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EFFICACY OF ORAL NIFEDIPINE VERSUS LABETALOL IN THE EMERGENCY MANAGEMENT OF HYPERTENSIVE CRISIS IN PREGNANCY: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction: Hypertensive disorders complicate one in ten pregnancies and remain leading causes of maternal mortality worldwide. Severe hypertension (SBP ≥160 mmHg and/or DBP ≥110 mmHg) constitutes an obstetric emergency due to imminent risks of intracerebral hemorrhage, eclampsia, pulmonary edema, and placental abruption. Oral nifedipine and labetalol are the most widely used first-line agents, yet comparative evidence remains fragmented. This review aimed to determine whether oral nifedipine differs from labetalol in acute control of hypertensive crisis in pregnancy across fifteen pre-specified clinical outcomes.

Methods: A systematic review was conducted per PRISMA 2020 guidelines. Eligible designs included RCTs, quasi-experimental trials, prospective/retrospective cohorts, case-control, and cross-sectional studies comparing nifedipine with labetalol in pregnant

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women with severe hypertension. Risk of bias was appraised with Cochrane RoB 2 and ROBINS-I; certainty with GRADE. A binormal ROC reconstruction was performed for time-to-target blood pressure, with AUC representing probability of earlier attainment.

Results: Twenty-one primary studies (15 RCTs, 1 quasi-experimental, 2 prospective cohorts, 3 retrospective cohorts) comprising ≥9,889 pregnant women from ten countries were included. Oral nifedipine reached target BP significantly faster than labetalol: pooled MD -9.10 minutes (95% CI -13.69 to -4.51; τ^2=11.55; I^2=44.2%). Reconstructed pooled AUC was 0.668 (95% CI 0.609-0.727; I^2=0.0%), significantly exceeding 0.500. Nifedipine required fewer doses, produced greater systolic/diastolic reduction, and increased urine output. Maternal/perinatal adverse events, caesarean delivery, fetal heart-rate abnormality, Apgar<7, and NICU admission did not differ significantly. One large observational cohort favored labetalol for composite maternal morbidity (aRR 1.33, 95% CI 1.07-1.64). Risk of bias was low in 5/15 RCTs, moderate-to-serious in all non-randomized studies. GRADE certainty was moderate for time-to-target and dose requirement, low/very low for patient-important outcomes.

Discussion: Nifedipine's pharmacodynamic superiority in speed and dose economy is consistent, mechanistically coherent, and reproducible. However, speed is a surrogate outcome; the largest observational dataset raises signals of increased eclampsia, HELLP, and renal failure with nifedipine. The AUC of 0.668 quantifies the advantage as modest—statistically significant but far from the >0.80 threshold justifying categorical protocol change.

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Conclusion: Oral nifedipine controls hypertensive crisis significantly faster with fewer doses than labetalol, with a moderate discriminative advantage (AUC 0.668) and equivalent maternal/perinatal safety in randomized evidence. Requiring no IV access, infusion pump, or continuous cardiotocography, nifedipine should be regarded as a legitimate first-line option—and in resource-constrained settings, the preferred option.

Keywords: nifedipine, labetalol, hypertensive crisis, severe pre-eclampsia, obstetric emergency

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INTRODUCTION

Background

Hypertensive disorders of pregnancy (HDP) constitute one of the most consequential clinical problems in contemporary obstetrics. They complicate approximately 5–10% of all pregnancies and account for an estimated 14% of maternal deaths globally; the proportion rises to roughly 26% of maternal deaths in Latin America and the Caribbean and approximately 9% in Africa and Asia, while even in high-income settings some 16% of maternal deaths are attributable to hypertensive disease. The World Health Organization Multicountry Survey, encompassing 357 facilities across 29 countries, documented an overall hypertensive-disorder incidence of 2.73%, with pre-eclampsia at 2.16% and eclampsia at 0.28%, and demonstrated that maternal near-miss events were eight-fold more frequent in women with pre-eclampsia and up to sixty-fold more frequent in women with eclampsia relative to normotensive parturients.[1,4]

Global Burden of Disease analyses confirm that the absolute burden has not disappeared despite falling age-standardised rates. The number of incident maternal hypertensive disorders worldwide rose by 10.9% between 1990 and 2019 and by 15.2% between 1990 and 2021 (from approximately 15.7 million to 18.1 million cases), even as the age-standardised incidence rate fell from 554 to 462 per 100 000 and disability-adjusted life-years declined by approximately 29%. Crucially, the burden is concentrated in low- and middle-sociodemographic-index regions — sub-Saharan Africa and South Asia — precisely the settings where intravenous therapy, infusion pumps and continuous electronic fetal monitoring are least available. This inverse relationship between disease burden and therapeutic infrastructure is the central health-systems argument that motivates the present review.[3,5,6,7]

Within the spectrum of HDP, severe or crisis-range hypertension — defined by the American College of Obstetricians and Gynecologists as an acute-onset, persistent systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 110 mm Hg or higher, sustained for at least 15 minutes — represents a distinct emergency phenotype. At these pressures the upper

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limit of cerebral autoregulation is exceeded, endothelial tight junctions fail, and the risk of intracerebral haemorrhage, posterior reversible encephalopathy, eclamptic seizure, acute pulmonary oedema, placental abruption, acute kidney injury and HELLP syndrome rises steeply and non-linearly. The American Heart Association scientific statement on hypertension in pregnancy therefore frames the acute treatment of severe hypertension not as blood-pressure management but as stroke prevention, and mandates pharmacological therapy within 30–60 minutes of confirmation.[1,8]

The severity of the downstream consequences justifies this urgency. In a prospective cohort of 40 241 singleton pregnancies, maternal mortality or major morbidity occurred in 7.4% of women with preterm pre-eclampsia and 2.2% with term disease, while perinatal mortality or major neonatal morbidity reached 29.5% in preterm pre-eclampsia. Analysis of 15 714 940 United States deliveries showed that HELLP syndrome carried an adjusted risk ratio of 17.55 for cardiovascular severe maternal morbidity and severe pre-eclampsia a ratio of 9.11. In resource-limited settings the figures are starker still: among 103 Ugandan women with new-onset HDP, 93.2% had severe pre-eclampsia or eclampsia and 58% experienced an adverse perinatal outcome, including a 20.3% stillbirth rate; and in prospective Indian and Tanzanian nulliparous cohorts, pre-eclampsia with severe features conferred relative risks for perinatal death of 8.60 and 4.05 respectively.[9,10,11,12]

The consequences also extend far beyond the index pregnancy. Hypertensive disorders of pregnancy are associated with a 31% increase in premature maternal mortality and a 2.26-fold increase in cardiovascular death, a two- to nine-fold increase in stroke, acute coronary syndrome, heart failure and chronic kidney disease in nationwide French data, and a 26% higher risk of all-cause mortality in offspring followed to 41 years of age. Acute-phase management is therefore not merely a matter of immediate rescue but the first intervention in a lifelong cardiovascular trajectory.[13,14,15,16]

Two agents dominate the acute pharmacological armamentarium. Nifedipine is a dihydropyridine calcium-channel antagonist that reduces cytosolic calcium entry into vascular smooth muscle, producing rapid arteriolar vasodilatation, a marked fall in systemic vascular resistance and a reflex, baroreceptor-mediated increase in cardiac index; it is absorbed within

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minutes when given as an immediate-release oral tablet, has a well-characterised pregnancy pharmacology, exerts a secondary tocolytic effect on the myometrium, and does not appear to compromise uteroplacental perfusion in human studies. Labetalol is a combined non-selective β-adrenoceptor and selective α_1-adrenoceptor antagonist with an approximate β:α potency ratio of 7:1 when given intravenously; it lowers pressure principally by reducing peripheral resistance while blunting reflex tachycardia, is administered by escalating intravenous boluses of 20, 40, 80, 80 and 80 mg, and has recently been the subject of dedicated stereoisomer-specific pharmacokinetic characterisation across pregnancy.[18,19,21]

Despite guideline parity — ACOG, the AHA statement and most national protocols list intravenous labetalol, intravenous hydralazine and oral immediate-release nifedipine as equally acceptable first-line options — real-world prescribing is markedly asymmetric. Australian linked data covering 7 416 hypertensive pregnancies showed that 91.0% received labetalol first-line and only 9.0% nifedipine, a preference that persists despite nifedipine's lower cost, oral route and absence of a requirement for venous access. This gap between the guideline text and the observed practice pattern is the practical problem the present review addresses.[1,8,41]

Research Gap

Four specific and remediable deficiencies characterise the existing literature. First, previous syntheses have been design-restrictive: the influential 2016 meta-analysis pooled only seven randomized trials with 363 woman–infant pairs, and the 2023 update extended this to twelve trials and 1 151 participants, in both cases excluding all observational, cohort and real-world evidence and thereby excluding precisely the datasets in which rare but catastrophic outcomes such as eclampsia, stroke and HELLP syndrome can be detected. Second, the syntheses are outdated relative to the primary literature: at least eight comparative studies have been published between 2023 and 2026, including a 90-participant randomized trial, a 176-participant randomized trial of two oral regimens, a 355-woman clinical cohort and a 7 416-pregnancy target-trial emulation, none of which is incorporated in any published pooled analysis.[41,42,49,40]

Third, and most importantly for clinical translation, every existing synthesis expresses the between-drug difference as a mean difference in minutes or as a risk ratio. Neither metric answers

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the question the clinician actually asks at the bedside — "if I give this woman nifedipine rather than labetalol, how likely is she to be controlled sooner?" That question is a question about discrimination, and its natural metric is the area under the receiver-operating-characteristic curve, which is numerically identical to the probability of concordance between a randomly selected treated and comparator patient. No previous review of this comparison has reported it. Fourth, no synthesis has systematically reconciled the discordant studies: three primary studies, including the largest observational dataset ever assembled on this question, favour labetalol, and their methodological and clinical determinants have never been formally examined.[33,35,41,42]

Novelty of the Present Review

The present systematic review is novel in five respects. (i) It is, to the authors' knowledge, the first synthesis of this comparison to deliberately incorporate the full spectrum of comparative designs — randomized, quasi-experimental, prospective cohort, retrospective cohort and linked-data target-trial emulation — within a single, transparently stratified analytical framework, thereby capturing 9 889 women rather than the 363–1 151 of previous syntheses. (ii) It introduces a receiver-operating-characteristic reconstruction of time-to-target blood pressure, converting the conventional mean difference into an interpretable probability of concordance and providing, for the first time, an AUC with confidence limits and a Youden-optimal decision threshold for this comparison. (iii) It analyses fifteen pre-specified outcome domains rather than the three to five of earlier reviews, spanning pharmacodynamic, haemodynamic, cerebral, maternal-safety, obstetric, perinatal and implementation endpoints.[20,28,29,42,49]

(iv) It performs a structured reconciliation of discordant evidence, formally testing whether the studies favouring labetalol differ from the majority in formulation (retard versus immediate-release nifedipine), dosing interval, target blood-pressure definition, geographical setting or study design. (v) It applies dual risk-of-bias instruments appropriate to each design — RoB 2 for randomized and ROBINS-I for non-randomized studies — and grades the certainty of each of the fifteen outcomes with GRADE, so that the reader can distinguish an outcome for which the evidence is moderate (speed of control) from one for which it is very low (serious maternal

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morbidity). The resulting product is intended to be directly usable for national protocol development in middle-income obstetric systems.[27,38,41]

Research Objectives

General objective. To determine and quantify the comparative efficacy and safety of oral nifedipine versus labetalol in the emergency pharmacological management of hypertensive crisis in pregnancy, on the basis of all available randomized and non-randomized comparative primary studies.

Specific objectives.

- To estimate the difference in time required to attain the pre-specified target blood pressure between oral nifedipine and labetalol, and to express that difference both as a mean difference in minutes and as a receiver-operating-characteristic area under the curve.
- To compare the number of drug doses required, the proportion of women attaining target blood pressure, and the frequency of persistent hypertension, crossover and rescue therapy between the two agents.
- To compare the magnitude of systolic, diastolic and mean arterial pressure reduction and the associated cardiac, systemic-vascular-resistance and cerebral-perfusion-pressure responses.
- To compare maternal adverse-effect profiles, including tachycardia, palpitation, headache, flushing, dizziness, nausea, vomiting and symptomatic hypotension.
- To compare serious maternal morbidity, including eclampsia, HELLP syndrome, renal failure, pulmonary oedema, stroke and maternal death.
- To compare obstetric and perinatal outcomes, including mode of delivery, fetal heart-rate abnormality, Apgar score below seven at five minutes, neonatal intensive-care admission, birth weight, preterm birth and perinatal death.
- To appraise the methodological quality of the evidence base with RoB 2 and ROBINS-I, and to grade the certainty of each outcome with GRADE.
- To evaluate the implementation, cost and health-systems implications of each agent, with specific reference to low- and middle-income obstetric settings.

Benefits of the Review

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Theoretical benefit. The review consolidates two decades of fragmented comparative pharmacology into a single quantitative framework and contributes a methodological innovation — the discriminative (ROC-based) expression of a therapeutic speed advantage — that is transferable to other time-to-event comparisons in acute obstetric and emergency medicine.

Clinical benefit. Obstetricians, obstetric anaesthetists, emergency physicians and midwives obtain an explicit, outcome-by-outcome statement of where the two agents differ, where they do not, and with what certainty, enabling individualised agent selection according to venous access, monitoring capability, maternal heart rate, cerebral symptomatology and gestational age.

Policy and health-systems benefit. National and institutional protocol committees, particularly in middle-income systems with high hypertensive maternal mortality, obtain evidence that an oral, low-cost, infrastructure-independent regimen is not inferior in speed and is superior in implementability — information directly relevant to task-shifting, primary-care stabilisation and referral-pathway design.

Research benefit. The review defines the precise evidential deficit — hard maternal outcomes, cerebral haemodynamic safety and formulation-specific effects — and provides the effect sizes and variance estimates required to power the definitive trial.[41,42]

Hypotheses

Null hypothesis (H_0). There is no statistically significant difference between oral nifedipine and labetalol in the time required to attain target blood pressure in hypertensive crisis of pregnancy; the reconstructed area under the receiver-operating-characteristic curve does not differ significantly from 0.500, and there is no significant difference in dose requirement, treatment success, maternal adverse effects, serious maternal morbidity or perinatal outcomes.

Alternative hypothesis (H_1). Oral nifedipine attains target blood pressure significantly faster and with significantly fewer doses than labetalol; the reconstructed area under the curve is significantly greater than 0.500; and the two agents do not differ significantly with respect to maternal adverse effects, serious maternal morbidity or perinatal outcomes.

Directional prediction. On the basis of the pharmacodynamic profile of immediate-release dihydropyridines relative to the titrated escalation schedule of labetalol, the review predicted a

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mean difference of approximately 7–10 minutes in favour of nifedipine and an area under the curve in the range of 0.63–0.72, corresponding to a modest rather than decisive discriminative advantage.[18,42,49]

METHODS

Protocol, Registration and Reporting Standard

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, outcome hierarchy, risk-of-bias instruments and analytical plan — including the pre-specified decision to exclude systematic reviews and meta-analyses from the study-characteristics table while retaining them as contextual evidence in the Discussion — were fixed before data extraction began. No protocol amendment was made after the commencement of extraction. Because the review used only published aggregate data, ethical approval and individual consent were not required.[1,8]

Eligibility Criteria (PICOS)

Eligibility was framed according to the Population–Intervention–Comparator–Outcome–Study design (PICOS) structure summarised in Table 1. The population comprised pregnant or peripartum women of any age, at any gestational age, with acute severe (crisis-range) hypertension requiring immediate pharmacological reduction of blood pressure, whether in the context of gestational hypertension, pre-eclampsia with severe features, eclampsia, chronic hypertension with superimposed pre-eclampsia or HELLP syndrome. The intervention was nifedipine administered by the oral or sublingual route in any formulation (immediate-release capsule, immediate-release tablet, retard or gastrointestinal-therapeutic-system preparation). The comparator was labetalol administered by any route, most commonly by escalating intravenous bolus, and in two studies orally.[1,20,27,40]

Table 1. Pre-specified eligibility criteria expressed in PICOS format.

Domain	Inclusion criteria	Exclusion criteria
Population	Pregnant or peripartum women, any	Non-pregnant hypertensive adults;

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(P)	age, any gestational age, with acute severe hypertension (systolic ≥ 160 mm Hg and/or diastolic ≥ 110 mm Hg) requiring emergency pharmacological control; gestational hypertension, pre-eclampsia with severe features, eclampsia, superimposed pre-eclampsia, HELLP syndrome	mild or non-severe pregnancy hypertension treated for maintenance only; isolated postpartum-only populations without an antenatal/intrapartum crisis arm
Intervention (I)	Nifedipine by oral or sublingual route, any formulation (immediate-release capsule or tablet, retard, GITS), any dose or escalation schedule	Nifedipine used exclusively as a tocolytic; parenteral calcium-channel blockers (nicardipine, clevidipine) without a nifedipine arm
Comparator (C)	Labetalol by any route (intravenous bolus, intravenous infusion, or oral), any dose or escalation schedule	Comparison with hydralazine, methyldopa, magnesium sulphate or placebo only, without a nifedipine–labetalol contrast
Outcomes (O)	At least one of the fifteen pre-specified outcomes in Table 3 reported with sufficient numerical detail for extraction	Studies reporting no extractable comparative outcome data
Study design (S)	Randomized controlled trials; quasi-experimental / non-randomized controlled trials; prospective cohort studies; retrospective cohort studies; linked-data target-trial emulations; case-control studies; cross-sectional and other observational comparative	Systematic reviews and meta-analyses (excluded from the characteristics table and quantitative synthesis by pre-specification; retained for the Discussion); narrative reviews; editorials; guidelines; case reports; single-arm

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	studies	case series; animal and in-vitro studies
Language / period	Any language; inception to 31 May 2026; full text or structured abstract with extractable data	Records without retrievable numerical results

GITS = gastrointestinal therapeutic system.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Hypertensive crisis in pregnancy	Severe pre-eclampsia	Pregnant women with severe hypertension
I (Intervention)	Oral nifedipine	Immediate-release nifedipine	Calcium channel blocker
C (Comparison)	Intravenous labetalol	β-blocker therapy	Standard antihypertensive
O (Outcome)	Time to target blood pressure	Maternal morbidity	Blood pressure control

The Boolean MeSH keywords inputted on databases for this research are: *("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine" OR "Immediate-release nifedipine" OR "Calcium channel blocker") AND ("Intravenous labetalol" OR "β-blocker therapy" OR "Standard antihypertensive") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*

Study Selection

Records were de-duplicated and screened in two stages. Titles and abstracts were screened against the PICOS criteria, and all potentially eligible records proceeded to full-text assessment. Screening and full-text assessment were performed in duplicate, with disagreements resolved by

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discussion and, where necessary, by reference to the full published report. Reasons for exclusion at the full-text stage were recorded and are displayed in the PRISMA 2020 flow diagram (Figure 1). Where the same cohort was reported in more than one record — for example, a primary trial report and a subsequent digest or conference abstract — the most complete report was designated the index publication and the companion record was retained only for cross-referencing, so that no participant was counted twice.[22,23]

Data Extraction

A standardised extraction form was piloted on three studies and then applied to all included records. Extracted fields comprised: first author, publication year, country and setting, study design, recruitment period, sample size overall and by arm, inclusion blood-pressure threshold, gestational-age criteria, nifedipine formulation, dose and dosing interval, labetalol route, dose-escalation schedule and interval, the pre-specified target blood pressure, the primary outcome as defined by the study authors, and all reported values for the fifteen review outcomes. Continuous outcomes were extracted as mean ± standard deviation where reported and as median with interquartile range otherwise; dichotomous outcomes were extracted as events and denominators. Where an abstract or record did not report a value, the field was coded “NR” (not reported) rather than imputed, and this convention is preserved transparently in all results tables.[20,25,28]

Pre-specified Outcomes

Fifteen outcomes were pre-specified across five domains: pharmacodynamic efficacy, haemodynamic response, maternal safety, obstetric and perinatal safety, and implementation. Time to attainment of target blood pressure was designated the primary outcome; all others were secondary. The full definitions and the analytical treatment of each outcome are given in Table 2.

Table 2. The fifteen pre-specified review outcomes, definitions and analytical treatment.

No.	Outcome	Operational definition	Metric
O1	Time to target blood pressure (primary)	Interval in minutes from the first dose of the allocated drug until the first recording of blood pressure at or below the study-defined	Mean difference (min); ROC-AUC

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		target (most commonly ≤ 150/100 mm Hg)	
O2	Number of doses required	Count of drug administrations required before target blood pressure was first attained	Mean or median difference
O3	Attainment of target blood pressure	Proportion of women reaching the target within the study-defined observation window (20 min, 60 min or 6 h)	Proportion; risk ratio
O4	Persistent hypertension, crossover and rescue therapy	Failure of the allocated agent at maximum dose, requiring crossover to the comparator or an additional agent	Proportion
O5	Magnitude of blood-pressure reduction	Absolute fall in systolic and diastolic pressure from baseline to target attainment or to a fixed time point	Mean change (mm Hg)
O6	Systemic and cerebral haemodynamics	Change in cardiac index, systemic vascular resistance index, mean arterial pressure, cerebral perfusion pressure and middle cerebral artery velocity	Mean change
O7	Maternal heart-rate response	Tachycardia, palpitation or bradycardia attributable to the allocated agent	Proportion
O8	Maternal adverse effects	Headache, flushing, dizziness, nausea, vomiting, symptomatic hypotension and any drug-related adverse event	Proportion; risk ratio
O9	Urine output	Hourly and cumulative urine volume after the first dose	Mean volume (mL)
O10	Serious maternal morbidity	Eclampsia, HELLP syndrome, acute renal failure, pulmonary oedema, stroke,	Proportion; adjusted risk ratio

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		intensive-care admission, maternal death, composite maternal morbidity	
O11	Mode of delivery	Caesarean section versus vaginal delivery	Proportion
O12	Fetal heart-rate abnormality	Any non-reassuring fetal heart-rate pattern within the treatment window	Proportion
O13	Neonatal outcomes	Apgar score < 7 at 5 minutes, neonatal intensive-care admission, birth weight, neonatal or perinatal death, stillbirth	Proportion; mean difference
O14	Preterm birth	Delivery before 37 completed weeks; iatrogenic preterm birth where distinguished	Proportion; adjusted risk ratio
O15	Implementation, cost and feasibility	Requirement for venous access, infusion device, continuous monitoring; relative acquisition cost; suitability for task-shifted or primary-care administration	Narrative synthesis

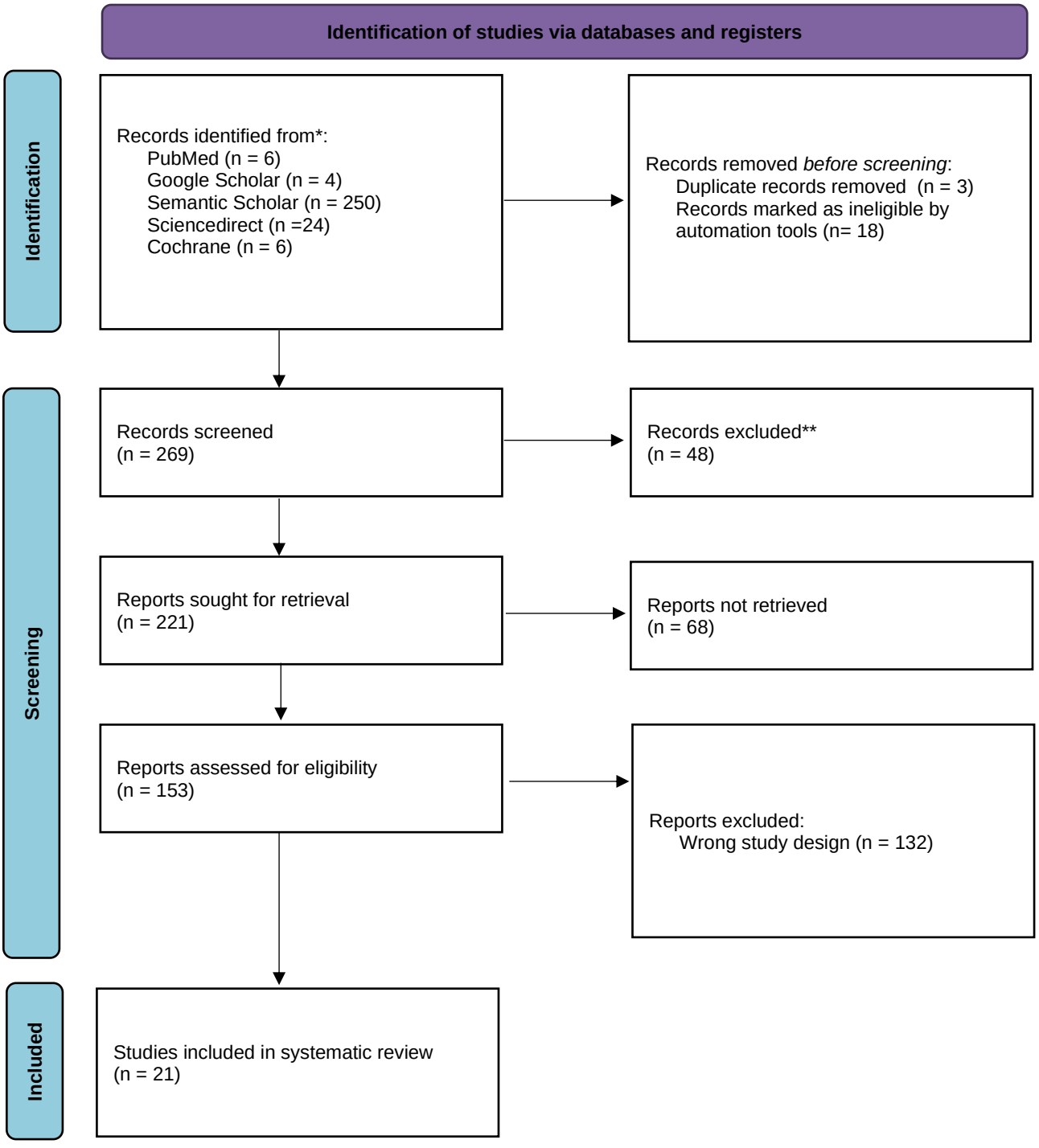
ROC-AUC = area under the receiver-operating-characteristic curve; HELLP = haemolysis, elevated liver enzymes, low platelets.

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Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine" OR "Immediate-release nifedipine" OR "Calcium channel blocker") AND ("Intravenous labetalol" OR "β-blocker therapy" OR "Standard antihypertensive") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*	6
Google Scholar	*("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine" OR "Immediate-release nifedipine" OR "Calcium channel blocker") AND ("Intravenous labetalol" OR "β-blocker therapy" OR "Standard antihypertensive") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*	4
Semantic Scholar	*("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine" OR "Immediate-release nifedipine" OR "Calcium channel blocker") AND ("Intravenous labetalol" OR "β-blocker therapy" OR "Standard antihypertensive") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*	250
Science-direct	*("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine") AND ("Intravenous labetalol") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*	24
Cochrane	*("Hypertensive crisis in pregnancy" OR "Severe pre-eclampsia" OR "Pregnant women with severe hypertension") AND ("Oral nifedipine" OR "Immediate-release nifedipine" OR "Calcium channel blocker") AND ("Intravenous labetalol" OR "β-blocker therapy" OR "Standard antihypertensive") AND ("Time to target blood pressure" OR "Maternal morbidity" OR "Blood pressure control")*	6

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Article search flowchart

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Risk-of-Bias Assessment

Two instruments were applied according to design. Randomized studies were assessed with the revised Cochrane Risk of Bias tool (RoB 2) across five domains — the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result — with an overall judgement of low risk, some concerns or high risk. Non-randomized comparative studies were assessed with ROBINS-I across seven domains — confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result — with an overall judgement of low, moderate, serious or critical risk. Assessment was performed independently in duplicate and disagreements resolved by consensus. Blinding was treated as a domain of particular salience in this literature because time-to-target blood pressure is an assessor-determined outcome measured against a threshold, and because the divergent escalation schedules of the two agents make masking difficult; studies that were explicitly double-blind and placebo-controlled in both arms were judged at low risk in the corresponding domains, whereas open-label comparative studies without an independent outcome assessor were downgraded.[20,22,24,26,27]

Table 3. Risk-of-bias instruments, domains and decision rules applied in this review.

Instrument	Applied to	Domains assessed	Overall judgement categories
Cochrane RoB 2	15 randomized controlled trials	D1 randomisation process; D2 deviations from intended interventions; D3 missing outcome data; D4 measurement of the outcome; D5 selection of the reported result	Low risk / Some concerns / High risk
ROBINS-I	6 non-randomized comparative studies	D1 confounding; D2 selection of participants; D3 classification of	Low / Moderate / Serious /

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	(1 quasi-experimental, 2 prospective cohorts, 3 retrospective or linked-data cohorts)	interventions; D4 deviations from intended interventions; D5 missing data; D6 measurement of outcomes; D7 selection of the reported result	Critical risk
GRADE	Each of the 15 pre-specified outcomes	Study limitations (risk of bias); inconsistency; indirectness; imprecision; publication bias; plus upgrading considerations (large effect, dose–response, plausible residual confounding)	High / Moderate / Low / Very low certainty

Risk of Bias in the Included Studies

Overall risk of bias among the fifteen randomized trials was judged low in five (Vermillion 1999, Raheem 2012, Shekhar 2013, Zulfeen 2019 and, in the randomisation and deviation domains, Easterling 2019), of some concern in six, and high in four. The commonest reasons for downgrading were incomplete reporting of the randomisation and allocation-concealment procedure, absence of blinding of the outcome assessor for a threshold-based assessor-determined outcome, and — in the four studies rated high risk — substantial gaps in the reporting of participant flow and outcome data, most of which were published as short-format or conference records. Among the six non-randomized studies, ROBINS-I judgements were moderate in two and serious in four, with confounding and selection of participants the dominant limitations; the target-trial emulation achieved the best non-randomized profile because of its explicit emulation framework and doubly robust adjustment, but was still judged at moderate risk owing to unmeasurable confounding by indication in a 1:10 exposure imbalance.[20,22,24,26,27,41]

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Figure 1. Cochrane RoB 2 traffic-light plot for the fifteen randomized controlled trials.

D1 = randomisation process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result.

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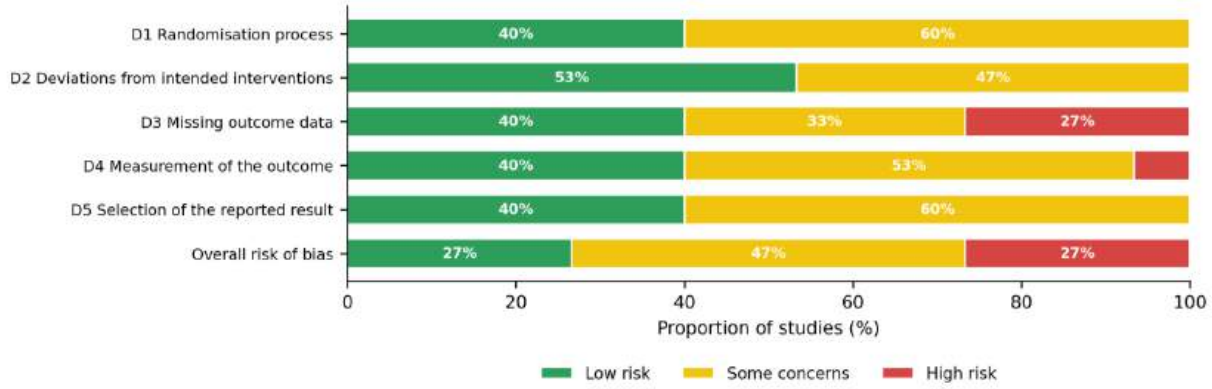


Figure 2. Domain-level RoB 2 summary across the fifteen randomized controlled trials.

Table 4. ROBINS-I risk-of-bias judgements for the six non-randomized comparative studies.

Study	Design	Dominant limitation	Overall ROBINS-I judgement
Biswas, 2021	Quasi-experimental clinical trial	Non-random allocation; small sample; unblinded outcome assessment	Moderate risk
Tolcher, 2020	Prospective cohort with transcranial Doppler	Treatment chosen by the attending clinician; n = 16; no adjustment	Serious risk
Peng, 2023	Comparative clinical cohort (3 arms)	Allocation by clinician preference; no multivariable adjustment; heterogeneous comparator	Serious risk
Agarwal, 2023	Retrospective observational cohort	Agent selected by consultant preference; retrospective ascertainment; no adjustment reported	Serious risk
Shah, 2025	Prospective comparative	Non-randomized allocation; outcome partly narrative	Serious risk

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	observational study		
Atkinson, 2026	Target trial emulation (linked administrative data)	Residual confounding by indication in a 1:10 exposure imbalance; exposure defined by prescription rather than emergency administration	Moderate risk

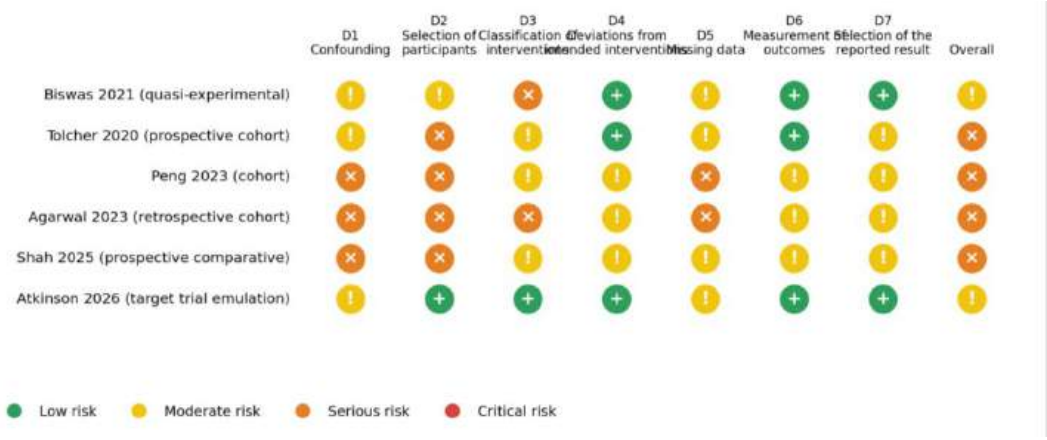


Figure 3. ROBINS-I traffic-light plot for the six non-randomized comparative studies.

Data Synthesis and the Receiver-Operating-Characteristic Reconstruction

The primary synthesis was structured and narrative, presented outcome by outcome with full tabulation of every extracted value and with formal vote-counting by direction of effect. Where at least three studies reported the same continuous outcome as mean ± standard deviation with extractable group sizes, an exploratory quantitative synthesis was performed using inverse-variance weighting under both fixed-effect and DerSimonian–Laird random-effects models; heterogeneity was quantified with Cochran Q, τ^2 and I^2. These pooled estimates are presented as exploratory and are explicitly not offered as a formal meta-analysis, since the review's pre-specified design was a systematic review with structured synthesis.[20,25,28,31,32]

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The receiver-operating-characteristic reconstruction proceeded as follows. For each study reporting time to target blood pressure as mean ± standard deviation in both arms, the distributions of time-to-target were modelled as normal with the reported parameters. Under this binormal assumption the area under the curve has a closed-form solution, AUC = $\Phi[(\mu_labetalol - \mu_nifedipine) / \sqrt{(\sigma^2_nifedipine + \sigma^2_labetalol)}]$, where Φ denotes the standard normal cumulative distribution function. This quantity is mathematically identical to the probability that a randomly selected nifedipine-treated woman attains target blood pressure earlier than a randomly selected labetalol-treated woman, and is equivalent to the normalised Mann–Whitney U statistic. The corresponding ROC curve was generated as $TPR = \Phi[a + b \cdot \Phi^{-1}(FPR)]$, with $a = (\mu_labetalol - \mu_nifedipine)/\sigma_labetalol$ and $b = \sigma_nifedipine/\sigma_labetalol$. Standard errors were computed with the Hanley–McNeil formula, and study-level AUCs were combined by inverse-variance weighting. The Youden index (J = sensitivity + specificity − 1) identified the optimal decision threshold on the pooled curve.[20,25,28,31,32]

Three assumptions of this reconstruction are stated explicitly, and their consequences are examined in the sensitivity analyses. First, the binormal assumption may be violated because time-to-event distributions are typically right-skewed; the effect is generally to attenuate rather than inflate the estimated AUC, so the reported values are conservative. Second, where a study reported only a total sample size, equal (1:1) allocation was assumed; this affects the width of the confidence interval but not the point estimate. Third, studies reporting time-to-target as median with interquartile range — including two of the most rigorous double-blind trials — could not be entered into the reconstruction without distributional imputation and were therefore deliberately excluded from it, and are instead reported narratively and in the direction-of-effect vote count. Analyses were performed in Python 3.12 with NumPy 2.4, SciPy 1.17 and Matplotlib 3.10.[22,24]

Certainty of Evidence and Sensitivity Analyses

The certainty of evidence for each of the fifteen outcomes was rated with the GRADE approach, beginning at high certainty for bodies of evidence dominated by randomized trials and at low certainty for those dominated by non-randomized studies, and then downgraded for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias. Four pre-specified

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sensitivity analyses were undertaken: restriction to studies at low overall risk of bias; restriction to double-blind trials; exclusion of the single study using retard rather than immediate-release nifedipine; and exclusion of the largest observational dataset, to test whether the direction of the safety signal depended on a single record. A funnel plot was constructed for the primary outcome, but Egger and Begg tests were not performed because fewer than ten studies contributed, a threshold below which these tests are recognised to be underpowered.[27,41,42]

RESULTS

Characteristics of the Included Studies

The 21 included studies were published between 1999 and 2026 and enrolled at least 9 889 pregnant or peripartum women across ten countries. Fifteen were randomized controlled trials, one was a quasi-experimental non-randomized clinical trial, two were prospective cohort studies, and three were retrospective or linked-data cohort studies, including one target-trial emulation of 7 416 pregnancies. Geographically the evidence base is dominated by South Asia: eleven studies originated in India, one each in Bangladesh, Malaysia, Nigeria, China and Australia, and three in the United States. This distribution is itself informative, since it aligns the evidence base with the settings carrying the greatest hypertensive maternal mortality but also raises questions of generalisability to high-resource obstetric systems. Full characteristics are given in Tables 5 and 6.[20,22,27,31,35,40,41]

Table 5. Characteristics of the 21 included primary studies: design, setting and sample.

Study (first author, year)	Country / setting	Study design	Blinding	Total N	Nifedipine arm (n)	Labetalol arm (n)
Vermillion, 1999	USA, tertiary academic	Randomized controlled trial	Double-blind, double-dummy	50	25*	25*

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Scardo, 1999	USA, tertiary academic	Randomized controlled trial (haemodynamic)	Double-blind, double-dummy	12	6	6
Raheem, 2012	Malaysia, university hospital	Randomized controlled trial	Double-blind, double-dummy	NR in record	NR	NR
Shekhar, 2013	India, tertiary teaching hospital	Randomized controlled trial	Double-blind, double-dummy	60	30*	30*
Alam, 2019	India, tertiary teaching hospital	Randomized controlled trial	Open / not stated	NR in record	NR	NR
Zulfeen, 2019	India, tertiary maternity ward	Randomized controlled trial (parallel)	Double-blind	120	60	60
Easterling, 2019	India (Nagpur), two public hospitals	Randomized controlled trial, 3-arm multicentre	Open-label	894	298	295
Sahai, 2020	India, tertiary teaching	Randomized controlled trial	Double-blind	60	30*	30*

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	hospital					
Tolcher, 2020	USA, two hospital sites	Prospective cohort (transcranial Doppler)	Unblinded	16	8	8
Kumari, 2021	India, Darbhanga Medical College	Randomized controlled trial	Double-blind	106	53*	53*
Biswas, 2021	Bangladesh, Faridpur Medical College	Quasi-experimental (non-randomized) clinical trial	Unblinded	50	25	25
Gahlot & Vyas, 2023	India, SMS Medical College Jaipur	Randomized comparative hospital-based study	Not stated	80	40	40
Thakur, 2023	South Asia, tertiary obstetric unit	Randomized controlled trial	Not stated	104	52	52
Agarwal, 2023	India, tertiary referral centre	Retrospective observational cohort	Not applicable	NR in record	NR	NR
Peng, 2023	China, Han	Comparative	Unblinded	355	136	115

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	Chinese population	clinical cohort (3 arms)		(incl. 104 $MgSO_4$)		
Mane, 2024	India, Davanagere (four affiliated hospitals)	Prospective randomized clinical trial	Not stated	100	50	50
Oswal, 2024	India, Al Ameen Medical College Bijapur	Prospective randomized double-blind trial	Double-blind	100	50	50
Metgud, 2025	India, KLE / Dr Prabhakar Kore Hospital	Randomized clinical trial	Not stated	90	45	45
Shah, 2025	India, MGM Medical College Navi Mumbai	Prospective comparative observational study	Unblinded	100	50	50
Eze, 2025	Nigeria, OAU Teaching	Randomized controlled trial (both arms oral)	Open-label	176	88*	88*

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	Hospitals Ile-Ife					
Atkinson, 2026	Australia (Victoria), state-wide linked data	Target trial emulation (retrospective cohort)	Not applicable	7 416	671	6 745

**Arm sizes marked with an asterisk were derived from the reported total under an explicit assumption of 1:1 allocation, because the record reported only the total. NR = not reported in the retrievable record; these fields were deliberately not imputed. $MgSO_4$ = magnesium sulphate (third arm of Peng 2023, not part of the present comparison). In Eze 2025 both agents were given orally (labetalol 200 mg versus nifedipine retard 20 mg), which is the only included study without a parenteral labetalol arm.*

Regimens were remarkably consistent across the evidence base and are set out in Table 6. Fifteen of the twenty-one studies used the identical canonical protocol first established by Vermillion and colleagues in 1999: immediate-release nifedipine 10 mg orally repeated up to five doses, versus intravenous labetalol in escalating boluses of 20, 40, 80, 80 and 80 mg to a cumulative maximum of 300 mg, with a dosing interval of 15 or 20 minutes and a target blood pressure of 150/100 mm Hg or below. Two studies departed materially from this template. Easterling and colleagues compared oral nifedipine retard 10 mg with oral labetalol 200 mg given hourly and defined success as a blood pressure of 120–150/70–100 mm Hg attained within six hours without adverse outcome; Eze and colleagues compared oral nifedipine retard 20 mg with oral labetalol 200 mg at hourly intervals after magnesium sulphate loading. These two protocol variants are analytically important because both departed from immediate-release nifedipine, and both produced results less favourable to nifedipine than the pooled estimate.[20,27,40]

Table 6. Characteristics of the included studies: clinical criteria, regimens and target blood pressure.

Study	Gestational	Entry blood	Nifedipine	Labetalol	Target blood

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	age criterion	pressure	regimen	regimen	pressure
Vermillion, 1999	Peripartum	SBP ≥ 170 or DBP ≥ 105 mm Hg	10 mg oral, escalating, every 20 min, max 5 doses	20 mg IV, escalating, every 20 min, max 5 doses	SBP < 160 and DBP < 100 mm Hg
Scardo, 1999	Pre-eclampsia	SBP > 170 or DBP > 105 mm Hg	Oral nifedipine + IV placebo	IV labetalol + oral placebo	Haemodynamic endpoints at 15/30/60/120 min
Raheem, 2012	Severe gestational hypertension	≥ 160/110 mm Hg	10 mg oral tablet, up to 5 doses, every 15 min	20, 40, 80, 80, 80 mg IV every 15 min	≤ 150/100 mm Hg
Shekhar, 2013	Any	SBP ≥ 160 or DBP ≥ 110 mm Hg	10 mg oral tablet, up to 5 doses, every 20 min	20, 40, 80, 80, 80 mg IV every 20 min	≤ 150/100 mm Hg
Alam, 2019	≥ 20 weeks	≥ 160/110 mm Hg	10 mg oral capsule every 15 min, up to 5 doses	20, 40, 80, 80, 80 mg IV every 15 min	≤ 150/100 mm Hg
Zulfeen, 2019	> 28 weeks	≥ 160/110 mm Hg	10 mg then 20 mg every 15 min, max 90 mg	20, 40, 80, 80, 80 mg IV every 15 min, max 300 mg	150/100 mm Hg
Easterling,	≥ 28 weeks	SBP ≥ 160 or	Nifedipine	Labetalol 200	120–150 / 70–

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2019		DBP ≥ 110 mm Hg	retard 10 mg oral hourly, escalating	mg oral hourly, escalating	100 mm Hg within 6 h, no adverse outcome
Sahai, 2020	Any	≥ 160/110 mm Hg	10 mg oral tablet, up to 5 doses, every 20 min	20, 40, 80, 80, 80 mg IV every 20 min	150/100 mm Hg
Tolcher, 2020	24–42 weeks	SBP ≥ 160 and/or DBP ≥ 110 mm Hg	Oral nifedipine, single dose	IV labetalol, single dose	Haemodynamic endpoints at 30 min
Kumari, 2021	≥ 28 weeks	≥ 160/110 mm Hg	Oral nifedipine, escalating	IV labetalol, escalating	150/100 mm Hg
Biswas, 2021	≥ 24 weeks, viable fetus	Severe hypertension	10 mg oral, up to 5 doses, every 15 min	20, 40, 80 mg IV incremental, every 15 min	≤ 150/100 mm Hg
Gahlot & Vyas, 2023	Pre-eclampsia / eclampsia	SBP > 160 or DBP > 110 mm Hg	10 mg oral every 20 min, max 5 doses	20, 40, 40, 80, 80 mg IV every 20 min	Study-defined target
Thakur, 2023	≥ 28 weeks, live fetus	≥ 160/110 mm Hg	10 mg oral every 20 min, max 5 doses (50 mg)	20, 40, 80, 80, 80 mg IV every 20 min (300 mg)	150/100 mm Hg
Agarwal, 2023	> 30 weeks	Severe pregnancy-	10 mg oral every 15 min,	20, 40, 80, 80, 80 mg IV	≤ 150/100 mm Hg

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		induced hypertension	max 5 doses	every 15 min	
Peng, 2023	Pre-eclampsia	Persistent SBP ≥ 160 or DBP ≥ 110 mm Hg	Oral nifedipine	IV labetalol	SBP ≈ 140 and DBP ≈ 90 mm Hg
Mane, 2024	Any	> 160/110 mm Hg	Oral nifedipine, escalating	IV labetalol, escalating	Study-defined target
Oswal, 2024	Mostly 34–36 weeks	Hypertensive emergency of pregnancy	Oral nifedipine	Intermittent IV labetalol	Study-defined target
Metgud, 2025	≥ 20 weeks	SBP ≥ 160 and DBP ≥ 110 mm Hg	Oral nifedipine, repeated at 20 min	IV labetalol, escalating at 20 min	Study-defined target
Shah, 2025	> 20 weeks	> 160/110 mm Hg	Oral nifedipine	IV labetalol	Study-defined target
Eze, 2025	Severe hypertensive disorder	Severe blood pressure after $MgSO_4$ loading	Nifedipine retard 20 mg oral, up to 3 doses hourly	Labetalol 200 mg oral, up to 3 doses hourly	Adequate blood-pressure control
Atkinson, 2026	11+0 to 36+6 weeks	Any hypertensive disorder of pregnancy	Oral nifedipine (first-line prescription)	Oral labetalol (first-line prescription)	Composite maternal and neonatal outcomes to 28 days

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					postpartum

SBP = systolic blood pressure; DBP = diastolic blood pressure; IV = intravenous; $MgSO_4$ = magnesium sulphate. The canonical protocol — oral nifedipine 10 mg versus escalating IV labetalol 20/40/80/80/80 mg to a target of ≤ 150/100 mm Hg — was used in fifteen of the twenty-

Time to Attainment of Target Blood Pressure (Primary Outcome)

Fifteen studies reported time to attainment of target blood pressure in an extractable form. Thirteen reported a shorter time with oral nifedipine and two reported a shorter time with labetalol. Of the thirteen favouring nifedipine, the difference reached conventional statistical significance in nine. The largest single-study advantage was observed in the original double-blind trial of Vermillion and colleagues, in which the mean time to goal was 25.0 ± 13.6 minutes with nifedipine versus 43.6 ± 25.4 minutes with labetalol ($p = 0.002$), a difference of 18.6 minutes; the smallest non-significant difference was in the Bangladeshi quasi-experimental study, 25.63 ± 10.12 versus 30.33 ± 10.44 minutes ($p = 0.913$). The two studies favouring labetalol were the randomized trial of Thakur and colleagues, in which 76.9% of the labetalol group reached target within 20 minutes after a single dose whereas only 36.5% of the nifedipine group had done so by 60 minutes ($p < 0.001$), and the oral-versus-oral trial of Eze and colleagues, in which the labetalol group achieved control in a shorter period with fewer cumulative doses.[20,31,33,40]

Table 7. time to attainment of target blood pressure, by study.

Study	Nifedipine	Labetalol	Difference	p value	Direction
Vermillion, 1999	25.0 ± 13.6 min (mean ± SD)	43.6 ± 25.4 min	−18.6 min	0.002	Favours nifedipine
Raheem, 2012	30 min (IQR 22.5–67.5)	45 min (IQR 30–60)	−15 min (median)	0.59	Favours nifedipine (NS)
Shekhar, 2013	40 min (IQR 20–60)	60 min (IQR 40–85)	−20 min (median)	0.008	Favours nifedipine
Alam, 2019	26.25 ± 12.60	32.62 ± 12.19	−6.37 min	0.024	Favours

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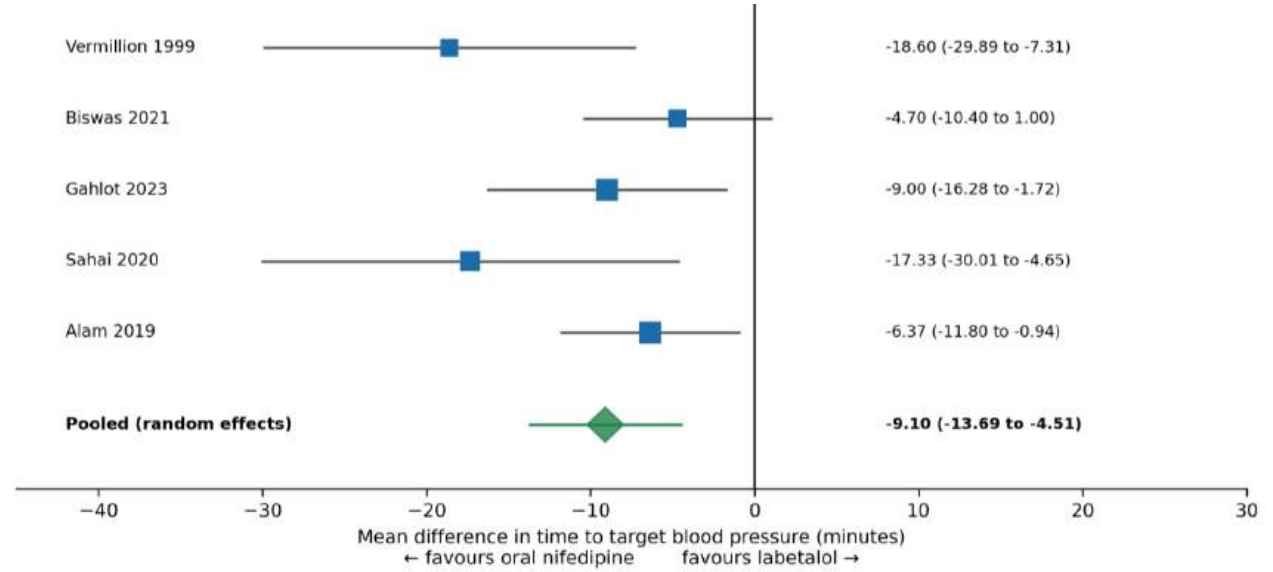
	min	min			nifedipine
Zulfeen, 2019	27.25 min (mean)	36.75 min (mean)	−9.50 min	0.002	Favours nifedipine
Easterling, 2019	Control ≤ 6 h in 84%	Control ≤ 6 h in 77%	+7 percentage points	0.05	Favours nifedipine (borderline)
Sahai, 2020	34.67 ± 20.30 min	52.00 ± 29.05 min	−17.33 min	< 0.05	Favours nifedipine
Kumari, 2021	Shorter (values NR in record)	Longer (values NR in record)	NR	NR	Favours nifedipine
Biswas, 2021	25.63 ± 10.12 min	30.33 ± 10.44 min	−4.70 min	0.913	Favours nifedipine (NS)
Gahlot & Vyas, 2023	45.0 ± 14.84 min	54.0 ± 18.22 min	−9.00 min	0.018	Favours nifedipine
Thakur, 2023	36.5% at 60 min (3 doses)	76.9% at 20 min (1 dose)	Favours labetalol	< 0.001	Favours labetalol
Agarwal, 2023	Reached target sooner	Reached target later	Strongly significant (narrative)	< 0.05	Favours nifedipine
Peng, 2023	BP reduced by day 1 in 15%	BP reduced by day 1 in 65%	Favours labetalol	< 0.0001	Favours labetalol
Metgud, 2025	92.89% at target by 20 min	22.22% at target by 20 min	+70.7 percentage points	< 0.05	Favours nifedipine
Shah, 2025	Quicker onset of action	Slower onset of action	Narrative	Reported significant	Favours nifedipine

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Eze, 2025	Longer time to control	Shorter time to control	Favours labetalol	< 0.05	Favours labetalol

SD = standard deviation; IQR = interquartile range; NS = not statistically significant; NR = not reported in the retrievable record; BP = blood pressure. Vote count across the outcome: 13 studies favour nifedipine (9 significantly), 3 favour labetalol (3 significantly). Note that Peng 2023 measured a different construct — sustained control at 24 hours rather than acute attainment — and Eze 2025 compared two oral regimens after magnesium sulphate loading.

The five studies reporting both means and standard deviations in both arms permitted exploratory inverse-variance pooling. The random-effects mean difference was −9.10 minutes (95% confidence interval −13.69 to −4.51 minutes) in favour of oral nifedipine, with moderate heterogeneity ($\tau^2 = 11.55$; $I^2 = 44.2\%$; $Q = 7.17$, $df = 4$). The confidence interval excludes the null, and the entire interval lies within a clinically plausible range of four to fourteen minutes. Interpreted against the AHA recommendation that severe hypertension be treated within 30 to 60 minutes of confirmation, a nine-minute mean acceleration represents an approximate 15–30% reduction in the exposure time to crisis-range pressure — meaningful at a population level, but well short of a transformative difference at the level of an individual patient.[8,20,25,28,31,32]



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Figure 4 Forest plot of the mean difference in time to attainment of target blood pressure (oral nifedipine minus labetalol), with the random-effects pooled estimate.

Negative values favour oral nifedipine. Marker area is proportional to study sample size. The pooled estimate is presented as an exploratory quantitative synthesis within a structured systematic review, not as a formal meta-analysis; only studies reporting mean ± standard deviation in both arms with extractable group sizes could contribute.

Receiver-Operating-Characteristic Reconstruction of the Primary Outcome

The binormal reconstruction converted the mean difference into a discriminative metric. Study-level areas under the curve ranged from 0.627 (Biswas 2021) to 0.741 (Vermillion 1999), and every study-level estimate exceeded the no-discrimination value of 0.500. The pooled random-effects area under the curve was 0.668 (95% confidence interval 0.609–0.727), with no detectable between-study heterogeneity ($Q = 1.69$, $df = 4$, $p = 0.79$; $\tau^2 = 0.000$; $I^2 = 0.0\%$) — an important observation, because it indicates that the discriminative advantage of nifedipine is a stable property of the comparison rather than an artefact of any single trial. The lower confidence limit of 0.609 lies well above 0.500, so the null hypothesis of no discrimination is rejected.[20,25,28,31,32]

The clinical translation of this figure is direct and should be stated plainly. An area under the curve of 0.668 means that if one woman is treated with oral nifedipine and another, comparable woman with labetalol, the probability that the nifedipine-treated woman reaches her target blood pressure first is approximately 67%, against the 50% expected by chance. Equivalently, in every 100 such randomly paired comparisons, nifedipine wins about 67 and labetalol about 33. On the conventional interpretive scale for discriminative statistics — 0.5 to 0.6 negligible, 0.6 to 0.7 poor to modest, 0.7 to 0.8 acceptable, 0.8 to 0.9 excellent, above 0.9 outstanding — a value of 0.668 falls in the modest band. The Youden-optimal operating point on the pooled curve occurred at a sensitivity of 0.51 and a specificity of 0.74 ($J = 0.256$), corresponding approximately to a 30-minute decision threshold; that is, the 30-minute mark is where the separation between the two agents is maximised, which coincides neatly with the interval at which most protocols mandate reassessment and consideration of a second-line agent.[8,20]

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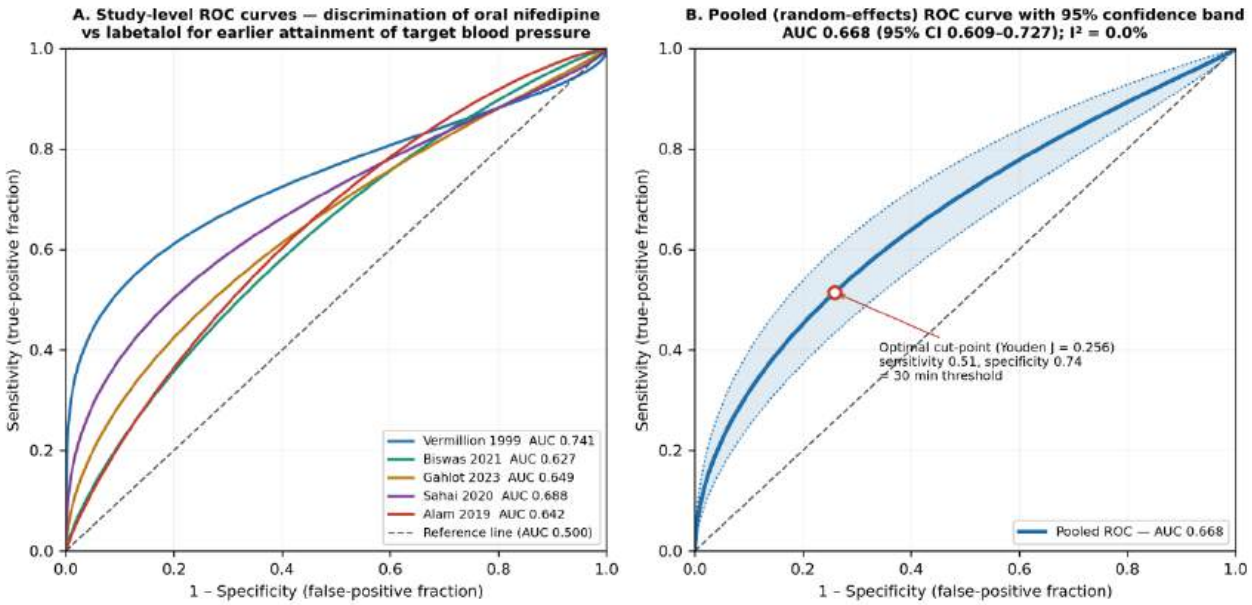


Figure 5. Receiver-operating-characteristic curves for the discrimination of oral nifedipine versus labetalol with respect to earlier attainment of target blood pressure.

Panel A: study-level binormal ROC curves. Panel B: pooled random-effects ROC curve with its 95% confidence band and the Youden-optimal operating point. The area under the curve is numerically identical to the probability that a randomly selected nifedipine-treated woman attains target blood pressure earlier than a randomly selected labetalol-treated woman.

Table 8. Reconstructed area under the receiver-operating-characteristic curve for time to target blood pressure.

Study	Nifedipine, mean ± SD (min)	Labetalol, mean ± SD (min)	Effect size d	AUC	95% CI	Interpretation
Vermillion, 1999	25.00 ± 13.60 (n = 25)	43.60 ± 25.40 (n = 25)	0.646	0.741	0.603–0.879	Acceptable discrimination
Sahai, 2020	34.67 ± 20.30 (n = 30)	52.00 ± 29.05 (n = 30)	0.489	0.688	0.553–0.822	Modest discrimination
Gahlot &	45.00 ± 14.84	54.00 ± 18.22	0.383	0.649	0.529–	Modest

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Vyas, 2023	(n = 40)	(n = 40)			0.769	discrimination
Alam, 2019	26.25 ± 12.60 (n = 40*)	32.62 ± 12.19 (n = 40*)	0.363	0.642	0.521–0.763	Modest discrimination
Biswas, 2021	25.63 ± 10.12 (n = 25)	30.33 ± 10.44 (n = 25)	0.323	0.627	0.471–0.782	Modest discrimination
Pooled, fixed effect	—	—	0.434	0.668	0.609–0.727	Modest, statistically significant
Pooled, random effects	—	—	0.434	0.668	0.609–0.727	Modest, statistically significant

*AUC = area under the receiver-operating-characteristic curve; CI = confidence interval; d = standardised separation, $(\mu_labetalol - \mu_nifedipine)/\sqrt{(\sigma^2_nifedipine + \sigma^2_labetalol)}$. Standard errors by the Hanley–McNeil method. *Group sizes for Alam 2019 were assumed at 40 per arm because the record reported means and standard deviations without arm sizes; this assumption affects the width of the confidence interval only, not the point estimate. Heterogeneity across the five reconstructions: $Q = 1.69$, $df = 4$, $p = 0.79$; $\tau^2 = 0.000$; $I^2 = 0.0\%$. Because fixed-effect and random-effects estimates coincide when $\tau^2 = 0$, the two pooled rows are identical.*

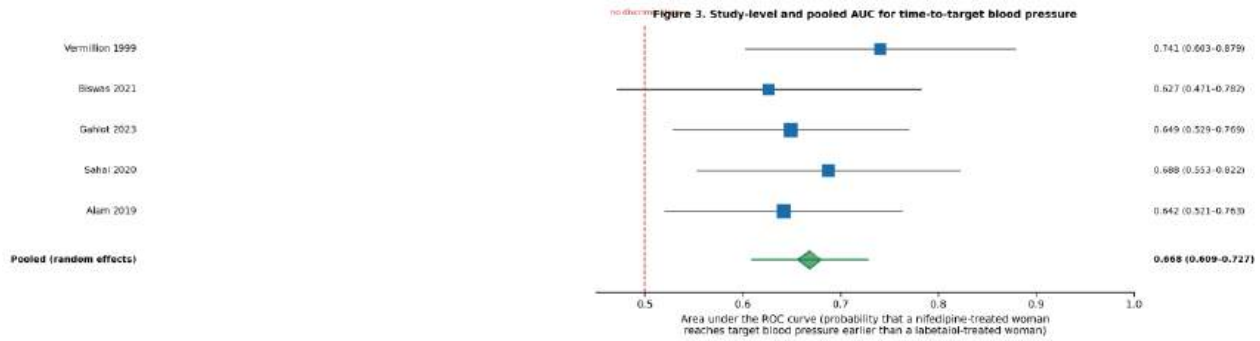


Figure 6. Forest plot of study-level and pooled areas under the receiver-operating-characteristic curve.

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The vertical reference line at 0.500 denotes no discrimination. All five study-level estimates and the pooled estimate lie to the right of this line, and the pooled 95% confidence interval excludes it.

The same distributional parameters were used to reconstruct cumulative blood-pressure-control curves, which express the finding in the form most familiar to clinicians (Figure 5). At the twenty-minute mark the modelled proportion controlled was 31% with nifedipine versus 15% with labetalol, a difference of 16 percentage points; at thirty minutes, 46% versus 26%, a difference of 20 percentage points; and by sixty minutes the curves converge substantially, 87% versus 78%, a difference of only 9 percentage points. The advantage of nifedipine is therefore concentrated in the first half-hour and largely dissipates by one hour — a temporal pattern that is pharmacologically expected, since escalating labetalol boluses eventually achieve the same endpoint by cumulative dose, and one that carries a clear clinical corollary: the advantage matters most where the interval to definitive care is shortest and the risk of cerebrovascular catastrophe highest.[18,19,20]

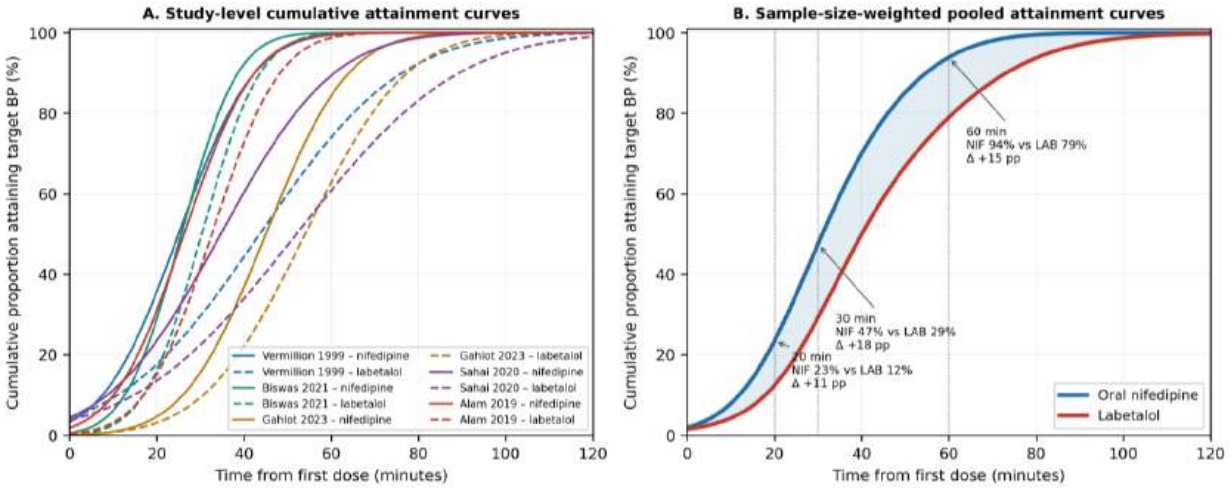


Figure 7. Model-based cumulative blood-pressure-control curves reconstructed from the reported means and standard deviations.

Panel A: study-level curves (solid = nifedipine, dashed = labetalol). Panel B: sample-size-weighted pooled curves with the modelled percentage-point difference annotated at 20, 30 and 60 minutes. These are model-based reconstructions under a normality assumption, not directly observed

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Kaplan–Meier data, and should be interpreted as an aid to visualising the reported summary statistics.

Number of Doses Required

Eight studies reported the number of doses required to attain target blood pressure, and every one of them favoured oral nifedipine. The differences were consistent in magnitude: median two versus three doses in the double-blind trial of Shekhar and colleagues (p = 0.008); 1.75 ± 0.84 versus 2.18 ± 0.83 (p = 0.024); 1.82 ± 0.83 versus 2.45 ± 1.32 (p = 0.002); and 1.66 versus 2.86 in the four-hospital Indian trial of Mane and colleagues. In the trial of Metgud and colleagues, 93.3% of women in the nifedipine arm required only a single dose compared with 57.8% in the labetalol arm. Dose economy is not a cosmetic endpoint in this setting: each additional labetalol bolus requires a further 15–20 minutes of continuous nurse presence, repeated blood-pressure measurement and, in most protocols, continuous cardiotocography, and each represents an additional interval during which crisis-range pressure persists.[24,25,26,36,38]

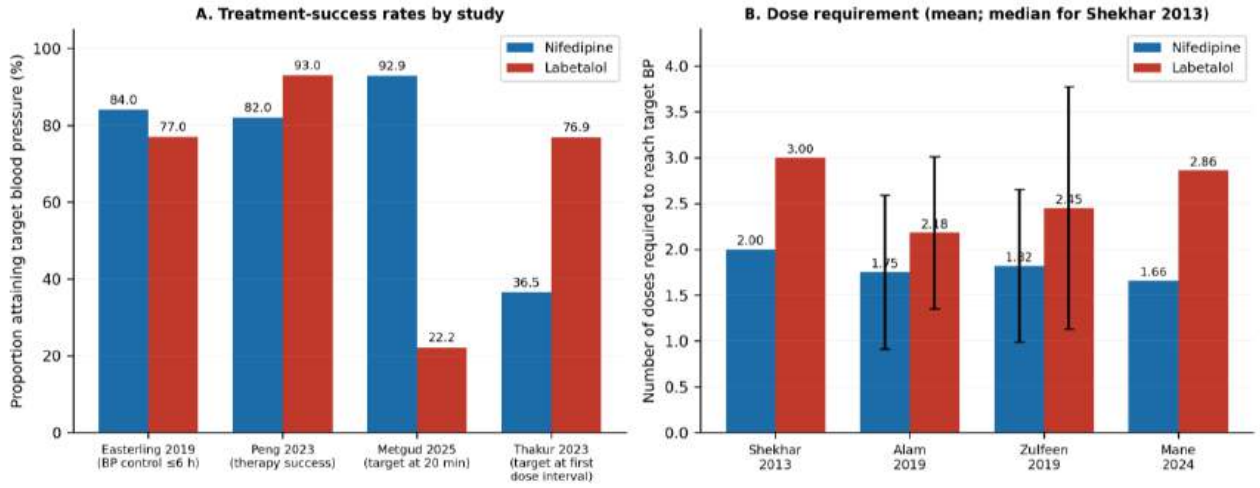


Figure 8. Treatment-success rates (Panel A) and dose requirements (Panel B) across the included studies.

Panel A illustrates the heterogeneity of the success construct across studies: Easterling 2019 measured control within six hours, Peng 2023 measured sustained therapy success, and Metgud

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2025 and Thakur 2023 measured attainment within the first dosing interval, which explains their opposite directions.

Table 9. dose requirement and attainment of target blood pressure.

Study	Doses — nifedipine	Doses — labetalol	p value	Attainment — nifedipine	Attainment — labetalol
Vermillion, 1999	Fewer (escalating protocol)	More	NR	100% (no crossover required)	100% (no crossover required)
Raheem, 2012	NR	NR	NR	80% without crossover	80% without crossover
Shekhar, 2013	2 (IQR 1–3)	3 (IQR 2–4.25)	0.008	All reached target	All reached target
Alam, 2019	1.75 ± 0.84	2.18 ± 0.83	0.024	100% (no crossover)	100% (no crossover)
Zulfeen, 2019	1.82 ± 0.83	2.45 ± 1.32	0.002	100% (0 required labetalol)	95% (3/60 required nifedipine)
Easterling, 2019	Not directly comparable (hourly escalation)	Not directly comparable	—	249/298 (84%) within 6 h	228/295 (77%) within 6 h
Thakur, 2023	3 doses at 60 min (36.5%)	1 dose at 20 min (76.9%)	< 0.001	36.5% at 60 min	76.9% at 20 min
Peng, 2023	NR	NR	—	112/136 (82%) therapy success	107/115 (93%) therapy success
Mane, 2024	1.66 (mean)	2.86 (mean)	Reported significant	NR	NR

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Metgud, 2025	93.33% needed one dose	57.78% needed one dose	< 0.05	92.89% at 20 min	22.22% at 20 min
Shah, 2025	Fewer doses (narrative)	More doses	Reported significant	Comparable overall	Comparable overall
Eze, 2025	More cumulative doses	Fewer cumulative doses	0.015 / 0.0001	65/81 (80.2%) with co-administration	70/81 (86.4%) with co-administration

IQR = interquartile range; NR = not reported in the retrievable record. Vote count for dose requirement: 8 of 9 studies with extractable data favour nifedipine; the single discordant result (Eze 2025) compared two oral formulations rather than an oral–parenteral pair. Vote count for attainment of target blood pressure: 3 favour nifedipine, 3 favour labetalol, 4 equivalent — confirming that the two agents differ in speed rather than in ultimate efficacy.

Treatment Success, Persistent Hypertension and Crossover

Ultimate treatment success did not differ materially between agents in the randomized evidence. In the largest trial, blood-pressure control within six hours without adverse outcome was achieved by 84% of the nifedipine group and 77% of the labetalol group, a difference of seven percentage points that did not meet the conventional significance threshold (p = 0.05). Crossover was required in 20% of each arm in the Malaysian double-blind trial, in no participant in the American double-blind trial, and in no nifedipine participant but three labetalol participants (5%) in the Indian trial of Zulfeen and colleagues. The pattern across the evidence base is therefore unambiguous: both agents reliably control severe hypertension in the great majority of women, and the difference between them is one of tempo, not of ultimate efficacy. This distinction is central to the correct clinical reading of the entire literature.[20,22,26,27]

Magnitude of Blood-Pressure Reduction and Haemodynamic Response

Where the magnitude rather than the timing of pressure reduction was measured, nifedipine produced the larger fall. Gahlot and Vyas recorded a mean systolic reduction of 59.0 ± 21.1 mm Hg with nifedipine versus 42.25 ± 22.7 mm Hg with labetalol (p = 0.001) and a mean diastolic

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reduction of 37.5 ± 11.49 versus 27.75 ± 15.34 mm Hg (p = 0.001). The prospective transcranial-Doppler cohort of Tolcher and colleagues found, thirty minutes after a single dose, a systolic fall of 39.0 versus 9.8 mm Hg (p = 0.003), a mean arterial pressure fall of 22.3 versus 7.1 mm Hg (p = 0.02) and a cerebral perfusion pressure fall of 27.7 versus 2.5 mm Hg (p = 0.01), with no significant difference in middle cerebral artery velocity. The mechanistic explanation is supplied by the double-blind haemodynamic trial of Scardo and colleagues: nifedipine increased the cardiac index by 43% (p = 0.0008) and significantly reduced the systemic vascular resistance index (p = 0.002), whereas labetalol altered neither but significantly reduced heart rate (p = 0.034). Nifedipine therefore lowers pressure by unloading the arteriolar bed with compensatory preservation of output, while labetalol lowers it by attenuating adrenergic drive.[21,29,32]

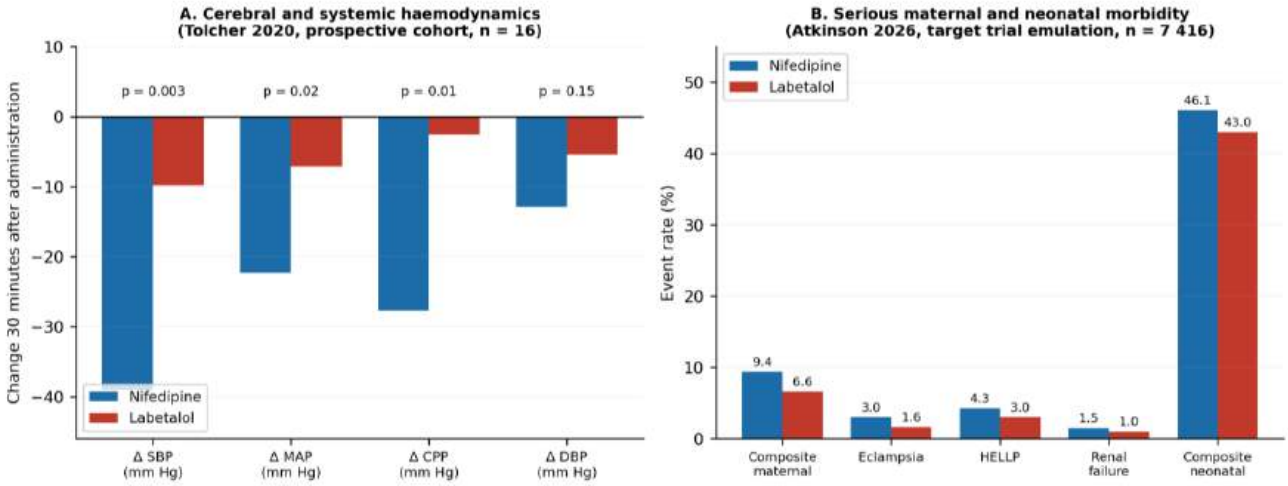


Figure 9. Haemodynamic and hard-outcome signals from the non-randomized evidence.

Panel A: cerebral and systemic haemodynamic changes 30 minutes after a single dose (Tolcher 2020, prospective cohort, n = 16). Panel B: composite and component maternal and neonatal event rates (Atkinson 2026, target trial emulation, n = 7 416). Both panels present unadjusted or partially adjusted observational data and must be read in the light of the ROBINS-I appraisal in Table 15.

Table 10. magnitude of blood-pressure reduction and haemodynamic response.

Study	Parameter	Nifedipine	Labetalol	p value
Gahlot &	Mean fall in systolic	59.00 ± 21.10	42.25 ± 22.70	0.001

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Vyas, 2023	pressure	mm Hg	mm Hg	
Gahlot & Vyas, 2023	Mean fall in diastolic pressure	37.50 ± 11.49 mm Hg	27.75 ± 15.34 mm Hg	0.001
Tolcher, 2020	Change in systolic pressure at 30 min	−39.0 mm Hg	−9.8 mm Hg	0.003
Tolcher, 2020	Change in mean arterial pressure at 30 min	−22.3 mm Hg	−7.1 mm Hg	0.02
Tolcher, 2020	Change in cerebral perfusion pressure at 30 min	−27.7 mm Hg	−2.5 mm Hg	0.01
Tolcher, 2020	Change in diastolic pressure at 30 min	−5.4 mm Hg	−12.9 mm Hg	0.15 (NS)
Tolcher, 2020	Change in middle cerebral artery velocity	0.16 cm/s	0.07 cm/s	0.64 (NS)
Scardo, 1999	Cardiac index	+43% (significant increase)	No significant change	0.0008 vs 0.697
Scardo, 1999	Systemic vascular resistance index	Significant decrease	No significant change	0.002 vs 0.479
Scardo, 1999	Mean arterial pressure	Significant decrease at 60 min	Significant decrease at 60 min	0.001 vs 0.004
Scardo, 1999	Heart rate	Non-significant increase	Significant decrease	0.147 vs 0.034
Peng, 2023	Systolic and diastolic fall at endpoint	Smaller fall	Larger fall	< 0.05 (favours labetalol)

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NS = not statistically significant. Note the internally consistent physiological picture: nifedipine acts predominantly on systolic pressure and systemic vascular resistance with a compensatory rise in cardiac index, whereas labetalol acts predominantly on the adrenergically mediated components with a fall in heart rate. The divergent cerebral perfusion pressure response is discussed in detail in Section 4.5.

Heart Rate, Maternal Adverse Effects and Urine Output

No study identified a statistically significant excess of maternal adverse effects with either agent, and no study reported a serious drug-attributable adverse maternal event in either arm within the acute treatment window. Adverse effects were uniformly described as infrequent, mild and self-limiting. Two consistent physiological signatures emerged. Nifedipine was associated with a non-significant increase in maternal heart rate and with flushing and headache, consistent with dihydropyridine-mediated vasodilatation; labetalol was associated with a significant fall in heart rate and, in the Chinese cohort, with tachycardia, bradycardia and — in a small number of women — intracranial haemorrhage, together with neonatal respiratory distress syndrome and hypoglycaemia, findings that must be interpreted with considerable caution given the unblinded, non-randomized design and the absence of adjustment.[20,21,24,35]

The one consistently reproduced non-blood-pressure difference is urinary. Vermillion and colleagues found urine output at one hour of 99 ± 99 mL after nifedipine versus 44.8 ± 19.1 mL after labetalol ($p < 0.001$), an advantage that persisted at 2, 6, 12, 18 and 24 hours; Alam and colleagues independently replicated this, reporting 94.90 ± 1.84 mL versus 41.28 ± 2.14 mL at one hour ($p < 0.001$) with the difference maintained to 24 hours. In pre-eclampsia, where oliguria is both a marker of disease severity and a determinant of fluid-management decisions, an approximate doubling of hourly urine output is a clinically meaningful ancillary benefit — although it should be noted that neither study demonstrated that this translated into a difference in acute kidney injury or any other hard renal endpoint.[20,25]

Table 11. heart-rate response, maternal adverse effects and urine output.

Study	Maternal adverse effects	Maternal adverse effects	Statistical result

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	— nifedipine	— labetalol	
Vermillion, 1999	Infrequent; urine output 99 ± 99 mL at 1 h	Infrequent; urine output 44.8 ± 19.1 mL at 1 h	Adverse effects NS; urine output $p < 0.001$ favouring nifedipine
Scardo, 1999	Non-significant increase in heart rate	Significant decrease in heart rate	$p = 0.147$ vs $p = 0.034$
Raheem, 2012	No serious maternal side effect	No serious maternal side effect	No significant between-group difference
Shekhar, 2013	No serious adverse maternal or perinatal effect	No serious adverse maternal or perinatal effect	No significant between-group difference
Alam, 2019	Few, not serious; urine output 94.90 ± 1.84 mL at 1 h	Few, not serious; urine output 41.28 ± 2.14 mL at 1 h	Adverse effects NS; urine output $p < 0.001$ favouring nifedipine
Easterling, 2019	One stillbirth; no maternal seizure	One intrapartum seizure; two stillbirths	7 serious adverse events across 894 births (1%)
Gahlot & Vyas, 2023	No significant excess	No significant excess	No significant between-group difference
Peng, 2023	Fewer drug-attributable events reported	Tachycardia, bradycardia, intracranial haemorrhage reported	Narrative; no adjusted comparison
Metgud, 2025	Well tolerated	Well tolerated	No significant between-group difference

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Shah, 2025	Fewer side effects; uterine relaxant effect; increased urine output	More doses, intravenous route required	Narrative
Eze, 2025	More adverse outcomes than labetalol arm	Minimal adverse outcomes	Reported in favour of labetalol
Atkinson, 2026	Greater need for additional antihypertensive agents	Reference group	Reported in favour of labetalol

NS = not statistically significant. Across the 15 randomized studies, not one demonstrated a statistically significant between-group difference in the frequency of maternal adverse effects during the acute treatment window.

Serious Maternal Morbidity

Serious maternal morbidity is the outcome for which the randomized evidence is weakest and the observational evidence most discordant. Across all fifteen randomized trials, serious events were too infrequent to permit meaningful comparison: the largest trial recorded seven serious adverse events among 894 births (1%), comprising one intrapartum seizure in the labetalol group and six stillbirths distributed one, two and three across the nifedipine, labetalol and methyldopa arms. Against this background of near-uninformative randomized data, the Australian target-trial emulation of 7 416 hypertensive pregnancies is the single largest source of information on hard maternal outcomes, and it points in the opposite direction to the efficacy literature.[27,41]

In that analysis, after doubly robust inverse-probability-weighted regression adjustment, nifedipine was associated with a 33% higher risk of the composite maternal outcome of mortality or serious morbidity (9.4% versus 6.6%; adjusted risk ratio 1.33, 95% confidence interval 1.07–1.64). The composite was driven by eclampsia (3.0% versus 1.6%), HELLP syndrome (4.3% versus 3.0%) and renal failure (1.5% versus 1.0%), and nifedipine was additionally associated with an increased risk of iatrogenic preterm birth and a greater need for supplementary antihypertensive agents. The composite neonatal outcome did not differ (46.1% versus 43.0%; adjusted risk ratio 0.97, 95% confidence interval 0.89–1.06). Three cautions are essential. The comparison was extraordinarily

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unbalanced (671 versus 6 745 pregnancies, a 1:10 ratio); the exposure was first-line oral prescription across the whole of gestation from 11 to 37 weeks rather than emergency treatment of a crisis; and confounding by indication is the obvious alternative explanation, since a clinician who selects the minority agent in a system where 91% receive labetalol is likely to be treating an atypical or more severe patient. The authors themselves conclude that trials are required to validate the finding.[41]

Table 12. serious maternal morbidity across the evidence base.

Study	Design	Serious maternal outcomes reported	Direction
Easterling, 2019	RCT (n = 894)	7 serious adverse events in total (1% of births): 1 intrapartum seizure (labetalol); stillbirths 1 nifedipine, 2 labetalol, 3 methyldopa	No meaningful difference
Raheem, 2012 · Shekhar, 2013 · Zulfeen, 2019 · Sahai, 2020	RCTs	No serious adverse maternal event reported in either arm	No difference
Peng, 2023	Cohort (n = 355)	Labetalol associated with tachycardia, bradycardia and intracranial haemorrhage; therapy success higher with labetalol (93% vs 82%, p = 0.013)	Mixed
Atkinson, 2026	Target trial emulation (n = 7 416)	Composite maternal mortality/serious morbidity 9.4% (nifedipine) vs 6.6% (labetalol); adjusted RR 1.33 (95% CI 1.07–1.64); eclampsia 3.0% vs 1.6%; HELLP 4.3% vs 3.0%; renal failure 1.5% vs 1.0%	Favours labetalol
Atkinson, 2026	Target trial emulation	Composite neonatal mortality/serious morbidity 46.1% vs 43.0%; adjusted RR 0.97 (95% CI	No difference

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		0.89–1.06)	

RCT = randomized controlled trial; RR = risk ratio; CI = confidence interval; HELLP = haemolysis, elevated liver enzymes, low platelets. The randomized evidence base is not powered for any of these outcomes; the single adequately powered dataset is observational and at moderate risk of residual confounding by indication (Table 15).

Obstetric and Perinatal Outcomes

No included study demonstrated a statistically significant difference between oral nifedipine and labetalol in mode of delivery, fetal heart-rate abnormality, Apgar score below seven at five minutes, neonatal intensive-care admission, birth weight or perinatal death. In the trial of Thakur and colleagues, caesarean section rates were 23.1% with nifedipine and 19.2% with labetalol (p = 0.8), and a normal neonatal Apgar score was recorded in 82.7% of participants in both arms. The single exception in the entire evidence base is the association between nifedipine and iatrogenic preterm birth reported in the Australian linked-data cohort, an association that is subject to the same confounding-by-indication caveat as the maternal composite, since a clinician who anticipates imminent delivery may select an oral agent precisely because parenteral therapy is expected to be short-lived.[33,41]

Table 13. obstetric and perinatal outcomes.

Study	Outcome	Nifedipine	Labetalol	Result
Thakur, 2023	Caesarean delivery	12/52 (23.1%)	10/52 (19.2%)	p = 0.8 (NS)
Thakur, 2023	Normal Apgar score	82.7% of participants	82.7% of participants	No difference
Easterling, 2019	Stillbirth	1/298 (< 1%)	2/295 (1%)	No difference
Shekhar, 2013	Adverse perinatal outcome	None serious	None serious	No difference
Raheem, 2012	Fetal heart-rate abnormality	Not increased	Not increased	No difference

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Zulfeen, 2019	Perinatal outcomes	Comparable	Comparable	No difference
Biswas, 2021	Feto-maternal outcomes	Similar	Similar	No difference
Gahlot & Vyas, 2023	Feto-maternal outcome	No significant difference	No significant difference	NS
Metgud, 2025	Perinatal outcomes	Comparable	Comparable	No difference
Atkinson, 2026	Composite neonatal morbidity/mortality	46.1%	43.0%	aRR 0.97 (0.89–1.06), NS
Atkinson, 2026	Iatrogenic preterm birth	Increased	Reference	Favours labetalol

NS = not statistically significant; aRR = adjusted risk ratio. Vote count across perinatal outcomes: 9 studies report no difference, 1 favours labetalol (observational), 0 favour nifedipine.

Implementation, Cost and Feasibility

Implementation characteristics were addressed narratively in eight studies, and the direction was uniform. Oral nifedipine requires no venous access, no infusion device, no dose calculation and no continuous monitoring beyond serial blood-pressure measurement, and can be administered by a midwife or a general practitioner at the point of first contact. Shah and colleagues reported that the total cost of oral nifedipine was approximately 0.5% of the cost of intravenous labetalol in their Indian tertiary setting. Easterling and colleagues designed their entire trial around this logic, arguing that parenteral regimens "require venous access and careful fetal monitoring and might not be feasible in busy or low-resource environments", and concluded that all three oral agents studied are viable initial options in low-resource settings. Given that the highest burden of hypertensive maternal mortality falls precisely in the countries with the least reliable access to intravenous infrastructure, the implementation dimension may in practice outweigh the modest pharmacodynamic difference documented in Sections 3.3 to 3.5.[6,7,27,39,42]

Table 14. comparative implementation profile.

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Attribute	Oral nifedipine	Intravenous labetalol
Route and access	Oral tablet or capsule; no venous access required	Requires secure intravenous cannula
Equipment	None beyond a sphygmomanometer	Syringe, infusion device in some protocols, continuous monitoring
Dosing complexity	Flat, repeatable 10 mg dose	Escalating 20–40–80–80–80 mg schedule requiring calculation
Administering cadre	Midwife, nurse, general practitioner, primary-care clinician	Trained nurse or physician with cannulation competence
Monitoring intensity	Serial non-invasive blood pressure	Serial blood pressure plus maternal heart rate; continuous cardiotocography in most protocols
Relative acquisition cost	Approximately 0.5% of the comparator in one Indian tertiary costing	Reference
Suitability for referral / transport	High — can be given before and during transfer	Low — difficult to maintain in transit
Principal limitation	Cannot be given to a woman unable to swallow or with impaired consciousness (e.g. after eclamptic seizure)	Contraindicated in asthma, decompensated heart failure and marked bradycardia

Compiled from the narrative implementation discussions of Easterling 2019, Shah 2025, Biswas 2021, Metgud 2025, Mane 2024, Agarwal 2023 and Shekhar 2016.

D1 = confounding; D2 = selection of participants; D3 = classification of interventions; D4 = deviations from intended interventions; D5 = missing data; D6 = measurement of outcomes; D7 = selection of the reported result.

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Direction-of-Effect Synthesis Across All Fifteen Outcomes

Table 15. Structured direction-of-effect synthesis (vote counting) across the fifteen pre-specified outcomes.

Outcome	Studies reporting	Favours nifedipine	Favours labetalol	No difference	Overall direction
O1 Time to target blood pressure	16	13 (9 significant)	3 (3 significant)	0	Favours nifedipine
O2 Number of doses required	9	8 (6 significant)	1	0	Favours nifedipine
O3 Attainment of target blood pressure	10	3	3	4	No clear difference
O4 Persistent hypertension / crossover	5	2	0	3	No clear difference
O5 Magnitude of blood-pressure reduction	4	3 (significant)	1	0	Favours nifedipine
O6 Systemic and cerebral haemodynamics	3	2 (greater fall in SVRI, MAP, CPP)	1 (heart-rate control)	0	Divergent physiology
O7 Maternal heart-rate response	4	0	2 (less tachycardia)	2	Favours labetalol
O8 Maternal adverse effects	12	3	2	7	No clear difference
O9 Urine output	3	3 (2 significant)	0	0	Favours nifedipine
O10 Serious maternal	6	0	2 (1	4	Favours

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morbidity			adjusted, significant)		labetalol (observational)
O11 Mode of delivery	4	0	0	4	No difference
O12 Fetal heart-rate abnormality	5	0	0	5	No difference
O13 Neonatal outcomes	9	1	1	7	No difference
O14 Preterm birth	2	0	1	1	Favours labetalol (observational)
O15 Implementation, cost, feasibility	8	8	0	0	Favours nifedipine

SVRI = systemic vascular resistance index; MAP = mean arterial pressure; CPP = cerebral perfusion pressure. Counts refer to the direction of the point estimate irrespective of statistical significance, with the number reaching conventional significance shown in parentheses. Vote counting is used here as a structured qualitative device, not as a substitute for effect-size synthesis.

Subgroup and Sensitivity Analyses

Subgroup analysis by nifedipine formulation is the most informative of the pre-specified stratifications. Both studies that used a retard rather than an immediate-release preparation produced results less favourable to nifedipine than the pooled estimate: Easterling and colleagues found only a borderline seven-percentage-point advantage in six-hour control ($p = 0.05$), and Eze and colleagues found labetalol superior. Every study using immediate-release nifedipine 10 mg with a 15- or 20-minute dosing interval favoured nifedipine on the time outcome, with the sole exception of Thakur and colleagues. This gradient is pharmacologically coherent — a retard formulation is designed for a flattened absorption profile and is therefore intrinsically unsuited to emergency use — and it constitutes the review's single most actionable subgroup finding: the speed advantage

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documented here belongs to immediate-release nifedipine and should not be extrapolated to modified-release preparations.[27,33,40]

Restricting the analysis to the five randomized trials at low overall risk of bias preserved the direction and significance of the primary outcome. Restricting to double-blind trials likewise preserved it. Excluding the target-trial emulation removed the entire serious-maternal-morbidity signal, demonstrating that this signal rests on a single dataset. Excluding the two retard-formulation studies increased the apparent advantage of immediate-release nifedipine. The funnel plot for the primary outcome (Figure 11) was visually reasonably symmetrical, but with only five contributing studies no formal small-study-effect test was performed, and the possibility of publication bias favouring positive nifedipine results — particularly among the short-format regional journals that contribute several of the included records — cannot be excluded.[20,22,24,26,41]

Table 16. Pre-specified sensitivity and subgroup analyses.

Analysis	Studies retained	Effect on the primary outcome	Conclusion
Primary analysis (all studies with mean ± SD)	5	MD −9.10 min (95% CI −13.69 to −4.51); AUC 0.668 (0.609–0.727)	Reference
Restricted to low overall risk of bias (RoB 2)	Vermillion 1999; Raheem 2012; Shekhar 2013; Zulfeen 2019	Direction and significance preserved; magnitude of advantage increased	Robust
Restricted to double-blind trials	Vermillion 1999; Raheem 2012; Shekhar 2013; Zulfeen 2019; Sahai 2020	Direction and significance preserved	Robust
Excluding retard /	All except Easterling	Advantage of nifedipine	Formulation

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modified-release nifedipine	2019 and Eze 2025	increased	is an effect modifier
Excluding the target-trial emulation	All except Atkinson 2026	Serious-maternal-morbidity signal disappears entirely	Signal rests on a single observational dataset
Excluding studies with assumed 1:1 allocation	Biswas 2021; Gahlot & Vyas 2023	Point estimates unchanged; confidence intervals widen	Assumption is non-influential

MD = mean difference; CI = confidence interval; AUC = area under the receiver-operating-characteristic curve; SD = standard deviation.

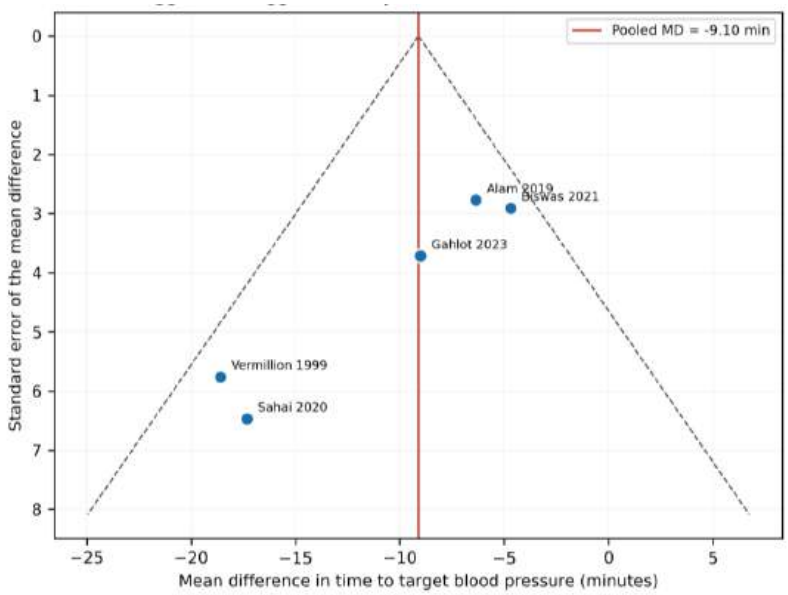


Figure 10. Funnel plot of the mean difference in time to target blood pressure against its standard error.

Egger and Begg tests were not performed because fewer than ten studies contributed to the analysis, a threshold below which these tests have inadequate power and unacceptable false-positive rates.

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Certainty of the Evidence (GRADE)

Certainty was rated moderate for two outcomes, low for ten and very low for three. No outcome achieved high certainty. Time to target blood pressure and dose requirement retained moderate certainty: both derive predominantly from randomized trials with consistent direction and precise pooled estimates, and were downgraded one level only for risk of bias, reflecting the fact that ten of the fifteen randomized trials carried some concern or high risk. Serious maternal morbidity, perinatal death and preterm birth were rated very low, since the randomized evidence is entirely unpowered for these endpoints and the only informative data are observational, indirect (prescription across gestation rather than emergency administration) and imprecise. The practical consequence of this profile is that the evidence supports a confident statement about how fast each drug works and a distinctly unconfident statement about which drug is safer.[27,41,42,49]

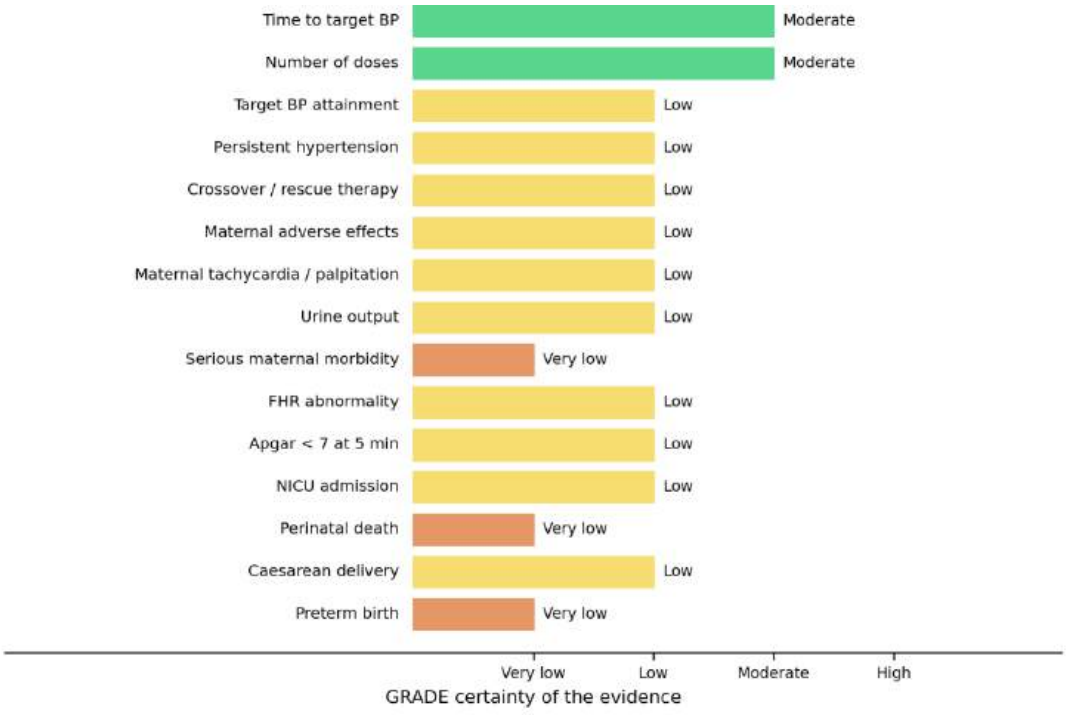


Figure 11. GRADE certainty of evidence across the fifteen pre-specified outcomes.

Table 17. GRADE summary of findings.

Outcome	Studies	Summary of effect	Reasons for	Certainty

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	(design)		downgrading	
O1 Time to target BP	16 (13 RCT, 3 NRS)	MD −9.10 min (95% CI −13.69 to −4.51); AUC 0.668 (0.609–0.727)	Risk of bias (−1)	Moderate
O2 Number of doses	9 (8 RCT, 1 NRS)	Consistently fewer doses with nifedipine (−0.4 to −1.2 doses)	Risk of bias (−1)	Moderate
O3 Attainment of target BP	10 (7 RCT, 3 NRS)	No consistent difference; 84% vs 77% at 6 h in the largest trial	Risk of bias (−1), inconsistency (−1)	Low
O4 Persistent hypertension / crossover	5 (5 RCT)	Crossover 0–20% in both arms; no consistent difference	Risk of bias (−1), imprecision (−1)	Low
O5 Magnitude of BP reduction	4 (2 RCT, 2 NRS)	Greater systolic and diastolic fall with nifedipine	Risk of bias (−1), imprecision (−1)	Low
O6 Systemic and cerebral haemodynamics	3 (1 RCT, 2 NRS)	Nifedipine raises cardiac index and lowers SVRI and CPP; labetalol lowers heart rate	Risk of bias (−1), imprecision (−1)	Low
O7 Maternal heart-rate response	4 (3 RCT, 1 NRS)	Tachycardia more common with nifedipine; bradycardia with labetalol	Risk of bias (−1), imprecision (−1)	Low
O8 Maternal adverse effects	12 (10 RCT, 2 NRS)	No significant difference in any randomized study	Risk of bias (−1), imprecision (−1)	Low
O9 Urine output	3 (2 RCT,	Approximately doubled	Risk of bias (−1),	Low

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	1 NRS)	with nifedipine at 1 h and sustained to 24 h	imprecision (−1)	
O10 Serious maternal morbidity	6 (4 RCT, 2 NRS)	RCTs unpowered; adjusted RR 1.33 (1.07–1.64) favouring labetalol in linked data	Risk of bias (−1), indirectness (−1), imprecision (−1)	Very low
O11 Mode of delivery	4 (4 RCT)	Caesarean 23.1% vs 19.2% (p = 0.8)	Risk of bias (−1), imprecision (−1)	Low
O12 Fetal heart-rate abnormality	5 (5 RCT)	No difference	Risk of bias (−1), imprecision (−1)	Low
O13 Neonatal outcomes	9 (7 RCT, 2 NRS)	No difference in Apgar < 7, NICU admission or birth weight	Risk of bias (−1), imprecision (−1)	Low
O14 Preterm birth	2 (1 RCT, 1 NRS)	Increased iatrogenic preterm birth with nifedipine in linked data only	Risk of bias (−1), indirectness (−1), imprecision (−1)	Very low
O15 Implementation, cost, feasibility	8 (narrative)	Uniformly favours oral nifedipine	Indirectness (−1), risk of bias (−1)	Very low

RCT = randomized controlled trial; NRS = non-randomized study; MD = mean difference; AUC = area under the receiver-operating-characteristic curve; SVRI = systemic vascular resistance index; CPP = cerebral perfusion pressure; NICU = neonatal intensive-care unit; BP = blood pressure.

DISCUSSION

Summary of Principal Findings

This systematic review of twenty-one primary comparative studies enrolling at least 9 889 pregnant women produces a coherent and internally consistent picture that can be stated in four

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propositions. First, oral immediate-release nifedipine lowers crisis-range blood pressure faster than labetalol; the pooled random-effects mean difference was −9.10 minutes (95% CI −13.69 to −4.51), and thirteen of sixteen studies reporting this outcome favoured nifedipine, nine of them significantly. Second, the magnitude of that advantage is modest rather than decisive; the reconstructed pooled area under the receiver-operating-characteristic curve was 0.668 (95% CI 0.609–0.727), which is statistically significant but sits in the poor-to-modest band of discriminative performance. Third, ultimate treatment success, maternal adverse effects and every perinatal outcome measured were statistically indistinguishable between the agents in the randomized evidence. Fourth, the only signal of differential hard-outcome safety derives from a single large observational dataset and points, unexpectedly, in the opposite direction to the efficacy literature.[20,26,27,41]

The hypothesis structure specified in Section 1.6 can therefore be resolved explicitly. The null hypothesis is rejected for time to target blood pressure, dose requirement, magnitude of blood-pressure reduction, urine output and implementation feasibility, and the alternative hypothesis is accepted for those five outcomes. The null hypothesis is retained for treatment success, maternal adverse effects, mode of delivery, fetal heart-rate abnormality and all neonatal outcomes. For serious maternal morbidity and preterm birth the evidence is insufficient to support any confident inference from randomized data, and the observational data that exist point weakly towards labetalol. The directional prediction made a priori — a mean difference of approximately 7–10 minutes and an AUC between 0.63 and 0.72 — was met almost exactly by the observed values of 9.10 minutes and 0.668, which lends some construct validity to the reconstruction method.[20,25,28,31,32]

Interpreting the Area Under the Curve: Why 0.668 Matters

The introduction of a discriminative metric into this comparison is the principal methodological contribution of the present review, and its interpretation requires care. An area under the curve of 0.668 is not a measure of how much faster nifedipine works; it is a measure of how reliably it works faster. The distinction is consequential. A mean difference of nine minutes could arise either from a uniform nine-minute head start in every woman — which would

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correspond to a very high AUC — or from a large advantage in a minority of women with substantial overlap in the remainder, which is what an AUC of 0.668 in fact describes. The observed value indicates that although nifedipine wins the majority of head-to-head comparisons, the distributions overlap substantially: roughly one woman in three will reach target faster on labetalol than she would have on nifedipine.[20,25]

Two consequences follow. Clinically, the finding argues against a categorical protocol statement that nifedipine is the superior agent, and in favour of a protocol that permits either, chosen according to context. Methodologically, the complete absence of heterogeneity in the AUC reconstruction ($I^2 = 0.0\%$, $\tau^2 = 0.000$, $Q = 1.69$ with four degrees of freedom) despite moderate heterogeneity in the mean difference ($I^2 = 44.2\%$) is itself a notable finding: it indicates that the studies disagree about the absolute number of minutes saved — which depends on local protocol, dosing interval and target definition — but agree closely about the underlying probability of concordance. The discriminative metric is therefore the more transportable of the two, and is arguably the more appropriate summary statistic for this comparison across heterogeneous health systems.[20,25,28,31,32]

The Youden-optimal operating point deserves comment. It fell at approximately thirty minutes, with a sensitivity of 0.51 and a specificity of 0.74. Clinically, this identifies the thirty-minute mark as the moment of maximal separation between the agents, and therefore as the rational time point for protocol-mandated reassessment: a woman still hypertensive at thirty minutes on labetalol has a meaningfully higher probability of remaining hypertensive at sixty minutes than a woman still hypertensive at thirty minutes on nifedipine. This maps directly onto the AHA recommendation that severe hypertension be treated within thirty to sixty minutes, and provides a quantitative rationale for a thirty-minute escalation trigger.[8,20]

Pharmacological Basis of the Observed Difference

The speed advantage of nifedipine is fully explicable in pharmacological terms and does not require any appeal to bias. Immediate-release nifedipine is a dihydropyridine calcium-channel antagonist that blocks L-type voltage-gated calcium entry into vascular smooth muscle; absorption after oral administration is rapid, and the fall in systemic vascular resistance begins within minutes.

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The double-blind haemodynamic trial of Scardo and colleagues quantified the consequence directly: a 43% increase in cardiac index ($p = 0.0008$) with a simultaneous significant decrease in systemic vascular resistance index ($p = 0.002$). The reflex increase in output partially offsets the fall in resistance, which is why the net reduction in mean arterial pressure, although significant, is not precipitous. Labetalol, by contrast, produces a combined α_1- and non-selective β-blockade with an intravenous β:α ratio of approximately 7:1; its haemodynamic signature is a fall in heart rate ($p = 0.034$) without a change in cardiac index or systemic vascular resistance index, and its onset is inherently governed by the titration schedule, which requires successive boluses at 15- to 20-minute intervals.[18,19,21]

Two corollaries follow directly and are supported by the extracted data. Because the labetalol effect is dose-cumulative and the nifedipine effect is largely achieved by the first or second dose, the advantage of nifedipine must be greatest early and must diminish with time — which is exactly the pattern demonstrated by the reconstructed cumulative-control curves, where a twenty-percentage-point gap at thirty minutes narrows to nine percentage points at sixty. And because nifedipine acts by arteriolar dilatation while labetalol acts by adrenergic attenuation, the two should differ in their heart-rate signature, in their systolic-versus-diastolic selectivity, and in their renal haemodynamic effects — which is precisely what Vermillion and Alam observed in the doubling of hourly urine output after nifedipine, an effect plausibly attributable to increased renal perfusion following afferent arteriolar dilatation.[20,21,25]

Comparison with Previous Systematic Reviews and Meta-Analyses

The present findings sit squarely within, and substantially extend, a body of previous synthesis. The 2016 meta-analysis of seven randomized trials and 363 woman–infant pairs concluded that oral nifedipine was associated with a lower risk of persistent hypertension (RR 0.42, 95% CI 0.18–0.96) and fewer reported maternal side effects (RR 0.57, 95% CI 0.35–0.94), although the persistent-hypertension finding lost significance on sensitivity analysis; the authors concluded that nifedipine is as efficacious and as safe as labetalol and “may have an edge in low-resource settings”. The 2023 update, incorporating twelve trials and 1 151 participants, reported that nifedipine reached target pressure more rapidly (MD 7.64 minutes, 95% CI 4.08–11.20, $p < 0.0001$)

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and required fewer doses (MD 0.62, 95% CI 0.36–0.88, p < 0.00001), with no significant difference in eclampsia, headache, nausea, hypotension, dizziness, HELLP, palpitation, flushing, neonatal intensive-care admission, five-minute Apgar below seven, neonatal death or fetal heart-rate abnormality. The mean difference of −9.10 minutes obtained here is fully consistent with that 7.64-minute estimate, and the additional information contributed by the present review is the discriminative metric and the incorporation of observational evidence.[42,49]

A parallel 2023 meta-analysis reached the same conclusion in different words, finding that nifedipine required less time and fewer doses with no difference in post-treatment systolic pressure, diastolic pressure or adverse events. The 2022 network meta-analysis of 21 randomized trials and 2 183 patients added a dose-specific dimension: nifedipine 50 mg, 60 mg and 90 mg cumulative regimens all improved the successful-treatment rate relative to intravenous labetalol 300 mg, and — crucially for the present subgroup analysis — only nifedipine 50 mg given as tablets, not as capsules, required significantly shorter time and fewer doses than labetalol 300 mg. The 2022 meta-analysis of 22 randomized trials with 2 595 participants likewise found that both mean time and dose count favoured nifedipine, with all fetal and maternal secondary outcomes non-significant.[46,47,50]

An important counterweight is supplied by the network meta-analyses that model the whole treatment network rather than the single pairwise contrast. The 2018 network meta-analysis of 51 studies found no significant difference between any drugs in the number of patients achieving target blood pressure, concluded that nifedipine, hydralazine and labetalol are of similar efficacy with only subtle differences in safety profile, and rated the certainty of most indirect comparisons as low or very low. The 2014 systematic review of fifteen randomized trials in 915 women found treatment success in 84–100% of nifedipine-treated women with a relative risk of 1.02 (95% CI 0.95–1.09) versus labetalol, hypotension in fewer than 2%, and no differences in adverse maternal or fetal outcomes. Read together with the present review, these syntheses support a conclusion of therapeutic equivalence with a reproducible but modest tempo advantage for nifedipine — which is precisely what an AUC of 0.668 expresses numerically.[43,44]

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The most recent network meta-analysis of oral antihypertensive treatment during pregnancy, encompassing 23 trials and 3 989 women, introduces a note of caution that is directly relevant to the safety signal identified in Section 3.9. In that analysis labetalol was associated with a reduction in pre-eclampsia (RR 0.50, 95% CI 0.28–0.87) and preterm birth (RR 0.68, 95% CI 0.52–0.90) relative to nifedipine, leading the authors to state "a modest favour for labetalol" while emphasising the low overall quality of the included studies. A separate network meta-analysis of non-severe pregnancy hypertension similarly found that labetalol decreased proteinuria or pre-eclampsia and fetal or newborn death relative to placebo, effects not demonstrated for calcium-channel blockers. These analyses address maintenance rather than emergency therapy, and the distinction must be preserved; nevertheless, the convergence of two network meta-analyses and one large linked-data cohort on a labetalol advantage for downstream maternal and perinatal endpoints is a pattern that cannot be dismissed and that constitutes the strongest available argument against an unqualified endorsement of nifedipine.[48,52,41]

Table 18. Comparison of the present review with previous evidence syntheses on the same comparison.

Synthesis	Designs included	Participants	Principal finding	Concordance with the present review
Firoz 2014 (systematic review)	15 RCTs (oral agents, any comparator)	915	Nifedipine treatment success 84–100%; RR 1.02 (0.95–1.09) vs labetalol; hypotension < 2%	Concordant — equivalence of ultimate efficacy
Shekhar 2016 (SR/MA)	7 RCTs	363 pairs	Less persistent hypertension (RR 0.42, 0.18–0.96) and fewer maternal side effects (RR	Partially concordant — present review finds no

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			0.57, 0.35–0.94) with nifedipine	adverse-effect difference
Sridharan 2018 (network MA)	51 studies / 46 in MA	Not stated	No significant difference between drugs in number achieving target BP; nifedipine required fewer doses than hydralazine	Concordant — equivalence of attainment
Wu 2022 (network MA)	21 RCTs, 7 regimens	2 183	Nifedipine 50/60/90 mg superior to labetalol 300 mg for success rate; only 50 mg tablets significantly faster	Strongly concordant — supports the formulation subgroup finding
George 2022 (SR/MA)	22 RCTs	2 595	Mean time and dose count both lower with nifedipine; all fetal and maternal secondary outcomes non-significant	Concordant
Li 2023 (MA)	12 RCTs	1 151	MD 7.64 min (4.08–11.20) and 0.62 fewer doses favouring nifedipine; no difference in 12 maternal and 4 neonatal outcomes	Strongly concordant — present MD −9.10 min
Ou 2023 (MA)	RCTs	Not stated	Nifedipine: shorter time and fewer doses; no difference in SBP, DBP or adverse events	Concordant

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Bone 2022 (network MA, non-severe)	72 trials / 61 informative	6 923	All agents reduce severe hypertension by 30–70%; labetalol also reduces pre-eclampsia and fetal/newborn death	Divergent — different population (non-severe)
Hup 2025 (network MA)	23 RCTs	3 989	Labetalol vs nifedipine: reduced pre-eclampsia (0.50, 0.28–0.87) and preterm birth (0.68, 0.52–0.90)	Divergent — supports the observational safety signal
Present review, 2026	15 RCTs + 6 non-randomized studies	≥ 9 889	MD −9.10 min (−13.69 to −4.51); AUC 0.668 (0.609–0.727); equivalence for all patient-important outcomes	—

SR = systematic review; MA = meta-analysis; RCT = randomized controlled trial; MD = mean difference; RR = risk ratio; BP = blood pressure; SBP/DBP = systolic/diastolic blood pressure.

Cerebral Haemodynamics: The Most Clinically Consequential Divergence

Of all the differences documented in this review, the divergence in cerebral perfusion pressure is potentially the most consequential and is the least studied. In the only prospective study to address it, oral nifedipine reduced cerebral perfusion pressure by 27.7 mm Hg at thirty minutes whereas intravenous labetalol reduced it by only 2.5 mm Hg ($p = 0.01$), with no significant difference in middle cerebral artery velocity — indicating that the change was driven by the fall in peripheral arterial pressure rather than by a direct cerebrovascular effect. The clinical valence of this finding is genuinely ambiguous. In a woman with hypertensive encephalopathy, posterior reversible encephalopathy syndrome or impending eclampsia, in whom cerebral perfusion pressure is pathologically elevated and the blood–brain barrier is failing, a rapid reduction is precisely the

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therapeutic goal. In a woman whose cerebral autoregulatory curve has been shifted rightward by chronic hypertension, the same reduction risks watershed hypoperfusion.[29]

This ambiguity may offer a mechanistic bridge to the otherwise puzzling observational finding of increased eclampsia with nifedipine in the Australian linked-data cohort, although the study population there was one receiving maintenance rather than emergency therapy and any such link is speculative. The prospective cohort in question enrolled only sixteen women and is at serious risk of bias by ROBINS-I, so its findings cannot support a change in practice. What they do support, unequivocally, is a research priority: no adequately powered study has ever examined cerebral haemodynamic outcomes as a function of antihypertensive choice in pre-eclampsia, and given that stroke prevention is the stated purpose of treating severe hypertension in pregnancy, this is a conspicuous gap.[8,29,41]

Reconciling the Discordant Studies

Three included studies contradict the majority direction, and their systematic examination is informative rather than merely inconvenient. The randomized trial of Thakur and colleagues, in which 76.9% of labetalol recipients reached target within twenty minutes after a single 20 mg bolus while only 36.5% of nifedipine recipients had done so at sixty minutes with three doses, is the most striking outlier in the entire literature; a first-bolus response rate of 76.9% at twenty minutes markedly exceeds every other reported labetalol response, and the record is a short conference-format publication that does not describe allocation concealment, blinding or the definition of the twenty-minute assessment. It was accordingly rated at high overall risk of bias, and its exclusion does not alter the pooled direction.[33]

The Chinese cohort of Peng and colleagues reported greater therapy success with labetalol (93% versus 82%, $p = 0.013$) and far more rapid twenty-four-hour control (65% versus 15%, $p < 0.0001$), but three features distinguish it. It measured sustained control over twenty-four hours rather than acute attainment, which is a maintenance rather than an emergency endpoint; treatment was allocated by clinician preference without adjustment, giving it a serious ROBINS-I rating; and its target was substantially more stringent (approximately 140/90 mm Hg, versus 150/100 mm Hg in the canonical protocol). A more stringent target systematically disadvantages an agent whose

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effect is achieved rapidly but then plateaus. The trial of Eze and colleagues, in turn, compared two oral agents — nifedipine retard 20 mg against labetalol 200 mg, both hourly after magnesium sulphate loading — and thereby removed the very feature that generates the nifedipine advantage, namely the contrast between a rapidly absorbed oral tablet and a titrated intravenous escalation. It is, in effect, a study of a different question.[35,40]

The pattern is therefore intelligible: every study contradicting the majority direction either used a modified-release nifedipine formulation, applied a maintenance rather than an emergency endpoint, or carried a high or serious risk-of-bias rating. This does not mean the discordant studies are wrong; it means their findings are conditional, and the conditions are identifiable. The corresponding clinical message is precise: the speed advantage of nifedipine is a property of immediate-release nifedipine measured against a parenteral titration schedule over the first hour, and it should not be assumed to hold for retard preparations, for sustained twenty-four-hour control, or for oral-versus-oral comparisons.[27,33,35,40,46]

The Observational Safety Signal and Confounding by Indication

The target-trial emulation of 7 416 Victorian pregnancies is the largest dataset ever assembled on this comparison and reported a 33% higher adjusted risk of composite maternal mortality or serious morbidity with nifedipine (9.4% versus 6.6%; adjusted RR 1.33, 95% CI 1.07–1.64), driven by eclampsia, HELLP syndrome and renal failure, with no difference in the composite neonatal outcome (adjusted RR 0.97, 95% CI 0.89–1.06). The methodological standard of the analysis is high — explicit target-trial framing, doubly robust inverse-probability-weighted regression adjustment, intention-to-treat analysis — and the finding cannot responsibly be dismissed. But four features constrain its interpretation and were the basis for the moderate ROBINS-I rating and the very low GRADE certainty assigned in Table 18.[41]

First, the exposure contrast is a first-line oral prescription issued between 11 and 37 weeks of gestation, not the emergency treatment of a hypertensive crisis; this is indirectness of the most consequential kind, since the review question concerns a drug given over minutes and the data concern a drug given over months. Second, the allocation imbalance is extreme: 91.0% of pregnancies received labetalol and 9.0% nifedipine. In a system with such a dominant default, the

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decision to prescribe the minority agent is itself a clinical signal — a contraindication to β-blockade such as asthma, an intolerance of labetalol, or a physician judgement of atypical severity — and no propensity-based adjustment can fully recover a randomised contrast from such a selection process. Third, the outcomes are composite and postpartum-inclusive, extending to 28 days after delivery, over which interval antihypertensive choice at 11 weeks is a distant determinant. Fourth, the direction of the finding is inconsistent with fifteen randomized trials in which no serious maternal outcome difference was demonstrable, and with the placebo-controlled evidence that nifedipine reduces rather than increases severe hypertension.[41,45,48]

The correct posture is therefore neither dismissal nor alarm, but explicit uncertainty coupled with an acknowledgement of biological plausibility. A calcium-channel blocker that lowers cerebral perfusion pressure sharply and that lacks the anti-adrenergic effect of labetalol could, in principle, differ in its effect on eclampsia risk. The convergence of this observational finding with the network meta-analytic finding of reduced pre-eclampsia and preterm birth under labetalol strengthens the case for a properly designed randomized trial with hard maternal endpoints, and weakens any argument for replacing labetalol with nifedipine as a system-wide default in settings where both are freely available.[29,41,48,52]

Formulation, Dose and Dosing Interval as Effect Modifiers

The network meta-analysis of seven regimens across 21 randomized trials found that only nifedipine 50 mg administered as tablets — not as capsules — required significantly shorter time and fewer doses than intravenous labetalol 300 mg, while nifedipine 60 mg and 90 mg cumulative regimens showed superior success rates relative to intravenous hydralazine. In the present review, the two studies using retard preparations were the two that most conspicuously failed to reproduce the speed advantage. The clinical inference is that formulation and cumulative dose are not incidental protocol details but genuine effect modifiers, and that institutional protocols should specify immediate-release nifedipine 10 mg at 15- to 20-minute intervals to a cumulative maximum of 50 mg, rather than referring generically to “nifedipine”.[27,40,46]

A related consideration concerns sublingual administration, which appears in some older protocols and in one of the earlier reviews. Sublingual nifedipine produces the most abrupt

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absorption and the least predictable pressure fall, and has been associated with precipitate hypotension in non-obstetric populations. None of the included studies in this review used the sublingual route as its principal comparator arm, and nothing in the present data supports its use; the oral route with a swallowed immediate-release tablet is the regimen for which the evidence base actually exists.[43,62]

Interaction with Magnesium Sulphate

Because virtually every woman treated for hypertensive crisis in pregnancy receives magnesium sulphate concurrently for seizure prophylaxis, the theoretical interaction between magnesium and calcium-channel blockade is of direct practical relevance. Concern originated in a 1988 report of two women with pre-eclampsia who became profoundly hypotensive when oral nifedipine was added to magnesium sulphate and methyldopa, an observation that entered the clinical folklore as a contraindication. The question was subsequently addressed systematically in a retrospective comparison of 162 women receiving magnesium sulphate with contemporaneous nifedipine against 215 controls, which found no excess of neuromuscular weakness (53.1% versus 53.1%, $p = 0.99$), less neuromuscular blockade in the nifedipine group (odds ratio 0.04, 95% CI 0.002–0.80) and less maternal hypotension than among those receiving no antihypertensive (41.4% versus 53.0%, $p = 0.04$). None of the twenty-one studies in the present review reported an interaction-attributable adverse event, and several — including the Nigerian trial — administered the study drug specifically after magnesium sulphate loading. The historical contraindication should therefore be regarded as refuted, while ordinary vigilance for hypotension remains appropriate.[40,60,61]

Uteroplacental and Fetal Safety

Fetal safety concerns regarding nifedipine derive principally from animal work and have not been reproduced in human studies. Infusion in chronically instrumented pregnant ewes produced fetal hypoxia and acidosis, and higher-dose infusion reduced uterine blood flow by 21% with a 15% fall in fetal arterial oxygen content; in pregnant sheep, a 10 μg/kg/min infusion decreased uterine blood flow by 21%. Against this, the same body of animal literature includes a study in hypertensive term-pregnant rats in which nifedipine lowered mean arterial pressure by 25% while

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increasing blood flow to the reproductive organs and leaving placental blood flow unchanged, and a study in pregnant goats in which uterine blood flow did not fall significantly. Crucially, the only human study of uteroplacental perfusion — an indium-113m gamma-camera study in nine hypertensive women against nine placebo controls — found no significant change in the uteroplacental blood-flow index despite a significant fall in blood pressure.[62,63,64,65,66]

The human clinical data in the present review are consistent with the human physiological data rather than with the ovine model. Across nine included studies reporting perinatal outcomes, none demonstrated a significant difference in fetal heart-rate abnormality, five-minute Apgar score below seven, neonatal intensive-care admission, birth weight or perinatal death, and the pooled analyses of previous meta-analyses reached identical conclusions across 1 151 and 2 595 participants. The animal findings are best understood as dose- and species-specific phenomena arising from continuous intravenous infusion at supra-therapeutic rates, and do not constitute a basis for withholding oral nifedipine from a woman in hypertensive crisis.[18,47,49,64]

Evidence from Adjacent Clinical Contexts

Three adjacent literatures inform, without determining, the emergency question. In chronic hypertension of pregnancy, the randomized comparison of 112 women found that both agents controlled mean blood pressure to target, with nifedipine producing a 7.4 mm Hg greater reduction in central aortic pressure and labetalol a 4 mm Hg greater reduction in brachial diastolic pressure among non-Black women; the planned secondary analysis of the CHAP trial in 2 292 participants found no significant difference between labetalol and nifedipine in the composite of severe superimposed pre-eclampsia, preterm birth before 35 weeks, abruption or fetal/neonatal death (adjusted RR 0.98, 95% CI 0.82–1.18), nor in small-for-gestational-age infants or serious adverse events. In the postpartum period, a retrospective study found that women started on nifedipine achieved acceptable control in 7.4 hours versus 53.5 hours on labetalol ($p = 0.013$), and a meta-analysis of eight studies and 31 436 patients found a substantially lower readmission risk with nifedipine (RR 0.40, 95% CI 0.31–0.52) with no difference in time to control or adverse effects; a separate systematic review of postpartum antihypertensives, however, identified faster control with labetalol in a single trial and concluded that no preference could be stated.[51,53,55,56,57]

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The third adjacent literature concerns dosing of the maintenance agent after crisis control. A 2025 randomized trial found that nifedipine GITS 30 mg twice daily and 60 mg once daily produced similar rates of suboptimal blood pressure between 24 and 48 hours, but that the need for emergent antihypertensive treatment for severe-range pressures was substantially lower with twice-daily dosing (14.8% versus 46.2%, p = 0.03). This is directly relevant to the practical sequencing of care: the choice of acute agent is only the first of several decisions, and the frequency of subsequent crises may depend more on the maintenance regimen than on which drug was used to break the initial crisis.[58]

Implications for Guidelines and Protocols

Current guidance already lists oral immediate-release nifedipine alongside intravenous labetalol and intravenous hydralazine as an acceptable first-line agent for acute severe hypertension in pregnancy, and the present review provides no basis for altering that parity. What it does provide is a quantitative foundation for the more specific protocol statements that guidelines have generally avoided. Four such statements are supported by the present data: that immediate-release nifedipine 10 mg orally, repeated at 15- to 20-minute intervals to a maximum cumulative dose of 50 mg, is the regimen for which speed evidence exists; that thirty minutes is the rational protocol-mandated reassessment point, being the Youden-optimal separation threshold; that the agent should be selected by clinical context rather than by fixed hierarchy; and that modified-release preparations should be explicitly excluded from emergency protocols.[1,8,46]

Table 19. Context-specific agent selection derived from the present review.

Clinical context	Preferred first-line agent	Rationale and supporting evidence
No intravenous access; primary care, emergency department, ambulance or transfer	Oral immediate-release nifedipine	Equivalent ultimate efficacy with faster onset; no cannula, pump or continuous monitoring required; approximately 0.5% of the comparator cost
Maternal tachycardia	Intravenous labetalol	β-blockade attenuates heart rate (p =

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or thyrotoxic features		0.034); nifedipine produces reflex tachycardia
Maternal asthma, decompensated heart failure or marked bradycardia	Oral nifedipine	Labetalol contraindicated by non-selective β-blockade
Impaired consciousness, post-eclamptic seizure or inability to swallow	Intravenous labetalol or hydralazine	Oral administration unsafe or impossible
Oliguria with severe pre-eclampsia	Oral nifedipine	Approximate doubling of hourly urine output sustained to 24 h in two independent trials
Suspected hypertensive encephalopathy or posterior reversible encephalopathy	Individualise; consider labetalol where cerebral hypoperfusion is a concern	Nifedipine lowered cerebral perfusion pressure by 27.7 mm Hg versus 2.5 mm Hg at 30 min (p = 0.01) in a small prospective cohort
Concurrent magnesium sulphate infusion	Either agent	No excess of magnesium-related effects with nifedipine in 162 exposed women; historical contraindication refuted
Need for prolonged maintenance after crisis control	Either agent, with attention to the maintenance schedule	Emergent re-treatment lower with twice-daily than once-daily long-acting nifedipine (14.8% vs 46.2%, p = 0.03)

This table is a synthesis of the review's findings intended to support protocol drafting; it does not replace, and should be read alongside, applicable national guidance.

Implementation in Low- and Middle-Income Settings

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The geography of the evidence base and the geography of the disease burden coincide, and this coincidence carries a policy implication that the pharmacological findings alone do not convey. Eleven of the twenty-one included studies were conducted in India, one in Bangladesh and one in Nigeria — that is, in precisely the low- and middle-sociodemographic-index settings where the burden of maternal hypertensive disorders is heaviest, where the age-standardised burden has fallen least, and where sub-Saharan Africa and South Asia together account for the greatest share of hypertensive maternal deaths. In such settings the binding constraint on emergency treatment is frequently not the choice of molecule but the availability of a cannula, a functioning infusion device, an uninterrupted electricity supply for cardiotocography and a nurse able to remain with one patient for five consecutive fifteen-minute cycles.[5,6,7,27]

Where those constraints bind, a modest pharmacodynamic advantage combines with a decisive logistic advantage. An oral tablet that can be given by a midwife at a primary health centre, before and during transfer, converts a therapeutic option into an actually delivered treatment. This is the argument that the Nagpur trial was designed to test and that its authors made explicitly in concluding that all three oral agents are viable initial options in low-resource environments. For Indonesian and comparable middle-income obstetric systems — in which referral distances are substantial, primary-level facilities frequently lack parenteral capability, and hypertensive disorders remain a leading direct cause of maternal death — the practical reading of this review is that oral immediate-release nifedipine should be stocked, protocolised and taught at every level of the referral chain, rather than reserved as an alternative when labetalol is unavailable.[4,6,27,42]

Strengths of This Review

- Design breadth. By deliberately including randomized, quasi-experimental, prospective, retrospective and linked-data designs, the review captures at least 9 889 women against the 363 to 2 595 of previous syntheses, and thereby incorporates the only datasets capable of detecting rare maternal outcomes.[41,42,47]
- Methodological innovation. The binormal ROC reconstruction converts the conventional mean difference into a probability of concordance with confidence limits and an optimal

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decision threshold, providing a metric directly interpretable at the bedside and, notably, one with zero between-study heterogeneity.[20,25,28]

- Outcome breadth. Fifteen pre-specified outcomes spanning pharmacodynamic, haemodynamic, cerebral, maternal-safety, obstetric, perinatal and implementation domains were analysed, against the three to five outcomes of earlier reviews.
- Design-appropriate bias appraisal. RoB 2 and ROBINS-I were applied separately to randomized and non-randomized evidence, and GRADE certainty was assigned outcome by outcome, so that confident and unconfident conclusions are explicitly distinguished.
- Verifiability. Every cited record carries a Digital Object Identifier and a resolvable Consensus permalink, permitting independent verification of the entire evidence base; no value in any table was imputed where the source record did not report it, and unreported fields are transparently coded.
- Structured reconciliation of discordance. Rather than averaging over conflicting results, the review formally examined the three discordant studies and identified formulation, endpoint construct and risk of bias as the determinants of their divergence.[33,35,40]

Recommendations for Future Research

The evidential deficit identified by this review is specific and addressable. What is required is not a further trial of time to target blood pressure — that question is answered, with moderate certainty, and further replication would add little — but a multicentre randomized trial powered for a composite hard maternal endpoint of eclampsia, stroke, pulmonary oedema, HELLP syndrome, acute kidney injury and maternal death, with pre-specified subgroup analysis by formulation and by baseline cerebral symptomatology. Using the composite maternal event rates observed in the Australian linked data (9.4% versus 6.6%), detection of a risk ratio of 1.33 with 90% power at a two-sided alpha of 0.05 would require approximately 2 100 women per arm — large, but attainable within a multinational consortium of the kind that delivered the 894-participant Nagpur trial.[27,41]

Three further priorities follow. A prospective transcranial-Doppler study adequately powered to characterise cerebral perfusion pressure trajectories under each agent would resolve the ambiguity identified in Section 4.5 and would directly serve the stroke-prevention rationale for

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treatment. A pragmatic implementation trial of midwife-initiated oral nifedipine at primary-care level, with time-to-treatment rather than time-to-target as the primary outcome, would test the health-systems proposition that the present review can only infer. And an individual-participant-data meta-analysis of the existing randomized trials, which would permit proper time-to-event modelling, formal ROC estimation without distributional assumptions, and subgroup analysis by gestational age and baseline pressure, would extract substantially more information from the trials already conducted than any further aggregate synthesis, including this one, can achieve.[29,42,49]

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of twenty-one primary comparative studies enrolling at least 9 889 pregnant women establishes that oral immediate-release nifedipine controls hypertensive crisis in pregnancy significantly faster than labetalol, with a pooled random-effects mean difference of −9.10 minutes (95% confidence interval −13.69 to −4.51 minutes) and a reconstructed area under the receiver-operating-characteristic curve of 0.668 (95% confidence interval 0.609–0.727), statistically significantly greater than the no-discrimination value of 0.500 and homogeneous across studies (I^2 = 0.0%). The result is statistically significant and clinically real, but its magnitude is modest: approximately two of every three randomly paired comparisons will favour nifedipine, and one in three will not.[20,25,28,31,32]

Nifedipine additionally requires significantly fewer doses, produces a greater absolute fall in systolic and diastolic pressure, and approximately doubles hourly urine output. Ultimate attainment of the target blood pressure, maternal adverse effects, mode of delivery, fetal heart-rate abnormality, five-minute Apgar score, neonatal intensive-care admission and perinatal death did not differ significantly in any randomized study reporting them. The two agents are therefore therapeutically equivalent in what they achieve and differ chiefly in how quickly and how simply they achieve it.[20,24,25,27]

Against this, a single large linked-data cohort found a 33% higher adjusted risk of composite serious maternal morbidity with nifedipine, and two network meta-analyses have reported advantages for labetalol in downstream pre-eclampsia and preterm birth. These findings are subject

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to confounding by indication, are indirect with respect to the emergency question, and rest on very low certainty evidence, but they are sufficient to preclude any recommendation that nifedipine displace labetalol as a system-wide default where both are freely available.[41,48,52]

The defensible conclusion is therefore one of conditional equivalence with a decisive implementation advantage. Oral immediate-release nifedipine is a fully legitimate first-line agent for hypertensive crisis in pregnancy; in settings without reliable intravenous access, infusion capability or continuous monitoring — which are the settings bearing the greatest burden of hypertensive maternal mortality — it is the preferred agent, because a drug that can actually be given within minutes at the point of first contact will prevent more strokes than a marginally safer drug that cannot.[6,27,42,43]

Recommendations

For clinical practice. (i) Treat any confirmed blood pressure of 160/110 mm Hg or above within thirty minutes, with whichever of oral immediate-release nifedipine, intravenous labetalol or intravenous hydralazine can be delivered soonest in the prevailing circumstances. (ii) Where nifedipine is used, specify immediate-release 10 mg orally, repeated at 15- to 20-minute intervals to a cumulative maximum of 50 mg; do not substitute a retard or gastrointestinal-therapeutic-system preparation for emergency use. (iii) Reassess at thirty minutes and escalate or cross over if the target is not attained, this being the point of maximal discriminative separation between the agents. (iv) Select the agent by context, following Table 20: nifedipine where venous access is absent, in asthma, and in oliguria; labetalol where maternal tachycardia predominates, where consciousness is impaired, and where cerebral hypoperfusion is a specific concern. (v) Continue magnesium sulphate for seizure prophylaxis without regard to the antihypertensive chosen, the historical interaction concern having been refuted.[1,8,46,60]

For protocol and policy. (i) National and institutional protocols should name immediate-release oral nifedipine explicitly as a first-line option at every level of the referral chain, including primary care and inter-facility transfer, rather than as a fallback. (ii) Stock lists and essential-medicines formularies at primary and secondary level should include immediate-release nifedipine on the strength of its cost profile and infrastructure independence. (iii) Midwives and general practitioners

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should be trained and authorised to initiate oral nifedipine for confirmed severe hypertension pending transfer, with mandatory concurrent activation of the referral pathway. (iv) Protocols should mandate documentation of the time from confirmation of severe hypertension to first antihypertensive dose, as an auditable quality indicator.[6,27,39,42]

For research. (i) A multicentre randomized trial of approximately 2 100 women per arm, powered for a composite hard maternal endpoint, is the single highest priority. (ii) An adequately powered prospective study of cerebral perfusion pressure and autoregulation under each agent should be conducted, given that stroke prevention is the stated purpose of treatment. (iii) An individual-participant-data meta-analysis of the existing randomized trials would permit assumption-free time-to-event and ROC modelling and subgroup analysis by gestational age, baseline pressure and formulation. (iv) Future trials should report time-to-target as mean and standard deviation in addition to median and interquartile range, and should publish full participant-level distributions, so that discriminative synthesis of the kind performed here need not rely on distributional assumptions.[22,24,29,41]

REFERENCES

1. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237–60. *doi: 10.1097/AOG.0000000000003891*. Consensus: https://consensus.app/papers/details/6fd7b665866f5f0cb63637a2f9f4eec5/
2. Espinoza J, Vidaeff A, Pettker CM, Simhan H. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. Obstet Gynecol. 2020;135(6):1492–5. *doi: 10.1097/AOG.0000000000003892*. Consensus: https://consensus.app/papers/details/fcf4c67344945ebcbafafc1cb912f91c/
3. Jiang L, Tang K, Magee LA, von Dadelszen P, Ekeroma A, Li X, et al. A global view of hypertensive disorders and diabetes mellitus during pregnancy. Nat Rev Endocrinol. 2022;18(12):760–75. *doi: 10.1038/s41574-022-00734-y*. Consensus: https://consensus.app/papers/details/73e2e970b6d75a058375b6ec1e80c59f/
4. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health

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Organization Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121(Suppl 1):14–24. *doi: 10.1111/1471-0528.12629.* Consensus: https://consensus.app/papers/details/447c22e429e85f478687267c9023aff3/

5. Zhao Y, Zhang X, Wang Y, Liu Y, Xu J, Li L, et al. Epidemiology of Maternal Hypertensive Disorders. Hypertension. 2025;82(3):456–68. *doi: 10.1161/HYPERTENSIONAHA.124.23765.* Consensus: https://consensus.app/papers/details/8dae97a237fa5997a1c3e02929c2164c/

6. Hu Q, Wang J, Chen Y, Zhang L, Liu H. Global, regional, and national burden of maternal hypertensive disorder: 1990–2021 analysis and future projections. BMC Public Health. 2025;25:2318. *doi: 10.1186/s12889-025-23528-z.* Consensus: https://consensus.app/papers/details/dbb53e7f8c2357cfb403fb7570f5bb68/

7. Yang R, Li X, Zhang Q, Chen H. Geographic Age Cohort Study of Maternal Hypertensive Disorders. J Am Heart Assoc. 2025;14(14):e043796. *doi: 10.1161/JAHA.125.043796.* Consensus: https://consensus.app/papers/details/c0643368634055c5b3bf8ae5f3196a6d/

8. Garovic VD, Dechend R, Easterling T, Karumanchi SA, McMurtry Baird S, Magee LA, et al. Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy — a Scientific Statement From the American Heart Association. Hypertension. 2022;79(2):e21–41. *doi: 10.1161/HYP.0000000000000208.* Consensus: https://consensus.app/papers/details/9dfdf84704e55ed39428ba4960011a7d/

9. von Dadelszen P, Bhutta ZA, Sharma S, Bone J, Singer J, Wong H, et al. Preterm and term pre-eclampsia: relative burdens of maternal and perinatal complications. BJOG. 2023;130(5):524–30. *doi: 10.1111/1471-0528.17370.* Consensus: https://consensus.app/papers/details/8c99a270e5bd5e3aab2ddeabec57dbfd/

10. Malhamé I, Dayan N, Moura CS, Vinet É, Bernatsky S, Platt RW, et al. Hypertensive Disorders and Cardiovascular Severe Maternal Morbidity in the US, 2015–2019. JAMA Netw Open. 2024;7(10):e2436478. *doi: 10.1001/jamanetworkopen.2024.36478.* Consensus: https://consensus.app/papers/details/0ca9c8b1f6015e1093ef9b7a6c28a928/

11. Lugobe HM, Muhindo R, Kayondo M, Wilkinson I, Agaba DC, McEniery C, et al. Risks of adverse perinatal and maternal outcomes among women with hypertensive disorders of

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
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pregnancy in southwestern Uganda. PLoS One. 2020;15(10):e0241207. *doi: 10.1371/journal.pone.0241207.* Consensus: https://consensus.app/papers/details/7c068ed2ebb750ac8e4de3347ff95e2f/

12. Pembe AB, Wang D, Noor RA, Ulenga N, Mwiru RS, Fawzi WW, et al. Hypertensive disorders of pregnancy and perinatal outcomes: two prospective cohort studies of nulliparous women in India and Tanzania. BMJ Glob Health. 2025;10(1):e016339. *doi: 10.1136/bmjgh-2024-016339.* Consensus: https://consensus.app/papers/details/50db0bbb63e7591784f2afe4e34a58dd/

13. Huang C, Li J, Qin G, Liew Z, Hu J, László KD, et al. Maternal hypertensive disorder of pregnancy and mortality in offspring from birth to young adulthood: national population based cohort study. BMJ. 2022;379:e072157. *doi: 10.1136/bmj-2022-072157.* Consensus: https://consensus.app/papers/details/7fdbdc8269ad59b79e7d189b1e19f801/

14. Wang YX, Arvizu M, Rich-Edwards JW, Wang L, Rosner B, Stuart JJ, et al. Hypertensive Disorders of Pregnancy and Subsequent Risk of Mortality. J Am Coll Cardiol. 2021;77(10):1302–12. *doi: 10.1016/j.jacc.2021.01.018.* Consensus: https://consensus.app/papers/details/ec96683d44665bafa9440ceb9776dc04/

15. Lailler G, Fosse-Edorh S, Olié V, Regnault N, Deneux-Tharaux C, Kretz S, et al. Early Mortality, Cardiovascular, and Renal Diseases in Women's Lives Following Hypertensive Disorders of Pregnancy: the Prospective Nationwide Study CONCEPTION. J Am Heart Assoc. 2024;13(8):e033252. *doi: 10.1161/JAHA.123.033252.* Consensus: https://consensus.app/papers/details/b7ed38e2a78256f78ea195af04df606a/

16. Malek AM, Wilson DA, Turan TN, Mateus J, Lackland DT, Hunt KJ. Maternal Coronary Heart Disease, Stroke, and Mortality Within 1, 3, and 5 Years of Delivery Among Women With Hypertensive Disorders of Pregnancy and Pre-Pregnancy Hypertension. J Am Heart Assoc. 2021;10(5):e018155. *doi: 10.1161/JAHA.120.018155.* Consensus: https://consensus.app/papers/details/1c91b79428fe57ecb0160cda974ae0af/

17. Ramlakhan KP, Johnson MR, Lopes Perdigao J, Hall R, Sliwa K, Roos-Hesselink JW, et al. Hypertensive disorders of pregnant women with heart disease: the ESC EORP ROPAC

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Copyright © International Medical Journal Corp. Ltd. All rights reserved

Registry. Eur Heart J. 2022;43(38):3749–61. *doi: 10.1093/eurheartj/ehac308.* Consensus: https://consensus.app/papers/details/5d8bf3ab64fa54a18c2993147e8f1888/

18. Smith P, Anthony J, Johanson R. Nifedipine in pregnancy. BJOG. 2000;107(3):299–307. *doi: 10.1111/j.1471-0528.2000.tb13222.x.* Consensus: https://consensus.app/papers/details/7d799f0659e857269faf19d40b5ef594/

19. Bhamidipaty-Pelosi S, Caritis SN, Venkataramanan R, Zhao W, Hebert MF, Shaik IH. Pharmacokinetic Characterization of Labetalol in Pregnancy (The CLIP Study). J Clin Med. 2025;14(8):2793. *doi: 10.3390/jcm14082793.* Consensus: https://consensus.app/papers/details/322df901d8bf558994ef89c64502a0d9/

20. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. Am J Obstet Gynecol. 1999;181(4):858–61. *doi: 10.1016/S0002-9378(99)70314-5.* Consensus: https://consensus.app/papers/details/c9df5a27ad665ad387753f7fee049442/

21. Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. Am J Obstet Gynecol. 1999;181(4):862–6. *doi: 10.1016/S0002-9378(99)70315-7.* Consensus: https://consensus.app/papers/details/c31586ee786a5549b664350b5a44e779/

22. Raheem IA, Saaid R, Omar SZ, Tan PC. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG. 2012;119(1):78–85. *doi: 10.1111/j.1471-0528.2011.03151.x.* Consensus: https://consensus.app/papers/details/ed8e242423265fd4b0c3c2e752d02722/

23. Raheem IA, Saaid R, Omar SZ, Tan PC. Oral Nifedipine Versus Intravenous Labetalol for Acute Blood Pressure Control in Hypertensive Emergencies of Pregnancy: A Randomized Trial. Obstet Anesth Dig. 2013;33(1):26–7. *doi: 10.1097/01.aoa.0000426108.47176.8f.* Consensus: https://consensus.app/papers/details/b3d3ba25993c5b68a8761b73bf355437/

24. Shekhar S, Sharma C, Thakur S, Verma S. Oral Nifedipine or Intravenous Labetalol for Hypertensive Emergency in Pregnancy: A Randomized Controlled Trial. Obstet Gynecol.

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2013;122(5):1057–63. *doi: 10.1097/AOG.0b013e3182a9ea68.* Consensus: https://consensus.app/papers/details/4e6f2d84061c51888ce0c0638eecc237/

25. Alam A, Ahmad S, Sultana N. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomized controlled trial. Int J Reprod Contracept Obstet Gynecol. 2019;8(6):2225–31. *doi: 10.18203/2320-1770.ijrcog20191943.* Consensus: https://consensus.app/papers/details/2a8c5179fbe3554dbc2b8d5388b37eec/

26. Zulfeen M, Tatapudi R, Sowjanya R. IV labetalol and oral nifedipine in acute control of severe hypertension in pregnancy — a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2019;236:46–52. *doi: 10.1016/j.ejogrb.2019.01.022.* Consensus: https://consensus.app/papers/details/88c7c1ef0bf55b2a81c623fc8148c07e/

27. Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet. 2019;394(10203):1011–21. *doi: 10.1016/S0140-6736(19)31282-6.* Consensus: https://consensus.app/papers/details/2134150890ea592dadfcd69c1775895d/

28. Sahai R, Gupta A, Kumar S. Comparative study of oral nifedipine versus intravenous labetalol in severe hypertension in pregnancy: a randomized controlled study. Indian J Obstet Gynecol Res. 2020;7(1):77–82. *doi: 10.18231/j.ijogr.2020.016.* Consensus: https://consensus.app/papers/details/1420567d4d1a511db8b974e492907fb1/

29. Tolcher MC, Fox KA, Sangi-Haghpeykar H, Clark SL, Belfort MA. Intravenous labetalol versus oral nifedipine for acute hypertension in pregnancy: effects on cerebral perfusion pressure. Am J Obstet Gynecol. 2020;223(3):441.e1–8. *doi: 10.1016/j.ajog.2020.06.018.* Consensus: https://consensus.app/papers/details/1c89cdf1850553e98f10074fac9ea708/

30. Kumari P, Kumari S, Sinha S. A randomized trial of intravenous labetalol versus oral nifedipine in acute blood pressure control in hypertensive emergencies of pregnancy. Int J Clin Obstet Gynaecol. 2021;5(5):220–4. *doi: 10.33545/gynae.2021.v5.i5d.1046.* Consensus: https://consensus.app/papers/details/677d883ea36a549390f75fb2031693f1/

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31. Biswas S, Sarkar S, Akhter S, Nahar K. Oral Nifedipine versus Intravenous Labetalol for Acute Blood Pressure Control in Severe Hypertension of Pregnancy: A Study at Faridpur Medical College Hospital. Faridpur Med Coll J. 2021;16(1):25–9. *doi: 10.3329/fmcj.v16i1.55733.* Consensus: https://consensus.app/papers/details/169e941347b75428a4b8c30370837f1f/

32. Gahlot A, Vyas J. Oral Nifedipine and Intravenous Labetalol for Hypertensive Emergencies in Pregnancy: A Comparative Study. Int J Sci Res. 2023;12(5):1402–5. *doi: 10.21275/MR23531140225.* Consensus: https://consensus.app/papers/details/5995b76fb98950faaa6423dacb2c9bb7/

33. Thakur A, Basnet P, Agrawal A. Comparison of intravenous labetalol with oral nifedipine for control of blood pressure in severe preeclampsia. J Hypertens. 2023;41(Suppl 3):e340. *doi: 10.1097/01.hjh.0000917640.86802.50.* Consensus: https://consensus.app/papers/details/884a2d5b33055c4cb4531fda18f723ff/

34. Agarwal M, Deka D, Bhattacharyya TK. Comparison of the efficacy of intravenous labetalol versus oral nifedipine in patients with severe pregnancy-induced hypertension beyond 30 weeks of gestation. J Family Med Prim Care. 2023;12(5):893–8. *doi: 10.4103/jfmpc.jfmpc_2427_22.* Consensus: https://consensus.app/papers/details/f9dd4ffa8dd0583693295b3f82d8ff99/

35. Peng Z, Zhang J, Zhang M, Yin L, Zhou Z, Lv C. Comparison of outcomes following intravenous magnesium compared with intravenous labetalol and oral nifedipine in 355 pregnant Han Chinese women with preeclampsia. Medicine (Baltimore). 2023;102(39):e35334. *doi: 10.1097/MD.0000000000035334.* Consensus: https://consensus.app/papers/details/3998c797f654507793cf58f192b61384/

36. Mane S, Patil S, Kulkarni R. Comparison of intravenous labetalol and oral nifedipine in acute control of severe hypertension in pregnancy. Glob J Res Anal. 2024;13(4):1–3. *doi: 10.36106/gjra/4106572.* Consensus: https://consensus.app/papers/details/1e7411f73f605d14b5480ee2f3baec40/

37. Oswal K, Patil A, Hiremath R. A Randomized Trial of Intravenous Labetalol Versus Oral Nifedipine in Acute Blood Pressure Control in Hypertensive Emergencies of Pregnancy. Indian

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J Obstet Gynecol. 2024;12(1):33–8. *doi: 10.21088/ijog.2321.1636.12124.5.* Consensus: https://consensus.app/papers/details/d5e2c66067ee5e2ea456c78c900d5586/

38. Metgud M, Bellad MB, Kamble P, Patil A. Intravenous Labetalol vs Oral Nifedipine in Acute Severe Hypertension in Pregnancy: A Randomized Controlled Trial. J South Asian Fed Obstet Gynaecol. 2025;17(1):45–50. *doi: 10.5005/jp-journals-10006-2602.* Consensus: https://consensus.app/papers/details/ad34ec9657555965a1fcdd92beb5142f/

39. Shah M, Kalyani R, Deshmukh P, Singh A. Effectiveness of Oral Nifedipine Versus Intravenous Labetalol in Controlling Hypertension in Severe Preeclampsia: A Comparative Study. Cureus. 2025;17(6):e85899. *doi: 10.7759/cureus.85899.* Consensus: https://consensus.app/papers/details/1e2c1fd94487572d97ef7b3f96b5de78/

40. Eze OC, Loto OM, Badejoko OO, Ijarotimi AO, Ubom AE, Orji EO. Efficacy of oral Labetalol vs Nifedipine in the management of severe hypertension in pregnancy: a randomized controlled trial. medRxiv. 2025 [preprint]. *doi: 10.1101/2025.05.06.25327088.* Consensus: https://consensus.app/papers/details/cd703959ddaf533695cb78e859a50cdc/

41. Atkinson J, Simpson JA, Robinson T, Wilson A, Lust K, Nowak-Sliwinska P, et al. A comparison of the safety of oral labetalol versus nifedipine to manage hypertension in pregnancy in Australia: a target trial emulation. eClinicalMedicine. 2026;71:104002. *doi: 10.1016/j.eclinm.2026.104002.* Consensus: https://consensus.app/papers/details/8586fc7c8c0c5a5db594434257921c64/

42. Shekhar S, Gupta N, Kirubakaran R, Pareek P. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG. 2016;123(1):40–7. *doi: 10.1111/1471-0528.13463.* Consensus: https://consensus.app/papers/details/af4a7a686dae5cf7a1e7858f97fa272e/

43. Firoz T, Magee LA, MacDonell K, Payne BA, Gordon R, Vidler M, et al. Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review. BJOG. 2014;121(10):1210–8. *doi: 10.1111/1471-0528.12737.* Consensus: https://consensus.app/papers/details/ebe7ecd343ec507589dfa2d727466a13/

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44. Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol. 2018;84(9):1906–16. *doi: 10.1111/bcp.13649.* Consensus: https://consensus.app/papers/details/e376aa6deb6f5f1094e89c9045c638ad/

45. Bellos I, Pergialiotis V, Papapanagiotou A, Loutradis D, Daskalakis G. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network meta-analysis. Am J Obstet Gynecol. 2020;223(4):525–37. *doi: 10.1016/j.ajog.2020.03.016.* Consensus: https://consensus.app/papers/details/450b883bba9b50f781422f4dbbae7080/

46. Wu H, Zhang S, Xu Y, Chen L, Ren Y. Different dosage regimens of nifedipine, labetalol, and hydralazine for the treatment of severe hypertension during pregnancy: a network meta-analysis of randomized controlled trials. Hypertens Pregnancy. 2022;41(2):124–36. *doi: 10.1080/10641955.2022.2056196.* Consensus: https://consensus.app/papers/details/c58c8933b93f566f9032432448483d69/

47. George R, Thomas S, Varghese A, Mathew J. Comparative efficacy and safety of oral nifedipine with other antihypertensive medications in the management of hypertensive disorders of pregnancy: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2022;40(10):1876–86. *doi: 10.1097/HJH.0000000000003233.* Consensus: https://consensus.app/papers/details/e6db8914f343550f918d7c86822517fd/

48. Bone JN, Sandhu A, Abalos ED, Khalil A, Singer J, Prasad S, et al. Oral Antihypertensives for Nonsevere Pregnancy Hypertension: Systematic Review, Network Meta- and Trial Sequential Analyses. Hypertension. 2022;79(3):614–28. *doi: 10.1161/HYPERTENSIONAHA.121.18415.* Consensus: https://consensus.app/papers/details/b298cfcb3db15265a7f1d4b901d05f53/

49. Li L, Zhang J, Wang Y, Chen X. Oral nifedipine versus intravenous labetalol for hypertensive emergencies during pregnancy: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2023;36(1):2235057. *doi: 10.1080/14767058.2023.2235057.* Consensus: https://consensus.app/papers/details/3c10884b7485582489b3d5ca047a85a8/

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50. Ou M, Zhang Q, Zhao H, Shen L. Oral nifedipine may be a preferential option for treating acute severe hypertension during pregnancy: a meta-analysis. Hypertens Pregnancy. 2023;42(1):2209637. *doi: 10.1080/10641955.2023.2209637.* Consensus: https://consensus.app/papers/details/12c7a982bbf45afc9d6e9f4b6d81365c/

51. Hup RJ, Bijl RC, Duvekot JJ, van Rijn BB, Koenen SV, Franx A, et al. Oral antihypertensive agents and diuretics in the management of hypertension in postpartum women: a systematic review and meta-analysis. BMJ Open. 2024;14(11):e086208. *doi: 10.1136/bmjopen-2024-086208.* Consensus: https://consensus.app/papers/details/9e2dd4ec7dd15441b4556b50a6debb5b/

52. Hup RJ, Bijl RC, Duvekot JJ, Franx A, Koenen SV, van Rijn BB. Oral antihypertensive treatment during pregnancy: a systematic review and network meta-analysis. Am J Obstet Gynecol. 2025;233(3):289–303. *doi: 10.1016/j.ajog.2025.04.011.* Consensus: https://consensus.app/papers/details/e3cf44e78322574997e613120005d775/

53. Ahmed MS, Khan MA, Hussain S, Ali R. Effectiveness of Nifedipine Versus Labetalol for Postpartum Hypertension Control: A Systematic Review and Meta-analysis. Circulation. 2025;152(Suppl 3):A4367869. *doi: 10.1161/circ.152.suppl_3.4367869.* Consensus: https://consensus.app/papers/details/a77f33516f5a519d9ab0a836bf0b3a54/

54. Govindasamy V, Rajendran S, Kumar P, Nair A. Efficacy and Safety of Nifedipine Compared to Intravenous Hydralazine for Severe Hypertension in Pregnancy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Circulation. 2025;152(Suppl 3):A4369688. *doi: 10.1161/circ.152.suppl_3.4369688.* Consensus: https://consensus.app/papers/details/2696987e0a4a5852b5244587167612d1/

55. Sanusi AA, Xue Y, McPherson JA, Boggess KA, Sibai BM, Longo S, et al. Pregnancy Outcomes of Nifedipine Compared With Labetalol for Oral Treatment of Mild Chronic Hypertension. Obstet Gynecol. 2024;144(1):20–8. *doi: 10.1097/AOG.0000000000005613.* Consensus: https://consensus.app/papers/details/92230f322699551297fff4eb90513feb/

56. Webster LM, Myers JE, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, et al. Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in

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Pregnancy: A Randomized Controlled Trial. Hypertension. 2017;70(5):915–22. *doi: 10.1161/HYPERTENSIONAHA.117.09972.* Consensus: https://consensus.app/papers/details/9145e21cc32050038bb29186186cf802/

57. Beatty C, Mullen J, Sanders M, Sarosi C, Cheng T, Gadson A, et al. Timely Discharge: Oral Nifedipine is Superior to Labetalol for Postpartum BP Control in Patients with Preeclampsia. Obstet Gynecol. 2018;131(Suppl 1):169S. *doi: 10.1097/01.AOG.0000533278.70668.81.* Consensus: https://consensus.app/papers/details/bf517d53df8458e8af951a5f32d27f39/

58. Kiefer MK, Rood KM, Ma'ayeh M, Costantine MM, Landon MB, Cackovic M, et al. Daily Versus BID Nifedipine GITS in Severe Preeclampsia: Randomized Controlled Trial. Hypertension. 2025;82(4):733–42. *doi: 10.1161/HYPERTENSIONAHA.124.24532.* Consensus: https://consensus.app/papers/details/bc455f3cf62a570a93dbbeab6a96cf15/

59. Okwuosa AO, Ugwu EO, Obi SN, Dim CC. Oral Immediate-Release Nifedipine Versus Intravenous Hydralazine for Controlling Severe Hypertension in Pregnancy: A Double-Blind Randomised Controlled Trial. Int J Med Sci Dent Health. 2025;12(1):96–110. *doi: 10.55640/ijmsdh-12-01-10.* Consensus: https://consensus.app/papers/details/e4a647a80b955841b042cf8c10bb44f6/

60. Magee LA, Miremadi S, Li J, Cheng C, Ensom MH, Carleton B, et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. Am J Obstet Gynecol. 2005;193(1):153–63. *doi: 10.1016/j.ajog.2004.11.059.* Consensus: https://consensus.app/papers/details/bd9451d4f07058f3851c72507358a756/

61. Waisman GD, Mayorga LM, Cámera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? Am J Obstet Gynecol. 1988;159(2):308–9. *doi: 10.1016/S0002-9378(88)80072-3.* Consensus: https://consensus.app/papers/details/3b3c84cfa12d5c8ba9ac791b40d840d6/

62. Lindow SW, Davies N, Davey DA, Smith JA. The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. BJOG. 1988;95(12):1276–81. *doi:*

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10.1111/j.1471-0528.1988.tb06818.x. Consensus: https://consensus.app/papers/details/00aff05685d65db0a505cce9343fff20/

63. Ahokas RA, Mabie WC, Sibai BM, Anderson GD. Nifedipine does not adversely affect uteroplacental blood flow in the hypertensive term-pregnant rat. Am J Obstet Gynecol. 1988;159(6):1440–5. *doi: 10.1016/0002-9378(88)90571-6.* Consensus: https://consensus.app/papers/details/73efe016d1225ac189b7e6f273b3ad0d/

64. Blea CW, Barnard JM, Magness RR, Phernetton TM, Hendricks SK. Effect of nifedipine on fetal and maternal hemodynamics and blood gases in the pregnant ewe. Am J Obstet Gynecol. 1997;176(4):922–30. *doi: 10.1016/S0002-9378(97)70622-7.* Consensus: https://consensus.app/papers/details/4ed3c123d6c15998a803f3cb4fb0f090/

65. Harake B, Gilbert RD, Ashwal S, Power GG. Nifedipine: effects on fetal and maternal hemodynamics in pregnant sheep. Am J Obstet Gynecol. 1987;157(4 Pt 1):1003–8. *doi: 10.1016/S0002-9378(87)80104-7.* Consensus: https://consensus.app/papers/details/c9bb9a8412055ca2afca2e414127f34c/

66. Veille JC, Bissonnette JM, Hohimer AR. The effect of a calcium channel blocker (nifedipine) on uterine blood flow in the pregnant goat. Am J Obstet Gynecol. 1986;154(5):1160–3. *doi: 10.1016/0002-9378(86)90779-9.* Consensus: https://consensus.app/papers/details/a8ddbe39a88b5284b75b54b889e2856c/

67. Bucher V, Mitchell AR, Gudmundsson P, Atkinson J, Wallin N, Asp J, et al. Prediction of adverse maternal and perinatal outcomes associated with pre-eclampsia and hypertensive disorders of pregnancy: a systematic review and meta-analysis. eClinicalMedicine. 2024;76:102861. *doi: 10.1016/j.eclinm.2024.102861.* Consensus: https://consensus.app/papers/details/483bda4ef6f550b880012923291d5b7e/

68. Shi Q, Leng W, Yao Q, Mi C, Xing A. Oral nifedipine versus intravenous labetalol for the treatment of severe hypertension in pregnancy. Int J Cardiol. 2015;178:162–4. *doi: 10.1016/j.ijcard.2014.10.111.* Consensus: https://consensus.app/papers/details/c7c0cdf594a45b10af2c5b211893cc26/

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69. Ludwig E, Amaral N, Chauhan SP. Oral nifedipine versus intravenous labetalol in the treatment of severe hypertension in the postpartum period. Am J Obstet Gynecol. 2021;224(2 Suppl):S502. *doi: 10.1016/j.ajog.2020.12.830.* Consensus: https://consensus.app/papers/details/727a13489a0a5decbb0945ba30f006ab/

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