

## VERAPAMIL USE IN CHRONIC HYPERTENSION PREGNANT WOMEN : A SYSTEMATIC REVIEW

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### ABSTRACT

**Background:** Verapamil is a medication that has been approved for the treatment of high blood pressure, abnormal heart rhythm, or angina (chest discomfort or shortness of breath).

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 115 articles, whereas the results of our search on SagePub brought up 21 articles. The results of the search conducted for the last year of 2013 yielded a total 11 articles for PubMed and 8 articles for SagePub. In the end, we compiled a total of 5 papers, 3 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.

**Conclusion:** Verapamil can be taken during pregnancy, although it is not commonly used. If patients need to take verapamil to treat high blood pressure, usually will be switched to different medicine. There are limited study and research about verapamil and its use to treat chronic hypertension in pregnancy woman.

**Keyword:** Verapamil, Chronic Hypertension, Pregnancy

## INTRODUCTION

Hypertensive disorders of pregnancy are a leading cause of maternal, fetal, and newborn mortality and morbidity, worldwide. As such, a large proportion of antenatal care is devoted to their detection. It is established that antihypertensive therapy is better than placebo or no antihypertensive therapy (placebo/no therapy) at decreasing the risk of severe maternal hypertension. A strategy of blood pressure (BP) control in pregnancy with antihypertensive therapy reduces severe hypertension without adversely affecting fetal/newborn death or illness, fetal growth restriction, or preterm birth. Importantly, severe hypertension is associated with heightened maternal and fetal/newborn risk, similar to (and independent of) preeclampsia, making severe hypertension an outcome worthy of avoidance, and not just one worthy of detection and treatment. Many national and international clinical practice guidelines now advocate BP control in pregnancy.<sup>1-3</sup>

The choice of antihypertensive therapy in pregnancy remains controversial. In previous direct comparisons, no antihypertensive has been shown to be superior to others, even among the most commonly recommended: labetalol, other  $\beta$ -blockers, nifedipine, and methyldopa. However, there is substantial uncertainty around point estimates of effect, due (at least in part) to the limited number of high-quality randomized controlled trials (RCTs) comparing drugs directly.<sup>4</sup>

Hypertension in pregnancy includes a range of conditions, most notably preeclampsia, a form of hypertension unique to pregnancy that occurs de novo or may be superimposed on chronic hypertension. The other forms, chronic and gestational hypertension, usually have more benign courses. Preeclampsia, a pregnancy-specific disorder characterized by hypertension ( $\geq 140/90$  mm Hg) and proteinuria ( $\geq 300$  mg in a 24-hour urine), affects 3–4% of all pregnancies worldwide. However, recent obstetric literature questions the importance of kidney injury (as demonstrated by proteinuria) in the diagnosis of preeclampsia, suggesting that a subclass of “non-proteinuric preeclampsia” should be added or that detection of proteinuria should not be mandatory for a preeclampsia diagnosis. Risk factors include primiparity, previous preeclampsia, increased maternal body mass index (BMI) before pregnancy, ethnicity (black women are more at risk), multiple gestations, and underlying medical conditions such as renal disease and diabetes mellitus. Preeclampsia is a condition that involves numerous and constant interactions among the placental, immunologic, and cardiovascular systems. It is a syndrome associated with impaired early placentation and dysfunctional trophoblast development, defective placental angiogenesis, and an exaggerated maternal systemic inflammatory response. Risks to the fetus include premature delivery, growth retardation, and death. Treatment of severe hypertension is necessary to prevent cerebrovascular, cardiac, and renal complications in the mother.<sup>5</sup>

Chronic hypertension in pregnancy is defined by the American College of Obstetrics and Gynecology (ACOG) as blood pressure  $\geq 140$  mm Hg systolic and/or 90 mm Hg diastolic before pregnancy or, in recognition that many women seek medical care only once pregnant, before 20 weeks of gestation, use of antihypertensive medications before pregnancy, or persistence of hypertension for  $>12$  weeks after delivery.<sup>6,7</sup>

Chronic hypertension needs to be distinguished from new-onset hypertensive complications of pregnancy such as preeclampsia (elevated blood pressure and proteinuria often accompanied by evidence of maternal organ injury and fetal compromise from placental dysfunction)<sup>2</sup> and gestational hypertension (elevated blood pressure alone after 20 weeks of gestation and most commonly in the mid to late third trimester without evidence or history of hypertension before pregnancy).<sup>6,7</sup>

The Food and Drug Administration (FDA) approved indications for verapamil include angina (chronic stable, vasospastic or Prinzmetal variant), unstable angina (crescendo, preinfarction), hypertension as add-on therapy, paroxysmal supraventricular tachycardia (PSVT) prophylaxis, and supraventricular tachycardia (SVT). Verapamil also has numerous non-FDA-approved indications. This activity outlines the indications, mechanism of action, administration methods, significant adverse effects, contraindications, toxicity, and monitoring, of verapamil so providers can direct patient therapy where it is indicated as part of the interprofessional team.<sup>8</sup>

Verapamil is a medication that has been approved for the treatment of high blood pressure, abnormal heart rhythm, or angina (chest discomfort or shortness of breath). It has also been used to treat headaches and migraines, coronary arteriosclerosis (when blood vessels near the heart become thick and stiff), and kidney disease. Verapamil is in a class of medications called calcium channel blockers.<sup>8</sup>

Sometimes when people find out they are pregnant, they think about changing how they take their medication, or stopping their medication altogether. However, it is important to talk with your healthcare providers before making any changes to how you take this medication. Uncontrolled high blood pressure during pregnancy has been associated with an increased chance of heart disease, kidney disease, and stroke in the pregnant person.<sup>8</sup>

Some studies have reported a greater chance for preterm delivery (birth before week 37) or low birth weight (weighing less than 5 pounds, 8 ounces [2500 grams] at birth) with the use of calcium channel blockers, including verapamil.

However, it is not known if these issues are caused by verapamil, the condition being treated, other medications, or other factors. Uncontrolled high blood pressure during pregnancy has been associated with growth restriction (babies that are smaller than usual) and a higher chance of preterm delivery. Two studies did not find long term effects in heart function of 40 newborns after prenatal exposure to verapamil later in pregnancy to treat high blood pressure or premature labor. People with high blood pressure have a greater chance of developing pre-eclampsia (high blood pressure and problems with organs, such as the kidneys) that can lead to seizures (called eclampsia).<sup>8</sup>

**METHODS**

**Protocol**

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

**Criteria for Eligibility**

For the purpose of this literature review, we review published literature about the use of verapamil for pregnant women with chronic hypertension. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

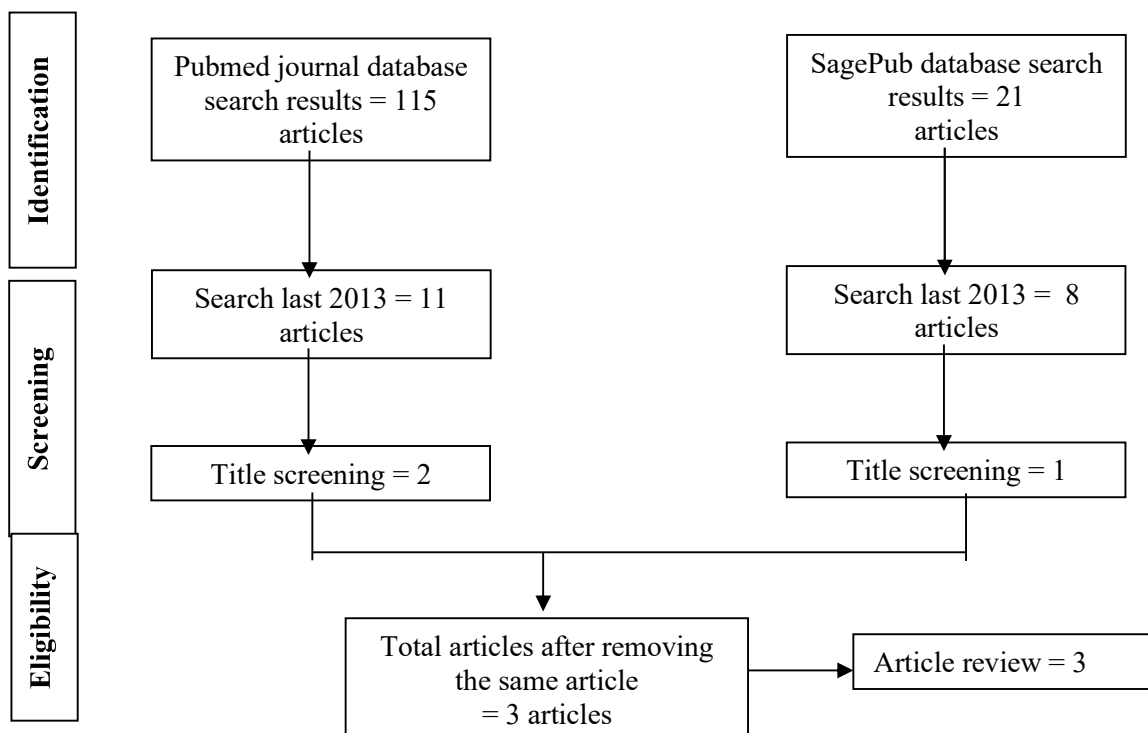
In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

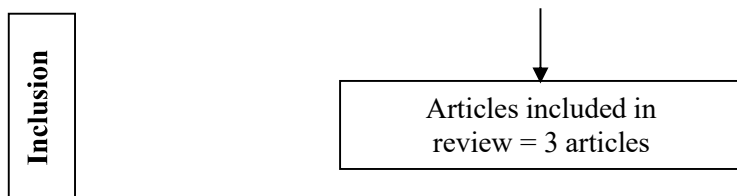
**Search Strategy**

We used "verapamil" and "hypertension" "pregnant" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((("verapamil"[MeSH Terms] OR "verapamil"[All Fields] OR "verapamil s"[All Fields]) AND ("pregnant"[All Fields] OR "pregnantis"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])) AND (2013:2023[pdat])* used in searching the literature.

**Data retrieval**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.





**Figure 1. Article search flowchart**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 115 articles, whereas the results of our search on SagePub brought up 21 articles. The results of the search conducted for the last year of 2013 yielded a total 11 articles for PubMed and 8 articles for SagePub. In the end, we compiled a total of 3 papers, 2 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Ardissino et al<sup>9</sup> (2022) showed that beta blocker and calcium channel blocker both be efficacious for lowering blood pressure in pregnancy butr this genetic genetic evidence suggests that BB use may lower birthweight. Conversely, CCB use may reduce risk of pre-eclampsia and eclampsia without impacting gestational diabetes risk or birthweight. These data support further study on the effects of BBs on birthweight.

Tita, et al<sup>10</sup> (2022) showed that in pregnant women with mild chronic hypertension, a strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes than a strategy of reserving treatment only for severe hypertension, with no increase in the risk of small-for-gestational-age birth weight.

**Table 1. The litelature include in this study**

Author	Origin	Method	Sample	Result
Adissino et al, 2022 <sup>9</sup>	United Kingdom	Randomized retropective sutdy	4.743 patients	Although not reaching the conventional threshold for statistical significance, genetically-proxied BB was associated with reduced risk of pre-eclampsia (OR per 10 mmHg SBP reduction 0.27, 95%CI 0.06–1.19, <i>p</i> = 0.08) and increased risk of gestational diabetes (OR per 10 mmHg SBP reduction 2.01, 95%CI 0.91–4.42, <i>p</i> = 0.08), and significantly associated with lower birthweight of first child (beta per 10 mmHg SBP reduction – 0.27, 95%CI – 0.39 to – 0.15, <i>p</i> = 1.90 × 10 <sup>-5</sup> ). Genetically-proxied CCB was

				associated with reduced risk of pre-eclampsia and eclampsia (OR 0.62, 95%CI 0.43–0.89, $p = 9.33 \times 10^{-3}$ ), and was not associated with gestational diabetes (OR 1.05, 95% CI 0.76–1.45, $p = 0.76$ ) or changes in birthweight of first child (beta per 10 mmHg SBP reduction 0.02, 95%CI –0.04–0.07, $p = 0.54$ ).
<b>Tita et al, 2022<sup>10</sup></b>	United Kingdom	Randomized retrospective study	2.408 patients	A total of 2408 women were enrolled in the trial. The incidence of a primary-outcome event was lower in the active-treatment group than in the control group (30.2% vs. 37.0%), for an adjusted risk ratio of 0.82 (95% confidence interval [CI], 0.74 to 0.92; $P < 0.001$ ). The percentage of small-for-gestational-age birth weights below the 10th percentile was 11.2% in the active-treatment group and 10.4% in the control group (adjusted risk ratio, 1.04; 95% CI, 0.82 to 1.31; $P = 0.76$ ). The incidence of serious maternal complications was 2.1% and 2.8%, respectively (risk ratio, 0.75; 95% CI, 0.45 to 1.26), and the incidence of severe neonatal complications was 2.0% and 2.6% (risk ratio, 0.77; 95% CI, 0.45 to 1.30). The incidence of any preeclampsia in the two groups was 24.4% and 31.1%, respectively (risk ratio, 0.79; 95% CI, 0.69 to 0.89), and the incidence of preterm birth was 27.5% and 31.4% (risk ratio, 0.87; 95% CI, 0.77 to 0.99).
<b>Bateman et al, 2015<sup>11</sup></b>	USA	Case control study	22.908 patients	Twenty two thousand nine hundred eight (0.91%) of pregnancies were exposed to calcium channel blockers during the final month of pregnancy. Neonatal seizures occurred in 53 (0.23%) infants born to mothers exposed to calcium channel blocker and 4,609 (0.18%) infants of unexposed women (unadjusted odds ratio (OR) 1.26, 95% confidence interval (CI) 0.96 to 1.65). After accounting for confounders, there was no increase in risk of neonatal seizures associated with calcium channel blocker

				exposure (OR 0.95, 95% CI 0.70 to 1.30). This null finding was robust across multiple sensitivity analysis.
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Bateman, et al<sup>11</sup> (2015) showed that in this large, carefully controlled, population-based cohort study, there was no significant increase in the risk of neonatal seizures in infants attributable to maternal calcium channel blocker exposure in late pregnancy. The results suggest that calcium channel blockers can be used by obstetricians in late pregnancy without excess concern about this neonatal complication.

**DISCUSSION**

The recent study showed that approximately 2% and 3% of new born in the manifest development suffer the birth defects which categorized in teratogen-induced malformations that percent due to expose the mother to a lot of factors as environmental or iatrogenic during pregnancy. A lot of problems can face the pregnant women due to the pathological changes that occur during the pregnancy one of this is hypertension which categorized one of the<sup>12</sup> most urgent case that may lead to hard problems, this Elevated Blood Pressure (BP) is due to preeclampsia either alone (pure) or “superimposed” on chronic vascular disease.

Calcium channel blockers prevent calcium from entering cells of the heart and blood vessel walls, resulting in lower blood pressure. Calcium channel blockers, also called calcium antagonists, relax and widen blood vessels by affecting the muscle cells in the arterial walls. Some calcium channel blockers have the added benefit of slowing heart rate, which can further reduce blood pressure, relieve chest pain (angina) and control an irregular heartbeat, for example verapamil.<sup>12</sup>

Calcium channel blockers (CCBs) (amlodipine, diltiazem, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, and verapamil) are mainly used for the treatment of hypertension and for the treatment and prophylaxis of angina. Additionally, nifedipine is used to treat Reynaud’s phenomenon and as a tocolytic to delay or prevent premature labour; nimodipine is used for the prevention and treatment of subarachnoid haemorrhage; verapamil is used to treat supraventricular arrhythmias and for the prophylaxis of cluster headaches. Topical diltiazem (2%) is used off-license to treat anal fissure.<sup>13</sup>

Rates of miscarriage do not appear to be increased following exposure to CCBs in early pregnancy. However, further research is required to confirm this finding. Available data do not support an increased risk of intrauterine death following exposure to nifedipine in pregnancy; however, further studies are required to confirm this and IUD/stillbirth risk for other CCBs. Data on rates of preterm delivery, fetal growth and neurodevelopmental outcomes are limited but do not raise any particular concerns.<sup>13</sup>

CCBs are routinely used in pregnancy to treat hypertension and may also be used in the management of threatened preterm labour. Exposure to a CCB at any stage in pregnancy would not usually be regarded as medical grounds for termination of pregnancy. In pregnancies complicated by maternal hypertension or threatened preterm labour, additional fetal monitoring may be required, depending on the clinical situation. Other risk factors may also be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.<sup>13</sup>

Verapamil is a non-dihydropyridine calcium channel blocker. Calcium channel blockers inhibit the entry of calcium ions into the slow L-type calcium channels in the myocardium and vascular smooth muscle during depolarization. This inhibition will produce relaxation of coronary vascular smooth muscle as well as coronary vasodilation, which is helpful in patients with hypertension. Verapamil also increases myocardial oxygen delivery, which helps patients with vasospastic angina. Verapamil correlates with negative chronotropic effects and decreased sympathetic nervous system activity.<sup>8</sup>

Verapamil can be administered either orally (sustained release or immediate release) or intravenously. It is possible to open sustained-release verapamil capsules, and the contents are sprinkled on one tablespoon of applesauce. Patients should receive instructions to swallow immediately with a full glass of cool water. For sustained verapamil products, take with food and swallow whole (they should not be chewed or crushed). When given intravenously, verapamil administration must be over at least a two-minute timeframe.<sup>8</sup>

Verapamil can cross the placenta, and use of verapamil during pregnancy may cause adverse effects on the fetus(e.g., bradycardia, heart block, hypotension). Women with HCM controlled with verapamil before pregnancy may continue therapy, but it is recommended to monitor the fetus for slow heart rate, low blood pressure, and heart block.<sup>14,15</sup>

Blood pressure is an essential indicator of how the patient with confirmed hypertension is doing with verapamil. The ASCVD risk and comorbidities of the patient require an evaluation to evaluate the specific blood pressure goal for the patient. If the patient with confirmed hypertension has known cardiovascular disease or a 10-year ASCVD risk greater

than or equal to 10%, then the recommended target blood pressure is less than 130/80 mm Hg - for patients without markers of increased ASCVD risk, a target blood pressure less than 130/80 is not a recommendation but is a reasonable goal.<sup>16</sup>

Like all calcium channel blockers, an overdose of verapamil can lead to negative inotropic and chronotropic effects, dilation of arterial vasculature, and hypotension. Additionally, verapamil's blockade of slow calcium channels in pancreatic beta cells can lead to inhibited insulin release, thereby causing hyperglycemia. If a patient experiences bradycardia with hypotension/metabolic acidosis and hyperglycemia is indicative of verapamil toxicity. The most serious complications from a verapamil overdose are bradycardia and hypotension, as both can lead to death if the patient is left untreated.<sup>17-19</sup>

If a patient presents with verapamil toxicity within 1 hour, two decontamination procedures exist; gastric lavage and single-dose activated charcoal. If a patient presents with verapamil toxicity after 1 hour of ingestion has elapsed, whole bowel irrigation using polyethylene glycol electrolyte solution is a viable decontamination procedure. According to experimental and clinical studies, ipecac and cathartics have not proven beneficial decontamination procedures.<sup>19</sup>

## CONCLUSION

Verapamil can be taken during pregnancy, although it is not commonly used. If patients need to take verapamil to treat high blood pressure, usually will be switched to different medicine. There are limited study and research about verapamil and its use to treat chronic hypertension in pregnancy woman.

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