Tropical Journal of Pharmaceutical Research May 2021; 20 (5): 1055-1059
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i5.24

Original Research Article

Calcium and vitamin D supplementation in pre-eclampsia: Analysis of effectiveness and safety

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Sent for review: 15 October 2020 *Revised accepted: 20 April 2021*

Abstract

Purpose: *To evaluate the impact of calcium and vitamin D (vit D) supplementation initiated at early pregnancy in high-risk women on reduction of preeclampsia risk.*
Methods: *This prospective cohort study involved 492 pregnant women who had experienced pre-eclampsia or eclampsia in their current pregnancy (high risk) and were either on calcium (1000 mg/day) as well as vit D (400 IU/day) supplementation at early pregnancy or none. All the included pregnant women received standard doses of calcium (1500 mg/day) and vit D (600 IU/day) supplementation post 20 gestation weeks till childbirth. The primary outcome was pre-eclampsia characterized by hypertension as well as proteinuria.*
Results: *From March 10, 2015 to February 24, 2018, each of the 246 pregnant women were assigned to the calcium/vit D group versus control group with no calcium/vit D. In the calcium/vit D group, 26.45 % developed preeclampsia compared to 32.11 % in control group with a Risk ratio [RR] of 0.82 (95 % confidence interval [CI], 0.62-1.08; p 0.167). No serious adverse events were related to calcium or vit D.*
Conclusion: *Calcium/vit D supplementation during early pregnancy did not demonstrate any significant reduction in pre-eclampsia. Large, high-quality studies with higher patient numbers are needed for adequate testing of impact of calcium/vit D on pre-eclampsia.*

Keywords: *Calcium supplement, Pre-eclampsia, Pregnancy, Vitamin D supplement*

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INTRODUCTION

Pre-eclampsia, characterized by hypertension and proteinuria appearing post-20 gestation weeks, is a multi-factorial disease in association with perinatal and maternal morbidity and mortality around the world, along with neurological diseases, abnormal renal functioning and liver disorders [1–3]. Nearly 2 – 10% of all pregnancies are complicated by pre-eclampsia and this rate is greater in lower resource settings [3]. Prior studies demonstrated that pre-eclampsia might lead to increased prevalence of risk-factors of cardiovascular diseases, including insulin metabolism impairment, metabolic syndrome, endothelial dysfunction, microalbuminuria, oxidative stress and inflammatory factors [2,4].

In a cross-sectional study in 29 countries of Asia, Africa, Middle East, and the Latin America, pre-eclampsia or eclampsia was noted in nearly 25.9% of pregnant women with serious maternal outcomes (like near miss or maternal death), with direct causative effect in 20 % of maternal deaths reported [5]. Hence, maternal morbidity and mortality from pre-eclampsia/eclampsia is of priority worldwide.

Prior studies showed calcium and vitamin D deficiency amid pregnancy might be independent risk factors for pre-eclampsia [6,7]. A study conducted by Haugen *et al* [8] demonstrated a 27 % pre-eclampsia risk reduction in women on 10 - 15 µ/day vitamin D supplements in comparison to women on no supplements. Another study showed significant pre-eclampsia risk reduction with calcium supplements ((≥1 g/day) in pregnant women especially on low calcium diets [9]. Such a role of vit D and calcium in preeclampsia was supported in a recent systematic review [10]. These discoveries brought about the speculation that early vit D or calcium supplementation could be beneficial in reducing preeclampsia risk.

As per our knowledge, no study that assessed effect of calcium and vit D supplementation at early pregnancy on pre-eclampsia was conducted. This prospective study goal is to evaluate the impact of calcium and vit D supplementation initiated at early pregnancy in high-risk women on preeclampsia risk reduction.

METHODS

Ethical approval and consent

This prospective cohort study was performed at the antenatal clinic of the Department of Obstetrics and Gynecology of the institute from March 10, 2015 to February 24, 2018. The hospital's review board approval was received (approval no. 2015CWCH1038). Patient confidentiality was strictly maintained. The guidelines set forth in the Helsinki Declaration [11] was followed. Informed consent was taken from all the participants. The study adhered to the research laws of China.

Study cohorts

The study population included pregnant women older than 18 years old, with pre-eclampsia or eclampsia in their current pregnancy (high risk) and were on calcium (1000 mg/day) as well as vit D (400 IU/day) supplementation at early pregnancy (8 weeks of gestation). The control group included high-risk pregnant women with no calcium or vit D supplementation at early pregnancy (until 20 gestation weeks). The pregnant women in our hospital are usually advised to take calcium and vit D supplementation at doses of 1500 mg/day and 600 IU/day respectively. Post 20 gestation weeks and all the included pregnant women followed the same till childbirth. The doses are as per recommendations by World Health Organization (WHO) [12] and Institute of Medicine (IOM) [13]. Participants were advised to take no extra calcium supplementation. Paracetamol was recommended in case of analgesics, if needed whereas non-calcium-based antacids in case of antacids.

Data collection

Clinical as well as demographic data of included pregnant women were noted from the medical records (charts review). The exclusion criteria included multiple pregnancies, fetal malformations, polyhydramnios, diabetes, renal disease, chronic hypertension, urolithiasis, cardiovascular disease, or 140/90 mmHg or higher blood pressure at the first visit.

Outcome measurements

The primary outcome was pre-eclampsia characterized by hypertension as well as proteinuria. The secondary outcomes were a composite.

Statistical analyses

Values are denoted as percentages in case of categorical variables, whereas means and standard deviations in case of continuous variables. Risk ratios (RR) with 95% confidence interval (CI) was used to compare categorical variables that was performed using Medcalc for windows, version 15.0 (MedCalc Software, Ostend, Belgium). All data were analyzed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

RESULTS

In the present study 492 pregnant women were enrolled; 246 women each were allocated to the calcium/vit D group and control group with no calcium/vit D. The clinical and demographic data of the participants were recorded and compared, which were comparable between the groups, including age, systolic/diastolic blood pressure, body mass index, and prior medical history (all $p > 0.05$; Table 1).

Table 1: Clinical/demographic characteristics

Characteristic	Group A (calcium + vit D, n=246)	Group B (no calcium or Vit D, n=246)
Maternal age (yrs)	30.22 ± 4.98	29.84 ± 4.62
Body mass index (BMI; kg/m^2)	29.32 ± 6.6	29.41 ± 6.4
BMI>30	108 (43.9%)	112 (45.53%)
Baseline blood pressure, mmHg		
Systolic	125 ± 18.13	125.32 ± 19.24
Diastolic	82.2 ± 11.62	82.9 ± 12.81
Prior medical history		
Severe pre-eclampsia*	205 (83.33%)	216 (87.8%)
Eclampsia	54 (21.95%)	61 (24.48%)
HELLP syndrome	37 (15.04%)	52 (21.14%)
Live birth	118 (47.97%)	111 (45.12%)

HELLP = Hemolysis, elevated liver enzymes, as well as low platelet count; *systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg; values are shown as mean ± standard deviation or numbers with percentages

Table 2: Primary and secondary outcomes data

Outcome	Group A (calcium plus vit D, %)	Group B (no calcium or vit D, %)	Risk ratio (CI)	*P*-value
Primary outcome				
Pre-eclampsia	65/246 (26.42)	79/246 (32.11)	0.82 (0.62-1.08)	0.167
Secondary outcome				
Pre-eclampsia and/or pregnancy loss at any gestation	89/246 (36.18)	108/246 (43.90)	0.82 (0.66-1.02)	0.082
Gestational proteinuria	72/246 (29.27)	85/246 (34.55)	0.85 (0.65-1.09)	0.209
Gestational hypertension	169/246 (68.7)	181/246 (73.58)	0.93 (0.83-1.05)	0.233
Severe gestational hypertension	83/246 (33.74)	90/246 (36.59)	0.92 (0.73-1.17)	0.509
Early onset preeclampsia*	39/246 (15.85)	40/246 (16.26)	0.98 (0.65-1.46)	0.902
Severe preeclampsia	54/246 (21.95)	61/246 (24.80)	0.89 (0.64-1.22)	0.456
Increased Uric acid values	19/26 (73.08)	17/24 (70.83)	1.03 (0.73-1.46)	0.86
Liver failure	9/51 (17.65)	8/62 (12.9)	1.37 (0.57-3.29)	0.484
Renal failure**	7/51 (13.73)	6/62 (9.68)	1.42 (0.51-3.96)	0.504
Moderately severe thrombocytopenia	14/61 (22.95)	13/76 (17.11)	1.34 (0.68-2.64)	0.394
Eclampsia§	6/246 (2.44)	10/246 (4.07)	0.60 (0.22-1.63)	0.315
HELLP syndrome	11/65 (16.92)	9/79 (11.39)	1.49 (0.66-3.36)	0.342
ICU admission >24 h	3/246 (1.22)	4/246 (1.63)	0.75 (0.17-3.32)	0.705
Placental abruption	11/246 (4.47)	8/246 (3.25)	1.38 (0.56-3.36)	0.485
Maternal death	0	0	-	-
Caesarean section	152/246 (61.79)	136/246 (55.28)	1.12 (0.96-1.29)	0.144
Early preterm birth*	48/246 (19.51)	59/246 (23.98)	0.81 (0.58-1.14)	0.23
Preterm birth*** (<37 weeks' gestation)	104/246 (42.28)	112/246 (45.53)	0.93 (0.76-1.13)	0.468
	56/217 (25.81)	61/204 (29.90)	0.86 (0.63-1.17)	0.349
Birthweight <2500 g	8/217 (3.69)	14/204 (6.86)	0.54 (0.23-1.25)	0.15
Apgar score <7 at 5 min	46/217 (21.2)	39/204 (19.12)	1.10 (0.76-1.62)	0.596
Neonatal ICU admission/Perinatal death	27/246 (10.98)	32/246 (13.01)	0.84 (0.52-1.36)	0.489
	97/246 (39.43)	99/246 (40.24)	0.98 (0.79-1.22)	0.854
Stillbirth	58/246 (23.58)	62/246 (25.20)	0.94 (0.69-1.28)	0.674
Severe pre-eclampsia complications index$^{\delta}$				
Severe maternal morbidity and mortality index‡¶				

CI = 95% confidence interval; HELLP=hemolysis, elevated liver enzymes, as well as low platelet count; ICU=intensive care unit; *<32 weeks'; gestation; **Creatinine >120 mmol/L; ***<37 weeks' gestation; §All patients with eclampsia had pre-eclampsia too; δSevere pre-eclampsia complications index constitutes at least one of the following: eclampsia, early-onset pre-eclampsia, severe pre-eclampsia, HELLP syndrome, placental abruption, or severe gestational hypertension; ‡Severe maternal morbidity and mortality index constitutes at least one of the following: ICU or special care unit admission, eclampsia, HELLP syndrome, placental abruption, renal failure, or death

The results of primary as well as secondary outcomes were presented in Table 2. In case of primary outcome, participants in the calcium/vit D group showed lower preeclampsia prevalence (65/246; 26.42 %) when compared to control group (79/246; 32.11 %) with 18 % reduction (RR 0.82 [CI 0.62-1.08]; *p* = 0.167), which is insignificant. None of the differences in secondary outcomes between the groups were significant. The prevalence of pre-eclampsia and/or pregnancy loss at any gestation, was 36.18 % in the calcium/vit D group and 43.9 % in the control group (RR 0·82 [CI 0·66-1·02]), with borderline significance. The differences in the composite outcomes (severe pre-eclampsia complications index as well as severe maternal morbidity and mortality index) were not significant. Serious adverse events from the records were noted. None of them were related to the calcium or vit D.

DISCUSSION

This prospective study did not demonstrate any significant pre-eclampsia reduction with calcium/vit D supplementation amid early pregnancy. This study is not like the earlier studies on either calcium or vit D supplementation for pre-eclampsia prevention. In this study, an attempt was made to identify the impact of calcium and vit D at early pregnancy (that is amid defective placentation which is presumed to is thought to start off the preeclampsia pathway) on pre-eclampsia development later in pregnancy in spite of higher doses of calcium and/or Vit D supplementation continued from 20 gestation weeks till birth, as suggested by WHO [14].

The secondary outcome of pre-eclampsia and/or loss of pregnancy at any gestation deserves discussion since loss of pregnancy may be associated with pre-eclampsia. This result may overcome preeclampsia result confounding by early impact of calcium/vit D on loss of pregnancy and could be a good marker of general impact of calcium/vit D supplementation. With calcium/vit D supplements, 18% risk reduction was noted in the above-mentioned secondary outcome.

Meaningful statistical analysis was not possible for serious outcomes as they are too little in number. Such a lower prevalence of serious outcomes is not out of the ordinary as all the included participants were on higher doses of calcium and vit D supplementation from 20 gestation weeks, which are known to decrease the rate of severe pre-eclampsia complications. In addition, the decreased rate of poor outcomes might also be due to higher quality of care given to the pregnant women due to study participation as showed by the way that, in spite of there being a higher prior pre-eclampsia prevalence, the eclampsia prevalence was found to be lower (2.44% in calcium/vit D group; 4.07% in control group).

As per our knowledge, this study is the first to assess the effect of calcium and vit D supplementation at early pregnancy on pre-eclampsia. One study [15] on calcium supplement usage in early pregnancy was reported where antioxidant as well as calcium supplementation initiated at 8 – 12 gestation weeks reduced prevalence of pre-eclampsia (6.8 vs 29 %; p = 0.043) in comparison to placebo group. The outcomes are indicative of the role of calcium in reducing.

Limitations of the study

The results of this study might not be generalizable as it is a single center study with a limited number of patients involved. There is a chance of information bias as well as recall bias since only a few patients were asked to supply their data when such information was not available in their medical records.

CONCLUSION

Calcium/vit D supplementation amid early pregnancy did not demonstrate any significant reduction pre-eclampsia. The present study results suggest that a large, high-quality studies with higher patient numbers are needed for adequate testing of impact of calcium/vit D on pre-eclampsia.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All the authors contributed equally to this work.

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