Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Comparison of terbutaline and atosiban as tocolytic agents in intrauterine repair of myelomeningocele: a retrospective cohort study

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Received 30 June 2023; accepted 4 March 2024
Available online 22 March 2024

KEYWORDS
Atosiban;
Perinatology;
Myelomeningocele;
Terbutaline;
Tocolysis

Abstract
Background: Myelomeningocele (MMC) is a neural tube defect disease. Antenatal repair of fetal MMC is an alternative to postnatal repair. Many agents can be used as tocolytics during the in utero fetal repair such as β2-agonists and oxytocin receptor antagonists, with possible maternal and fetal repercussions. This study aims to compare maternal arterial blood gas analysis between terbutaline or atosiban, as tocolytic agents, during intrauterine MMC repair.
Methods: Retrospective cohort study. Patients were divided into two groups depending on the main tocolytic agent used during intrauterine MMC repair: atosiban (16) or terbutaline (9). Maternal arterial blood gas samples were analyzed on three moments: post induction (baseline, before the start of tocolysis), before extubation, and two hours after the end of the surgery.
Results: Twenty-five patients were included and assessed. Before extubation, the terbutaline group showed lower arterial pH (7.347 ± 0.05 vs. 7.396 ± 0.02 for atosiban, $p = 0.006$) and higher arterial lactate (28.33 ± 12.76 mg.dL^{-1} vs. 13.06 ± 6.35 mg.dL^{-1}, for atosiban, $p = 0.001$) levels.
Conclusions: Patients who received terbutaline had more acidosis and higher levels of lactate, compared to those who received atosiban, during intrauterine fetal MMC repair.

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https://doi.org/10.1016/j.bjane.2024.844495

Introduction

Myelomeningocele (MMC) is a neural tube defect disease, and this malformation affects approximately 3.4 pregnancies per 10,000 in the USA.[1] The surgical repair can be performed with an antenatal intrauterine approach or on the first days after childbirth. Intrauterine surgery reduces the exposure of fetal neural tissues to the intrauterine environment, which potentially can decrease the incidence and the intensity of neurological deficits.[2] In 2011, the MOMS trial (Management of Myelomeningocele Study) showed better neurological outcomes for children undergoing an antenatal repair compared to postnatal treatment. However, the study also showed an increased risk of premature labor and maternal hemorrhage during delivery.[3]

One of the most important perioperative goals in intrauterine MMC repair is the avoidance of uterine contractions and placental abruption. Uterine relaxation can be achieved by using tocolytic agents. Many agents can be used such as magnesium sulfate, calcium channel blockers (nifedipine), non-steroidal anti-inflammatory drugs (indomethacin), β2-agonists (terbutaline) and oxytocin receptor antagonists (atosiban),[4] and the choice is based on subjective criteria like institutional protocols, availability, costs and physicians' preference.

Terbutaline is a β2-agonist widely used as a tocolytic drug for preterm labor[5] and is associated with tachycardia, arrythmias, hyperglycemia, hypokalemia, and hypocalcemia.[6] Lactic acidosis and hyperlactatemia have also been associated with β2-agonists even in the absence of hypoperfusion or shock.[7] Atosiban is an oxytocin and vasopressin receptor antagonist as effective as β2-agonists,[8] with a higher uterine specificity and less systemic side effects.[9] Despite the higher cost, UK's Royal College of Obstetricians and Gynaecologists (RCOG) recommends oxytocin antagonists as one of the first choices for preterm labor management.[10] There are some studies comparing betamimetics and atosiban for preterm labor, but there is no study comparing them for in utero MMC repair. We hypothesized that terbutaline is associated with more side effects than atosiban, especially lactic acidosis and hyperlactatemia.

The primary objective of this study was to evaluate maternal arterial blood gas differences between terbutaline or atosiban use as the main tocolytic agent during intrauterine MMC repair.

Methods

This was a retrospective cohort study. Patients submitted to intrauterine fetal MMC surgical repair in a low-income country tertiary care obstetrics center (Obstetric Clinic of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo), from November of 2017 to January of 2020, were included. The study was approved by the Ethics in Research Committee of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAAE: 03681918.2.0000.0068, n° 3.077.257, December 12, 2018; Chairperson Dr. Alfredo Jose Mansur) and is registered at ClinicalTrials.gov (NCT04468568).

Patients were candidates and underwent the surgical procedure when they fulfilled the following criteria: single pregnancy of fetus with MMC, older than 18 years of age, normal karyotype fetuses, with gestational age between 19 and 26 weeks and with American Society of Anesthesiologists (ASA) physical status equal to II. The patients who were submitted to an open intrauterine fetal MMC surgical repair under the institutional standard perioperative management and had arterial blood gas analysis done for the three aimed timepoints were included in the study. Patients who had undergone the fetal MMC repair surgery but did not receive the perioperative institutional standard of care or did not have arterial blood gas analysis done for all three aimed timepoints were not included. The exclusion criteria were patient's decision to withdraw from the study or who would not wish to participate and, therefore, would not sign the consent form. This was a retrospective cohort study (patients were included after their exposure to a factor, and the outcome happened after the exposure, however the data collection was performed retrospectively). The patients were contacted and asked about their agreement to participate in the study when they returned to the hospital to deliver their babies (weeks after the intrauterine fetal MMC repair surgery), or when they should be returning for the delivery (by phone, in case of fetal demise). Consent was obtained, authorizing the research team to gather the data from patient`s charts and data base.

Patients were organized into two groups, depending on which tocolytic agent was used as first line during the surgical procedure: Terbutaline Group (Terbutaline: 2.5 mg in 500 mL of normal saline, as intravenous [IV] infusion, at a rate of 150 mcg.h^{-1} for 24 hours) or Atosiban Group (atosiban: IV loading dose of 6.75 mg and IV maintenance of 300 mcg.min^{-1} for the first 3 hours, followed by an IV infusion of 100 mcg.min^{-1} for 21 hours). The tocolytic agent was initiated 15–30 minutes before starting the surgical incision.

The standardized perioperative management for all open fetal MMC repair surgeries was performed according to institutional protocol and based on previous studies.[11] With the exception of the main tocolytic agent, all perioperative care was the same for all patients, with no modifications. Terbutaline or atosiban were part of the protocol, and the choice for one of them was based on availability on the day of the procedure.

Patients were previously consulted for a pre-anesthesia assessment by an anesthesiologist, in the ward. The anesthetic technique was a combination of general anesthesia and epidural anesthesia. Initially, patients were monitored with standard noninvasive monitors (ECG, pulse oximetry and noninvasive blood pressure). Two large bore peripheral IV catheters were inserted (14–18G) under local anesthesia, followed by administration of IV metoclopramide 10 mg and ranitidine 50 mg for aspiration prophylaxis. A thoracic epidural catheter (T11–T12, T12–L1 or L1–L2 level) was placed under mild sedation (fentanyl 50–100 mcg), in the sitting position, followed by epidural injection of fentanyl 100 mcg. Patients were laid on supine position with left uterine displacement with a wedge and had Bispectral Index (BIS) and the neuromuscular block monitor installed. They were preoxygenated for 5–7 minutes, induced with IV fentanyl 4–6

mcg.kg^{-1}, lidocaine 1.5 mg.kg^{-1}, propofol 1−2 mg.kg^{-1} and rocuronium 1.2 mg.kg^{-1} and intubated in a rapid sequence intubation (RSI) with endotracheal tube size 6.5−7.0. The target for $EtCO_2$ was in a range of 28−30 mmHg and FiO_2 > 50%. Monitorization was completed with esophageal temperature probe, bladder catheter and invasive blood pressure monitoring through a radial artery catheter. Fifteen to thirty minutes before the skin incision, patients received antibiotic prophylaxis with cefazolin 2g IV and the first line tocolytic was initiated (terbutaline or atosiban). General anesthesia was maintained with sevoflurane at 1 MAC and increased to 2−3 MAC for tocolysis supplementation when the procedure started. Bolus of IV nitroglycerine (100 mcg) was given in case of insufficient tocolysis.

Fetal monitoring was performed by the obstetrics team through echocardiography and fetal heart rate vigilance. Fetal anesthesia was supplemented by intramuscular (IM) injection of fentanyl 10−20 mcg.kg^{-1} and pancuronium 0.1 −0.3 mg.kg^{-1} (fetal weight based), if needed, although this was not required for any of the cases.

Maternal systolic blood pressure was maintained at the patient's baseline levels, avoiding decreases of more than 10% of the baseline for systolic blood pressure. Metaraminol was used as vasopressor in a continuous infusion (2.5−10 mg.h^{-1}) or intermittent bolus (200 mcg) regimen.[12,13] A restrictive fluid management strategy was adopted to avoid postoperative pulmonary edema, aiming a total perioperative fluid intake of 500−2000 mL. Normothermia (36°−37.5°C) was aimed during the entire procedure.

Once the myelomeningocele repair was finished and the uterus was closed, a loading dose of IV magnesium sulfate (5g in 20 minutes) was given, and sevoflurane was decreased to 1 MAC. Magnesium sulfate was maintained for 5 hours in an infusion of 1 g.h^{-1}. Neuromuscular block was reversed with sugammadex, patients received dipyrone 2 g IV, ondansetron 4 mg IV and an epidural dose of morphine 2 mg, for postoperative analgesia. At the Postanesthesia Care Unit (PACU), tocolysis was switched to oral nifedipine 80 mg daily and vaginal progesterone 400 mg daily for long term tocolysis, until the delivery.

Three arterial blood gas samples were routinely collected, as part of the standard of care protocol: after induction and intubation, before starting the tocolytic agent infusion (baseline); at the end of the surgical procedure (before extubation); and at PACU discharge, (typically 2 hours after surgery is finished). Samples were sent immediately, in standard proper syringes, to the laboratory for processing and results (ABL800, Radiometer).

All patients had their medical records assessed for demographic characteristics (age, Body Mass Index − BMI, gestational age), primary outcomes (pH and lactate measures) and secondary outcomes (pCO_2, bicarbonate and Base Excess [BE] levels, total fluid intake, estimated blood loss and vasopressor consumption as surrogate variables for intraoperative hemodynamic instability and poor peripheral tissue perfusion). The patients were also analyzed for their delivery related outcomes: preterm labor and premature rupture of membranes incidence, gestational age, newborn weight, newborn umbilical artery pH, newborn Apgar scores.

The variables were tested for normality (Kolmogorov-Smirnov Test of Normality). Data were expressed as mean ± Standard Deviation (SD) (for normally distributed variables), median (minimum − maximum) (for not normally distributed variables), and as percentages (for categorical variables) and a *p*-value lower than 0.05 was considered significant. Study data were collected and managed using REDCap (Research Eletronic Data Capture)[12] and were analyzed using the Mann-Whitney *U* (for non-parametric continuous variables), Student's *t* (for parametric continuous variables), and Chi-Square test for categorical variables. SPSS Statistics software was used for statistical analysis.

Results

Twenty-five patients were included in the study: 16 in the Atosiban Group and 9 in the Terbutaline Group (Fig. 1).

Baseline maternal demographic data are shown in Table 1 and had no difference between groups.

Maternal arterial blood gas analysis results are shown in Table 2. Baseline values were similar between both groups. The Terbutaline group had lower pH and Base Excess (BE) values at the end of the surgery, and also lower bicarbonate and BE levels at PACU discharge, with higher levels of lactate at the end of the surgery and at PACU discharge.

Table 3 shows that the estimated blood loss, total fluid intake and amount of vasopressor used were similar between the groups.

Table 4 shows the outcomes for the moment of delivery (preterm labor and premature rupture of membranes incidence, gestational age, newborn weight, newborn umbilical artery pH, newborn Apgar scores). One patient from the Terbutaline group was excluded from this analysis, due to the fact that the fetus had a demise during the intrauterine surgery. The groups presented no differences for delivery related outcomes.

Discussion

The aim of this study was to compare maternal arterial blood gas features between two tocolytic agents, during intrauterine fetal MMC surgical repair. Terbutaline is widely used as a tocolytic agent in preterm labor,[5] however it is a unspecific drug for uterine muscle receptors. Hence, it is postulated that the use of terbutaline could be associated with systemic maternal effects such as acidosis and increased arterial lactate levels. The mechanism is not completely clear, but can be due to stimulation of β-adrenergic receptors leading to a variety of metabolic effects such as increased adenylate cyclase activity, lipolysis, free fatty acids and increased glycogenolysis and gluconeogenesis.[7] Atosiban is a selective oxytocin receptor antagonist and seems to have less systemic effects.

Atosiban has less cardiovascular effects when compared to β2-agonist agents.[8,14] A large multicentric randomized trial with 742 patients compared atosiban and β2-agonist agents for preterm labor. Authors found equivalent clinical effectiveness with fewer side effects in the Atosiban Group. They evaluated maternal side effects such as cardiovascular issues, hypotension, nausea, hyperglycemia, and hypokalemia, as well as fetal outcomes. However, they did not study maternal arterial blood gas changes.[8] In our study, in a fetal surgery situation, findings for lower pH values and higher

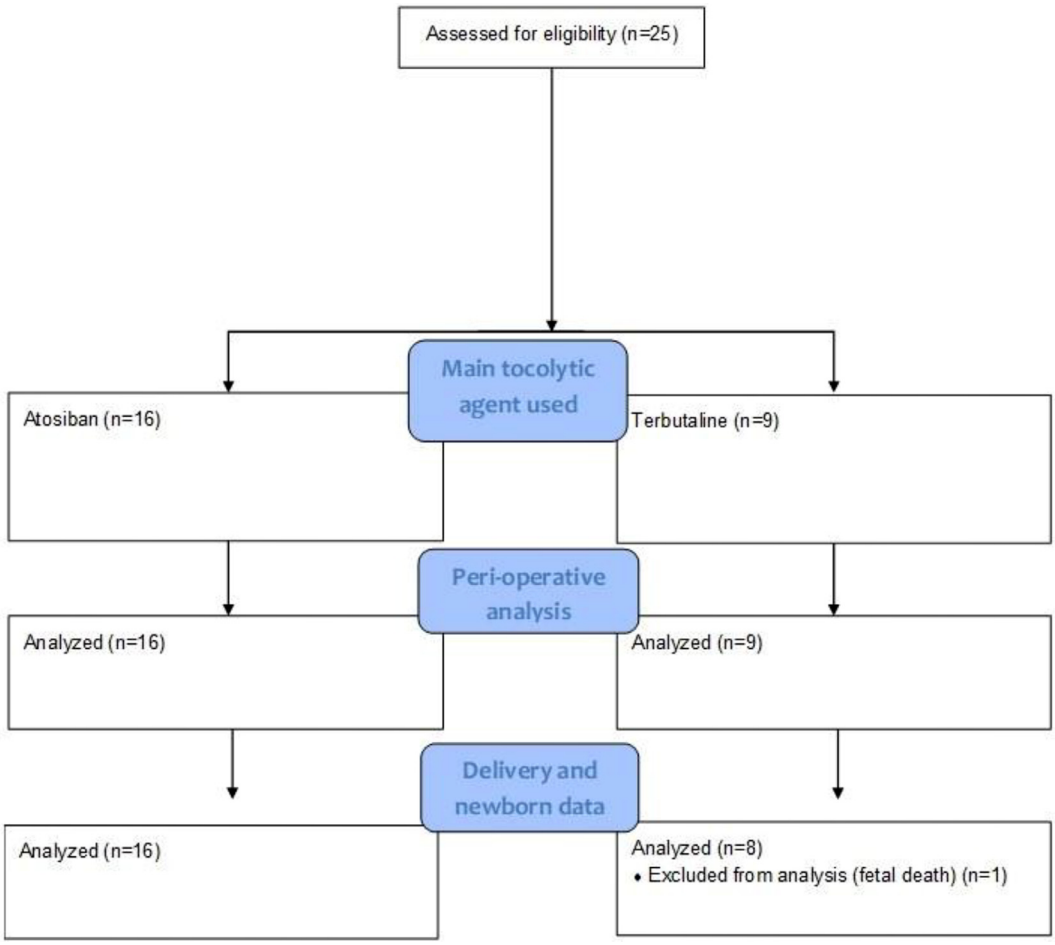

Figure 1 Flow diagram.

lactate levels in maternal arterial blood samples at the end of the surgery, for the patients who received terbutaline, were significant. There was a significant decrease in pH at the end of the surgery, as well as in bicarbonate, BE and pCO_2 values before discharge at the PACU, which can indicate metabolic acidosis and a compensatory respiratory response. Lactate levels were significantly higher after the procedure. Estimated blood loss, fluid intake and amount of vasopressor (surrogate outcomes for tissue hypoperfusion) were also compared between the groups and showed no difference. Manrique et al., in a retrospective cohort using atosiban for tocolysis for spina bifida repair with fetoscopy surgery, found no changes in maternal blood gases even after CO_2 insufflation.[15] Based on their results, the blood gas differences found in our study might have been due to a non-specific activation of adrenergic receptors by terbutaline.[16]

Some degree of adrenergic stimulation can be found in neonates of mothers who received β2-agonist agents.[14] However, a systematic review with the most used drugs for acute tocolysis did not show differences in efficacy to inhibit uterine contractions. On the other hand, they also found no differences for neonatal outcomes, which the authors attributed to small sample sizes and heterogeneity of included studies.[17] In our results, delivery and neonatal outcomes were statistically similar between groups. However, one critical event of fetal death during the immediate

Table 1 Maternal baseline demographic data.

	Groups		
Variables	Atosiban (n = 16)	Terbutaline (n = 9)	*p*
Maternal age (years)	29.06 ± 6.83	27.11 ± 5.58	0.473
Weight (kg)	69.31 ± 12.89	76.11 ± 10.79	0.194
Height (cm)	158.81 ± 6.59	163.89 ± 5.44	0.062
BMI ($kg.m^{-2}$)	27.30 ± 3.99	28.36 ± 4.09	0.529
Gestational age (weeks)	24.37 ± 1.08	24.44 ± 1.67	0.900
Surgery length (minutes)	244.37 ± 41.46	247.77 ± 41.46	0.845

Student's *t*-test. Data is shown as Mean ± SD.

Table 2 Maternal arterial blood gas analysis.

Variables	Groups		p[a]
	Atosiban (n = 16)	Terbutaline (n = 9)	
pH			
Baseline	7.395 ± 0.03	7.371 ± 0.04	0.110
Before extubation	7.396 ± 0.02	7.347 ± 0.05	**0.003**
PACU	7.382 ± 0.03	7.352 ± 0.04	**0.029**
pCO_2 (mmHg)			
Baseline	33.73 ± 1.83	35.73 ± 2.78	0.051
Before extubation	33.03 ± 2.51	35.33 ± 5.70	0.194
PACU	33.92 ± 3.10	29.20 ± 4.99	**0.015**
Bicarbonate ($mEq.L^{-1}$)			
Baseline	20.30 ± 0.93	20.22 ± 1.12	0.899
Before extubation	19.87 ± 1.29	18.84 ± 2.32	0.165
PACU	19.72 ± 1.12	15.87 ± 3.03	**0.0001**
Base excess			
Baseline	−3.40 ± 1.15	−3.87 ± 1.76	0.426
Before extubation	−3.73 ± 1.28	−5.66 ± 2.40	**0.014**
PACU	−4.14 ± 1.04	−8.12 ± 3.37	**0.0002**
Lactate ($mg.dL^{-1}$)			
Baseline	12.66 ± 3.57	17.55 ± 9.72	0.098
Before extubation	13.06 ± 6.35	28.33 ± 12.76	**0.0004**
PACU	13.73 ± 4.96	44.66 ± 18.9	**< 0.00001**

[a] Student *t*-test.
Data is shown as Mean ± SD.

postoperative period was described with one of the patients who received terbutaline. Despite this event not representing statistical significance for our results, a fetal demise is clinically relevant[3] and further studies are required to elucidate if β2-agonist agents can be directly related to unfavorable neonatal events.

Other tocolytic agents are available for use and their indication is based on maternal side effects, fetal effects, safety, costs, and approval by regulatory agencies. Atosiban use is not allowed by regulatory agencies in North America. β2-agonists and nifedipine are considered safe for the fetus but have maternal side effects.[14] There is no intravenous presentation for nifedipine in some countries which limits its intraoperative use. Magnesium sulfate, an alternative agent, is associated with tachyarrhythmias, drug interactions, pulmonary edema, and prolonged neuromuscular block. A prospective cohort study with 30 fetal procedures has shown more complications related to magnesium compared to atosiban and the authors suggest using atosiban as the drug of choice for open fetal surgeries.[18] Indomethacin is associated with constriction of the ductus arteriosus and there is evidence of that effect on fetuses during the intraoperative period among mothers who received preoperative indomethacin.[19] However, Novoa y Novoa et al., in a systematic review, concluded that information about the best regimen for tocolysis for open repair of myelomeningocele is still insufficient given the heterogeneity, lack of consistent design and multiple confounders of the studies.[20]

The current study has considerable limitations. It is a non-randomized study, and the anesthesia care provider was not blinded to the tocolytic agent used. There were no criteria for the choice of tocolytic agents, other than availability: when atosiban was available at the hospital pharmacy, it was used. When it was not available due to its high cost, terbutaline was used. This was the consequence of the irregular funding conditions for the hospital (a public institution). The retrospective nature of this study can justify some caveats about its results. Given the surgical procedure has its perioperative management strictly standardized by an institutional protocol, and the review of the medical records demonstrated that no deviations of the protocol were made, it is fair to assume that the only difference between the groups was the tocolytic agent used. The small number of

Table 3 Fluid and hemodynamic management.

	Groups		*p*[a]
	Atosiban (n = 16)	Terbutaline (n = 9)	
Crystalloids (mL)	1321.87 ± 536	1655.55 ± 655	0.181
Estimated blood loss (mL)	987.5 ± 471.2	755.4 ± 462.8	0.246
Metaraminol consumption (mg)	21.58 ± 6.26	19.17 ± 9.12	0.441

[a] Student *t*-test.
Data is shown as Mean ± SD.

Table 4 Delivery and newborn data.

	Groups		*p*
	Atosiban (n = 16)	Terbutaline (n = 8)	
Newborn weight (g)	2207.50 ± 735.92	2102.37 ± 637.36	0.739[a]
Newborn umbilical artery pH	7.222 ± 0.03	7.244 ± 0.07	0.477[a]
Gestational age (weeks)	33.9 ± 4.3	33.2 ± 2.63	0.722[a]
Apgar score on 1st minute	8 (4 − 9)	8 (8 − 9)	0.101[b]
Apgar score on 5th minute	9 (6 − 10)	9 (4 − 10)	0.631[b]
Apgar score on 10th minute	9.14 ± 0.86	8.75 ± 1.03	0.350[a]
Preterm labor	10 (62.50%)	6 (75.00%)	0.540[c]
Premature rupture of membranes	5 (31.25%)	4 (50.00%)	0.371[c]

[a] Student's *t*-test.
[b] Mann-Whitney test.
[c] Chi-square test.
Data is shown as Mean ± SD, Median (minimum − maximum) or n (%).

patients is also a considerable limitation. However, fetal MMC intrauterine repair is not a frequent performed procedure. Its sporadic nature creates difficulty to achieve more cases for a much larger study. A retrospective cohort carried out in Spain enrolled 29 patients between 2011 and 2016, seven for open surgery and 22 for fetoscopy surgery.[15] Even with the small sample size, a difference on the outcomes was observed.

The first case of antenatal intrauterine open surgery for fetal myelomeningocele was performed at our hospital in 2015[21] and atosiban use was limited due to its high cost. After the execution of this study and the critical event that happened in one of the cases, the institutional protocol for the in utero MMC repair surgery was revised. As atosiban had shown a safer profile, terbutaline was excluded from the standard of care for this specific procedure.

Conclusions

In conclusion, patients undergoing antenatal intrauterine fetal MMC repair surgery who received terbutaline as the main tocolytic agent had higher levels of arterial lactate and lower levels of arterial pH at the end of the procedure when compared to patients who received atosiban, with no differences for delivery and neonatal outcomes. The lactic acidosis founded seemed to be partially compensated by a respiratory alkalosis shown by a pCO_2 decrease. The literature is heterogeneous about tocolytics and outcomes for fetal surgery and their use is often based on the experience and previous knowledge from preterm labor tocolysis, and this study, even with a small sample size and its limitations, can be a starting point for more studies. Larger randomized clinical trials comparing the perioperative maternal and fetal impacts of terbutaline, atosiban and other tocolytic agents in fetal surgeries are necessary to have more evidence about safety and efficacy of each drug.

What is known

Fetal Myelomeningocele (MMC) antenatal repair is a potentially preferable alternative when compared to postnatal repair.

One of the most important perioperative goals in intrauterine MMC repair is the avoidance of uterine contractions and placental abruption, by using tocolytic agents.

What is new

This study compares maternal arterial blood gas analysis between terbutaline and atosiban when they are used as tocolytic agents during intrauterine myelomeningocele surgical repair.

Patients who received terbutaline had more acidosis and higher levels of arterial lactate during in uterus fetal MMC surgical repair.

Conflicts of competing interest

The authors declare no conflicts of interest.

Funding

The authors have no sources of funding to declare for this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2024.844495.

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