Efficacy of Long Term Indomethacin Therapy in Prolonging Pregnancy After Fetoscopic Laser Surgery for Twin-to-Twin Transfusion Syndrome: a Collaborative Cohort Study

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Abstract

Objective: To evaluate the efficacy of long-term indomethacin therapy (LIT) in prolonging pregnancy and reducing spontaneous preterm birth (PTB) in patients undergoing fetoscopic laser surgery (FLS) for the management of twin-to-twin transfusion syndrome (TTTS). Design: Retrospective cohort study of prospectively collected data. Setting: Collaborative multicenter study Population: 557 consecutive TTTS cases that underwent FLS Methods: LIT was defined as indomethacin use for at least 48 hours. Log-binomial regression was used to estimate the relative risk (RR) of PTB in LIT compared to non-LIT group. Cox regression was used to evaluate the association between LIT use and FLS-to-delivery survival. Main outcome measures: gestational age (GA) at delivery Results: Among the 411 pregnancies included, a total of 180 patients (43.8%) received LIT after FLS and 231 patients (56.2%) did not. Median GA at fetal intervention did not differ between groups (20.4 weeks). Median GA at delivery was significantly higher in the LIT group (33.6 weeks) compared to the non-LIT group (31.1weeks), $p<0.001$. FLS-to-delivery interval was significantly longer in the LIT group ($P<0.001$). The risk of PTB prior to 34, 32, 28, and 26 weeks gestation were all significantly lower in the LIT group compared to the non-LIT group (RR=0.69, 0.51, 0.37, and 0.18, respectively). The number needed to treat (NNT) with LIT to prevent one PTB<32 weeks gestation was 4, and to prevent one PTB<34 weeks was 5. Conclusion: Long-term indomethacin after FLS for TTTS was found to be associated with prolongation of pregnancy and reducing the risk for PTB.

Short title: Long term indomethacin in TTTS treated with FLS

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Abstract

Objective: To evaluate the efficacy of long-term indomethacin therapy (LIT) in prolonging pregnancy and reducing spontaneous preterm birth (PTB) in patients undergoing fetoscopic laser surgery (FLS) for the management of twin-to-twin transfusion syndrome (TTTS).

Design: Retrospective cohort study of prospectively collected data.

Setting: Collaborative multicenter study

Population: 557 consecutive TTTS cases that underwent FLS

Methods: LIT was defined as indomethacin use for at least 48 hours. Log-binomial regression was used to estimate the relative risk (RR) of PTB in LIT compared to non-LIT group. Cox regression was used to evaluate the association between LIT use and FLS-to-delivery survival.

Main outcome measures : gestational age (GA) at delivery

Results: Among the 411 pregnancies included, a total of 180 patients (43.8%) received LIT after FLS and 231 patients (56.2%) did not. Median GA at fetal intervention did not differ between groups (20.4 weeks). Median GA at delivery was significantly higher in the LIT group (33.6 weeks) compared to the non-LIT group (31.1weeks), p<0.001. FLS-to-delivery interval was significantly longer in the LIT group (P <0.001). The risk of PTB prior to 34, 32, 28, and 26 weeks gestation were all significantly lower in the LIT group compared to the non-LIT group (RR=0.69, 0.51, 0.37, and 0.18, respectively). The number needed to treat (NNT) with LIT to prevent one PTB<32 weeks gestation was 4, and to prevent one PTB<34 weeks was 5.

Conclusion: Long-term indomethacin after FLS for TTTS was found to be associated with prolongation of pregnancy and reducing the risk for PTB.

Tweetable abstract:

Long term indomethacin used after fetoscopic laser surgery for twin-to-twin transfusion syndrome is effective in prolonging pregnancy and reducing the risk for preterm birth; especially extreme preterm birth.

Keywords: Indomethacin, long term indomethacin, fetoscopic laser, twin-to-twin transfusion, monochorionic diamniotic, twin

Main text

Introduction

Twin-to-twin transfusion syndrome (TTTS) affects approximately 10-15% of monochorionic diamniotic twin pregnancies (MCDA). [1]Fetoscopic laser surgery (FLS) has become the standard treatment for managing these pregnancies. [2] Despite the apparent success of FLS, spontaneous preterm birth (sPTB) remains to be a major complication and a challenge that determines perinatal morbidity and survival, [3,4] with a reported gestational age (GA) at delivery of 31 to 33 weeks of gestation. [5,6] sPTB accounts for almost 48% of these deliveries [7] which has been largely related to preterm labor and preterm prelabor rupture of membranes (PPROM) with occurrence to as high as 53% in some reports.[5,8,9] Up to date, effective PTB preventative measures in this population are lacking.

Indomethacin, a non-specific cyclooxygenase (COX) inhibitor, is a commonly used tocolytic agent. The three proposed mechanisms of action include COX blockage, uterine calcium efflux blockage, which reduces uterine resting tone, and the hydrophobic effect on cervical matrix metalloproteinases (MMP), which prevents further softening and shortening. [10,11] Long-term indomethacin therapy (LIT) (>48 hours, and not beyond 32 weeks gestation) used under strict follow-up guidelines has shown effectiveness in stabilizing cervical length (CL) in dichorionic diamniotic twin (DCDA) pregnancies with a short cervix. [12] The safety of LIT in the setting of the short cervix in singleton pregnancies has been demonstrated in a cohort study which showed no significant differences in fetal and neonatal complications compared to a matched control group.[13]

The hypothesis of our study was that LIT prolongs pregnancy and reduces the risk for sPTB in the setting of TTTS treated with FLS.

Materials and Methods

This was a retrospective cohort study of prospectively collected data of consecutive TTTS cases that underwent FLS at two fetal treatment centers between 2012 and 2018. The study was approved by the institutional review boards of both participating institutions (University of Maryland, Baltimore [UMB], MD and Baylor College of Medicine [BCM], Houston, TX). The study results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies. [14]

Preoperative evaluation and management

Patients referred for evaluation of TTTS, underwent comprehensive ultrasound examination, including biometry measurements with Doppler studies for the diagnosis and staging of TTTS based on the Quintero system, [15] performed by registered diagnostic medical sonographers supervised by experienced fetal medicine specialists. All cases with TTTS Stage II or higher were offered surgical intervention, as were Stage-I cases if they presented with a short cervix of less than 25 mm or symptomatic polyhydramnios. Patients undergoing FLS at UMB were started on the LIT protocol (see below in the LIT protocol section for details).

Operative procedure

FLS was performed using a single port fetoscope under either local anesthetic in conjunction with intravenous sedation or regional anesthesia. The entry technique used was either the Seldinger or sharp trocar method. The placental vascular equator was identified, and a diode laser used to ablate all intertwin vascular anastomoses using selective or sequential selective method followed by equatorial dichorionization 'Solomon technique' [16] if technically feasible. When needed, amnioinfusion was performed to improve visualization. If amniodrainage was necessary, it was performed following the coagulation phase of the procedure.

Postoperative evaluation and management

Patients remained in the hospital for a minimum of 24 hours. Daily ultrasound exams were performed while patients remained in the hospital. After discharge, patients were either followed with weekly scans by the fetal center if feasible or returned to the referring provider with recommended follow-up care per institutional protocol. The decision for delivery was based on the referring physician's assessment. Information about pregnancy outcomes was collected prospectively either from the patients or the referring physicians as a part of follow-up care.

LIT protocol

LIT was administered as a standard regimen using oral indomethacin of 100 mg loading dose, then 50 mg every 6 hours for up to 48 hours, followed by a maintenance dose of 25 mg every 6 hours thereafter. The minimum duration was 48 hours and not beyond 32 weeks gestation. LIT ultrasound surveillance included weekly evaluation of the maximum vertical pocket (MVP) and Doppler flow studies (ductus arteriosus [DA], ductus venosus, and atrioventricular valves). These weekly scans were continued as long as patients were still using indomethacin. LIT was stopped if 1. The patient was returned to the referring provider, where performing the weekly LIT ultrasound surveillance was not feasible, knowing that cervical length was stable. This category is referred to as "stable clinical status" throughout the paper, 2. LIT complications, including DA constriction, defined as the DA peak systolic velocity exceeded the 95^{th} percentile for GA, and/or the DA pulsatility index (PI) was $< 5^{\text{th}}$ percentile for GA, or oligohydramnios defined as MVP of less than 2 cm, 3. PPROM, and 4. Reaching 32 weeks gestation.[13]

Study groups and outcome measures

LIT in the setting of TTTS treated with FLS was used routinely after FLS in one of the participating institutions (UMB), while TTTS cases from the second institution (BCM) did not receive LIT. Exclusion criteria included triplet gestations, pregnancies that underwent cervical cerclage placement, postoperative complications that resulted in dual twin demise, obstetrical and medical indicated deliveries at less than 32 weeks gestation (did not encounter PTL or PPROM), and patients with missing records. Collected data included preoperative, operative, and postoperative variables, delivery information, and perinatal survival.

Preoperative variables included maternal characteristics (age, parity, race, previous PTB, BMI), TTTS stage using the Quintero criteria, CL (measured transvaginally), recipient's MVP, presence of anterior placenta, and presence of selective fetal growth restriction (sFGR). Operative variables included GA at FLS, size of trocar outer sheath in mm, number of anastomoses ablated, whether or not complete dichorionization was performed, the occurrence of chorioamnion membrane separation (CAS), and septostomy (intertwin membrane disruption). Postoperative variables included GA at delivery, live births, and neonatal survival. The primary outcome measure was GA at delivery. Secondary outcome measures included FLS-to-delivery interval, live births, and neonatal survival.

Statistical analysis

Study data were deidentified and imported into the statistical software. Results are reported as mean $\pm$ standard deviation (SD), median (interquartile range [IQR]), or number (percentage). Normal distribution was determined by Shapiro-Wilk test. Categorical variables were compared using the Pearson's chi-square or Fisher's exact test. Continuous variables were compared using an unpaired t -test for normally distributed data or the Wilcoxon rank-sum test for not normally distributed data. Pearson correlation was used to assess linear correlation between two continuous variables.

Log-binomial regression was used to directly estimate relative risks (RRs) of PTB, very PTB, and extremely PTB. Significant variables in bivariate analysis were incorporated into a log-binominal regression model to determine which factors were independent risk factors of the primary outcome (PTB) and estimate adjusted RR. The number needed to treat (NNT) was calculated using pooled absolute risk reduction for PTD.

A secondary analysis was performed to evaluate FLS-to-delivery duration. Kaplan–Meier curve was used to visualize the FLS-to-delivery survival function for each group, and equality of survival functions between groups was tested using the log-rank test. Cox regression analysis was used to estimate hazard ratios (HRs) for FLS-to-delivery survival. Multivariate stepwise backward Cox regression was used to identify significant independent maternal characteristics, pre-operative variables, and operative variables that predict FLS-to-delivery survival and estimate adjusted HR.

Trocar outer sheath diameter and total number of anastomoses were categorized into quartiles, age was categorized into <35 and [?]35 (advanced maternal age), BMI was categorized into <25 (underweight or normal), 25 – 30 (overweight), and [?]30 (obese), parity was categorized into 0, 1, and 2 or more, MVP was categorized into <8 (oligohydramnios or normal), 8 – 12 (polyhydramnios), [?]12 (severe polyhydramnios), and GA at FLS was categorized into <18 weeks, 18 – 24 weeks, and [?]24 weeks in log-binomial and Cox regression models to allow non-linear relationships. The p- value <0.05 was considered statistically significant. Statistical analysis was performed using the Stata 16 software.[17]

Results

A total of 557 FLS procedures were performed during the study period. In this study, a total of 146 pregnancies were excluded. (Figure 1) The distribution of the excluded pregnancies was similar between the two centers (Table 1). After applying the exclusion criteria, 411 pregnancies were included in the final analysis; of those, 180 pregnancies received LIT (43.8%) and 231 did not (56.2%).

Maternal characteristics and preoperative variables

There were no statistically significant differences in maternal age, prior PTB, sFGR, CL <25 mm, presence of anterior placenta, and Quintero staging between the two groups (Table 2). Preoperative significant differences between groups were race, of which 69.3% were white in the LIT group *vs.* 54.5% in the non-LIT group (p<0.001), BMI with the median of 23.95 (IQR: 21 – 29.4) in the LIT group *vs.* 28.2 (IQR: 25.4 – 34.2) in the non-LIT group (p<0.001), parity with the median of 1 (IQR: 0 – 1) in the LIT group *vs.* 1 (IQR: 0 – 2) in the non-LIT group (p<0.001), and recipient MVP with the median of 11 (IQR: 9.3 – 13.3) in the LIT group *vs.* 10.1 (IQR 8.5 – 12.45) in the non-LIT group (p=0.006) (Table 2).

Operative variables

Median GA at the time of FLS was 20.4 weeks which was similar between groups. The use of Solomon technique and CAS did not differ significantly between groups. Trocar outer sheath diameter was different between groups (median of 3.33 mm [IQR: 3.33 – 4] in the LIT group*vs.* 3.2 mm [IQR: 3.1 – 3.8] in the non-LIT group, p<0.001), total number of anastomoses were higher in the LIT group (median of 13 [IQR: 10 – 18] vs. 11 [IQR: 8 – 13], p<0.001), and occurrence of postoperative septostomy was more common in the non-LIT group (24.8% vs. 6.1%, p<0.001) (Table 3).

Postoperative variables

Gestational age at delivery was significantly different between the groups with median GA at delivery of 33.6 weeks (IQR: 31.2 – 35.3) in the LIT groups *vs.* 31.1 weeks (IQR: 28.57 – 34) in the non-LIT group (*P* <0.001). PTB < 26 weeks (1.1% in the LIT group *vs.* 6.1% in the non-LIT group), extreme PTB < 28 weeks (5.6% in the LIT group *vs.* 15.2% in the non-LIT group), PTB < 32 weeks (27.8% in the LIT group*vs.* 54.1% in the non-LIT), and PTB < 34 weeks (50.6% in the LIT group *vs.* 73.6% in the non-LIT) were all significantly higher in the non-LIT group (p=0.010, p=0.002, p<0.001, and p<0.001, respectively), Figure 2. FLS to delivery duration was significantly higher in the LIT group than in the non-LIT group with the median of 90 days (IQR: 70.35 – 108.85)*vs.* 76 days (IQR: 49 – 98), respectively (p<0.001) (Table 4).

The risk of PTB prior to 34, 32, 28, and 26 weeks was significantly lower in the LIT group compared to the non-LIT group (RR=0.69, 0.51, 0.37, and 0.18, respectively). Multivariate regression analysis showed race, BMI, parity, MVP, trocar outer sheath diameter, total number of anastomoses, and septostomy, are not associated with PTB while indomethacin use is a protective factor against PTB. (Table 5) The number needed to treat (NNT) with LIT to prevent one PTB<32 weeks gestation was 4 (95% CI: 3.82 to 3.94), and to prevent one PTB<34 weeks was 5 (95% CI: 4.32 to 5.12).

Kaplan-Meier curve showed a significantly longer FLS-to-delivery duration in the LIT group compared to the non-LIT group (Log-rank test for equality of survival functions: p<0.001, Figure 3). Multivariate stepwise backward Cox regression showed CL < 25mm, GA at intervention, LIT, and CAS were independent predictors of FLS-to-delivery survival. (Table 6) LIT remained a statistically significant predictor for longer

FLS-to-delivery survival, even after adjusting for CL < 25mm, GA at intervention, and CAS (adjusted HR: 0.68, 95% CI: 0.55 – 0.83).

There were no significant differences in live birth rates between the two groups. Neonatal survival (>28 days) of at least one newborn was increased in the LIT group compared to the non-LIT group (98.9% vs. 95.7%), although this increase was not statistically significant (p=0.05). (Table 4)

LIT group characteristics

A total of 180 pregnancies received LIT in the cohort (43.8%). Median GA at the start of LIT was 20.4 weeks (IQR: 18.4 – 22.3), and at the stop was 24.4 weeks (IQR: 22.2 – 26.6), with a median duration of 21 days (IQR: 15.4 – 33.95). Reasons to stop LIT in descending order were: stable clinical status (149 cases, 83%), 32 weeks gestation (13 cases, 7%), PPROM (13 cases, 7%), and fetal complications (4 cases, 2%). Fetal complications included 3 fetuses (1.5%) with constriction of DA and one fetus (0.5%) with oligohydramnios (Table 7). All four cases of fetal complications were resolved after stopping LIT. The neonatal intensive care unit (NICU) chart review showed that the patient with resolved oligohydramnios fetus delivered at 30 weeks and the newborn had only prematurity-related respiratory distress syndrome (RDS). The three patients with resolved DA constriction fetuses were delivered at 32.4 weeks, 33.6 weeks, and 34.1 weeks. The first two newborns had RDS and bronchopulmonary dysplasia (BPD), while the third newborn had no complications. None of them required surgical intervention. All four were discharged home in stable condition. PPROM rate in the LIT cohort was 28.2% (n=49) with a mean GA at PPROM of 29.6 weeks (IQR: 27.5 – 31.3). There was a moderate positive correlation, both between the duration of LIT and duration of FLS-to-PPROM (r=0.48, p=0.002) and between the duration of LIT and duration of FLS-to-delivery (r=0.33, p<0.001).

Discussion

This is the first study to evaluate the efficacy of LIT in prolonging pregnancy and reducing the risk of sPTB in the setting of TTTS treated with FLS. The main findings of the study were that the LIT group had a significantly longer pregnancy with a median of 2 weeks, longer FLS-to-delivery interval with a median of 2 weeks, 31% reduction in risk of PTB (GA less than 34 weeks), 52% reduction in risk of very PTB (GA less than 32 weeks), and 67% and 84% reduction in risk of extreme PTB (GA less than 28 and 26 weeks, respectively), and higher neonatal survival compared to the non-LIT group. Cox regression analysis showed that LIT is a significant predictor for prolongation of pregnancy following FLS, even after adjustment for CL, GA at FLS, and chorioamnion separation. The NNT with LIT to prevent one PTB<32 weeks gestation was 4, and to prevent one PTB<34 weeks was 5.

PTB has been a major determinant for outcomes after FLS, with significant risk factors including PPROM, short preoperative CL, intraoperative amnioinfusion, and an increased number of anastomoses.[7,18] Other reported risk factors include septostomy[19-22] and chorioamnion separation.[23-26] In our study, the multivariate regression analysis showed that none of these factors were significant independent predictors for PTB while LIT was the only significant independent protective factor in preventing PTB. Early gestational age at intervention (<18 weeks), on the other hand, has not been found to increase the risk for PTB in this population[27], similarly to what our study showed.

The most common etiology for PTB is spontaneous PTB in 48 percent of patients. [18] Effective PTB prevention measures in multiple gestations, in general, and in MCDA complicated with TTTS undergoing FLS, in specific, have not yet been defined. In multiple gestation with a normal or short cervix, interventions such as other forms of tocolytics, cerclage, progesterone, pessary, routine hospitalization, or bed rest have not been proven to prolong pregnancy or improve neonatal morbidity and mortality. [10,28-40]In the setting of TTTS treated with FLS with short preoperative CL, cervical cerclage did not prolong pregnancy in a retrospective, multicenter cohort study. [41] Our study showed that LIT use significantly increased the FLS-to-delivery interval regardless of the length of the cervix and gestational age of the surgery.

The efficacy of short-term antenatal indomethacin use is well reported in the literature. In singleton pregnancies in the setting of preterm labor, a 2015 metanalysis of two randomized trials showed indomethacin compared to placebo was significantly effective in reducing the risk of delivery within 48 hours of initiation. [42] In the setting of exam-indicated cerclage, indomethacin along with antibiotics significantly prolonged pregnancy for more than 28 days.[43] In twin pregnancies, a retrospective matched case-control study previously reported that LIT stabilizes cervical length in DCDA twin gestations with short CL. [12] It is important to emphasize that our study demonstrated that LIT reduces the risk of extreme prematurity by 67% and 84% (GA less than 28 and 26 weeks, respectively).

PPROM has been reported to be as high as 53% after FLS.[5,8,9] In PPROM generally, sequence of events modulates metalloproteinases (MMPs) expression, secretion, and activation by local and infiltrating cells synchronously with myometrial and cervical changes. This leads to the progressive loss of the mechanical properties and tensile strength of the amniotic membranes and eventually to their rupture. [44-49] Similar cascade of events has been shown in amniotic membranes following FLS. [50] In our study, longer duration of LIT use was associated with longer FLS-to-delivery interval. This effect of LIT has significant rationale given that indomethacin has multiple vectors of impact, including tocolysis, uterine relaxation, biochemical cervical stabilization, and hydrophobic effect on MMPs. [11]

In terms of indomethacin safety, data on fetal effects have been conflicting, with the main concerns being oligohydramnios and constriction of ductus arteriosus, both of which have been shown to resolve within 48 hours of stopping the medication.[51,52] Neonatal effects associated with antenatal use of indomethacin have also been controversial, mostly related to the prematurity associated adverse events aside from the use of indomethacin. In a meta-analysis including randomized trials, there were no statistically significant differences in adverse events between cases with indomethacin use and controls [53] while a systematic review of case-control pairs that were not matched for GA or birth weight showed an increase in neonatal morbidity.[54] Other reported fetal and neonatal outcome data are mainly in the form of case reports and case series.[55-62] Turan et al. investigated the safety of LIT in a matched case-control analysis considering the effects of GA and birth weight on neonatal morbidities. That study showed no significant increase in neither fetal nor neonatal complications in cases underwent LIT. [13] In the current study, there were only four indomethacin-related fetal complications, including one oligohydramnios and three DA constrictions. All four resolved after stopping LIT, and all four newborns were discharged home in stable condition.

Our study has several strengths. To the best of our knowledge, this is the first study reporting on the effect of LIT in prolonging pregnancy and reducing the risk of sPTB in monochorionic pregnancies complicated by TTTS that required FLS. The study was conducted in two experienced, high volume fetal centers. The data were collected from all consecutive patients who underwent FLS which minimizes the selection bias. The data were collected prospectively as an ongoing process, which reduces recollection bias and missing data. The establishment of a vigorous, standardized LIT protocol allowed for uniformly proper follow-up of these patients. The sample size was large enough to assess the effect of the most relevant risk factors in a regression model.

We acknowledge the limitations of our study, including the retrospective nature of the study. The study was conducted in two different centers; therefore, different institutional practices or techniques might have impacted the outcomes despite following similar procedural indications and follow-up protocols between the two participating institutions. Other limitations include the lack of neonatal outcomes comparisons between the groups aside from perinatal survival.

In conclusion, in the setting of TTTS treated with FLS, LIT; defined as indomethacin use for more than 48 hours and not beyond 32 weeks gestation; was significantly effective in prolonging pregnancy with a median of 2 weeks and reducing the risk of PTB particularly the risk of extreme prematurity, which has the highest impact on neonatal outcomes. Future prospective randomized trials are required to confirm our findings and investigate the effect of LIT in other clinical settings such as in patients with short cervical length.

Disclosure of interests

None declared. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

HJM and OMT conceived the study and designed the protocol. HJM and NP collected the data. HJM wrote the first draft of the paper. OMT and HT were involved in the statistical analysis and drafting the results. EK, JE, AS, AN, RD, MB, MC, and CH were all involved in critical analysis of the data. All authors contributed significantly to critical revisions of successive drafts of the manuscript. HJM and OMT are the guarantors of the review.

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Tables

Table 1. The distribution of excluded pregnancies by centers

Exclusion criteria	UMB N (262)	BCM N (295)	Total N (557)
Triplet gestation	16 (6.1%)	17 (5.8%)	33 (5.9%)
Cerclage placement	9 (3.4%)	13 (4.4%)	22 (3.9%)
Dual twin demise	8 (3.0%)	10 (3.4%)	18 (3.2%)
Indicated delivery < 32 weeks	20 (7.6%)	19 (7.2%)	39 (7%)
Missing data	18 (6.8%)	16 (5.4%)	34 (6.1%)
Total n	71 (27%)	75 (25.4%)	146 (26.2%)
Data are given as n (%) UMB: University of Maryland, Baltimore; BCM: Baylor College of Medicine	Data are given as n (%) UMB: University of Maryland, Baltimore; BCM: Baylor College of Medicine	Data are given as n (%) UMB: University of Maryland, Baltimore; BCM: Baylor College of Medicine	Data are given as n (%) UMB: University of Maryland, Baltimore; BCM: Baylor College of Medicine

Table 2 . Maternal characteristics and preoperative variables comparisons between the groups

Preoperative Variable	LIT N (180)	Non-LIT N (231)	P value
Maternal age *(years)*	30 (25.5. – 34.5)	29 (25 – 33)	0.07
Parity	1 (0 – 1)	1 (0 – 2)	<0.001
Race, *n (%)*			<0.001
White	124 (69.3%)	126 (54.5%)	
Black	24 (13.4%)	22 (9.5%)	
Hispanic	6 (3.4%)	72 (31.2%)	
Other	25 (14.0%)	11 (4.8%)	
Prior PTB, *n (%)*	17 (9.8%)	31 (13.4%)	0.27
BMI (kg/m^2)	23.9 (21 – 29.4)	28.2 (25.4 – 34.2)	<0.001
sFGR, *n (%)*	80 (47.1%)	103 (45.0%)	0.68
CL < 25 mm, *n (%)*	11 (6.1%)	21 (9.4%)	0.22
Anterior placenta, *n (%)*	71 (39.4%)	102 (44.2%)	0.34
Recipient MVP (*cm)*	10.1 (8.5 – 12.45)	11 (9.3 – 13.3)	0.006
Quintero staging, *n (%)*			0.16
I	32 (17.8%)	27 (11.7%)	
II	62 (34.4%)	70 (30.3%)	
III	75 (41.7%)	118 (51.1%)	
IV	11 (6.1%)	16 (6.9%)	

Preoperative Variable	LIT N (180)	Non-LIT N (231)	P value
Data are given as median (IQR) and n (%) PTB: preterm birth, BMI: body mass index, sFGR: selective fetal growth restriction, CL: cervical length, MVP: maximum vertical pocket	Data are given as median (IQR) and n (%) PTB: preterm birth, BMI: body mass index, sFGR: selective fetal growth restriction, CL: cervical length, MVP: maximum vertical pocket	Data are given as median (IQR) and n (%) PTB: preterm birth, BMI: body mass index, sFGR: selective fetal growth restriction, CL: cervical length, MVP: maximum vertical pocket	Data are given as median (IQR) and n (%) PTB: preterm birth, BMI: body mass index, sFGR: selective fetal growth restriction, CL: cervical length, MVP: maximum vertical pocket

Table 3 . Operative variables comparisons between the groups

Operative Variable	LIT N (180)	Non-LIT N (231)	P value
GA at FLS *(weeks)*	20.4 (18.4 – 22.3)	20.4 (18.5 – 22.57)	0.53
GA at FLS< 18 *(weeks)*	31 (17.2%)	41 (17.7%)	0.89
Trocar outer sheath diameter *(mm)*	3.2 (3.1 – 3.8)	3.33 (3.33 – 4)	<0.001
Number of anastomoses	13 (10 – 18)	11 (8 – 13)	<0.001
Solomon technique, *n (%)*	129 (74.6%)	181 (80.1%)	0.19
Septostomy, *n (%)*	11 (6.1%)	57 (24.8%)	<0.001
CAS, *n (%)*	14 (7.8%)	31 (13.7%)	0.60
Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery, CAS: chorioamnion separation	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery, CAS: chorioamnion separation	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery, CAS: chorioamnion separation	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery, CAS: chorioamnion separation

Table 4 . Postoperative variables comparisons between the groups

Postoperative Variable	LIT N (180)	Non-LIT N (231)	P value
GA at delivery *(weeks)*	33.6 (31.2 – 35.3)	31.1 (28.57 – 34)	<0.001
GA at delivery <26 weeks, *n (%)*	2 (1.1%)	14 (6.1%)	0.01
GA at delivery <28 weeks, *n (%)*	10 (5.6%)	35 (15.2%)	0.002
GA at delivery <32 weeks, *n (%)*	50 (27.8%)	125 (54.1%)	<0.001
GA at delivery <34 weeks, *n (%)*	91 (50.6%)	170 (73.6%)	<0.001
FLS-to-delivery *(days)*	90 (70.35 – 108.85)	76 (49 – 98)	<0.001
At least one live birth, *n (%)*	179 (99.4%)	231 (100%)	0.26

Postoperative Variable	LIT N (180)	Non-LIT N (231)	P value
At least one neonatal survival (>28 days), *n (%)*	178 (98.9%)	221 (95.7%)	0.05
Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery	Data are given as median (IQR) and n (%) GA: gestational age, FLS: fetoscopic laser surgery

Table 5. Relative risk for PTB in the LIT group vs. non-LIT group

Variable	**GA < 26 weeks**
	Univariate model RR (95% CI)
LIT	0.18 (0.04 - 0.8)
Parity	
0	Ref.
1	0.8 (0.23 - 2.76)
2	1.52 (0.5 - 4.58)
Race	
White	Ref.
Black	-
Hispanic	1.92 (0.72 - 5.12)
Other	-
BMI	
Normal	Ref.
Overweight	1.06 (0.35 - 3.21)
Obese	0.68 (0.2 - 2.34)
Recipient MVP	
Normal	Ref.
Polyhydramnios	0.76 (0.1 - 6.12)
Severe polyhydramnios	1.86 (0.24 - 14.15)
Trocar outer shea	
< 3.1	Ref.
3.1 – 3.33	0.48 (0.12 - 1.89)
3.33 – 3.8	0.44 (0.05 - 3.56)
3.8	1.45 (0.48 - 4.36)
Anastomoses	
< 9	Ref.
9 – 12	1.19 (0.33 - 4.28)
12 – 15	0.75 (0.17 - 3.26)
15	0.8 (0.21 - 3.12)
Septostomy	1.16 (0.34 - 3.96)
RR: relative risk; CI: confidence interval EXPLAIN OTHER ABBREVIATIONS	RR: relative risk; CI: confidence interval

Table 6. Hazard ratio for FLS-to-delivery survival

Variable
LIT
CL < 25mm
Chorioamnion separation
GA at FLS *(weeks)*

LIT: long-term indomethacin therapy, CL: cervical length, GA: gestational age, FLS: fetal laser surgery HR: hazard ratio, C

Table 7. Characteristics of the LIT group

LIT Group Characteristics, n=180

GA at LIT start *(weeks)*
GA at LIT stop *(weeks)*
Reasons LIT stopped, *n (%)*
Stable clinical status *
32 weeks
PPROM
Fetal complications DA constriction Oligohydramnios
LIT duration *(days)*

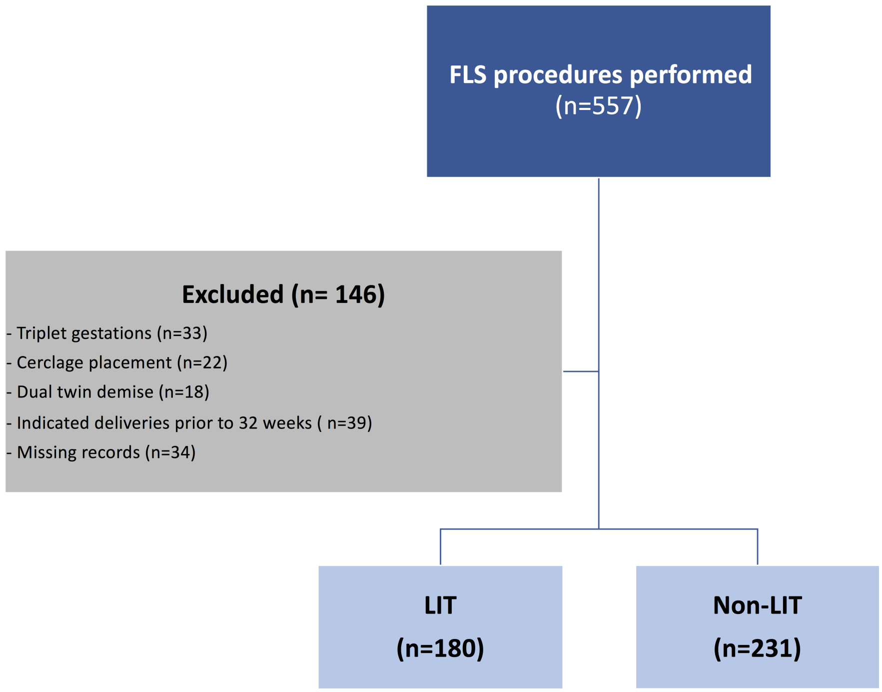
Data are given as median (IQR) and n (%) *The definition can be seen in the methods section under LIT protocol GA: ges

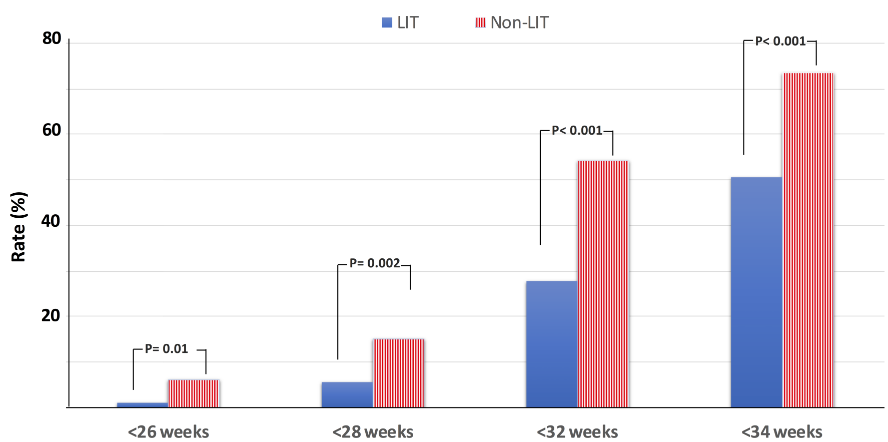
Figures legends

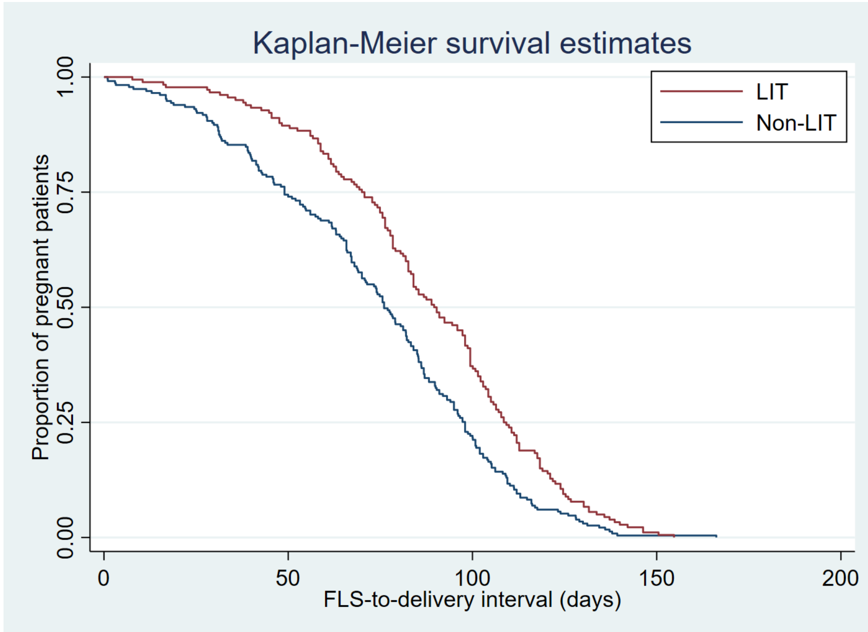
Figure 1. Flow diagram of study population

Figure 2. The rate of preterm births before 26, 28, 32, and 34 weeks gestation by long-term indomethacin (LIT) and non-LIT groups

Figure 3. The probability of staying pregnant after fetoscopic laser surgery (FLS) by long-term indomethacin (LIT) and non-LIT groups


FLS procedures performed
(n=557)
Excluded (n= 146)
- Triplet gestations (n=33)
- Cerclage placement (n=22)
- Dual twin demise (n=18)
- Indicated deliveries prior to 32 weeks (n=39)
- Missing records (n=34)
LIT
(n=180)
Non-LIT
(n=231)


LIT
Non-LIT
Rate (%)
80
60
40
20
P= 0.01
P= 0.002
P< 0.001
P< 0.001
<26 weeks
<28 weeks
<32 weeks
<34 weeks


Kaplan-Meier survival estimates
Proportion of pregnant patients
0.00
0.25
0.50
0.75
1.00
0
50
100
150
200
FLS-to-delivery interval (days)
LIT
Non-LIT