# The effect of different phenylephrine infusion rates on uteroplacental blood flow during cesarean delivery under spinal anesthesia

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**Introduction**
Hypotension associated with spinal anesthesia is more common and profound in the pregnant population, resulting in adverse effects to both the mother and the fetus. It is now widely accepted that the vasopressor of choice during cesarean delivery is phenylephrine. However, an overdose of phenylephrine may cause reflex bradycardia and decreased maternal and fetal cardiac output. In contrast, lower phenylephrine doses may not be adequate to avoid or control hypotension. The optimal phenylephrine dose and its direct effect on uteroplacental blood flow are yet to be determined.
**Aim of the work**
This study aimed to examine the direct effect of different phenylephrine infusion rates on uterine blood flow during cesarean delivery spinal anesthesia. Assessment of uteroplacental blood flow was performed using Doppler ultrasound of the uterine artery from which uterine blood flow indices were obtained, namely, peak systolic velocity (PSV) and pulsatility index (PI).
**Materials and methods**
This is a prospective, randomized double-blind study. We included 90 age-matched American Society of Anesthesiologists (ASA) I or II parturients with term singleton pregnancies admitted for elective cesarean delivery under spinal anesthesia. We excluded candidates with hypertension, cardiovascular or cerebrovascular disease, type 1 diabetes mellitus, allergy or hypersenstivity to phenylephrine, known fetal abnormalities, intrauterine growth retardation, and any contraindication to spinal anesthesia. The patients were distributed randomly into three equal groups ($n = 30$ each). Groups 25, 50, and 75 received 25, 50, and 75 μg/min phenylephrine infusion, respectively, after spinal anesthesia was administered. The maternal uterine artery was identified by colored Doppler ultrasound and pulsed-wave Doppler was used to measure PSV and calculate PI before spinal anesthesia and at 5 and 15 min after the block was performed. Maternal hemodynamics and measures of fetal well-being (Apgar score and umbilical venous pH) were also recorded.
**Results**
PI at 15 min after spinal anesthesia was significantly higher in group 75 in comparison with the baseline value ($P < 0.05$) and also in comparison with groups 50 and 25 ($P < 0.05$). Furthermore, the percentage of decrease in PSV, compared with the baseline, was also significantly higher in group 75 compared with the other two groups at both 5 and 15 min ($P < 0.05$). Group 75 also showed a significantly higher incidence of hypertension and bradycardia in comparison with both the other groups. However, the number of hypotensive episodes as well as nausea and vomiting was significantly higher in group 25 compared with the other two groups ($P < 0.05$). There was no significant difference in fetal outcome among the different groups.
**Conclusion and recommendations**
At a dose of 75 μg/min, phenylephrine induced a significant reduction in uteroplacental blood flow as evidenced by decreased PSV compared with baseline values and an increase in PI compared with the other two groups. This decrease in uteroplacental blood flow was not associated, however, with poor fetal outcome. Further studies are needed to address the correlation between uteroplacental blood flow and fetal outcome with different phenylephrine doses in patients with uteroplacental insufficiency.

**Keywords:**
cesarean delivery, peak systolic velocity, phenylephrine, pulsatility index, spinal anesthesia

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## Introduction

Spinal anesthesia provides a fast and high-quality motor and sensory block in women undergoing cesarean delivery [1]. However, hypotension associated with spinal anesthesia is more common and profound in the pregnant population, resulting in adverse effects to both the mother and the fetus [2]. Many preventive strategies have been described to decrease the incidence

and extent of hypotension including intravenous fluid preloading or coloading, [3] low spinal anesthesia [4], and different vasopressor regimens [5].

In recent years, it has been widely accepted that the vasopressor of choice during cesarean delivery is phenylephrine [6–8]. However, the optimal regimen or infusion rate to be used during delivery is still undetermined. Although large doses of phenylephrine are often required because of increased baroreceptor sensitivity, [9] there are concerns that these large doses might cause reflex bradycardia, with consequent reduction of maternal cardiac output (CO) and uterine blood flow (UBF) 0.10 Another concern is that, at these large doses, phenylephrine may cause uteroplacental vasoconstriction, also resulting in further decrease in UBF [10].

Previous studies, which compared different infusion regimens for phenylephrine administered during ceserian delivery, have observed maternal blood pressure and heart rate (HR) changes as well as noninvasive monitoring of maternal CO [11–13] Their assumption was that maternal CO correlates closely with uteroplacental blood flow. However, estimation of total CO does not necessarily reflect regional blood flow in the uterus and placenta [14]. We have not found any earlier studies that examined the impact of increasing infusion rates of phenylephrine on uteroplacental circulation.

Pulsatility indices (PIs) reflect the impedance to blood flow in the uteroplacental circulation because of changes in vascular resistance. Thus, they are used to monitor high-risk pregnancies and pathological PIs serve as indicators of fetal distress [15]. Direct noninvasive measurements of arterial flow velocity in the uterine artery are obtained by combining Doppler and B-mode techniques with simultaneous measurements of local blood flow and vessel diameter [16].

The aim of this prospective randomized study was to examine the direct effect of different phenylephrine infusion rates on UBF, when used after spinal anesthesia during cesarean delivery, using the uteroplacental Doppler assessment technique. We also studied their effects on maternal hemodynamics and fetal outcome.

## Materials and methods

After obtaining approval from our department's ethics committee, our study was carried out over a period of 14 months from September 2011 till December 2012 in Kasr El Aini hospital. We carried out a prospective randomized double-blind study on 90 American Society of Anesthesiologists (ASA) I or II parturients with term singleton pregnancies admitted for elective cesarean delivery under spinal anesthesia. Exclusion criteria were preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, Type 1 diabetes mellitus, allergy or hypersenstivity to phenylephrine, known fetal abnormalities, intrauterine growth retardation, and any contraindication to spinal anesthesia.

All women provided informed consent to participate in the study. Patients were assigned randomly to one of three different phenylephrine infusion regimens: Phenylephrine 25 μg/min (group 25, $n$ = 30), phenylephrine 50 μg/min (group 50, $n$ = 30), and phenylephrine 75 μg/min (group 75, $n$ = 30). The infusions were prepared in identical 50 ml syringes containing phenylephrine at a concentration of 25, 50, and 75 μg/ml by a physician not involved in the study. Each syringe was identified by a study number according to a computer-generated randomization. The patient and the attending anesthesiologist were blinded to the study group.

All patients were fasting at least 8 h before arriving to the operating room. Upon arrival to the operating room, standard monitors were attached to the patient including noninvasive blood pressure, pulse oximetry, and ECG. Patients were allowed to rest in the supine position slightly tilted to the left 15° for a few minutes, during which baseline systolic blood pressure (SBP) and HR were measured by averaging three consecutive readings taken 1 min apart.

The maternal uterine artery was identified by colored Doppler ultrasound (Voluson 730 Pro; GE Healthcare, USA) at the apparent cross-over with the external iliac arteries by the obstetrician involved in the study. Pulsed-wave Doppler was used to obtain blood-velocity waveforms (with a 3.75 MHz convex transabdominal probe). The angle of the probe to the artery was determined. The Doppler probe was kept immobile once a stable signal was obtained. A baseline reading of the peak systolic velocity (PSV) was recorded. Pulsatility index (PI = peak systolic velocity–end-diastolic velocity/mean velocity during cardiac cycle) was measured from the waveform profile of blood velocity. Three consecutive correctly imaged blood-velocity waveforms were analyzed and the mean PI value was calculated.

After baseline readings, we inserted an 18 G intravenous catheter and started an intravenous infusion of 500 ml of lactated Ringer's solution using a pressurized infusion system over a period of 5–10 min, after which no intravenous fluids were administered until delivery of the fetus. Spinal anesthesia was then initiated in

the sitting position. After infiltrating the skin with lidocaine, a 25 G atraumatic pencil point spinal needle (Uniever; Unisis Corp., Japan) was inserted at level $L_{3-4}$ or the $L_{4-5}$ interspace. Hyperbaric bupivacaine 0.5% 10–12.5 mg and fentanyl 15 μg were then injected intrathecally.

Immediately after the block, the patients were turned supine with left uterine tilt. Noninvasive SBP and HR measurements were taken every minute for 10 min and then every 2.5 min. Immediately after the intrathecal injection, the infusion of the study drug was started at a rate of 1 ml/min and continued until delivery of the fetus. The infusion was connected to the intravenous line at the most proximal port to the patient. Subsequently and until the time of uterine incision, we adjusted the rate of infusion according to each 1 min measurement of SBP. The infusion was discontinued if SBP became higher than the baseline SBP reading. Hypotension requiring intervention was defined as SBP less than 80% of baseline or SBP less than 90 mmHg for two consecutive readings and was treated by administering 100 μg bolus of phenylephrine. If no improvement was observed in two consecutive readings, a bolus of ephedrine 6 mg was administered. Bradycardia (HR < 50 bpm) for two consecutive readings, which was associated with SBP greater than or equal to baseline, was treated by discontinuation of the phenylephrine infusion and administration of atropine 0.6 mg.

Doppler measurements from the same uterine artery were obtained by the same obstetrician after 5 and 15 min of the spinal block initiation. When the angle of the probe had not changed, the PSV from each measurement after the start of phenylephrine infusion was compared with the baseline PSV value and the percentage change was recorded. The PI values were also calculated at the same time points.

The presence of nausea and vomiting was assessed at 5 min intervals until 20 min after spinal injection. The upper sensory level of anesthesia was measured at 5, 10, and 20 min after the placement of spinal anesthesia by assessing loss of pinprick discrimination. After delivery of the fetus, oxytocin 5–10 IU was administered by a slow intravenous injection, followed by an infusion over the next 2 h of 25 IU in 1 l of lactated Ringer's solution.

The attending pediatrician, who was blinded to the study group, assessed and recorded 1 and 5 min Apgar scores. Umbilical venous blood gases were obtained from a double-clamped segment of umbilical cord after delivery using a blood gas analyzer (Premier 3000; GEM Systems, USA). Obstetric data collected included skin incision to delivery and uterine incision and to delivery times.

The primary outcome measure was change in PSV and PI with different phenylephrine regimens after spinal anesthesia. Secondary outcomes included effects on SBP, HR, incidence of nausea and vomiting, and measures of fetal well-being.

### Statistical analysis

The data obtained are presented as mean ± SD, numbers and percentages as appropriate. Categorical variables were compared using the $\chi^2$-test with continuity correction. Comparisons of continuous variables were performed using mixed-design 'two-group univariate repeated measures' analysis of variance with post-hoc Dunnett's test for multiple comparisons against baseline values to further investigate any statistically significant findings. Statistical analysis was carried out using computer programs Microsoft Office Excel 2010 (Microsoft Corporation, New York, New York, USA) and SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). *P* value less than 0.05 was considered statistically significant.

## Results

We enrolled 90 women admitted for elective cesarean delivery under spinal anesthesia in the study, with 30 patients in each group. Patient demographic characteristics are shown in Table 1. There were no significant differences between the three groups in age, weight, height, and gestational age of pregnancy. The sensory level achieved was adequate in all patients and there was no significant difference in the block heights between the groups. Skin incision to delivery time and uterine incision to delivery time was comparable in the three groups.

In terms of UBF indices, there was a significant increase in the PI in group 75 at 15 min compared with the baseline value ($P < 0.05$) (Fig. 1). At the same time point (15 min), the PI was significantly higher in group 75 compared with groups 50 and 25 ($P < 0.05$).

**Table 1 Demographic and operative data**

| | Group 25 (*n* = 30) | Group 50 (*n* = 30) | Group 75 (*n* = 30) |
|---|---|---|---|
| Age (years) | 31.1 ± 4.2 | 32.3 ± 3.9 | 30.7 ± 4.6 |
| Weight (kg) | 77.2 ± 9.9 | 74.6 ± 8.3 | 73.5 ± 9.6 |
| Height (cm) | 162 ± 5.3 | 160 ± 5.9 | 159 ± 4.8 |
| Gestational age (weeks) | 39.3 ± 1.4 | 39.4 ± 1.5 | 39.2 ± 1.5 |
| Highest sensory block (dermatome) | T4 (T2–T6) | T4 (T3–T5) | T5 (T3–T6) |
| Skin incision to delivery time (min) | 10.4 ± 2.5 | 11.1 ± 2.7 | 10.8 ± 2.2 |
| Uterine incision to delivery time (s) | 95.4 ± 19.1 | 98.5 ± 18.6 | 93.1 ± 17.3 |

Data are mean ± SD or median (range).

The percentage change (decrease) in PSV compared with baseline was also significantly higher in group 75 compared with the other two groups at both 5 and 15 min ($P < 0.05$) (Figure 2).

Maternal hemodynamics variables are shown in Table 2. There was no significant difference in baseline SBP and HR between the three groups. The number of patients with hypotensive episodes was significantly higher in group 25 compared with the other two groups ($P < 0.05$ vs. group 50, $P < 0.01$ vs. group 75). The number of patients requiring ephedrine boluses was also significantly higher in group 25 ($P < 0.05$). Group 75 showed a significantly higher incidence of hypertension and bradycardia in comparison with both the other groups ($P < 0.05$). The incidence of nausea and vomiting was significantly higher in group 25 compared with the other groups ($P < 0.05$).

Serial SBP and HR values for 20 min after the onset of spinal anesthesia among groups are shown in Figures 3 and 4. Group 25 showed significantly lower SBP values compared with the other two groups starting from the third minute until the 20th minute. The decrease in HR, although greater in group 75, did not reach statistical significance between groups.

Neonatal data are summarized in Table 3. Umbilical venous pH values and Apgar scores at 1 and 5 min were comparable in the three groups. No neonates had an Apgar score less than 7 at 5 min. None of the neonates required tracheal intubation or admission to the neonatal ICU.

## Discussion

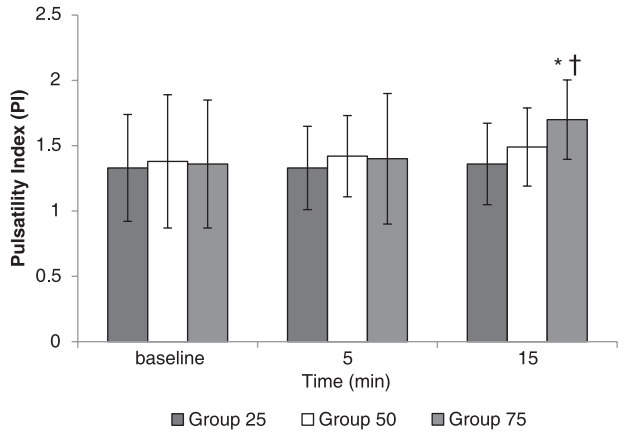
Recent studies have agreed that phenylephrine is the preferred drug for prophylaxis against hypotension during elective cesarean section under spinal anesthesia [6–8]. Unfortunately, the debate has not been settled yet as to which dose and which mechanism of delivery offer the best fetal and maternal outcomes. To the best of our knowledge, this is the first study that examines the direct effect of different phenylephrine infusion regimens on uteroplacental blood flow in patients undergoing elective cesarean delivery under spinal anesthesia.

Our data showed that the 75 μg/min phenylephrine infusion regimen resulted in decreased uteroplacental blood flow as evidenced by a significant decrease in PSV in the uterine artery compared with the baseline value, as well as a significant increase in PI indicating increased vascular resistance. The 50 and 25 μg/min infusion regimens were not associated with significant changes in UBF indices.

Contradictory results were found on the effect of high-dose phenylephrine on maternal CO. Doherty *et al.* [17] found that a 120 μg/min phenylephrine infusion did not result in a significant decrease in CO in comparison with a 120 μg phenylephrine bolus. However, Stewart *et al.* [13] found that fixed high doses of phenylephrine effusion (100 μg/min) exposed the mother to unnecessarily high doses of phenylephrine. This further led to a significant decrease in CO of up to 20% as well as a baroreceptor-mediated bradycardia.

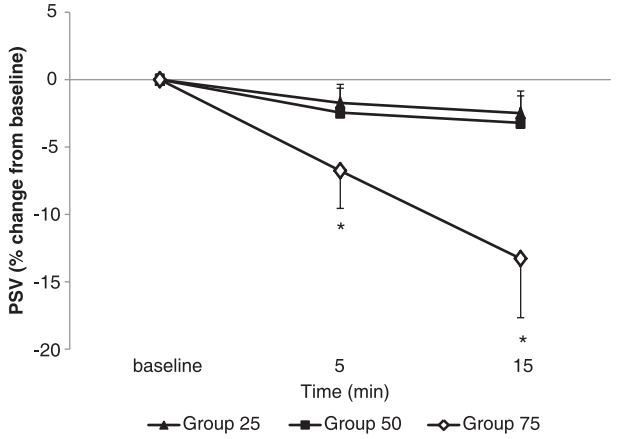
Previous work has shown that SBP does not necessarily correlate to changes in maternal CO [18]. In the initial phase of phenylephrine infusion, SBP can be

**Figure 1**




Changes in pulsatility index (PI) after spinal anesthesia (data are mean ± SD). *$P < 0.05$ versus baseline. †$P < 0.05$ versus the other two groups.

**Figure 2**




Changes in peak systolic velocity (PSV) after spinal anesthesia (data are mean ± SD). Changes are shown as percent of baseline. *$P < 0.05$ versus the other two groups.

maintained at the expense of reflex bradycardia and hence minor changes in CO cannot be solely assessed by SBP reading. Thus, the current trend shifted to measurement of CO as an indirect method of evaluating uteroplacental blood flow [13,18].

Furthermore, depending solely on maternal CO to assess uteroplacental blood flow has its own drawbacks. Different methods of CO measurements are used. The pulse waveform analysis monitor (LiDCO*plus*) offers continuous CO monitoring [19]. However, this method requires arterial line placement, which is not recommended during hemodynamic instability, [20] and has been shown to produce CO assessment errors of greater than 33% during cardiac surgery [21]. Others have used the suprasternal Doppler technique for CO measurement [13]. It is a noninvasive and well-validated method [22], yet intermittent, needs special training, and yields a 10% underestimate of the actual CO [13].

Most importantly, uteroplacental blood flow can be compromised by local uterine/placental factors not necessarily reflected by CO changes. This is especially significant in patients with a preoperative risk of uteroplacental compromise, for example placental ischemia, embolization, or thrombosis as in antiphospholipid syndrome, or fetal intrauterine growth retardation (IUGR), etc. The direct assessment of UBF indices using colored Doppler ultrasound that we used in our study offers an alternative solution to the aforementioned drawbacks.

The advantage of PI is that it reliably reflects changes in uteroplacental vascular resistance, and at the same time, is independent of the angle of insonation that improves reproducibility between measurements at different time points. However, previous work has shown that significant changes in systolic blood flow velocity can occur without concurrent changes in PIs [16]. This discrepancy may be explained by the way in which PIs are calculated (peak systolic velocity–end-diastolic velocity/mean velocity during cardiac cycle). If the systolic and mean blood flow decrease while the diastolic blood flow remains unchanged, there will be a decrease in overall blood flow that will not be reflected by the PI because the numerator and the denominator are changed in the same direction. This is why we chose to measure PSV as a more accurate measure of actual UBF.

**Table 2 Maternal hemodynamics and incidence of nausea and vomiting**

| | Group 25 ($n$ = 30) | Group 50 ($n$ = 30) | Group 75 ($n$ = 30) |
|---|---|---|---|
| Baseline SBP (mmHg) | 133.8 ± 5.9 | 132.5 ± 6.5 | 131.2 ± 5.3 |
| Baseline HR (bpm) | 86.3 ± 8.2 | 83.9 ± 7.4 | 84.2 ± 8.1 |
| Hypotension (SBP decrease>20% from baseline) | 16 (53.3)* | 6 (20) | 4 (13.3) |
| Phenylephrine bolus required | 8 (26.6) | 5 (16.6) | 4 (13.3) |
| Phenylephrine and ephedrine bolus required | 8 (26.6)* | 1 (3.3) | 0 (0) |
| Hypertension (SBP increase>20% from baseline) | 0 (0) | 1 (3.3) | 7 (23.3)* |
| Bradycardia (HR < 50 bpm) | 0 (0) | 0 (0) | 6 (20)* |
| Nausea or vomiting | 9 (30)* | 2 (6.6) | 1 (3.3) |

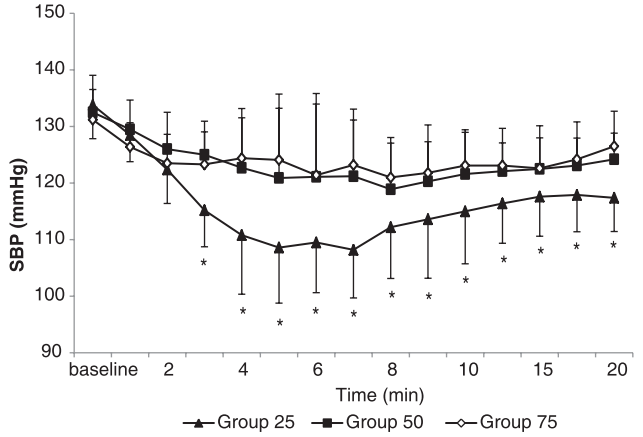
Data are mean ± SD or $n$ (%); bpm, beats per minute; HR, heart rate; SBP, systolic blood pressure; *$P$ < 0.05 versus the other two groups.

**Table 3 Neonatal data**

| | Group 25 ($n$ = 30) | Group 50 ($n$ = 30) | Group 75 ($n$ = 30) |
|---|---|---|---|
| Umbilical venous pH | 7.35 ± 0.04 | 7.34 ± 0.04 | 7.34 ± 0.03 |
| 1 min Apgar score <7 | 5 (16.6) | 3 (10) | 4 (13.3) |
| 5 min Apgar score <7 | 0 (0) | 0 (0) | 0 (0) |

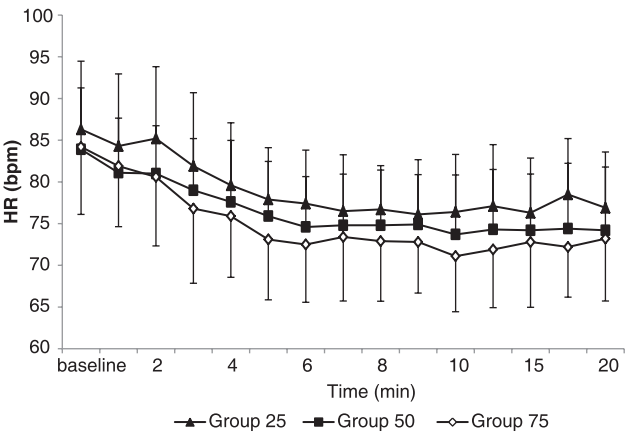
Data are mean ± SD or $n$ (%).

**Figure 3**




Changes in systolic blood pressure (SBP) after spinal anesthesia (data are mean ± SD). *$P$ < 0.05 versus the other two groups.

**Figure 4**




Changes in heart rate (HR) after spinal anesthesia (data are mean ± SD).

The high-dose phenylephrine group (75 μg/min) also showed a significantly higher number of hypertension and bradycardia episodes, necessitating further intervention and discontinuation of the infusion. Despite the fact that reactive hypertension can be unpredictable, that is occurring with any phenylephrine dose, [12] its incidence was proven to be dose dependent [12,13]. Hence, avoidance of maternal exposure to high doses of phenylephrine is always a requirement. Allen *et al*. [12] found that an infusion regimen of 100 μg/min provides less maternal hemodynamic control and stability compared with all the other regimens studied including 25 and 75 μg/min doses.

Hypotension episodes were significantly more frequent in patients of the low-dose phenylephrine group (25 μg/min) requiring intervention and introduction of ephedrine in such patients. SBP decreased below 80% of its baseline. This showed inadequate prophylaxis against hypotension with such a dose. This was in agreement with the findings of Ngan *et al*. [23], who found that as the dose of phenylephrine infusion decreased, hemodynamic control was reduced. The same group showed significantly more episodes of nausea and vomiting. Studies have shown that the increased variability of blood pressure in this category of patients is the main reason for these symptoms [11,23].

We found that the 50 μg/min group provided the balance between prophylaxis against hypotension on the one hand and the lack of hypertension and bradycardia on the other. Allen *et al*. [12] reported that the fixed-rate infusion of 25–50 μg/min was associated with more hemodynamic stability and fewer hypertension episodes in elective cesarean section spinal anesthesia when compared with the higher doses of 100 μg/min. This in turn avoids uteroplacental vasoconstriction and hypoperfusion and hence disturbance in fetal acid–base balance.

There was no difference in the umbilical venous blood gases between the different groups despite the occurrence of hypertension or hypotension. This is in agreement with the results of previous studies [12,13] showing no difference in fetal outcomes between patients receiving variable doses of phenylephrine. This is probably because of the transient nature of blood pressure changes and the prompt intervention during the study. Caution needs to be exercised when interpreting these data as they can only be applied to healthy elective cesarean section patients. There is no available information on the effect of variable phenylephrine doses in hemodynamically unstable patients and their fetal outcomes.

The decrease in uteroplacental blood flow in our study was not associated with poor Apgar score results; yet, our patients had no preoperative uteroplacental compromise. Further studies are needed to address the correlation between uteroplacental blood flow and fetal outcome with different phenylephrine doses in patients with uteroplacental insufficiency.

Nevertheless, our study had some limitations. First, the use of a fixed predelivery crystalloid coload may have affected the outcome. Yet, we included the coload procedure in order to standardize the results. Coloading has shown, in some studies, although controversial, a decrease in the overall dose of vasopressors, hemodynamic changes, incidence of hypotension, as well as nausea and vomiting [3,24]. Second, we used a fixed-dose plan to determine the ideal dose needed for a balance between hypotension prophylaxis and hypertension avoidance. Fixed-rate phenylephrine provides a simpler mechanism for assessment of the doses required; yet, the initiation dose may not necessarily be the appropriate maintenance dose. Hence, future studies are needed to address variable rate infusion regimens, on a treat-to-target basis, in this patient population.

## Conclusion

We showed a significant decrease in uteroplacental blood flow with a phenylephrine dose of 75 μg/min. This was not associated with poor fetal outcome in our healthy parturients. Nevertheless, this could prove to be significant in emergency interventions in patients with uteroplacental blood flow compromise. Further studies are required to address this issue.

## Acknowledgements

**Conflicts of interest**

There are no conflicts of interest.

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