

Contemporary Vasopressor Strategies for Spinal-Induced Hypotension in Preeclamptic Patients: Maternal Hemodynamics and Neonatal Outcomes

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Abstract

Spinal anesthesia is widely favored for cesarean delivery in patients with preeclampsia, yet sympathetic blockade can still produce clinically important hypotension in a population with abnormal vascular tone and potentially compromised uteroplacental perfusion. The optimal rescue vasopressor remains debated because phenylephrine, norepinephrine, and ephedrine differ in alpha- and beta-adrenergic activity, effects on maternal heart rate and cardiac output, placental transfer, and fetal metabolic consequences. This narrative review examines intermittent bolus phenylephrine, norepinephrine, and ephedrine for spinal-induced hypotension in preeclamptic parturients, with emphasis on maternal hemodynamics and neonatal outcomes. Phenylephrine provides reliable arterial pressure restoration and has a long record of obstetric use, but pure alpha-adrenergic vasoconstriction can cause reflex bradycardia and reduce cardiac output. Ephedrine supports heart rate and cardiac output through mixed direct and indirect sympathomimetic actions, but repeated dosing may cause tachycardia, tachyphylaxis, and greater placental transfer; in low-risk cesarean populations it has been associated with less favorable fetal acid-base status than phenylephrine. Norepinephrine combines potent alpha-adrenergic vasoconstriction with modest beta1 activity and generally preserves heart rate and cardiac output better than phenylephrine. Preeclampsia-specific randomized trials and recent meta-analyses suggest that all three agents can restore blood pressure effectively, while norepinephrine may reduce bradycardia relative to phenylephrine and tachycardia relative to ephedrine without a demonstrated disadvantage in umbilical blood gas or Apgar outcomes. However, direct preeclampsia-specific evidence remains smaller and more heterogeneous than the literature in healthy elective parturients, and prophylactic infusion data should not be extrapolated uncritically to rescue bolus treatment. Vasopressor selection should therefore be individualized according to baseline heart rate, severity of hypertension, ventricular function, fetal status, concurrent magnesium and antihypertensive therapy, and the magnitude of the hypotensive episode. Larger dose-equivalence trials focused on preeclampsia are needed to determine whether the hemodynamic advantages of norepinephrine translate into clinically important maternal or neonatal benefit.

Keywords: Preeclampsia; Spinal anesthesia; Cesarean delivery; Hypotension; Phenylephrine; Norepinephrine; Ephedrine; Vasopressors

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1. Introduction

Preeclampsia is a multisystem hypertensive disorder of pregnancy characterized by new-onset hypertension after 20 weeks of gestation with proteinuria and/or maternal organ dysfunction. Its pathophysiology includes abnormal placentation, endothelial dysfunction, altered angiogenic signaling, increased vascular resistance, and variable intravascular volume status [1-4]. These features create a hemodynamic phenotype that differs substantially from uncomplicated pregnancy and make abrupt reductions in arterial pressure potentially

important for both maternal organ perfusion and an already vulnerable uteroplacental circulation.

For cesarean delivery, neuraxial anesthesia is generally preferred to general anesthesia when no contraindication exists because it avoids airway instrumentation, reduces exposure to general anesthetic drugs, and permits the mother to remain awake. Contemporary reviews support the safety of spinal anesthesia even in severe preeclampsia when coagulation status, neurologic symptoms, and overall clinical condition are appropriate [5]. Importantly, several comparative studies have shown that patients

with severe preeclampsia may experience less frequent or less profound spinal-induced hypotension than healthy normotensive parturients, probably because of higher baseline vascular tone and altered sympathetic physiology [6-8]. Lower incidence, however, does not imply that hypotension is benign when it occurs.

Spinal anesthesia produces rapid sympathetic blockade, venous pooling, and decreased systemic vascular resistance. In cesarean delivery, these effects are superimposed on aortocaval compression and the large cardiovascular changes of late pregnancy [9-12]. Maternal hypotension can cause nausea, vomiting, dizziness, impaired consciousness, and, when severe or prolonged, compromised uteroplacental perfusion and fetal acid-base disturbance. Modern obstetric anesthesia therefore treats blood-pressure control as an active component of spinal anesthesia rather than a complication to be addressed only after prolonged hypotension [10-15].

The choice of vasopressor has evolved considerably. Ephedrine was historically preferred because of concern that direct alpha-adrenergic agonists would reduce uterine blood flow [16-18]. Subsequent human studies and meta-analyses shifted practice toward phenylephrine because of more predictable blood-pressure control and more favorable fetal acid-base findings in many low-risk elective cesarean populations [19-23]. More recently, norepinephrine has emerged as an attractive alternative because its modest beta1-adrenergic activity may preserve maternal heart rate and cardiac output better than phenylephrine while retaining potent alpha-mediated vasoconstriction [29-40].

The evidence becomes less straightforward when the clinical question is restricted to preeclampsia. Baseline vascular resistance, antihypertensive treatment, magnesium therapy, fetal growth restriction, prematurity, and placental dysfunction can all modify the physiological response to spinal anesthesia and vasopressors. The aim of this narrative review is therefore to compare intermittent bolus phenylephrine, norepinephrine, and ephedrine for the management of spinal-induced hypotension in preeclamptic patients undergoing cesarean delivery, focusing on maternal hemodynamic effects, adverse events, fetal and neonatal outcomes, and practical implications. Prophylactic infusion evidence is discussed where it clarifies pharmacology or comparative safety, but is distinguished from therapeutic rescue-bolus use throughout the review.

2. Preeclampsia and Spinal-Induced Hypotension

2.1 Hemodynamic phenotype of preeclampsia

Preeclampsia is not a uniform hemodynamic state. Some patients demonstrate high systemic vascular resistance with relatively low cardiac output, whereas others, particularly earlier in the disease process or

with less severe disease, may have more variable patterns. Endothelial dysfunction, vasoconstrictor sensitivity, capillary leak, and reduced effective circulating volume can coexist with hypertension [1-4]. Consequently, arterial pressure alone does not fully describe cardiovascular reserve. A vasopressor that restores systolic blood pressure at the cost of marked bradycardia or a fall in cardiac output may be physiologically different from one that restores pressure while better preserving flow.

Clinical studies comparing severely preeclamptic and normotensive parturients consistently challenge the assumption that preeclampsia necessarily increases susceptibility to spinal hypotension. Aya and colleagues reported less spinal-induced hypotension in severe preeclampsia than in healthy parturients, and subsequent work in preterm cesarean delivery reached a similar conclusion [6,7]. Other comparative data also show relative hemodynamic stability after spinal anesthesia in preeclampsia [8]. These observations are clinically reassuring, but they should not be interpreted as a reason to accept large pressure reductions. Preeclamptic placentas may already have impaired perfusion, and maternal cerebral, renal, and cardiac complications can coexist with the hypertensive disorder.

2.2 Why spinal anesthesia remains appropriate

Historically, severe preeclampsia raised concern that neuraxial sympathectomy might provoke dangerous hypotension. Accumulating evidence has instead supported spinal anesthesia as a practical and often advantageous technique when platelet count, coagulation status, and other clinical factors permit [5,9]. Avoidance of difficult or hypertensive airway responses is particularly relevant in preeclampsia, where airway edema and exaggerated pressor responses to laryngoscopy can increase risk. The principal intraoperative requirement is therefore not avoidance of spinal anesthesia, but anticipatory hemodynamic management with close blood-pressure surveillance and immediately available vasopressor therapy.

2.3 Defining and monitoring post-spinal hypotension

Definitions of spinal-induced hypotension vary across trials, complicating comparisons. Common thresholds include systolic arterial pressure below 80% of baseline, an absolute systolic pressure below 90 or 100 mmHg, or a combination of relative and absolute criteria [10-15]. International consensus for routine cesarean delivery emphasizes maintaining systolic pressure close to baseline and avoiding reductions below 80% of baseline [10]. In preeclampsia, however, blindly restoring pressure to a markedly hypertensive preoperative value may be undesirable. The clinically relevant target is adequate

maternal and uteroplacental perfusion without provoking severe reactive hypertension.

Frequent noninvasive blood-pressure measurements are essential during the first minutes after intrathecal injection because hemodynamic changes can develop rapidly. Heart rate is equally informative. Bradycardia after a pure alpha agonist can indicate a strong baroreflex response and may accompany reduced cardiac output, whereas tachycardia can reflect inadequate vasoconstriction, beta stimulation, anxiety, pain, blood loss, or excessive ephedrine exposure. In selected high-risk patients, advanced hemodynamic monitoring can clarify whether pressure restoration is accompanied by preservation of stroke volume and cardiac output, although such monitoring is not required routinely [26,29,55].

3. Vasopressor Pharmacology in Obstetric Anesthesia

3.1 Phenylephrine

Phenylephrine is a predominantly alpha1-adrenergic agonist that increases systemic vascular resistance and arterial pressure rapidly after intravenous administration. Its direct mechanism and short onset make it easy to titrate in small boluses. In obstetric anesthesia, phenylephrine became the reference vasopressor after randomized trials and meta-analyses showed effective blood-pressure control and, compared with ephedrine, generally higher umbilical arterial pH in healthy elective cesarean delivery [19-23]. These fetal acid-base findings helped overturn the earlier preference for ephedrine.

The principal physiological limitation of phenylephrine is reflex bradycardia. Increased arterial pressure activates the baroreflex, reducing heart rate; because phenylephrine lacks meaningful beta1 support, cardiac output can fall when the reduction in heart rate is substantial. Direct hemodynamic studies demonstrate that phenylephrine may restore systolic pressure while lowering heart rate and cardiac output [26-29]. In a patient whose baseline heart rate is already low, or in whom maintenance of forward flow is a priority, repeated boluses can therefore be less attractive despite excellent pressure efficacy.

3.2 Norepinephrine

Norepinephrine is a potent alpha-adrenergic agonist with modest beta1-adrenergic activity. At the small doses used in obstetric anesthesia, its alpha effect provides vasoconstriction while beta1 stimulation can attenuate reflex slowing of the heart and support cardiac output. The pivotal randomized comparison by Ngan Kee and colleagues demonstrated that norepinephrine maintained blood pressure effectively while producing higher heart rate and cardiac output and less bradycardia than

phenylephrine in healthy parturients [29]. Subsequent dose-response, bolus, infusion, systematic-review, and meta-analytic studies have generally confirmed this hemodynamic profile [30-40].

Norepinephrine is more potent than phenylephrine on a microgram-for-microgram basis, so direct numerical dose comparison is misleading. Dose-finding studies estimate that small norepinephrine boluses in the low microgram range can provide effects comparable with much larger phenylephrine doses [32,35,36]. Preparation and dilution therefore require meticulous attention. The clinical advantage of norepinephrine is not simply a higher blood pressure; rather, it is the possibility of restoring vascular tone with less bradycardia and less reduction in cardiac output.

3.3 Ephedrine

Ephedrine has mixed alpha- and beta-adrenergic activity and also increases endogenous catecholamine release. It tends to increase heart rate and contractility in addition to vascular tone. These properties explain its historical popularity for spinal hypotension, particularly when hypotension is accompanied by bradycardia [16-20]. Ephedrine remains useful and should not be considered obsolete, especially when a low heart rate suggests that chronotropic support is desirable.

Its limitations are equally important. Ephedrine can produce tachycardia, has a less immediately titratable relationship between dose and vascular response, and may develop tachyphylaxis after repeated administration. It also crosses the placenta more readily than phenylephrine and can stimulate fetal metabolism. Human placental-transfer studies provide a plausible explanation for the lower umbilical pH observed with ephedrine in many elective low-risk trials [20,21]. Yet this fetal acid-base disadvantage is not consistently reproduced in high-risk or preeclamptic populations, where disease-related placental physiology and the smaller available evidence base complicate interpretation [24,25].

3.4 Dose equivalence and the importance of bolus strategy

The terms “phenylephrine,” “norepinephrine,” and “ephedrine” do not describe a single intervention because dose, timing, indication, and route strongly influence outcome. Rescue boluses given after a documented hypotensive episode answer a different clinical question from prophylactic boluses or continuous infusions started immediately after spinal injection. Prophylactic infusion studies tend to reduce the overall burden of hypotension in healthy elective patients, whereas rescue-bolus studies are more directly relevant to a protocol in which the study drug is administered only when hypotension occurs [10,15,51,54].

Dose-response data also suggest that preeclamptic patients may require smaller vasopressor doses than normotensive parturients. In a comparative phenylephrine study, the estimated ED₅₀ for treatment of the first hypotensive episode was approximately one-third lower in severe preeclampsia than in normotensive pregnancy [43]. This finding supports careful titration rather than automatic transfer of dose regimens established in healthy elective populations. It also provides a physiologic reason to compare equipotent or clinically calibrated doses rather than nominally similar bolus sizes.

4. Clinical Evidence in Preeclamptic Parturients

4.1 Phenylephrine versus ephedrine

The broad obstetric literature strongly influenced the transition from ephedrine to phenylephrine. Early quantitative reviews and later meta-analyses found that both agents can treat spinal hypotension, but phenylephrine was associated with higher umbilical arterial pH when used therapeutically in many elective cesarean populations [19,22,23]. Placental-transfer work demonstrated greater fetal exposure to ephedrine and greater evidence of fetal metabolic stimulation [21]. These data established a compelling biological and clinical case for phenylephrine in routine low-risk obstetric anesthesia.

The preeclampsia-specific evidence is more nuanced. A randomized study in severe preeclampsia with fetal compromise found no significant difference between phenylephrine and ephedrine in umbilical arterial base excess, pH, lactate, or Apgar scores [25]. A high-risk meta-analysis similarly concluded that the available evidence was insufficient to establish a clear neonatal superiority of one drug in compromised populations [24]. Thus, the often-repeated statement that ephedrine necessarily worsens fetal acid-base status should be qualified when applied to preeclampsia. The low-risk evidence remains important, but the magnitude and clinical relevance of the difference may not be identical in placental disease.

4.2 Norepinephrine versus phenylephrine

Norepinephrine was initially evaluated largely in healthy elective parturients. Randomized infusion and bolus studies showed comparable blood-pressure control with less bradycardia and better maintenance of heart rate and cardiac output than phenylephrine [29,32-36]. Systematic reviews and meta-analyses generally found similar neonatal acid-base outcomes between the two drugs, while maternal bradycardia favored norepinephrine [38-40]. A large pragmatic non-inferiority trial further demonstrated non-inferior umbilical arterial pH with norepinephrine compared with phenylephrine across a broad cesarean population [40].

Direct evidence in preeclampsia is now more informative. In a randomized double-blind trial, Mohta and colleagues compared phenylephrine and norepinephrine for treatment of post-spinal hypotension in preeclamptic patients and found broadly similar maternal and neonatal outcomes, with the expected heart-rate differences between drugs [41]. A prophylactic infusion trial in preeclampsia also reported less bradycardia with norepinephrine while supporting its blood-pressure efficacy [42]. A 2024 meta-analysis restricted to preeclamptic patients concluded that norepinephrine and phenylephrine were similarly effective for blood-pressure control and neonatal outcomes, with lower maternal bradycardia under norepinephrine [48].

The most recent randomized rescue-bolus trial specifically enrolled preeclamptic women with severe features who developed hypotension after spinal anesthesia. Both norepinephrine and phenylephrine effectively rescued hypotensive events, but norepinephrine better preserved heart rate and cardiac output and produced less bradycardia [55]. Although the sample was small, the study directly addresses the clinical question that matters most for intermittent rescue treatment in severe preeclampsia and strengthens the physiological argument for norepinephrine in patients susceptible to phenylephrine-induced bradycardia.

4.3 Direct three-agent comparisons

Direct randomized comparisons of phenylephrine, norepinephrine, and ephedrine in preeclampsia are uncommon. Wang and colleagues compared bolus norepinephrine, phenylephrine, and ephedrine for maternal hypotension during cesarean delivery in preeclamptic parturients [37]. Blood-pressure efficacy was broadly comparable, but adverse-effect profiles differed in the expected direction: phenylephrine tended toward more bradycardia, ephedrine toward more tachycardia, and norepinephrine provided an intermediate chronotropic profile. The value of this design is that it compares the three drugs within a single disease-specific population rather than inferring across unrelated trials.

The 2025 network meta-analysis by Badran and colleagues synthesized randomized evidence specifically in preeclamptic patients and found no decisive difference in mean arterial pressure restoration among norepinephrine, phenylephrine, and ephedrine, while phenylephrine carried more bradycardia and norepinephrine showed favorable elements of maternal and umbilical acid-base outcomes [52]. A separate 2025 systematic review focusing on intermittent bolus vasopressors in preeclamptic cesarean delivery reached a similarly cautious conclusion: all three agents are effective, but

their adverse-effect profiles differ and the evidence is not sufficient to declare a universally best drug [53].

4.4 What prophylactic evidence contributes-and what it does not

Prophylactic vasopressor trials provide important information about comparative pharmacology, dose-response behavior, and fetal safety. Norepinephrine infusion studies, prophylactic bolus dose-finding work, and contemporary network meta-analyses consistently demonstrate that norepinephrine can prevent spinal hypotension effectively and usually causes less bradycardia than phenylephrine [33,42,44-47,50,54]. Continuous prophylactic infusions of either norepinephrine or phenylephrine also reduce the incidence of hypotension compared with waiting for hypotension to occur in many low-risk elective settings [15,51,54].

Nevertheless, prophylaxis and rescue should remain conceptually separate. A drug administered before blood pressure falls is being evaluated for prevention; the same drug given after a fall is being evaluated for treatment. The optimal dose and the balance between hypotension and reactive hypertension may therefore differ. This distinction is particularly important in preeclampsia, where the baseline pressure may be elevated and unnecessary prophylactic vasoconstriction could overshoot the desired target. Evidence from prophylactic infusion studies should support mechanistic reasoning, not replace direct rescue-bolus evidence.

4.5 Synthesis of contemporary meta-analytic evidence

Recent evidence syntheses increasingly separate healthy elective populations from high-risk or preeclamptic patients. A 2024 network meta-analysis of high-risk cesarean deliveries found no statistically definitive difference in hypotensive episodes among phenylephrine, norepinephrine, and ephedrine, although phenylephrine ranked highly for preventing hypotension and norepinephrine showed a favorable bradycardia profile [49]. A preeclampsia-specific 2024 meta-analysis found lower bradycardia with norepinephrine than phenylephrine with comparable fetal outcomes [48]. The 2025 preeclampsia network meta-analysis extended the comparison to all three agents and again emphasized broadly similar pressure efficacy with differing adverse-effect patterns [52].

Broader 2025 network evidence in cesarean delivery supports continuous phenylephrine or norepinephrine infusion as highly effective preventive approaches, with no consistent neonatal pH difference between the two drugs and more bradycardia under phenylephrine [54]. These findings strengthen confidence in norepinephrine's obstetric safety but should not obscure the narrower question of intermittent rescue boluses in preeclampsia. For that

question, the total number of direct randomized participants remains modest, and confidence intervals around uncommon maternal and neonatal outcomes are necessarily wide.

5. Maternal Hemodynamic and Adverse-Effect Outcomes

5.1 Restoration of arterial pressure

All three drugs can restore maternal arterial pressure after spinal-induced hypotension when appropriate doses are used. Differences in apparent efficacy may therefore reflect potency, dose selection, timing, and retreatment rules as much as intrinsic pharmacology. Phenylephrine typically provides a rapid and predictable increase in systemic vascular resistance. Norepinephrine produces a similarly rapid alpha-mediated pressor response at much smaller microgram doses. Ephedrine can also be effective, but its indirect component and beta stimulation can make the relationship between repeated boluses and blood-pressure response less linear [18,29,32,36,37].

For preeclamptic patients, avoiding both undertreatment and overshoot is important. Severe reactive hypertension can be undesirable in a disease already associated with cerebral and cardiovascular complications. The lower phenylephrine dose requirement demonstrated in severe preeclampsia suggests that dose calibration should account for the disease state [43]. Repeated one-size-fits-all boluses derived from normotensive populations may expose some patients to unnecessary vasoconstriction or bradycardia.

5.2 Heart rate, bradycardia, and tachycardia

Heart-rate behavior is one of the clearest differentiators among the three drugs. Phenylephrine commonly causes reflex bradycardia; norepinephrine causes less because modest beta1 activity offsets some baroreflex slowing; ephedrine more often increases heart rate [26,29,37-42,48,52,55]. These effects are not merely cosmetic. A low heart rate during phenylephrine treatment can coincide with reduced cardiac output, while excessive tachycardia during ephedrine treatment can increase myocardial oxygen demand and may be poorly tolerated in susceptible patients.

This pattern supports phenotype-based selection. Hypotension with marked bradycardia is a poor setting for repeated pure alpha agonism without considering chronotropic support. Conversely, hypotension accompanied by significant tachycardia may be a poor setting for repeated ephedrine. Norepinephrine can occupy a useful middle ground when preservation of heart rate and vascular tone are both desired. The 2026 severe-preeclampsia rescue trial is particularly relevant because it demonstrated superior preservation of heart rate with norepinephrine at the same time that pressure rescue remained comparable [55].

5.3 Cardiac output and systemic vascular resistance

Blood pressure is the product of flow and vascular resistance, so equivalent pressure does not guarantee equivalent hemodynamics. Phenylephrine can raise systemic vascular resistance while reducing heart rate and cardiac output. Norepinephrine also raises vascular resistance but tends to preserve cardiac output better because of its beta₁ effect [29,55]. This distinction may matter in preeclampsia, where cardiac phenotype varies and some patients have impaired diastolic function, pulmonary edema risk, or limited ability to tolerate abrupt changes in afterload.

Direct cardiac-output studies in preeclampsia remain limited. Consequently, a theoretical hemodynamic advantage should not be converted automatically into a claim of superior clinical outcome. The available evidence supports norepinephrine as a rational choice when cardiac-output preservation is desired, but larger trials are needed to determine whether modest short-term differences in flow translate into reduced maternal symptoms, organ injury, or neonatal morbidity.

5.4 Nausea, vomiting, arrhythmia, and reactive hypertension

Maternal nausea and vomiting during spinal anesthesia are closely linked to hypotension and reduced cerebral and gastrointestinal perfusion. Effective prevention or rapid treatment of hypotension therefore reduces nausea and vomiting regardless of the specific vasopressor [10,12,15]. High-risk network evidence suggests that phenylephrine and norepinephrine may be associated with less nausea or vomiting than ephedrine in some comparisons [49], although event definitions and prophylactic strategies vary.

Clinically significant arrhythmias are uncommon in the randomized literature, but drug-specific chronotropic effects remain relevant. Ephedrine can provoke tachycardia; phenylephrine can provoke bradycardia; norepinephrine can cause either bradycardia or tachycardia depending on dose and baseline physiology, though marked bradycardia is generally less frequent than with phenylephrine [37-42,48,52,55]. Reactive hypertension is possible with all three agents when dosing exceeds physiological need. This reinforces the importance of repeated reassessment rather than automatic sequential bolusing.

6. Fetal and Neonatal Outcomes

6.1 Placental transfer and fetal acid-base status

The fetal acid-base debate has shaped obstetric vasopressor practice for decades. Animal work initially generated concern that alpha agonists might reduce uteroplacental blood flow [17]. Human evidence later demonstrated that maintaining maternal

pressure with phenylephrine is not inherently harmful and that ephedrine, despite its beta activity, can produce lower umbilical arterial pH in elective cesarean delivery [19-23]. The placental-transfer study by Ngan Kee and colleagues showed greater transfer of ephedrine and evidence of enhanced fetal metabolic activity, providing a mechanistic basis for this observation [21].

In preeclampsia, however, fetal acid-base findings are less uniform. Severe placental disease, fetal growth restriction, prematurity, urgency of delivery, and pre-existing fetal compromise may exert effects that are larger than modest drug-related differences. The randomized high-risk phenylephrine-versus-ephedrine trial found similar umbilical arterial acid-base values [25], and high-risk meta-analysis did not establish a clear neonatal winner [24]. Recent preeclampsia-specific syntheses suggest that norepinephrine is at least comparable with phenylephrine and ephedrine and may show favorable umbilical pH in some analyses, but the evidence remains imprecise [48,49,52,53].

6.2 Apgar scores and immediate neonatal condition

Apgar scores are easy to collect and clinically familiar but are relatively insensitive for detecting subtle drug-related physiological differences. Most comparative vasopressor trials report similar 1- and 5-minute Apgar outcomes among phenylephrine, norepinephrine, and ephedrine when maternal hypotension is treated promptly [25,29,37,40-42,48,52,55]. This consistency is reassuring but should not be interpreted as proof that all fetal effects are identical.

Umbilical arterial pH, base excess, lactate, and, where available, neonatal intensive-care admission provide additional context. Current evidence does not demonstrate a reproducible clinically important neonatal disadvantage with norepinephrine. The large pragmatic norepinephrine-versus-phenylephrine trial established non-inferiority for umbilical arterial pH in a broad cesarean population [40], and newer preeclampsia-specific evidence remains consistent with neonatal comparability [41,48,52,55].

6.3 Why preeclampsia-specific fetal evidence matters

It is tempting to extrapolate from thousands of healthy elective parturients to preeclampsia, but this can be misleading. Preeclampsia is frequently accompanied by placental insufficiency, altered uterine vascular resistance, preterm delivery, and fetal growth restriction. The same maternal blood-pressure change may therefore have a different fetal consequence. Moreover, urgent or non-elective delivery introduces confounding by fetal condition before the vasopressor is given.

Future trials should therefore report pre-delivery fetal status, gestational age, growth restriction, umbilical artery Doppler findings where clinically available, decision-to-delivery interval, total vasopressor exposure, and standardized cord blood gas sampling. Without this context, a small between-group difference in pH may be difficult to attribute to the drug rather than to the obstetric disease or the timing of delivery.

7. A Practical Perioperative Approach

7.1 Prevention and preparation

Management begins before spinal injection. Baseline blood pressure should be measured carefully, ideally using repeated readings rather than a single anxious preoperative value. The anesthesia team should review the severity of preeclampsia, antihypertensive therapy, magnesium administration, symptoms of severe features, fluid status, platelet count, fetal status, and urgency of delivery. Left uterine displacement, appropriate fluid administration, frequent blood-pressure measurement, and immediately prepared vasopressors remain fundamental [5,9-15].

General consensus in routine elective cesarean delivery favors proactive prevention of spinal hypotension, usually with an alpha-adrenergic vasopressor [10,14,15]. In preeclampsia, however, the lower observed incidence and reduced vasopressor requirement justify a more individualized approach. A prophylactic infusion can be appropriate in selected patients and has supporting evidence for both phenylephrine and norepinephrine [42,54], but routine aggressive prophylaxis should not be assumed necessary for every hypertensive patient. The target is stable perfusion, not normalization to an arbitrarily high pre-spinal pressure.

7.2 Selecting the rescue vasopressor by hemodynamic phenotype

When hypotension occurs, drug selection can be guided by the accompanying heart rate and the clinical context. Phenylephrine is a strong option when rapid vasoconstriction is needed and heart rate is normal or elevated. Norepinephrine is attractive when similar pressor efficacy is desired with less tendency toward bradycardia or reduction in cardiac output. Ephedrine remains reasonable when hypotension is accompanied by clinically important bradycardia and beta-adrenergic support is advantageous. None of these rules should be treated as absolute, and local formulation, clinician familiarity, and medication safety systems are important considerations.

The literature demonstrates why dose equivalence matters. Studies have used phenylephrine boluses commonly in the tens of micrograms, norepinephrine in the low single-digit to low double-digit microgram range, and ephedrine in milligram doses [25,32,35-

37,41,43,55]. The purpose of citing these regimens is to explain trial interpretation, not to prescribe a universal bedside dose. Institutional protocols should determine drug preparation and dosing, with special attention to norepinephrine dilution because small concentration errors can produce large clinical effects.

7.3 Reassessment after each bolus

A rescue bolus should be followed by prompt reassessment of systolic pressure, mean pressure, heart rate, symptoms, surgical events, and the possibility of ongoing blood loss. Repeated hypotension despite apparently adequate vasopressor dosing should trigger evaluation of block height, aortocaval compression, hemorrhage, medication effects, and other causes rather than endless repetition of the same bolus. Likewise, reactive hypertension or marked bradycardia should prompt dose adjustment or a change in agent.

This feedback-based approach is particularly important in preeclampsia, where the therapeutic window may be narrower. The phenylephrine dose-response study demonstrates lower requirements in severe preeclampsia [43], while the newer norepinephrine data suggest that pressure can be restored with better preservation of heart rate and cardiac output [55]. Together, these findings favor titration to response rather than fixed escalation detached from the patient's physiology.

7.4 Fluids, magnesium, and antihypertensive therapy

Vasopressor treatment should not be considered in isolation from fluid strategy. Excessive crystalloid loading is undesirable in preeclampsia because endothelial dysfunction and reduced colloid oncotic pressure increase pulmonary edema risk. Modern management therefore emphasizes judicious fluid administration combined with vasopressors rather than large-volume preload [5,11-15]. The appropriate amount depends on fasting status, hemorrhage, urine output, cardiac function, and the broader obstetric context.

Magnesium sulfate can contribute to vasodilation and may influence neuromuscular and cardiovascular responses, while labetalol and other antihypertensive drugs alter baseline heart rate and vascular tone. These treatments can modify the apparent effect of a rescue vasopressor and should be documented in clinical trials. A patient receiving beta blockade who develops hypotension and bradycardia may not respond physiologically in the same way as a patient with untreated tachycardia and high vascular resistance. Future comparative work should stratify or adjust for these co-interventions more consistently.

7.5 A pragmatic intermittent-bolus framework

For a preeclamptic patient who develops spinal-induced hypotension, a pragmatic framework is:

confirm the pressure fall and clinical context; assess heart rate and symptoms; correct positioning and obvious mechanical contributors; administer the locally standardized rescue vasopressor appropriate to the hemodynamic phenotype; reassess within the short interval expected for drug effect; repeat or change therapy if hypotension persists; and avoid overshoot into severe hypertension. Fetal status and the progress of delivery remain part of the same decision pathway.

This framework is intentionally not a prescriptive dosing guideline. The literature does not yet establish one universally superior intermittent-bolus regimen for preeclampsia. The most defensible current position is that phenylephrine, norepinephrine, and ephedrine are all effective pressors; norepinephrine offers a consistent advantage in heart-rate preservation compared with phenylephrine; ephedrine provides greater chronotropic support but has fetal metabolic and tachycardia concerns; and the best agent depends on the patient's immediate physiology and the dose used [37,41,48,52,53,55].

8. Obstacles and Limitations

The literature has several limitations that prevent a definitive ranking of the three vasopressors. First, the largest evidence base comes from healthy term parturients undergoing elective cesarean delivery, whereas the population of interest is preeclamptic and often preterm or otherwise high risk. Extrapolation is biologically plausible but not equivalent to direct evidence. Disease-specific meta-analyses have improved this situation, yet they remain dependent on a relatively small number of trials [24,48,49,52,53].

Second, hypotension definitions, baseline blood-pressure methods, vasopressor doses, retreatment intervals, and endpoints vary. A trial using a systolic threshold of 80% of baseline is not directly interchangeable with one using an absolute threshold, and a 50-microgram phenylephrine bolus cannot be compared fairly with an arbitrary norepinephrine dose without considering relative potency. Some studies evaluate prevention, others treatment, and others combine the two. This clinical heterogeneity can dilute or exaggerate apparent drug differences.

Third, "preeclampsia" includes a wide spectrum of disease. Trials differ in severity, gestational age, fetal growth restriction, antihypertensive exposure, magnesium therapy, and urgency of cesarean delivery. These factors influence maternal hemodynamics and fetal acid-base status independently of the vasopressor. Small trials may therefore be balanced imperfectly even after randomization.

Fourth, many studies are powered for maternal hypotension or heart-rate outcomes rather than uncommon clinically important neonatal events. Similar Apgar scores and mean umbilical pH do not exclude small differences in rare severe acidosis,

neonatal intensive-care admission, or longer-term neonatal outcomes. Conversely, statistically significant differences in cord pH may be too small to have clinical significance. Interpretation should therefore consider both effect size and clinical context.

Finally, norepinephrine research has expanded rapidly, and practice has sometimes moved faster than the disease-specific evidence. Its hemodynamic advantages are consistent, but claims of universal superiority would be premature. The 2026 severe-preeclampsia rescue trial is directly relevant but included only 40 patients [55]. Larger multicenter studies using standardized equipotent bolus protocols are required before a specific norepinephrine regimen can be regarded as definitively optimal for preeclampsia.

9. Future Directions

Future research should prioritize direct, adequately powered comparisons in preeclamptic patients rather than continued reliance on extrapolation from healthy elective cesarean delivery. Trials should stratify preeclampsia with and without severe features, document gestational age and fetal growth restriction, and standardize the definition of post-spinal hypotension. Because baseline hypertension varies widely, studies should predefine clinically sensible lower and upper blood-pressure limits rather than use only a single relative threshold.

Dose equivalence is a central research need. Sequential allocation and dose-response methods have clarified relative potency in general obstetric populations [32,35,43,44,47], but preeclampsia-specific equipotent comparisons remain limited. A multicenter trial comparing calibrated intermittent boluses of phenylephrine, norepinephrine, and ephedrine could evaluate not only treatment success but also number of repeat boluses, time outside the target pressure range, bradycardia, tachycardia, reactive hypertension, nausea and vomiting, and total vasopressor exposure.

Maternal hemodynamic research should move beyond arterial pressure alone. Noninvasive cardiac-output monitoring could determine whether the heart-rate and cardiac-output advantages of norepinephrine are consistent across different preeclamptic phenotypes and whether they have clinical consequences [29,55]. Maternal cerebral symptoms, pulmonary edema, myocardial injury, acute kidney injury, and postoperative recovery are uncommon but meaningful endpoints for larger collaborative studies.

Neonatal assessment should be equally rigorous. Standardized umbilical arterial and venous blood gases, lactate, Apgar scores, resuscitation requirements, and neonatal intensive-care admission should be reported together with the pre-delivery fetal condition. Longer-term neonatal outcomes are rarely

studied and may not be feasible in every trial, but registry linkage or pragmatic follow-up could determine whether small physiological differences at delivery have lasting relevance.

Finally, future studies should evaluate decision algorithms rather than only individual drugs. A heart-rate-guided strategy, for example, could compare phenylephrine in tachycardic patients, norepinephrine in those with normal heart rate, and ephedrine or combined chronotropic support in bradycardic patients against a single-agent strategy. Such precision hemodynamic management may prove more clinically useful than asking whether one vasopressor is universally best for every preeclamptic patient.

10. Conclusion

Intermittent bolus phenylephrine, norepinephrine, and ephedrine are all capable of treating spinal-induced hypotension during cesarean delivery in patients with preeclampsia. Phenylephrine offers rapid and predictable alpha-adrenergic vasoconstriction and extensive obstetric experience, but its tendency to produce reflex bradycardia and reduce cardiac output is clinically relevant. Ephedrine provides useful beta-adrenergic and chronotropic support, but repeated administration may cause tachycardia and greater fetal drug exposure; the fetal acid-base disadvantage seen in low-risk populations is less consistently demonstrated in preeclampsia. Norepinephrine provides effective pressure restoration with better preservation of heart rate and cardiac output than phenylephrine in many studies and has not shown a reproducible neonatal disadvantage.

The preeclampsia-specific evidence therefore supports norepinephrine as an increasingly compelling alternative, particularly when avoidance of bradycardia or preservation of cardiac output is important, but it does not establish universal superiority. Differences in disease severity, baseline heart rate, antihypertensive and magnesium therapy, fetal condition, dose equivalence, and whether the drug is used prophylactically or therapeutically all influence the balance of benefit and risk. Current practice is best served by rapid recognition of hypotension, careful dose titration, and hemodynamic phenotype-based vasopressor selection. Larger multicenter trials focused specifically on intermittent rescue boluses in preeclampsia are needed to define the optimal agent and dose with greater certainty.

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Conflicts of Interest

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References

1. **American College of Obstetricians and Gynecologists (2020):** Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. *Obstetrics & Gynecology*, 135(6): e237-e260.
<https://doi.org/10.1097/AOG.0000000000003891>
2. **Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R (2010):** Pre-eclampsia. *The Lancet*, 376(9741): 631-644.
[https://doi.org/10.1016/S0140-6736\(10\)60279-6](https://doi.org/10.1016/S0140-6736(10)60279-6)
3. **Rana S, Lemoine E, Granger JP, Karumanchi SA (2019):** Preeclampsia: Pathophysiology, challenges, and perspectives. *Circulation Research*, 124(7): 1094-1112.
<https://doi.org/10.1161/CIRCRESAHA.118.313276>
4. **Erez O, Romero R, Jung E et al. (2022):** Preeclampsia and eclampsia: The conceptual evolution of a syndrome. *American Journal of Obstetrics and Gynecology*, 226(2S): S786-S803.
<https://doi.org/10.1016/j.ajog.2021.12.001>
5. **Henke VG, Bateman BT, Leffert LR (2013):** Focused review: Spinal anesthesia in severe preeclampsia. *Anesthesia & Analgesia*, 117(3): 686-693.
<https://doi.org/10.1213/ANE.0b013e31829eef5>
6. **Aya AGM, Mangin R, Vialles N et al. (2003):** Patients with severe preeclampsia experience less hypotension during spinal anesthesia for elective cesarean delivery than healthy parturients: A prospective cohort comparison. *Anesthesia & Analgesia*, 97(3): 867-872.
<https://doi.org/10.1213/01.ANE.0000073610.23885.F2>
7. **Aya AGM, Vialles N, Tanoubi I et al. (2005):** Spinal anesthesia-induced hypotension: A risk comparison between patients with severe preeclampsia and healthy women undergoing preterm cesarean delivery. *Anesthesia & Analgesia*, 101(3): 869-875.
<https://doi.org/10.1213/01.ANE.0000175229.98493.2B>
8. **Nikooseresht M, Seifrabiei MA, Hajian P, Abdi S (2016):** Comparing the hemodynamic effects of spinal anesthesia in preeclamptic and healthy

- parturients during cesarean section. *Anesthesiology and Pain Medicine*, 6(3): e11519. <https://doi.org/10.5812/aapm.11519>
9. **Pirenne V, Dewinter G, Van de Velde M (2023):** Spinal anaesthesia in obstetrics. *Best Practice & Research Clinical Anaesthesiology*, 37(2): 101-108. <https://doi.org/10.1016/j.bpa.2023.03.006>
10. **Kinsella SM, Carvalho B, Dyer RA et al. (2018):** International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. *Anaesthesia*, 73(1): 71-92. <https://doi.org/10.1111/anae.14080>
11. **van Dyk D, Dyer RA, Bishop DG (2022):** Spinal hypotension in obstetrics: Context-sensitive prevention and management. *Best Practice & Research Clinical Anaesthesiology*, 36(1): 69-82. <https://doi.org/10.1016/j.bpa.2022.04.001>
12. **Hasanin A, Mokhtar AM, Badawy AA, Fouad R (2017):** Post-spinal anesthesia hypotension during cesarean delivery, a review article. *Egyptian Journal of Anaesthesia*, 33(2): 189-193. <https://doi.org/10.1016/j.egja.2017.03.003>
13. **Loubert C (2012):** Fluid and vasopressor management for Cesarean delivery under spinal anesthesia: Continuing Professional Development. *Canadian Journal of Anesthesia*, 59(6): 604-619. <https://doi.org/10.1007/s12630-012-9705-9>
14. **Chooi C, Cox JJ, Lumb RS et al. (2017):** Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database of Systematic Reviews*, 8: CD002251. <https://doi.org/10.1002/14651858.CD002251.pub3>
15. **Fitzgerald JP, Fedoruk KA, Jadin SM, Carvalho B, Halpern SH (2020):** Prevention of hypotension after spinal anaesthesia for caesarean section: A systematic review and network meta-analysis of randomised controlled trials. *Anaesthesia*, 75(1): 109-121. <https://doi.org/10.1111/anae.14841>
16. **Rout CC, Rocke DA (1994):** Prevention of hypotension following spinal anesthesia for caesarean section. *International Anesthesiology Clinics*, 32(2): 117-135. <https://doi.org/10.1097/00004311-199432020-00010>
17. **Ralston DH, Shnider SM, deLorimier AA (1974):** Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. *Anesthesiology*, 40(4): 354-370. <https://doi.org/10.1097/00000542-197404000-00009>
18. **Macarthur A, Riley ET (2007):** Obstetric anesthesia controversies: Vasopressor choice for postspinal hypotension during cesarean delivery. *International Anesthesiology Clinics*, 45(1): 115-132. <https://doi.org/10.1097/AIA.0b013e31802b8d53>
19. **Lee A, Ngan Kee WD, Gin T (2002):** A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. *Anesthesia & Analgesia*, 94(4): 920-926. <https://doi.org/10.1097/00000539-200204000-00028>
20. **Cooper DW, Carpenter M, Mowbray P et al. (2002):** Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*, 97(6): 1582-1590. <https://doi.org/10.1097/00000542-200212000-00034>
21. **Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK (2009):** Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*, 111(3): 506-512. <https://doi.org/10.1097/ALN.0b013e3181b160a3>
22. **Lin FQ, Qiu MT, Ding XX, Fu SK, Li Q (2012):** Ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean section: An updated meta-analysis. *CNS Neuroscience & Therapeutics*, 18(7): 591-597. <https://doi.org/10.1111/j.1755-5949.2012.00345.x>
23. **Xu C, Liu S, Huang Y et al. (2018):** Phenylephrine vs ephedrine in cesarean delivery under spinal anesthesia: A systematic literature review and meta-analysis. *International Journal of Surgery*, 60: 48-59. <https://doi.org/10.1016/j.ijsu.2018.10.039>
24. **Heesen M, Rijs K, Hilber N et al. (2019):** Ephedrine versus phenylephrine as a vasopressor for spinal anaesthesia-induced hypotension in parturients undergoing high-risk caesarean section: Meta-analysis, meta-regression and trial sequential analysis. *International Journal of Obstetric Anesthesia*, 37: 16-28. <https://doi.org/10.1016/j.ijoa.2018.10.006>
25. **Dyer RA, Emmanuel A, Adams SC et al. (2018):** A randomised comparison of bolus phenylephrine and ephedrine for the management of spinal hypotension in patients with severe preeclampsia and fetal compromise. *International*

- Journal of Obstetric Anesthesia, 33: 23-31.
<https://doi.org/10.1016/j.ijoa.2017.08.001>
26. **Dyer RA, Reed AR, van Dyk D et al. (2009):** Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. *Anesthesiology*, 111(4): 753-765.
<https://doi.org/10.1097/ALN.0b013e3181b437e0>
27. **Habib AS (2012):** A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. *Anesthesia & Analgesia*, 114(2): 377-390.
<https://doi.org/10.1213/ANE.0b013e3182373a3e>
28. **Kuhn JC, Hauge TH, Rosseland LA, Dahl V, Langesaeter E (2016):** Hemodynamics of phenylephrine infusion versus lower extremity compression during spinal anesthesia for cesarean delivery: A randomized, double-blind, placebo-controlled study. *Anesthesia & Analgesia*, 122(4): 1120-1129.
<https://doi.org/10.1213/ANE.0000000000001174>
29. **Ngan Kee WD, Lee SWY, Ng FF, Tan PE, Khaw KS (2015):** Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. *Anesthesiology*, 122(4): 736-745.
<https://doi.org/10.1097/ALN.0000000000000601>
30. **Carvalho B, Dyer RA (2015):** Norepinephrine for spinal hypotension during cesarean delivery: Another paradigm shift? *Anesthesiology*, 122(4): 728-730.
<https://doi.org/10.1097/ALN.0000000000000602>
31. **Mets B (2016):** Should norepinephrine, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesthesia & Analgesia*, 122(6): 1707-1714.
<https://doi.org/10.1213/ANE.0000000000001239>
32. **Ngan Kee WD (2017):** A random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology*, 127(6): 934-941.
<https://doi.org/10.1097/ALN.0000000000001880>
33. **Ngan Kee WD, Lee SWY, Ng FF, Khaw KS (2018):** Prophylactic norepinephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. *Anesthesia & Analgesia*, 126(6): 1989-1994.
<https://doi.org/10.1213/ANE.0000000000002243>
34. **Vallejo MC, Attaallah AF, Elzamzamy OM et al. (2017):** An open-label randomized controlled clinical trial for comparison of continuous phenylephrine versus norepinephrine infusion in prevention of spinal hypotension during cesarean delivery. *International Journal of Obstetric Anesthesia*, 29: 18-25.
<https://doi.org/10.1016/j.ijoa.2016.08.005>
35. **Puthenveetil N, Sivachalam SN, Rajan S, Paul J, Kumar L (2019):** Comparison of norepinephrine and phenylephrine boluses for the treatment of hypotension during spinal anaesthesia for caesarean section: A randomised controlled trial. *Indian Journal of Anaesthesia*, 63(12): 995-1000.
https://doi.org/10.4103/ija.IJA_481_19
36. **Mohta M, Dubey M, Malhotra RK, Tyagi A (2019):** Comparison of the potency of phenylephrine and norepinephrine bolus doses used to treat post-spinal hypotension during elective caesarean section. *International Journal of Obstetric Anesthesia*, 38: 25-31.
<https://doi.org/10.1016/j.ijoa.2018.12.002>
37. **Wang X, Mao M, Liu S, Xu S, Yang J (2019):** A comparative study of bolus norepinephrine, phenylephrine, and ephedrine for the treatment of maternal hypotension in parturients with preeclampsia during cesarean delivery under spinal anesthesia. *Medical Science Monitor*, 25: 1093-1101.
<https://doi.org/10.12659/MSM.914143>
38. **Xu S, Shen X, Liu S, Yang J, Wang X (2019):** Efficacy and safety of norepinephrine versus phenylephrine for the management of maternal hypotension during cesarean delivery with spinal anesthesia: A systematic review and meta-analysis. *Medicine*, 98(5): e14331.
<https://doi.org/10.1097/MD.00000000000014331>
39. **Heesen M, Hilber N, Rijs K et al. (2020):** A systematic review of phenylephrine vs. noradrenaline for the management of hypotension associated with neuraxial anaesthesia in women undergoing caesarean section. *Anaesthesia*, 75(6): 800-808. <https://doi.org/10.1111/anae.14976>
40. **Ngan Kee WD, Lee SWY, Ng FF, Lee A (2020):** Norepinephrine or phenylephrine during spinal anaesthesia for Caesarean delivery: A randomised double-blind pragmatic non-inferiority study of neonatal outcome. *British Journal of Anaesthesia*, 125(4): 588-595.
<https://doi.org/10.1016/j.bja.2020.05.057>
41. **Mohta M, Lakshmi R, Chilkoti GT, Agarwal R, Malhotra RK (2021):** A randomised double-blind comparison of phenylephrine and norepinephrine for the management of postspinal hypotension in pre-eclamptic patients undergoing caesarean section. *European Journal of Anaesthesiology*, 38(10): 1077-1084.
<https://doi.org/10.1097/EJA.0000000000001461>

42. **Guo L, Qin R, Ren X et al. (2022):** Prophylactic norepinephrine or phenylephrine infusion for bradycardia and post-spinal anaesthesia hypotension in patients with preeclampsia during Caesarean delivery: A randomised controlled trial. *British Journal of Anaesthesia*, 128(5): e305-e307. <https://doi.org/10.1016/j.bja.2022.01.027>
43. **Hu LJ, Mei Z, Shen YP et al. (2022):** Comparative dose-response study of phenylephrine bolus for the treatment of the first episode of spinal anesthesia-induced hypotension for cesarean delivery in severe preeclamptic versus normotensive parturients. *Drug Design, Development and Therapy*, 16: 2189-2198. <https://doi.org/10.2147/DDDT.S368480>
44. **Xu W, Drzymalski DM, Ai L et al. (2021):** The ED50 and ED95 of prophylactic norepinephrine for preventing post-spinal hypotension during cesarean delivery under combined spinal-epidural anesthesia: A prospective dose-finding study. *Frontiers in Pharmacology*, 12: 691809. <https://doi.org/10.3389/fphar.2021.691809>
45. **Li Y, Shuai B, Huang H (2023):** Prophylactic intravenous norepinephrine for the prevention of hypotension during spinal anesthesia for elective cesarean section: A systematic review and dose-response meta-analysis of randomized controlled trials. *Frontiers in Pharmacology*, 14: 1247214. <https://doi.org/10.3389/fphar.2023.1247214>
46. **Xue X, Lv X, Ma X et al. (2023):** Prevention of spinal hypotension during cesarean section: A systematic review and Bayesian network meta-analysis based on ephedrine, phenylephrine, and norepinephrine. *Journal of Obstetrics and Gynaecology Research*, 49(7): 1651-1662. <https://doi.org/10.1111/jog.15671>
47. **Guo L, Xu X, Qin R et al. (2023):** Prophylactic norepinephrine and phenylephrine boluses to prevent postspinal anesthesia hypotension during cesarean section: A randomized sequential allocation dose-finding study. *Drug Design, Development and Therapy*, 17: 1547-1555. <https://doi.org/10.2147/DDDT.S406671>
48. **Ahmed S, Ahmad E, Fatima E et al. (2024):** Efficacy and safety of norepinephrine versus phenylephrine for post-spinal hypotension in preeclamptic patients: A systematic review and meta-analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 303: 91-98. <https://doi.org/10.1016/j.ejogrb.2024.10.012>
49. **Zhao S, Chen Q, Qin P, Liu L, Wei K (2024):** Comparison of vasopressors for management of hypotension in high-risk caesarean section under neuraxial anesthesia: A systematic review and network meta-analysis. *BMC Anesthesiology*, 24(1): 447. <https://doi.org/10.1186/s12871-024-02819-9>
50. **Kang H, Sung TY, Jee YS et al. (2024):** A comparison of norepinephrine versus phenylephrine to prevent hypotension after spinal anesthesia for cesarean section: Systematic review and meta-analysis. *Journal of Personalized Medicine*, 14(8): 803. <https://doi.org/10.3390/jpm14080803>
51. **Garg H, Narayanan MRV, Khanna P, Yalla B (2024):** Comparison of phenylephrine bolus and infusion regimens on maternal and fetal outcomes during cesarean delivery: A systematic review and meta-analysis. *Anesthesia & Analgesia*, 139(6): 1144-1155. <https://doi.org/10.1213/ANE.0000000000007156>
52. **Badran AS, Shata KS, Elgammal A et al. (2025):** Comparison of phenylephrine, ephedrine, and norepinephrine for the prevention and treatment of spinal-induced hypotension in preeclamptic patients undergoing caesarean section: A systematic review and network meta-analysis. *Indian Journal of Anaesthesia*, 69(6): 526-539. https://doi.org/10.4103/ija.ija_62_25
53. **Gunawan MFB, Soetomo CT, Richard R, Darmayasa PB, Suastika AV (2025):** Dissecting vasopressor efficacy in the management of maternal hypotension in preeclamptic cesarean delivery: A systematic review of randomized controlled trials. *Maternal-Fetal Medicine*, 7(4): 234-243. <https://doi.org/10.1097/FM9.0000000000000314>
54. **Imai E, Kataoka Y, Watanabe J et al. (2025):** Norepinephrine vs. phenylephrine for spinal hypotension in cesarean section: A network meta-analysis. *Journal of Anesthesia*, 39(6): 849-868. <https://doi.org/10.1007/s00540-025-03528-4>
55. **Zou L, Li H, Shi Y, Xi N, Chen Y (2026):** The hemodynamic effects of bolus norepinephrine and phenylephrine in the treatment of hypotensive events in preeclamptic women with severe features following spinal anesthesia during cesarean section: A randomized controlled trial. *Frontiers in Pharmacology*, 17: 1783419. <https://doi.org/10.3389/fphar.2026.1783419>