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

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Condensation : Expectant management is a safe option compared to immediate intrauterine fetoscopic photocoagulation of placental anastomoses for stage 1 twin-twin transfusion syndrome.

Short title: expectant versus laser for stage 1 TTTS

At a glance

Question : Should stage 1 twin twin transfusion syndrome (TTTS) be managed primarily with intrauterine fetoscopic photocoagulation of placental anastomosis or expectantly?

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

Meaning: Expectant management is a safe option in stage 1 TTTS.

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

ABSTRACT

Background: Fetoscopic laser coagulation of the inter-twin anastomotic chorionic vessels is the first-line treatment for twin-to-twin transfusion syndrome (TTTS). However, in stage 1 TTTS, the risks of intrauterine surgery may be higher than those of the natural history of the condition.

Objective: To compare immediate surgery and expectant follow-up in stage 1 TTTS.

Design: We conducted a multicentric randomized trial recruiting from 2011 to 2018 with a 6-month postnatal follow-up. The study was conducted in 9 fetal medicine centers in Europe and the USA.

Asymptomatic women, with stage-1 TTTS at between 16 and 26 weeks, a cervix >15mm 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, percutaneous laser coagulation of anastomotic vessels was performed within 72 hours. In patients allocated to expectant management, weekly ultrasound follow-up was planned. Rescue fetoscopic coagulation of anastomoses was offered if the syndrome worsened during follow-up, either because of progression to a higher Quintero stage or because of maternal complications of polyhydramnios. Primary outcome was survival at 6 months

without severe neurological 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 were allocated to expectant management and 59 to immediate laser. Intact survival was 84/109 (77%) and 89/114 (78%) ($P=0.88$) and severe neurological morbidity occurred in 5/109 (4.6%) and 3/114 (2.6%) ($P=0.49$) in the expectant and immediate surgery groups respectively. In patients followed expectantly, 24/58 (41%) cases remained stable with dual intact survival in 36/44 (86%) at 6 months. Intact survival was lower following surgery than in non-progressive cases, although non-significantly (78% and 71% following immediate and rescue surgery respectively).

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

Clinical trial registration: NCT01220011

INTRODUCTION

Twin-to-twin transfusion syndrome complicates 10-15% of monochorionic pregnancies and it is a major contributor to perinatal mortality and morbidity (1,2). Its prenatal diagnosis is defined by oligohydramnios in one twin and a polyuric polyhydramnios in the co-twin and is well standardized (3). Left untreated, the condition leads to miscarriage, early preterm birth, neurological damage or in utero fetal demise of one or both twins (4). Fetoscopic laser coagulation (SFLC) of inter-twin anastomoses on the chorionic plate was proven the best first-line treatment for TTTS compared to amnioreduction through an RCT which included 142 women (3,5). However, the benefits of surgery for early stages (i.e. Quintero stage 1) of the disease could not be specifically assessed, given the small number of cases included, and remains therefore debated since the risks of intrauterine surgery, including 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 that of the natural history 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 amniotic fluid, together with a visible bladder in the donor twin and the absence of

Doppler anomalies in either twins, Observed evolutions include regression, stability through to worsening of the fetal condition or of maternal symptoms (preterm labor, pain, dyspnea). Khalil et al. summarized the results of these studies in a meta-analysis of observational, non-randomized cases, showing that overall progression occurred in 27% (range: 10%-50%) of cases, without separating progression in Quintero staging and maternal/obstetric symptoms (12). In a large multicentric retrospective analysis of stage 1 TTTS, Emery et al found a 60% rate of progression in Quintero stage (13). It appears therefore founded to balance the risk of rapid aggravation with that of severe complications post-surgery. We conducted a randomized controlled trial comparing expectant management and heightened surveillance with intrauterine surgery in stage-1 TTTS.

METHODS

Participants

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

TTTS was defined on ultrasound by the association of polyhydramnios in one sac (deepest vertical pocket (DVP) >10 cm when gestational age >20 weeks and >8 cm before 20 weeks) and oligohydramnios in the other (DVP <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, i.e. a positive end diastolic flow in the umbilical arteries, a positive "A" wave in the ductus venosus (10). Women with symptoms related to polyhydramnios (contractions, dyspnea or orthopnea) and/or a cervical length measured ≤ 15 mm by ultrasound were excluded, as well as cases diagnosed <16+0/7 weeks and >26+6/7 weeks. We also excluded cases with PPROM prior to enrollment, prior 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 expectant weekly follow-up or immediate laser, as performed in patients randomized in the trial. However, in this case, the decision for either primary management protocol was based solely on parental preference.

Randomization and intervention procedures

Following information on the trial, eligible patients 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.

Patients allocated to immediate surgery were operated within 72h following randomization. Surgery was performed percutaneously in all cases, using a 1.3 or 2 mm semi-rigid fetoscope or a 3.3 mm rigid 3-channel fetoscope (Karl Storz SE & Co. KG, Tuttlingen, Germany). Maternal anesthesia is obtained by local injection of xylocaine or epidural, possibly with conscious sedation (remifentanil or midazolam). The fetoscope is inserted through a 8-12 Fr trocar placed in the polyhydramniotic cavity under ultrasound control. Placental inter-twin anastomoses are coagulated using a Diode or Nd:YAG

(Dornier MedTech GmbH, Wessling, Germany) laser aiming for the vascular equator.

Excess amniotic fluid was removed at the end of the procedure.

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 $<27+0/7$ weeks, emergency fetoscopic laser was considered as first-line treatment. In cases $\geq 27+0/7$ weeks, amnioreduction and steroids for lung maturation were the most usual first-line treatment.

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

Outcomes

The primary outcome was defined by infant survival at 6 months postnatal without severe neurological morbidity. Severe neurological morbidity was defined by an abnormal neurological examination at 6 months (severe neurodevelopmental delay or abnormal motor examination), intraventricular hemorrhage (IVH) grade 3/4 on postnatal ultrasound

and MRI, periventricular leukomalacia (PVL) on postnatal ultrasound and MRI, bilateral blindness or deafness.

Secondary outcomes include extra-neurologic severe complications of prematurity at 6 months (any of necrotizing enterocolitis \geq stage 2, bronchopulmonary dysplasia, renal failure, retinopathy of prematurity), maternal and obstetrical morbidity including

Miscarriage (spontaneous delivery $<$ 24 weeks), PPRM, preterm birth $<$ 28 weeks and $<$ 32 weeks placental abruption and chorioamnionitis.

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

Statistical analysis

Previous reports published at the time of designing the trial reported perinatal survival rates of 71-77% in stage 1 pregnancies managed expectantly (16,17) and intact survival of 64% following laser (stage 1 and 2) (3). We aimed to detect a 15% clinically relevant difference (a difference between 60% and 75%) in survival without neurological damage at 6 months between groups. With 80% power and a 2-sided $\alpha=0.05$, 100 pregnancies (i.e. 200 fetuses) in each study group would be sufficient to detect such a difference, adjusting for the correlation between twins using an intra-cluster correlation of 0.3,

estimated from the primary trial by Senat et al. (3). No interim analyzes were planned. However, given the slow accrual rate after 7 years, the data monitoring committee decided to stop the trial at 117/200 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 3 hypotheses for the remaining data: i) that it would follow the treatment effect postulated by the initial design; ii) that it would follow the effect found at end of recruitment and iii) that it would follow the null hypothesis of no difference between randomization arms (18).

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

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

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

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

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

RESULTS

Patients

The data monitoring committee made the decision to stop the trial in May 2018, while 117 of 164 eligible cases consented to inclusion between April 2011 and March 2018, showing increasing difficulties to recruit (Supplementary data Fig. A). 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 trial design was 11%. Under the hypothesis that the remaining data would follow the same trend as the data observed so far, conditional power was 0.1%, suggesting futility and further validating the decision to stop the trial before completion. Under the null hypothesis, conditional power was also 0.1%.

117 women (234 twins) were enrolled in the trial: 58 were allocated to expectant follow-up and 59 to immediate surgery (Figure 1). Maternal and obstetric characteristics at randomization were similar between the two allocation arms (Table 1). The characteristics of women included in the trial were compared to those that declined (N=47 pregnancies). Both populations were similar except that non-randomized women were diagnosed at an earlier gestational age, with slightly larger inter-twin discordance in

abdominal circumference and smaller deepest vertical pocket in the recipient twin. This report is based on the 6-months outcome, available in 223/234 infants: 11 (4.7%) infants were lost to follow-up between 28 days or discharge and 6 months and were excluded for the analysis of 6-month outcomes.

Progression of the disease

In patients allocated to expectant management, the disease progressed in 34/58 (59%) cases, requiring rescue surgery, while it remained stable in 24/58 (41%) (Table 2). Indications for rescue surgery were progression to stage 3 or 4 of the disease in 19/34 (59%), maternal symptoms of polyhydramnios in 7/34 (21%), cervical shortening in 6/34 (18%) and twin anemia-polycythemia sequence (TAPS) in 2/34 (6%). Progression was managed either by percutaneous laser in 29/34 (85%) cases, or by amnioreduction in 5/34 (15%) cases. After 26 weeks, progression was treated by amnioreduction (median=27.0 weeks, IQR=26.3-27.1), whereas laser was performed when progression was identified under 26 weeks (median=21.3 weeks, IQR=23.0-25.0). The median time interval between randomization and the diagnosis of progression was 9 days (IQR=5-18). Two cases required intrauterine transfusion: 1 for TAPS following rescue laser surgery and one

for acute anemia following the demise of the co-twin. One pregnancy was terminated at 25 weeks following the demise of one twin with an anemic co-twin.

All patients allocated to immediate laser were operated within 72h of randomization. Surgery was transplacental in 5/59 (8%) cases. 2 cases were converted to simple amniodrainage because of intraoperative technical difficulties that precluded laser coagulation of anastomotic vessels. Post-operative TAPS occurred in one patient and was managed by cord coagulation of the anemic twin showing ischemic/hemorrhagic brain lesions.

Primary outcome

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

Miscarriages occurred in 1 case following immediate laser and 4 cases in pregnancies randomized to expectant management. Dual loss and single loss per pregnancy occurred within similar proportions in 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 neurological anomalies at 6 months included severe neurodevelopmental delay (N=2), encephalopathy in 2 cases, one of which is possibly syndromic, delayed motor function (N=3) and severe social behavior delay in one 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 respectively): none displayed severe neurological anomalies at 6 months.

In pregnancies managed expectantly, the rate of intact survival after rescue therapy for disease progression did not differ significantly compared to pregnancies that did not progress (Table 3): the risk ratio of death or severe neurological anomalies associated with rescue surgery was 2.14 (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 non-progressive cases: the rate of dual survival at 6 months was 86% in non-progressive cases and 69% in progressive cases. However, intact survival was close for immediate surgery (78%) and

for rescue therapy following initially expectant management (71%). The proportions of 0, 1 and 2 survivors per pregnancy were also similar in these two groups (Tables 2 and 3).

Secondary outcomes

The rate of PPROM <32 weeks was significantly higher in the immediate laser group, with a RR=2.9 (1.24-6.78). In the expectant management group, only 1/24 (4%) case of PPROM <32 weeks occurred in pregnancies that did not progress, whereas 4/34 (15%) ruptured following rescue therapy (Table 3). In non-progressive 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 non-progressive and progressive cases respectively (P=0.34, data not shown).

There were no severe maternal adverse events. However, 3/59 (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 post-operatively: 1/59 (2%) in the immediate laser group, and 3/34 (9%) following rescue surgery in the expectant management group.

The median gestational age at delivery was 32.8 and 32.3 weeks in the expectant management and immediate laser groups respectively (P=0.689). Preterm birth occurred with similar distributions across gestational age in both groups (Table 1). The time interval between randomization and delivery was similar in both groups (Fig 2, P=0.448). In perinatal survivors, severe complications of preterm birth were 14/97 (14.43%) and 22/99 (22.22%) in the expectant and immediate surgery groups respectively (P=0.222). In the cohort declining randomization where 21/47 (45%) and 26/47 (55%) 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 (supplementary data)

Risk-factors for progression

Given the difference in outcomes between patients that progressed and those that did not, we sought to identify risk factors for progression within the cases allocated to expectant management. We took advantage of the cohort of women that declined to participate and performed analyzes 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 BMI, given technical difficulties anticipated in anterior placentas, we checked for an association between 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, deepest vertical pocket in the recipient twin, discordance in abdominal circumference. However, none of these characteristics were found significantly associated with progression (Table 4).

COMMENT

Main finding:

Our study did not identify a clinically important difference in perinatal outcome between expectant management and primary surgery for stage-1 TTTS. We have shown that 41% of stage-1 cases will remain stable and lead to the birth of two live-born neonates with a normal 6-months outcome in over 86% of the cases. When surgery was performed survival was lower, though in line with what is reported in large recent series (9,20,21). Importantly, the outcome following rescue surgery performed for progression of the condition was similar to that of primary surgery. We could not identify any meaningful predictor of progression, which developed within 2 weeks of the diagnosis.

Meaning:

The classification used to define the various forms of the condition named twin-to-twin transfusion syndrome was put up in 1999 based-upon simple and reproducible components which made it the basis of all cohort studies and RCTs reported to date. Attempts to refine the potential of stage-1 to worsen relied upon detailed assessment of fetal cardiac function (22–27). Although those classifications accounting for more parameters may contribute to the knowledge of the underlying pathophysiology of the

disease, they did not prove superior to the primary staging to decide upon clinical management and they require specific skills that are not widely available.

Neurological morbidity in the survivors was similar in both groups. The evolution of TTTS includes late miscarriage and severe prematurity in relation 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 prior to 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 it survives, the development of ischemic-hemorrhagic lesions in 20% of the survivors (28). This risk, particularly that to the co-twin, constitutes the strongest basis for offering primary surgery in stage-1 TTTS (29). In this trial, spontaneous fetal demise occurred in 17% of cases randomized to expectant management, including one double demise in the sub-group that did not progress. This confirms the high-risk of TTTS, even at an early stage. The overall perinatal survival in this trial was above 80% in both groups, close to 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 and N=49 expectant management), Emery et al. found a

significantly lower survival rate following expectant management of 66% compared to an overall survival of 87% following laser (13). A previous report had suggested that laser could be protective of neurological injury (13). However, neurological morbidity was not less following intrauterine surgery, and this is likely to be related to a higher PPROM rate that is associated with infection and inflammation-related neurological morbidity.

We were surprised by the difficulties to recruit among eligible patients since laser endoscopic surgery is the undisputed first-line treatment of 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 of aggravation of 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 preterm ruptures of the membranes. Since both were rated at around 20% in the pre-inclusion counselling, the even distribution of choice is likely to reflect opposite utility preferences that are common in fetal medicine and constitute an obstacle to randomization which cannot substitute parental responsibility despite the balance in probabilities and the presence of clinical equipoise (30–32).

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', a question that remained debated in most national guidelines (33,34). This is at odds with previously published cohorts and systematic reviews of non-randomized studies suggesting a benefit to immediate surgery (11,35) as well as SMFM guidelines (36). However, since the trial was not designed as an equivalence trial and because of potential lack of power, immediate laser 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 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 termination of the trial. In addition, the results observed in the group of patients who declined randomization and chose either one of the two management options, are similar to the group randomized. We acknowledge that randomization was not stratified by center, leading to imbalance in inclusions between centers; however, this was deliberate from start, not to slow inclusions which 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 presenting no maternal symptoms, a long cervix and access to a surgical center within 48 hours.

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TABLES AND FIGURES

Table 1. Baseline characteristics of the study population.

| Characteristic | Expectant N=58 | Immediate Laser N=59 | Total randomized N=117 | Non-random. for refusal N=47 | P-value* |
|--|-------------------|----------------------------|------------------------------|------------------------------------|----------|
| Maternal age – years (IQR) | 31.5 (27,35) | 31 (28,34.5) | 31 (28,35) | 32 (29,34) | 0.627 |
| Nulliparous – no. (%) | 24 (41.38%) | 21 (35.59%) | 45 (38.46%) | 14 (29.79%) | 0.369 |
| BMI – (IQR) | 24.1 (21.5,28.7) | 22.8 (21,26.8) | 23.4 (21.2,28.2) | 23.4 (21.7,26) | 0.45 |
| Assisted reproductive technology – no. (%) | 1 (1.72%) | 4 (6.78%) | 5 (4.27%) | 5 (10.64%) | 0.152 |
| Gestational age at inclusion – wks | 21.5 (19.9,23.6) | 20.7 (19,22.7) | 20.9 (19.6,23.1) | 19.7 (18.4,21.9) | 0.004 |
| Deepest vertical pocket in the donor sac – cm (IQR) | 2 (1,2) | 1.6 (1,2) | 2 (1,2) | 1.7 (1,2) | 0.504 |
| Deepest vertical pocket in the recipient sac – cm (IQR) | 10 (10,11) | 10.2 (9.25,11.5) | 10 (10,11) | 9.7 (8.6,10.5) | 0.005 |
| Abdominal circumference discordance – % (IQR) | 6.25 (3.06,11.5) | 7.49 (3.6,13) | 7.06 (3.32,12.6) | 11.3 (5.17,15.9) | 0.021 |
| Cervical length – mm (IQR) | 38 (35,42.8) | 39 (35,44.5) | 39 (35,44) | 40 (34.8,44) | 0.983 |
| Anterior placenta – no. (%) | 14 (24.14%) | 19 (32.2%) | 33 (28.21%) | 13 (27.66%) | 1 |

*P-value is for comparison of randomized and non-randomized patients

BMI: body-mass index; wks: weeks

Table 2. Perinatal outcomes compared between patients randomized to expectant or immediate laser

| Outcome | Expectant | Immediate Laser | Risk Ratio (95% CI) | P value |
|---|-------------------------|-------------------------|------------------------|---------|
| Outcomes per fetus | N=116 fetuses | N=118 fetuses | | |
| Primary outcome – no. (%) | 25 (22.94%) | 25 (21.93%) | 0.956 (0.532-1.72) | 0.881 |
| Components of primary outcome | | | | |
| Death ≤6 months – no. (%) | 20 (18.35%) | 22 (19.3%) | 1.05 (0.541-2.05) | 0.882 |
| Neurological anomaly at 6 months – no. (%) | 5 (4.59%) | 3 (2.63%) | 0.574 (0.117-2.81) | 0.493 |
| Severe complications of PTB* | 14 (14.43%) | 22 (22.22%) | 1.54 (0.762-3.11) | 0.222 |
| Outcomes per pregnancy | N=58 pregnancies | N=59 pregnancies | | |
| Gestational age at birth – wks (IQR) | 32.8 (30.1-34.8) | 32.3 (29.1-34.7) | | 0.689 |
| gestational age at birth - no. (%) | | | | 0.662 |
| <24 wks | 3 (5.17%) | 2 (3.39%) | | |
| ≥24 and <28 wks | 8 (13.79%) | 6 (10.17%) | | |
| ≥28 and <32 wks | 12 (20.69%) | 18 (30.51%) | | |
| ≥32 wks | 35 (60.34%) | 33 (55.93%) | | |
| PPROM <32 wks – no. (%) | 6 (10.53%) | 18 (30.51%) | 2.9 (1.24-6.78) | 0.011 |
| Number of twins alive at birth per pregnancy – no. (%) | | | | 0.442 |
| 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 days or discharge – no. (%) | | | | 0.952 |
| 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 months – no. (%) | | | | 0.819 |
| 0 | 6 (11.11%) | 6 (10.53%) | | |
| 1 | 7 (12.96%) | 10 (17.54%) | | |
| 2 | 41 (75.93%) | 41 (71.93%) | | |

* any of necrotizing enterocolitis ≥ stage 2 (37), bronchopulmonary dysplasia, renal failure, retinopathy of prematurity, sepsis. Proportions are computed within perinatal survivors (N=97 and N=99 neonates in the expectant and immediate laser groups respectively)

PPROM: Preterm premature rupture of membranes

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 – no. (%) | 6 (13.64%) | 19 (29.23%) | 2.14 (0.685-6.71) | 0.19 |
| Components of primary outcome | | | | |
| Death ≤6 months – no. (%) | 6 (13.64%) | 14 (21.54%) | 1.58 (0.486-5.13) | 0.447 |
| Neurological anomaly at 6 months – no. (%) | 0 (0%) | 5 (7.69%) | NA | NA |
| Severe complications of PTB* | 4 (9.52%) | 10 (18.18%) | 1.91 (0.643-5.67) | 0.26 |
| Outcomes per pregnancy | N=24 pregnancies | N=34 pregnancies | | |
| Gestational age at birth – wks (IQR) | 34.3 (30.6-35) | 32.3 (28.7-34.5) | | 0.305 |
| gestational age at birth - no. (%) | | | | 0.908 |
| <24 wks | 1 (4.17%) | 2 (5.88%) | | |
| ≥24 and <28 wks | 3 (12.5%) | 5 (14.71%) | | |
| ≥28 and <32 wks | 4 (16.67%) | 8 (23.53%) | | |
| ≥32 wks | 16 (66.67%) | 19 (55.88%) | | |
| PPROM <32 wks – no. (%) | 1 (4.35%) | 5 (14.71%) | 3.38 (0.422-27.1) | 0.385 |
| Number of twins alive at birth per pregnancy – no. (%) | | | | |
| 0 | 1 (4.17%) | 0 (0%) | | 0.005 |
| 1 | 0 (0%) | 9 (26.47%) | | |
| 2 | 23 (95.83%) | 25 (73.53%) | | |
| Number of twins alive at 28 days or discharge – no. (%) | | | | |
| 0 | 3 (12.5%) | 3 (8.82%) | | 0.026 |
| 1 | 0 (0%) | 8 (23.53%) | | |
| 2 | 21 (87.5%) | 23 (67.65%) | | |
| Number of twins alive at 6 months – no. (%) | | | | |
| 0 | 3 (13.64%) | 3 (9.38%) | | 0.054 |
| 1 | 0 (0%) | 7 (21.88%) | | |
| 2 | 19 (86.36%) | 22 (68.75%) | | |

* any of necrotizing enterocolitis ≥ stage 2, bronchopulmonary dysplasia, renal failure, retinopathy of prematurity, sepsis. Proportions are computed within perinatal survivors (N=42 and N=55 neonates in the non-progressive and rescue therapy groups respectively)

PPROM: Preterm premature rupture of membranes

Table 4. Prognostic factors for disease progression in patients initially managed expectantly. Analyses were conducted using both the randomized and non-randomized population. Unless a specific cut-off was available, continuous variables were divided at the median.

| Variable | No progression N=44 | Rescue therapy N=40 | Risk Ratio (95% CI) | P value |
|--|--------------------------------|--------------------------------|--------------------------------|----------------|
| Gestational age at randomization <20.9 wks | 22 (50%) | 19 (47.5%) | 0.95 (0.612-1.47) | 0.831 |
| Cervical length <39 mm | 18 (45%) | 19 (50%) | 1.11 (0.696-1.77) | 0.821 |
| Cervical length <30 mm | 2 (5%) | 3 (7.89%) | 1.58 (0.279-8.94) | 0.671 |
| DVP recipient >10 cm | 17 (38.64%) | 13 (32.5%) | 0.841 (0.47-1.5) | 0.65 |
| Discordance in abdominal circumference >8.8% | 22 (51.16%) | 19 (47.5%) | 0.928 (0.599-1.44) | 0.827 |
| Nulliparous | 15 (34.09%) | 16 (40%) | 1.17 (0.671-2.05) | 0.653 |
| Anterior placenta | 13 (29.55%) | 10 (25%) | 0.846 (0.418-1.71) | 0.807 |
| BMI > 23.8 | 14 (42.42%) | 20 (55.56%) | 1.31 (0.8-2.14) | 0.338 |
| BMI > 25 | 13 (39.39%) | 18 (50%) | 1.27 (0.744-2.17) | 0.469 |

BMI: body-mass index; DVP: deepest vertical pocket; wks: weeks

Figure 1. Flow chart of the study population; TOP: termination of pregnancy; IUFD: in utero fetal demise; NND: neonatal death; LFU: lost to follow-up.

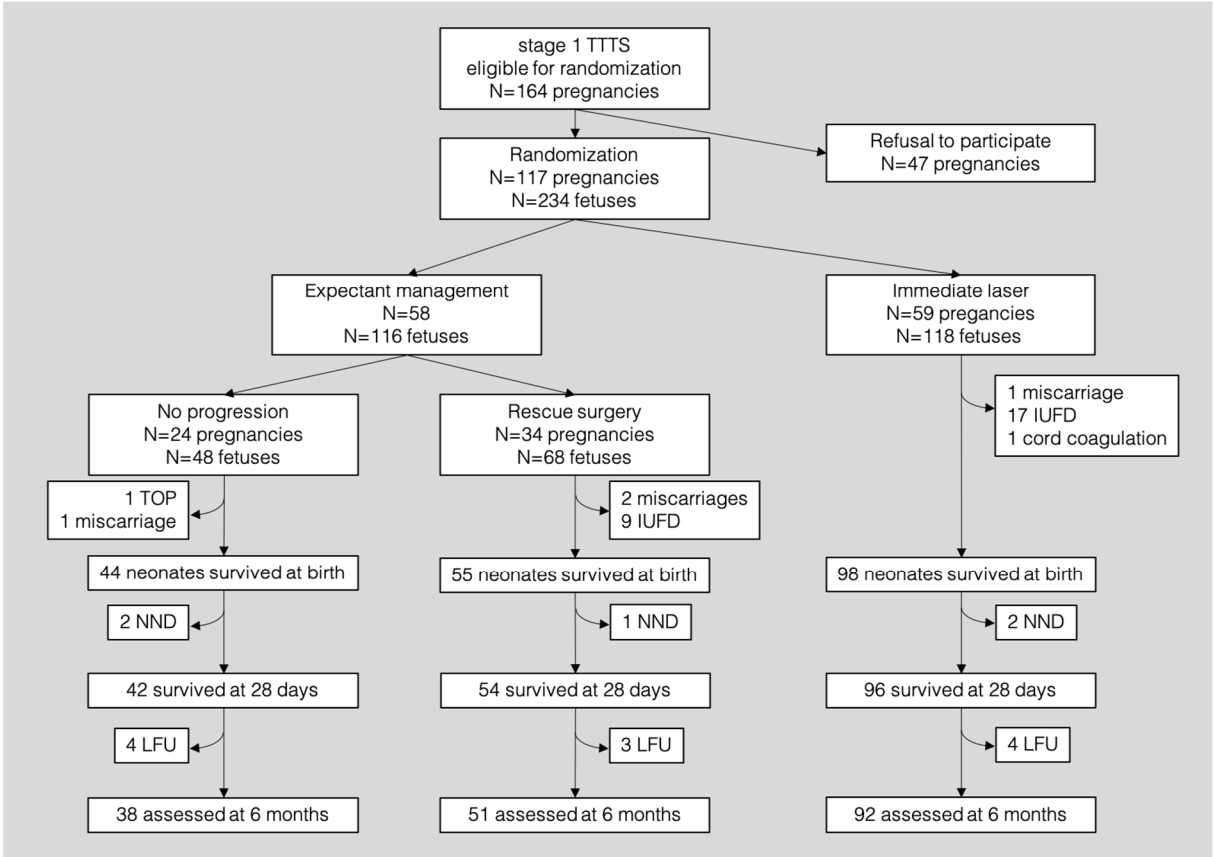


Figure 2. Kaplan Meier curves for time interval between randomization and delivery. E: Expectant (purple line); L: Laser (red line)

