Original Article

Maternal and Neonatal Outcomes Associated with Different Anesthetic Techniques in Cesarean Delivery for Multiple Gestations: A Retrospective Study of 1,057 Patients

Patchareya Nivatpumin MD[1], Tripop Lertbunnaphong MD[2], Wanna Srirojanakul MD[1], Sarasate Eiamtanasate MD, PhD[1], Patcha Papaisarn MD[1], Donpicha Woonprasert MD[1]

[1] Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2] Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: The aim of the present study was to examine maternal and neonatal outcomes of cesarean delivery for multiple gestations using different anesthetic techniques.

Materials and Methods: A retrospective chart review of 1,057 pregnant women with multiple gestations undergoing cesarean delivery in 10-year period (August 2006 to December 2015) was performed. Patient demographic characteristics, choices of anesthesia, intra-operative data and complications were collected. Maternal and neonatal complications were compared between spinal anesthesia [SA] and general anesthesia [GA].

Results: A total of 984 (93.1%) patients received SA, whereas 73 (6.9%) received GA. The incidence of intra-operative maternal hypotension and the proportion of patients requiring vasopressors were higher in the SA than GA group ($p<0.001$). The intra-operative estimated blood loss volume was significantly higher in the GA than SA group ($p = 0.007$). Among peripartum complications, the rate of postpartum hemorrhage ($p = 0.003$), the rate of blood transfusion ($p = 0.001$), and the rate of hysterectomy ($p<0.001$) were significantly higher in the GA than SA group. However, there was no difference in the incidence of uterine atony between the two groups. The neonatal Apgar scores at 1 and 5 minutes of first- and second-born neonates were significantly higher in the SA than GA group ($p<0.001$). Although the neonatal death rate was not significantly different between the groups, the rate of birth asphyxia was significantly higher in first- and second-born neonates from women in the GA group ($p<0.001$).

Conclusion: General anesthesia in women with multiple gestations undergoing cesarean delivery is associated with more complications than SA. Since this is a retrospective study, whether SA is a preferable anesthetic of choice in these patients needs further study.

Keywords: Multiple gestations, Anesthetic technique, Cesarean delivery, Maternal outcome, Neonatal outcome, Hysterectomy

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The incidence of multiple gestations has risen during the last 30 years because of an increased use of fertility drugs, which cause a higher rate of multiple ovulations, as well as an increased use of assisted reproductive technology[1]. Multiple-gestation pregnancy is considered high-risk because of the differences in maternal physiology compared with singleton pregnancy. Multiple gestations result in exaggeration of the anatomical and physiological changes that occur during pregnancy. The enlarged uterus causes profound supine hypotensive syndrome, especially in higher-order multiple gestations[2].

Correspondence to:
Nivatpumin P. Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand
Phone: +66-2-4197978, **Fax:** +66-2-4113256
E-mail: patchareya.niv@mahidol.ac.th

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Moreover, multiple gestations increase the risk of postpartum hemorrhage due to uterine atony and the need for blood transfusion[3-5].

Spinal anesthesia [SA] has been acknowledged as an anesthetic technique of choice for cesarean delivery for singleton pregnancy because of its prompt onset of action, reliability, postoperative pain control, and lower mortality rate when compared with general anesthesia [GA][6]. However, SA may be associated with a higher incidence of hypotension, which can result in fetal hypoxia and acidosis[7]. In contrast, numerous studies have shown that GA in cesarean delivery is associated with a higher incidence of uterine atony, postpartum hemorrhage, and blood transfusion[3,8,9]. Nevertheless, GA is used in some pregnant women undergoing cesarean delivery who have contraindications for SA, such as patients in an emergency situation, those with coagulopathy, and those with a low platelet count.

The effects of SA versus GA in multiple gestations have not been compared in the literature. The objective of the present study was to elucidate the maternal and neonatal outcomes occurring after the use of different anesthetic techniques in women with multiple gestations undergoing cesarean delivery.

Materials and Methods

This retrospective cohort study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand (protocol approval number Si. 204/2016). The electronic medical records of patients who delivered in Siriraj Hospital during the 10-year period from August 2006 to December 2015 were identified using the International Classification of Diseases, 10th revision [ICD-10]. The keywords used in this study were "twin" and "triplet". The cesarean delivery procedure was coded using ICD-9-CM (clinical modification). The inclusion criterion was cesarean delivery in women with multiple gestations. The exclusion criteria were a gestational age of <24 weeks, quadruplets, incomplete medical records, performance of both vaginal and cesarean delivery, performance of cesarean delivery under epidural or combined spinal-epidural anesthesia, and failed spinal anesthesia.

The following maternal demographic and clinical data were recorded: age, body mass index, gestational age, parity, maternal comorbidities, and American Society of Anesthesia [ASA] physical status. Two different anesthetic methods (SA and GA) were compared. Intra-operative complications such as maternal hypotension, the amounts of fluids and vasopressors used, and the estimated blood loss volume were also recorded. Hypotension was defined as a maternal systolic blood pressure of <20% of the pre-operative value. Maternal desaturation was defined as an oxygen saturation of <95%. The following neonatal data were recorded: birth weight, the uterine incision-to-delivery time, and the Apgar score. Birth asphyxia was defined as Apgar score of <7 at 5 minutes. Peripartum complications, namely the rate of blood transfusion, number of patients who developed uterine atony, number of patients who developed postpartum hemorrhage, and incidence of hysterectomy, were collected. Patients who received second- or third-line uterotonic drugs such as methylergonovine (Expogin®; LBS Laboratory Ltd., Bangkok, Thailand) or prostaglandin E2 (Nalador®; Patheon Italia SpA, Frosinone, Italy), both of which were used in our institute during the study, were considered to have uterine atony. Postpartum hemorrhage was defined as an estimated blood loss volume of >1,000 ml from the intra-operative period to 24 hours postoperatively. Postoperative pulmonary edema was defined as desaturation (oxygen saturation of <95%) with abnormal lung signs including rales or crepitation, radiographic evidence of pulmonary edema, or postoperative treatment with diuretics.

Statistical analysis

Sample size calculation was based on the findings of Trojner-Brejar et al[10]. In their study, the incidence of postpartum hemorrhage in twin pregnancy was 6%. Calculation was made with the confidence level (1-α) of 95% and allowable error 0.015; accordingly, 963 patients were required. Ten percent were included to compensate for possible data loss during the study. The sample size of 1,060 patients was required.

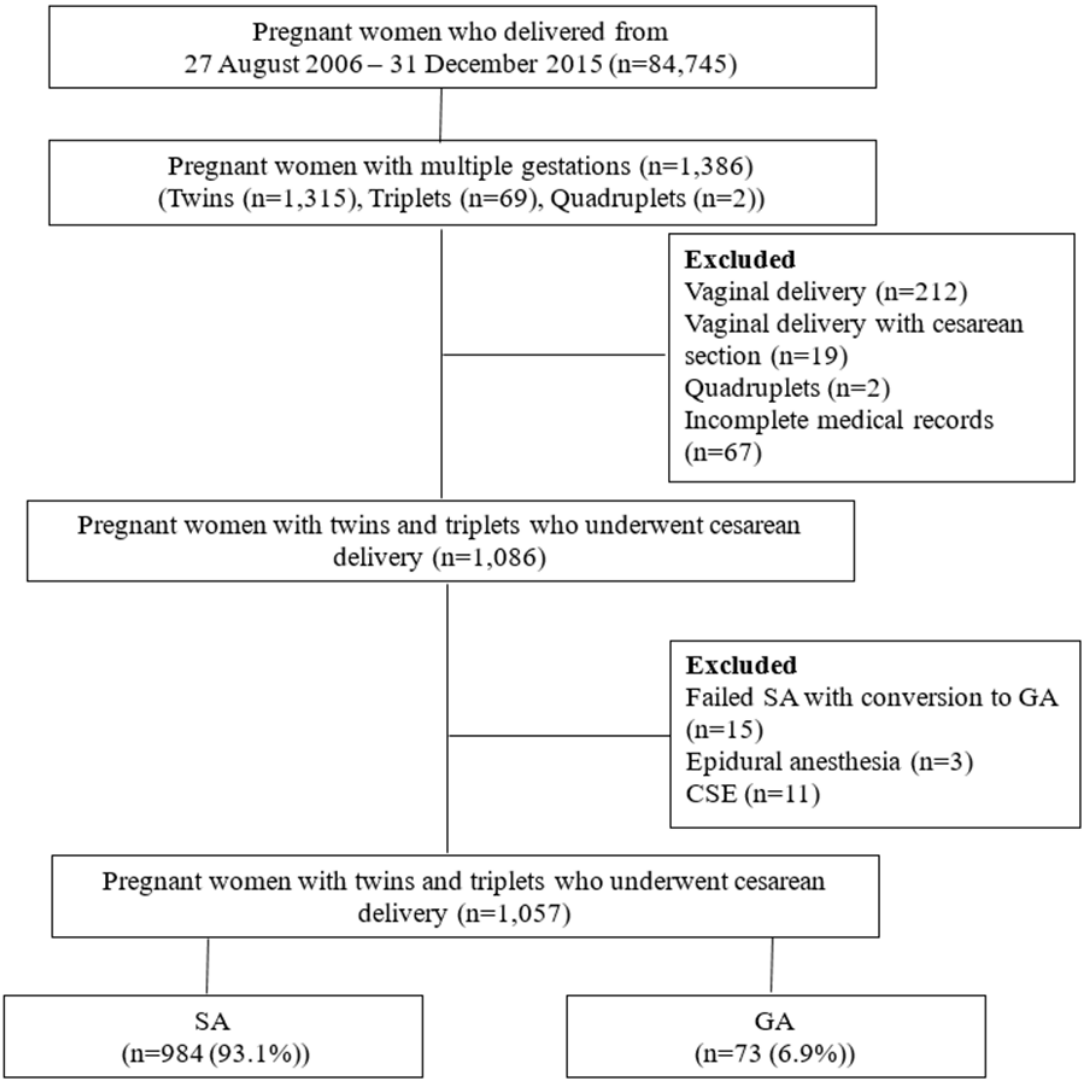
All analyses were performed using PASW statistics [SPSS] version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical data are presented as number and percentage. The Chi-square test and Fisher's exact test were used to compare categorical data between the two groups. The independent t-test was used to compare continuous data. The odds ratio and 95% confidence interval were calculated for peripartum complications. A *p*-value of <0.05 was considered statistically significant.

Results

Among 84,745 charts of pregnant women delivered from August 2006 to December 2015, we

identified 1,386 (1.6%) pregnant women with multiple gestations who were eligible for the present study. We excluded patients with vaginal delivery, vaginal delivery with cesarean section and patients with incomplete medical records. Two patients were excluded due to a quadruplet pregnancy. Eleven patients were excluded due to the performance of combined spinal and epidural anesthesia, and three of these patients underwent cesarean delivery under epidural anesthesia. Fifteen patients who underwent failed SA and were converted to GA were excluded from the study. Finally, 1,057 patients were analyzed. The numbers of patients who underwent cesarean delivery under SA and GA were 984 (93.1%) and 73 (6.9%), respectively (Figure 1). No patients were at a gestational age of <24 weeks. Table 1 shows the maternal demographic and clinical characteristics.

The intra-operative data and anesthetic-related complications are shown in Table 2. Patients who received SA had a higher incidence of intra-operative hypotension, greater need for intra-operative vasopressors, and higher amount of fluid



SA = spinal anesthesia; GA = general anesthesia; CSE = combined spinal-epidural anesthesia

Figure 1. Study population.

Table 1. Maternal clinical and demographic characteristics

	Spinal anesthesia (n = 984)	General anesthesia (n = 73)	*p*-value
Mean maternal age (year)	31±5.8	30±6.8	0.794
Maternal age of >35 year	200 (20.3)	17 (23.3)	0.545
Body mass index (kg/m^2)	28±4.5	29±4.3	0.346
Gestational age (week)	35±2.3	34±3.5	<0.001*
Gestational age of <32 week	66 (6.7)	16 (21.9)	<0.001*
Nulliparous	597 (60.7)	41 (56.2)	0.458
Type of pregnancy			
Twin	945 (96.0)	61 (83.6)	<0.001*
Triplet	39 (4.0)	12 (16.4)	
Natural pregnancies	804 (81.7)	55 (75.3)	0.179
Maternal comorbidities			
Gestational diabetes	71 (7.2)	4 (5.5)	0.577
Gestational hypertension	37 (3.8)	2 (2.7)	1.000
Preeclampsia	106 (10.8)	19 (26.0)	<0.001*
ASA physical status			
II	938 (95.3)	58 (79.5)	<0.001*
III	46 (4.7)	13 (17.8)	
IV	0 (0.0)	2 (2.7)	
Hematocrit	35.7±3.6	34.7±3.6	<0.019*
Platelet count (mm^3)	217,180±66,907	220,432±97,609	0.845

The data are presented as mean ± standard deviation or n (%)
*p<0.05 indicates statistical significance
ASA = American Society of Anesthesiologists

Table 2. Intraoperative data and anesthetic-related complications

	Spinal anesthesia (n = 984)	General anesthesia (n = 73)	*p*-value
Hypotension	740 (75.2)	17 (23.3)	<0.001*
Bradycardia	13 (1.3)	1 (1.4)	1.000
Desaturation	0 (0.0)	1 (1.4)	0.069
Vasopressor used	738 (75.0)	16 (21.9)	<0.001*
Ephedrine used	637 (64.7)	6 (8.2)	<0.001*
Amount of ephedrine (mg)	18.4±11.8	20±8.8	0.740
Norepinephrine used	370 (37.6)	12 (16.4)	<0.001*
Amount of norepinephrine (mcg)	15.8±13.8	17.8±14.0	0.639
2nd- and 3rd-line uterotonic agents used			
Ergotamine	476 (48.4)	34 (46.6)	0.767
Prostaglandin	43 (4.4)	5 (6.8)	0.372
Total intravenous fluid (mL)	1,323±703	1,149±662	0.034*
Estimated blood loss (mL)	534±265	832±915	0.007*

The data are presented as mean ± standard deviation or n (%)
* p<0.05 indicates statistical significance

administration. However, the intra-operative estimated blood loss volume was significantly higher in patients who received GA. All patients in the GA group underwent endotracheal intubation, and one patient encountered difficult airway management. Twenty-one patients (2.1%) in the SA group experienced high spinal block (block level up to the second thoracic vertebra). Nonetheless, no patients required intubation after high spinal block.

Table 3 shows the neonatal characteristics.

Table 3. Neonatal characteristics

	Spinal anesthesia (n = 2,007)	General anesthesia (n = 158)	*p*-value
Birth weight (g)			
1st-born	2,267±466	1,987±631	<0.001*
2nd-born	2,199±476	1,953±608	<0.001*
3rd-born	1,660±573	1,691±476	0.866
Uterine incision-to-delivery time (min)			
1st-born	1.6±1.0	1.1±0.8	<0.001*
2nd-born	2.9±1.4	2.2±0.9	<0.001*
3rd-born	4.0±1.8	3.4±0.6	0.281
Apgar score at 1 min			
1st born	8.4±1.3	6.2±2.7	<0.001*
2nd born	8.1±1.5	5.8±2.9	<0.001*
3rd born	7.5±2.3	5.5±1.9	0.007*
Apgar score at 5 min			
1st-born	9.5±1.0	8.1±2.3	<0.001*
2nd-born	9.4±1.2	8.0±2.5	<0.001*
3rd-born	8.8±2.3	7.8±1.9	0.210
Birth asphyxia			
1st-born	18 (1.8)	13 (17.8)	<0.001*
2nd-born	24 (2.4)	13 (17.8)	<0.001*
3rd-born	3 (0.3)	2 (2.7)	0.579

The data are presented as mean ± standard deviation or n (%)
* $p<0.05$ indicates statistical significance
Birth asphyxia was defined as an Apgar score of <7 at 5 minutes

Table 4. Peripartum complications (n = 1,057)

	Spinal anesthesia (n = 984)	General anesthesia (n = 73)	*p*-value	Crude OR (95% CI)
Uterine atony	482 (49.0)	35 (47.9)	0.864	0.9 (0.6 to 1.5)
Postpartum hemorrhage	76 (7.7)	13 (17.8)	0.003*	2.6 (1.4 to 4.9)
Blood transfusion	40 (4.1)	10 (13.7)	0.001*	3.7 (1.8 to 7.8)
Hysterectomy	4 (0.4)	4 (5.5)	<0.001*	14.4 (3.5 to 58.8)
ICU admission	5 (0.5)	12 (16.4)	<0.001*	38.5 (13.1 to 112.8)
Postoperative pulmonary edema	2 (0.2)	6 (8.2)	<0.001*	43.9 (8.7 to 221.8)
Neonatal death	16 (1.6)	3 (4.1)	0.139	2.6 (0.7 to 9.1)

The data are presented as n (%) unless otherwise indicated
* $p<0.05$ indicates statistical significance
Uterine atony was defined as the use of more than one uterotonic agent
Postpartum hemorrhage was defined as maternal blood loss of >1,000 mL
ICU = intensive care unit; OR = odds ratio; CI = confidence interval

There was a significantly shorter uterine incision-to-delivery time in the GA than SA group. In contrast, the Apgar score of the first- and second-born neonates at 1 and 5 minutes were significantly lower in the GA than SA group. Additionally, a higher proportion of first- and second-born neonates had birth asphyxia in the GA than SA group.

Peripartum complications are shown in Table 4. Overall incidence of postpartum hemorrhage was 8.4% (89 in 1,057 patients). Total of 8 patients encountered peripartum hysterectomy. No difference was found in the rate of peripartum hysterectomy

between twins (6 patients) and triplets (2 patients). No maternal death occurred in our study.

Discussion

In the present study, patients with multiple gestations who underwent cesarean delivery under GA had a higher incidence of intra-operative blood loss, postpartum hemorrhage, blood transfusion, hysterectomy, intensive care unit [ICU] admission, postoperative pulmonary edema, and neonatal birth asphyxia. Previous reports have indicated that women with a singleton pregnancy who undergo cesarean delivery under GA experience greater blood loss, postpartum hemorrhage, and blood transfusion than those who undergo SA, and our data regarding multiple pregnancies were consistent with those regarding singleton pregnancies[8,9,11]. These findings suggest that GA is associated with a higher risk of obstetric bleeding, possibly due to the inhalation anesthetic used, which results in poorer uterine muscle contraction than in SA[11].

Moreover, pre-operative patient conditions in GA group appeared more severe than that of patients in SA group. That is, the higher proportion of patients with ASA classification III-IV and lower of the hematocrit level were found in GA group, which may result in the higher rate of blood transfusion.

SA is the most popular choice of anesthesia in cesarean delivery. The present study data show that >90% of women with multiple gestations underwent cesarean delivery under SA. In singleton pregnancies, SA offers more advantages than GA, including better postoperative pain control and a lower mortality rate[6]. Not surprisingly, the present study revealed that SA was associated with significantly more maternal hypotension and a higher proportion of patients who required vasopressor agents. A previous meta-analysis showed the same results[11]. Not only does SA induce a higher rate of hypotension in the third trimester of pregnancy, but a higher rate of hypotension is also found in women with multiple gestations undergoing surgery in the second trimester[12].

Nevertheless, the neonatal Apgar score and proportion of neonates with birth asphyxia among first- and second-born neonates were lower in parturients receiving GA than those receiving SA, although the uterine incision-to-delivery time was significantly shorter in the GA group. A possible explanation is that patients receiving GA have a higher preoperative risk. The GA group contained a higher proportion of patients with comorbidities including pre-operative anemia, preeclampsia, and a higher ASA physical status classification. These factors may have had negative effects on the fetus. Additionally, the proportion of triplet gestations was significantly higher in the GA than SA group. Triplet pregnancies are associated with more maternal comorbidities such as preeclampsia and thrombocytopenia[2,13]. Another explanation is the choice of anesthesia, which was made at the individual attending anesthetist's discretion. Some patients with preeclampsia had coagulopathy or thrombocytopenia, necessitating avoidance of regional anesthesia. Moreover, in patients undergoing emergency cesarean section because of pre-operative fetal distress, GA is the preferred technique because SA takes a longer period of time to perform than GA.

Although the rate of uterine atony was not different between the groups, peripartum complications such as the rate of hysterectomy were significantly higher in the GA than SA group (5.6% and 0.4%, respectively). This may have resulted from the higher intra-operative blood loss volume in the GA group. The literature presents conflicting data regarding the increasing rate of hysterectomy in multiple pregnancies. Whiteman et al and Bodelon et al found that multiple pregnancies were not associated with a higher rate of peripartum hysterectomy, but Bateman et al reported a higher rate of hysterectomy after cesarean delivery in multiple pregnancies[14-16]. The present study did not show a difference in the rate of hysterectomy between twin and triplet pregnancies. The rate of hysterectomy in our study was 8 of 1,057 (0.76%) patients, which is similar to the findings of the above-mentioned study (0.71% to 0.82%)[16]. They included all obstetrics patients, including those with abnormal placentation, who had a higher chance of hysterectomy. In the present study, we collected data of patients with multiple gestations and an enlarged uterus, which may cause uterine atony, a higher intraoperative bleeding volume, and a higher rate of postpartum hemorrhage.

The rates of ICU admission and postoperative pulmonary edema were significantly higher in the GA than SA group. Because of the more severe preoperative comorbidities in patients undergoing GA, such as preeclampsia, attending anesthetists may choose GA over SA. However, the main reason for ICU admission in the present study was not documented. A previous study of patients with preeclampsia also reported a higher rate of ICU admission in parturients undergoing cesarean delivery receiving GA[17].

The main limitation of this study is that the choice of anesthesia for cesarean delivery in

patients with multiple pregnancies in our institute may lack standardization depending on the individual decision of the attending anesthetist. Another limitation is the lack of randomization of the anesthetic technique because this was a retrospective review, potentially introducing bias or resulting in incomplete data.

Conclusion

More adverse maternal and neonatal outcomes were found in women with multiple gestations undergoing cesarean delivery under GA than SA. However, GA was used in multiple gestations with more complicated pre-operative conditions and lower gestational age comparing with SA. Further study should be carried out to verify the result of this retrospective study.

What is already known on this topic?

Patients undergoing cesarean delivery can be successfully done under either general anesthesia or regional anesthesia. Both techniques lead to different maternal and neonatal outcomes. Singleton pregnancies that undergo cesarean delivery under GA experience greater blood loss, postpartum hemorrhage, and blood transfusion than those who undergo SA.

What this study adds?

This study revealed more adverse maternal outcomes were found in women with multiple gestations undergoing cesarean delivery under GA than SA such as higher intra-operative estimated blood loss volume, higher rate of postpartum hemorrhage and peripartum hysterectomy. The neonatal Apgar scores at 1 and 5 minutes of first- and second-born neonates were significantly lower in the GA than SA group. Also, the rate of birth asphyxia was significantly higher in first- and second-born neonates from women in the GA group.

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Trial registration

ClinicalTrial.gov as NCT02846129.

Potential conflicts of interest

The authors declare no conflict of interest.

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