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Vitamin D and Pre-eclampsia

Kawtar Nassar*, Wafae Rachidi, Saadia Janani and Ouafa Mkinsi

Department of Rheumatology, Ibn Rochd University Hospital, University of Medicine and Pharmacy of Casablanca, Morocco

***Corresponding author:** Nassar K, 33, Avenue du 2mars, Résidence Youssef Appartement 2, 1er étage, Casablanca, Morocco, Tel: +212 662080302; E-mail: kawtarnassar@yahoo.fr

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Abstract

Pre-eclampsia is a pregnancy disorder, usually occurs during the third trimester, and manifested by hypertension and proteinuria. Several alterations of calcium metabolism have been described. Poor Vitamin D status has been described in pregnancy women in several countries, and that has been associated with an increased risk lower birth weight, type 1 diabetes and asthma, and it is one of risk factors of preeclampsia. Previous studies report an association between vitamin D deficiency and hypertension, including the pregnancy-specific preeclampsia. It has been reported that women taking supplements containing vitamin D pre-pregnancy, in the first trimester and in late pregnancy had a lower risk of developing preeclampsia than those who did not. The aim of our study is to review the association between vitamin D statues during pregnancy, specially the pre-eclampsia risk.

Keywords: Pre-eclampsia; Vitamin D; Pregnancy; Supplementation; Complications

Introduction

Preeclampsia is pregnancy-specific syndroma, characterized by high blood pressure induced and proteinuria after 20 weeks gestation [1]. It complicates 2-8% of all pregnancies, accounts for 25% of all maternal deaths, and perinatal morbidity and mortality [2,3]. Disorders of calcium metabolism, including hypocalciuria and low vitamin D level, have been consistently described, during clinical disease in pregnancy women who later developed preeclampsia [4-6]. Despite maternal vitamin D deficiency has been observed during pregnancy, with rates varying by sunlight and ethnicity [7,8], and the involvement of pro-inflammatory cytokine [9]. The etiology of pre-eclampsia is unknown. Abnormal trophoblastic invasion, inflammatory changes, oxidative stress, and immunological factors are all potential contributing factors [10]. The attention has been drawn to vitamin D as a possible etiological factor in pre-eclampsia, during it, the metabolism of vitamin D in placental tissue is altered, and previously studies reported lower maternal serum vitamin D and its active metabolite concentrations in women after diagnosis of pre-eclampsia, or before clinical diagnosis. Otherwise, it is uncertain whether there is a critical window for exposure during pregnancy that increases the risk of pre-eclampsia. Our objective is to determine the association between maternal vitamin D status during pregnancy, its protective effect and the pre-eclampsia risk.

Methods

We performed a systematic review and where possible combined study results using meta-analysis to estimate the combined effect size. Major electronic databases (including Database of Abstracts of Reviews of Effect, Cochrane Database of Systematic Reviews) were searched from inception up to June 2014 covering both published and grey literature. Bibliographies of selected papers were hand-searched for additional references.

Current Status of Knowledge

Physiopathology of preeclampsia

Preeclampsia is a gestational complication that classically appears from the start of the second trimester and which is specific to humans, and resulting in serious maternal and fetal morbidity and mortality. It is a disease of the maternal endothelium, which is placental origin [11]. Despite recent progress toward the understanding of the pathophysiology of preeclampsia, the disorder remains a challenge with no preventive therapy and effective treatment limited to delivery to terminate pregnancy and the disorder.

Molecular data confronted with pathological studies directed towards a pathophysiological diagram including several successive stages: Defective uterine vascular remodeling (due to a lack of trophoblastic invasion) responsible for hypo-perfusion of the intervillous space, placental hypoxia and oxidative stress inducing dysfunction of syncytiotrophoblast, a maternal endothelial dysfunction associated with various substances released by the placenta into the maternal circulation (free radicals, oxidized lipids, cytokines, sVEGFR-1,angiogenic dysregulation factors, especially EG-VEGF) and leading to the clinical signs of the disease [12].

As a result, the most promising biomarkers for preeclampsia are associated with alterations in angiogenic factors as either an etiology or a byproduct of disease development. As in spontaneous preterm birth, combinations of biomarkers are thought to have stronger test characteristics than individual biomarkers alone [13]. Specifically, the ratios of sFlt-1/PlGF, and of PlGF/sEng as well as the combination of sFlt-1, PlGF, and sEng [14] have stronger ability to predict preeclampsia than any individual biomarkers alone. On the journey of discovering the underlying mechanisms that cause pre- eclampsia, vitamin D deficiency has been linked with an increased risk of preeclampsia [14].

Vitamin D and pregnancy

Vitamin D is a pro hormone derivative from cholesterol. It has two origins: Endogenous and exogenous. Endogenous synthesis, skin provitamin D3 is made from 7-dehydrocholesterol in the deep layers of the skin under the effect of ultraviolet UVB (290-315 nm) obtained from lanolin. This form is the main source of vitamin D. $1,25(OH)_2$ vitamine D is an active form. It plays a key role in calcium-phosphorus homeostasis and bone metabolism, but it is also involved in numerous others tissues. The activated $1,25(OH)_2$ vitamine D mediates its actions through specific vitamin D receptors (VDR), which are expressed in both decidua and trophoblast.

Recent pregnancy-related studies indicate that vitamin D inhibits the messenger RNA transcription of inflammatory cytokine genes (TNFa, interferon- g, and IL-6) in trophoblast cell culture systems. Vitamin D insufficiency is characterized, since 2005, by 25(OH)D concentration less than 75 nmol/L (or 30 ng/mL) [15].

During pregnancy, there is a metabolism changes of vitamin D and calcium occur to provide fetal calcium necessary for its bone development. The fetal skeleton construction requires about 30 grams of calcium during pregnancy, 80% during the third quarter [16]. The process of active transfer of calcium and phosphorus maternefoetal seems to be stimulated by a protein secreted locally, having action similar to parathyroid hormone (PTHrP) and the active derivative of vitamin D; 1,25 (OH) vitamin D, 1 alpha hydroxylase which ensures placental synthesis from 1,25 (OH) vitamin D [17]. During pregnancy, vitamin D may play a role in implantation and placental function potentially due to angiogenic, immunomodulatory, and anti-inflammatory effects. It could also interfere with many mechanisms involved in preeclampsia's pathogenesis including trophoblastic invasion as well as blood pressure control and proteinuria. Occurrence of preeclampsia and gestational diabetes seems to be linked to vitamin D deficiency but recent data in the literature are contradictory [18].

Vitamin D supplementation during pregnancy is controversial. Some societies consider it unnecessary and others recommend up to 2000 UI/d and there is no reported case of teratogenicity linked with vitamin D intake [18,19].

The effect of vitamin D in preeclampsia

Several studies have reported increased risk of preeclampsia when 25-hyrdoxyvitamin D levels are low [19]. It may protect from preeclampsia through influences on immune modulation and vascular function. The National Institutes of Health has funded several ongoing trials to assess the extent to which vitamin D supplementation during pregnancy may prevent perinatal complications [20]. Maternal vitamin D deficiency is associated with a 5-fold increase in the odds of preeclampsia compared with normotensive controls [21].

The prevalence of vitamin D insufficiency was very high with more than 3 quarters (78%) of all subjects having a serum 25(OH)D level<30 ng/ml, in pregnant women receiving care at the Dhaka Medical College Hospital with preeclampsia (n=33), eclampsia (n=79), and normal pregnancy (controls, n=76). The mean serum 25(OH)D level was 24.86 ng/ml in controls, 23.96 ng/ml in pre-eclamptic women, and 21.56 ng/ml in eclampsia patients.

Comparing to those who had a serum 25(OH)D level of ≥30 ng/ml, the odds ratio (95% CI) of developing preeclampsia and eclampsia in mothers with vitamin D insufficiency were 3.9 (95% CI=1.18-12.87) and 5.14 (95% CI=1.98-13.37), respectively (adjusting for age, BMI and duration of pregnancy) [22]. A case-cohort study among women enrolled at 12 US sites from 1959 to 1966 in the Collaborative Perinatal Project. In serum collected at ≤26 weeks' gestation, from 717 women who later developed preeclampsia (560 mild and 157 severe cases) and from 2986 mothers without preeclampsia. Half of women in the subcohort had 25-hydroxyvitamin D (25(OH)D)>50 nmol/L.

Maternal 25(OH)D 50 to 74.9 nmol/L was associated with a reduction in the absolute and relative risk of preeclampsia and mild preeclampsia compared with 25(OH)D<30 nmol/L in the crude analysis but not after adjustment for confounders, including race, pre-pregnancy body mass index, and parity. For severe preeclampsia, 25(OH)D ≥ 50 nmol/L was associated with a reduction in three cases per 1000 pregnancies and a 40% reduction in risk, compared with 25(OH)D<50 nmol/L [23]. Serum $1,25(OH)_2$ vitamin D, total fractional urinary calcium excretion, and IGF-I concentrations were significantly lower in the preeclampsia group than in the normal group in the Halhali and al study, without significant differences in serum parathormone levels [23].

One prospective observational study compared mothers who had used vitamin D supplements before and/or during pregnancy with those who had not taken any vitamin D supplementation at any of these times, with an overall adjusted OR for preeclampsia of 0.83 (95% CI 0.75-0.92) for supplementation in the first trimester of pregnancy, with or without previous or later supplementation. When it was combined in a meta-analysis, the overall estimate suggested 19% lower odds (95% CI 25-13%, $p = 2.4 \times 10^{-8}$) of pre-eclampsia for mothers taking vitamin D supplements during pregnancy when averaged across dosages [24].

In ALSPAC, there were 99 incident cases of pre- eclampsia. Pre-eclampsia incidence was the highest for mothers with 25(OH)D<25 nmol/l and lowest for those with >75 nmol/l [25]. Other recent meta-analyses of observational studies also support an association between maternal serum 25(OH)D levels and pre-eclampsia, although in contrast to current study, neither of them restricted their analyses to confounder-adjusted studies and one of them included studies that measured concentrations at the time of pre-eclampsia [25,26].

There are several mechanisms by which vitamin D could potentially prevent or at least delay the progression to pre-eclampsia. One potential mechanism relates to a defective control of effector T cells by regulatory T cells. This can lead to poor placental invasion, which in turn leads to the release of placental-derived vasoconstrictor factors and consequent maternal hypertension and proteinuria. Calcitriol is believed to be important in maintaining and restoring immune homeostasis and tolerance. Vitamin D receptors on immune cells express key enzymes involved in the hormonal activation and catabolism of vitamin D metabolites, suggesting that the availability and effectiveness of Calcitriol can be directly regulated by the cells of the immune system [21,27].

Vitamin D receptors on the heart and blood vessels suggest vitamin D has a cardio-protective effect, and Calcitriol can influence endothelial and vascular smooth-muscle cell function as well as controlling inflammation and affecting the regulation of blood pressure through influences on the renin-angiotensin-aldosterone system. Direct effects on the arterial wall by calcitriol may be important by preventing cholesterol uptake by macrophages and vascular smooth muscle proliferation; an athermanous pathology that is acutely observed in utero-placental vessels in women with pre-eclampsia [28,29].

Management and treatment of preeclampsia

The treatment of preeclampsia consists of ending the pregnancy. The only curative treatment is currently represented by the termination of pregnancy allows both the extraction of the fetus and placenta. In some cases, medical termination of pregnancy can sometimes be discussed in case of major severity and because of the prognosis and postnatal maternal risk [30]. Sibai established recommendations (expectant or grant) for the management of severe preeclampsia before 34 weeks of amenorrhea [31].

Corticosteroids for lung maturity have to be prioritized depending on the term. Antihypertensive drugs are used to limit maternal complications, especially neurological form. Calcium pump inhibitors are usually indicate as a first line choice. Magnesium sulfate needs to be administered with care and strict monitoring. Aspirin has shown efficacy in preventing pre-eclampsia with a 10% incidence reduction. It must be started between the 12th and 14th week of amenorrhea with a dose of 75 to 160 mg once daily, especially for high risk population [32].

Randomized controlled trials (RCTs) comparing high-dose (at least 1 g daily of calcium) or low-dose calcium supplementation during pregnancy with placebo or no calcium, collected from eligibility and trial quality, extracted and double-entered data, found that Calcium supplementation (≥1 g/day) is associated with a significant reduction in the risk of pre-eclampsia, particularly for women with low calcium diets. It also reduces preterm birth and the occurrence of the composite outcome 'maternal death or serious morbidity'. It also reduces preterm birth and the occurrence of the composite outcome 'maternal death or serious morbidity'. The option of lower-dose supplements (500 to 600 mg/day) might be considered in preference to no supplementation, especially in the malnourished and young patents [33]. The vitamin D dose recommended is colechalciferol 100 000 UI in the seventh month of pregnancy, or calcifediol supplementation of 400 to 800 UI / day. That prevents children rickets. It also promotes long-term changes in bone growth.

1000 UI daily to the third trimester also appear possible within normal maternal and cord blood and even reduces the risk of neonatal hypocalcaemia, with a frequency 5.1% to 1.9%.

A randomized controlled U.S. study compared the daily administration of 400, 2000 or 4000 UI of vitamin D3 in pregnant women between 12 and 16 weeks of pregnancy until delivery. Supplementation with vitamin D to 4,000 UI daily is more effective to maintain plasma levels of 25 (OH) D sufficient (>32 ng/ml), regardless of ethnicity, and without toxicity [34].

Conclusion

Pre-eclampsia is potentially a life-threatening condition for both mother and fetus. Knowledge of the pathophysiology advances slowly and should provide help to develop new areas of research. Delivery of the placenta remains the only cure, but is often associated with severe prematurity for the neonate. Vitamin D is a promising candidate for preeclampsia prevention, and there is an urgent need for well-controlled randomized trials to test its effectiveness and safety.

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