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A systematic review of association between vitamin D levels and pre-eclampsia in pregnant womens - An old problem revisited

Lata Kanyal Butola*[1], Anjali Vagga[1], Ranjit Ambad[2], Deepika Kanyal[3], Jayshri Jankar[1]

[1]Department of Biochemistry, Jawaharlal Nehru Medical College, DMIMS, Sawangi, Meghe, Wardha, Maharashtra, India
[2]Department of Biochemistry, Datta Meghe Medical Sciences, Wanadongri, Nagpur, Maharashtra, India
[3]Department of Hospital Administration, Jawaharlal Nehru Medical College, DMIMS, Sawangi, Meghe, Wardha, Maharashtra, India

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ABSTRACT

The beneficial effects of sunlight in preventing bone-related disorders have been well-known for centuries. Vitamin D is a modified steroid, synthesised under the influence of sunlight in the skin. Low Vitamin D status has associated with a higher risk of pre-eclampsia in pregnant womens. The aim of this study was to undertake a systematic review of different studies investigating the association between Vitamin D levels and pre-eclampsia in pregnant womens. A systematic review was undertaken. MEDLINE, PUBMED, EMBASE, Google Scholar were searched. The review protocol was designed to answer the question. Search terms (Preeclampsia and Vitamin D or 1,25 dihydroxy vitamin D). The search was confined to peer-reviewed articles that were published in English and contained an abstract. Reference list of journal articles were also screened for additional citations fitting our search criteria. Twenty-Seven studies were included in the systematic review that investigates the association between Vitamin D and pre-eclampsia. The present systematic review concludes that maternal vitamin D deficiency in pregnancy is significantly associated with an elevated risk of preeclampsia. Pregnant womens should take vitamin D supplementation, expose themselves into the sunlight, and they should be physically active. Further taking Vitamin D supplementation in early pregnancy may be a simple way to reduce the risk of these adverse pregnancy outcomes.

*Corresponding Author

Name: Lata Kanyal Butola
Phone: +91-7892390212
Email: Kanyallata1010@gmail.com

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INTRODUCTION

Vitamin D is endogenously produced by the exposure of skin to sunlight, and it gets absorbed from the foods containing or supplemented with Vitamin D. Vitamin D is a group of steroid hormones originating from both diet and sunlight, and it also plays an important role in immunity and many aspects of cell functioning, and it is necessary for calcium and phosphorous metabolism. Vitamin D3, which is derived from skin synthesis by exposure to 7-dehydrocholesterol, concentrated in the basal and stratum spinosum stratums, to ultraviolet B (UV-B) radiation, is the main source of

Vitamin D in humans (~90 percent). (Rafi, 2014; Dhok *et al.*, 2020). Vitamin D is hydroxylated to form 25 hydroxyvitamin D [25(OH) vitamin D] in the liver. (Hollis, 2005) Maternal vitamin D deficiency is a popular public concept Decreased rates of low vitamin D status are found worldwide in pregnant mothers. (Halicioglu *et al.*, 2012) The major causes of deficiency are poor nutrition, lack of exposure to sunlight, decreased vitamin D synthesis. (Gusain and Butola, 2020) Vitamin D has been correlated with numerous pregnancy developments, such as gene regulation and early placental pregnancy expression, fetomaternal immunological tolerance, and anti-inflammatory responses. (Shin *et al.*, 2010) Vitamin D deficiency is recognized as a global health issue in the world. (Jha *et al.*, 2020) In terms of its involvement in preeclampsia-associated pathophysiology, vitamin D deficiency has recently become more acute. (Hyppönen *et al.*, 2013) Vitamin D has an immunosuppressive role in modulating pro-inflammatory reactions and reducing oxidative stress in PE, promoting angiogenesis through vascular endothelial growth factor (VEGF) and gene regulation, and reducing blood pressure through the renin-angiotensin system. It has been documented that vitamin D deficiency in healthy women is correlated with increased secretion of proinflammatory cytokines. In vitro studies have shown that 1, 25(OH)2 D3 could modulate IL-6 and TNF-α expression by suppressing NF-κB. (Robinson *et al.*, 2010; Holick, 2007) It has also been shown that vitamin D prevents activation and proliferation of T cells and stimulates IL-10 secretion and T-regulatory cell production, which are important for normal placental implantation in maternal immune tolerance. (Wei *et al.*, 2012) Preeclampsia (PE) is a pregnancy-specific condition that affects several body systems, characterized by elevated blood pressure, proteinuria and elevated maternal and fetal mortality and morbidity after 20 weeks of pregnancy. (James *et al.*, 2010; Roberts and Hubel, 2009; Laine *et al.*, 2013) There are many factors in the development and progression of preeclampsia, such as maternal constitutional, angiogenetic, endothelial, syncytiotrophoblastic,(STMP) causes and inflammatory activation.

Vitamin D Physiology and Metabolism

Vitamin D is a classic steroid hormone involved in calcium homeostasis. The two major sources of Vitamin D are Vitamin D2 (Ergocalciferol) and Vitamin D3 (Cholecalciferol). (Gezmish and Black, 2013) D3 is the major source of human vitamin D (~90%) extracted from skin synthesis by exposure to ultraviolet B (UV-B) radiation of 7-dehydrocholesterol concentrated in the stratum basale and stratum spinosum. Latitude, season, aging, use of sunscreen, and pigmentation of the skin affect skin development of Vitamin D3. Naturally, fish liver oil, fatty fish, egg yolks, and liver contain large quantities of vitamin D. Vitamin D2 is derived from the diet and is contained in fungi from ultraviolet ergosterol irradiation. The two metabolites are transferred to the vitamin D binding protein (DBP) in the blood. (Barrett and McElduff, 2010) To become biologically active, these inactive Vitamin D metabolites must undergo a two-step hydroxylation process. Initially, vitamin D2 and D3 are hydroxylated in the maternal liver to form the inactive steroid precursor 25-hydroxy-vitamin D (25[OH]D) via the action of vitamin D 25-hydroxylase, a cytochrome P450 enzyme (CYP27A1). The main circulating and stored source of vitamin D is 25[OH]D. Further hydroxylation occurs through the action of 25-hydroxyvitamin D -1-alpha-hydroxylase found in the maternal kidneys and placenta to form the active metabolite 1,25 hydroxy-vitamin D[1,25[OH]2D to enable biological activation. In a physiological regulatory loop, this mechanism in the kidneys is closely regulated by the parathyroid hormone, serum calcium and phosphorous levels. (Gezmish and Black, 2013) The serum 25(OH)D concentration is approximately 15 to 65ng / ml, and the circulating half-life of 25(OH)D is 2 to 3 weeks. The detection of 25-hydroxy-vitamin D (25[OH]D) is involved in calculating serum vitamin D levels. Due to the latter having a half-life of many minutes, we calculate 25[OH]D in comparison to the active 1,25[OH]D, compared to 3 weeks for the former. (Roberts and Hubel, 2009) The circulating 1,25(OH)2D concentration is strictly regulated primarily by PTH, phosphate, and calcium. Vitamin D,25(OH)D and 1,25(OH)2D are bound to vitamin D-binding protein (DBP) in circulation, a specific high-affinity transport protein also known as a serum or Gc-globulin group-specific portion. D concentrations of 1,25[OH]2 are far higher once pregnancy begins. (Hollis *et al.*, 2011) However, there is a growing consensus that vitamin D intakes above the current recommendations may be associated with better health outcomes. (Ambad *et al.*, 2020)

METHODS

Search Strategy

The review protocol was designed to answer the question "What are the effects of Vitamin D concentration during pregnancy on pre-eclampsia women?" We conducted a literature search using MEDLINE electronic database to identify published studies until Sep 2020. Search terms (Preeclampsia and Vitamin D or 1,25 dihydroxy vitamin D).

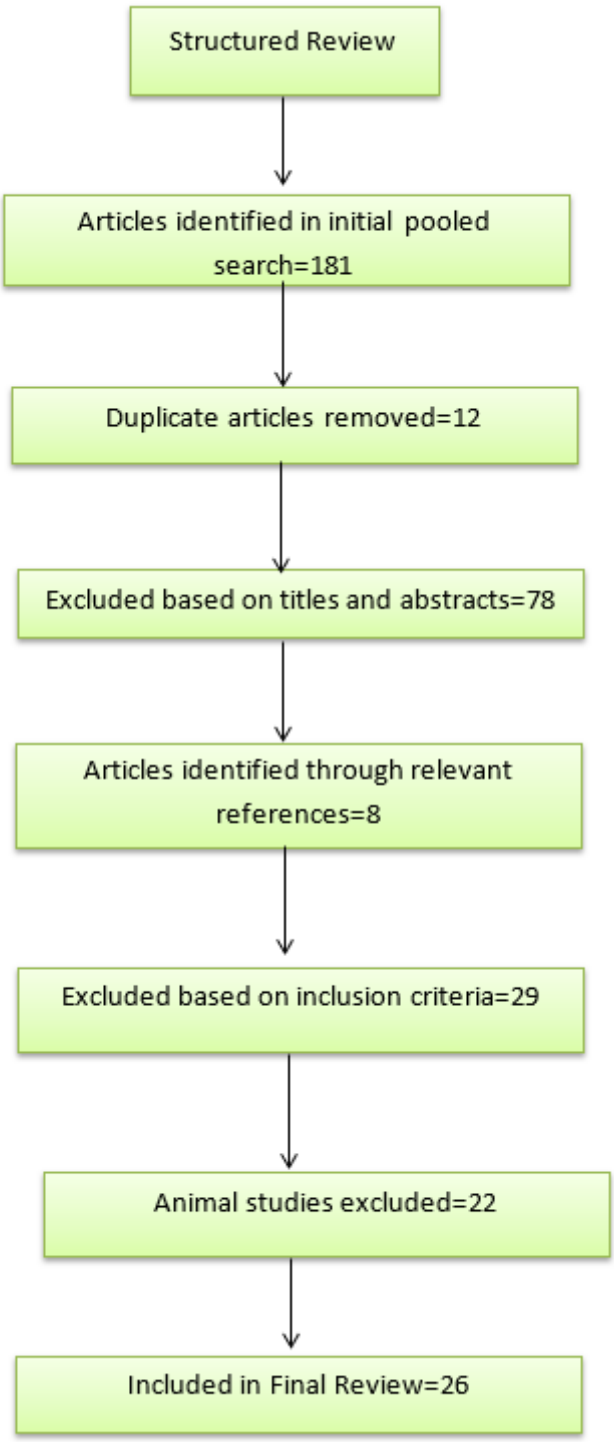

Figure 1: Flowchart of the search strategy and selection process

Table 1: Characteristics of Included Reports

Author, year	Study-design	Subject
(Baker *et al.*, 2010)	Nested Case-control study	Total Cases-3992 Women's 51-Severe preeclampsia 198-controls
(Benachi *et al.*, 2020)	Nested Case-control study (FEPED Study)	Cases-83, Controls-319
(Yuan *et al.*, 2019)	Nested Case-control study and meta-analysis	Cases-122, Control-488
(Singla *et al.*, 2015)	Case-control study	Cases-74, Controls-100
(Pashapour *et al.*, 2019)	Case-control study	Cases-80, Controls-80
(Abedi *et al.*, 2014)	Case-control study	PE Cases-59, Controls-59
(Ullah *et al.*, 2013)	Case-control study	Total cases-112 P.E-33, Eclampsia-79, Control-76
(Sonuga *et al.*, 2017)	Case-control study	Cases-60, Controls-60
(Baca *et al.*, 2016)	Cohort study	Cases-650, Controls-2327
(Achkar *et al.*, 2015)	Nested Case-control study	Cases-169, Controls-1975
(Gidlöf *et al.*, 2015)	Nested Case-control study	Cases-37, Controls-120
(Goel *et al.*, 2016)	prospective case-control	Cases(P.E and Eclampsia)-42, Controls-50
(Bodnar *et al.*, 2014)	Case-Cohort study	Case-717, Control-2986
(Biggio *et al.*, 2013)	Nested case-control study	Case subsets- a- 100 cases with preeclampsia. b-100 women with spontaneous preterm birth 35 weeks, Control- 200 women
(Mohaghegh *et al.*, 2015)	Case-control study	Case=41, Control=50
(Rezaei *et al.*, 2014)	Case-control study	Cases=50, Controls=100
(Karamali *et al.*, 2015)	Double-blind placebo-controlled clinical trial	Case=60 pregnant women at risk for pre-eclampsia. Subjects are divided into two groups. Group I- 30(Receiving 50000IU Vitamin D supplement). Group II-30 (Receive placebo, every 2 weeks from 20 to 32 weeks of gestation)
(Sadin *et al.*, 2015)	Case-control study	Case=40, Control=40
(Ghomian *et al.*, 2015)	Case-control study	Case=70, Control=70
(Scholl *et al.*, 2013)	Prospective cohort study	Cases=1141
(Bener *et al.*, 2013)	Cohort study	n=1873
(Shand *et al.*, 2010)	Prospective cohort study	n=221
(Robinson *et al.*, 2010)	Case-control study	Cases=50, Controls=100
(Bodnar *et al.*, 2007)	Nested case control study	Cases=55, Control=219
(Tamblyn *et al.*, 2017)	Cross-sectional study	Cases=22, Control=20
(Hamedanian *et al.*, 2019)	Case-control study	Cases=60, Controls=60

Table 2: Association between Pre-Eclampsia and Vitamin D levels in studies

Author, year	Key Findings of the studies	Result
(Baker *et al.*, 2010)	Decreased vitamin D levels in women with PE vs Controls. Vitamin D deficiency in Pre eclampsia.	Cases-51 Women's, P.E-75nmol/Liter, Control-98nmol/Liter (p=0.01)
(Benachi *et al.*, 2020)	The risk for preeclampsia with vitamin D levels≥30ng/ml in the first trimester was decreased but did not statistical significance.	Cases-83, Cases - 20.1±9.3 Control-22.3±11.1ng/ml (p=0.09)
(Yuan *et al.*, 2019)	Low Vitamin D concentration in pregnancy was significantly associated with preeclampsia risk.	Cases-43.3nmol/L, Control-47.5nmol/L (p=.014)
(Singla *et al.*, 2015)	High prevalence of hypovitaminosis D among pregnant women in India. Decreased vitamin D levels in women with P.E.	Mean serum vitamin D was lower among the cases compared to controls. P.E Cases=9.7±4.95ng/ml Controls=14.8±6.68ng/ml P=0.0001
(Pashapour *et al.*, 2019)	Vitamin D deficiency had a statistically significant relationship with preeclampsia and supports the hypothesis that vitamin D deficiency may be a risk factor for preeclampsia.	OR=4.79, CI=1.45-9.87, P=0.01
(Abedi *et al.*, 2014)	Low Vitamin D levels in Iranian women because of particularly life style.	P.E Cases=17.48±13.58 ng/ml, Healthy controls-22.98±11.36, P=0.001
(Ullah *et al.*, 2013)	High prevalence of Vitamin D insufficiency in Bangladesh	Controls-24.86ng/ml Pre-eclampsia-23.96ng/ml Control-21.56ng/ml OR-3.9(95%CI=1.18-12.87)
(Sonuga *et al.*, 2017)	P.E women had lower levels of Vitamin D	Vitamin D at 20 weeks-cases-24.5±4.6, controls-36.59±5.1. Vitamin D levels at 30 weeks-cases-23.3±3.9, controls-34.14±3.7. Post-partum Vitamin D levels- cases-21.7±5.5, controls- 32.62±3.2 P=<0.05

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Table 2 continued

Author, year	Key Findings of the studies	Result
(Baca *et al.*, 2016)	20 weeks of gestation, serum Vitamin D was measured. Vitamin D deficiency increases the risk of severe and mild forms of preeclampsia.	95% CI, vitamin D levels less than 25nmol/L Case-6.12(4.57-11.21), Controls-15.18(7.67-18.83) P=0,007
(Gidlöf *et al.*, 2015)	The findings of their study indicates that preeclampsia was not more common in women with vitamin D deficiency in early pregnancy.	Cases-52.2±20.5 nmol/L, Controls-48.6±20.5nmol/L P=0.3
(Goel *et al.*, 2016)	Mean serum 25(OH)D levels were significantly less in cases.	Cases-6.7236ng/ml, Controls-9.8862ng/ml P=0.004
(Bodnar *et al.*, 2014)	Maternal Vitamin D deficiency may be a risk factor for severe pre-eclampsia, but it is not associated with pre-eclampsia overall or its mild subtypes.	Adjuster RD-0.003, 95% CI-.005,.0002 and a 40% reduction in risk (adjusted RR .65, 95%CI,43, .98)
(Bodnar *et al.*, 2014)	Neither vitamin D insufficiency nor deficiency.	89 PE, 90 SPB and 177 controls had valid measurements. PE=27.4ng/ml Controls=28.6±12.6 ng/ml p=0.46 SPB= 28.8±13.2 p=0.92
(Mohaghegh *et al.*, 2015)	Vitamin D levels was deficient in P.E Women's	Case=15.2±13.6 ng/ml, Control=23.3±15.3 ng/ml p=0.001
(Rezaei *et al.*, 2014)	Vitamin D level of most pregnant womens was lower than normal. According to these findings, vitamin D deficiency can be considered as a risk factor for preeclampsia.	Cases=11.0±9.4ng/ml, Controls=16.3±10.0 P=0.003
(Karamali *et al.*, 2015)	Pregnant women who receive Vitamin D supplements had significantly increased serum Vitamin D levels compared to placebo, which reduces the risk of developing PE.	(+17.92±2.28Vs +0.27±3.19ng/ml p0.001)
Ghomian *et al.* (2015)	Vitamin D deficiency was found in both groups.	Case=5.5±3.32, Controls=8.05±4.81 p=0.001

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Table 2 continued

Author, year	Key Findings of the studies	Result
(Scholl *et al.*, 2013)	Women who are vitamin D insufficient develop secondary hyperparathyroidism, which is associated with an increased risk of pre-eclampsia.	18.4% of women whose 25(OH)D concentration were 20ng/ml. Risk of preeclampsia was increases 2.86-Fold (95% CI:1.28, 6.41 fold) early in gestation in these women.
(Sadin *et al.*, 2015)	Pre-eclampsia can cause a decrease in the serum level of 25(OH)D.	60% of pre-eclamptic women were Vitamin D Deficient, and 40% were insufficient. Cases=10.09±6.66ng/ml Controls=15.73±5.85ng/ml p=0.002
(Bener *et al.*, 2013)	Maternal Vitamin D deficiency in pregnancy is significantly associated with an elevated risk of pre-eclampsia.	PE=(OR 1.75, CI 1.16-2.58, p=0.010)
(Shand *et al.*, 2010)	Vitamin D deficiency and insufficiency were common in women at high risk of PE.	42.6nmol/L, IQR 32.7-72.4 p=0.21
(Achkar *et al.*, 2015)	Maternal Vitamin D deficiency in early pregnancy may be an independent risk factor for PE.	Cases=47.2±17.7nmol/L, Controls=52.3±17.2nmol/L p=< .0001 Adjusted Odds ratio, 2.23;95%Confidence Interval, 1.29-3.83.
(Robinson *et al.*, 2010)	Decreased level of Vitamin D at the time of diagnosis of Early-onset severe preeclampsia.	Case=18ng/ml, Controls=32ng/ml p< 0.001
(Bodnar *et al.*, 2007)	Vitamin D deficiency may be an independent risk factor for pre-eclampsia.	Geometric mean 45.4nmlo/l and 95% CI, 38.6-53.4nmol/L,vs 53.1 and 47.1-59.9nmol/L, p< 0.01
(Tamblyn *et al.*, 2017)	P.E is associated with decreased activation, increased catabolism and impaired placental uptake of 25(OH)D3	Cases=17.7±54.7nmol/L, Controls=20.8±44.3nmol/L p=< 0.0001
(Hamedanian *et al.*, 2019)	Serum Vitamin D levels are significantly lower in pregnant womens with pre-eclampsia.	Cases=6.88±9.46ng/ml, Controls= 13.41±8.05ng/ml p=0.688

The search was confined to peer-reviewed articles that were published in English and contained an abstract. Reference list of journal articles were also screened for additional citations fitting our search criteria.

Inclusion Criteria

1. Clinical data on Vitamin D concentration in association with pre-eclampsia in any global setting.
2. Subjects that included pregnant participants aged 18years and above without medical co-morbidities.

Exclusion Criteria

1. Review
2. Editorials letters
3. Commentaries
4. Case report
5. Animal studies
6. Article with unavailable data
7. Pre-eclampsia articles which do not include Vitamin D or Vitamin D articles which do not include PE as a primary or secondary outcome.

RESULTS

The structured literature search resulted in 181 articles. 12 Duplicate articles were removed, 17 articles were excluded based on titles and abstracts, 8 articles were identified through relevant reference, 29 articles were excluded based on inclusion criteria, 22 animal studies were excluded, and 26 relevant articles were selected according to the inclusion and exclusion criteria. The reviewed studies included 21 case-control studies, 4 cohort studies, 1 double-blinded placebo study and 1 cross-sectional study. Only the articles in English were considered in the study. A detailed summary of the search strategy and the result is presented in Figure 1 and Tables 1 and 2.

DISCUSSION

During pregnancy, vitamin D deficiency has been associated with a range of severe and long-term offspring health problems, including impaired growth, skeletal problems, type 1 diabetes, asthma and schizophrenia. Vitamin D has been involved in providing essential signals among placental trophoblast models in gene regulation and expression in early placental development. There is concern regarding vitamin D deficiency that the absence of these signals may play a critical role in placental development at Stage I, contributing to the eventual identification of Stage II and preeclampsia diagnosis. Pre-eclampsia pathogenesis includes a variety of biological processes that may be directly or indirectly impaired by vitamin D, including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation and hypertension. In a major prospective study on vitamin D and preeclampsia performed by (Scholl *et al.*, 2013), a two-fold increase in the incidence of preeclampsia was found to be less than 20 ng/ml in circulating vitamin D concentrations. Several studies have shown an increased risk of preeclampsia with maternal vitamin D deficiency or insufficiency, as well as low total vitamin D intake. (Scholl *et al.*, 2013) A case-control study performed by (Sadin *et al.*, 2015) included 40 preeclampatic women aged 18 to 45 years in the study. In their report, 60% of preeclampatic women were vitamin D deficient with a level of vitamin D below 10ng / ml, and 40% were vitamin D deficient. Maternal vitamin D deficiency, including its effects on placental function and inflammatory response, is a common public health issue during pregnancy. (Shin *et al.*, 2010) In early 2007, (Bodnar *et al.*, 2007) observed the association between pre-eclampsia and vitamin D, claiming that a 50nmol / l decrease in vitamin D concentration doubles the risk of PE in pregnant women. (Bodnar *et al.*, 2007) A study conducted by (Sadin *et al.*, 2015) reported that the maternal 25(OH)D concentration was less than 10ng / ml, correlated with a 15-fold increase in the odds ratio of pre-eclampsia (adjusted OR, 14.98; 95 percent CI, 4.01-55.95). (Sadin *et al.*, 2015) In a broad cohort sample, 1873 pregnant women participated and were divided into 4 groups, and serum levels of vitamin D were calculated using other parameters. In pregnant women, half of the pregnant women surveyed had Vitamin D deficiency and preeclampsia (OR 1.75, CI 1.16-2.58; P=0.010). (Bener *et al.*, 2013) Since the research included a prospective longitudinal study of 221 participants, out of which 28 participants developed preeclampsia (42.6nmol / l, IQR 32.7-72.4,p=0.21), their study indicates that vitamin D deficiency and insufficiency were prevalent in groups of women at high risk of preeclampsia. (Shand *et al.*, 2010) A nested case-control study showed preeclampsia lowers Vitamin D concentration at a mean gestational age of 14 weeks. Women with 25(OH)D < 30nmol/L had a greater risk of developing PE(Adjusted odds ratio, 2.23;95%confi-

dence interval,1.29-3.83). (Achkar *et al.*, 2015) Vitamins supplementation therapy in pregnancy could help in reducing the incidence of gestational hypertension/preeclampsia. (Ambad *et al.*, 2020)

CONCLUSION

The present systematic review revealed that maternal vitamin D deficiency in pregnancy is significantly associated with an elevated risk of preeclampsia. Pregnant womens should take vitamin D supplementation, expose themselves into the sunlight, and they should be physically active. Further taking Vitamin D supplementation in early pregnancy may be a simple way to reduce the risk of these adverse pregnancy outcomes.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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