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Anesthesia-Related Factors Associated with Preterm Labor and Delivery after Open Fetal Surgery

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Keywords
Preterm labor · Preterm delivery · Fetal surgery · Anesthesia

Abstract
Background: Fetal surgery, such as for meningomyelocele repair, has a clear clinical fetal benefit. In patients who undergo in utero repair of meningomyelocele, for example, there is reduced long-term disease morbidity. However, despite the beneficial effects of early intervention, women who undergo fetal interventions have an increased risk of preterm labor and delivery. Several surgery-related factors have been described but no specific anesthesia-related factors. ***Objective:*** The aim of this study was to determine if any aspects of the perioperative anesthetic management influenced maternal complications following in utero surgery. ***Methods:*** This was a retrospective chart review of the anesthetic management of mothers and fetuses who presented for open and fetoscopic myelomeningocele repair, between 2011 and 2015, at Texas Children's Fetal Center®. ***Results:*** Forty-six women underwent open or fetoscopic repair of neural tube defects at our institution. We found the maternal heart rate in the postoperative period to be associated with a higher likelihood of preterm labor, but not delivery. The odds of having preterm delivery was higher for nulliparous patients and those with lower intraoperative diastolic pressure. ***Conclusions:*** Our findings confirm what has been previously reported regarding the association of nulliparity with preterm delivery. Additionally, this study highlights the importance of maintaining stable perioperative hemodynamics during the intraoperative and postoperative phases of care for patients undergoing in utero surgery.

Introduction

Fetal surgery and interventions offer the unique opportunity for in utero treatment of congenital conditions, with otherwise significant morbidity and mortality. These therapeutic innovations were first studied in nonhuman models, and then transferred to human studies [1].

In utero procedures are typically performed on fetuses for a variety of conditions. Following the findings of the Management of Myelomeningocele Study (MOMS), myelomeningocele repair became the most common indication for open fetal surgery.

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The mode of anesthesia offered to the mother and fetus during fetal intervention depends on the procedure. The goals of the anesthetic management during fetal surgery include avoidance of hypotension, hypoxia, and acidosis. The ultimate goal is to ensure that uteroplacental blood flow remains adequate throughout the operation. For open fetal surgery, the mothers commonly receive general anesthesia plus neuraxial anesthesia via an epidural catheter. The latter is placed primarily for postoperative pain management. The fetus receives anesthesia and analgesia in 2 distinct ways: through transplacental transfer of volatile anesthetics and opioids from the mother, and the direct intramuscular administration of opioids and muscle relaxants. During fetal surgery, fetal well-being is continually monitored either with fetal echocardiography, scalp electrodes, umbilical blood sampling, or pulse oximetry [2–5].

Mothers undergoing in utero procedures are at risk for the following complications: pulmonary edema, hemorrhage, preterm labor, and preterm delivery. One of the tenets of fetal surgery is maintaining maternal safety and reducing fetal morbidity and mortality. Ultimately, preterm labor and delivery remain the most commonly feared complications following open fetal surgery.

This exploratory, hypothesis-generating pilot study aimed to determine if any aspects of the perioperative anesthetic management influenced maternal complications following in utero surgery.

Materials and Methods

Study Population

We performed a retrospective chart review of the anesthetic management of mothers and fetuses who presented for open and fetoscopic myelomeningocele repair, between 2011 and 2015, at Texas Children's Fetal Center®. The Baylor College of Medicine Institutional Review Board approved this study, and the need for informed consent was waived.

Data Collection

For each case, the electronic medical record (EMR) was queried for patient demographics (including age, parity, and gestational age), indication for inutero surgery, preoperative hemodynamic variables (blood pressure and heart rate), intraoperative factors (duration of surgery, maternal intravenous opioid use, maximum sevoflurane concentration, mean maternal vasopressor dose, frequency of maternal vasopressor administration, magnesium dose, total amount of crystalloid administered, fetal drugs and doses administered, hemodynamic variables, and oxygen saturation), postoperative factors (mean duration of epidural infusion, number of times epidural concentration was changed, duration of magnesium tocolysis, use of other tocolytics, fetal heart rate, hemodynamic variables, presence of side effects (itching, nausea, and vomiting), duration of time from end of surgery to start of oral intake, and occurrence of maternal and fetal complications (placental abruption, chorioamniotic separation, preterm premature rupture of membranes [PPROM], chorioamnionitis, oligohydramnios, uterine dehscence, preterm labor, preterm delivery, infection, hemorrhage, pulmonary edema, pulmonary embolism, and need for fetal resuscitation).

Preterm delivery was defined as delivery before 37 weeks of gestation. Preterm labor was defined as regular uterine contractions resulting in cervical change before 37 weeks of gestation.

Regarding hemodynamic variables, the baseline vital signs were obtained from the first set of vital signs recorded on the day of surgery. Intraoperative vital signs were recorded every 30 min, with a preference for arterial blood pressure readings over manual blood pressure readings. Postoperatively, the vitals were recorded hourly for the first 24 h. The average for both the intraoperative and postoperative vitals was then inputted for analysis.

Table 1. Baseline demographics and surgery-related characteristics of study population

Variables	*N* (%)
Maternal age (*n* = 45)	
19–30 years	32 (71.1)
31–45 years	13 (28.9)
Maternal weight (*n* = 43)	
70 kg or less	16 (37.2)
71–100 kg	25 (58.1)
101 kg and over	2 (4.7)
Nulliparity (*n* = 44)	
Yes	14 (31.8)
No	30 (68.2)
History of Cesarean section (*n* = 45)	
Yes	8 (17.8)
No	37 (82.2)
Duration of surgery – maternal (*n* = 43)	
0–120 min	0 (0.0)
121–240 min	10 (23.3)
241–480 min	29 (67.4)
481–600 min	4 (9.3)
Epidural duration (*n* = 41)	
1–2 days	5 (12.2)
3–4 days	35 (85.4)
5 days or more	1 (2.4)
Gestational age at delivery (*n* = 42)	
24–30 weeks	6 (14.3)
31–34 weeks	8 (19)
35–36 weeks	11 (26.2)
37–40 weeks	17 (40.5)
Duration of surgery – fetal (*n*= 41)	
0 min (aborted procedure)	2 (4.9)
Less than 30 min	16 (39)
31–60 min	13 (31.7)
61–90 min	3 (7.3)
Greater than 91 min	8 (17.1)
Fetal heart rate – mean (postoperative) (*n* = 39)	
100–119 bpm	8 (20.5)
120–160 bpm	31 (79.5)

Table 2. Characteristics associated with preterm labor

Variable	Preterm labor = no		Preterm labor = yes		*p* value
	N	mean ± SD	*N*	mean ± SD	
Maternal-related factors					
Maternal age, years	18	29.1±4.9	25	28.2±6.4	0.46
Maternal weight, kg	17	76.9±16.6	25	76.2±10.8	0.90
Duration of surgery – maternal, min	18	322±101	25	294±73.8	0.43
Epidural duration, days	16	3.2±0.7	24	3.0±0.7	0.44
Number of times epidural changed	16	1.4±1.0	24	1.3±1.1	0.72
Maximum sevoflurane concentration, %	18	4.2±0.9	25	3.71±0.6	0.14
Maternal total opioid dose (morphine equivalents, mg)	18	17.8±7.7	25	16.9±8.2	0.85
Intraoperative average systolic blood pressure, mm Hg	18	104±8.4	25	104±5.8	0.80
Intraoperative average diastolic blood pressure, mm Hg	18	61.1±5.7	25	58.7±4.6	0.27
Intraoperative average heart rate, bpm	18	80.7±10.1	25	84.2±10.5	0.30
Intraoperative average SpO_2, %	18	98.6±0.9	25	98.8±1.2	0.44
Postoperative average systolic blood pressure, mm Hg	16	99.7±8.8	24	102±13.9	0.70
Postoperative average diastolic blood pressure, mm Hg	16	56.3±5.0	24	57.7±6.4	0.36
Postoperative average heart rate, bpm	16	80.4±10.4	24	88.6±11.5	**0.02**
Postoperative average SpO_2, %	16	97.7±1.2	24	97±1.6	0.15
Fetal-related factors					
Mean fetal heart rate, bpm	16	127±14.2	22	129±7.9	0.76
Delivery weight, g	11	3,010±369	21	1,960±672	**<0.0001**
Gestational age at time of procedure, weeks	18	24.3±1.1	25	24.2±1.3	0.94
Duration of surgery – fetal, min	17	64.5±75.9	24	56±51.9	0.36

Variable	Preterm labor = no		Preterm labor = yes		*p* value
	N	*n* (%)	*N*	*n* (%)	
Maternal-related factors					
Nulliparity	18	3 (17)	25	10 (40)	0.18
History of Cesarean section	18	6 (33)	25	1 (4)	**0.02**
Side effect (itching)	16	7 (44)	25	8 (32)	0.52
Side effect (nausea)	16	10 (63)	25	9 (36)	0.10
Side effect (vomiting)	16	5 (31)	25	4 (16)	0.28
Fetal-related factor					
Intraoperative fetal bradycardia	18	6 (33)	25	2 (8)	**0.05**

Bold type denotes significance. SD, standard deviation.

Statistical Analysis

Categorical variables were analyzed using Fisher's test, and the Mann-Whitney U test was used to compare continuous variables. The Mann-Whitney U test was used as the data are not normally distributed. Categorical data are expressed as frequencies (percentages); continuous data are expressed as mean/standard deviation (SD) and median/ranges. A p value <0.05 was determined to be statistically significant. Multivariate logistic regression models were used to assess the significant risk factors affecting pain management and pregnancy outcome, namely, the probability of having an epidural rate change, preterm delivery, and preterm labor. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

From January 2011 to December 2015, 46 women underwent open or fetoscopic repair of neural tube defects at our institution. Table 1 presents the baseline demographics and surgery-related characteristics of these patients. All procedures were performed between 21 and 26 weeks, and the majority of the mothers were younger than 30 years and multiparous.

After adjusting for potential confounders, the only independent risk factor for preterm labor (Table 2) was maternal heart rate in the postoperative period (from

Table 3. Characteristics associated with preterm delivery

Variable	Preterm delivery = no		Preterm delivery = yes		*p* value
	N	mean ± SD	*N*	mean ± SD	
Maternal-related factors					
Maternal age, years	18	29±4.9	25	28.3±6.4	0.57
Maternal weight, kg	18	75.6±15.5	24	77.1±11.6	0.49
Duration of surgery – maternal, min	17	335±99.7	26	286±72.4	0.06
Epidural duration, days	18	3±0.8	22	3.1±0.5	0.64
Number of times epidural changed	18	1.3±1.0	22	1.4±1.1	0.87
Cervical Length, mm	18	40.9±7.2	25	38.1±8.2	0.15
Maximum sevoflurane concentration, %	18	3.9±0.7	25	3.9±0.9	0.83
Maternal total opioid dose (morphine equivalents, mg)	18	19.7±8.3	25	15.5±7.2	0.12
Intraoperative average systolic blood pressure, mm Hg	18	103±8.3	25	104±5.9	0.87
Intraoperative average diastolic blood pressure, mm Hg	18	62.3±4.5	25	57.8±4.9	**0.01**
Intraoperative average heart rate, bpm	18	81.1±10.0	25	83.9±10.6	0.54
Intraoperative average SpO_2, %	18	98.7±0.9	25	98.7±1.2	0.95
Postoperative average systolic blood pressure, mm Hg	18	99.8±8.6	22	102±14.3	0.76
Postoperative average diastolic blood pressure, mm Hg	18	56.3±4.9	22	57.8±6.6	0.31
Postoperative average maternal heart rate, bpm	18	82.7±11.7	22	87.5±11.5	0.16
Postoperative average SpO_2, %	18	97.4±1.4	22	97.1±1.5	0.57
Fetal-related factors					
Mean fetal heart rate, bpm	15	128±13.5	23	128±9.0	0.90
Delivery weight, g	11	3,010±376	21	1,970±675	**<0.0001**
Gestational age at time of procedure, weeks	18	24.4±1.2	25	24.2±1.2	0.58
Duration of surgery – fetal, min	16	70.3±74.1	25	52.6±53.8	0.80

Variable	Preterm delivery = no		Preterm delivery = yes		*p* value
	N	*n* (%)	*N*	*n* (%)	
Maternal-related factors					
Nulliparity	18	1 (5.6)	25	12 (48)	**0.003**
History of Cesarean section	18	5 (28)	25	2 (8)	0.11
Side effect (itching)	18	8 (44)	23	7 (30)	0.52
Side effect (nausea)	18	9 (50)	23	10 (43)	0.76
Side effect (vomiting)	18	5 (28)	23	4 (17)	0.47
Fetal-related factor					
Intraoperative fetal bradycardia	18	4 (22)	25	4 (16)	0.70

Bold type denotes significance. SD, standard deviation.

the conclusion of surgery until discharge). There was no relationship between the maximum concentration of sevoflurane and preterm labor. Even though there was a significant difference in intraoperative fetal bradycardia, this finding was more likely in the group without preterm labor and not a risk factor for having preterm labor. Intraoperative diastolic blood pressure and nulliparity were found to be statistically significant risk factors for preterm delivery (Table 3). Perioperative hemodynamic variables (except as listed above), the need for fetal resuscitation, maternal total opioid dose, and duration of postoperative epidural analgesia were not significantly different between the groups of patients that developed preterm labor or preterm delivery (Tables 2, 3).

On regression analysis, only the maternal heart rate in the postoperative period was associated with a higher likelihood of preterm labor (Table 4). The odds of having preterm labor was 1.12 times higher, with increased heart rate (88.6 ± 11.5) in the postoperative period, adjusting for maternal age and weight, gestational age at time of procedure, fetal bradycardia, nulliparity, and maximum sevoflurane concentration.

Using regression analysis, after adjusting for maternal age, maternal weight, and gestational age at the time of procedure, the odds of having preterm delivery was 16.8

Table 4. Multivariate logistic regression for having preterm labor

Variable	Odds ratio	95% confidence interval	*p* value
Maternal-related factors			
Maternal age	1.14	0.93–1.40	0.22
Maternal weight	0.97	0.90–1.05	0.50
Nulliparity (yes/no)	5.36	0.54–53.29	0.15
History of cesarean section (yes/no)	0.17	0.01–3.10	0.23
Maximum sevoflurane concentration	0.43	0.11–1.73	0.23
Postoperative average heart rate	1.13	1.02–1.25	**0.02**
Fetal-related factors			
Gestational age at time of procedure	0.94	0.40–2.17	0.88
Intraoperative fetal bradycardia (yes/no)	0.27	0.02–4.20	0.35

Table 5. Multivariate logistic regression for having preterm delivery

Variable	Odds ratio	95% confidence interval	*p* value
Maternal-related factors			
Maternal age	1.08	0.91–1.28	0.36
Maternal weight	1.00	0.94–1.07	0.92
Nulliparity (yes/no)	16.80	1.09–258.85	**0.04**
Duration of surgery – maternal	1.00	0.99–1.00	0.69
Intraoperative average diastolic blood pressure	0.82	0.68–0.99	**0.04**
Fetal-related factor			
Gestational age at time of procedure	0.90	0.43–1.91	0.79

Table 6. Factors associated with change in epidural (rate/concentration)

Variable name	Changes* = 0		Changes* = 1 or 2		*p* value
	N	*n* (%)	*N*	*n* (%)	
Side effect (itching)	9	4 (44)	32	10 (31)	0.69
Side effect (nausea)	9	1 (11)	32	17 (53)	**0.05**
Side effect (vomiting)	9	0 (0)	32	9 (28)	0.17

Bold type denotes significance.* Number of changes to epidural.

times higher for nulliparous patients. A one-unit increase in intraoperative diastolic blood pressure was associated with a 17.7% lower chance of preterm delivery (Table 5).

The epidural duration was typically 3–4 days. The presence of nausea was the most common, statistically significant factor that precipitated epidural change (change in rate or concentration change) (Table 6). There was no association between changes in the epidural rate or concentration and the mean fetal heart rate, or postoperative hemodynamic values.

In our cohort, there were no cases of maternal hemorrhage or pulmonary embolism, and the rates of infection and pulmonary edema were minimal (less than 3 and 7%, respectively). Obstetric (OB) complications, such as placental abruption, chorioamnionitis, chorioamniotic separation, PPROM, oligohydramnios, and uterine dehiscence, were also reviewed. There was no significant dif-

ference in the incidence of preterm labor and delivery between those who had or did not have OB complications. History of prior cesarean delivery was significant for preterm labor, but not preterm delivery (Tables 2, 3).

Discussion/Conclusion

There are a myriad of indications for open fetal surgery. Myelomeningocele repair was the most common at our institution, and this is consistent with the positive results of the MOMS trial published in 2011[6–8]. In line with recommendations from this trial, most of the in utero surgical procedures in our cohort were conducted between 24 and 26 weeks.

Common complications of open fetal surgery include preterm labor and preterm delivery, which was also evident in our study. Tocolytic therapy is central to the management of open fetal surgery due to the known risk of preterm labor. Like in our study, magnesium is the most common tocolytic used during these interventions [9]. The magnesium dosing used was: a loading dose of 4–6 g, followed by an infusion of 2 g/h; and magnesium was continued postoperatively for a median of 3 days. The supplemental tocolytics that were occasionally administered in the postoperative period were indomethacin and nifedipine.

The common assumption is that preterm labor and delivery occur due to manipulation of the gravid uterus, in conjunction with the fetus's surgical stimulation, and possible noxious stimuli in the fetus. Noxious stimuli to the fetus have been proposed as an etiology of preterm labor and delivery due to the release of stress hormones, which subsequently stimulate uterine contractions [10]. Additional risk factors for preterm labor and delivery include infection, inflammation, uteroplacental insufficiency, uterine overdistension, and placental abnormalities, among others [11].

Chorioamnionitis and placental abruption were, however, not found to be risk factors for either preterm labor or delivery. We did identify anesthesia-related factors that were associated with preterm labor or preterm delivery.

The odds of having preterm labor was higher with increasing maternal heart rate, that is, with a mean heart rate greater than 88 bpm (88.6 ± 11.5), in the postoperative period. While no previous studies have shown a direct link between maternal heart rate and preterm labor, it is well established that stress does contribute to the incidence of preterm labor. Of note, the maximum heart rate was 101 beats per minute in the preterm labor group of patients. Following surgery, all patients received patient-controlled epidural analgesia, consisting of 0.1% bupivacaine with 10 μg/mL of fentanyl, following surgery, and pain control was adequate. All the medication therapy changes were due to side effects such as itching, nausea, or vomiting, and not inadequate pain control. The total intraoperative maternal opioid consumption was used as a surrogate for pain scores in this study due to a lack of documentation of the actual pain scores in the EMR.

Fetal heart rate, a potential marker for the effect of noxious stimuli or stress, has been previously associated with preterm labor and delivery. However, in our study, intraoperative fetal bradycardia was more commonly seen in patients who did not have preterm labor. Of note, all persistent intraoperative fetal bradycardia episodes were immediately treated with epinephrine, with prompt resolution. There was no consistent documentation of fetal heart rates postoperatively.

In our study, preterm delivery was more likely in nulliparous women. This finding confirms what has been previously reported [11–13]. Other pregnancy history-related causes include previous preterm delivery and multiple gestation pregnancies [11–13].

The mean intraoperative diastolic pressure was also associated with preterm delivery. Interestingly, this was not due to a decrease in systemic vascular resistance from higher sevoflurane concentration as would be expected. On the contrary, in our study, we found that a lower maximum sevoflurane concentration was likely in patients with preterm delivery. The maximum sevoflurane concentration between the groups with and without preterm labor and delivery was above normal physiologic ranges. This supraphysiologic dosing was to achieve adequate uterine relaxation, as determined by the surgical team.

Regression analysis revealed that the odds of having preterm delivery were 17.7% lower with a one-unit increase in the intraoperative diastolic blood pressure. Intraoperative phenylephrine infusions are commonly administered to patients undergoing fetal surgery to maintain the systolic blood pressure within 20% of baseline pre-surgery values. Our findings highlight the importance of ensuring that the intraoperative diastolic pressure, and not just the systolic blood pressure, remains within 20% of baseline. The diastolic pressure is indeed what determines the uterine perfusion pressure, and inadequate uterine perfusion pressure is a known risk factor for preterm labor and delivery [11]. The majority of the study cohort received vasoactive therapy with phenylephrine and ephedrine during surgery, but no vasopressors were administered postoperatively.

The authors do note that there is a disparity between the effects of postoperative maternal heart rate and intraoperative diastolic blood pressure on preterm labor and preterm delivery. All patients received tocolytic therapy, which could disrupt the progression from preterm labor to preterm delivery. Also, if the sample size was greater than 46 patients, perhaps a notable difference would have been observed in both preterm labor and preterm delivery.

Preterm labor and delivery were similar for those who had or did not have OB complications. History of prior cesarean delivery was a risk factor for preterm labor, but not preterm delivery.

This study highlights the importance of maintaining stable perioperative hemodynamics during the intraoperative and postoperative phases and may help guide the perioperative management of patients undergoing in utero surgery. Added emphasis on maintaining the intraoperative diastolic pressure and postoperative heart rate, within 20% of baseline values, may positively influence the outcome of pregnancies following in utero surgery. Previous studies have examined procedure-related complications [14], but to the authors' knowledge, no study has specifically examined perioperative anesthesia-related factors that may influence the incidence of complications following in utero surgery.

This study has some limitations. It is retrospective; however, a prospective study to examine which factors precipitate preterm labor and delivery may be considered unethical. Retrospective studies may also be critiqued for having inaccurate data; however, the data points analyzed in this study were all obtained from the EMR, thereby decreasing incorrect measurements. Given the retrospective nature of this study, not all data points were available, leading to a higher potential for type I and II errors. Other limitations include the relatively small sample size, making it challenging to detect complications that may have a relatively low incidence. More studies will be needed to confirm that the differences we noted are valid and not due to chance.

Our findings do suggest that critical intraoperative management of both systolic and diastolic pressures should be considered during in utero fetal surgery. Considerations for postoperative anxiolysis should also be entertained to prevent elevated heart rates in the postoperative period.

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Statement of Ethics

Baylor College of Medicine Institutional Review Board approval was obtained before the completion of this research study (H-38624). This study complies with the guidelines for human studies and was conducted in accordance with the World Medical Association Declaration of Helsinki. A waiver of written patient consent was granted because this was a chart review study without patient identifiers.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.A. and O.O. contributed to the design and implementation of the research study. T.A., J.K., and K.A.W. contributed to data collection. T.A., H.Z., A.N., and O.O. contributed to the analysis of the data and the writing of the manuscript.

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