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ORIGINAL ARTICLE

The impact of gestational age and fetal weight on the risk of failure of spinal anesthesia for cesarean delivery

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Short title: Spinal dosing and preterm cesarean delivery

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ABSTRACT

Background: There are limited data about spinal dosing for cesarean delivery in preterm parturients. We investigated the hypothesis that preterm gestation is associated with an increased incidence of inadequate spinal anesthesia for cesarean delivery compared with term gestation.

Methods: We searched our perioperative database for women who underwent cesarean delivery under spinal or combined spinal-epidural anesthesia with hyperbaric bupivacaine ≥10.5 mg. The primary outcome was the incidence of inadequate surgical anesthesia needing conversion to general anesthesia or repetition or supplementation of the block. We divided patients into four categories: <28, 28 to <32, 32 to <37 and ≥37 weeks of gestation. The chi-square test was used to compare failure rates and a multivariable regression analysis was performed to investigate potential confounders of the relationship between gestational age and failure.

Results: A total of 5015 patients (3387 term and 1628 preterm) were included. There were 278 failures (5.5%). The incidence of failure was higher in preterm versus term patients (6.4% vs. 5.1%, P=0.02). Failure rates were 10.8%, 7.7 %, 5.3 % and 5 % for <28, 28 to <32, 32 to <37 and ≥37 weeks of gestation, respectively. In the multivariable model, low birth weight (P<0.0001), gestational age (P=0.03), ethnicity (P=0.02) and use of combined spinal-epidural anesthesia (P<0.0001) were significantly associated with failure.

Conclusions: At standard spinal doses of hyperbaric bupivacaine used in our practice (≥10.5 mg), there were higher odds of inadequate surgical anesthesia in preterm parturients. When adjusting for potential confounders, low birth weight was the main factor associated with failure.

Keywords: Anesthesia, Spinal, Combined spinal-epidural, Cesarean delivery, Gestation age, Failed anesthesia

Introduction

Pregnancy is associated with increased spread of spinal anesthesia.[1] Pregnant women at term require a smaller dose of intrathecal local anesthetic than non-pregnant women to produce the same level of spinal block.[2-4] The physiologic changes of pregnancy such as changes in spinal curvature,[5] decreased cerebrospinal fluid (CSF) volume caused by the distention of epidural veins as a result of inferior vena cava obstruction by the gravid uterus,[6] and enhanced sensitivity of neural tissue to local anesthetics may play a role in these observations.[7, 8] While many studies have examined the difference between pregnant and non-pregnant women in the relative spread of spinal block for surgical anesthesia,[2-4] there are limited data reviewing adequate spinal dosing for preterm (<37 weeks of gestation) versus term (≥37 weeks of gestation) patients. A previous study[9] demonstrated that hyperbaric bupivacaine 11.25 mg provided adequate spinal block to T4 for women at term but failed to provide the same level in 84% of preterm women undergoing cesarean delivery. Our clinical observation also suggests that our standard doses of intrathecal bupivacaine might fail to achieve adequate sensory block for surgery in some preterm patients. However, altering the dose of intrathecal bupivacaine in preterm parturients is not common practice. Therefore, we performed this retrospective database analysis to investigate the hypothesis that preterm gestation is associated with an increased risk of failed spinal anesthetic for cesarean delivery compared with term gestation.

Methods

After IRB approval, we retrospectively retrieved data from the Duke Perioperative Anesthesia Database for women who underwent cesarean delivery under spinal or combined spinal-epidural (CSE) anesthesia from 2003–2012. Duke University Medical Center is a university teaching hospital with a delivery rate of approximately 3500 deliveries/year. A dedicated group of nine obstetric anesthesiologists provides round-the-clock coverage for the labor and delivery ward. First and second year anesthesia residents and a daytime certified registered nurse anesthetist (CRNA) staff the labor and delivery ward. Third-year residents also have an elective obstetric anesthesia rotation and when present provide daytime coverage.

We searched for patients who received our standard doses of local anesthetic (≥10.5 mg of 0.75% wt/vol hyperbaric bupivacaine with fentanyl 15 µg and morphine 0.1–0.2 mg) and were 152–183 cm in height. Inadequate surgical anesthesia after initial spinal dose (failure) was the primary outcome. Failure was defined as the need to repeat the spinal technique to obtain adequate block height (T6–T2), convert to general anesthesia secondary to pain within 60 min of skin incision, augment the initial block with epidural lidocaine before or within 30 min of skin incision (if the CSE technique was used), or supplement by inhalation or intravenously with at least two of the following within 60 min of skin incision: nitrous oxide, fentanyl (>100 µg), ketamine, midazolam or propofol. Patients who received epidural labor analgesia before cesarean delivery were excluded. Anesthetic records were reviewed to confirm reasons for failure and its management. We divided patients into four categories according to gestational age: <28 weeks (extremely preterm), 28 to <32 (very preterm), 32 to <37 weeks (moderate to late preterm), and ≥37 weeks (term).[10] We also collected information about the highest recorded block level. This is recorded in our electronic medical record as follows: T10–T7, T6–T2 and ≥T1.

Statistical analysis

The Cochrane-Armitage (CA) trend test, chi-square test and Kruskal-Wallis test were used to compare patient characteristics and intraoperative variables between those with failed blocks versus those with successful blocks, and between the different gestational age groups. We performed a multivariable logistic regression analysis to account for potential confounders of the relationship between gestational age and failed blocks. We considered the following potential confounders: age, body mass index (BMI), ethnicity, low birth weight (<2500 g), priority of cesarean delivery (scheduled or non-scheduled), block type (spinal or CSE), provider performing the block (resident, fellow, CRNA or attending) and hyperbaric bupivacaine dose. Before analysis, we evaluated the relationship between the empirical logit of failure on the deciles of the continuous covariates to determine if the relationship was non-linear. We identified a non-linear relationship for gestational age, and we used our defined four-category gestational age variable in the multivariable model. For birth weight, we found evidence of a threshold effect near the standard definition of low birth weight (<2500 g) with those below the threshold having an elevated empirical odds of failure compared with those above the threshold; hence we utilized a binary birth weight covariate in our models. None of the other continuous variables demonstrated departures from linearity and were used as continuous covariates in the multivariable models. Model fit of the multivariable logistic regression model was assessed via the Hosmer-Lemeshow goodness of fit test, and the C-index. We also performed three sensitivity analyses: one excluding cases in which failure was identified by augmentation of the initial block with epidural lidocaine when a CSE technique was used; a second restricting the analysis to cases where the neuraxial block was spinal; and a third including the experience of the provider performing the block as an additional potential confounder. Analysis was performed in SAS version 9.4 (SAS Inc., Cary, NC, USA) and statistical significance was assessed at $P<0.05$.

Results

A total of 5015 patients (3387 term and 1628 preterm) fulfilled the inclusion criteria and were included in the analysis. The most common dose of hyperbaric bupivacaine administered was 12 mg (61.7%), followed by 11.25 mg (23.0%), 10.5 mg (9.1%), 13.5 mg (3.8%), 12.75 mg (1.9%) and 15 mg (0.5 %). Overall, there were 278 failed anesthetics (5.5%). Spinal anesthesia was used in 80.7 % of cases [238 (87.3%), 320 (88.9%), 799 (82.7%) and 2698 (81.1%) for patients at <28, 28 to <32, 32 to <37 and ≥37 weeks of gestation, respectively] and CSE was used in 19.3 % of cases. There was a trend for greater use of CSE as gestational age increased (*P*<0.0001). Doses of intrathecal bupivacaine were larger in patients who received CSE compared with those who received a single-shot spinal anesthetic (*P*<0.0001). Fifty-four percent of cesarean deliveries were scheduled and 46 % unscheduled. There was a decreasing trend in unscheduled cesarean deliveries with increasing gestational age [252 (90.7%), 304 (83.3%), 680 (69.3%) and 1047 (30.9%) for patients < 28, 28 to <32, 32 to <37 and ≥37 weeks of gestation respectively, CA trend *P*<0.0001].

Patient demographics and intraoperative characteristics according to block failure are shown in Table 1. Augmentation of CSE with epidural lidocaine accounted for 130 (46.8%) of failures, followed by supplementation of spinal anesthetic with intravenous adjuvants with or without nitrous oxide (*n*=50, 18.0%), conversion to general anesthesia (*n*=41, 14.8%), repetition of spinal anesthesia (*n*=41, 14.8%), and supplementation of CSE with epidural lidocaine and intravenous adjuvants or nitrous oxide (*n*=16, 5.8%). The most common reasons for failure according to gestational age, type of block and birth weight are shown in Table 2.

We found a decreasing trend of failure with increasing gestational age (CA trend *P*<0.0001). Overall, the failure rate was greater in preterm versus to term patients (6.4% vs. 5.1%, *P*=0.01). The failure rates were 10.8%, 7.7%, 5.3% and 5% for patients <28, 28 to <32, 32 to <37 and ≥37 weeks of gestation respectively (*P*=0.0002). After Bonferroni adjustment for multiple comparisons, the failure rate was lower in women at 32 to <37 weeks and ≥37 weeks gestation compared with those <28 weeks of gestation (*P*=0.004 and *P*=0.0003, respectively), but there was no difference in failure rates for other pairwise gestational age comparisons. In the multivariable model (C-Index 0.78, HL GOF *P* value =0.2, Table 3), low birth weight (*P*<0.0001), gestational age (*P*=0.03), use of CSE (*P*<0.0001) and ethnicity (*P*=0.02) were significantly associated with failure. There was a moderate correlation between the continuous measures of gestational age and low birth weight (Spearman's rho = 0.45), but there was no evidence of collinearity or interaction between the variables in the model. An analysis replacing BMI with height and weight in the final model identified the same significant factors and found no significant association between patient height or weight and the rate of failure (*P*=0.19 and *P*=0.63, respectively).

In the sensitivity analysis, when cases where the epidural catheter was topped-up with lidocaine were excluded, the failure rates were 8.8%, 5.6%, 3.0% and 2.3% for patients <28, 28 to <32, 32 to <37 and ≥37 weeks of gestation, respectively (CA trend *P*<0.0001). In this analysis, after Bonferroni adjustment for multiple comparisons, patients at 32 to <37 and ≥37 weeks of gestation had lower failure rates than patients at <28 weeks of gestation (*P*=0.0002 and *P*<0.0001, respectively). There was also a difference in the failure rate between patients at 28 to <32 and ≥37 weeks of gestation (*P*=0.0011). In the multivariable logistic regression analysis (C-Index 0.67, HL GOF *P* value =0.37, Table 3), only low birth weight and use of CSE (both *P*<0.0001) were significantly associated with increased odds of failure, whereas gestational age (*P*=0.06) and ethnicity (*P*=0.73) were no longer significant. Similar results were obtained when the analysis was restricted to cases performed under spinal anesthesia (model not reported).

Data for the experience of the provider performing the block were missing in 17% of included cases; therefore this variable was not included in the main model, but we performed an additional sensitivity analysis including this variable. In the multivariable model including provider type (C-Index 0.785, HL GOF *P* value = 0.14), low birth weight (*P*<0.0001), block type (*P* <0.0001), ethnicity (*P* =0.03) and provider level (*P* <0.004), were significantly associated with odds of failure, but gestational age was not (*P*=0.17). Pairwise comparisons showed lower failure rate with CRNAs compared to residents (OR 0.42, 95 % CI 0.25 to 0.69, *P*=0.0008), but there was no statistically significant difference for the other pairwise comparisons.

Discussion

In this retrospective database analysis, at the standard spinal doses of hyperbaric bupivacaine used in our practice, there was a higher likelihood of inadequate surgical anesthesia during cesarean delivery for preterm compared with term parturients. Extremely preterm patients (gestational age <28 weeks) had the highest incidence of failure. However, when adjusting for potential confounders, low birth weight had a larger effect size than gestational age in the main model, and its significant association with failure was consistent in all sensitivity analyses, whereas the association with gestational age was no longer statistically significant in the sensitivity analyses performed.

A previous study of women undergoing cesarean delivery under CSE anesthesia by James et al.,[9] reported that a dose of 0.5% hyperbaric bupivacaine 11.25 mg provided an anesthetic block to T4 in 100% of term women, but failed to provide a T4 level in 84% of preterm women. The latter group required supplemental epidural local anesthetic. Preterm women who developed adequate sensory block were at the upper end of the preterm gestational age limit.[9] The authors also found a strong linear correlation between increasing gestational age and block height.

Previous studies [2-4] reported that pregnant women require less local anesthetic than non-pregnant women and suggested that this is related to the physiological and hormonal changes in pregnancy. Uterine enlargement and inferior vena cava obstruction result in distention of the epidural veins leading to a decrease in volume of both subarachnoid and epidural spaces.[6] The enlargement of the epidural veins also may lead to compression of the theca displacing CSF from the subarachnoid space.[6] It has been proposed that these changes alter the distribution of drugs injected into the CSF and subarachnoid dose requirements.[11] Increased prostaglandin concentrations in both blood and CSF during pregnancy may also alter susceptibility of nerves to local anesthetics and may contribute to the reduction of local anesthetic requirement seen in pregnancy.[12] Changes in spinal curvature during pregnancy such as the caudal shift of the apex of lumbar lordosis and reduction of the typical thoracic kyphosis may influence the spread of local anesthetic solutions, leading to higher sensory level in the pregnant patient.[5] Preterm women have a smaller uterus than women at term and presumably have less vena caval compression, less engorgement of epidural veins and therefore larger epidural and subarachnoid space volumes, which could serve as an explanation for our findings. In fact, when we controlled for potential confounders in our multivariable model, low birth weight was significantly associated with increased odds of inadequate blocks, and this was consistent in all the three sensitivity analyses performed, whereas gestational age was associated with a smaller effect size compared with low birth weight in the main model and was no longer significantly associated with failure in the sensitivity analyses. While it may be assumed that the global increase in intra-abdominal pressure is a potential mechanism for increased intrathecal drug spread during pregnancy, a recent study challenges this theory.[13] In that study, intra-abdominal pressure was measured via a bladder catheter after establishing a T4 sensory block and at the end of the surgery in parturients having elective cesarean delivery with single-shot spinal anesthesia; the authors found no association between maximum sensory block level and pre-incisional intra-abdominal pressure.[13]

We found that the use of CSE anesthesia was associated with an increased risk of failure compared with the single-shot spinal technique, despite the use of larger intrathecal doses with CSE. This effect was still present in the sensitivity analysis when cases that were classified as failure based on epidural administration of lidocaine were excluded. The reason for this is unclear, but might be related to a delay in moving the patient from the sitting to the supine position when using hyperbaric bupivacaine. While previous studies suggested that there is no difference in block level,[14] or even higher levels with CSE compared with single-shot spinal anesthesia,[15] in those studies blocks were performed with patients in the lateral position, whereas the sitting position is routinely used in our practice. However, other factors must have contributed to the failures since topping up the epidural catheter with lidocaine in some of those cases was not successful in achieving adequate anesthesia and other interventions were needed. We also found that ethnicity was significantly associated with failure in our multivariable model. In a study examining mode of anesthesia for preterm cesarean delivery, Butwick et al. reported that non-Caucasian race was associated with greater use of general anesthesia than neuraxial anesthesia,[16] although they but did not examine the failure rate of neuraxial anesthesia by ethnicity. The reason for this association of ethnicity with failure in our study is unclear, but ethnic differences in neuraxial anatomy have been previously reported[17] and might be a contributing factor.

There are some limitations to our study. It was a single center retrospective study. Because it was a retrospective analysis, we cannot ascertain from the patient charts the reasons for augmentation with epidural lidocaine when a CSE technique was used. In some cases the lidocaine bolus was administered before or shortly after the onset of surgery. While we assumed this was because of an inadequate block, the exact reasons are not clear. It is also possible that in some of these cases, a lower dose of hyperbaric bupivacaine was used with the intention to augment the block with epidural lidocaine if needed. We therefore performed a sensitivity analysis excluding cases in which failure was assumed based only on topping-up the epidural catheter with lidocaine and this analysis showed comparable results to the main analysis. Similarly, the reason and threshold for administration of supplemental analgesics was not available and could have varied among different providers. We tried to address this limitation by including only patients who received at least two supplemental analgesics intraoperatively. The dose of hyperbaric bupivacaine was not strictly controlled among groups, however 62% of patients received hyperbaric bupivacaine 12 mg. The narrow range of doses, with only 6 % of patients receiving doses higher than 12 mg, might also account for the fact that the dose of local anesthetic was not found to be a factor associated with failure in our analysis. While we collected information on the highest recorded block level, we cannot ascertain that this was the level recorded after the initial failed block or after repeating or supplementing the block. Furthermore, these data were missing in 6 % of cases. While we categorized cases into scheduled and unscheduled, the degree of urgency of unscheduled cases was not included in the analysis. Data about the experience of the provider performing the block were missing in a number of cases, which prevented us from including this variable in the main model. However, the results of the sensitivity analysis including this variable yielded comparable results to the main model.

In conclusion, at standard doses of spinal bupivacaine for cesarean delivery used in our practice, the rate of inadequate spinal block was higher in preterm compared with term patients. Our analysis suggests that low birth weight is the major factor responsible for the increased risk of failure.

Disclosure

This study received no external funding and the authors have no conflicts of interest to declare.

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Table 1 Patient demographics

	No Failure (*n*=4737)	Failure (*n*=278)	*P* value
Age (years)	30 [24–34]	31 [26–35]	0.10
Ethnicity			<0.0001
Caucasian	1976 (41.7%)	110 (39.6%)	
African American	1634 (34.5%)	133 (47.8%)	
Other	1127 (23.8%)	35 (12.6%)	
Body mass index(kg/m^2)	32.0 [27.9–37.2]	32.5 [27.9–40.3]	0.05
Gestational age (weeks)			<0.0001
<28 weeks	249 (5.3%)	30 (10.8%)	
28 to <32 weeks	337 (7.1%)	28 (10.1%)	
32 to <37 weeks	934 (19.7%)	50 (18.0%)	
≥37 weeks	3217 (67.9%)	170 (61.2%)	
Bupivacaine dose(mg)	11.77 ± 0.6	11.84 ± 0.8	0.33
Unscheduled cesarean delivery	2149 (45.4%)	134 (48.2%)	0.37
Birth weight (g)*	3292.5 [2770–3755]	3095 [2315–3515]	<0.0001
Low birth weight (<2500 g)*	851 (18.3%)	87 (32.2%)	<0.0001
Anesthetic method (spinal)	3941 (84.8%)	114 (41.0%)	<0.0001
Highest recorded block level[†]			<0.0001
≥T1	26 (0.6%)	1 (0.4%)	
T6-T2	3922 (88.0%)	183 (76.6%)	
T10-T7	510 (11.4%)	55 (23.0%)	
Provider level[#]			<0.0001
Attending	419 (10.7%)	38 (16.6%)	
Fellow	28 (0.7%)	4 (1.8%)	
Resident	2733 (69.6%)	169 (73.8%)	
CRNA	746 (19.0%)	18 (7.9%)	

Data presented as median [IQR], mean ± SD, or number (%).
*Missing for 95 (1.9%), [†]Missing for 318 (6.3%), [#]Missing for 860 (17%).
CRNA: certified registered nurse anesthetist

Table 2 Distribution of failure by gestational age, type of neuraxial block and birth weight

Management of Failure	**According to gestational age**			
	<28 weeks (*n*=30)	28 to <32 weeks (*n*=28)	32 to <37 weeks (*n*=52)	≥37 weeks (*n*=172)
Block repeated	6 (20.0%)	5 (17.9%)	3 (6.0%)	27 (15.9%)
Converted to GA	7 (23.3%)	6 (21.4%)	12 (24.0%)	16 (9.4%)
Spinal with IV adjuvants/N_2O	8 (26.7%)	8 (28.6%)	11 (22.0%)	23 (13.5%)
CSE with epidural lidocaine and IV adjuvants/ N_2O	3 (10%)	1 (3.6%)	3 (6.0%)	9 (5.3%)
CSE with epidural lidocaine	6 (20.0%)	8 (28.6%)	21 (42.0%)	95 (55.9%)

	According to type of neuraxial block	
	Spinal (*n*=114)	CSE (*n*=164)
Block repeated	35 (30.7%)	6 (3.7%)
Converted to GA	29 (25.4%)	12 (7.3%)
Spinal with IV adjuvants/N_2O	50 (43.9%)	-
CSE with epidural lidocaine and IV adjuvants/ N_2O	-	16 (9.8%)
CSE with epidural lidocaine	-	130 (79.3%)

	According to birth weight	
	Low birth weight (*n*=87)	Normal birth weight (*n*=183)
Block repeated	12 (13.8%)	26 (14.2%)
Converted to GA	23 (26.4%)	17 (9.3%)
Spinal with IV adjuvants/N_2O	22 (25.3%)	27 (14.8%)
CSE with epidural lidocaine and IV adjuvants/ N_2O	5 (5.8%)	11 (6.9%)
CSE with epidural lidocaine	25 (28.7%)	102 (55.7%)

Data are number (%)
GA: general anesthesia; IV: intravenous; N_2O: nitrous oxide; CSE: combined spinal-epidural.

Table 3 Multivariable logistic regression model

Covariable	Odds Ratio (95% CI)	*P* value
Main Model		
Gestational age (weeks, reference group: ≥37 weeks)		0.03
<28 weeks	1.56 (0.89,2.71)	0.12
28 to <32 weeks	0.93 (0.52,1.62)	0.80
32 to <37 weeks	0.71 (0.47, 1.04)	0.08
Age (years)	1.01 (0.99, 1.03)	0.31
Body mass index (kg/m^2)	1.00 (0.98, 1.01)	0.61
Ethnicity (reference group: Caucasian)		0.02
African American	1.08 (0.80, 1.46)	0.61
Other	0.60 (0.40, 0.89)	0.01
Hyperbaric bupivacaine dose (mg)	0.92 (0.75, 1.12)	0.41
Priority: scheduled vs. unscheduled	0.93 (0.69, 1.26)	0.63
Anesthetic technique: CSE vs. spinal	9.36 (7.05, 12.47)	<0.0001
Low birth weight (<2500 g)	2.46 (1.65, 3.64)	<0.0001
Sensitivity analysis excluding cases where failure was accounted for by epidural lidocaine		
Gestational age (weeks, reference group: ≥37 weeks)		0.06
<28 weeks	1.81 (0.92, 3.49)	0.08
28 to <32 weeks	1.06 (0.53, 2.07)	0.86
32 to <37 weeks	0.79 (0.46, 1.31)	0.37
Age (years)	1.01 (0.98, 1.02)	0.59
Body mass index (kg/m^2)	1.00 (0.98, 1.02)	0.78
Ethnicity (reference group: Caucasian)		0.73
African American	0.97 (0.65, 1.44)	0.88
Other	0.82 (0.73, 1.25)	0.43
Hyperbaric bupivacaine dose (mg)	0.92 (0.70, 1.18)	0.51
Priority: scheduled vs. unscheduled	0.93 (0.62, 1.41)	0.74
Anesthetic technique: CSE vs. spinal	2.08 (1.34, 3.16)	0.0008
Low birth weight (<2500 g)	2.97 (1.79, 4.92)	<0.0001
Sensitivity analysis including provider level for subset where data were available		
Gestational age (weeks, reference group: ≥37 weeks)		0.17
<28 weeks	1.18 (0.62, 2.24)	0.62
28 to <32 weeks	0.78 (0.41, 1.49)	0.45
32 to <37 weeks	0.68 (0.44, 1.05)	0.08
Age (years)	1.01 (0.99, 1.04)	0.28
Body mass index (kg/m^2)	1.00 (0.98, 1.02)	0.87
Ethnicity (reference group: Caucasian)		0.03
African American	1.02 (0.73, 1.41)	0.91
Other	0.56 (0.36, 0.89)	0.01
Hyperbaric bupivacaine dose (mg)	0.92 (0.72, 1.16)	0.46
Priority: scheduled vs. unscheduled	1.08 (0.77, 1.52)	0.65
Anesthetic technique: CSE vs. spinal	8.51 (6.22, 11.64)	<0.0001
Low birth weight (<2500 g)	2.53 (1.64, 3.88)	<0.0001
Provider level (reference group: Resident)		0.004

Attending	1.18 (0.79, 1.75)	0.42
Fellow	1.46 (0.46, 4.63)	0.52
CRNA	0.42 (0.25, 0.69)	0.0008

CI: confidence interval; CSE: combined spinal epidural; CRNA: certified registered nurse anesthetist

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Highlights

- We retrospectively reviewed our perioperative cesarean delivery database
- Spinal anesthesia failure rate was higher in preterm versus term patients
- The highest risk of failure at gestational age <28 weeks of gestation
- Low birth weight was the main factor associated with failure