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Association between depression and hypertensive disorders during pregnancy: an integrative review

Relación entre depresión y trastornos hipertensivos durante el embarazo: una revisión integrativa

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Sabrina Chapuis-de-Andrade^{1,2*}, Aline Parisotto³, Bartira Ercília Pinheiro da Costa¹, Ivan Carlos Ferreira Antonello¹

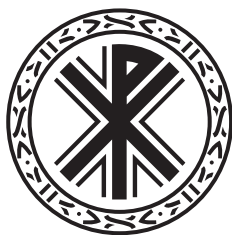
¹ Postgraduate Program in Medicine and Health Sciences. Pontifical Catholic University of Rio Grande do Sul. Porto Alegre.

² Research fellow from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brazil (Capes).

³ School of Medicine. Pontifical Catholic University of Rio Grande do Sul. Porto Alegre.

* Correspondencia: Sabrina Chapuis-de-Andrade. Avenida Ipiranga, 6690. 90619-900 Porto Alegre. Brazil.

E-mail: sabrinachapuis@gmail.com



ABSTRACT

The etiology of hypertension, especially in pregnancy, is various and complex, involving both genetic and psychological factors. The aim of this study was to investigate the association between depression and hypertensive disorders in pregnancy. Its original contribution is to broadly address these types of hypertensive disorders. We conducted an integrative literature review and identified relevant studies from four databases, including *MEDLINE*, *LILACS*, *SciELO* and *EMBASE*. Qualitative and original studies in English, Spanish and Portuguese (Brazilian) published between the years of 2005-2016 were included. Studies were selected by titles, abstracts and full texts, and its quality was evaluated by three researchers independently. Data showed that depression was associated to hypertensive disorders in pregnancy. Women with severe depressive symptoms have higher risk to develop preeclampsia. The use of antidepressants also showed a large association to the hypertensive disorders in pregnancy. Conclusion: Current evidence indicates association between depression and hypertensive disorders in pregnancy. Physical care and mental health care of women is essential for a physiological and safe pregnancy.

KEYWORDS: *hypertension, hypertension, pregnancy-induced hypertension, preeclampsia, depressive disorder, review.*

RESUMEN

La etiología de la hipertensión, especialmente en el embarazo, es variada y compleja, involucrando factores genéticos y psicológicos. El objetivo de este estudio fue investigar la asociación entre la depresión y los trastornos hipertensivos en el embarazo. Su contribución original es el enfoque ampliado sobre estos tipos de trastornos hipertensivos. Realizamos una revisión bibliográfica integradora y identificamos estudios relevantes de cuatro bases de datos, que incluyen *MEDLINE*, *LILACS*, *SciELO* y *EMBASE*. Se incluyeron estudios cualitativos y originales en inglés, español y portugués (brasileño) publicados entre los años 2005-2016. Los estudios fueron seleccionados

por títulos, resúmenes y textos completos, y su calidad fue evaluada por tres investigadores de forma independiente. Los datos mostraron que la depresión estaba asociada a trastornos hipertensivos en el embarazo. Las mujeres con síntomas depresivos graves tienen un mayor riesgo de desarrollar preeclampsia. El uso de antidepresivos también mostró una gran asociación con los trastornos hipertensivos en el embarazo. Conclusión: la evidencia actual indica asociación entre la depresión y los trastornos hipertensivos en el embarazo. El cuidado físico y el cuidado de la salud mental de las mujeres es esencial para una gestación fisiológica y segura.

PALABRAS CLAVE: hipertensión, hipertensión inducida en el embarazo, preeclampsia, trastorno depresivo, revisión por expertos.

INTRODUCTION

Pregnancy is considered one of the most important moments in a woman's life. As a physiological phenomenon, the World Health Organization (WHO) defines gestation as a natural manifestation that triggers physiological, social and emotional changes [38]. Moreover, it is a time that provides several physical and psychological transformations, preparing the pregnant woman for the baby's birth. These alterations are such that some imbalances can occur, leading to the development of diseases.

Gestational hypertension is one of the most common cause of maternal morbidity and mortality [37]. It has been estimated that around 5-10 % of pregnant women will develop this disorder [30]. Pregnancy-induced hypertension has classically been classified as: chronic hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension and gestational hypertension without proteinuria (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy 2000, [21]), being preeclampsia/eclampsia the most substantial effect on maternal and newborn health [27].

Regarding mental health, depression is one of the most prevalent complications during pregnancy [3, 10, 40]. It is defined as a clinical syndrome, with a multifactorial etiology (Diagnostic and statistical manual of mental disorders, 2013). The magnitude of such a problem is so great that WHO recognizes depression as one of the major causes of morbidity and disability among young adults. Studies estimate that depression affects around 16 % of pregnant women [40]. The effects of this condition are numerous, since depression can affect the pregnant woman's self-care and, consequently, cause problems to the newborn.

Both hypertension and depression place women in greater need of care, since these conditions can lead to important dysfunctions in the body. Furthermore, the association between depression and hypertension is an important factor that should be evaluated during pregnancy. Of note, studies about psychological factors, such as depression and/or depressive symptoms associated to the risk of gestational hypertension, have increased in the last years [30, 20]. However, this relation is still unclear.

The aim of this study was to search for evidence available in the literature related to depression and hypertensive disorders in pregnancy to answer the question: *Is there any association between depression and hypertensive disorders?* This review attempts to clarify if the intensity of depressive symptoms is related to a higher prevalence of hypertensive disorders and whether the use of antidepressants is related to this outcome or not.



MATERIALS AND METHODS

The present research was conducted through an integrative literature review on the topic of depression and hypertension during pregnancy. This methodology allows a better understanding of issues already addressed by previous research. Moreover, it indicates which aspects need to be investigated in further studies [15].

This review considered the following steps: definition of the research question; selection of the inclusion and exclusion criteria of the studies; selection of databases and descriptors for the search; studies analysis; results interpretation and presentation of the review. The search for studies was conducted on December 2018.

The databases consulted were: *Medical Literature Analysis and Retrieval System Online (MEDLINE)*, *Literature in the Health Sciences in Latin America and the Caribbean (LILACS)*, *Scientific Electronic Library Online (SciELO)* and *EMBASE*.

For the search, descriptors were used related to depression and gestational hypertension, according to the Health Sciences Descriptors (DECS) and the Medical Subject Headings (MeSH). Only English, Spanish and Portuguese (Brazilian) clinical studies were included, published between the years of 2005 and 2016.

The exclusion criteria considered were review articles, hypotheses, validation studies of scales, editorials and conference abstracts.

After the search, articles were assessed first by the title, followed by summary and careful reading of the full text. Data collection instrument used for analysis of the results was based on the article identification: Author/year/country; main characteristics of participants and main results.

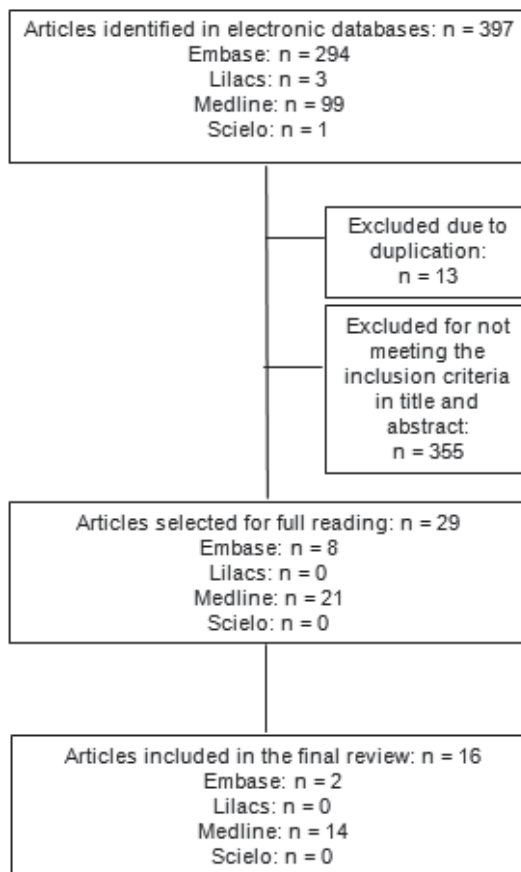
RESULTS

Of the 397 different clinical studies conducted in women regarding depression and hypertension in pregnancy, 16 were included in the final analysis (Flow Chart 1).

Of the 381 studies that were excluded, 41 were review, 11 were in languages other than English, Spanish or Portuguese (Brazilian), one was a hypothesis study and the others were not related to the aim of this review.

The final sample of studies included in this research is presented in Table 1.





Flow Chart 1: Selection of studies included in the review.

Table 1. Studies included in integrative review

Author / year / country	Main characteristics of participants	Study design	Main results
Rouleau CR, <i>et al.</i> 2016. Canada.	n = 287; MA: 31.5; GA: First evaluation: 14.9; Second evaluation: 32.4.	Prospective longitudinal study.	In early pregnancy, women without gestational hypertension showed higher mean of depressive symptoms (5.7) than women with gestational hypertension (5.5). However, in late pregnancy women with gestational hypertension showed higher means (6.5 x 5.3)
Yedid Sion M, <i>et al.</i> 2016. Israel.	n = 256312; MA: Depression: 32.05; No depression: 28.56; GA: Depression: 37.99; No depression: 39.02.	Retrospective cohort study.	There was no significant difference between depressed and non-depressed women regarding preeclampsia incidence.



Author / year / country	Main characteristics of participants	Study design	Main results
Franco RC, <i>et al.</i> 2015. Brazil.	n = 105; MA: 24; GA: third trimester.	Cross-sectional study.	Depression is the risk factor for the occurrence of gestational arterial hypertension (OR 8.69).
Lutsiv O, <i>et al.</i> 2015. Canada.	n = 70605 women; 50.3% were overweight/ obese; MA: 30.1. GA: >20.	Retrospective cohort study.	Normal weight (Body Mass Index - BMI, 18.5-24.9kg/m ²): 2.2 % depressed women had gestational hypertension and 1.5 % presented preeclampsia; Overweight/obese (BMI ≥25 kg/m ²): 5.5 % depressed women had gestational hypertension and 3.1 % presented preeclampsia.
Avalos LA, <i>et al.</i> 2015. USA.	n = 21589; Electronic medical records of pregnant Kaiser Permanente Northern California members. MA: Not informed. GA: all pregnancy.	Retrospective population-based cohort study.	Women who took antidepressant medications had increased risk of preeclampsia, compared to women with untreated depression or no depression.
Thombre MK, <i>et al.</i> 2015. USA.	n = 1371; MA: 28.7. GA: 16-27.	Retrospective subcohort study.	Women's lifetime history of depression symptoms was associated with a 2.3-fold higher risk of preeclampsia. Women with comorbid anxiety and depressive disorder had a higher blood pressure (systolic: linear regression coefficient [β]= 3.0, 95 % confidence interval [CI]=0.2-5.7; diastolic, β =2.3, 95 % CI=0.1-4.4).
Winkel S, <i>et al.</i> 2015. Germany.	n = 283 25.8% were overweight; MA: 28.2 GA: >12.	Prospective longitudinal study.	Overweight (BMI ≥25 kg/m ²): Women with overweight had significantly higher systolic and diastolic blood pressure compared to women with normal or underweight (crude: β =6.3 and β =4.5; adjusted: β =6.2 and β =4.6). No significant associations of overweight with anxiety liability and depression liability were apparent (linear regression: all p>0.05; results on request).
Palmsten K, <i>et al.</i> 2013. USA.	n = 100942; MA: 25.2. GA: Not informed.	Retrospective cohort study.	The risk of preeclampsia was 5.4 % among women with depression and no antidepressant exposure. Compared with these women, the risk for preeclampsia was higher among those receiving some antidepressants.
Katon WJ, <i>et al.</i> 2012. USA.	n = 2398; MA: 30.5; GA: 23.3.	Prospective study.	Women with preexisting hypertension had higher risk of depression (OR=1.55) compared to women without hypertension. No differences were seen in risk of depression in women with pregnancy-induced hypertension or preeclampsia/eclampsia compared to those without hypertension.
Palmsten K, <i>et al.</i> 2012. Canada.	n = 69448; MA: 31. GA: >10.	Retrospective cohort study.	The risk of preeclampsia in depressed women not treated with antidepressants (2.4 %) was similar to that in women without depression (2.3 %). The use of antidepressants was associated with a higher risk of preeclampsia.



Author / year / country	Main characteristics of participants	Study design	Main results
De Vera MA, Bérard A. 2012. Canada.	n = 13376; 1216 women with pregnancy-induced hypertension and with no history of hypertension before pregnancy; 10 controls for each case; MA: 27.3; GA: 36.3.	Case-control.	The use of antidepressants during pregnancy had 1.5-fold increased risk of pregnancy-induced hypertension.
Kharaghani R, <i>et al.</i> 2012. Iran.	n = 312; 156 women with preeclampsia and 156 women without any history of preeclampsia. MA: 28.4; GA: 35.7.	Case-control.	Women with mild depression had a 1.8-fold increased risk for preeclampsia while moderate to severe depression had a 2.5-fold higher risk compared to no depression women.
Bansil P, <i>et al.</i> 2010. USA.	n = 32156438; 244939 women with depression diagnosis; MA: 29.5; GA: all pregnancy.	Retrospective cohort study.	Women with depression had a 1.5-fold higher risk for Preeclampsia/hypertension compared to women without depression.
Toh S, Mitchell AA, <i>et al.</i> 2009. USA.	n = 5731 MA: 32. GA: all pregnancy.	Retrospective cohort.	Gestational hypertension was present in 9.0 % of the women who were not treated with selective serotonin reuptake inhibitors (SSRIs) and 19.1 % of the women who were treated with SSRIs. Preeclampsia occurred in 2.4 % of women who were not treated with SSRIs, 3.7 % in women who were exposed to SSRIs only during the first trimester, and 15.2 % in women who continued SSRI treatment beyond the first trimester.
Vollebregt KC, <i>et al.</i> 2008. The Netherlands.	n = 3679 nulliparous women; MA: 29.9; GA: all pregnancy.	Prospective community-based cohort study.	The incidence of pre-eclampsia and gestational hypertension was 3.5 and 4.4 %. Depression had no effect on the incidence of pre-eclampsia or gestational hypertension.
Qiu C, <i>et al.</i> 2007. Peru.	n = 676 339 preeclamptic women and 337 normotensive controls. MA: 26.2; GA: all pregnancy.	Case-control.	Women with moderate and severe depression had a 2.3-fold and a 3.2-fold increased risk of preeclampsia, respectively, compared with non-depressed women.

MA=Maternal age (years); Gestational age (weeks).

Most studies were a retrospective cohort study. Case-control studies typically involved depressive women who were compared to non-depressive women. One cross-sectional and four prospective community-based cohort studies were identified.

Regarding publication year, most studies are recent. Publication year was concentrated from 2012 ahead.

In the 16 studies, a total of 32,703,552 women were analyzed, predominantly from North America - USA and Canada. Only two studies were from Europe, two were from Latin America and two other



from Asia. The average age of participants was 25.21 years old. Gestational age most analyzed was third trimester.

In general, depression was associated to gestational hypertension, especially preeclampsia. Depression severity also contributed to increase the risk of hypertensive disorders in pregnancy, according to authors.

Some studies explored the association between the use of antidepressants and the risk of gestational hypertension and preeclampsia [1, 5, 19, 18]. According to that, women who take antidepressants have a 1.5-fold increased risk of pregnancy-induced hypertension [5].

Two studies also evaluate Body Mass Index (BMI). A study showed that depressed women who are also overweight or obese have a higher risk of gestational hypertension and preeclampsia [35]. However, another study found no significant association between overweight and depression susceptibility, but showed higher blood pressure in overweight women [41].

Only two studies presented no significant association between depression and hypertensive disorders in pregnancy [35, 41].

DISCUSSION

By conducting this review, we found that the association between depression and the risk of gestational hypertension was high. In general, women with depressive symptoms were more likely to develop a hypertensive disorder. Especially, moderate and severe depression were around two times more associated with this outcome. Such associations can be explained by the woman's lifestyle, neither based on healthy lifestyle habits [28], changes in the immune system, nor changes in the autonomic nervous system and the hypothalamic-pituitary-adrenal axis [25] nor the increase in the release of pro-inflammatory markers [16].

Corroborating our findings, a recent meta-analysis also showed the association between depressions with a moderately increased risk of preeclampsia [11]. Of note, our integrative review included not only preeclampsia as an outcome, but also the others hypertensive disorders in pregnancy. However, most studies rather focus on preeclampsia comprehension given its high rate of complications for pregnant women and the fetus.

On the other hand, a prospective community-based cohort study from 2008 with nulliparous women and a singleton pregnancy did not find any significant difference between having or not depression and incidence of hypertensive disorders [35]. These data are consistent with the main analyses from a systematic review and meta-analysis conducted in 2010 [9]. It should also be noted that most studies included in this integrative review were more recent, from years 2015 and 2016. Only one study did not find association between depressive symptoms and preeclampsia diagnosis and it is from Israel [41]. Additionally, it is important to consider cultural differences when we are thinking about psychological symptoms. Western and Eastern women can view the fact of being depressed, for example, in different ways. In our society, based on capitalist models, women are required to follow patterns that are not always easy to reach. Consequently, this can lead to important psychological changes such as the manifestation of more intense depressive symptoms; even because social pressure has an important role in human behavior, especially regarding psychological symptoms [33]. Moreover, during



pregnancy, a period of great transformation in a woman's life, this fact can intensify even more, causing other pathologies, like the alteration of the arterial pressure.

Regarding antidepressants use, some studies also showed association with a higher risk of hypertensive disorders in pregnancy. According to a recent systematic review, some antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, have been associated to a higher risk of pregnancy complications, including preeclampsia [17]. It is important to consider that antidepressants use may be related to higher severity of depressive symptoms, interacting as a confounding factor in this case. However, the results of the studies analyzed indicate the importance of taking into account the current scenario, which is worrying since it is known that the percentage of pregnant women who use these drugs is quite high. In the United States, for example, antidepressant medication reaches more than eight percent of pregnant women [34]. It is understood that depression reaches a large number of people and that women are especially affected by it [38]. Additionally, in this situation, the risks of untreated depression with medication during pregnancy are much greater than the adverse effects that the antidepressants can trigger. It is known, for example, that there are adverse perinatal outcomes, besides direct risks to the fetus [4], depending on the severity of the depressive symptoms. However, medication is not the only option for treating depression. Since there are serious adverse effects that the use of antidepressants can cause in pregnant women, such as hypertensive disorders, it is important to foster alternative treatments, for example, psychotherapy. For this reason, it is essential for the woman to be accompanied by a qualified professional team that can identify risk factors for mental health, such as depressive symptoms, even in a lighter intensity, given the complications that this disease can cause.

Another important risk factor for gestational hypertension cited in some of studies included in this review was the association not only with depression, but also with high BMI. Obesity and depression have been cited as the most prevalent comorbidities of gestation [29, 7]. Both are associated with complications of pregnancy, including gestational hypertension or preeclampsia, and can take the development of many pregnancy adverse outcomes [14]. Obesity is widely known as a risk factor for the development of hypertension [6, 26]. However, the correlation between higher BMI associated to depression and the development of gestational hypertension has not been fully established yet. Whereas some studies show that to be a little overweight is a risk factor for hypertensive disorders [8, 31]; others do not find this association [24]. We found two articles that studied the correlation between BMI, depression and gestational hypertension. Lutsiv O, *et al.* proved that being obese and depressed increases the prevalence of comorbidities during pregnancy, including gestational hypertension and preeclampsia [14]. Winkel, *et al.* also showed a significant association between BMI and hypertensive disorders in pregnancy, which appears to be somewhat more relevant in relation to anxiety and depression [36].

CONCLUSIONS

This review demonstrates that, in general, depression is associated with hypertensive disorders in pregnancy. Women with more severe depressive symptoms have particularly higher risks of preeclampsia. Antidepressant use and higher BMI also showed high odd ratios, relating to hypertensive



disorders in pregnancy. However, there are important limitations in this review: the number of studies included was small, although samples were large. The age of women in the studies was different, although most were about thirty years old. Gestational age was different, too. Nevertheless, the third gestational trimester was the most studied. Additionally, the instruments and scales used to assess depression in women were different, making it difficult to compare them, despite everything was validated to the used language.

Considering this limitations, other studies are necessary based in scales more widely disseminated, as Beck Depression Inventory (BDI) or Diagnostic and Statistical Manual of Mental Disorders (DSM) for depression diagnosis, for example. Furthermore, it is clear that a more frequent follow-up of the pregnant women is fundamental not only in relation to physical but also psychological changes, since serious outcomes can occur in these cases.

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NORMAS DE ADMISIÓN Y PRESENTACIÓN DE LAS COLABORACIONES ADMISSION AND PRESENTATION STANDARDS FOR CONTRIBUTIONS

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