randomization and delivery with at least 1 twin alive was studied using Kaplan-Meier analyses and log-rank tests and censoring cases with dual fetal death or termination of the pregnancy.

A prognostic analysis was conducted to identify potential predictors for disease progression in cases initially managed expectantly. The RRs were computed for all the potential risk factors. Given the lack of a consensual cutoff and the small sample size precluding more advanced modeling, the continuous variables were dichotomized at the median.

All analyses were performed using R (R foundation for statistical computing, Vienna, Austria) and the packages geepack and lme4.

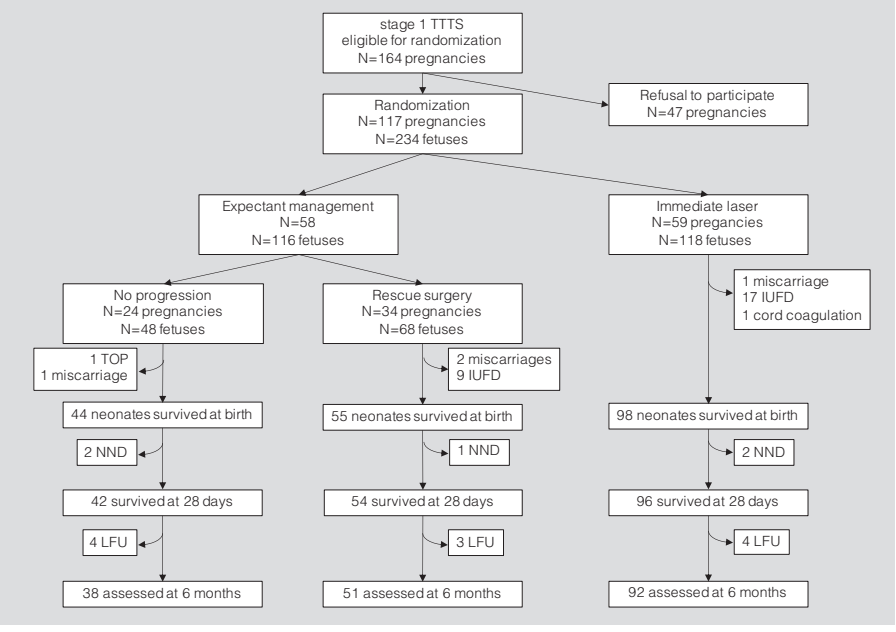
This trial was registered with clinicaltrials.gov under number NCT01220011 before the start.

Results

Patients

The data monitoring committee made the decision to stop the trial in May 2018 when 117 of 164 eligible cases consented to inclusion between April 2011 and March 2018, showing the increasing difficulties to recruit (Supplemental Figure). Based on the primary outcome, the conditional power under the most favorable hypothesis that the remaining data would follow any of the alternate hypotheses postulated by the trial design was 11%. Under the

FIGURE 1
Flowchart of the study population



IUFD, in utero fetal demise; *LFU,* lost to follow-up; *NND,* neonatal death; *TTTS,* twin-twin transfusion syndrome; *TOP,* termination of pregnancy.

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TABLE 1
Baseline characteristics of the study population

Characteristic	Expectant (n=58)	Immediate laser (n=59)	Total randomized (n=117)	Nonrandom for refusal (n=47)	*P* value[a]
Maternal age (y), median (IQR)	31.5 (27−35)	31 (28−34.5)	31 (28−35)	32 (29−34)	.627
Nulliparous, n (%)	24 (41.38)	21 (35.59)	45 (38.46)	14 (29.79)	.369
BMI (kg/m^2), median (IQR)	24.1 (21.5−28.7)	22.8 (21.0−26.8)	23.4 (21.2−28.2)	23.4 (21.7−26.0)	.45
Assisted reproductive technology, n (%)	1 (1.72)	4 (6.70)	5 (4.27)	5 (10.64)	.152
Gestational age at inclusion (wk), median (IQR)	21.5 (19.9−23.6)	20.7 (19.0−22.7)	20.9 (19.6−23.1)	19.7 (18.4−21.9)	.004
Deepest vertical pocket in the donor sac (cm), median (IQR)	2 (1−2)	1.6 (1−2)	2 (1−2)	1.7 (1−2)	.504
Deepest vertical pocket in the recipient sac (cm), median (IQR)	10 (10.0−11.0)	10.2 (9.25−11.5)	10 (10.0−11.0)	9.7 (8.6−10.5)	.005
Abdominal circumference discordance, percentage, median (IQR)	6.25 (3.06−11.5)	7.49 (3.6−13)	7.06 (3.32−12.6)	11.3 (5.17−15.9)	.021
Cervical length (mm), median (IQR)	38 (35.0−42.8)	39 (35.0−44.5)	39 (35.0−44.0)	40 (34.8−44.0)	.983
Anterior placenta, n (%)	14 (24.14)	19 (32.2)	33 (28.21)	13 (27.66)	1.0

BMI, body mass index; *IQR*, interquartile range.

[a] *P* value is for comparison between the randomized and nonrandomized patients.

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hypothesis that the remaining data would follow the same trend as the data observed so far, the conditional power was 0.1%, suggesting futility and further validating the decision to stop the trial before completion. Under the null hypothesis, the conditional power was also 0.1%.

A total of 117 women (234 twins) were enrolled in the trial: 58 were allocated to the expectant follow-up group and 59 to the immediate surgery group (Figure 1). The maternal and obstetrical characteristics at randomization were similar between the 2 allocation arms (Table 1). The characteristics of the women included in this trial were compared with those who declined recruitment (n=47 pregnancies). Both populations were similar except that the nonrandomized women were diagnosed at an earlier gestational age, with slightly larger intertwin discordance in the abdominal circumference and a smaller DVP in the recipient twin. This report is based on the 6-month outcome, available for 223 or 234 infants: 11 (4.7%) infants were lost to follow-up between 28 days or discharge and 6 months, and they were excluded from the analysis of the 6-month outcomes.

Progression of the disease

In patients allocated to expectant management, the disease progressed in 34 of 58 (59%) cases, requiring rescue surgery, whereas it remained stable in 24 of 58 (41%) cases (Table 2). The indications for rescue surgery were progression to stage 3 or 4 of the disease in 19 of 34 (59%) cases, maternal symptoms of polyhydramnios in 7 of 34 (21%) cases, cervical shortening in 6 of 34 (18%) cases, and TAPS in 2 of 34 (6%) cases. Progression was managed either by percutaneous laser surgery in 29 of 34 (85%) cases, or by amnioreduction in 5 of 34 (15%) cases. After 26 weeks' gestation, progression was treated by amnioreduction (median, 27.0 weeks; interquartile range [IQR], 26.3−27.1), whereas laser surgery was performed when progression was identified under 26 weeks' gestation (median, 21.3 weeks; IQR, 23.0−25.0). The median time interval between randomization and the

TABLE 2
Perinatal outcomes compared between patients randomized to expectant or immediate laser treatment

Outcome	Expectant	Immediate laser	Risk ratio (95% CI)	*P* value
Outcomes per fetus	n=116 fetuses	n=118 fetuses		
Primary outcome, n (%)	25 (22.94)	25 (21.93)	0.956 (0.532–1.72)	.881
Components of primary outcome				
Death at ≤6 mo, n (%)	20 (18.35)	22 (19.30)	1.05 (0.541–2.05)	.882
Neurologic anomaly at 6 mo, n (%)	5 (4.59)	3 (2.63)	0.574 (0.117–2.81)	.493
Severe complications of PTB[a], n (%)	14 (14.43)	22 (22.22)	1.54 (0.762–3.11)	.222
Outcomes per pregnancy	n=58 pregnancies	n=59 pregnancies		
Gestational age at birth (wk), median (IQR)	32.8 (30.1–34.8)	32.3 (29.1–34.7)		.689
Gestational age at birth, n (%)				.662
<24 wk	3 (5.17)	2 (3.39)		
≥24 and <28 wk	8 (13.79)	6 (10.17)		
≥28 and <32 wk	12 (20.69)	18 (30.51)		
≥32 wk	35 (60.34)	33 (55.93)		
PPROM at <32 wk, n (%)	6 (10.53)	18 (30.51)	2.9 (1.24–6.78)	.011
Number of twins alive at birth per pregnancy, n (%)				.442
0	1 (1.72)	4 (6.78)		
1	9 (15.52)	10 (16.95)		
2	48 (82.76)	45 (76.27)		
Number of twins alive at 28 d or discharge, n (%)				.952
0	6 (10.34)	6 (10.17)		
1	8 (13.79)	10 (16.95)		
2	44 (75.86)	43 (72.88)		
Number of twins alive at 6 mo, n (%)				.819
0	6 (11.11)	6 (10.53)		
1	7 (12.96)	10 (17.54)		
2	41 (75.93)	41 (71.93)		

CI, confidence interval; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes; *PTB*, preterm birth.

[a] Any of the following: necrotizing enterocolitis ≥stage 2,[20] bronchopulmonary dysplasia, renal failure, retinopathy of prematurity, or sepsis. The proportions were computed among the perinatal survivors (n=97 and n=99 neonates in the expectant and immediate laser groups, respectively).

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diagnosis of progression was 9 days (IQR, 5–18). Two cases required intrauterine transfusion: 1 for TAPS following rescue laser surgery and 1 for acute anemia following the demise of the co-twin. One pregnancy was terminated at 25 weeks' gestation following the demise of 1 twin with an anemic co-twin.

All patients allocated to immediate laser surgery were operated on within 72 hours of randomization. The surgery was transplacental in 5 of 59 (8%) cases. Two cases were converted to a simple amniodrainage because of intraoperative technical difficulties that precluded laser coagulation of the anastomotic vessels. Postoperative TAPS occurred in 1 patient and was managed by cord coagulation of the anemic twin showing ischemic or hemorrhagic brain lesions.

Primary outcome

The rates of overall survival without severe neurologic morbidity at 6 months were 77% and 78% in the expectant and immediate surgery groups, respectively (Table 2). The rates of severe neurologic morbidity between the groups were close: 4.6% and 2.6% in pregnancies managed initially as expectant and by immediate surgery, respectively. Death at <6 months occurred in 20 of 116 (18.3%) expectant cases and 22 of 118 (19.3%) immediate surgery cases, mostly prenatally. Intrauterine fetal demise accounted for the losses in 9 of 20 (45%) expectant cases and 17 of 22 (77%) immediate surgery cases. There were no deaths between discharge and 6 months.

Miscarriages occurred in 1 case following immediate laser surgery and in 4 cases in pregnancies randomized to expectant management. Dual loss and single loss per pregnancy occurred within similar proportions across both groups: at 6 months, the rates of dual survivors were 76% and 72% in the expectant and immediate surgery groups, respectively. All cases of cerebral injury were diagnosed postnatally. Severe neurologic anomalies at 6 months included severe neurodevelopmental delay (n=2); encephalopathy in 2 cases, 1 of which is possibly syndromic; delayed motor function (n=3); and severe social behavior delay in 1 child raised in a very deprived environment. There were 19 perinatal survivors following intrauterine demise of the co-twin (10 and 9 in immediate laser and expectant management groups, respectively): none of them displayed severe neurologic anomalies at 6 months.

In pregnancies managed expectantly, the rate of intact survival after rescue therapy for disease progression did not differ significantly compared with pregnancies that did not progress (Table 3): the RR of death or severe neurologic anomalies associated with rescue surgery was 2.14 (95% CI, 0.685−6.71). However, the survival rate per pregnancy, in terms of 0, 1, or 2 survivors, was lower following rescue therapy than in nonprogressive cases: the rate of dual survival at 6 months was 86% in the nonprogressive cases and 69% in the progressive cases. However, intact survival rate was close for the immediate surgery (78%) and for the rescue therapy cases following initially expectant management (71%). The proportions of 0, 1, and 2 survivors per pregnancy were also similar between these 2 groups (Tables 2 and 3).

Secondary outcomes

The rate of PPROM at <32 weeks' gestation was significantly higher in the immediate laser group, with an RR of 2.9 (95% CI, 1.24−6.78). In the expectant management group, only 1 of 24 (4%) cases of PPROM at <32 weeks' gestation occurred in pregnancies that did not progress, whereas in 4 of 34 (15%) cases, the membranes ruptured following rescue therapy (Table 3). In nonprogressive pregnancies, delivery occurred 2 weeks later than in pregnancies that required rescue therapy, although this difference was not statistically significant. The median time between randomization and delivery was 12.6 weeks (95% CI, 10.3−15.6) and 10.8 weeks (95% CI, 9.14−12) in the nonprogressive and progressive cases, respectively (P=.34) (data not shown).

There were no severe maternal adverse events. However, 3 of 59 (5%) cases of placental abruption were suspected in the immediate laser group, requiring emergency delivery (none in the expectant group). Four cases of chorioamnionitis following PPROM occurred postoperatively: in 1 of 59 (2%) cases in the immediate laser group and in 3 of 34 (9%) cases following rescue surgery in the expectant management group.

The median gestational age at delivery was 32.8 and 32.3 weeks' gestation in the expectant management and immediate laser groups, respectively (P=.689). Preterm birth occurred with similar distributions across gestational age in both groups (Table 2). The time interval between randomization and delivery was similar in both groups (P=.448) (Figure 2). In the perinatal survivors, severe complications of preterm birth were observed in 14 of 97 (14.43%) and 22 of 99 (22.22%) cases in the expectant and immediate surgery groups, respectively (P=.222).

In the cohort that declined randomization in which 21 of 47 (45%) and 26 of 47 (55%) cases elected to have immediate surgery or expectant management, respectively, both the incidence of rescue procedures following initial expectancy and perinatal survival and morbidity were similar to those outcome measures in the randomized women (Supplemental Table).

Risk factors for progression

Given the difference in outcomes between the patients who progressed and those who did not, we sought to identify the risk factors for progression within the cases allocated to expectant management. We used the cohort of women who declined to participate and performed analyses on the total population of patients initially managed expectantly, thus adding 26 cases to the 58 cases randomized to expectant management.

Because we were concerned that rescue therapy would be offered preferentially to patients with a posterior placenta or low body mass index, given the technical difficulties anticipated in anterior placentas, we checked for an association between the placental location and rescue therapy: no difference was found in the proportion of anterior placentas between pregnancies that required rescue therapy and those that did not (Table 4). Candidate risk factors for progression were gestational age at randomization, cervical length, nulliparity, DVP in the recipient twin, and discordance in abdominal circumference. However, none of these characteristics were found to be significantly associated with progression (Table 4).

Comment

Principal findings

Our study did not identify a clinically important difference in the perinatal outcomes between the expectant management and primary surgery cohorts for stage 1 TTTS. We have shown that 41% of stage 1 cases will remain stable and lead to the birth of 2 live-born neonates with a normal 6-month outcome in more than 86% of the cases. When surgery was performed, the survival was lower, although in line with what is reported in a large recent series.[9,21,22] Importantly, the outcome following rescue surgery performed for progression of the condition was similar to that of the primary surgery cohort. We could not identify any meaningful predictors of progression, which developed within 2 weeks of the diagnosis.

Meaning

The classification used to define the various forms of TTTS was generated in 1999 based on simple and reproducible components, which became the basis of all cohort studies and RCTs reported to date. Attempts to refine the potential of

TABLE 3
Perinatal outcomes in patients randomized to expectant management according to the prenatal course following randomization

Outcome	No progression	Rescue therapy	Risk ratio (95% CI)	*P* value
Outcomes per fetus	n=48 fetuses	n=68 fetuses		
Primary outcome, n (%)	6 (13.64)	19 (29.23)	2.14 (0.685–6.71)	.19
Components of primary outcome				
Death at ≤6 mo, n (%)	6 (13.64)	14 (21.54)	1.58 (0.486–5.13)	.447
Neurologic anomaly at 6 mo, n (%)	0 (0.0)	5 (7.69)	NA	NA
Severe complications of PTB[a], n (%)	4 (9.52)	10 (18.18)	1.91 (0.643–5.67)	.26
Outcomes per pregnancy	n=24 pregnancies	n=34 pregnancies		
Gestational age at birth (wk), median (IQR)	34.3 (30.6–35)	32.3 (28.7–34.5)		.305
Gestational age at birth, n (%)				.908
<24 wk	1 (4.17)	2 (5.88)		
≥24 and <28 wk	3 (12.50)	5 (14.71)		
≥28 and <32 wk	4 (16.67)	8 (23.53)		
≥32 wk	16 (66.67)	19 (55.88)		
PPROM at <32 wk, n (%)	1 (4.35)	5 (14.71)	3.38 (0.422–27.1)	.385
Number of twins alive at birth per pregnancy, n (%)				.005
0	1 (4.17)	0 (0.0)		
1	0 (0.0)	9 (26.47)		
2	23 (95.83)	25 (73.53)		
Number of twins alive at 28 d or discharge, n (%)				.026
0	3 (12.5)	3 (8.82)		
1	0 (0.0)	8 (23.53)		
2	21 (87.5)	23 (67.65)		
Number of twins alive at 6 mo, n (%)				.054
0	3 (13.64)	3 (9.38)		
1	0 (0.0)	7 (21.88)		
2	19 (86.36)	22 (68.75)		

CI, confidence interval; *IQR*, interquartile range; *NA*, not applicable; *PPROM*, preterm premature rupture of membranes; *PTB*, preterm birth.

[a] Any of the following: necrotizing enterocolitis ≥stage 2, bronchopulmonary dysplasia, renal failure, retinopathy of prematurity, or sepsis. The proportions were computed among the perinatal survivors (n=42 and n=55 neonates in the nonprogressive and rescue therapy groups, respectively).

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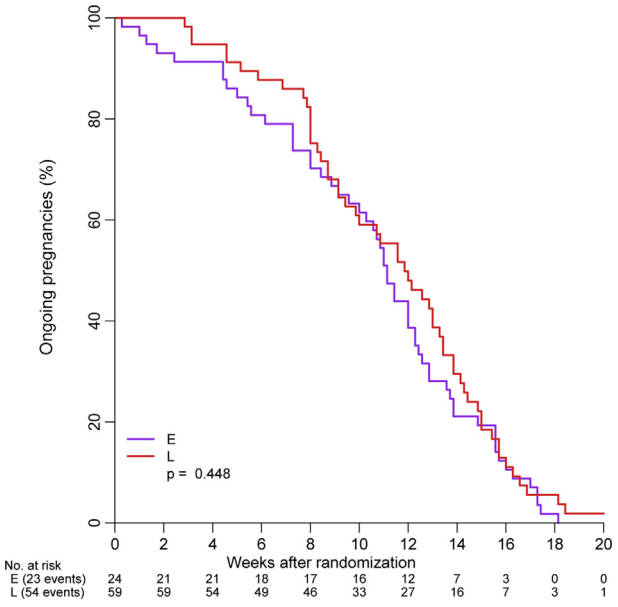
stage 1 progression relied on detailed assessment of the fetal cardiac function.[23–28] Although the classifications that take more parameters into account may contribute to the knowledge of the underlying pathophysiology of the disease, they did not prove to be superior to the primary staging when deciding on clinical management and they require specific skills that are not widely available.

Neurologic morbidity in the survivors was similar for both groups. The evolution of TTTS includes late miscarriage and severe prematurity in conjunction with polyhydramnios-related uterine contractility and cervical changes. Despite weekly surveillance of the cases managed expectantly, late miscarriage occurred in 5% of the cases. This was not different following fetal surgery whenever performed. Unexpected fetal demise before placental surgery is considered the biggest threat because it could lead to exsanguination of the co-twin in the shared placenta. This leads to the death of the co-twin in 40% of the cases and when the co-twin survives, it leads to the development of ischemic-hemorrhagic lesions in 20% of the survivors.[29] This risk, particularly to the co-twin, constitutes the strongest basis for offering primary surgery in stage 1

FIGURE 2
Kaplan-Meier curves for time interval between randomization and delivery



E, expectant (*purple line*); *L*, laser (*red line*).

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TTTS.[30] In this trial, spontaneous fetal demise occurred in 17% of the cases randomized to expectant management, including 1 double demise in the subgroup that did not progress. This confirms the high risk of TTTS, even at an early stage. The overall perinatal survival in this trial was more than 80% in both groups, close to the reported survival rates of 79% and 68% following expectant and immediate surgery, respectively, in a meta-analysis published in 2016.[12] However, in a large cohort of 94 cases (n=45 laser surgery and n=49 expectant management), Emery et al[13] found a significantly lower survival rate of 66% following expectant management than an overall survival rate of 87% following laser surgery. A previous report had suggested that laser surgery could be protective against neurologic injury.[13] However, neurologic morbidity rates were not lower following intrauterine surgery, and this is likely to be related to a higher PPROM rate that is associated with infection and inflammation-related neurologic morbidity.

We were surprised by the difficulties to recruit among eligible patients because laser endoscopic surgery is the undisputed first-line treatment for TTTS and the alternative was a very close surveillance, which would only postpone the same treatment, and no placebo or experimental treatment was proposed. Interestingly, the distribution of choices in the group that declined randomization was even between the 2 options. This suggests that the risks for aggravation of the fetal well-being and unexpected fetal death inherent to expectant management can be viewed as equal to those related to surgery, including fetal loss and PPROM. Because both were rated at approximately 20% in the preinclusion counseling, the even distribution of choice is likely to reflect opposite utility preferences that are common in fetal medicine and which constitute an obstacle to randomization that cannot

TABLE 4
Prognostic factors for disease progression in patients initially managed expectantly

Variable	No progression (n=44)	Rescue therapy (n=40)	Risk ratio (95% CI)	*P* value
Gestational age at randomization of <20.9 wk	22 (50.0)	19 (47.5)	0.95 (0.612–1.47)	.831
Cervical length of <39 mm	18 (45)	19 (50.0)	1.11 (0.696–1.77)	.821
Cervical length of <30 mm	2 (5.0)	3 (7.89)	1.58 (0.279–8.94)	.671
DVP recipient of >10 cm	17 (38.64)	13 (32.5)	0.841 (0.47–1.5)	.65
Discordance in abdominal circumference >8.8%	22 (51.16)	19 (47.5)	0.928 (0.599–1.44)	.827
Nulliparous	15 (34.09)	16 (40)	1.17 (0.671–2.05)	.653
Anterior placenta	13 (29.55)	10 (25.0)	0.846 (0.418–1.71)	.807
BMI >23.8 kg/m^2	14 (42.42)	20 (55.56)	1.31 (0.8–2.14)	.338
BMI >25 kg/m^2	13 (39.39)	18 (50.0)	1.27 (0.744–2.17)	.469

Analyses were conducted using both the randomized and nonrandomized population. Unless a specific cutoff was available, continuous variables were divided at the median. Data are presented as number (percentage).

BMI, body mass index; *CI*, confidence interval; *DVP*, deepest vertical pocket.

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substitute parental responsibility, despite the balance in probabilities and the presence of clinical equipoise.[31–33]

Clinical implications

The results of this trial suggest that for asymptomatic women with a long cervix and access to a surgical center within 48 hours, expectant management is a reasonable option for stage 1 TTTS cases presenting before 26 weeks' gestation, an issue that remained debated in most national guidelines.[34,35] This is in contrast to previously published cohorts and systematic reviews of nonrandomized studies, which suggest a benefit to immediate surgery,[11,36] as well as in contrast to the Society for Maternal-Fetal Medicine guidelines.[37] However, as this trial was not designed as an equivalence trial and because of a potential lack of power, immediate laser surgery may still be considered an option.

Research implications

Given the difficulties to recruit in this trial, we doubt that a second confirmatory trial can be conducted. We failed to identify prognostic markers for disease progression. However, such markers would be valuable to identify in patients with stage 1 TTTS at risk of progression. Identifying an even higher risk population would possibly allow better planning and allocation of monitoring and surgical resources.

Strengths and weaknesses

This RCT was terminated for failure to recruit after including 58% of the planned number of cases expected to address the primary objective. However, conditional power analysis suggested futility, hence validating the termination of the trial. In addition, the results observed in the group of patients who declined randomization and chose either 1 of the 2 management options are similar to the results of the group that was randomized. We acknowledge that randomization was not stratified by center, leading to an imbalance in the inclusions between centers; however, this was deliberate from start, not to slow inclusions that we foresaw as potentially difficult.

Conclusion

This trial has shown that in stage 1 TTTS, expectant management with heightened weekly surveillance is reasonable without compromising the outcome of 59% of the cases that will progress and require surgery. However, this option is restricted to a selected population of stage 1 TTTS cases that present with no maternal symptoms, a long cervix, and have access to a surgical center within 48 hours. ■

Acknowledgments

We acknowledge the contributions of Dick Oepkes, MD; Julie Moldenhauer, MD; Jan Deprest, MD; Jerome Massadier, MD; and Christian Bamberg, MD.

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Author and article information

From the Department of Obstetrics and Maternal-Fetal Medicine, Hôpital Necker-Enfants Malades, AP-HP and EA7328, Université de Paris, Paris, France (Drs Stirnemann, Bussieres, and Ville); Department of Obstetrics and Fetal Therapy, Leiden University Medical Center, Leiden, the Netherlands (Dr Slaghekke); Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA (Dr Khalek); Department of Obstetrics and Gynecology, NUN, INRAE, UMR 1280, PhAN, University Hospital of Nantes, Nantes, France (Dr Winer); The Fetal Center, University of Texas Health Science Center, Houston, TX (Dr Johnson); Department of Obstetrics and Gynecology, University Hospitals Leuven and Department of Development and Regeneration, Biomedical Sciences, Katholieke Universiteit Leuven, Leuven, Belgium (Dr Lewi); Fetal Medicine Unit, Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Lyon, France (Dr Massoud); Department of Public Health, UMR 1168, UVSQ INSERM, GIRCI IdF—UFR Médecine Paris-Ile-de-France-Ouest, Université de Versailles St-Quentin-en-Yvelines, Versailles, France (Dr Aegerter); Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany (Dr Hecher); and Department of Gynecology-Obstetrics, Hôpital Bicêtre AP-HP and Université Paris-Sud, Paris-Saclay Medical School and CESP Centre for Research in Epidemiology and Population Health, Université Paris-Saclay, Université Paris-Sud, UVSQ, INSERM, Villejuif, France (Dr Senat).

Received Aug. 28, 2020; revised Nov. 17, 2020; accepted Nov. 18, 2020.

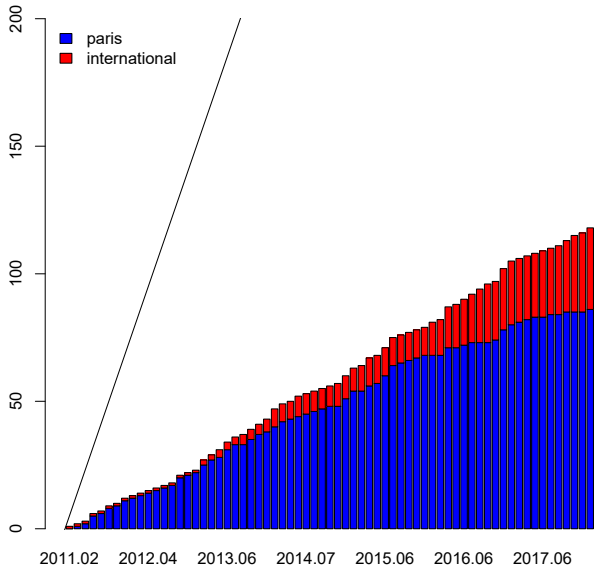
Contributor affiliations: From the Department of Obstetrics and Fetal Therapy, Leiden University Medical Center, Leiden, the Netherlands (Dr Oepkes); Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Philadelphia, PA (Dr Moldenhauer); Department of Obstetrics and Gynecology, University Hospitals Leuven and Department of Development and Regeneration, Biomedical Sciences, Katholieke Universiteit Leuven, Leuven, Belgium (Dr Deprest); Fetal Medicine Unit, Hôpital Femme Mère Enfants, Hospices Civils de Lyon, Lyon, France (Dr Massardier); and University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany (Dr Bamberg).

The authors report no conflict of interest.

This clinical trial is registered under number NCT01220011.

Corresponding author: Julien Stirnemann, MD. julien.stirnemann@aphp.fr

SUPPLEMENTAL FIGURE
Accrual rate



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SUPPLEMENTAL TABLE

Comparison between randomized and nonrandomized cases

Outcome	Nonrandomized	Randomized	Risk ratio (95% CI)	*P* value
Outcomes per fetus	n=94 fetuses	n=234 fetuses		
Primary outcome, n (%)	12 (13.79)	50 (22.42)	2.14 (0.685–6.71)	
Components of primary outcome				
Death at ≤6 mo, n (%)	11 (12.64)	42 (18.83)	1.58 (0.486–5.13)	.447
Neurologic anomaly at 6 mo, n (%)	1 (1.15)	8 (3.59)	3.12 (0.38–25.7)	.29
Severe complications of PTB[a], n (%)	11 (13.41)	36 (18.37)	1.37 (0.641–2.93)	.417
Outcomes per pregnancy	n=47 pregnancies	n=117 pregnancies		
Gestational age at birth (wk), median (IQR)	33.6 (31.5–34.4)	32.4 (29.7–34.7)		.741
Gestational age at birth, n (%)				.289
<24 wk	3 (6.52)	5 (4.27)		
≥24 and <28 wk	3 (6.52)	14 (11.97)		
≥28 and <32 wk	7 (15.22)	30 (25.64)		
≥32 wk	33 (71.74)	68 (58.12)		
PPROM at <32 wk, n (%)	5 (10.64)	24 (20.69)	1.94 (0.789–4.79)	.175
Severe complications of PTB[a] n (%)	11 (13.41)	36 (18.37)	1.37 (0.641–2.93)	.417
Number of twins alive at birth per pregnancy, n (%)				.431
0	1 (2.17)	5 (4.27)		
1	4 (8.70)	19 (16.24)		
2	41 (89.13)	93 (79.49)		
Number of twins alive at 28 d or discharge, n (%)				.494
0	4 (8.70)	12 (10.26)		
1	4 (8.70)	18 (15.38)		
2	38 (82.61)	87 (74.36)		
Number of twins alive at 6 mo, n (%)				.411
0	4 (9.30)	12 (10.81)		
1	3 (6.98)	17 (15.32)		
2	36 (83.72)	82 (73.87)		

CI, confidence interval; *IQR*, interquartile range; *PPROM*, preterm premature rupture of membranes; *PTB*, preterm birth.

[a] Any of the following: necrotizing enterocolitis stage 2, bronchopulmonary dysplasia, renal failure, retinopathy of prematurity, or sepsis. The proportions were computed among the perinatal survivors (n.42 and n.55 neonates in the nonprogressive and rescue therapy groups, respectively).

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