



Review article

Nocturnal blood pressure alterations in patients with preeclampsia – Do they really matter? A systematic review of the literature



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ABSTRACT

The significance of blood pressure alterations during night-time has been already recorded in essential hypertension and several studies have been conducted to guide current clinical practice. To date, however, there is no consensus regarding the need for screening patients with preeclampsia for nocturnal hypertension as evidence in this field remain scarce. The purpose of this study is to accumulate current data in this field and serve as a pilot for the conduct of future studies. The present systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We used the Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases in our primary search along with the reference lists of electronically retrieved full-text papers. Overall, six studies were included in our systematic review that recruited 487 pregnant women. Their methodological quality was evaluated as average according to the Newcastle-Ottawa criteria. The majority of those studies pointed towards significant differences in nocturnal blood pressure patterns among patients with preeclampsia and controls. However, its clinical value in determining pregnancy outcomes remains unknown as only one small case control study investigated outcomes of patients with severe preeclampsia and different patterns of nocturnal blood pressure and reported that differences were non-significant. Concluding, current evidence supports that nocturnal hypertension seems to be more prevalent in cases complicated by preeclampsia; however, its clinical usefulness in determining pregnancy outcomes remains, to date, unknown.

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Introduction

The incidence of preeclampsia is approximately 3.1% according to the findings of a population-based study that was based in a cohort of 456,000 singleton deliveries [1]. The disease is usually sub-grouped to early and late onset preeclampsia based on the cut-off of 34 weeks of gestation [1]. Although early onset preeclampsia is generally more aggressive and results in severe maternal morbidity and neonatal mortality, late preeclampsia is more difficult to diagnose as its rather indolent course may result in significant false negative diagnoses. Several pathways have been implicated in the pathophysiology of the disease [2]. Decidual vasculopathy and inadequate trophoblastic invasion is the predominant theory and is supported by pathology results that designate the presence of impaired spiral artery remodeling and endothelial dysfunction [3–5]. More specifically, it has been clarified that in preeclamptic women cytotrophoblasts do not manage to invade adequately both the myometrium and the vessel lumen. This leads to lack of spiral artery remodeling that fails to result in a low-resistance vascular system [6].

In healthy adults blood pressure (BP) follows a circadian pattern and during nighttime a normal nocturnal “BP dipping” is generally anticipated with a cut-off of a 10% reduction in mean BP to be considered as normal during night [7]. Reduction of sympathetic tone and elevation of the vagal activity at night lead to this circadian blood pressure pattern [8]. Previous researchers observed that nocturnal hypertension may be the result of inadequate renal sodium handling or impaired sympathetic/parasympathetic reflexes during nighttime [9]. The opposite effect is characterized as nocturnal hypertension and seems to provide substantial information as a prognostic index of adverse cardiovascular events. Specifically, two previous meta-analyses in the field of essential hypertension observed that after adjustment for 24-h systolic blood pressure (SBP), the nocturnal systolic blood pressure effectively predicted coronary events, strokes, cardiovascular mortality, and total mortality as well as cardiac and carotid structural abnormalities [10,11].

To date, although several researchers have studied the incidence of nocturnal hypertension in pregnant women, firm consensus is lacking concerning its impact on antenatal and perinatal maternal as well as neonatal outcomes. The purpose of the present systematic review is to accumulate the existing evidence, point the heterogeneity in outcome reporting and measures of outcome reporting among the existing studies and provide directions for future research in this field.

Materials and methods

The present systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Types of studies and patients

The eligibility criteria for the inclusion of studies were predetermined. We selected all observational studies (prospective and retrospective) as well as randomized trials that reported the

outcome of interest (nocturnal alterations in blood pressure) as a dependent variable (primary/secondary outcome) or independent variable (prognostic index). Conference proceedings and abstracts were also considered to be eligible, provided that the outcome of interest was available within their context. When consecutive studies were published from the same research center and referred to outcomes from an identical or partially identical series of patients, we chose to include the most recent study in which data for quantitative synthesis were available. Case reports, short case-series (<20 patients), as well as experimental animal studies and reviews were excluded.

Information sources and search methods

We used the Medline (1966–2019), Scopus (2004–2019), Clinicaltrials.gov (2008–2019), EMBASE (1980–2019), Cochrane Central Register of Controlled Trials CENTRAL (1999–2019) and Google Scholar (2004–2019) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set at January 31, 2018. Our search strategy included the text words “nocturnal; sleep; night; blood pressure; hypertension; preeclampsia; pregnancy” and is briefly presented in Fig. 1 Appendix 2.

Two independent reviewers (V.P. and N.K) were involved in the search strategy and data selection process. Studies were screened and evaluated in three consecutive stages. Firstly, deduplication of retrieved articles was performed and following that the titles and abstracts of all electronic articles were reviewed to assess their eligibility. Articles that were considered to be relevant were retrieved in full text and the final decision concerning their inclusion was taken. Potential discrepancies concerning the reviewers’ opinion on eligibility of retrieved articles were resolved by consensus from all authors.

Data extraction

Data extraction was performed using a modified data form that was based in Cochrane’s data collection form for intervention reviews for RCTs and non-RCTs (Appendix 1) [13]. We sought to investigate the diagnostic accuracy of nocturnal blood pressure alterations (elevated nocturnal blood pressure, absence of the “dipping” effect) in predicting antenatal and perinatal maternal and neonatal complications as well as the potential differences in nocturnal blood pressure patterns among pregnant women with uncomplicated pregnancies and those with hypertensive disorders of pregnancy. Adverse pregnancy outcomes that were considered to be correlated with nocturnal blood pressure alterations (and for which data were sought) were the onset and severity of preeclampsia, intrauterine growth restriction, preterm birth and neonatal outcomes including birthweight, 5’ Apgar score, neonatal morbidity and neonatal mortality (Appendix 2).

Quality assessment

The methodological quality of the included studies was assessed by two independent reviewers (V.P and I.B). The Newcastle-Ottawa Scale (NOS) was used in this stage. The scale examines the risk of bias in observational studies by evaluating the

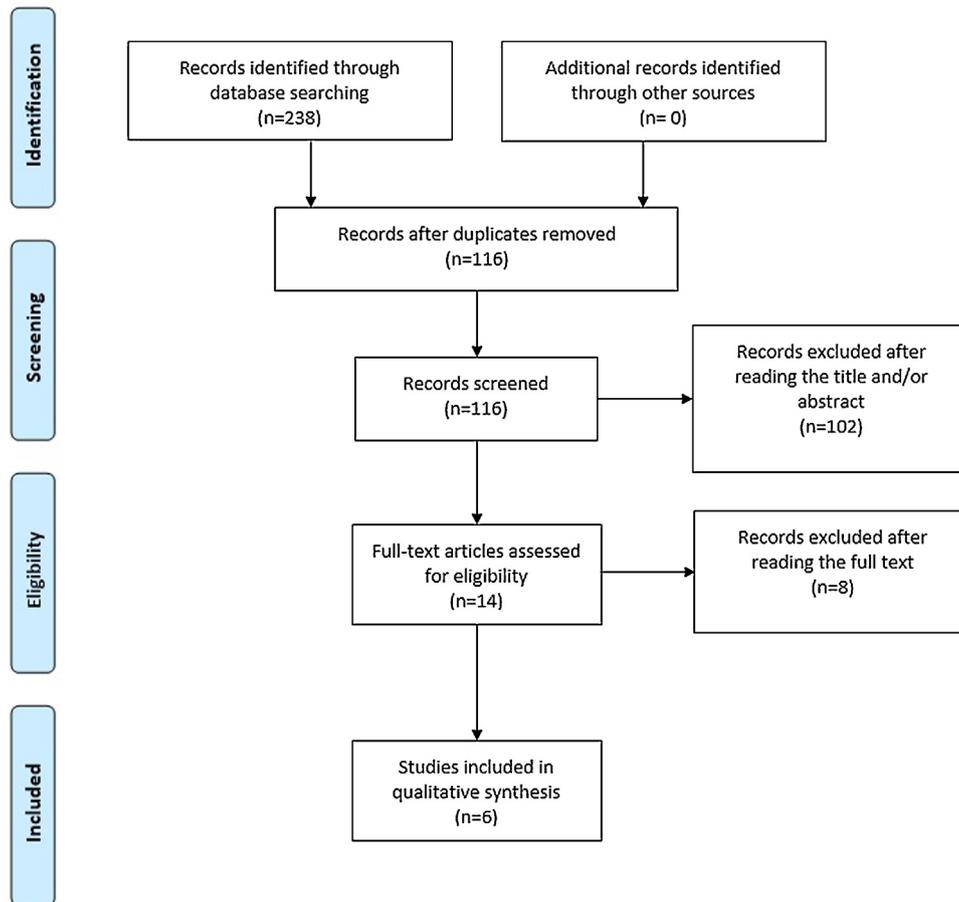


Fig. 1. Search plot diagram.

selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest.

Definitions

Gestational hypertension was defined as the presence of systolic blood pressure ≥ 140 mmHg or of diastolic blood pressure ≥ 90 mmHg on two separate readings following the completion of the 20th week of gestation. Preeclampsia was defined as the simultaneous presence of gestational hypertension and proteinuria (≥ 300 mg of protein in a 24 h urine sample). Essential hypertension was defined as the presence of a systolic blood pressure ≥ 140 mmHg or of a diastolic blood pressure ≥ 90 mmHg on two separate readings before the completion of the 20th week of gestation or when it was diagnosed prior to pregnancy and/or following the completion of the puerperium.

Quantitative analysis

Meta-analysis of collected data was initially designed to investigate the diagnostic accuracy of nocturnal blood pressure alterations in detecting adverse pregnancy outcomes (incidence of hypertensive disorders of pregnancy, fetal growth restriction, preterm birth and adverse neonatal outcomes). Meta-analysis of mean differences in nocturnal blood pressure was also designed to investigate potential differences among healthy pregnant women and women with hypertensive disorders of pregnancy. However, the significant heterogeneity in terms of selected population and outcome reporting (Table 1) precluded the conduct of quantitative analysis.

Results

Excluded studies

Two studies were excluded from the present systematic review as they did not investigate the correlation of nocturnal blood pressure disorders with the antenatal course of pregnant women. Specifically, Lazdam et al investigated the impact of preeclampsia on blood pressure characteristics during the post-partum period and at 6–13 years follow-up [14]. Miyamoto et al evaluated the pathophysiological background of nocturnal hypertension in preeclamptic patients, but did not investigate the association of nocturnal hypertension with preeclampsia or with the perinatal maternal and/or neonatal outcome [15].

Included studies

Overall, six studies were included in our systematic review. Among those, four case control studies and two cohorts were identified that recruited 487 pregnant women (Table 1) [16–21]. The results of the quality assessment analysis are presented in Table 2. The overall risk of bias was evaluated to be moderate to low.

Salazar M. et al observed in 2018 that nocturnal hypertension during mid-pregnancy significantly increased the odds of developing preeclampsia (OR 5.32, 95%CI 1.48–19.10) [16]. However, diurnal hypertension was not considered as significant predictive factor even when it was combined with abnormal nocturnal blood pressure measurements ($p = .012$ for nocturnal hypertension and $p = .547$ when they were combined). The same research team

Table 1
Study characteristics (preeclampsia vs controls).

| Date; Author | Type of study | Patient n | Inclusion criteria |
|---------------------|---------------|------------------|--|
| 2018; Salazar | Case control | 13 vs 74 | Pregnant women in the second trimester of pregnancy that referred to a high-risk pregnancy department due to comorbidities such as obesity, diabetes, hypertension, chronic kidney disease and others, or by findings detected during the current pregnancy (gestational diabetes, pregnancy hypertension, and twins). |
| 2016; Salazar | Case control | 22 vs 65 | Pregnant women that had completed the 20 th gestational week and did not have medical history of hypertension and/or were not under antihypertensive drug therapy. |
| 2013; Karkkainen | Cohort | 28 vs 32 | Pregnant women with either hypertensive disorders during their pregnancy or eventually uncomplicated pregnancies |
| 2007; Bouchlariotou | Case control | 31 vs 20 | Pregnant women that had completed the 32 nd week of gestation and did not have pre-existing chronic hypertension, diabetes, chronic renal or liver disease, vasculitis, systemic infection, recent major surgery or trauma and with von Willebrand disease |
| 2007; Steyn | Case control | 20 vs 14 vs 10 * | Patients with severe preeclampsia |
| 2001; Brown | Cohort | 65 vs 93 ‡ | Pregnant women who were in third trimester and suffered from hypertensive disorders of pregnancy and received or did not receive antihypertensive medication. |

*Numbers refer to women with normal mean diastolic blood pressure and a day-night diastolic difference ≥ 0 vs those that had abnormal (≥ 90 mmHg) diastolic blood pressure and a day-night diastolic difference < 0 or normal diastolic blood pressure and a day-night diastolic difference ≥ 0 vs those that had mean diastolic blood pressure ≥ 90 mmHg and a day-night diastolic difference < 0 .

‡Numbers refer to normal sleep BP vs nocturnal hypertension.

reported two years earlier that normotensive women with high risk pregnancy that presented nocturnal or masked hypertension had increased risk of developing preeclampsia (OR 4.72, 95% CI, 1.25–19.43, OR 7.46, 95% CI, 2.11–23.36, respectively) [17].

In 2013, Karkkainen H. et al compared differences in nocturnal patterns of blood pressure among healthy pregnant individuals and women with gestational hypertension or preeclampsia and observed that the latter group had significantly increased systolic and diastolic pressure (nocturnal systolic dipping 11 ± 4 vs 7 ± 8 , $p < .031$, nocturnal diastolic dipping 13 ± 4 vs 8 ± 6 , $p < .001$) [18].

Brown M. et al conducted a prospective cohort study in 2001 to investigate differences in nocturnal hypertension rates among women with preeclampsia and pregnant women with gestational/essential hypertension. A double blinded protocol was used to ensure that both pregnant women and clinicians did not have access to BP measurements. The authors observed that nocturnal hypertension was less prevalent in the latter group ($p < .0001$) [20]. They also reported that sleep hypertensive patients had significantly increased incidence of renal insufficiency, renal dysfunction, thrombocytopenia as well as episodes of severe hypertension ($p < .05$).

The actual pathophysiological pathways that correlate nocturnal hypertension to preeclampsia have not been fully elucidated. In 2008, however, Bouchlariotou et al investigated the association of nocturnal hypertension with biomarkers of endothelial damage and observed soluble vascular cellular adhesion molecule-1 (sVCAM-1) levels were increased among women with preeclampsia and nocturnal hypertension compared to women with preeclampsia that had a normal nocturnal dipping effect [19].

Similarly, when addressing the impact of nocturnal hypertension on perinatal maternal and neonatal pregnancy outcomes evidence is still lacking. Only a small case control study that included 44 patients with severe preeclampsia investigated differences in terms of delivery < 34 weeks, NICU admission rates, abnormal umbilical doppler patterns and cesarean section rates [21]. The authors reported that they did not observe significant differences among those that had normal and abnormal diastolic BP with either increased or decreased day-night BP differences. A mild, but significant difference in gestational age at delivery was noted that favored pregnancies with normal diastolic blood pressure and increased day-night diastolic pressure difference (33.4 ± 1.8 vs 32.2 ± 2.5 vs 31.9 ± 2.5 weeks $p = .02$).

Discussion

In our systematic review we observed that current evidence concerning the impact of nocturnal hypertension on the antenatal pregnancy course is extremely scarce and accompanied by wide heterogeneity in terms of outcome reporting and outcome reporting measures. Nevertheless, all studies seem to support that nocturnal hypertension is more prevalent in patients with preeclampsia, compared to controls and patients with gestational or essential hypertension. The correlation between altered nocturnal patterns of blood pressure and adverse pregnancy outcomes as well as with the risk of morbidity during the antenatal period has been poorly investigated; hence, definitive conclusions and a firm consensus concerning the optimal screening and

Table 2
Newcastle-Ottawa assessment scale.

| Newcastle-Ottawa Assessment Scale | | | | | | | | | |
|-----------------------------------|--|-------------------------------------|---------------------------|---|---------------|-------------------------------|-----------------------------------|---------------------------------------|-------|
| Date; Author | Selection Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome of interest not present at start of study | Comparability | Outcome Assessment of outcome | Adequacy of duration of follow up | Adequacy of completeness of follow up | Total |
| 2018; Salazar | ★ | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 8 |
| 2016; Salazar | ★ | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 8 |
| 2013; Karkkainen | ★ | ★ | ★ | – | ★ | ★ | ★ | – | 6 |
| 2007; Bouchlariotou | ★ | ★ | ★ | – | ★ | ★ | ★ | ★ | 7 |
| 2007; Stein | ★ | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 8 |
| 2001; Brown | ★ | ★ | ★ | – | ★ | ★ | ★ | – | 6 |

management of preeclamptic patients that have increased blood pressure at night is missing.

On the other hand, the significance of nocturnal hypertension during the pregnancy course is not a novel matter of concern as it has been already underlined in 1990 by Oney and Mayer-Sabellek who observed that women that suffered from severe preeclampsia were more prone to present reversed circadian rhythm and nocturnal hypertension than healthy pregnant women [22]. The same authors supported that hypertensive emergencies had a higher incidence at night. As a consequence, they suggested intense nighttime blood pressure observation and adaptation of antihypertensive medication. Brown noted that sleep hypertension was quite frequent among preeclamptic pregnant women and women suffering from pregnancy-induced hypertensive disorders. According to the same study, maternal renal and liver function as well as birth weight were also negatively influenced in women who suffered from nocturnal hypertension [23]. Ditisheim et al observed that nocturnal and masked hypertension were still obvious six to twelve weeks postpartum. Preeclamptic women were also diagnosed with statistically higher nocturnal blood pressure compared to women with normal pregnancies [24]. Lazdam et al reported that women with early onset preeclampsia, had a significant risk of developing sustained diurnal and nocturnal hypertension at 6–13 years postpartum, compared to women with late onset preeclampsia [14]. Both studies pointed the need of following-up and managing these women following labor to prevent future cardiovascular disease.

The actual factors that may influence the presence and severity of nocturnal hypertension in pregnancy as well as its correlation with the severity and onset of preeclampsia remain unknown. In their recent study, Lv et al observed that excessive umbilical coiling might be a predisposing factor; however, the actual pathophysiological explanation behind this association remains unknown [25].

Strengths and weaknesses of the study

Our systematic review accumulates for the first time in the literature all existing data concerning the prevalence of nocturnal hypertension in preeclampsia. The qualitative assessment of included studies revealed that the possibility of bias was moderate to low; hence, possibility of selection bias was significantly reduced. On the other hand, the heterogeneity of included studies in terms of reported outcomes and studied population rendered impossible the accumulation of data in a meta-analysis. Moreover, the sample size that was used in the majority of included studies was relatively small; thus, putting into question the potential external validity of their findings. Therefore, it is impossible to establish safe conclusions which could help reach consensus concerning the optimal screening strategy of patients with gestational hypertension

Implications for future research

Given the findings of our systematic review, nocturnal blood pressure alterations seem to be a promising index for future research in the field of preeclampsia. Unfortunately, several gaps exist which preclude safe conclusions and these deserve further investigation. We believe that identification of the prevalence of these alterations in the three trimesters of pregnancy is of extreme importance as it will help researchers investigate their diagnostic accuracy in detecting women at risk of developing hypertensive disorders of pregnancy.

Moreover, future cohort studies are needed to provide robust evidence concerning the association of these alterations with maternal and neonatal outcomes. Ideally, these studies should stratify pregnant women according to the severity of their hypertensive disorder (gestational hypertension, late onset preeclampsia and early onset preeclampsia) and use both univariate and multivariate analysis in order to help determine the actual prognostic accuracy of nocturnal blood pressure alterations.

Controlled trials would be also useful to evaluate whether women with gestational hypertension that becomes more intense at night may actually benefit from a more rigorous or an alternate medical approach. Thus said, the actual timing of administration of anti-hypertensive therapy may significantly alter the severity of the disease and, therefore, result in different maternal and neonatal outcomes. If this would prove to be true 24-h ambulatory blood pressure monitoring should be unanimously instituted to all pregnant women with gestational hypertensive disorders, to optimize diurnal and nocturnal blood pressure control.

Concluding, nocturnal hypertension seems to be more prevalent in cases complicated by preeclampsia; however, its clinical usefulness in determining pregnancy outcomes and its prognostic significance in preeclamptic patients remains to date unknown. Current evidence seems to support that its presence is more evident among cases with severe, early onset preeclampsia; however, it remains unknown whether this is manifested from the first trimester of pregnancy and if it is associated with worsening of perinatal outcome. Future studies are needed to evaluate the predictive accuracy of nocturnal hypertension during the antenatal period and these should consistently measure nighttime blood pressure in all trimesters pregnancy to help reach definitive conclusions.

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Disclosure of conflicts of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejogrb.2019.05.028>.

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