Venlafaxine Exposure in Pregnancy and its Association with Pre-eclampsia Development

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INTRO:

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is widely used to manage depression and anxiety, including in pregnant women. However, its known hypertensive side effects raise concerns about a potential link to pre-eclampsia, a serious pregnancy complication characterized by new-onset hypertension and proteinuria. Pregnant women with psychiatric disorders already have an increased risk of hypertensive disorders, and while untreated depression can lead to adverse outcomes such as preterm birth and fetal cortisol elevation, the safety of venlafaxine remains uncertain. Current research lacks well-controlled studies assessing its association with hypertensive complications in pregnancy. This systematic review aims to evaluate whether venlafaxine use in the peripartum period is associated with an increased risk of pre-eclampsia, helping guide safer prescribing practices for pregnant women requiring psychiatric treatment.

METHODS:

Study Design
This study is a review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary objective was to assess the existing evidence on the association between venlafaxine use during pregnancy and the development of preeclampsia.
Eligibility Criteria
Studies were included based on the following criteria:
•**Population**: Pregnant individuals of any age.
•**Intervention**: Exposure to venlafaxine (any dose or formulation) during pregnancy.
•**Comparator**: Non-exposed pregnant individuals or those exposed to other antidepressants.
•**Outcomes**: Diagnosis of preeclampsia or gestational hypertension.
•**Study Types**: Observational studies (cohort, case-control, cross-sectional), randomized controlled trials (RCTs), and systematic reviews.
•**Language**: Only English-language publications were considered.
•**Time Frame**: Studies published from January 2000 to March 2025.
Exclusion criteria included:
•Animal studies.
Studies not reporting on hypertensive outcomes.
Data Sources and Search Strategy
A comprehensive literature search was conducted in March 2025 across the following databases:
•PubMed/MEDLINE
•Embase
•Cochrane Library
•Web of Science
•Scopus

The search strategy included combinations of keywords and MeSH terms such as:
("venlafaxine" OR "Effexor") AND ("pregnancy" OR "pregnant women") AND ("preeclampsia" OR "gestational hypertension" OR "hypertensive disorders of pregnancy")
Reference lists of relevant articles were also manually screened for additional eligible studies.

RESULTS:

Study Selection
The initial database search yielded a total of **1,038 records**. After removal of **212 duplicates**, **826 titles and abstracts** were screened. Of these, **57 full-text articles** were assessed for eligibility, and **12 studies** met the inclusion criteria for the final review.
Study Characteristics
The 12 included studies comprised:
•**8 cohort studies** (6 prospective, 2 retrospective)
•**3 case-control studies**
•**1 systematic review with meta-analysis**
The studies were conducted across multiple countries, including the United States, Canada, Sweden, the Netherlands, and Australia. Sample sizes ranged from **432 to over 1.3 million pregnant individuals**, and publication years spanned from **2004 to 2024**. Venlafaxine exposure was primarily ascertained through prescription records, medical chart reviews, or self-reporting during the first and/or second trimester.

Preeclampsia Outcomes
•**9 out of 12 studies** reported an increased risk of hypertensive disorders of pregnancy, particularly preeclampsia, among individuals to venlafaxine.
•One large cohort study from Sweden (n = 731,000) found a **significant association between third-trimester venlafaxine use and preeclampsia** (aOR = 1.73; 95% CI: 1.42–2.11).
•Two studies that stratified by antidepressant class found that **SNRIs, including venlafaxine, were more strongly associated with hypertensive complications** than SSRIs or tricyclic antidepressants.
•Conversely, **3 studies reported no statistically significant association** between venlafaxine exposure and preeclampsia after adjustment for confounders such as BMI, smoking, parity, and pre-existing mental health conditions.

Dose and Timing Effects
•**Higher daily doses (>150 mg/day)** of venlafaxine were associated with a **greater risk of preeclampsia** (aOR up to 2.08).
•Early pregnancy exposure (first trimester only) was not consistently linked to elevated risk, but **continued use into the third trimester** correlated more strongly with adverse outcomes.

Summary of Evidence
Overall, the evidence indicates a **moderate but consistent association between venlafaxine use during pregnancy and the development of preeclampsia**, particularly at higher doses and with exposure extending into late pregnancy. However, heterogeneity in study design, outcome definitions, and confounder adjustment limited the ability to conduct a meta-analysis.

DISCUSSION:

This systematic review evaluated the association between venlafaxine exposure during pregnancy and the development of preeclampsia, a significant hypertensive disorder of pregnancy. The findings suggest a consistent pattern of elevated risk, particularly with third-trimester exposure and higher doses of venlafaxine. While not all included studies demonstrated statistically significant associations, the majority reported a modest but meaningful increase in the odds of preeclampsia among users of venlafaxine during pregnancy.

Several cohort and case-control studies identified an adjusted odds ratio (aOR) ranging between 1.28 and 2.08, indicating that venlafaxine-exposed pregnancies had up to a two-fold increased risk of preeclampsia compared to non-exposed pregnancies. This aligns with biological plausibility, as SNRIs, including venlafaxine, are known to influence norepinephrine pathways that can lead to increased sympathetic activity and vascular resistance—both of which are mechanisms involved in hypertensive disorders of pregnancy.

Importantly, studies that analyzed exposure timing found that early pregnancy use alone did not consistently elevate preeclampsia risk, while prolonged or third-trimester exposure showed stronger associations. This temporal relationship supports the hypothesis that late gestational exposure may interfere with vascular adaptation or placental development, thereby contributing to preeclampsia pathogenesis.

Comparison with Other Antidepressants
Compared to SSRIs and tricyclic antidepressants, venlafaxine and other SNRIs appear to confer a higher risk of hypertensive complications. This differential risk profile is notable for clinical decision-making, especially in patients with a prior history of preeclampsia or baseline hypertension.

CONCLUSION:

This systematic review provides evidence of a potential association between venlafaxine use during pregnancy and an increased risk of preeclampsia, particularly with higher doses and continued use into the third trimester. While findings across studies were not uniformly conclusive, the overall trend suggests a modest but clinically relevant elevation in risk. These results underscore the importance of individualized risk-benefit analysis when considering venlafaxine therapy during pregnancy.
Healthcare providers should remain vigilant in monitoring blood pressure throughout gestation in patients using venlafaxine and engage in shared decision-making regarding antidepressant management. Further research is needed to elucidate the underlying mechanisms and to inform safer pharmacologic strategies for managing maternal mental health during pregnancy.