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Original Article

Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: A systematic review and updated meta-analysis

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ABSTRACT

Objectives: Because of the immune modulatory effects of vitamin D3 in preeclampsia, we intend to have a systematic review and meta-analysis on association of both 25-hydroxy vitamin D (25-OHD) level (parametric approach) and 25-OHD deficiency (non-parametric approach) with preeclampsia. As well, for the parametric part, we used receiver operating characteristic (ROC) curve model.
Materials and methods: We used Web of Science, PubMed and Science Direct data bases through searching in titles. Google Scholar search engine was used in order to find missing papers. Finally 23 studies were imported. Both random and fixed models were reported.
Results: Based on the forest plot, lower levels of 25-OHD were significantly associated with risk of preeclampsia (fixed and random $P < 0.001$). Based on the forest plot, vitamin D deficiency (25-OHD < 20 ng/ml) was significantly associated with risk of preeclampsia (fixed $P < 0.0001$; random $P = 0.0029$; fixed OR = 1.33; random OR = 1.54). Based on ROC curve results, we found 2 cutoffs of 10.60 and 20.05 ng/ml.
Conclusion: Women with vitamin D deficiency at cutoff 20 ng/ml are more at risk of preeclampsia. This association can be specific up to 90% at 10.60 ng/ml cutoff. Treatment of vitamin D deficiency is necessary before pregnancy.

Introduction

Background

Reproductive immunology is of the conviction that pregnancy is a kind of transplantation called as semi-allograft. The immune tolerance induced by natural killer (NK) cells, impedes rejection of this transplantation. In a successful pregnancy, immune system not only does not reject embryo, but also protects the transplantation [1,2]. Other than immune tolerance, adhesive factors [3], angiogenic factors and hormonal balance play roll in pregnancy maintenance [4,5]. Of course such other factors are extremely associated immune system. For example, estrogen/progesterone balance is in near contact with T-helper1/T-helper2 balance [6]. Another instance which is the topic of our present paper is vitamin D3. Other than nutritional value, this vitamin is an endocrine hormone. As well, other than being a hormone, vitamin D3 is an immune mediator [7,8]. Failure of the immune processes mentioned before, results in blood supplying insufficiency of fetus and preeclampsia. Hence preeclampsia is associated with immune system [1].

Rationale

Regulatory T cells (Treg) are another immune cells involved in physiology of pregnancy [1]. Tregs ($CD4^+CD25^+$) play role in immune modulation. Proliferation and differentiation of these lymphocytes are controlled by forkhead box P3 (*FOXP3*) gene [9,10]. *FOXP3* expression is controlled by transforming growth factor beta (TGF-β). Other than TGF-β, this gene is affected by vitamin D3. Therefore, vitamin D receptor (*VDR*) will be another involved gene in preeclampsia and other pregnancy complications [11,12]. It

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seems that vitamin D deficiency results in down regulation of Treg population [13–15].

Objectives

Because of the immune modulatory effects of vitamin D3 in preeclampsia, we intend to have a systematic review and meta-analysis on association of both 25-hydroxy vitamin D (25-OHD) level (parametric approach) and 25-OHD deficiency (non-parametric approach) with preeclampsia. As well, for the parametric part, we are intend to use receiver operating characteristic (ROC) curve model.

Methods

Study selection

In the present paper we used Web of Science, PubMed and Science Direct data bases through searching in titles. We found 30, 16 and 25 documents respectively (n = 71). After exclusion of duplicates and conference abstracts, 30 papers remained (n = 30). Then content wise, 17 papers were finally selected (n = 17). Google Scholar search engine was used in order to find missing papers. Hereby 5 papers were manually added (n = 23). After data summarizing (Table 1), only studies with complete information of numerical findings imported for meta-analysis (other papers were used for qualitative systematic review). Because of high number of figures, the flowchart is not shown. PROSPERO web site, was used for finding other meta-analyses.

Eligibility criteria

We had content (topic) and numerical criteria. Contentwise, papers about administration of vitamin D supplements were excluded. Quantitywise, we needed the concentration of 25-OHD (ng/ml) in both groups. For vitamin D deficiency our regarded cutoff point was 20 ng/ml.

Statistical analyses

In order to design our meta-graphs, the software comprehensive meta-analysis version 2 (Biostat, US) was used. We intended to design two forest plots for both parametric (20-OHD level) and Odds ratio based (non-parametric approach at cutoff 25-OHD <20 ng/ml) information. The effect size instructions were "mean ± SD" and "exposed and unexposed for cases and controls" respectively. Because of 10 simultaneous studies in each forest plot, we considered pooled P value of 0.005 instead of 0.05 to control false significance (Bonferroni's correction).

Heterogeneity and publication bias

In order to detect heterogeneity and publication bias, I^2 and funnel plots were used respectively. The forest plots were reported based on both fixed and random effect models. For odds ratio based meta-graphs (our non-parametric part of analysis), Yate's correction was used in order to homogenize the odds ratios from each side toward OR = 1. This correction procedure was done manually [16].

Additional analyses

Meta-regression plot was used to show impact of study type in effect size. For this aim, case–control, nested case–control (NCC) and cohort studies were ranked 0, 1 and 2 respectively based on prospectiveness (the level of having prospective nature). In addition, ROC curve was designed through software GraphPad Prism version 6 (GraphPad, US) to evaluate medical diagnosis accuracy of

Table 1
Summarized information of the imported studies.

Study name	Study type	Type of PE*	Trimester of 25-OHD evaluation	Country	Patient number	Health number	Patient 25-OHD (SD) ng/ml	Health 25-OHD (SD) ng/ml	Patient 25-OHD <20 ng/ml	Health 25-OHD <20 ng/ml	Effect size group for meta-graph
Bodnar, 2007	NCC	NM/All	Early/first	US	49	216	18 (2.4)	21.2 (2.4)	NM	NM	Mean/SD
Baker, 2010	NCC	Severe	Mid/second	US	44	198	30 (11.2)	39.2 (12)	11	19	Both
Shand, 2010	Cohort	No control	Cohort	Canada	161	28	NM	NM	80	17	Excluded
Robinson, 2013	NCC	Severe	Early/first	US	40	40	16.9 (NM)	33.2 (NM)	NM	NM	Excluded
Scholl, 2013	Cohort	NM/All	Cohort	US	69	1072	NM	NM	31	360	2 by 2 table
Ullah, 2013	Case-control	Preeclampsia Eclampsia	After admission	Bangladesh	33 79	76	23.96 (2.62) 21.56 (2.32)	24.86 (2.04)	NM NM	NM	Mean/SD
Yu, 2013	Case-control	Early PE Late PE	Early/first	UK	30 60	1000	12.90 (NM) 15.71 (NM)	18.75 (NM)	NM	NM	Excluded
Bodnar, 2014	Cohort	NM/All	Cohort	US	717	3068	NM	NM	432	1749	2 by 2 table
Gernand, 2014	Cohort	LDA-CT	Cohort	US	NA	NA	NA	NA	NA	NA	Excluded
Lechtermann, 2014	Cohort	NM/All	Cohort	Germany	25	43	18.2 (NM)	33.3 (NM)	NM	NM	Excluded
Reeves, 2014	Cohort	No control	Cohort	US	NA	NA	NA	NA	NA	NA	Excluded
Rezaei, 2014	Case-control	Severe	Mid/second	Iran	50	100	NM	NM	40	75	2 by 2 table
Wetta, 2014	NCC	NM/All	Mid/second	UK	89	177	27.4 (14.4)	28.6 (12.6)	NM	NM	Mean/SD
Achkar, 2015	NCC	NM/All	Early/first	Canada	169	1975	18.8 (6.4)	20.8 (7.8)	103	909	Both
Bakacak, 2015	Case-control	Preeclampsia Eclampsia	Mid/second	Turkey	83 32	40	19.3 (4.31) 18.5 (5.47)	23.7 (5.93)	NM	NM	Mean/SD
Gidlöf, 2015	NCC	NM/All	Early/first	Sweden	37	120	NM	NM	14	62	2 by 2 table
Singla, 2015	Case-control	Mild/severe	Mid/second	India	74	100	9.7 (4.94)	14.8 (6.68)	NM	NM	Mean/SD
Bärebring, 2016	Cohort	No control	First/third	Sweden	NA	NA	NA	NA	NA	NA	Excluded
Djekic-Ivankovic, 2016	Case-control	NM/All	Delivery	Serbia	30	30	NM	NM	29	23	2 by 2 table
Goel, 2016	Case-control	NM/All	NM	India	42	50	6.72 (3.81)	9.88 (6.03)	42	46	Both
Mirzakhani, 2016	Cohort	NM/All	Cohort	US	NA	NA	NA	NA	NA	NA	Excluded
Hashemipour, 2017	Case-control	NM/All	NM	Iran	74	75	10 (6.4)	11.2 (6.4)	68	65	Both
Zhao, 2017	Cohort	Severe	Cohort	China	139	11012	32.8 (11.7)	37.7 (14.1)	123	8559	Both

*PE = preeclampsia; SD = standard deviation; 25-OHD = 25-hyroxy vitamin D; NCC = nested case–control; NM = not mentioned; E = eclampsia; LDA-CT = low-dose aspirin clinical trial; NA = not applicable.

25-OHD level in preeclampsia. Of course this analysis was based on 25-OHD level of each group of each study, with same weights. Nmol/lit values were converted to ng/ml through the online source http://www.vitamindservice.com/node/91.

Results

Selection results

The imported studies were Bodnar, 2007 [14], Baker, 2010 [17], Shand, 2010 [18], Robinson, 2013 [19], Scholl, 2013 [20], Ullah, 2013 [21], Yu, 2013 [22], Bodnar, 2014 [23], Gernand, 2014 [24], Lechtermann, 2014 [25], Reeves, 2014 [26], Rezaei, 2014 [27], Wetta, 2014 [28], Achkar, 2015 [29], Bakacak, 2015 [30], Gidlöf, 2015 [31], Singla, 2015 [32], Bärebring, 2016 [33], Djekic-Ivankovic, 2016 [34], Goel, 2016 [35], Mirzakhani, 2016 [36], Hashemipour, 2017 [37], Zhao, 2017 [38]. Summary information of the imported studies are shown in Table 1. Among the selected papers, 10 of them were imported for parametric analysis and 10 of them were imported for non-parametric analysis. The studies of Ullah et al. and Bakacak et al. had two subgroups of preeclampsia and eclampsia. We chose the first subgroup for meta-analysis.

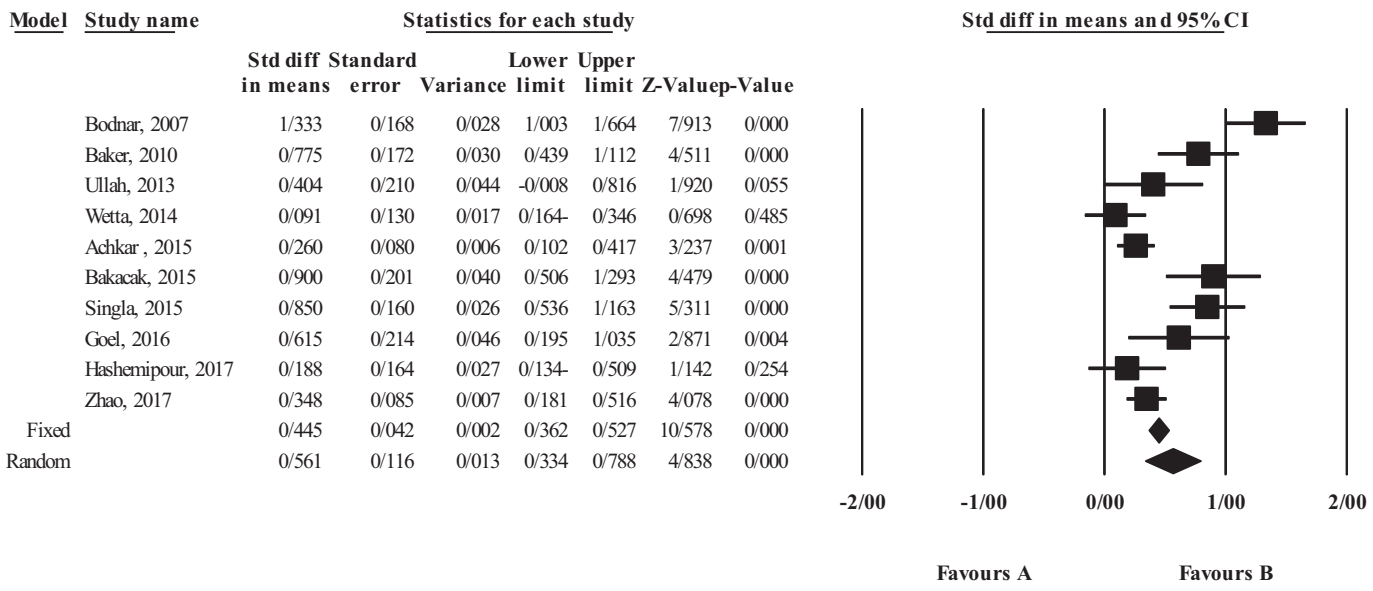

Fig. 1. Forest plot of 25-OHD. Favours B shows the protective effects of positive standard difference in means. Fixed $I^2 = 85.0\%$.

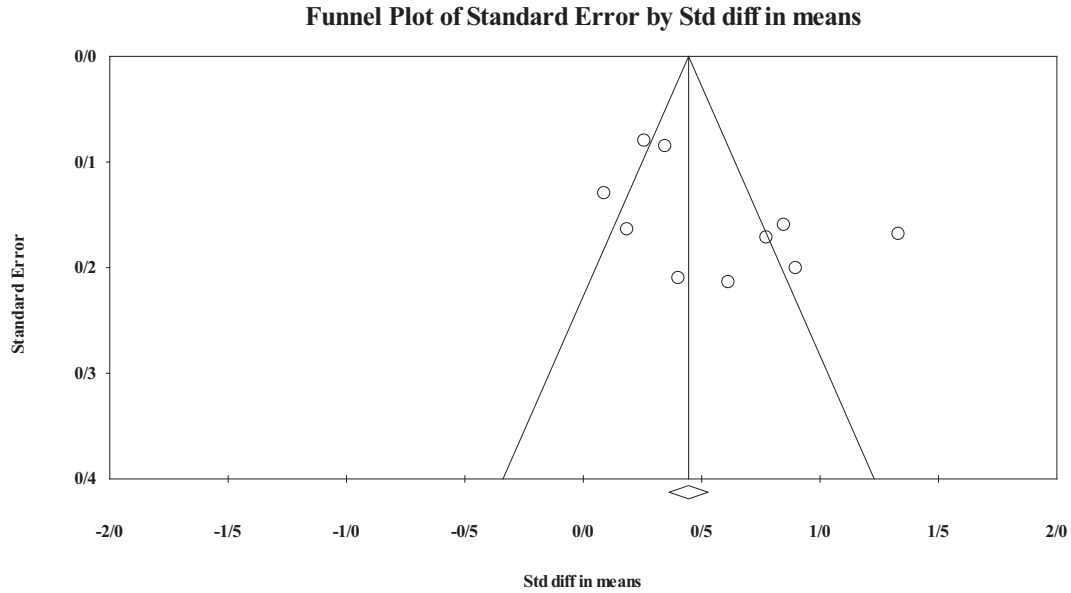

Fig. 2. Funnel plot of 25-OHD (fixed).

Parametric results

Based on the forest plot, lower levels of 25-OHD were significantly associated with risk of preeclampsia (fixed and random P < 0.001) (Fig. 1). There was a heterogeneity (fixed $I^2 = 85.0\%$) and there was publication bias based on the funnel plot (Fig. 2).

Non-parametric results

Based on the forest plot, vitamin D deficiency (25-OHD < 20 ng/ml) was significantly associated with risk of preeclampsia (fixed P < 0.0001; random P = 0.0029; fixed OR = 1.33; random OR = 1.54) (Fig. 3). There was a mild heterogeneity (fixed $I^2 = 57.7\%$), but there was no publication bias based on fixed funnel plot (of course random funnel plot had it) (Figs. 4 and 5). The meta-regression plot shows that this effect size would be lower in prospective studies, of course this finding was not significant (slope P = 0.08) (Fig. 6).

ROC curve results

This model has been used for evaluation of medical diagnosis accuracy of 25-OHD level in diagnosis/prediction of preeclampsia.

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Baker (2010)	2/869	1/243	6/620	2/471	0/0135
	Scholl (2013)	1/647	1/008	2/692	1/990	0/0466
	Bodnar (2014)	1/139	0/965	1/344	1/540	0/1236
	Rezaei (2014)	1/221	0/538	2/769	0/477	0/6331
	Achkar (2015)	1/806	1/310	2/489	3/608	0/0003
	Gidlof (2015)	0/613	0/289	1/299	1/277-	0/2015
	Djekic-Ivankovic (2016)	5/255	0/820	33/674	1/751	0/0800
	Goel (2016)	6/247	0/313	124/555	1/200	0/2302
	Hashemipour (2017)	1/506	0/525	4/321	0/762	0/4463
	Zhao (2017)	2/127	1/270	3/563	2/867	0/0041
Fixed		1/336	1/174	1/520	4/394	0/0000
Random		1/540	1/159	2/047	2/976	0/0029

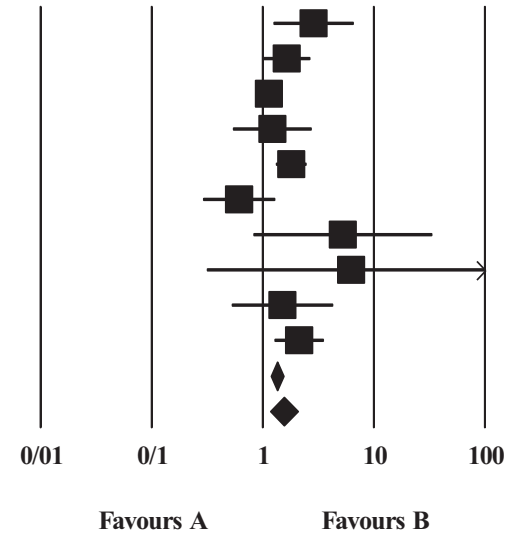

Fig. 3. Forest plot of vitamin D deficiency. The odds ratios are Yate's corrected. Favours B shows the protective effects of sufficient vitamin D. Fixed $I^2 = 57.7\%$.

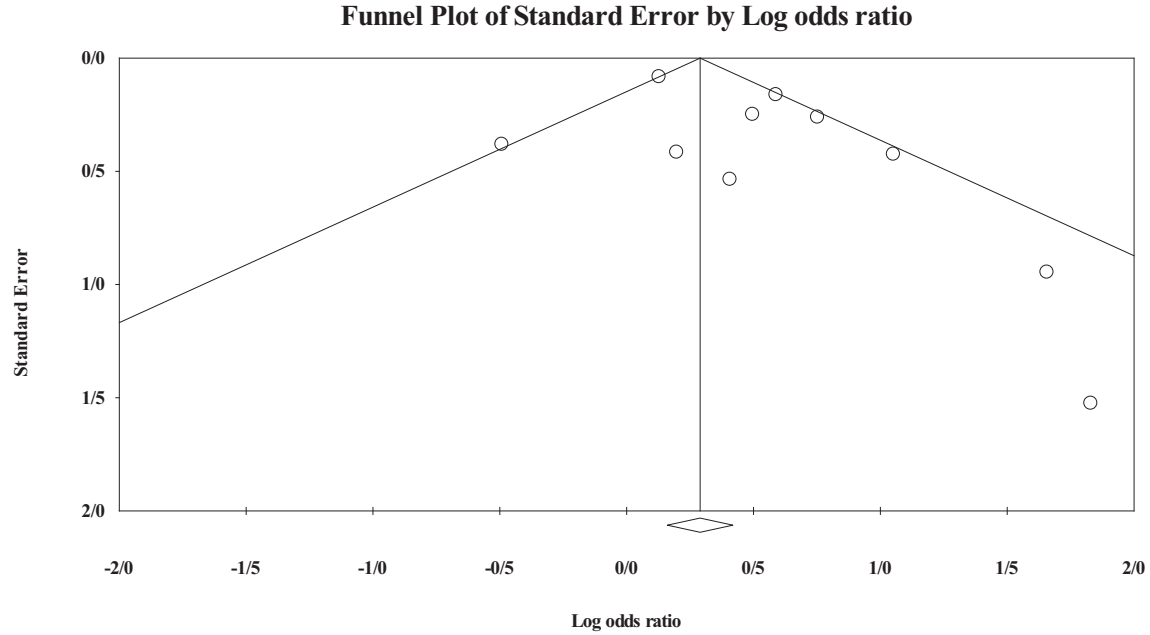

Fig. 4. Fixed model funnel plot of vitamin D deficiency.

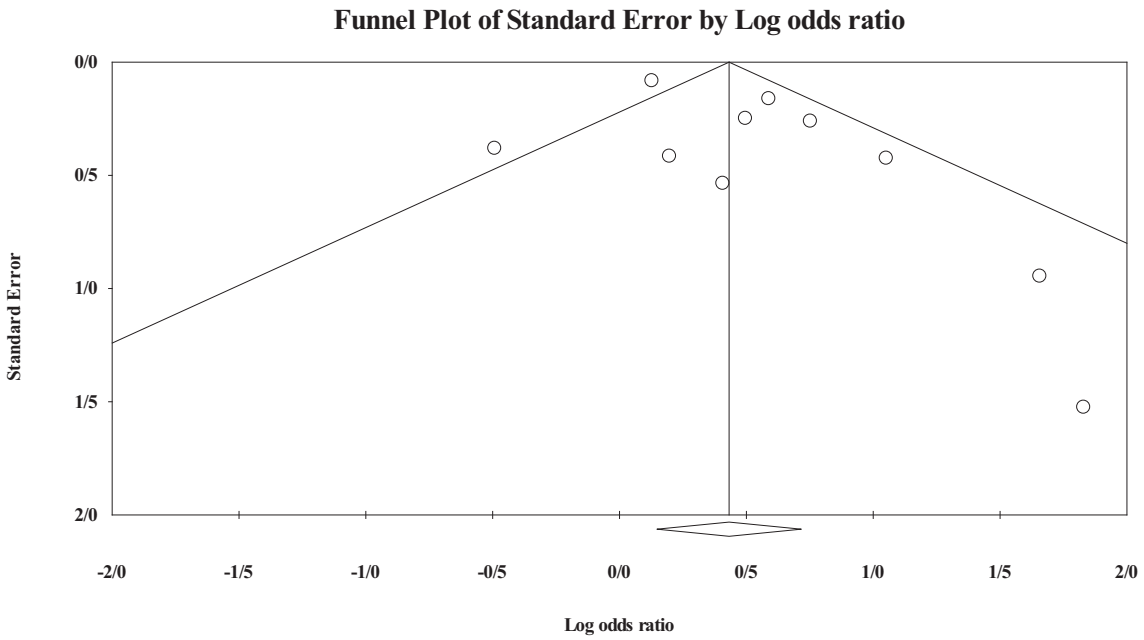

Fig. 5. Random model funnel plot of vitamin D deficiency.

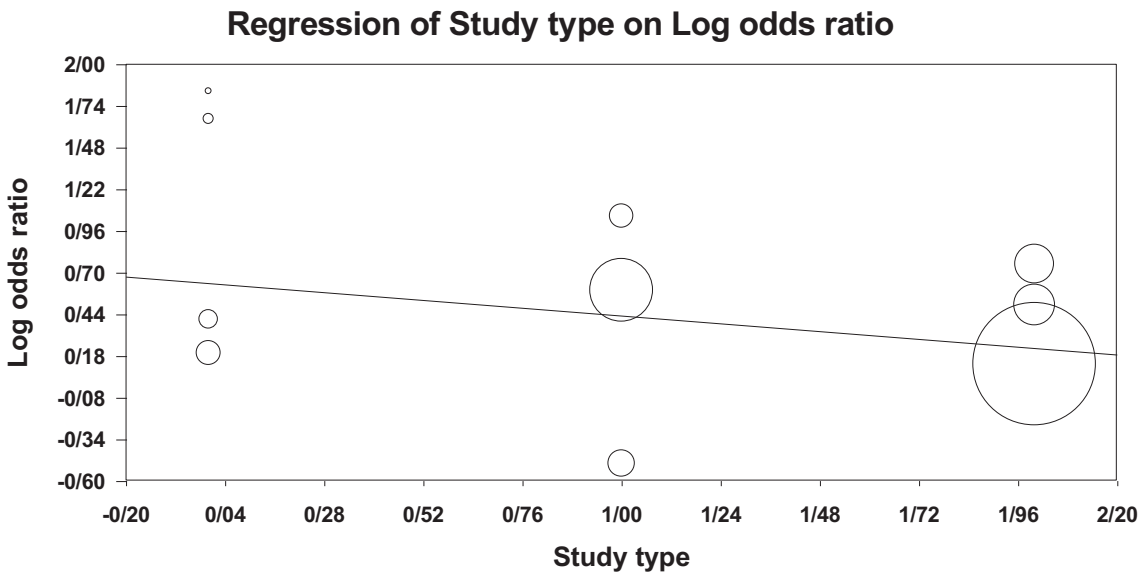

Fig. 6. Effect of prospectiveness on effect size. Fixed model slope P value = 0.08. (Case–control = 0; NCC = 1; cohort = 2).

Based on this, we found 2 cutoffs of 10.60 and 20.05 ng/ml. Cutoff 9.79 had up to 100% specificity (Table 2 and Fig. 7). Of course this specificity was in comparison to the control groups, not other diseases and disorders. As well, this 100% specificity will not be clinically occurred because we should regard confidence intervals.

Discussion

Interpretation of the results

Parametric results

All the studies imported in the forest plot, had protective effect directions (standard difference in means > 0) (Fig. 1). It shows that lower levels of vitamin D is associated with risk of preeclampsia in approximately all populations. Although there was a high heterogeneity, but it was not important to us; because this heterogeneity depended on ethnicities, *FOXP3* and *VDR* allele genetic reservoirs, sun exposure condition of the country, season of evaluation, etc. of each study. Because of such bias, further interpretation is not possible.

Non-parametric results

This forest plot is more reliable. The fixed funnel plot showed no publication bias. It shows that vitamin D deficiency at cutoff 20 ng/ml is definitely associated with risk of preeclampsia. The pooled odds ratio was acceptable (of course it was adjusted with Yate's correction).

ROC curve results

Because of high heterogeneity of the studies in 25-OHD levels, we preferred to design this curve without any weight. The first bold

Table 2
Diagnostic accuracy of serum 25-OHD in preeclampsia.

Cutoff	Sensitivity%	Specificity%	Likelihood ratio
<8.210	10/00	100/0	
<9.790	20/00	100/0	
<9.940	20/00	90/00	2/000
<10.60	**30/00**	**90/00**	**3/000**
<13.00	30/00	80/00	1/500
<16.40	30/00	70/00	1/000
<18.40	40/00	70/00	1/333
<19.05	50/00	70/00	1/667
<20.05	**60/00**	**70/00**	**2/000**
<21.00	60/00	60/00	1/500
<22.45	60/00	50/00	1/200
<23.83	60/00	40/00	1/000
<24.41	70/00	40/00	1/167
<26.13	70/00	30/00	1/000
<28.00	80/00	30/00	1/143
<29.30	80/00	20/00	1/000
<31.40	90/00	20/00	1/125
<35.25	100/0	20/00	1/250
<38.45	100/0	10/00	1/111

The chosen cutoffs based on peaks of likelihood ratio are shown in bold.

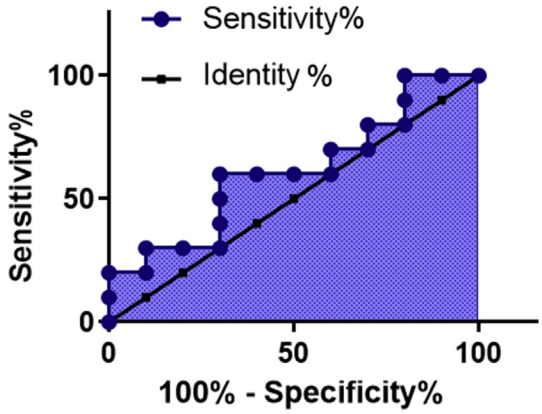

Fig. 7. ROC curve of 25-OHD level. (Area = 61%).

cutoff of Table 2 is more reliable, because the second bold cutoff is not matched with the non-parametric results (both of them are at cutoff 20 ng/ml, but the specificities seem different). Hence at cutoff 20, Fig. 3 is more reliable than the blue-colored part of Table 2.

Summary of evidence

Previously, role of vitamin C and vitamin E had been imported in a meta-analysis. Based on that, combined supplementation of vitamin C and vitamin E was not protective for preeclampsia [39]. For vitamin D, a meta-analysis conducted in 2013 suggested that vitamin D supplementation can reduce risk of preeclampsia [40]. There were 3 ongoing meta-analyses in PROSPERO about vitamin D and preeclampsia [41–43]. For vitamin D deficiency a meta-analysis was conducted in 2013 showed that vitamin D deficiency increased risk of preeclampsia. There was no parametric analysis in that study [44].

Epidemiological findings in Iran

Badfar et al. (2017) performed a meta-analysis on prevalence of vitamin D deficiency in pregnant women. Their meta-regression plot showed that vitamin deficiency was increasing from 1995 to 2016. The prevalence of vitamin D deficiency based on cutoffs 10 and 20 ng/ml were respectively 42.42% and 55.84%. Based on our findings, vitamin D supplementation is needed in Iran [45]. A meta-analysis conducted by Azami et al. (2017) showed that vitamin D level in Iranian pregnant women was 15.02 ng/ml [46].

Limitations

Different ethnicities and genetic reservoirs of *FOXP3* and *VDR*, different countries, different types of preeclampsia, different times and conditions of vitamin D evaluation, and as well different brands and qualities of kits in different studies. All of these, resulted in the heterogeneity of the imported studies.

Conclusion

Women with vitamin D deficiency at cutoff 20 ng/ml are more at risk of preeclampsia. This association can be specific up to 90% at 10.60 ng/ml cutoff. Treatment of vitamin D deficiency is necessary before pregnancy. Cohort studies are suggested for evaluation of positive predictive value at cutoff 10 in groups of supplement treated and untreated. Evidence-based findings should be updated in text books.

Conflict of interest

None.

Acknowledgement

This meta-analysis is a part of thesis entitled “Association of *FOXP3* gene polymorphisms with risk of preeclampsia”. The registration number is A-10-1869-1. The ethical code of this thesis is IR.LUMS.REC.1396.394.

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