REVIEW

Vitamin D and the prevention of preeclampsia: A systematic review

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Abstract: To identify the effect of Vitamin D in reducing the risk of preeclampsia in pregnant women. The review was conducted from December 2011 to March 2012 at the University of Sheffield. Studies were included from the Medline data base, Web of Science (Web of Knowledge), Ovid database and Google Scholar. Studies were limited to published literature only; published between January 1992 to March 2012. A total of seven studies were selected for this review based on the inclusion criteria. One was non-randomized clinical trial, three were cohort studies and three were nested case-control studies. The clinical trial showed a positive association between Vitamin D supplements and the reduction of preeclampsia risk in pregnant women. In addition, one large cohort and two nested case-control studies also showed a protective effect of vitamin D in preventing the risk of preeclampsia. However, the other two cohort studies and a nested case-control study could not find any association between vitamin D levels and the risk of preeclampsia in pregnant women. The studies included in this review show conflicting results about the association of vitamin D levels and the risk of preeclampsia. However, in this review more than half of the studies showed a positive link between Vitamin D deficiencies and Preeclampsia. There is a clear need for further trials and other robust studies to identify the effect of Vitamin D on preeclampsia.

Keywords: Preeclampsia, hypertension, vitamin D and pregnancy induced hypertension.

INTRODUCTION

Vitamin D is known to have a preventive effect for several diseases. The benefits are also evident in pregnancy for preventing diseases by increasing serum calcium levels (Basile *et al*, 2006). The effect of Vitamin D has been studied on cardiovascular diseases (Bischoff-Ferrari *et al*, 2011). However, little is known about the effect of Vitamin D on hypertension, particularly on pregnancy-induced hypertension (Preeclampsia). There are several studies that have shown a positive association of Vitamin D deficiency with Preeclampsia (Baker *et al*, 2010 and Haugen *et al*, 2009) whilst other studies have shown no association (Shand *et al*, 2010). As a result, there have been conflicting results about the association of taking a Vitamin D supplement with the risk of developing Preeclampsia in pregnancy (Urrutia, 2012). There is a lack of evidence from clinical trials in this area of research. Only one clinical trial was conducted in 1994, which took into account the effect of vitamin D on preeclampsia as a subgroup analysis. However, the sample for the subgroup analysis was small (Ito *et al*, 1994).

A Cochrane review was conducted in 2012 on the effect of Vitamin D on the outcome of pregnancy including Preeclampsia, however, the results were inconclusive and further research was recommended (De-Regil, 2012). Other studies recommended the need for clinical trials on this topic to produce concrete evidence. It has been observed that the number of observational studies has increased in the last decade on this topic, yet the results are not definitive. Therefore, the purpose of this review was to generate evidence on the topic and analyse the findings to come to a conclusion. The objective of the review was to identify the effect of Vitamin D in reducing the risk of Preeclampsia in pregnant women.

METHODS

Criteria for the selection of studies in this review

This review was conducted on the studies published during 1992 to 2012. The studies were selected on the basis of the following indices.

Type of studies

The reviewers' first preference was to include all clinical trials with randomization but only one non-randomised clinical trial was found, published in 1994 (Ito *et al*, 1994). Thus, the reviewers preferred another strong observational study design (cohort) to be included in the review. However, only two cohort studies were found according to the inclusion criteria. Therefore, the inclusion criteria were further expanded to include case control studies in order to have sufficient evidence to answer the research question. Only nested case control studies were included which were expected to have a stronger design than the other case control studies in the presence of the controlled environment of the cohort and

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fewer chances of recall bias and other bias associated with this study design. The researchers did not include other case control and descriptive studies in this review.

Type of population

Studies on pregnant women of any age group, with singleton or multiple pregnancies, irrespective of gestational week, and parity were included.

Type of interventions

Vitamin D was given alone or in combination with other micronutrients irrespective of dose, time and duration (clinical trial). For observational studies it was measured by blood test during pregnancy.

Outcome of interest

Preeclampsia (reviewers excluded those studies where outcome was other types of pregnancy induced hypertension such as Gestational hypertension, Eclampsia and HELLP syndrome).

Search methods for identification of studies

The review was conducted from December 2011 to March 2012. Sources were used at the School of Health and Related Research Library (ScHARR) and other libraries at the University of Sheffield. Only published sources were chosen to conduct this review. Multiple online sources were searched including Medline (Pubmed), Web of Science/web of knowledge, Ovid database, Cochrane Review and Google Scholar. Only those studies were included which were published during previous twenty years (from January 1992 to March 2012). The purpose for applying this criterion was to take account of all relevant literature published in the previous two decades to include recent as well as slightly older studies, which might have implications for today's health care practice. However, a very few studies were found relevant to this topic, most of them were observational and there was only one non-randomised clinical trial, published in 1994 (Ito *et al*, 1994). This indicates a gap in this research area and more RCTs are needed to have better evidence in determining the role of Vitamin D against pregnancy induced hypertension. One non-randomized clinical trial and four observational studies were also included in this review.

The following limits applied on search criteria

1) Only English studies (the resources were not available to translate other literature)
2) Types of study: a clinical trial, cohort studies and case control (all other studies such as surveys, case reports, case series, cross sectional and papers presented at conferences were excluded).
3) Key word searching field: abstract and article
4) Duration: From 1992 to 2012 (before that period studies may had more ethical issues and be no longer applicable).

Searching was done by putting different keywords with MeSH terms and included vitamin D and pregnancy induced hypertension, fat soluble vitamins and toxemia of pregnancy, nutritional deficiency and high blood pressure during pregnancy, Role of food supplements in prevention of high blood pressure during pregnancy.

Searched literature was reviewed by two independent reviewers for the inclusion or exclusion criteria. Data were collected about study setting, study design, targeted population, intervention/exposure and the desired outcome. In addition, methodological components were extracted to apply quality checks.

Appendix I

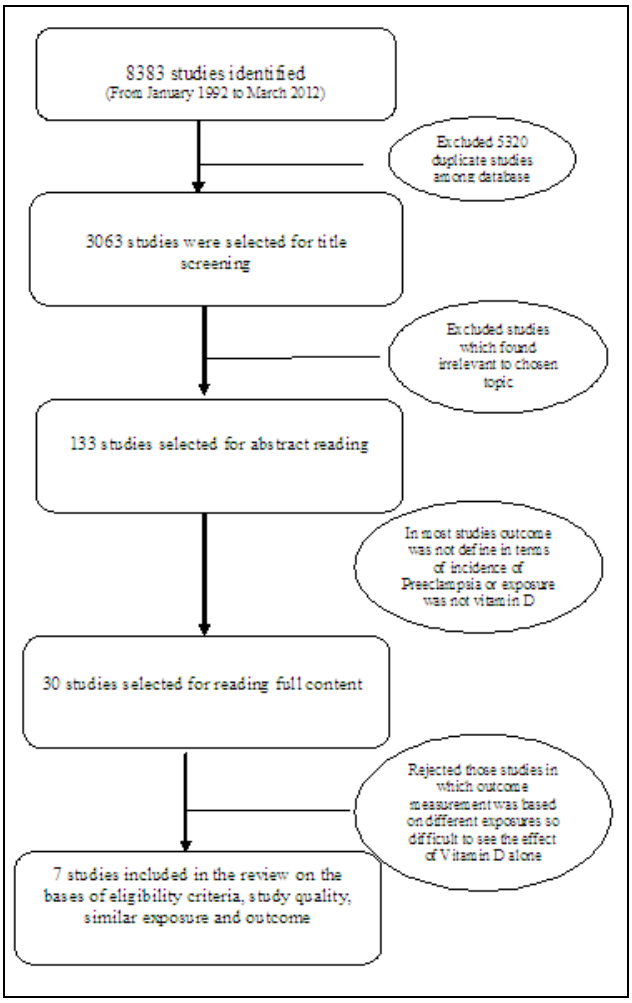

Fig. 1: Study selection flow diagram

Selection of studies

The studies were reviewed independently by two reviewers, one reviewer was a medical scientist and had some clinical experience in the field of Obstetrics & Gynecology and other was consultant in clinical Radiology.

Fig. 1 shows the whole sequential process for selecting the studies. Selection of studies was done in three different steps. In the first step, selection of studies was based on only reading titles, studies were included if they looked appropriate on a title basis. Further selection was based on an abstract level and the selected articles were further screened for methodological appropriateness and the outcome of interest. In the final stage, full articles were read and only those articles were included in the review that fulfilled all the eligibility criteria. The searching process was conducted twice to prevent any error due to the selection process. Secondary electronic searches were also done by the reviewer using references from selected articles but no new articles found.

Methodological quality assessment

Different guidelines and checklists were applied to assess the quality of studies. CONSORT guidelines (The Trend statement) were used to assess quality of clinical trial and STORBE checklist applied for observational studies.

RESULTS

A total of 8383 studies were extracted on initial searching of different electronic databases. Those studies found to be irrelevant to the topic were excluded by the reviewer, conducted on the non pregnant women or used the study design which was not included in the inclusion criteria of this review (cross-sectional and descriptive studies such as case report/case series or ecological study design).

Only one clinical trial was considered to be included in the review, which matched the review objective (M. Ito *et al*, 1994). Three cohort studies were also included because of same exposure and outcome. Preference was given to the nested case control studies over the case control studies and three studies were included in this review because of the stronger design. Overall, seven studies have been included in this review to identify the role of Vitamin D in prevention of Preeclampsia. On the level of abstract; one study was found to be relevant to the topic but was under publication so it was not included.

Major characteristics of the selected studies

Table1 shows the important characteristic of studies included in the review.

Study setting: All the studies were conducted on pregnant women in different countries. Four Studies were conducted in the United States of America, one in Canada, one in Norway and one in Japan.

Study population: Total participants were 26,924 with the range of sample size from 170 to 23,423 participants in the selected studies. All studies were conducted on pregnant women aged 17 to 44 years (normal fertility age); two studies did not provide information on the age of study participants. High-risk pregnant women for developing preeclampsia were taken in two studies as a study population while all the others were carried out on low risk pregnant women. Recruitment of the participants was mainly done in first trimester of pregnancy between 10 to 20 weeks of gestation and follow up continued till delivery of the baby.

Study design: Most of the included studies were observational; three cohorts, three-nested case control (conducted within cohort studies) and one was experimental (non randomized clinical trial).

Type of exposure: Vitamin D was not taken as a single exposure in half of the studies so the effect was identified on the subgroup. Most of the studies measured vitamin D along with calcium and diet containing all the essential nutrients.

Outcome of Interest: Preeclampsia was the main outcome of interest in most of the studies. In some studies data were also collected for adverse outcome of pregnancy and Gestational hypertension.

Quality assessment of methodology

One trial was selected for this review in which outcome was preeclampsia and intervention was calcium along with vitamin D3 (Ito *et al*, 1994). The trial was conducted on 876 pregnant women, divided into 2 groups, 210 in the intervention group and 666 women in a control group. The intervention group was selected on the basis of high risk. It was further divided into four more groups; in group A calcium was given from 22 weeks of gestation and Vit D3 (dose 0.5µg/3 days) from 30 week of gestation till delivery. Group B took calcium only. Group C and group D were based on low risk group, took calcium and received conventional care respectively. Preeclampsia was assessed at the time of delivery by reviewing participants charts on the basis of BP measurement and proteinuria by dipstick. Pregnant women with blood pressure high > 140/90 at 20 weeks' gestation and protenuria at the time of enrolment were excluded.

The results of this clinical trial suggest that overall incidence of Preeclampsia was significantly higher (X^2 =4.4, P-value =<0.04) in the control group than in the protocol group 113/666 (16.9%) and 23/210 (10.9%). However, when sub group analysis was performed within the intervention groups, group A (which was on Vitamin D3 and calcium) showed a higher incidence of preeclampsia 3/7 (42.9%) compared to group D (which was not taking anything but still included in the intervention group because it consisted of high risk pregnant women), where the incidence was 16/182 (8.8%). Nevertheless, the sample was small in the sub group so the conclusion may not be appropriate.

Cohort studies

Three cohort studies were also included to provide better evidence on association of vitamin D with preeclampsia. One was done on a small sample size (227) of high risk singleton pregnant women for preeclampsia selected at a specialist antenatal clinic. This Prospective cohort study was part of a large ongoing EMMA (Evaluating Maternal Markers of Acquired risk of pre-eclampsia) study in Canada. However, this study did not include a true representative population because the cohort was taken from the high-risk population so results cannot be generalized. Another study conducted on a relatively larger sample size with 1718 pregnant women included a truly exposed cohort from the community. Both studies selected the unexposed cohort from the same population.

Results of one cohort study (Shand *et al*, 2010) suggest that there is no significant association between the first half of pregnancy serum 25OHD (25-hydroxycholecalciferol) level and subsequent development of preeclampsia. Median concentration of serum 25OHD level was 50.2 nmol/l (Interquartile range (IQR) =35.8-68.0) in the 161 women who had not developed preeclampsia while it was 42.6 nmol/l (IQR 32.7-72.4, P value= 0.21) among preeclamptic women. There was also no statistical significant association found between both groups after taking cutoff points at <37.5, <50 or <75 vitamin D levels. Odds ratios were 0.91 (CI=0.31-2.62), 1.39 (CI=0.54-3.53), 0.57 (CI=0.19-1.66) at <37.5, <50 or <75 levels respectively. However, small sample size and small proportion of preeclamptic women were the

Table 1: Major Characteristics of included studies along with their presented data and estimated results (ordered by study design and year of publication)

Clinical Trial								
Study	Population	Age group	Total participants	Vit D dosage	Intervention n/N	Controls n/N	OR	95% CI
Ito *et al* (1994)	Pregnant women	17 to 42 years	876	0.5 µg/3 days (Vitamin D3 given with Calcium)	210/876	666/876	0.60[a]	0.37-0.97[a]
Cohort studies								
Study	Population	Age group	Total participants	Exposure categories	N	OR	95% CI	
Haugen*et al* (2009) (Norwegian Mother and Child Cohort Study)	nulliparous pregnant women	<20 to >40 years	23,423	1. Total Vitamin D intake: (15-20 µ/d compared with <5 µ/d)		0.76	0.60-0.95	
				2. Vitamin D from food supplement: (10-15µ/d compared with no supplements)		0.73	0.58-0.92	
Shand *et al* (2010) (EMMA study)	High risk pregnant women for Pre - eclampsia	≥18 years	221[b]	1. Vitamin D Insufficient gp : (Serum 25OHD <75 nmol/l)	21/28	0.57[c]	0.19-1.66	
				2. Vitamin D deficient gp : (Serum 25OHD <50 nmol/l)	17/28	1.39[c]	0.54-3.53	
				3. Vitamin D deficient gp : (Serum 25 OHD <37.5 nmol/l)	10/28	0.91[c]	0.31-2.62	
Oken *et al* (2007) (Project Viva study)	Pregnant women	Fertility age	1718	Women with preeclampsia [d](Vit D) =mean (SD) =466 (183)	59/1718	0.99	0.87-1.13	
				Women with gestational hypertension (Vit D) =mean (SD) =542(262)	119/1718	1.11	1.01-1.21	

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Nested case control studies								
Study	Population	Age group	Total participants	Cases (Preeclamptic women)	Control (Normotensive women)	Identified factors	OR	95% CI
Camille *et al* (2010)	Cohort of 9930 Pregnant women of Massachusetts General Hospital Obstetric Maternal Study	Fertility age	170 of 9930 of cohort study	39	131		2.49 (Univariate)	0.89-6.90
							1.35 (Multivariate)[e]	0.40-4.50
Baker *et al* (2010)	cohort of 3992 women who had previously given blood for routine genetic multiple marker screening and subsequently delivered at the University of North Carolina-Chapel Hill	23 to 34 years	241 samples of 3992 women	43	198 (matched by race/ethnicity)	Serum25 (OH) D level (nmol/liter) 50–74.9	1.53 (Unadjusted)	0.67-3.49
							2.16 (Adjusted)[f]	0.86-5.40
						<50	3.63 (Unadjusted)	1.52-8.65
							5.41 (Adjusted)[f]	2.02-14.52
Bodnar *et al* (2007)	1198 women in the cohort of Pregnancy Exposures and Preeclampsia Prevention Study	14 to 44 years	275 samples of 1198 women	55	220 non-Preeclamptic women	Early-pregnancy maternal 25 (OH) D concentration Less than 37.5 nmol/liter	5.0 (adjusted)	1.7-14.1
						Serum 25 (OH) D levels at less than 22 wk	2.4 (adjusted)	1.1-5.4

[a]In the trial Vitamin D3 given with Calcium (OR &CI were calculated by the reviewer)
[b]Results of Serum 25OHD were available for 227 women whose pregnancy outcomes were known but 6 women were excluded from the analysis because of different reasons
[c]Multivariate analysis adjusted for maternal age, ethnicity, parity, BMI, season, multivitamin use and smoking status, at each concentration of serum 25OHD
[d]Vitamin D measured in IU which Intake from foods + supplements
[e]Multivariate adjustment for body mass index, nonwhite race, and summer blood collection
[f]Adjusted for season of blood draw, maternal age, multiparity, body mass index, and gestational age at serum collection

limitations of this study. Moreover, information about diet and dose of vitamin D supplements were not taken in account and serum 25OHD concentration was measured at only one point in the time of pregnancy.

In the second study (Oken *et al* 2007) only 3% developed preeclampsia and there was no difference in the mean level of vitamin D between preeclamptic and healthy women (mean +SD=466+183, 496+210). Adjusted odds of developing preeclampsia for vitamin D were 0.99 with 95% CI=0.87-1.13 (insignificant CI) showing that higher intake of vitamin D did not affect on preeclampsia. Furthermore, an interesting finding of this study that was the incidence of gestational hypertension increased with a higher intake of vitamin D (Odds Ratio (OR) =1.11, 95% CI=1.01-1.21) This study was stronger by comparison to the first study in its application of a validated SFFQ (Semi-quantitative Food Frequency Questionnaires) for diet and for a number of essential nutrients during pregnancy and its use of a larger sample larger sample.

Another large recently conducted cohort study on 23,423 participants (Haugen *et al* 2009) found strong evidence of 27% risk of reduction of preeclampsia in the Vitamin D

supplement group as compared to those unexposed (OR=0.73; CI=0.58-0.92). The supplement dose was set at 10-15 microg/day for participants and no supplement was given to the unexposed group.

Nested case control studies

Three nested case control studies were included in this review. All three studies had a standard case definition and they selected a control group from the same population. Two studies selected unmatched controls randomly while in one study computer generated matched controls for race/ethnicity were taken with a ratio of 4:1. Advance analysis was applied for the adjustment and results were reported in odds ratios and an adjusted mean.

One study (Camille *et al.*, 2010) reported no significant difference in the first trimester total 25 (OH) -D level among preeclamptic and non-preeclamptic women (27.4+1.9ng/mL versus 28.8+0.80ng/mL, p value=0.435). The same results were observed on univariate and multivariate analyses for 10ng/ml increase in 25(OH) D level; Univariate OR=2.5 (0.89 to 6.9), Multivariate OR=1.35 (0.40 to 4.5). No association between first trimester vitamin D level and subsequent preeclampsia was observed. However, there were some limitations such as the small sample size and measurement of vitamin D at a single time point.

The results of second study (Baker *et al*, 2010) contradicted with all the above studies, they demonstrated that the serum 25 (OH) D concentration was 23% lower among severely preeclamptic women as compared to the healthy women (median value 75 versus 98, p-value=0.01). Midgestation Vitamin D deficiency (25OHD <50 nmol/liter) was also more prevalent among cases compared to the controls (26% vs 10%; p value=0.01), unadjusted OR was 3.63 (95%CI=1.52-8.65; P value 0.004) and it was 5 folds higher after the adjustment; OR 5.41 (95%CI=2.02-14.52; P value 0.001). However, the serum 25 (OH) D concentration at 50-74.9 nmol/liter was; unadjusted OR 1.53 (0.67-3.49; p value 0.31) adjusted OR 2.16 (0.86-5.40; p value 0.10) (dose response relationship). This study showed a positive association and dose response relationship between lower levels of vitamin D and severe preeclampsia. But the study outcome only considered severe preeclampsia, did not considered preeclampsia. Furthermore, it did not measure other factors such as lifestyle differences between cases and control, and their intake of calcium and other vitamins and minerals.

The third study (Bodnar *et al.*, 2007) also showed a positive association between Vitamin D and preeclampsia and the results showed that serum 25 (OH) D level was 15% lower among preeclamptic women as compared to the control group (an adjusted geometric mean with 95%CI=45.4 (38.6-53.4 versus 53.1 (47.1-59.9, p value 0.01). An early pregnancy 25 (OH) D concentration at<37.5 nmol/liter was also associated with a 5-fold increase in the odds of preeclampsia (adjusted OR, 5.0; 95% CI, 1.7-14.1). According to this study vitamin D deficiency was a strong predictor for preeclampsia at less than 22 wk gestation and a monotonic dose response relationship was also observed. The limitations were there they did not measure vitamin D binding protein and these findings may reflect overestimation of vitamin D levels. They did not measure calcium intake, which could be a confounder although they performed a sensitivity analysis for it.

DISCUSSION

This review showed that Vitamin D deficiency is associated with preeclampsia, however, the evidence is limited and more trials are needed. Most of the studies with larger samples have shown the positive effect of vitamin D in the prevention of preeclampsia. Some studies have shown that Vitamin D has no effect on preeclampsia, while others have even shown an increased incidence of preeclampsia in the patients taking Vitamin D supplements (Hypponen, 2005). One old clinical trial, published in 1987 showed no association of combined vitamin D and calcium with the risk of preeclampsia (Marya *et al*, 1987). While a clinical trial published in 1994 has shown a protective effect of vitamin D on preeclampsia, the trial was 18years old and limited by sample size and the control of confounders (Ito *et al*, 1994). In addition, a recent cohort on a large population of 23,423 also found a positive association of vitamin D supplements with the prevention of preeclampsia (Marya *et al.*, 1987).

Furthermore, a review published in 2005 also suggested a positive association of vitamin D with preeclampsia based on observational studies and recommended the need for future clinical trials (Hypponen, 2005).

This review has selected of a limited number of studies with study design of either cohort of nested case-control, in addition to a clinical trial which was the only trial found relevant to the review. Only published data was included in the review and there is a possibility that important information available in other unpublished literature has not been considered.

CONCLUSION

In the presence of limited literature on the topic, this review has shown a positive association of Vitamin D deficiency with preeclampsia in pregnancy. However, more clinical trials are needed to quantify the effect of vitamin D on preeclampsia in pregnancy.

REFERENCES

Baker AM, Haeri S, Camargo CA Jr, Espinola JA and Stuebe AM (2010). A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *J. Clin. Endocrinol. Metab.,* **95**(11): 5105-5109.

Basile LA, Taylor SN, Wagner CL, Horst RL and Hollis BW (2006). The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. *Breastfeed Med.*, **1**(1): 27-35.

Bischoff-Ferrari H, Stähelin HB and Walter P (2011). Vitamin D effects on bone and muscle. *Int. J. Vitam. Nutr. Res.*, **81**(4): 264-672.

Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW and Roberts JM (2007). Maternal vitamin D deficiency increases the risk of preeclampsia. *J. Clin. Endocrinol. Metab.*, **92**(9): 3517-3522.

Camille E Powe, Ellen W Seely, Sarosh Rana, Ishir Bhan, Jeffrey Ecker, S Ananth Karumanchi and Ravi Thadhani (2010). First trimester vitamin D, vitamin D binding protein and subsequent preeclampsia. *Hypertension,* **56**(4): 758-763.

De-Regil LM, Palacios C, Ansary A, Kulier R and Peña-Rosas JP (2012). Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst. Rev.*, 15;2:CD008873.

Haugen M, Brantsaeter AL, Trogstad L, Alexander J, Roth C, Magnus P and Meltzer HM (2009). Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology.*, **20**(5): 720-726.

Hypponen E (2005). Vitamin D for the prevention of preeclampsia? A hypothesis. *Nutr. Rev.*, **63**(7): 225-232.

Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T and Okamura H (1994). Prevention of preeclampsia with calcium supplementation and vitamin D3 in an antenatal protocol. *Int. J. Gynaecol. Obstet.,* **47**(2): 115-120.

Marya RK, Rathee S and Manrow M (1987). Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. *Gynecol. Obstet. Invest*, **24**(1): 38-42.

Oken E, Ning Y, Rifas-Shiman SL, Rich-Edwards JW, Olsen SF and Gillman MW (2007). Diet during pregnancy and risk of preeclampsia or gestational hypertension. *Ann. Epidemiol.*, **17**: 663-668.

Shand AW, Nassar N, Dadelszen P Von, Innis SM and Green TJ (2010). Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. *BJOG,* **117**(13): 1593-1598.

Urrutia RP and Thorp JM (2012). Vitamin D in pregnancy: Current concepts. *Curr. Opin. Obstet. Gynecol.,* **24**(2): 57-64.