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PREGNANCY

ORIGINAL RESEARCH

Impact of preoperative second-trimester vaginal bleeding on operative factors and outcomes in patients undergoing laser for twin–twin transfusion syndrome

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Abstract

Introduction: Second-trimester vaginal bleeding has been associated with increased risk for preterm delivery after laser for twin–twin transfusion syndrome (TTTS), but its incidence and impact on operative factors and other outcomes is unknown.

Methods: A retrospective analysis of prospectively collected data from a monochorionic (MC) pregnancy registry at a Level III fetal care center was conducted. The records of patients with MC twins that underwent laser for TTTS between January 2013 and January 2024 were reviewed to determine the incidence of second-trimester vaginal bleeding prior to the laser procedure. Those without clear documentation of bleeding were excluded. Pregnancy characteristics and outcomes were then compared between patients who had second-trimester bleeding versus those who did not using Mann–Whitney *U*, chi-square, and Fisher's exact tests, as appropriate.

Results: Of 373 patients who underwent laser, 359 (96.2%) had clear documentation of whether they had second-trimester vaginal bleeding or not, including 30 (8.4%) who did and 329 (91.6%) who did not. Although demographic characteristics and survival outcomes were similar between groups, patients with second-trimester vaginal bleeding had longer median operating room times (61 vs. 50 min, $p = 0.032$), higher need for amnioexchange (33.3% vs. 14.3%, $p = 0.006$), and higher incidence of preterm premature rupture of membranes within 1 week after the laser procedure (16.7% vs. 3.3%, $p = 0.001$).

Conclusion: In our cohort, second-trimester vaginal bleeding was associated with a higher incidence of perioperative complications surrounding laser for TTTS. This information can be used to guide future studies and in counseling patients prior to the laser procedure.

KEYWORDS
amnioexchange, laser, PPROM, TTTS, vaginal bleeding

1 | INTRODUCTION

Twin–twin transfusion syndrome (TTTS) complicates approximately 6%–18% of monochorionic (MC) pregnancies and leads to significant morbidity and mortality [1, 2]. When technically feasible, fetoscopic laser surgery to coagulate anastomoses on the surface of the placenta is the preferred treatment modality for Stages II–IV TTTS and for cases of Stage I with risk factors for progression [3–6]. Survival after laser has improved over the last several decades with many high-volume centers reporting single survival above 90% and dual survival up to 70% [7].

Numerous studies have identified risk factors for fetal loss and preterm delivery after laser, including donor growth restriction, abnormal Dopplers, recipient cardiac dysfunction, short cervical length, and larger amnioinfusion volume [8–17]. Additionally, preoperative second-trimester vaginal bleeding has been reported as a risk factor for delivery within 4 weeks after fetoscopic laser for TTTS [18].

Vaginal bleeding prior to amniocentesis has been associated with opaque, discolored amniotic fluid [19]. Since the fetoscopic laser procedure relies on visualizing anastomoses through the amniotic fluid, preoperative vaginal bleeding may lead to more opaque fluid, presenting difficulties with the procedure (Figure 1). Opaque fluid may limit the ability to see the anastomoses on the surface of the placenta, therefore, limiting the ability to successfully ablate all of the vascular connections. When visualization is poor, amnioexchange may be undertaken to try to clear the amniotic fluid but may be associated with additional operative risk due to longer operating room times and need for large volume amnioinfusion and amnioreduction [20]. Furthermore, second-trimester vaginal bleeding has been associated with adverse pregnancy outcomes and increased risk of pregnancy loss after genetic amniocentesis [21–26].

We hypothesized that preoperative second-trimester vaginal bleeding would be associated with more difficulty during the fetoscopic laser and worse outcomes following the procedure. Our objective, therefore, was to determine the incidence of preoperative second-trimester vaginal bleeding prior to laser for TTTS and determine whether it was associated with perioperative complications and worse post-procedure outcomes.

2 | METHODS

After institutional review board approval (IRB# 09-007085), we conducted a retrospective analysis of prospectively collected data from a MC pregnancy registry at our Level III fetal care center [27]. Written informed consent was obtained from the participants prior to enrollment in the registry. Records of patients with MC twins who underwent laser for TTTS between January 2013 and January 2024 were reviewed to determine the incidence of second-trimester vaginal bleeding prior to the laser pro-

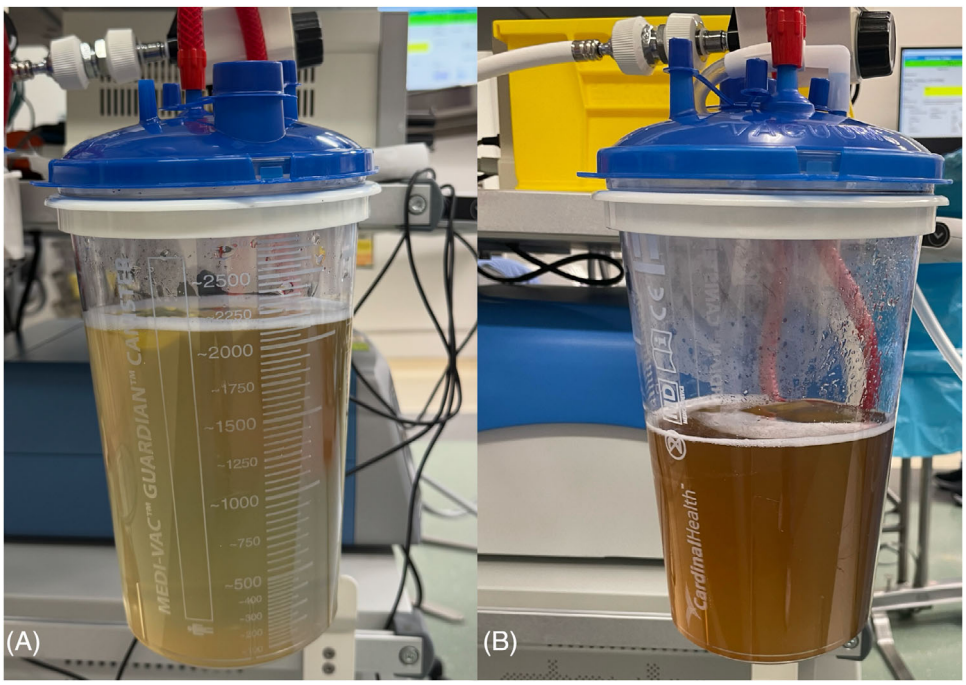

FIGURE 1 Photograph of amnioreduction fluid in a patient without second-trimester vaginal bleeding (A) and with second-trimester vaginal bleeding (B), both of whom underwent laser for twin–twin transfusion syndrome.

cedure. Those without clear documentation of whether bleeding occurred or not were excluded. Patients with first-trimester vaginal bleeding but without second-trimester vaginal bleeding were included in the no vaginal bleeding group. Higher order multiples were also excluded, but pregnancies with evidence of selective fetal growth restriction or concomitant twin anemia polycythemia sequence were not excluded if the pregnancies also met criteria for TTTS. Data were extracted from the registry and included maternal demographic characteristics, pregnancy details, operative details, and pregnancy outcome. Ultrasound evidence of subchorionic hemorrhage was not captured in the dataset.

A selective fetoscopic laser was performed in the standard fashion, ablating all donor–recipient anastomoses on the surface of the placenta [28]. Laser was offered in cases of Quintero Stages II–IV TTTS and also in select cases with Stage I TTTS at increased risk of pregnancy loss (i.e., massive polyhydramnios, elevated cardiovascular score, short cervix) [3, 6]. When deemed necessary, amnioexchange was performed at the discretion of the operating surgeon and involved removing 500 mL of amniotic fluid and replacing that with 500 mL of warmed Lactated Ringer's systematically until the fluid was clear enough to allow adequate visualization. Ultrasound was routinely performed on postoperative Day 1 and postoperative Day 7. Patients were generally followed locally after that time with weekly ultrasound assessments. In complicated cases, such as those with chorioamnion separation, additional ultrasound examinations were performed postoperatively at our center. Pregnancy outcomes in the registry were obtained through review of internal and external medical records.

Demographic characteristics included maternal age and body mass index (BMI). Pregnancy details included use of assisted reproductive technologies, preoperative cervical length, TTTS Quintero stage, estimated fetal weight (EFW) discordance, cardiovascular score, donor deepest vertical pocket (DVP), recipient DVP, and the presence of an anterior placenta (yes/no) [3, 6]. Operative details included gestational age at laser, operating room (OR) time, amnioexchange performed (yes/no), amnioinfusion volume, amnioreduction volume, ability to complete laser (yes/no), and number of anastomoses. Pregnancy outcome data included postoperative chorioamnion separation (yes/no), preterm premature rupture of membranes (PPROM) within 1 week of procedure, any PPROM, gestational age at PPROM, need for additional therapy, single fetal demise, dual fetal demise, gestational age at delivery, delivery less than 21 days after laser, delivery less than 28 days after laser, number of liveborn infants and residual anastomoses (yes/no). Operative time included surgical planning, fetoscopy, and amnioinfusion/amnioreduction time.

The two groups were stratified by whether preoperative second-trimester vaginal bleeding occurred and compared using Mann–Whitney *U*, chi-square, and Fisher's exact tests, as appropriate. Statistical analysis was performed using Stata version 16. $p < 0.05$ was considered statistically significant.

3 | RESULTS

Of 373 patients who underwent laser over the study period, 359 (96.2%) had clear documentation of whether they had second-trimester vaginal bleeding, including 30 (8.4%) who did and 329 (91.6%) who did not, respectively.

3.1 | Preoperative characteristics

Median maternal age (30.5 vs. 31.0), maternal BMI (29.7 vs. 28.1), use of assisted reproductive technologies (23.3% vs. 13.1%), preoperative cervical length (3.8 vs. 3.6 cm), EFW discordance (21% vs. 17%), cardiovascular score (5 vs. 4), donor DVP (0.9 vs. 0.9 cm), recipient DVP (9.0 vs. 9.6 cm), and percent with anterior placenta (33.3% vs. 43.8%) were similar between the two groups (all $p > 0.05$) (Table 1). There was also no difference in preoperative TTTS stage (Vaginal bleeding—Stage I: 13.3%, Stage II: 43.3%, Stage III: 40%, Stage IV: 3.3% vs. no vaginal bleeding—Stage I: 11.6%, Stage II: 55.6%, Stage III: 30.0%, Stage IV: 4.9%; $p = 0.482$) (Table 1).

3.2 | Operative characteristics

Although median gestational age at laser (19.0 vs. 20.1), inability to complete the laser (3.3% vs. 1.2%), median volume of amnioreduction (1262 vs. 1250 mL, $p = 0.844$), and median number of anastomoses (11 vs. 13) were also similar between groups, patients with second-trimester vaginal bleeding had longer median operating room times (61 vs. 50 min, $p = 0.032$), higher median amnioinfusion volumes (117.5 vs. 0 mL, $p = 0.028$), and higher need for amnioexchange (33.3% vs. 14.3%, $p = 0.006$) (Table 2).

3.3 | Outcome characteristics

The incidence of chorioamnion separation appeared higher in the group with second-trimester vaginal bleeding, but the finding was not statistically significant (23.3% vs. 11.6%, $p = 0.062$) (Table 2). The incidence of PPROM within 1 week of the laser procedure was higher

TABLE 1 Comparison of preoperative characteristics in patients undergoing laser for twin–twin transfusion syndrome with and without second-trimester vaginal bleeding.

	Vaginal bleeding, $n = 30$	No vaginal bleeding, $n = 329$	p value
Maternal age	30.5 [27.0–36.0]	31.0 [27.0–34.0]	0.768
Maternal BMI	29.7 [25.5–37.3]	28.1 [24.1–32.3]	0.111
Use of ART	7 (23.3%)	43 (13.1%)	0.120
Cervical length	3.8 [3.4–4.2]	3.6 [3.1–4.1]	0.153
TTTS stage			0.482
I	4 (13.3%)	38 (11.6%)	I
II	13 (43.3%)	183 (55.6%)	
III	12 (40%)	92 (30.0%)	
IV	1 (3.3%)	16 (4.9%)	
EFW discordance	21 [10–27]	17 [11–26]	0.506
Cardiac score	5 [2–8]	4 [2–7]	0.661
Donor DVP	0.9 [0.5–1.4]	0.9 [0.4–1.5]	0.821
Recipient DVP	9.0 [8.3–10.9]	9.6 [8.2–11.2]	0.687
Anterior placenta	10 (33.3%)	144 (43.8%)	0.269

Note: Results are given as median [interquartile range] or proportion.

Abbreviations: ART, assisted reproductive technologies; BMI, body mass index; DVP, deepest vertical pocket; EFW, estimated fetal weight; TTTS , twin twin transfusion syndrome.

in those with vaginal bleeding (16.7% vs. 3.3%, $p = 0.001$), even though the overall incidence of any PPROM was similar between the groups (23.3% vs. 12.5%, $p = 0.094$). The median gestational age at PPROM appeared to be lower in the vaginal bleeding group, but this also did not reach statistical significance (19.2 vs. 25.1 weeks, $p = 0.074$). There was no difference in need for additional therapy based on preoperative second-trimester vaginal bleeding (6.7% vs. 4.9%, $p = 0.654$) (Table 2).

Dual fetal demise occurred in 11 (3.1%) pregnancies, including 2 (6.7%) with second-trimester vaginal bleeding and 9 (2.7%) without ($p = 0.232$). Single fetal demise occurred in 66 (18.4%) pregnancies, including 7 (23.3%) with second-trimester vaginal bleeding and 59 (17.9%) without ($p = 0.456$). The median gestational age at delivery was similar between groups (34 vs. 34 weeks, $p = 0.559$). Furthermore, 4 (13.3%) patients in the vaginal bleeding group delivered at less than 21 days after the procedure compared to 27 (8.2%) in the no vaginal bleeding group ($p = 0.312$) and 4 (13.3%) patients with second-trimester vaginal bleeding delivered at less than 28 days following the procedure compared to 32 (9.7%) in the no vaginal bleeding group ($p = 0.524$). For survival outcomes, 2 (0.6%) patients were lost to follow-up, including 0 from the vaginal bleeding group and 2 (0.6%) from the no vaginal bleeding group. Dual and single infant survival to 28 days were similar between the two groups (Vaginal bleeding: dual 60%, single 26.7%; no vaginal bleeding: dual: 69.0%, single: 20.1%; $p = 0.544$) (Table 2).

As mentioned above, laser was not possible in five patients (1 [3.3%] in the vaginal bleeding group and four [1.2%] in the no vaginal bleeding group). Two of those pregnancies then had selective cord occlusion with single survival, one had spontaneous fetal demise of one fetus with single survival, and two had dual fetal demise.

Placental pathology with injection studies was performed on 141 available placentas with dual survivors and revealed residual anastomoses in 2/10 (20.0%) patients with second-trimester vaginal bleeding compared to 13/131 (9.9%) with no second-trimester vaginal bleeding ($p = 0.288$).

4 | DISCUSSION

In this study, we report that 8.4% of patients who underwent laser for TTTS in our center had preoperative second-trimester vaginal bleeding. Compared to those without, patients with second-trimester bleeding had longer operating room times, higher median amnioinfusion volume, higher need for amnioexchange, and higher incidence of PPROM within 1 week after the laser. While not statistically significant, they also appeared to have more postoperative chorioamnion separation (23.3% vs. 11.6%) and more residual anastomoses (20.0% vs. 9.9%).

Other authors have similarly found that second-trimester vaginal bleeding, or preoperative evidence of bleeding on ultrasound, is associated with complications after laser. Yamamoto et al. reported second-trimester

TABLE 2 Comparison of operative characteristics and outcomes in patients undergoing laser for twin–twin transfusion syndrome with and without second-trimester vaginal bleeding.

	Vaginal bleeding, $n = 30$	No vaginal bleeding, $n = 329$	p value
GA at laser	19.0 [18.2–21.0]	20.1 [18.2–21.6]	0.163
Unable to complete laser	1 (3.3%)	4 (1.2%)	0.355
OR time (minutes)	61 [48–75]	50 [39–63]	0.032
Amnioexchange performed	10 (33.3%)	47 (14.3%)	0.006
Amnioinfusion volume (mL)	117.5 [0–1000]	0 [0–500]	0.028
Amnioreduction volume (mL)	1262 [750–1750]	1250 [800–1800]	0.844
Number of anastomoses	11 [7–15]	13 [9–17]	0.080
Chorioamniotic membrane separation	7 (23.3%)	38 (11.6%)	0.062
PPROM			
Within 1 week	5 (16.7%)	11 (3.3%)	0.001
Any PPROM	7 (23.3%)	41 (12.5%)	0.094
GA at PPROM	19.2 [17.2–27.3]	25.1 [23.0–30.5]	0.074
Need for additional therapy	2 (6.7%)	16 (4.9%)	0.654
Fetal demise			
Single	7 (23.3%)	59 (17.9%)	0.456
Dual	2 (6.7%)	9 (2.7%)	0.232
Delivery close to laser			
≤21 days	4 (13.3%)	27 (8.2%)	0.312
≤28 days	4 (13.3%)	32 (9.7%)	0.524
GA at delivery (weeks)	34 [30.5–36.4]	34 [30.2–35.6]	0.559
28-day survival			0.544
0	4 (13.3%)	34 (10.3%)	
1	8 (26.7%)	66 (20.1%)	
2	18 (60.0%)	227 (69.0%)	
Lost to follow-up	0	2 (0.6%)	
Residual anastomoses	2/10 (20%)	13/131 (9.9%)	0.288

Note: Results are given as median [interquartile range] or proportion.

Abbreviations: GA, gestational age; OR, operating room; PPROM, preterm premature rupture of membranes.

vaginal bleeding was an independent risk factor for delivery within 4 weeks of laser procedure with a hazard ratio of 6.62 [18]. Additionally, Chmait et al. identified subchorionic hematoma as a risk factor for delivery within 21 days after laser with an odds ratio of 7.92 [29]. While there was no difference in preterm delivery within 21 or 28 days in our cohort, patients with second-trimester vaginal bleeding had a higher incidence of PPROM within 1 week of the procedure. This is a risk factor for preterm delivery and may cause some patients to opt for iatrogenic delivery due to associated risks [30]. Others opt for expectant management, given outcomes can remain favorable in many cases [30].

Other studies that have evaluated the risk of PPROM or preterm delivery after laser have not included second-trimester vaginal bleeding in the analysis. Short cervical length, earlier gestational age at laser, larger cannula size, higher number of anastomoses, larger amnioinfusion volume, and postoperative chorioamnion separation have been associated with post-laser PPROM and preterm delivery [10, 16, 26, 31–42]. Our study shows that amnioexchange was more commonly utilized in patients with preoperative vaginal bleeding. In our experience, the amniotic fluid in these cases can be brown and opaque, limiting visualization of anastomoses during the procedure (Figure 1). Amnioexchange can improve visualization by replacing dark amniotic fluid with warmed Lactated Ringer's solution. This may improve visualization and allow completion of the procedure but may also increase the rate of PPROM given the large volume infused. It may also increase the risk of postoperative chorioamnion separation. Interestingly, in our study and in others, the higher incidence of early PPROM was not necessarily associated with worse outcomes [34, 43]. In addition to the increased

need for amnioexchange, the higher percentage of patients with residual anastomoses in the vaginal bleeding group may suggest difficulties with visualization even though the finding was not statistically significant. Furthermore, although not clinically relevant in our cohort, it may prove relevant in a larger population.

Studies on interventions to prevent PPROM such as collagen plug placement have been conflicting [32, 43]. Similarly, cervical cerclage and pessary have not been shown to reduce preterm delivery after laser [15, 44]. Future studies are needed to evaluate potential risk-reducing interventions. While post-laser single and dual survival has improved over the past 25 years, PPROM and preterm delivery rates remain high and should be an area of focus. Advances in fetoscopic instrumentation or membrane tacking/sealing techniques may reduce the risk of chorioamnion separation and PPROM in the future. Additionally, studies on vaginal progesterone may prove that it is beneficial to reduce rates of preterm delivery [15]. Finally, modifications to improve visualization in cases with murky amniotic fluid, such as those with preoperative second-trimester bleeding, may improve outcomes. At this point, knowledge of the increased risk of PPROM within 1 week after laser in patients with preoperative second-trimester vaginal bleeding can be discussed in counseling but should not preclude laser surgery, given the poor outcome in expectantly managed cases of advanced TTTS. In cases with an anterior placenta, however, partial carbon dioxide insufflation to facilitate visualization may be considered [20, 45, 46].

The strength of this study is that it provides new information on how preoperative second-trimester bleeding impacts surgical approach and outcomes following laser for TTTS. It is not without limitations, however. Although this is a relatively large cohort of patients that had laser, the incidence of preoperative second-trimester bleeding was low at 8.4% resulting in only 30 patients with this finding. Additionally, the presence of second-trimester vaginal bleeding was obtained via patient history, maternal questionnaire, and/or review of prenatal records, therefore, the quantity and length of vaginal bleeding could not be determined. This prohibited analysis of the impact of amount of vaginal bleeding on outcomes. Finally, although PPROM and gestational age at delivery were reported, the indication for delivery was not thereby limiting the ability to make direct connections between the preoperative/operative course and subsequent pregnancy complications. Nonetheless, we believe that the findings of this study are useful in counseling patients and in identifying a population that may benefit from future research and surgical modifications.

5 | CONCLUSION

In our cohort, second-trimester vaginal bleeding occurred in 8.4% of patients who underwent laser for TTTS and was associated with a higher incidence of poor visualization during the procedure and increased risk of PPROM within 1 week. This information can be utilized to guide future studies and in counseling patients prior to the laser procedure.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

The study was reviewed and approved by the Children's Hospital of Philadelphia Institutional Review Board, IRB#09-007085. Patient consent to have data collected and compiled in the registry was obtained. The research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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