

The Association between Maternal Vitamin D Status in Gestation and Pre-Eclampsia

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Abstract

Preeclampsia is a complex and life threatening pregnancy disorder is major cause of maternal and neonatal morbidity and mortality. A growing body of evidence has demonstrated that low vitamin D is associated with the pathophysiology of preeclampsia. As such, identification of the mechanisms behind this relationship and placental vascular endothelial dysfunction presents itself as a significant modifiable disease risk factor, which if identified and managed appropriately, may make a significant impact in reducing the burden of disease.

Keywords: Vitamin D; Preeclampsia; Gestation; Pregnancy; Endothelial dysfunction

Introduction

Preeclampsia is a life threatening pregnancy disorder, which is classically characterised by hypertension and proteinuria and complicates 2-8% of all pregnancies [1]. The pathophysiology of preeclampsia is poorly understood, however, it is often described as a 2-stage process whereby Stage I is characterised by abnormal placental invasion and formation resulting in impaired placental perfusion. It is thought that reactive oxygen species and pro-inflammatory cytokines released from the ischaemic placenta result in oxidative stress and placental endothelial cell dysfunction [2,3]. This creates a pathophysiological state resulting in Stage II of preeclampsia with the clinical detection of hypertension, proteinuria and eventual organ damage [2].

In recent times, it has become increasingly evident that preeclampsia is no longer an isolated disease of pregnancy, but rather has a significant impact on the risk of subsequent maternal and paediatric cardiovascular disease [4,5]. Preeclampsia has been shown to be an independent risk factor for maternal cardiovascular disease 10 to 15 years after the affected pregnancy, with an increase in the risk of cardiovascular disease of similar magnitude to that of dyslipidaemia [4,6]. Furthermore, children of preeclamptic pregnancies have been found to have elevated blood pressure and increased cardiovascular risk later in life [7].

Current research highlights low levels of the steroid hormone vitamin D as a potentially significant independent risk factor for the development of preeclampsia and cardiovascular disease [3,8]. Vitamin D plays a critical role in vascular endothelial function, and deficiency leads to dysfunction in the preeclamptic placenta [3]. This review discusses vitamin D function in the placenta, deficiency of which increases the risk of preeclampsia, a significant cause of maternal and neonatal morbidity, and as such presents a potentially significant modifiable risk factor [9].

Vitamin D Physiology and Metabolism

Vitamin D is a steroid hormone classically involved in calcium homeostasis. The two main forms are vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol) (Table 1) [10,11]. The main source of vitamin D in humans (~90%) is in the form of vitamin D₃, which is derived from synthesis in the skin via exposure of 7-dehydrocholesterol, concentrated in the stratum basale and stratum

spinosum, to ultraviolet B (UV-B) radiation. Vitamin D₂ is obtained from the diet, and is derived from ultraviolet irradiation of ergosterol, found in fungi [11]. Both metabolites are transported in the blood bound to vitamin D binding protein (DBP) (Figure 1) [11,12]. These inactive vitamin D metabolites must undergo a two-step hydroxylation process to become biologically active [11]. Initially, vitamin D₂ and D₃ undergo hydroxylation in the maternal liver, via the action of vitamin D 25-hydroxylase enzyme (CYP27A1), to form the inactive steroid precursor 25-hydroxy-vitamin D (25[OH]D). 25[OH]D is the major circulating and stored form of vitamin D [10,11]. To enable biological activation, further hydroxylation occurs via the action of 25-hydroxyvitamin D-1- α -hydroxylase, found in the maternal kidneys and placenta, to form the active metabolite 1,25 hydroxy-vitamin D [1,25 [OH]₂D [10,11]. This process in the kidneys is tightly regulated by the parathyroid hormone, serum calcium and phosphorous levels in a physiological regulatory loop [11]. Measurement of serum vitamin D levels involve detection of 25-hydroxy-vitamin D (25[OH]D). We measure 25[OH]D in preference to the active 1,25[OH]₂D due to the latter having a half-life of several minutes, as compared to 3 weeks for the former [12]. 1,25[OH]₂D concentrations are much higher once pregnancy begins [13].

Mechanism of Vitamin D Action in the Placenta

In recent times it has been highlighted that vitamin D has many other important non-classic roles including placental and immunomodulatory functions [14]. Furthermore, vitamin D deficiency is becoming increasingly prevalent and has been linked to adverse pregnancy outcomes, including preeclampsia, insulin resistance, gestational diabetes mellitus, low birth weight (<2500 g) and high rate of Caesarean section [14-16]. The actions of the active metabolite, 1,25[OH]₂D, are mediated via binding to the vitamin D receptor

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| Name | Biological significance |
|--------------------------------------|---|
| Ergosterol | Found in fungi and is a biological precursor to vitamin D2 |
| Ergocalciferol | Derived from UV irradiation of ergosterol leading to the formation of vitamin D2 |
| 7-Dehydrocholesterol | Found in the skin (stratum basale and stratum spinosum) and leads to the production of cholecalciferol following UVB radiation |
| Vitamin D3 (Cholecalciferol) | Synthesised in the skin via exposure of 7-dehydrocholesterol to UVB radiation |
| 25-hydroxyvitamin D (Calcidiol) | Produced in the liver by the hydroxylation of vitamin D2 and D3. This is the inactive steroid precursor and the stored form in the body |
| 1,25 dihydroxyvitamin D (Calcitriol) | Produced in the kidney and/or placenta by the hydroxylation of calcidiol. This is the active form of vitamin D in the body |

Table 1: Vitamin D secosteroids and their synthesis [11]

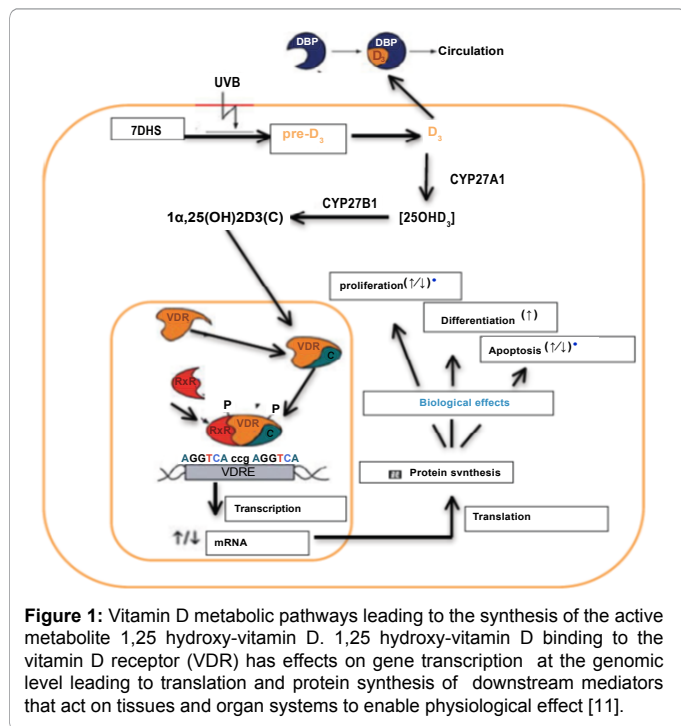
| Study type | Study details | Gestation when 25 (OH)D measured | Conclusion of the study | Reference |
|---------------------|---|---|---|-----------|
| Case- Control | Cases, n=12; Controls, n=24 | Mean 35.5 (0.6) weeks for cases and 36 (0.4) weeks for Controls. | No statistical significance observed | [24] |
| Nested case-Control | Cohort study, n=1198 women; Cases, n=55; Controls, n=220. All women nulliparous | Two occasions Before 22 weeks. Pre-delivery. | At <22 weeks a strong inverse relationship between preeclampsia and 25(OH)D was observed, p<0.02. | [9] |
| Cohort | N=1718 women; Cases, n= 59. | Not measured. | No significant difference was observed. | [25] |
| Nested case-Control | All white women with Type I diabetes. Cohort, n=151; Cases, n=23 and Controls, n=24. | Three visits Mean 12.2 (1.9) weeks Mean 21.6 (1.5) weeks Mean 31.5 (1.7) weeks | No statistical significant relationship was observed at any time point. | [26] |
| Nested case-Control | Cohort Size, n=3992 women. Cases, n=44 and Cohorts, n=201 | Between 15 and 20 weeks. | Lower 25(OH)D was associated with increased risk of severe preeclampsia. | [27] |
| Cohort | Norwegian mother and child cohort study, Norway. N=23,425 women. Cases, n=1267 | Not measured. | Lower total vitamin D intake associated with an increased risk of preeclampsia. P<0.001. | [20] |
| Nested case-Control | Cohort size, n=9930 women. Cases, n=39; Controls, n=131. | First trimester. | No significant relationship observed. p=0.43 | [28] |
| Case-Control | Cases, n=50 Controls, n=100 | Time of diagnosis, <34 weeks. | Lower 25(OH)D associated with increased risk of severe early preeclampsia. | [2] |
| Cohort | Cohort, n=221. Cases, n=28. | Between 10 and 20 weeks, 6 days (mean 18.7 (1.88) weeks). | No significant relationship observed. | [22] |
| Cross-sectional | Cohort, n=75, conducted in Pakistan. Cases, n= not provided. 26% covered their arms, hands and head; 76% also covered their face. | At delivery. | 50nmol/l maximum identified as the threshold relating to increased risk for preeclampsia. | [29] |
| Cohort | Cohort, n=466. Cases, n=7. | Between 11 and 14 weeks. | No significant relationship observed. p=0.51. | [30] |

Table 2: The association between maternal vitamin D status in gestation and maternal preeclampsia: observational studies.

(VDR), which is present in a diverse range of tissues. Sites of VDR expression include endothelial cells, cells of the innate and adaptive immune systems, pancreatic β -cells, the brain and reproductive tissues including placental trophoblast cells [17,18]. The VDR is a nuclear receptor for steroid hormones and mediates its action via two main methods, one of which is at the gene expression level and the other a more rapid non-genomic response involving signalling cascades [9]. Identified roles of vitamin D include induction of decidualisation in early pregnancy to enable implantation, angiogenesis, modulation of immune function and regulation of hormone function in pregnancy [19,20]. Human placental trophoblast cells both produce and respond to 1,25[OH]₂D, and the P450 cytochrome enzymes encoded by CYP27B1 (1 α -hydroxylase) and CYP24A1 (25-hydroxylase) genes are local regulators of 1,25[OH]₂D in these cells [3]. CYP24A1 encodes 25-hydroxylase, the vitamin D catabolizing enzyme, converting 25[OH]D and 1,25[OH]₂D to their inactive metabolites.

Recent studies have demonstrated that in preeclamptic placentas there is increased expression of this catabolizing enzyme, suggesting elevated degradation of active vitamin D in these placentas as compared to healthy placentas [3]. Furthermore, researchers have found reduced expressions of VDR and DBP in preeclamptic placentas as compared to normal placentas, providing direct evidence of disrupted vitamin D metabolism in the preeclamptic placenta [3].

Although the exact molecular mechanisms by which vitamin D deficiency affects the risk of developing preeclampsia is yet to be determined, there are a number of potential avenues by which they are hypothesised to occur. Reduced placental perfusion during Stage I may result in the placenta producing substances, including pro-inflammatory cytokines that initiate the ensuing multi-system sequelae characterising Stage II of preeclampsia [17,19]. Pro inflammatory cytokines such as tumour necrosis factor- α , (TNF- α) interleukin-6 (IL-6) and interferon- γ (IFN- γ), as well as the pro-inflammatory nuclear transcription factor nuclear factor- κ B (NF- κ B), are increased



in pregnant women with vitamin D deficiency [17,19]. Furthermore, vitamin D has been found to inhibit proliferation of T helper 1 (Th1) cells and reduce their production of pro-inflammatory cytokines IFN- γ , IL-2, and TNF- α [17]. Thus, hypothesising that maternal vitamin D deficiency predisposes to a pro-inflammatory state with increased levels of oxidative stress, leading to endothelial cell dysfunction, may have sound premise.

Vitamin D Deficiency and Vascular Endothelial Dysfunction

The diagnosis and management of vitamin D deficiency is a contentious issue with varying local practices [10]. The adequate level of serum 25(OH)D levels remains contested, with levels ranging from 80-250 nmol/L being considered vitamin D replete [11]; the majority of the literature supports the consensus of <50 nmol/L being classified as vitamin D deficient [10,11]. This can be further subclassified into three categories differentiated by severity; marginal (25-50 nmol/L), moderate (12.5-25 nmol/L), and severe (<12.5 nmol/L) [20].

In recent times, there have been a number of studies that have demonstrated a link between vitamin D deficiency and placental dysfunction in preeclampsia (Table 2), with particular emphasis on Stage I of preeclampsia as the key period during which vitamin D deficiency would have a significant impact. Bodnar et al demonstrated via a nested case control study that maternal vitamin D deficiency at less than 22 weeks' gestation was a strong independent risk factor for preeclampsia [9]. The authors hypothesise that potential mechanisms may include abnormal implantation in the absence of sufficient vitamin D leading to subsequent impaired placental perfusion and oxidative stress which results in the preeclamptic physiological sequelae [9]. Furthermore, similar results were reported by Robinson et al in another case control study where women with early onset severe preeclampsia were found to be significantly vitamin D deficient at the time of diagnosis [2]. Another observational study from Norway on 23,423 nulliparous pregnant women demonstrated that vitamin D

supplementation during pregnancy reduced the risk of preeclampsia by 27% [20]. These observational studies demonstrate a probable link between vitamin D deficiency during pregnancy and prevalence of preeclampsia, although the exact mechanism by which this occurs is yet to be determined.

However, there have been contradictory results from some studies with a prospective cohort study by Shand et al (n=221) finding no association between vitamin D deficiency and the incidence of preeclampsia in early pregnancy in a group of women identified as being at high risk of developing preeclampsia [21,22]. This conflicting result may have been due to the small sample size and selective patient subset. Furthermore, the quantification of vitamin D status during different gestational ages may have also contributed to the incongruent findings. In particular the authors looked at vitamin D concentrations between 10 to 20th week of pregnancy [22], whereas most studies show a significant association between lower concentrations of vitamin D and preeclampsia at the third trimester [23]. Therefore, studies assessing vitamin D levels at the first trimester and the subsequent risk of developing preeclampsia may conceal the true risk of such deficiency on development of preeclamptic disease later in the pregnancy. As such, studies may not be directly comparable at such varying gestation times.

Subsequently, in a prospective cohort study (n=697) assessing longitudinal vitamin D status in pregnancy has demonstrated a positive association between vitamin D deficiency at 24-26 weeks' gestation and preeclampsia [19]. Furthermore, Tabesh et al found that there was a significant association between vitamin D deficiency and the risk of developing preeclampsia on systematic review and meta-analyses of published observational studies [23].

It must be noted that these cross sectional studies have innate limitations, in that causal relationships are unable to be established [23]. Further research and stronger study design in the form of randomised clinical trials is required to elucidate the exact relationship between vitamin D and preeclampsia, although the feasibility of such studies in a patient cohort of pregnant women may be debatable.

Conclusion

It is clear that we can no longer consider vitamin D as a humble steroid hormone involved solely in mineral homeostasis - it has more complex actions than previously accredited with. In particular, we cannot ignore the multitude of evidence from observational studies linking vitamin D deficiency to preeclampsia. Further research is required to determine the exact mechanisms by which vitamin D influences placental formation, and in particular the role that vitamin D plays in Stage I of the development of preeclampsia, and the specific downstream molecular mechanisms involved in endothelial dysfunction.

The limitations of observational studies conducted to date have been discussed, highlighting the beneficial role a randomised clinical trial would play in providing us with definitive evidence based answers. Although, this may be technically difficult due to the nature of pregnancy and ethical obligations of patient safety, a careful study design can make this a reality. Other clinical questions that may be answered include the correct vitamin D analogue to test, the timing of vitamin D testing and ideal window of vitamin D supplementation in order to correctly diagnose deficiency and to effectively treat this deficiency in order to provide the greatest benefit for preventing the development of maternal preeclampsia.

If we were able to answer these clinical questions, and further identify the specific molecular and genetic mechanisms involved in the fetoplacental unit, we could better understand the intricate relationship between vitamin D deficiency and placental endothelial vascular dysfunction, thus allowing us to modify the development of long term maternal and paediatric adverse health outcome.

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