

# Periconceptional Folic Acid Supplementation and the Risk of Preeclampsia in Eastern Sudan: An Unmatched Case-Control Study

Gamal K Adam<sup>1</sup>, Nadiah AlHabardi<sup>2</sup>, Ishag Adam<sup>2</sup>

<sup>1</sup>Faculty of Medicine, Gadarif University, Gadarif, Sudan; <sup>2</sup>Department of Obstetrics and Gynecology, College of Medicine, Qassim University, Buraydah, Saudi Arabia

Correspondence: Nadiah AlHabardi, Department of Obstetrics and Gynecology, College of Medicine, Qassim University, Buraydah, Saudi Arabia, Email [n.alhabrdr@qu.edu.sa](mailto:n.alhabrdr@qu.edu.sa)

**Purpose:** This study aimed to investigate the association between periconceptional [before conception/pregnancy (preconception) through the first trimester (around 10–14 weeks)] folic acid supplementation and the risk of preeclampsia among pregnant women in Gadarif, eastern Sudan.

**Methods:** This was an unmatched case-control study (127 cases and 127 controls) conducted in 2024 at Gadarif Maternity Hospital in Gadarif, Eastern Sudan. The cases were pregnant women diagnosed with preeclampsia, while the controls were pregnant women without preeclampsia. Participants' sociodemographic and obstetrical data were assessed via a questionnaire. Multivariate binary analyses were also performed.

**Results:** Women with preeclampsia were less likely to have used periconceptional folic acid supplementation (12 [9.4%] vs 26 [20.5%],  $p = 0.016$ ). The univariate binary analysis showed that maternal age, gravidity, overweight/obesity, and periconceptional folic acid supplementation were significantly associated with preeclampsia. However, residence, internal displacement, couples' education, maternal occupation, maternal blood group, antenatal care, anemia, and number of fetuses in the current pregnancy were not associated with preeclampsia. The multivariate binary analysis showed that primigravida (adjusted odds ratio, AOR = 6.20, 95% confidence interval, CI 3.16–12.14), not taking periconceptional folic acid supplementation (AOR = 2.24, 95% CI 1.02–4.96), and being anemic (AOR = 1.94, 95% CI 1.10–3.40) were associated with an increased risk of preeclampsia. However, maternal age and being overweight or obese were confounding factors.

**Conclusion:** This study provides compelling evidence that periconceptional folic acid supplementation is significantly associated with a reduced risk of preeclampsia in eastern Sudan. It also reinforces the importance of primigravida and anemia as critical risk factors. These findings have direct public health implications, including intensified efforts to promote early, consistent folic acid supplementation, alongside targeted interventions for primigravida women and anemia management, to improve maternal and child health outcomes in the region.

**Keywords:** preeclampsia, folic acid, age, primigravida, anemia, Sudan

## Introduction

Preeclampsia is a pregnancy-specific disorder characterized by new-onset hypertension, proteinuria, or other signs of end-organ dysfunction after 20 weeks of gestation. It remains a significant cause of poor pregnancy outcomes worldwide.<sup>1</sup> Globally, preeclampsia contributes to approximately 46,000 maternal deaths annually, and tragically, it is also associated with about 500,000 fetal or newborn deaths each year.<sup>2</sup> The burden of preeclampsia is much higher among women in settings with limited resources, such as Sub-Saharan Africa (SSA).<sup>3</sup> In SSA, the overall estimated pooled incidence of preeclampsia was 13% (95% confidence interval, CI: 0.12–0.14).<sup>3</sup> The etiology of preeclampsia is complex and not fully understood, as it includes dietary habits and sociocultural, economic, and placental factors.<sup>3–6</sup> In

the absence of effective preventive or curative treatments beyond delivery, the identification of modifiable risk factors is emerging.

Recently, more attention has been paid to maternal dietary habits, particularly periconceptional folic acid supplementation and its protective role in preeclampsia.<sup>6–11</sup> Folic acid, a synthetic form of folate (vitamin B9), is an essential vitamin for cell division as well as deoxyribonucleic acid (DNA) synthesis and repair. Folic acid is widely recommended in the periconceptional period to prevent neural tube defects.<sup>4,5,12</sup> Beyond its documented role in neural development, emerging evidence suggests that folic acid may protect against other adverse pregnancy outcomes, including preeclampsia, by influencing endothelial function, reducing oxidative stress, and regulating homocysteine levels.<sup>9,13</sup> Elevated homocysteine levels, a consequence of folate deficiency, have been linked to endothelial damage and an increased risk of preeclampsia.<sup>9,14</sup> However, the literature shows contradictory results regarding the role of folic acid as a protective factor in preeclampsia. These conflicting results may be attributable to variations in study populations, methodological differences, and confounding factors. Some studies have shown that folic acid supplementation during early pregnancy has a protective effect against preeclampsia,<sup>8,10,11</sup> whereas others have found no effect.<sup>15–17</sup> However, most of these studies were conducted in high-income countries and non-African contexts, particularly those examining the mechanisms underlying such an association.<sup>4,9,13,18–22</sup> There is a relatively notable lack of research in SSA, where the lack of periconceptional folic acid supplementation and associated complications, such as preeclampsia and neural tube defects, are more prevalent.<sup>23</sup> Indeed, no study in Sudan has explored the role of periconceptional folic acid supplementation in preeclampsia. Crucially, a low prevalence (14.10%; 95% CI: 11.22–16.98) of preconceptional folic acid supplementation among women in SSA<sup>23</sup> and Sudan (3.7%) was reported.<sup>24</sup> In such settings, where healthcare resources may be limited and access to comprehensive antenatal care (ANC) can vary, understanding these associations is crucial.

Besides folic acid, other factors have been reported as risk factors for preeclampsia, such as age,<sup>25–28</sup> parity,<sup>28,29</sup> education,<sup>28,30</sup> occupation,<sup>27</sup> inadequate ANC,<sup>29,31</sup> maternal blood group,<sup>31</sup> high maternal body mass index (BMI),<sup>26,29,32</sup> multiple gestational pregnancies,<sup>30</sup> and anemia.<sup>8,28,29</sup> Identifying the risk factors for preeclampsia is essential for early detection, timely intervention, and improved pregnancy outcomes. Untreated preeclampsia can progress to eclampsia, which involves seizures. Both conditions (preeclampsia and eclampsia) can be life-threatening.<sup>1</sup>

Despite the notable lack of periconceptional folic acid supplementation<sup>24</sup> and the significant burden of preeclampsia,<sup>28,33,34</sup> there is a significant dearth of research investigating this association in the Sudanese context. Moreover, the ongoing war is devastating maternal and perinatal health.<sup>35</sup> Understanding the specific risk factors for preeclampsia in this population is essential for developing targeted prevention and management strategies.

In Sudan, where maternal and perinatal morbidity and mortality rates remain high,<sup>35</sup> understanding the local risk factors for preeclampsia is crucial for developing targeted interventions. Gadarif State in eastern Sudan faces unique challenges in the provision of maternal healthcare, and the prevalence and risk factors for preeclampsia in this region require specific investigation. It is essential to emphasize the inconsistent results across previous studies on the association between folic acid supplementation and preeclampsia, underscoring the need for context-specific research. Thus, this study investigates the association between periconceptional [before conception/pregnancy (preconception) through the first trimester (around 10–14 weeks)] folic acid supplementation and the risk of preeclampsia among women treated at Gadarif Maternity Hospital in Gadarif, eastern Sudan.

## Methods

### Study Design and Setting

This unmatched case-control study was conducted between June and December 2024 at Gadarif Maternity Hospital in Gadarif, Eastern Sudan. Gadarif is one of Sudan's 18 states; it has 2.5 million inhabitants.<sup>36</sup> Gadarif City is the capital of Gadarif State. Gadarif Maternity Hospital is located in the center of Gadarif City and is the main referral hospital for maternity care in Gadarif State. This governmental hospital provides obstetrical and gynecological services for all women, regardless of their residency in Gadarif State or in nearby states.

## Participants

The cases were pregnant women diagnosed with preeclampsia.<sup>37</sup> *Preeclampsia* is defined as follows:[the] occurrence of systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg on two occasions at least four hours apart in previously normotensive women with one of the following new-onset conditions at or after 20 weeks of gestation: proteinuria ( $\geq 30$  mg/mol protein or creatinine ratio;  $\geq 300$  mg/24 hour or  $\geq 2+$  dipstick), maternal organ dysfunction (eg, acute kidney injury, liver involvement, neurological complications, hematologic complications [platelets count  $< 150,000/\mu\text{L}$ ], disseminated intravascular coagulation, and hemolysis), and uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth).<sup>37</sup>

Cases were consecutively recruited upon diagnosis. The controls were pregnant women without preeclampsia or other diseases who delivered at the same hospital during the study period. One control was recruited for each case.

## Inclusion and Exclusion Criteria

In this case-control study, all pregnant women (gestational age  $> 20$  weeks) who attended the hospital were approached to participate after receiving full explanations of the study's objectives and all related ethical issues. After signing an informed consent form, all Sudanese pregnant women with singleton pregnancies were enrolled. Women who refused to give written informed consent and women with comorbidities, such as diabetes mellitus, chronic hypertension, renal disease, and thyroid disease, were excluded from the cases and the controls. Based on clinical examination, blood pressure, and laboratory tests (ie, the presence or absence of preeclampsia), a woman was categorized as a case or a control. During the study period, the desired sample size was achieved.

## Data Collection

In this study, the authors followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>38</sup> Data were collected using a structured questionnaire administered through face-to-face interviews with trained female medical officers. The questionnaire was developed based on similar studies.<sup>8,10,11,15,17,30</sup> The collected data included sociodemographic characteristics, such as maternal age in years, residence (urban or rural), internal displacement, couples' education, and maternal occupation. Medical histories included periconceptional folic acid supplementation (defined as taking folic acid supplements before conception and/or taking them in the first trimester) and preexisting medical conditions. Current pregnancy details comprised gravidity, maternal blood group, ANC attendance, and maternal height and weight, later expressed as a body mass index (BMI) category (underweight [ $< 18.5$  kg/m<sup>2</sup>], normal weight [ $18.5$ – $24.9$  kg/m<sup>2</sup>], overweight [ $25$ – $29.9$  kg/m<sup>2</sup>], and obese [ $\geq 30$ ] kg/m<sup>2</sup>).<sup>39</sup> Clinical measurements entailed weight and height. Periconceptional folic acid supplementation was assessed by direct questioning and, when possible, verified through ANC records or supplement packaging. Hemoglobin was measured by automated analysis (Sysmex KX-21, Japan), and anemia was defined as a hemoglobin level less than 11 g/dl.

## Sample Size Calculation

A total of 254 participants (pregnant women) were included in each study group (127 with preeclampsia vs 127 without preeclampsia) at a 1:1 ratio. This assumption was informed by Wang et al, who reported a lack of periconceptional folic acid supplementation of 33% in women with preeclampsia and 20% in those without.<sup>11</sup> Non-folic acid users are highly vulnerable to preeclampsia in African contexts, such as in the authors' neighboring Ethiopia.<sup>8</sup> The authors assumed that 37% of non-users might have preeclampsia compared to 21% of users. The sample size of 127 participants in each group was determined to detect a 5% difference at  $\alpha = 0.05$  with 80% power.

## Statistical Analysis

The data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 22.0 (SPSS Inc., New York, United States). Before the analysis, the data were double-entered and cross-checked to ensure accuracy. The proportions were expressed as frequencies (%). Continuous variables, such as age, hemoglobin, and BMI, were summarized as means with standard deviations (SDs), and categorical variables were summarized as frequencies

and percentages. Univariate binary analysis was performed with preeclampsia as the dependent variable. Sociodemographic variables were used as independent variables. These sociodemographic variables included age, BMI, residence, educational level, and occupation. Obstetrical variables included gravidity, maternal anemia, maternal overweight/obesity, maternal blood group, and periconceptional folic acid supplementation. Variables with a p-value  $\leq 0.20$  in univariate analyses were selected for multivariate binary analyses, with the model adjusted for covariates. AORs and 95% CIs were calculated to assess the strength and direction of the association. A two-sided P-value of  $<0.05$  was considered statistically significant.

## Results

In this study, 127 pregnant women (preeclampsia and controls) were enrolled in each arm of the study (preeclampsia and controls). Pregnant women with preeclampsia were younger ( $<30$  years) than the controls, 76 (59.8%) vs 58 (45.7%),  $p = 0.024$ ; had primigravida, 67 (52.8%) vs 21 (16.5%),  $p = <0.001$ ; were likelier to be overweight, 61 (48.0%) vs 50 (39.4%)  $p = 0.007$ ; and were obese, 49 (38.6%) vs 41 (32.3%),  $p = 0.010$ , compared to the controls, respectively. Notably, women with preeclampsia were less likely to have used periconceptional folic acid supplementation (12 [9.4%] 26 vs [20.5%],  $p = 0.016$ ). However, there was no significant difference between the two groups regarding residence, internal displacement, couples' education, maternal occupation, maternal blood group, ANC, anemia, or the number of fetuses in the current pregnancy (Table 1).

The univariate binary analysis revealed that maternal age, gravidity (primigravida), overweight/obesity, and periconceptional folic acid supplementation were significantly associated with preeclampsia ( $p < 0.05$ ). However, residence, internal displacement, couples' education, maternal occupation, maternal blood group, ANC, anemia, and the number of fetuses in the current pregnancy were not associated with preeclampsia ( $p\text{-value} > 0.05$ ). See Table 1.

**Table 1** Univariate Binary Analysis of the Factors Associated with Preeclampsia Among Pregnant Women, Eastern Sudan, 2024 (n = 254)

| Variable                     |              | Women with Preeclampsia, the Cases (Number = 127) | Women without Preeclampsia, the Control Group (Number = 127) | Odds Ratio (95.0% Confidence Interval) | P      |
|------------------------------|--------------|---------------------------------------------------|--------------------------------------------------------------|----------------------------------------|--------|
|                              |              | Frequency (Percentage)                            |                                                              |                                        |        |
| Age                          | ≥30 years    | 51 (40.2)                                         | 69 (54.3)                                                    | Reference                              |        |
|                              | <30 years    | 76 (59.8)                                         | 58 (45.7)                                                    | 1.77 (1.07–2.91)                       | 0.024  |
| Gravidity                    | Multigravida | 60 (47.2)                                         | 106 (83.5)                                                   | Reference                              |        |
|                              | Primigravida | 67 (52.8)                                         | 21 (16.5)                                                    | 5.63 (3.14–10.10)                      | <0.001 |
| Residence                    | Urban        | 57 (44.9)                                         | 67 (52.8)                                                    | Reference                              |        |
|                              | Rural        | 70 (55.1)                                         | 60 (47.2)                                                    | 1.37 (0.83–2.24)                       | 0.210  |
| Internal displacement        | No           | 105 (82.7)                                        | 110 (86.6)                                                   | Reference                              |        |
|                              | Yes          | 22 (17.3)                                         | 17 (13.4)                                                    | 1.35 (0.68–2.69)                       | 0.385  |
| Maternal education level     | >Secondary   | 34 (26.8)                                         | 43 (33.9)                                                    | Reference                              |        |
|                              | ≤Secondary   | 93 (73.2)                                         | 84 (66.1)                                                    | 1.40 (0.81–2.39)                       | 0.220  |
| Maternal occupational status | Employed     | 17 (13.4)                                         | 24 (18.9)                                                    | Reference                              |        |
|                              | Housewife    | 110 (86.6)                                        | 103 (81.1)                                                   | 1.50 (0.76–2.96)                       | 0.235  |

(Continued)

**Table 1** (Continued).

| Variable                                    |               | Women with Preeclampsia, the Cases (Number = 127) | Women without Preeclampsia, the Control Group (Number = 127) | Odds Ratio (95.0% Confidence Interval) | P     |
|---------------------------------------------|---------------|---------------------------------------------------|--------------------------------------------------------------|----------------------------------------|-------|
|                                             |               | Frequency (Percentage)                            |                                                              |                                        |       |
| Periconceptional folic acid supplementation | Yes           | 101 (79.5)                                        | 115 (90.6)                                                   | Reference                              |       |
|                                             | No            | 26 (20.5)                                         | 12 (9.4)                                                     | 2.46 (1.18–5.14)                       | 0.016 |
| Antenatal care                              | Adequate      | 12 (9.4)                                          | 15 (11.8)                                                    | Reference                              |       |
|                                             | Non adequate  | 115 (90.6)                                        | 112 (88.2)                                                   | 1.28 (0.57–2.86)                       | 0.542 |
| Body mass index groups                      | Normal weight | 17 (13.4)                                         | 36 (28.3)                                                    | Reference                              |       |
|                                             | Overweight    | 61 (48.0)                                         | 50 (39.4)                                                    | 2.58 (1.29–5.13)                       | 0.007 |
|                                             | Obese         | 49 (38.6)                                         | 41 (32.3)                                                    | 2.53 (1.24–5.15)                       | 0.010 |
| Blood groups                                | Not group O   | 81 (63.8)                                         | 78 (61.4)                                                    | Reference                              |       |
|                                             | O             | 46 (36.2)                                         | 49 (38.6)                                                    | 0.90 (0.54–1.50)                       | 0.697 |
| Anemia                                      | No            | 63 (49.6)                                         | 76 (59.8)                                                    | Reference                              |       |
|                                             | Yes           | 64 (50.4)                                         | 51 (40.2)                                                    | 1.51 (0.92–2.48)                       | 0.102 |

The results of the multivariate binary analysis showed that primigravida was significantly associated with an increased odds of preeclampsia (AOR = 6.20, 95% CI 3.16–12.14). Not taking periconceptional folic acid supplementation was independently associated with a more than twofold increased odds of preeclampsia (AOR = 2.24, 95% CI 1.02–4.96), and being anemic was associated with an increased risk of preeclampsia (AOR = 1.94, 95% CI 1.10–3.40). See [Table 2](#). Interestingly, after adjusting for other variables, including maternal age and overweight or obesity, which

**Table 2** Multivariate Binary Analysis of the Factors Associated with Preeclampsia Among Pregnant Women in Eastern Sudan, 2024 (n = 254)

| Variable                                    |               | Adjusted Odds Ratio | 95% Confidence Interval | P Value |
|---------------------------------------------|---------------|---------------------|-------------------------|---------|
| Age                                         | ≥30 years     | Reference           |                         |         |
|                                             | <30 years     | 0.83                | 0.45–1.55               | 0.576   |
| Gravidity                                   | Multigravida  | Reference           |                         |         |
|                                             | Primigravida  | 6.20                | 3.16–12.14              | <0.001  |
| Body mass index groups                      | Normal weight | Reference           |                         |         |
|                                             | Overweight    | 2.06                | 0.97–4.40               | 0.060   |
|                                             | Obese         | 1.81                | 0.81–4.03               | 0.142   |
| Anemia                                      | No            | Reference           |                         |         |
|                                             | Yes           | 1.94                | 1.10–3.40               | 0.020   |
| Periconceptional folic acid supplementation | Yes           | Reference           |                         |         |
|                                             | No            | 2.24                | 1.02–4.96               | 0.045   |

were significant in the univariate binary analysis, these factors were no longer independently associated with preeclampsia in the multivariate analysis. This suggests that other factors might have confounded their effects or that they acted through pathways captured by the independently significant variables.

## Discussion

The study's findings revealed an inverse association, indicating that adequate periconceptional folic acid intake protects against preeclampsia in this population. Specifically, not taking periconceptional folic acid supplementation independently increased the odds of preeclampsia by more than twofold. This supports a growing body of evidence suggesting that folic acid has a beneficial effect on preventing preeclampsia.<sup>8,10,11</sup> However, some studies have reported contradictory results.<sup>15–17</sup> In Ethiopia, an unmatched case-control study was conducted among 453 pregnant women (151 cases and 302 controls). According to this study, compliance with folic acid intake during pregnancy has a significant independent effect on the prevention of preeclampsia (AOR = 0.16, 95% CI: 0.08–0.29).<sup>8</sup> In China, Wang et al reported that compared to non-users, folic acid supplement users had a reduced risk of preeclampsia (AOR = 0.61, 95% CI: 0.43–0.87).<sup>11</sup>

Such contradictory results, even between systematic review and meta-analysis studies regarding the influence of folic acid on preeclampsia, could be explained by the time of starting folic acid, that is, pre- or postconception, or both, as in this study. Early and adequate folic acid supplementation can support optimal placental development, improve endothelial functioning, and reduce oxidative stress, thereby preventing the cascade of events that lead to preeclampsia.<sup>4,5</sup> Given that abnormal placentation often begins in the first trimester, the “periconceptional” period of supplementation is crucial, underscoring its potential to influence early developmental processes. However, most previous studies have focused on folic acid during early pregnancy rather than before conception, such as one study in China similar to this study.<sup>11</sup> Importantly, folic acid supplementation is essential for childbearing women before conception and during the first trimester of pregnancy.<sup>5</sup> Folic acid plays a crucial role in several biochemical processes necessary for healthy pregnancy outcomes, including the prevention of preeclampsia. The mechanisms by which folic acid supplementation is thought to reduce the risk of preeclampsia are multifaceted and primarily involve its role in one-carbon metabolism, endothelial functioning, and placental development. One of the commonly accepted mechanisms is the reduction of homocysteine levels.<sup>9</sup> Folic acid is an essential cofactor in the remethylation of homocysteine to methionine. High homocysteine (hyperhomocysteinemia) is recognized as an independent risk factor for preeclampsia. High homocysteine levels can lead to endothelial dysfunction, oxidative stress, and impaired nitric oxide bioavailability, all of which contribute to the abnormal vascular changes seen in preeclampsia.<sup>9,13</sup> By ensuring an adequate folate status, supplementation helps maintain normal homocysteine levels, thereby protecting the integrity of the maternal vasculature and improving blood flow to the placenta. Second, folic acid contributes to improving endothelial functioning.<sup>18</sup> Preeclampsia is characterized by widespread maternal endothelial dysfunction.<sup>19</sup> Folic acid has been shown to enhance the production and bioavailability of nitric oxide, a potent vasodilator, by increasing the availability of its cofactor, tetrahydrobiopterin.<sup>20</sup> Nitric oxide helps to relax blood vessels, regulate blood pressure, and improve blood flow.<sup>21</sup> By promoting nitric oxide synthesis and reducing the oxidative stress that can inactivate nitric oxide, folic acid helps maintain healthy vascular tone and prevents the vasoconstriction characteristic of preeclampsia. Finally, optimal placental development is crucial. Abnormal trophoblast invasion and impaired spiral artery remodeling during early pregnancy are fundamental for the pathogenesis of preeclampsia.<sup>22</sup> Folic acid is essential for rapid cell division, DNA synthesis, and methylation processes, which are crucial for the proper proliferation and invasion of the trophoblast into the maternal decidua.<sup>4,5</sup> Adequate periconceptional folic acid may support these early developmental processes, ensure proper placental formation and establish a robust uteroplacental blood supply, thus reducing the risk of subsequent placental ischemia and the release of the anti-angiogenic factors associated with preeclampsia. Williams et al also suggested a role in promoting placental angiogenesis.<sup>4</sup> Therefore, folic acid supplementation may reduce the risk of preeclampsia by lowering detrimental homocysteine levels, improving maternal endothelial functioning, and supporting healthy early placental development, all of which contribute to better uteroplacental perfusion and a reduced inflammatory response.

Besides folic acid, our study identified primigravidity as an independent and influential risk factor for preeclampsia. This finding is consistent with established epidemiological evidence in SSA, as primigravidae are known to have a higher risk of preeclampsia than multiparous women.<sup>1,28,29</sup> Our previous study in central Sudan included 54,339 singleton



deliveries of; 1,765 women with preeclampsia (giving a 3.2% incidence of preeclampsia) reported that primiparity (AOR = 3.3, 95% CI: 2.7–4.0) and anemia (AOR = 3.3, 95% CI: 2.8–3.9) were risk factors for preeclampsia.<sup>28</sup> This increased risk in first pregnancies is often attributed to the initial immunological adaptation to paternal antigens and the establishment of placental circulation.

Interestingly, in this study, anemia also emerged as an independent risk factor for preeclampsia. The relationship between anemia and preeclampsia is complex and bidirectional. Likewise, other studies from different contexts, including Sudan, have reported similar results.<sup>28,29,40</sup> For instance, our previous study in eastern Sudan revealed that severe anemia is associated with a higher risk for preeclampsia and poor perinatal outcomes.<sup>40</sup> This may indicate the close relationship between a lack of folic acid supplementation and anemia. In SSA, meta-analysis studies revealed that women who knew about anemia were 5.42 times likelier to exhibit compliance with iron and folic acid supplementation (IFAS) than those who had no knowledge of anemia.<sup>41</sup> Women who had no IFAS were almost two times likelier to develop anemia than those women who had IFAS.<sup>42</sup> In addition, our previous studies in central Sudan reported that using IFAS protected against anemia.<sup>43,44</sup> This finding underscores the importance of addressing nutritional deficiencies, including IFAS and anemia, as part of the comprehensive ANC in this region.

In addition, our univariate binary analysis showed that younger maternal age and being overweight or obese were associated with preeclampsia. However, these associations lost their significance in the multivariate binary analysis after adjusting for other variables. This suggests that their effects might be confounded by or mediated through other factors, such as primigravida status, unmeasured lifestyle factors, or sample size. However adequate, the primary outcome may not have been sufficient to reveal the independent effects of these secondary variables after extensive adjustment. For example, younger women are often primigravidae, and obesity is a known risk factor for various pregnancy complications, including preeclampsia.<sup>26,32</sup> Nevertheless, in this specific population, the independent contribution was not sustained. It is essential to mention that this study found no significant association between various sociodemographic and obstetric factors with the development of preeclampsia among the pregnant women studied. Such factors included age, residence, BMI, ANC, couples' education and occupation, and maternal blood group. Some of these factors, including age,<sup>25–28</sup> parity,<sup>28,29</sup> education,<sup>28,30</sup> occupation,<sup>27</sup> inadequate ANC,<sup>29,31</sup> maternal blood group,<sup>31</sup> high maternal BMI,<sup>26,32</sup> and multiple gestational pregnancies,<sup>30</sup> have been implicated in preeclampsia risks in other populations. Such contradictory results with this specific study population in eastern Sudan could be attributed to variations in the measurement of the studied variables' quality, such as education and ANC. That is, both education and ANC were measured in terms of how many years of education the women achieved and how many visits to ANC they made rather than the time of ANC initiation and the component of these essential variables. For example, in African contexts, including Sudan, maternal education did not influence the occurrence of preeclampsia and was less likely to be reflected in the workforce.<sup>29–31,34</sup>

## Implications of the Study

The findings of this study have direct implications for improving maternal and perinatal health in Gadarif, Eastern Sudan. Although the risk factors identified, such as a lack of folic acid supplementation and anemia, represent public health problems in Sudan,<sup>24,40,45</sup> they are preventable. For example, our systematic review and meta-analysis reported a high prevalence of anemia among pregnant women in Sudan, at 53.0% (95% CI = 45.9–60.1).<sup>45</sup> Given that not taking periconceptional folic acid supplementation significantly increases the risk of preeclampsia, healthcare providers at Gadarif Maternity Hospital should intensify their efforts to counsel all women of reproductive age about the importance of folic acid before and during early pregnancy. Targeted public health campaigns can promote the widespread use of folic acid. Furthermore, as primigravida and anemic women are at a higher risk, these groups require closer monitoring and prioritized interventions, including robust ANC to screen for and manage anemia effectively. Integrating these simple, cost-effective strategies into routine maternal healthcare is crucial for reducing preeclampsia rates and improving pregnancy outcomes in the region.

## Strengths and Limitations

Although this study offers valuable insights, it has limitations. One of the study's key strengths lies in its case-control design, which is well-suited to investigating rare outcomes, such as preeclampsia, and allows efficient recruitment of a sufficient number of cases (127 in this instance). This design is particularly valuable in resource-limited settings, where large prospective cohort studies might be impractical, especially during the ongoing war. Using a control group from the same hospital helped minimize selection bias, ensuring that both cases and controls were drawn from the same source population. The systematic collection of data from a major referral hospital enhances the representativeness of the findings for eastern Sudan. The inclusion of a diverse range of sociodemographic, obstetric, and clinical variables allowed a comprehensive assessment of potential risk factors. Crucially, the application of both univariate and multivariate binary analyses is a significant strength. By performing multivariate binary analysis, the authors were able to adjust for potential confounding factors, isolating the independent effects of primigravida status, periconceptional folic acid supplementation, and anemia on the risk of preeclampsia. This rigorous statistical approach provides greater confidence in the identified associations, particularly the independent protective effect of folic acid and the increased risk associated with primigravida status and anemia. The findings regarding primigravida status and anemia align with established knowledge,<sup>8,28,29</sup> reinforcing the study's validity in identifying known risk factors. Despite these strengths, the present study has limitations that must be mentioned to improve future research. The study used a single-center design at Gadarif Maternity Hospital, which is practical but limits the generalizability of the findings to the broader Sudanese population or to other healthcare settings. The observed associations might be specific to the patient population and the healthcare practices prevalent at this particular hospital. The data/information from the self-reported supplement use could enhance contextualization but introduce recall bias. The research did not take into account or regulate some possible confounders that might be relevant, eg, dietary folate intake, adherence patterns, and ANC initiation timing; consequently, internal validity might be reduced. While the multivariate analysis was adjusted for several confounders, unmeasured or residual confounding may still influence the results.<sup>6</sup> For example, socioeconomic factors not fully captured by "couples' education" or "maternal occupation" could play a role. The observation that overweight/obesity was not independently associated with preeclampsia in the multivariate binary analysis, despite being a well-known global risk factor,<sup>1</sup> might suggest confounding by other factors or a unique local context that warrants further investigation. Therefore, a prospective longitudinal study involving multiple centers and providing in-depth information on dietary patterns and socioeconomic factors is required to overcome these limitations.

## Conclusion

This case-control study revealed a significant inverse association between periconceptional folic acid supplementation and the risk of preeclampsia among pregnant women in eastern Sudan. Our findings demonstrate that not taking periconceptional folic acid supplementation independently increased the odds of preeclampsia by more than twofold. This strongly suggests the protective role of early folic acid intake in preventing this severe pregnancy complication in this population. Beyond folic acid, primigravida emerged as a robust independent risk factor, increasing the odds of preeclampsia by more than six times. Anemia also depicted a significant association, nearly doubling the risk. These findings highlight the importance of promoting early and consistent periconceptional folic acid supplementation as a simple, affordable, and effective public health intervention to reduce the burden of preeclampsia in eastern Sudan. Emphasis should also be placed on identifying and managing primigravid women and addressing anemia during pregnancy. Furthermore, studies exploring the interplay between folic acid, anemia, and preeclampsia would provide deeper insights into their complex relationships.

## Data Sharing Statement

The data supporting the current study's findings are available from the corresponding author upon reasonable request.



## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Faculty of Medicine, University of Gadarif, Eastern Sudan. The reference number is # 11,2023. Written informed consent was obtained from all the enrolled women in accordance with the Human Rights Declaration of Helsinki.

## Acknowledgment

We would like to thank the women who participated in the study. The researchers would like to thank the Deanship of Graduate Studies and Scientific Research at Qassim University for financial support (QU-APC-2026).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

There is no funding to report.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. World Health Organization. Pre-eclampsia. Available from: <https://www.who.int/news-room/fact-sheets/detail/pre-eclampsia>. Accessed 25 October 2025.
2. Cresswell JA, Alexander M, Chong MYC, et al. Global and regional causes of maternal deaths 2009–2020: a WHO systematic analysis. *Lancet Glob Heal*. 2025;626–634. doi:10.1016/S2214-109X(24)00560-6.
3. Jikamo B, Adefris M, Azale T, Alemu K. Incidence, trends and risk factors of preeclampsia in sub-Saharan Africa: a systematic review and meta-analysis. *PAMJ-One Heal*. 2023;11(1):1. doi:10.11604/PAMJ-OH.2023.11.1.39297
4. Williams PJ, Bulmer JN, Innes BA, Pipkin FB. Possible roles for folic acid in the regulation of trophoblast invasion and placental development in normal early human pregnancy. *Biol Reprod*. 2011;84(6):1148–1153. doi:10.1095/biolreprod.110.088351
5. Tola FS. The concept of folic acid supplementation and its role in prevention of neural tube defect among pregnant women: PRISMA. *Med*. 2024;103(19):E38154. doi:10.1097/MD.00000000000038154
6. Kinshella MLW, Pickerill K, Bone JN, et al. An evidence review and nutritional conceptual framework for pre-eclampsia prevention. *Br J Nutr*. 2023;130(6):1065–1076. doi:10.1017/S0007114522003889
7. Wantong H, Meng W, Zhang J, Jin L, Jin L. Periconceptional supplementation with folic acid or multiple micronutrients containing folic acid and the risk for hypertensive disorders in pregnancy. *Med Princ Pract*. 2024;33:578–586. doi:10.1159/000540322
8. Endeshaw M, Abebe F, Bedimo M, Asart A. Diet and Pre-eclampsia: a Prospective Multicentre Case-Control Study in Ethiopia. *Midwifery*. 2015;31(6):617–624. doi:10.1016/j.midw.2015.03.003
9. Kaldygulova L, Ukybassova T, Aimagambetova G, Gaiday A, Tussupkaliyev A. Biological Role of Folic Acid in Pregnancy and Possible Therapeutic Application for the Prevention of Preeclampsia. *Biomedicines*. 2023;11(2):272. doi:10.3390/biomedicines11020272
10. Liu C, Liu C, Wang Q, Zhang Z. Supplementation of folic acid in pregnancy and the risk of preeclampsia and gestational hypertension: a meta-analysis. *Arch Gynecol Obstet*. 2018;298(4):697–704. doi:10.1007/s00404-018-4823-4
11. Wang Y, Zhao N, Qiu J, et al. Folic acid supplementation and dietary folate intake, and risk of preeclampsia. *Eur J Clin Nutr*. 2015;69(10):1145–1150. doi:10.1038/ejcn.2014.295
12. World Health Organization. *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. 2016.
13. Lai WKC, Kan MY. Homocysteine-induced endothelial dysfunction. *Ann Nutr Metab*. 2015;67(1):1–12. doi:10.1159/000437098
14. Cotter AM, Molloy AM, Scott JM, Daly SF. Elevated plasma homocysteine in early pregnancy: a risk factor for the development of severe preeclampsia. *Am J Obstet Gynecol*. 2001;185(4):781–785. doi:10.1067/mob.2001.117304
15. Asres AW, Samuel S, Daga WB, et al. Association between iron-folic acid supplementation and pregnancy-induced hypertension among pregnant women in public hospitals, Wolaita Sodo, Ethiopia 2021: a case-control study. *BMC Public Health*. 2023;23(1):843. doi:10.1186/s12889-023-15794-6
16. Li Z, Ye R, Zhang L, Li H, Liu J, Ren A. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. *Hypertension*. 2013;61(4):873–879. doi:10.1161/HYPERTENSIONAHA.111.00230
17. Cui H, Zhang N, An JL, et al. Maternal folic acid supplementation to prevent preeclampsia: a systematic review and meta-analysis. *Complement Ther Med*. 2024;82(November 2023):103052. doi:10.1016/j.ctim.2024.103052
18. Doshi SN, McDowell IFW, Moat SJ, et al. Folic acid improves endothelial function in coronary artery disease via mechanisms largely independent of homocysteine lowering. *Circulation*. 2002;105(1):22–26. doi:10.1161/hc0102.101388
19. George EM, Granger JP. Endothelin: key mediator of hypertension in preeclampsia. *Am J Hypertens*. 2011;24(9):964–969. doi:10.1038/ajh.2011.99

20. Chalupsky K, Kračun D, Kanchev I, Bertram K, Görlach A. Folic Acid Promotes Recycling of Tetrahydrobiopterin and Protects Against Hypoxia-Induced Pulmonary Hypertension by Recoupling Endothelial Nitric Oxide Synthase. *Antioxid Redox Signal*. 2015;23(14):1076–1091. doi:10.1089/ars.2015.6329
21. Houston M, Hays L. Acute Effects of an Oral Nitric Oxide Supplement on Blood Pressure, Endothelial Function, and Vascular Compliance in Hypertensive Patients. *J Clin Hypertens*. 2014;16(7):524–529. doi:10.1111/jch.12352
22. Rana S, Lemoine E, Granger J, Karumanchi SA. Preeclampsia: pathophysiology, Challenges, and Perspectives. *Circ Res*. 2019;124(7):1094–1112. doi:10.1161/CIRCRESAHA.118.313276
23. Aweke MN, Fentie EA, Agimas MC, et al. Folic acid supplementation during preconception period in sub-Saharan African countries: a systematic review and meta-analysis. *PLoS One*. 2025;20(1):e0318422. doi:10.1371/journal.pone.0318422
24. Hassan AA, Hassan AM, Bashir AO, Adam GK, AlHabardi N, Adam I. Periconceptional folic acid usage and its associated factors in eastern Sudan: a cross-sectional study. *Women's Heal*. 2024;20:17455057231224176. doi:10.1177/17455057231224176
25. Cho JJ, Kim YY, Min KJ, et al. Prior cesarean section is associated with increased preeclampsia risk in a subsequent pregnancy. *BMC Pregnancy Childbirth*. 2015;15(1):24. doi:10.1186/s12884-015-0447-x
26. Saadat M, Nejad SM, Habibi G, Sheikhatvan M. Maternal and neonatal outcomes in women with preeclampsia. *Taiwan J Obstet Gynecol*. 2007;46(3):255–259. doi:10.1016/S1028-4559(08)60029-7
27. Kassa BG, Asnkew S, Ayele AD, Nigussie AA, Demilew BC, Mihirete GN. Preeclampsia and its determinants in Ethiopia: a systematic review and meta-analysis. *PLoS One*. 2023;18(11 November):e0287038. doi:10.1371/journal.pone.0287038
28. Adam I, Haggaz AED, Mirghani OA, Elhassan EM. Placenta previa and pre-eclampsia: analyses of 1645 cases at Medani Maternity Hospital, Sudan. *Front Physiol*. 2013;4:32. doi:10.3389/fphys.2013.00032
29. Meazaw MW, Chojenta C, Muluneh MD, Loxton D. Systematic and meta-analysis of factors associated with preeclampsia and eclampsia in sub-Saharan Africa. *PLoS One*. 2020;15(8):e0237600. doi:10.1371/journal.pone.0237600
30. Wolie Asres A, Tilahun AW, Addissie A. Factors associated with preeclampsia among pregnant women in Gojjam zones, Amhara region, Ethiopia: a case-control study. *Blood Press*. 2023;32(1). doi:10.1080/08037051.2023.2255687
31. Elmugabil A, Rayis DA, Ahmed MAM, Adam I, Gasim GI. O blood group as risk factor for preeclampsia among Sudanese women. *Maced J Med Sci*. 2016;4(4):603–606. doi:10.3889/oamjms.2016.108
32. Adam I, Elmugabil A, AlHabardi N. History of maternal migraine and its association with preeclampsia: a case-control study in a low-resource setting in Sudan, Africa. *Cephalalgia*. 2023;43(8):3000605231193823. doi:10.1177/03331024231196303
33. Adam GK, Bakheit KH, Adam I. Maternal and perinatal outcomes of eclampsia in Gadarif hospital, Sudan. *J Obstet Gynaecol*. 2009;29(7). doi:10.1080/01443610903150802
34. Adam I, Rayis DA, Alhabardi NA, Ahmed ABA, Sharif ME, Elbashir MI. Association between breastfeeding and preeclampsia in parous women: a case-control study. *Int Breastfeed J*. 2021;16(1):48.
35. Hassan AA, Adam I, Husain NE. War in Sudan: the impact on maternal and perinatal health. *Sudan J Med Sci*. 2023;18(3):268–271. doi:10.18502/sjms.v18i3.14094
36. UNICEF. Situation in Gedaref. 2022. Available from: <https://www.unicef.org/sudan/media/8651/file/Gedaref.pdf>. Accessed December 25, 2023.
37. ACOG Committee on Practice B. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol*. 2020;135(6):e237–e260. doi:10.1097/AOG.0000000000003891.
38. Cuschieri S. The STROBE guidelines. *Saudi J Anaesth*. 2019;13(Suppl 1):S31–S34. doi:10.4103/sja.SJA\_543\_18
39. WHO. Global Database on Body Mass Index. Available from: [http://apps.who.int/bmi/index.jsp?introPage=intro\\_3.html](http://apps.who.int/bmi/index.jsp?introPage=intro_3.html). Accessed December 28, 2016.
40. Ali AA, Rayis DA, Abdallah TM, Elbashir MI, Adam I. Severe anaemia is associated with a higher risk for preeclampsia and poor perinatal outcomes in Kassala hospital, eastern Sudan. *BMC Res Notes*. 2011;4. doi:10.1186/1756-0500-4-311.
41. Fite MB, Roba KT, Oljira L, Tura AK, Yadeta TA. Compliance with iron and folic acid supplementation (IFAS) and associated factors among pregnant women in Sub-Saharan Africa: a systematic review and metaanalysis. *PLoS One*. 2021;16(4 April):e0249789. doi:10.1371/journal.pone.0249789
42. Fite MB, Assefa N, Mengiste B. Prevalence and determinants of Anemia among pregnant women in sub-Saharan Africa: a systematic review and Meta-analysis. *Arch Public Heal*. 2021;79(1):219. doi:10.1186/S13690-021-00711-3
43. Abdullahi H, Gasim GI, Saeed A, Imam AM, Adam I. Antenatal iron and folic acid supplementation use by pregnant women in Khartoum, Sudan. *BMC Res Notes*. 2014;7(1):498. doi:10.1186/1756-0500-7-498
44. Elmugabil A, Adam I. Prevalence and Associated Risk Factors for Anemia in Pregnant Women in White Nile State, Sudan: a Cross-Sectional Study. *SAGE open Nurs*. 2023;9. doi:10.1177/23779608231173287.
45. Adam I, Ibrahim Y, Elhardello O. Prevalence, types and determinants of anemia among pregnant women in Sudan: a systematic review and meta-analysis. *BMC Hematol*. 2018;18(1):31. doi:10.1186/s12878-018-0124-1

## International Journal of Women's Health

### Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, editorials, reviews and commentaries on all aspects of women's healthcare including gynecology, obstetrics, and breast cancer. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-womens-health-journal>

**Dovepress**  
Taylor & Francis Group