Latest findings on labetalol in severe hypertension during pregnancy and in postpartum — a systematic review

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Abstract

Hypertension during pregnancy is a significant problem, with severe hypertension being an especially dangerous condition. As pharmacological treatment options are limited mostly due to the unknown effects of multiple drugs on the fetus, labetalol is one of the more frequently used therapies. The other popular substances are methyldopa, nifedipine and hydralazine. In this paper, the effectiveness and limitations of labetalol in hypertensive disorders of pregnancy are discussed based on the latest available original papers. As the accessible data implicates, labetalol has a high and proven ability to reduce blood pressure with non-severe side effects. The most common of which are headaches and nausea. The drug seems to be slightly less effective in blood pressure normalization than nifedipine, with inconclusive data about safety to the mother and her baby. However due to a small number of patients included in the presented studies, more high-population trials are necessary to give an unambiguous recommendation on its regular usage.

Key words: labetalol; severe hypertension; hypertension; pregnancy; gestation

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Introduction

Hypertension in pregnancy is a worldwide major contributing factor of maternal and fetal morbidity and mortality. Hypertensive disorders of pregnancy (HDPs) are the second leading cause of global maternal death behind maternal hemorrhage [1]. They have a per-pregnancy incidence rate of 7.3–7.4% [2, 3] and occur roughly in 15.5 million [4] women yearly and are defined as hypertension with the onset on, before or after the 20th week of gestation [5, 6]. These group of disorders relate to an increased risk of future maternal complications such as: cardiovascular diseases including chronic hypertension, type 2 diabetes, stroke, chronic kidney disease [2, 7–11]. They also have a negative effect on the pregnancy, with higher cesarean section risk, preterm delivery, low birth weight and ultimately perinatal mortality rates [12]. Pharmacological treatment greatly reduces the risk of complications, but drugs widely used in non-gravid patients are known to be teratogenic and only a few substances—methyldopa, calcium channel blockers and hydralazine, are widely seen as potentially safe for the fetus [13–16]. However, their effectiveness and safety profiles are not ideal, prompting the search for new and more effective therapies [17–19]. Labetalol (FDA C category), an antihypertensive agent with

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both alpha and beta-adrenergic receptor blocking capability, has become a crucial addition to the spectrum of anti-hypertensive therapies making it widely recommended among medical societies [14, 20]. However some authors are concerned about its potential to cause bradycardia, bronchoconstrictive effects, hypoglycemia and fetal growth retardation [17, 18, 20].

The aim of this paper was to confirm and define main side effects and effectiveness of labetalol when used for blood pressure reduction during severe hypertension in pregnancy and the postpartum period. The authors also try to answer the question: Should labetalol be the first-line drug in treating severe hypertension during the gestation period and in postpartum. This was done by exploring the latest clinical trials from around the world regarding the use of labetalol in severe hypertension, specifically in the rapid reduction of blood pressure.

Material and methods

In this review the PubMed registry was searched using specifically tailored search strategies. Key words used were "labetalol", "pregnancy", "hypertension", "severe hypertension" and appropriate MeSH terms. A manual reverse reference search was also set up to help find trials that were not identified by the PubMed search engine or not indexed in the registry. This strategy has highly increased the chance that all the sought-after papers were found. Also, the work by Alavifard et al. was used to identify some papers [15]. Only randomized controlled trials written in English were accepted. They had to include women (≥ 18 years old) with severe hypertension who were pregnant or postpartum, taking labetalol (either orally or intravenously) and who were later observed, with their parameters and potential drug side effects noted. Moreover, articles were accepted if they had more than 10 participants, included information about the dosage regimen and clearly stated a primary outcome that was related to the change of the systemic blood pressure. Hypertension etiology was not taken into account — for example whether it was pregnancy-induced, an exacerbation of a previously existing condition (chronic), or whether it appeared after delivery. Papers were not divided by this category because of the lack of information in the articles or different opinions of the authors on the inclusion criteria. In the authors opinion such a division would significantly and unnecessarily complicate the review process and its results. Articles published only as abstracts, pilot studies and unpublished manuscripts were not included. This analysis was performed using data from the last 20 years, with the cut-off set to 2003. This was done to ensure, on the one hand, that only the most recent data would be taken into account and, on the other hand, to have a population large enough for more precise conclusions to be drawn.

Among scientific communities, there was a prolonged debate about which criteria should be used to diagnose gestational hypertension [20]. The up-to-date consensus is that systolic blood pressure (SBP) ≥ 140–160 mm Hg and/or diastolic blood pressure (DBP) ≥ 90–110 mm Hg should be called mild hypertension, with severe hypertension defined by SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg [6, 19, 21, 22]. Although it must be noted that the criteria may vary between authors [20].

A blood pressure consistent with the consensus of SBP ≥ 160 mm Hg and/or DBP ≥110 mm Hg was determined for article acceptance. As the definition of severe hypertension has changed over the years, one of the older studies used a different cut-off. It was also included in this study (Ainuddin et al. ≥ 150/100 mm Hg). Three randomized controlled trials (RCTs) with patients in postpartum were accepted — Mukherjee et al., Dhali et al., Ainuddin et al. Ten papers on women with preeclampsia were accepted as an appropriate BP threshold was set.

Analyzed was the speed and effectiveness of labetalol. Major and minor side effects for the mother as well as the newborn were also discussed. These variables were compared to other agents used in severe hypertension in and directly after the gestation period such as nifedipine or hydralazine. Due to the differences in parameters that were collected by different studies, some parameters could not be calculated from the global population of this review (subgroup number stated in parenthesis or written directly after).

Access to some trials could not be obtained and therefore they were not included in this review (Dhananjaya et al. and Tariq et al.) [23, 24].

Results

The PubMed search identified 27 papers out of which only five met the criteria of this study. Eight trials were found independently from the database search. All the trials were performed in developing countries. Records were screened by one reviewer (Fig. 1, 2).

Most papers, with the exception of 3 [29, 30, 32], had a time-related outcome — they mea-

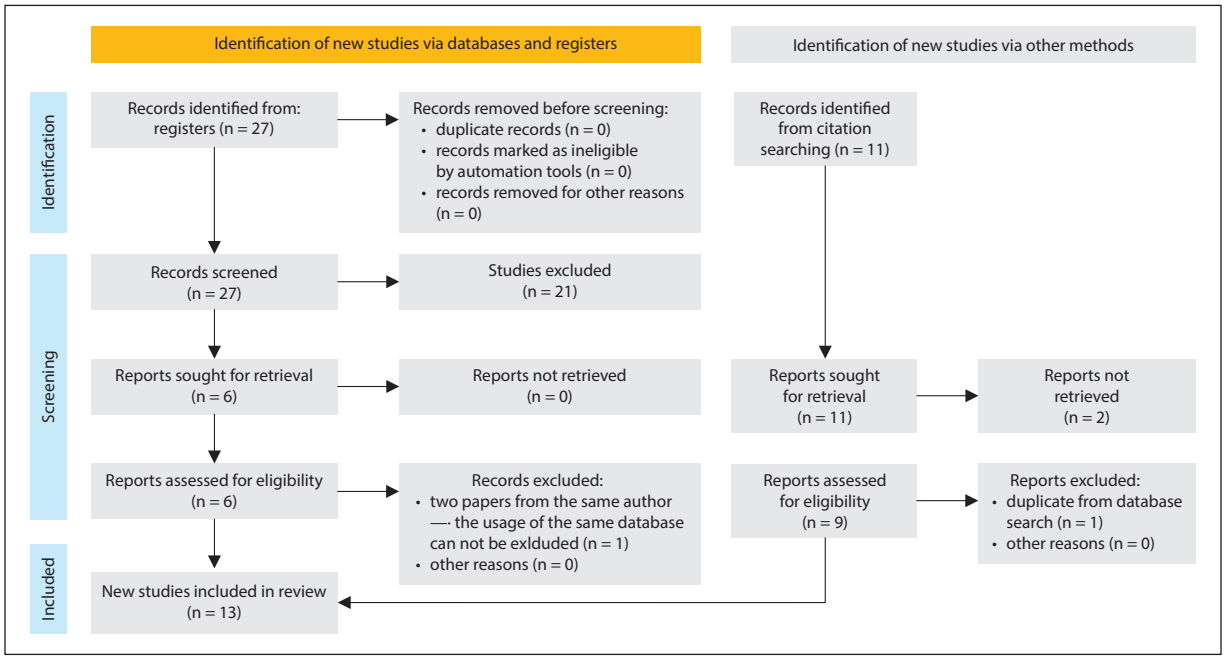

Figure 1. PRISMA flow diagram, data accessed on 09.2022 [25]

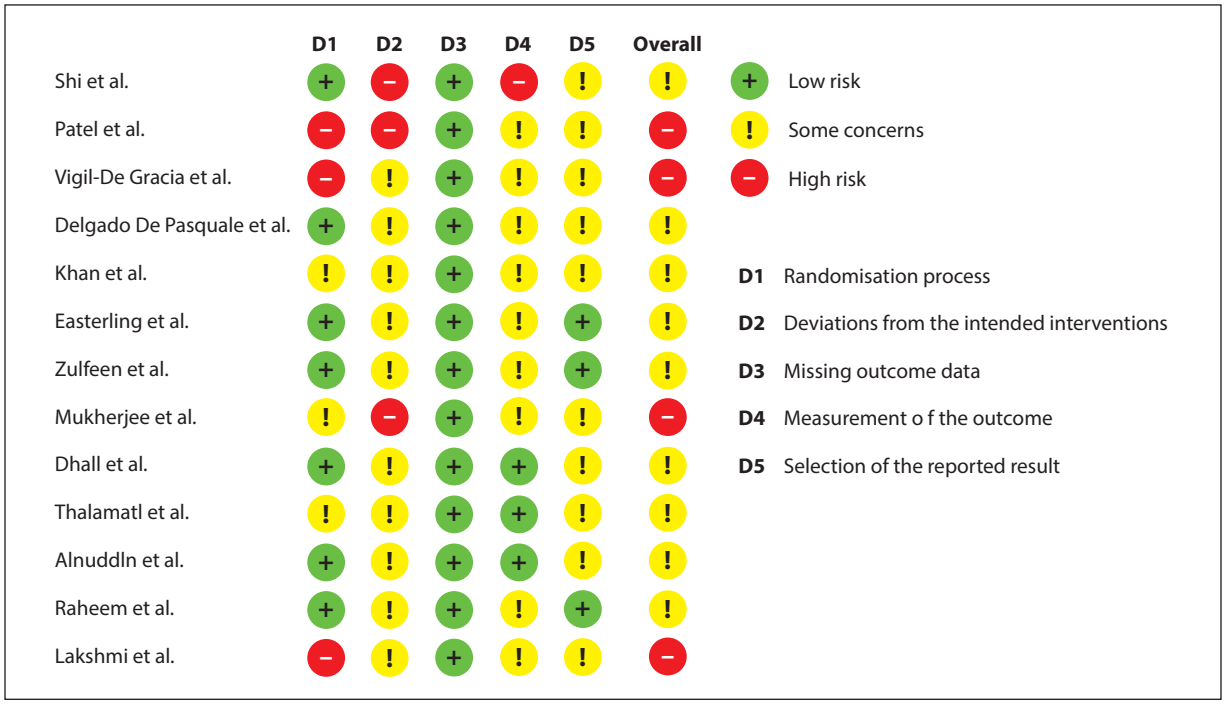

Figure 2. Risk of bias in each of the 5 assessed domains (RoB 2.0) [26]

sured how much time it took to achieve a successful lowering of BP to the pre-established target. In the majority, it was set to a BP lower than 150/100 mm Hg. Labetalol achieved a mean time of 41 minutes (calculated from 300 patients — 6 studies, SD = 4.99) to reduce the BP to that level. This value was calculated only from studies that clearly reported the time needed to achieve blood pressure control to lower than 150/100 mm Hg, as this was the most popular target set among the pooled papers. The fastest time of 35.6 minutes was reported by Ainuddin et al. and the longest

Table 1. Summarization and details of the pooled randomized controlled trials (RCT)

Author	Year of publication	Design	Population (labetalol)	Country	Escalation strategy (labetalol)	Primary outcome	Risk of bias (RoB 2) [26]
Shi et al. [27]	2016	RCT, double-blinded	73	China	20–40–80 mg *i.v.*; every 15 minutes	Time to achieve ≤ 150/100 mm Hg	Some concerns
Patel et al. [28]	2018	RCT, "envelope method"	76	India	20–40–80 mg *i.v.*; every 10 minutes	Time to achieve BP = 140/90 mm Hg	High
Vigil-De Gracia et al. [29]	2006	RCT, open-label	100	Panama	20–40–80 mg *i.v.*; every 20 minutes	Successful BP lowering and maternal hypotension	High
Delgado De Pasquale et al. [30]	2014	RCT, open-label	131	Panama	20–40–80 mg *i.v.*; every 15 minutes	Number of doses to obtain SBP ≤ 159 mm Hg and/or DBP ≤ 109 mm Hg	Some concerns
Khan et al. [31]	2017	RCT, not stated	39	Pakistan	20–40–80 mg *i.v.*; every 20 minutes	Mean MAP noted	Some concerns
Easterling et al. [32]	2019	RCT, open-label	295	India	200 mg oral; if BP higher than 155/105 mm Hg after 1 hour next 200 mg given (max 600 mg)	SBP 120–150 mm Hg, DBP 70–100 mm Hg, no adverse effects within 6 h	Some concerns
Zulfeen et al. [33]	2019	RCT, double blinded	60	India	20–40–80–80–80 mg *i.v.*; every 15 min	Time to achieve ≤ 150/100 mm Hg	Some concerns
Mukherjee et al. [34]	2015	RCT, open-label	30	India	20–20–20–40–40–80 mg *i.v.*; every 20 min, max 220 mg	Time until ≤ 150/100 mm Hg	High
Dhali et al. [35]	2012	RCT, open-label	50	India	30–40–80–80–80 mg *i.v.*; every 20 min	Time to achieve ≤ 150/100 mm Hg	Some concerns
Thalamati et al. [36]	2018	RCT, double-blinded	50	India	20–40–80–80–80 mg *i.v.*; every 15 min	Time to achieve SBP 140–155 mm Hg and DBP 90–100 mm Hg	Some concerns
Ainuddin et al. [37]	2019	RCT, open-label	62	Pakistan	100 mg oral; max 1200 mg as needed to control BP	Time to achieve SBP < 150 mm Hg and DBP 80–100 mm Hg with no severe hypertensive spikes for 72 h	Some concerns
Raheem et al. [38]	2011	RCT, double blinded	25	Malaysia	20–40–80–80–80 mg *i.v.*; every 15 min	Time to achieve blood pressure ≤ 150/100 mm Hg	Some concerns
Lakshmi et al. [39]	2012	RCT, open-label	50	India	20–40–80–80 mg *i.v.*; every 30 min or target BP achieved	Number of doses and time required to achieve reduction of 25% MAP	High

i.v. — intravenously; BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; MAP — mean arterial pressure

time of 45 minutes by Raheem et al. It must be noted that different papers used varying doses. In the RCT by Patel et al., the time to achieve the primary outcome of BP = 140/90 mm Hg was reported to be 12.63 min (SD = 7.19), which is more than 3 times faster than in any other trial, even though the target was set lower. This could be explained by using a significantly higher dose escalation regimen. However, it was fairly consistent with the other trials (20–40–80 mg *i.v.*; every 10 minutes). Except that the individual doses were administered more frequently. The mean dose number in this RCT to achieve BP control was 1.21. This is significantly less than the mean of 2.33 doses (524 patients, SD = 1.06) from all the studies that reported this information. It also must be remembered that different authors used varying doses and escalation strategies that could alter the results — for example higher doses could potentially mean the agent needs to be administered less frequently to achieve the desired effect.

The largest study in this review, which did not focus solely on time to effect, performed by Easterling et al. in 295 patients, did not specify a mean number of doses administered. However, it reported that 48% of women received a second dose and 22% a third dose. Nine women (3%) had to be given another drug, because labetalol could not adequately reduce the blood pressure. A therapy failure like this was not common among the other RCTs — mean of 3.91% (1002 women, SD = 2.77).

Labetalol was found to be a safe drug, with regard to adverse effects. Mostly minor problems were reported. Headaches were found to be the most

common problem with a prevalence of 7.81% (952 patients, SD = 13.32). Nausea was reported in 4.04% of women (890 patients, SD = 3.47). Maternal tachycardia occurred in 1.96% (SD = 1.52) of patients — this information was collected by only 5 papers, so the sample was limited to 329 people. Two incidents of hypotension as an effect of labetalol were observed. This relates to 0.42% and an SD of 0.46 (476 women). However, this occurrence rate cannot be precise as the calculation contains work by Vigil-De Gracia et al. where women were preloaded with 1000 ml of fluid (900 ml of Ringer's lactate with 100 mL of 25% albumins). This could have a positive impact on the occurrence of hypotension as none was reported in a sample of 100 women.

In the work by Ainuddin et al., one incidence of bronchospasm was observed, a potentially lethal side effect. Among 4 studies (474 women) that reported this kind of information there were 2 incidents of seizures observed.

Labetalol was also found to be a safe drug for the fetus. First minute Apgar score lower than 7 was recorded in 10.18% of 206 newborns (SD = 10.07) and 5-minute scores lower than 7 were observed in 6.43% of 661 newborns (SD = 3.27). Of the 686 of children, 18.36% had to be admitted to the intensive care unit after birth (SD = 14.76). Inclusion criteria varied upon papers or were not determined. Stillbirth occurred in 6.28% of 631 pregnancies (SD = 2.66).

Discussion

The goal of this paper was to establish and verify the effectiveness of labetalol as a blood pressure reducing drug. Data pooled from 13 RCT involving 1041 women clearly place labetalol in the group worth considering. It was found to be effective, as less than 4% of patients had to be given another drug to achieve safe blood pressure. What is also important is that it took effect relatively fast (mean of 41 min). This is especially crucial to ensure the shortest possible time that patients were exposed to extremely high, harmful blood pressures.

Labetalol was also found to cause mostly minor side effects that did not result in the need to halt the therapy, only were unpleasant to the patient. These included headaches (most common) or nausea. Maternal tachycardia that occurred in less than 2% of patients could be a compensatory mechanism to the decrease of blood pressure [40]. This theory is backed by the work by Easterling et al. where nifedipine, a more rapid antihypertension agent, showed significantly more (31% to 14%, $p < 0.0001$) tachycardiac incidences. Here the pre-loading strategy used by Vigil-De Gracia et al. could become helpful as no cases of hypotension and one of tachycardia were reported in his study. This may suggest that *i.v.* fluid solutions could reduce the incidence of these side effects. However, the safety of such actions must be further examined.

However, some major incidents were observed. There were 2 cases of seizures after the admission of the drug, including one woman who received earlier magnesium sulfate. Convulsions, being a severe side effect, must be closely watched for, but not enough data is available to draw binding conclusions from these two cases. Especially considering that these women could have easily developed eclampsia during the study. Also, one episode of bronchospasm was noted — it could have been expected with labetalol being a mixed alpha and beta-receptor blocker. Nevertheless it can be an important argument in the discussion to restrict usage of the drug in individuals susceptible to this kind of reaction, for example asthmatics [41].

In the literature, the drug is compared to other antihypertensives — in a recent network meta-analysis labetalol was found to be slightly less effective than nifedipine, while causing a similar amount of side effects [15]. Another meta-analysis found the calcium channel blocker to be associated with less side effects [16]. A work by Alavifard et al. showed that labetalol was superior to hydralazine in terms of effectiveness and safety. Awaludin et al. found hydralazine to be equally as effective as the betablocker, but often caused more heart palpitations [42]. Labetalol also did not cause more fetal side effects than other similar drugs like calcium channel blockers [42, 43]. This paper is unable to independently compare this beta-blocker to other antihypertensive drugs as such data was not gathered in this work.

This paper also cannot comment on safety concerns of labetalol raised by some authors (such as hypoglycemia, bradycardia, fetal growth retardation), as such information was not gathered in presented studies. One incident of bronchoconstriction was observed suggesting it can be a rare side effect of labetalol.

This review included some open-label trials, which increases the chance of bias. This was, to some extent, the result of logistical problems, as the compared drugs could have different routes of administration — oral or intravenous — which made them more difficult to mask. Some authors did not write why their RCTs were not blinded. No papers had a low chance of bias as calculated by RoB

2.0, always some kind of flaw was present. However, the effect of a potentially present bias could be limited as the most important parameters collected were numerical and arguably hardly influenced by the individual.

A few limitations of this systematic review can be identified. Although this paper incorporated 13 RCTs and over 1000 patients, most of them were small studies with less than 100 women. Therefore, there is a probability that rare side effects could have not been identified. Furthermore, no advanced synthesis of the data was performed, potentially limiting the value of the reporting done. Other drugs than labetalol were not incorporated in this paper which heavily limited the ability to directly compare them with labetalol.

Here must be mentioned the ethical dilemma in conducting RCTs in pregnancy, as there is a probability that a drug side effect could impair the child for life. This is especially concerning when using agents that do not have firmly established safety characteristics. This problem makes conducting studies on pregnant women much more difficult and complicated, as the safety of the participants and their child must be ensured Also, all the studies were performed in developing countries. This could potentially influence drug characteristics in regions of the world other than those where the studies were performed, as it is known that some substances tend to act differently in various populations [44]. There is no generally accepted consensus whether this effect also applies to labetalol [45].

Conclusion

Based on the data presented in this review labetalol seems to be a highly effective drug in lowering severe hypertension in pregnancy or postpartum. It is associated with few side effects, which mostly are not threatening to the patient and her child. Common side-effects of labetalol included nausea and headaches, but the latter's relation to the drug is unknown as such information was not gathered pre-study. Maternal tachycardia was also noted. As for severe side effects, one instance of bronchospasm and two cases of seizures after drug admission were observed.

There is a strong need for larger and more detailed studies on labetalol in severe hypertension in the gestational period and postpartum, as only one recent RCT encompassed over 200 patients. They are also needed because of the high discrepancy level between many of the trials cited in this paper, which in many cases prevents drawing final conclusions. Nonetheless, labetalol's efficacy as a hypotensive drug is thought to be sufficiently proven, as in every paper presented here, it was reported as highly effective for BP lowering while being safe at the same time. Considering all the data presented in this review, labetalol firmly confirmed its position as the first-line drug in the treatment of hypertension in the gestation or postpartum period; however, the results were not supportive for it to become a choice that stands out and should be chosen without considering its competitors. Efforts must be made to ensure its availability, so clinicians have more proven and safe therapy options, as in some countries (for example Germany, Poland) it is still unavailable for standard use.

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Author contributions

M.M. came up with the idea for this article, he also performed the literature search, data analysis and wrote the manuscript. J.Z.P. and J.D.K. critically revised this paper.

Conflict of interest

Authors declare no conflict of interest.

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