ORIGINAL ARTICLE

Flow patterns in the ductus arteriosus during open fetal myelomeningocele repair[†]

Lisa Howley[1]*, Cristina Wood[2], Sonali S. Patel[1], Michael V. Zaretsky[3,4], Timothy Crombleholme[4] and Bettina Cuneo[1]

[1]Department of Pediatric Cardiology, The Fetal Heart Program, Colorado Fetal Care Center, Colorado Institute for Maternal Fetal Health, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

[2]Department of Anesthesiology, Colorado Institute for Maternal Fetal Health, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

[3]Department of Maternal-Fetal Medicine, Colorado Institute for Maternal Fetal Health, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

[4]Department of Fetal Surgery, Colorado Institute for Maternal Fetal Health, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

*Correspondence to: Lisa Howley. E-mail: Lisa.howley@childrenscolorado.org

[†]Presented at the 33rd Annual Meeting of the International Fetal Medical and Surgical Society, September 7–11, 2014, Chatham, MA, USA.

ABSTRACT

Objective The objective of this study is to perform a longitudinal evaluation of blood flow patterns in the ductus arteriosus (DA) during the perioperative period in fetal myelomeningocele (MMC) surgical patients.

Method Serial fetal echocardiograms were reviewed in 10 MMC cases where mothers received indomethacin and intravenous and inhaled anesthesia. One-way analysis of variance was utilized to evaluate for differences in peak systolic velocity, end-diastolic velocity (EDV), time-averaged mean velocity (TAMV), and Pulsatility Index (PI) throughout the monitoring period. Regression analysis was performed to evaluate the relationship between PI and maternal hemodynamics and medications.

Results The DA TAMV and EDV increased between baseline and inhaled anesthesia and decreased between inhaled anesthesia and postoperative day 2. PI decreased to a nadir during inhaled anesthesia and then increased through postoperative day 2. Three distinct ductal flow patterns, characterizing degree of ductal constriction, were observed. Two fetuses exhibited a severely constricted ductal flow pattern with concurrent moderate tricuspid insufficiency and right ventricular dysfunction during inhaled anesthesia.

Conclusion Abnormal DA flow patterns culminating in significant DA constriction occurred during fetal MMC repair. Limiting maternal exposure to indomethacin, supplemental oxygen, and inhaled anesthesia may reduce the incidence and severity of DA constriction and perhaps reduce fetal cardiac dysfunction during open fetal surgery. © 2015 John Wiley & Sons, Ltd.

INTRODUCTION

Fetuses undergoing prenatal surgical repair of myelomeningocele (MMC) have improved neurologic outcomes with a 50% reduction in ventriculoperitoneal shunting compared with those repaired after birth.[1] However, as with any fetal procedure, there is an inherent risk of premature labor and delivery with prenatal MMC repair, particularly in the perioperative period. In order to reduce this risk, potent tocolytic agents such as indomethacin, magnesium, and nifedipine are widely used before and after fetal MMC repair to prevent premature labor. In addition to its powerful tocolytic properties, indomethacin is recognized to cause constriction of the fetal ductus arteriosus (DA), which has been most frequently reported in the third trimester of pregnancy.[2,3] Fetuses undergoing MMC repair are exposed not only to tocolytic agents but also to high-oxygen concentrations, which can cause DA constriction, and general inhalational agents such as desflurane, which are known to cause negative inotropic effects on the fetal heart. Although fetal surgical patients are routinely exposed to agents known to affect the DA, a longitudinal evaluation of the blood flow patterns in the fetal DA during the perioperative period has not been performed.

In this preliminary investigation, we sought to examine the presence, timing, and frequency of DA constriction before, during, and after prenatal MMC repair. We hypothesized that

a majority of fetuses would demonstrate at least mild evidence of DA constriction resulting from exposure to indomethacin, high maternal oxygen tension, and anesthetic agents.

METHODS

Following the Institutional Review Board (IRB) approval, the Colorado Institute for Maternal and Fetal Health database was queried for pregnancies diagnosed with fetal MMC between January 2012 and July 2014. Fetal echocardiograms and anesthesia records were reviewed at various time points before, during, and after MMC repair (specifically, at baseline, following indomethacin, intravenous anesthesia, inhaled anesthesia, and on postoperative days 1 and 2).

Institution protocol

The protocol for pregnancies with fetal MMC under consideration for open surgical repair is a multistep process which includes fetal assessment by obstetrical ultrasound, fetal echocardiogram, and magnetic resonance imaging, a multi-disciplinary counseling session and review of the findings by a multispecialty oversight committee. If inclusion criteria, as described in the MoMs trial[1] and the local MoMs-plus IRB-approved protocol for women with a BMI of up to $40 \, kg/m^2$ (a deviation from the original MoMs trial protocol, which excluded women with a $BMI \geq 35 \, kg/m^2$) are met, the expectant mother is admitted to the Maternal Fetal Care Center for fetal open MMC repair. The preoperative, intraoperative, and postoperative assessment and monitoring protocols are described in the succeeding text.

Preoperative management

The baseline ultrasound assessment including anatomical survey and fetal cardiac evaluation are described in Table 1. The technique for fetal echocardiography has been described

previously.[4] We considered a fetal heart rate below 120 beats per minute (bpm) or above 180 bpm to be abnormal. Semilunar and atrioventricular (AV) valve insufficiency was graded semiquantitatively by the width of the color flow insufficiency jet at its origin relative to the width of the atrium or great vessel: thus, mild, moderate, or severe insufficiency was diagnosed if the color flow jet width was <1/3, about 1/2, or >1/2 the width of the atrium or great vessel, respectfully. Left and right ventricular systolic function was qualitatively classified as normal or exhibiting mild, moderate, or severe dysfunction. We sampled the DA for five consecutive cardiac cycles using pulsed Doppler to obtain the peak, mean, and end-diastolic velocities and calculated the DA Pulsatility Index (PI) as (peak systolic velocity (PSV) − end-diastolic velocity (EDV))/time-averaged mean velocity (TAMV). The PSV, EDV, and TAMV were averaged for the five cardiac cycles to obtain a mean value for each. We defined DA flow patterns as previously described[5]: normal = PSV 0.50–1.4 m/s and EDV 0.06–0.3 m/s; DA constriction = increased PSV and EDV; and increased cardiac output = increased PSV and normal EDV. Fetal cardiac imaging was performed on a GE Voluson E8 (GE Healthcare, Wauwatosa, WI, USA) or a Philips IE33 (Philips Healthcare, Andover, MD, USA) ultrasound platform using 4–8 MHz curvilinear and phased array transducers. The echo-cardiograms were reviewed together by the two subspecialists experienced in fetal echocardiography (L. W. H. and B. F. C.) who performed the measurements offline using an Agfa Heartlab package (version2.14.03.SU1, Greenville, South Carolina) blinded to the interventions.

A dose of indomethacin (50 mg orally) is given to the expectant mother at bedtime but not later than midnight the evening prior to surgery and is followed at approximately 6 AM by a second dose (25 mg) consistent with the published protocol of the MoMS trial.[1] Immediately prior to the open MMC repair, fetal ventricular function, AV valve regurgitation,

Table 1 Fetal myelomeningocele repair evaluation timing and examination components

Time and frequency of testing	Assessed on OB ultrasound	Assessed on fetal echocardiogram
Baseline (once)	Fetal presentation and biometry Placenta location and AFI Level and size of spinal defect Lower extremity malformation Chiari malformation	Anatomy Heart rate and rhythm DA flow and velocity Ventricular function AV valve integrity
Preoperative (once)	Fetal position Placenta location	Heart rate and rhythm DA flow and velocity Ventricular function AV valve integrity
Intraoperative (every 15–30 min)		Heart rate and rhythm DA flow and velocity Ventricular function AV valve integrity
Postoperative day 1 (once)		Heart rate and rhythm DA flow and velocity Ventricular function AV valve integrity

MMC, myelomeningocele; AFI, amniotic fluid index; DA, ductus arteriosus; AV, atrioventricular.
Description of obstetrical and cardiac evaluation performed baseline, preoperatively, intraoperatively, and postoperatively for fetal MMC repair candidates.

and DA flow are rechecked using fetal echocardiography to assess for any changes secondary to indomethacin (Table 1).

Intraoperative management
Anesthesia

Preoperative evaluation, consent, and lumbar epidural are performed at the patient's bedside prior to moving to the operating room. Once in the operating room, standard ASA monitors are placed, and the expectant mother is preoxygenated with 100% inspired oxygen for 5 min. General endotracheal anesthesia with rapid sequence induction is then performed using propofol (2 mg/kg) and succinylcholine (1.5 mg/kg). The expectant mother is maintained on total intravenous anesthesia (TIVA) with propofol and remifentanil infusions, as well as a phenylephrine infusion to maintain blood pressure within 20% of baseline. Inspired oxygen is maintained at 50% during the maintenance phase per protocol. Immediately prior to hysterotomy, the TIVA is terminated and inhalation anesthesia is initiated with desflurane at 1.5–2 minimal alveolar concentration (MAC). The fetus receives intramuscular fentanyl (20 mcg/kg), atropine (20 mcg/kg), and rocuronium (2 mg/kg) for paralysis and analgesia. Upon closure of the hysterotomy, a magnesium bolus is initiated, the inhalation anesthetic is terminated, and TIVA is resumed until the surgery is completed. The lumbar epidural is dosed prior to extubation for postoperative pain management. The patient is then extubated when awake and taken to the recovery room for further monitoring. The epidural and magnesium infusions are maintained for 48 h postoperatively.

Maternal and fetal hemodynamic monitoring

The expectant mothers are monitored according to guidelines of the American Society of Anesthesia, which include electrocardiogram, noninvasive blood pressure, pulse oximetry, end-tidal CO_2, and direct blood pressure monitoring from a radial arterial line placed during induction of anesthesia. We also monitor the fetus continually in the operating room using echocardiography before, during, and after the open MMC

repair (Table 1). Fetal heart rate and ventricular function is assessed every 2 min during open hysterotomy. Complete hemodynamic data is collected every 15–30 min during administration of TIVA, during inhalation anesthesia (Table 2), and after the desflurane is discontinued and TIVA restarted. We specifically evaluate for changes in the DA flow pattern from baseline with each pharmacologic intervention.

Postoperative management

During the first 48 h after surgery, the magnesium infusion (as described earlier) is continued, and oral indomethacin (25 mg) is given every 6 h unless there was evidence of ductal constriction during surgery. During echocardiographic evaluation of the fetus, if there is evidence of DA constriction (elevated PSV and EDV and decreased PI), indomethacin is discontinued. The indomethacin is restarted only if uterine contractions occur despite tocolysis with magnesium. Forty-eight hours after the repair, the magnesium infusion is discontinued, and the expectant mother receives nifedipine (20 mg) every 6 h for ongoing tocolysis until delivery.

Statistical analysis

Data were evaluated for normality using Shapiro–Wilk testing. Summary statistics are presented, including mean and standard deviation. Group differences for heart rate, PSV, EDV, TAMV, and PI among all time points were evaluated by one-way analysis of variance testing. Post-hoc comparisons were performed with Tukey testing. Similarly, group differences in maternal hemodynamic and medication doses were also evaluated during delivery of inhaled anesthesia (0–30, 31–60, and 61+ min). Univariable regression analysis was performed to evaluate the relationship between PI and MAC of inhaled desflurane, percent inspired oxygen, maternal heart rate and blood pressure, and maternal phenylephrine administration during inhalation anesthesia. Data analysis was performed using the Statistical Analysis System (version 9.3; SAS Corporation, Cary, NC).

Table 2 Maternal hemodynamics, inspired oxygen, and medication and anesthetic doses throughout inhalational anesthesia during fetal myelomeningocele repair

	Inhaled anesthesia 0–30 min	Inhaled anesthesia 31–60 min	Inhaled anesthesia 61+ min	*p*-value
Heart rate (beats/min)	66.67 ± 10.80	71.43 ± 7.45	71.80 ± 4.73	0.3648
Systolic blood pressure (mmHg)	105.00 ± 5.48	108.86 ± 7.00	110.30 ± 12.75	0.5327
Diastolic blood pressure (mmHg)	57.50 ± 4.18	62.86 ± 5.79	64.20 ± 9.53	0.1849
Inspired oxygen (%)	55.00 ± 12.25	58.57 ± 14.06	50.00 ± 0	0.1943
Remifentanil (mcg/kg/min)	0	0.01 ± 0.05	0.09 ± 0.13	0.0809
Propofol (mcg/kg/min)	0	12.50 ± 46.77	45.00 ± 95.60	0.3321
Phenylephrine (mcg/kg/min)	1.07 ± 0.52	1.09 ± 0.66	0.66 ± 0.37	0.1588
Desflurane minimum alveolar concentration	1.68 ± 0.34	1.74 ± 0.27	1.37 ± 0.19	0.0058[a]
Percent desflurane (%)	12.22 ± 2.55	12.64 ± 1.91	10.00 ± 1.39	0.0073[a]

MMC, myelomeningocele.
[a]Inhaled anesthesia 61+ min group was significantly different from remaining groups.

RESULTS

Subject population

Of the 23 pregnancies referred to our institution for evaluation during the study period, 14 underwent open fetal MMC repair. Complete echocardiographic data were available in ten pregnancies, and these ten comprise the study cohort. Median gestational age of the cohort was $25^{0/7}$ ($23^{3/7}$–$25^{5/7}$). At baseline, all fetuses had structurally normal hearts with normal biventricular and valve function, and normal heart rates/rhythm. All fetuses survived the procedure, and mothers were discharged home on postoperative day four or five.

Fetal heart rates

Fetal heart rates did not significantly differ from baseline with each pharmacologic intervention ($p = 0.67$) (Table 3). There were no episodes of fetal tachycardia, bradycardia, or arrhythmia.

DA Doppler measurements

In all fetuses, both the DA TAMV and EDV increased significantly between baseline and the time of inhaled anesthesia (0.33 ± 0.03 m/s to 0.82 ± 0.43 m/s and 0.07 ± 0.01 m/s to 0.33 ± 0.25 m/s, respectively, $p < 0.001$). On the other hand, both DA TAMV and EDV decreased significantly between inhaled anesthesia and postoperative day 2 (0.82 ± 0.18 m/s to 0.34 ± 0.14 m/s and 0.39 ± 0.36 m/s and 0.09 ± 0.05 m/s, respectively, $p < 0.001$). While the DA PSV exhibited a similar trend, this did not reach statistical significance ($p = 0.05$) (Table 3).

Pulsatility Index

The DA Pulsatility Index was normal in all subjects prior to intervention. The PI decreased, indicating worsening DA constriction, at every time point through 60 min of inhaled anesthesia and then increased, indicating improved ductal flow, through postoperative day 2 ($p < 0.0001$) (Table 2 and Figure 1). An inverse relationship between mean DA PI and mean inhaled desflurane MAC was observed, although it was not statistically significant ($r = -0.49$, $p = 0.15$). Given this observation, univariable regression analysis was performed to evaluate the effects of percent inspired oxygen, maternal heart rate and blood pressure, and maternal phenylephrine administration during inhalation anesthesia on PI (data not shown). No significant associations were identified.

DA Doppler flow patterns

In addition to the normal baseline spectral Doppler pattern of the DA, there were three distinct ductal flow patterns seen during this study (Figure 2). All ten fetuses exhibited type I flow pattern after receiving indomethacin preoperatively, but this was the only alteration in ductal flow for two fetuses. The type I ductal flow pattern is characterized by an increased PSV, increased TAMV and normal EDV, resulting in a decreased PI. This pattern is similar to that seen in mild coarctation of the aorta.[5] Six fetuses progressed intraoperatively to type II, and the classical pattern of ductal constriction is characterized by elevated PSV, EDV, and TAMV and decreased PI. Only two

Table 3 Fetal heart rate and ductus arteriosus flow velocities throughout the fetal myelomeningocele repair monitoring period

	Baseline	Indomethacin	IV Anesthesia	Inhaled anesthesia 0–30 min	Inhaled anesthesia 31–60 min	Inhaled anesthesia 61+ min	Postoperative day 1	Postoperative day 2	p-value
Heart rate (beats/min)	145.9 ± 7.1	150.4 ± 7.7	133.8 ± 6.4	135.9 ± 11.5	142.7 ± 9.8	133.6 ± 11.3	136.4 ± 13.9	133.5 ± 9.5	0.6700
Peak systolic velocity (m/s)	0.88 ± 0.10	1.00 ± 0.43	1.33 ± 0.36	1.42 ± 0.67	1.33 ± 0.58	1.49 ± 0.33	0.96 ± 0.27	0.86 ± 0.30	0.0524
End-diastolic velocity (m/s)	0.07 ± 0.01	0.08 ± 0.04	0.15 ± 0.18	0.33 ± 0.25	0.39 ± 0.36	0.10 ± 0.06	0.15 ± 0.15	0.09 ± 0.05	<0.001[a]
Time-averaged mean velocity (m/s)	0.33 ± 0.03	0.49 ± 0.24	0.69 ± 0.29	0.79 ± 0.46	0.82 ± 0.43	0.82 ± 0.18	0.47 ± 0.25	0.34 ± 0.14	<0.001[b]
Pulsatility Index	2.47 ± 0.20	1.94 ± 0.23	1.87 ± 0.56	1.48 ± 0.40	1.30 ± 0.46	1.70 ± 0.18	1.98 ± 0.63	2.34 ± 0.29	<0.0001[b]

MMC, myelomeningocele.
[a]Significant differences between baseline and inhaled anesthesia 0–30 min and inhaled anesthesia 0–30 min and postoperative day 2.
[b]Significant differences between baseline and inhaled anesthesia 31–60 min and inhaled anesthesia 31–60 min and postoperative day 2.
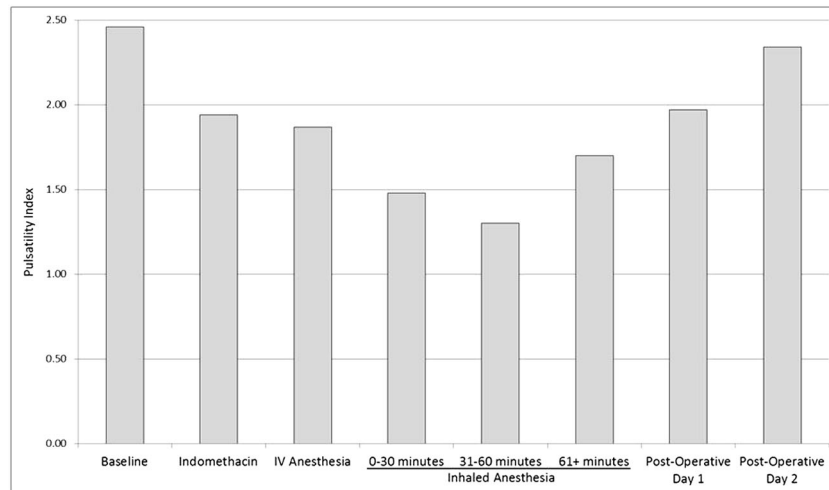
Figure 1 Ductus Arteriosus Pulsatility Index during MMC repair. Changes in Ductus Arteriosus Pulsatility Index over the preoperative, intraoperative, and postoperative period, reaching a nadir during fetal surgery at the time point when mother received inhaled anesthesia. Columns represent mean Pulsatility Index during the timepoint measured. MMC, myelomeningocele
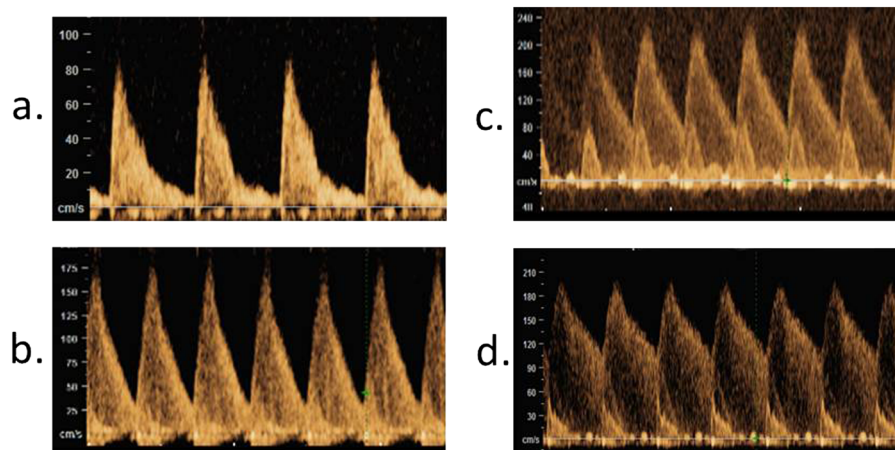

Figure 2 Ductus arteriosus doppler flow patterns. (a) Baseline prior to any fetal drug exposure. (b) Type I, increased PSV and persistent diastolic antegrade flow but a normal EDV, consistent with long segment mild DA constriction. (c) Type II, characterized by elevated PSV, EDV, and TAMV, consistent with significant ductal constriction. (d) Type III, characterized by further elevation of the EDV and TAMV, suggesting worsening DA constriction. PSV, peak systolic velocity; TAMV, time-averaged mean velocity; EDV, end-diastolic velocity; DA, ductus arteriosus

fetuses progressed further to type III, which is similar to type II but with a PI < 0.9 and the concomitant findings of ventricular dysfunction (see succeeding text).

AV valve and ventricular function

Ventricular and AV valve function were normal throughout all pharmacologic interventions except in the two with type III DA pattern. These fetuses developed moderate tricuspid insufficiency and mild to moderate RV dysfunction during inhalation anesthesia. Ventricular function was subjectively normalized in the affected fetuses within 4 h after the operation.

DISCUSSION

Although DA constriction has been previously reported during open fetal surgery,[6] this is the first study to systematically evaluate changes in DA Doppler flow patterns at baseline and before, during, and after open MMC repair. We used the PI to characterize changes in ductal flow, as the PI remains constant despite changes in gestational age[7] and is relatively angle independent.[8] We observed that DA constriction was evident in the preoperative period after indomethacin exposure and that DA constriction was most significant during maternal inhaled anesthesia. We speculate that our findings of progressive DA constriction may be the result of the combined effects of indomethacin, supplemental oxygen, and concurrent desflurane exposure and may be in part responsible for previous reports of fetal cardiac dysfunction during open fetal surgery.[6,9,10]

Histologically, the media layer of the DA is predominantly composed of layers of smooth muscle surrounded by few loose layers of elastic tissue.[11] Patency of the fetal DA is controlled by several factors, most importantly, low fetal oxygen tension

and cyclooxygenase-mediated products of arachidonic acid metabolism, primarily prostaglandin and prostacyclin.[11] In our study, Doppler flow abnormalities in the DA were detectable after the first dose of indomethacin. An efficacious tocolytic agent, indomethacin, inhibits prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase.[12–14] Indomethacin is known to be a potent vasoconstrictor of the DA, and its effects are independent of maternal indomethacin level and fetal gestational age.[15] We found in our study that the early DA flow abnormalities progressed to DA constriction in response to supplemental oxygen and intravenous anesthesia. While the intravenous agents, propofol and remifentanil, are not recognized to have vasoconstrictive properties,[16–18] we speculate that supplemental oxygen or phenylephrine, known vasoconstrictors of the DA,[19] may be responsible for progressive DA constriction observed in this study.

Only at the time of inhaled anesthesia with desflurane did we observe ventricular and AV valve dysfunction and severe DA constriction. Cardiac dysfunction during anesthesia with desflurane, a volatile agent frequently used in fetal surgery to provide adequate uterine relaxation, has been observed in up to 60% of open fetal surgeries.[6,9,10] The mechanism of cardiac dysfunction may be similar to that observed in pregnant ewes receiving 2–3 MAC of desflurane: maternal hypotension, decreased uterine blood flow, and fetal acidosis.[20] During our fetal surgeries, the average MAC of desflurane was lower at 1.5 MAC, and our maternal blood pressure was maintained with alpha agonists, which should maintain uterine blood flow. Higher doses of desflurane result in more maternal hypotension and increased vasopressor requirements to maintain placental perfusion pressure. This increased use of vasopressor in the setting of high-dose desflurane could synergistically lead to fetal cardiac dysfunction as seen in the rat model.[21] Thus, in addition to TIVA, the lower concentration of desflurane and resulting preserved maternal perfusion pressure may have contributed to the normal fetal heart rates and lower incidence of cardiac dysfunction observed in our study.

There are several limitations to this study. First, it is retrospective, and the cohort is small. Second, we were challenged in accurately assessing DA flow and AV valve and ventricular function at regular intervals because of fetal position and considerations for the ongoing surgical repair. Third, while we were able to measure maternal hemodynamics in the operating room, we could not assess the same parameters during baseline and postoperative periods. Although we speculate that prolonged exposure to inhalational anesthesia may contribute to the high incidence of ventricular dysfunction reported in other studies, the role of DA constriction in these studies has not been elucidated. Lastly, the direct effect of desflurane on the human fetal DA has not been well-characterized. Prospective studies evaluating the effects of pharmacologic and specific anesthetic interventions are warranted to assist in development of protocols that minimize DA constriction during open fetal MMC repair.

CONCLUSION

Abnormal DA flow patterns suggesting significant DA constriction during inhalational anesthesia were observed during open fetal MMC repair. Limiting maternal exposure to indomethacin, high levels of supplemental oxygen, and the duration and concentration of inhaled anesthetic agents may reduce the incidence or severity of DA constriction and perhaps decrease the incidence of fetal cardiac dysfunction during open fetal surgery.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Ductal constriction has been observed during fetal surgery.
- Up to 60% of fetuses undergoing fetal surgery have intraoperative cardiac dysfunction.
- Indomethacin, a tocolytic agent used in the perioperative period, has potent vasoconstrictive properties that may result in ductal constriction.

WHAT DOES THIS STUDY ADD?

- First longitudinal evaluation of flow patterns in the ductus arteriosus before, during, and after fetal myelomeningocele repair.
- Progressive ductal constriction observed with most severe constriction occurring during the time of inhaled anesthesia.

REFERENCES

1. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011;364 (11):993–1004.
2. Vermillion ST, Scardo JA, Lashus AG, et al. The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. Am J Obstet Gynecol 1997;177(2):256–9; discussion 59-61.
3. Moise KJ Jr. Effect of advancing gestational age on the frequency of fetal ductal constriction in association with maternal indomethacin use. Am J Obstet Gynecol 1993;168(5):1350–3.
4. Rychik J, Ayres N, Cuneo B, et al. American society of echocardiography guidelines and standards for performance of the fetal echocardiogram. J Am Soc Echocardiogr 2004;17(7):803–10.
5. Echocardiography in Pediatric and Congenital Heart Disease: From Fetus to Adult. Chichester, UK: Wiley Blackwell; 2009. p 796.
6. Rychik J, Tian Z, Cohen MS, et al. Acute cardiovascular effects of fetal surgery in the human. Circulation 2004;110(12):1549–56.
7. Tulzer G, Gudmundsson S, Sharkey AM, et al. Doppler echocardiography of fetal ductus arteriosus constriction versus increased right ventricular output. J Am Coll Cardiol 1991;18(2):532–6.
8. Hoskins PR, Loupas T, McDicken WN. An investigation of simulated umbilical artery doppler waveforms. I. The effect of three physical parameters on the maximum frequency envelope and on pulsatility index. Ultrasound Med Biol 1991;17(1):7–21.
9. Rychik J, Cohen D, Tran KM, et al. The role of echocardiography in the intraoperative management of the fetus undergoing myelomeningocele repair. Fetal Diagn Ther 2015;37(3):1–7.
10. Boat A, Mahmoud M, Michelfelder EC, et al. Supplementing desflurane with intravenous anesthesia reduces fetal cardiac dysfunction during open fetal surgery. Paediatr Anaesth 2010;20(8):748–56.
11. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation 2006;114 (17):1873–82.
12. Zuckerman H, Shalev E. Fetal and neonatal effects of indomethacin used as a tocolytic agent. Am J Obstet Gynecol 1985;153(6):712–3.

13. Sharpe GL, Larsson KS. Studies on closure of the ductus arteriosus. X In vivo effect of prostaglandin. Prostaglandins 1975;9(5):703–19.

14. Levy R, Matitiau A, Ben Arie A, *et al.* Indomethacin and corticosteroids: An additive constrictive effect on the fetal ductus arteriosus. Am J Perinatol 1999;16(8):379–83.

15. Moise KJ Jr, Huhta JC, Sharif DS, *et al.* Indomethacin in the treatment of premature labor. Effects on the fetal ductus arteriosus. N Engl J Med 1988;319(6):327–31.

16. Williams GD, Jones TK, Hanson KA, *et al.* The hemodynamic effects of propofol in children with congenital heart disease. Anesth Analg 1999;89(6):1411–6.

17. Masjedi M, Zand F, Kazemi AP, *et al.* Prophylactic effect of ephedrine to reduce hemodynamic changes associated with anesthesia induction with propofol and remifentanil. J Anaesthesiol Clin Pharmacol 2014;30(2):217–21.

18. Komatsu R, Turan AM, Orhan-Sungur M, *et al.* Remifentanil for general anaesthesia: A systematic review. Anaesthesia 2007;62(12):1266–80.

19. Smith GC. The pharmacology of the ductus arteriosus. Pharmacol Rev 1998;50(1):35–58.

20. Ngamprasertwong P, Michelfelder EC, Arbabi S, *et al.* Anesthetic techniques for fetal surgery: Effects of maternal anesthesia on intraoperative fetal outcomes in a sheep model. Anesthesiology 2013;118(4):796–808.

21. Griffin MJ, Breen PM, O'Connor JJ, *et al.* Desflurane, compared to halothane, augments phenylephrine-induced contraction in isolated rat aorta smooth muscle. Can J Anaesth 2001;48(4):361–8.