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Maternal Vitamin D deficiency and brain functions: a never-ending story

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A large number of observational studies highlighted the prevalence rates of vitamin D insufficiency and deficiency in many populations as pregnant women. Vitamin D is well known to have a crucial role in differentiation and proliferation, as well as neurotrophic and neuroprotective actions in the brain. It has been observed that this micronutrient can modulate the neurotransmission and synaptic plasticity. Recent results from animal and epidemiological studies indicated that maternal vitamin D deficiency is associated with a wide range of neurobiological disease including autism, schizophrenia, depression, multiple sclerosis or developmental defects. The aim of this review is to summarize the current state of knowledge on the effect of maternal vitamin D deficiency on brain functions and development.

1. Introduction

Challenges during pre-conception, foetal and early postnatal periods of life, such as nutritional and lifestyle imbalances, can cause the onset of diseases during adulthood; this concept is known as the Developmental Origins of Health and Disease (DOHaD). 1,2 These changes can occur via various mechanisms including the disruption of the placental function as well as epigenetic modifications such as histone modification, DNA methylations or non-coding RNAs and the consequences of which induce an alteration in the expression of key genes. 2,3 The perinatal period including gestation and lactation is considered as a critical period with high epigenome plasticity and sensitivity, during this time the mother is the only source of nutrients for the foetus. 4 Macronutrients like carbohydrates or proteins as well as micronutrients like minerals and vitamins are essential for the developing foetus and any imbalance induces functional changes and has long lasting health consequences for the offspring. 1,2,5 It is also interesting to note that several studies have reported that the foetus responds to external signals such as maternal nutritional stimuli in a gender-dependent manner suggesting that perinatal reprogramming is characterized by a sexual dimorphism. 1,2,6 In this context, the role of vitamin D (VD) in foetal development is widely studied. VD is not only known for its role in calcium homeostasis and foetal bone development, but also for its implication in many biological functions as a hormone. 7 Because of this, many studies have highlighted its skeletal and non-skeletal role during pregnancy such as foetal implantation as well as placental formation and function 8 or lung activity. 9–11 Interestingly, VD is also important for brain development and particularly in the dopamine system ontogeny, axonal connectivity and neuronal differentiation. 12 In the last decade, several studies have exposed the adverse consequences of a gestational VD deficiency (VDD) on brain development and the onset of neurological diseases in the stages of later life. The aim of this review is to assess the existing evidence of the impact of...
a maternal VDD on the neurodevelopment of offspring and its long-term neurological consequences.

2. Vitamin D

2.1. Biosynthesis, degradation and mechanisms of action of vitamin D

VD is a fat-soluble hormone that has both exogenous and endogenous origins. During endogenous synthesis, VD is produced in the skin under the action of ultraviolet B rays (UVB) and known as cholecalciferol or vitamin D3 (VD3). For the exogenous origin, VD can be found in different foodstuff. Particularly in animal-source food such as fish, fish oils, egg yolks, and beef liver under the form of VD3; and also in vegetables and mushrooms under the name of ergocalciferol or vitamin D2 (VD2) 13 (Fig. 1).

VD requires two hydroxylations in order to be biologically active. 13–15 The first step of VD activation takes place in the liver and generates 25-hydroxyvitamin D (25(OH)D), which represents the main circulating but inactive form of VD with a half-life of three to four weeks. 7,13,14 The adipose tissue is considered as a storage site for 25(OH)D as reported in rats, mice, and humans. 21 Then, 25(OH)D is transported to the kidneys, where the second step of VD activation will take place leading to the formation of 1,25-dihydroxyvitamin D (1,25(OH)2D) also called calcitriol, which is the main active form of VD. 13 Kidney production of 1,25(OH)2D is highly regulated by calcium and phosphorus levels, PTH (Parathyroid hormone) and FGF-23 (fibroblast growth factor 23). 7,13,14 1,25(OH)2D is involved in the activation of its own catabolism by inducing the expression of the ubiquitous enzyme: CYP24A1, which converts 1,25(OH)2D to 1,24,25(OH)3D, resulting in the inactive form of VD called calcitriol acid (Fig. 1). 7,13 In the context of this review, it has also been reported that there was a local activation and catabolism of VD in the central nervous system where CYP27B1 and CYP24A1 are expressed in several cell types such as neurons, astrocytes and other glial cells. 22

The active form of VD is known to have both genomic and non-genomic effects. 7,22,23 The genomic effects result from the binding of active VD to its nuclear receptor VDR (vitamin D receptor) which induces either the activation or repression of target gene (Fig. 1). 7,23 This gene regulation of VD via VDR has epigenetic effects as it modulates the expression of enzymes involved in methylation and acetylation. 23 In addition, VD also regulates the expression of micro-RNAs (miRs) which are small non-coding RNAs that are known for their role in post-transcriptional regulation of gene expression and gene silencing. 23–25 For the non-genomic effects, VD acts via a membrane receptor named Pdiα (Fig. 1). Binding and activation of this receptor by 1,25(OH)2D induces the activation of signal transduction pathways which will elicit rapid responses. 23,26–29

2.2. Biological roles of vitamin D

In addition to its primary role in the regulation and maintenance of phosphocalcic homeostasis, VD is known to have several other physiological functions in immune system and adipose tissue biology. 14,15,17,18–20 VD is also involved in regulation of immune and inflammatory responses. 27–31 More interestingly, VD is also considered an essential micronutrient for brain development during foetal life. 32 In accordance with its involvement in foetal neurodevelopment, the lack of VD in later life stages seems to be associated with the increased risk and course of many neurodegenerative and neuroinflammatory diseases as described below.

3. Vitamin D deficiency

3.1. Vitamin D status

The 25(OH)D represents the most abundant circulating form of VD. In addition to being in balance with the spare 25(OH)D, only a fraction of this metabolite is converted to active VD. Thus, the serum concentration of 25(OH)D is the best indicator of VD status. 17 A serum level greater than 30 ng/ml (75 nmol/L) is considered optimal, therefore, the VD standards have been established as follows: sufficiency >30 ng/ml (75 nmol/L), insufficiency 10–30 ng/ml (25–75 nmol/L), and deficiency <10 ng/ml (25 nmol/L). VD deficiency (VDD) or hypovitaminosis D is considered as a risk factor for many diseases such as cardiovascular 33 and autoimmune diseases 40, type 2 diabetes 41 and cancer. 42 VDD is now regarded as a global epidemic induced by many factors including a diet low in VD, inadequate exposure to the sun or obesity. 13,14

3.2. Vitamin D deficiency during perinatal period

The mother is the primary source of VD for the fetus and the placenta is a key structure in fetal development because of its involvement in the diffusion of nutrients such as 1,25(OH)2D and 25(OH)D from the mother to the fetus. Due to the presence of 1α-hydroxylase, 25(OH)D can be activated in both the trophoblast and the decidua. In addition to this enzyme, VDR is also found in the placenta, indicating that this structure not only produces but also responds to 1,25(OH)2D. 43,44 As it has been shown that VD modulates the synthesis of placental hormones involved in pregnancy such as human chorionic gonadotrophin (hCG) and also plays an important role in endometrial decidualization and thus foetal implantation. 44,45

A large proportion of pregnant women exhibit a VDD (8% to 100% in some parts of the world). 46 Several studies showed that maternal VDD induced foetal growth restriction. A prospective cohort that examined the impact of maternal VDD in a multi-ethnic population of 7,098 women found that low maternal 25(OH)D levels were associated with foetal growth restriction, low birth weight and increased risk of premature birth. 47 These results are correlated with several other studies. 48,49 Maternal VDD during pregnancy predisposes the offspring to several diseases such as childhood rickets and severe VDD in
the early stages of pregnancy was linked to an increased risk of childhood obesity. 5 In our group, we showed that a maternal VDD in mice was associated with a small birth weight in juvenile 5 weeks-old male offspring which was related to an increase of the spontaneuos activity and energy expenditure. 6 Interestingly, in adulthood, a High Fat Diet (HFD) combined with maternal VDD disrupted glucose homeostasis and adiposity in male offspring but not in females. 6 Under the same experimental conditions, a maternal VDD coupled with a HFD induced an increase in white adipose tissue inflammation as well as an increased adiposity in male offspring only, thus highlighting the sexual dimorphism in the response to a developmental VDD. 50 Maternal VDD is also associated with an increased risk of Type 1 diabetes in the offspring. 51,52 Maternal VD status also affects the epigenome of the foetus via different epigenetic mechanisms, particularly in the early stages of gestation, which can contribute to the onset and progression of diseases in adulthood. 53 VD exerts also a genomic effect in the developing brain by modulating the proliferation and differentiation of neural stem cells, regulating the development of the dopaminergic system and the release of neurotransmitters such as dopamine. It can also exhibit non-genomic actions by inducing an increase of extracellular Ca2+ uptake or by modulating kinase-activated signalling pathways in the developing cortex. Taken together, these data highlight the importance of VD and the fact that exposure to low levels of this micronutrient during foetal life alters brain development and predisposes offspring to various neurological disorders. 22,54,55 In the next sections of this review, an update on the impact of a maternal VDD on the onset of neurological and psychological disorders in the offspring has been presented.

4. The impact of maternal vitamin D deficiency on cerebral functions

4.1. Maternal vitamin D deficiency and brain development

VD is considered as a potent neurosteroid that acts via genomic and non-genomic effects. 56 Interestingly, the brain has the ability to metabolize VD due to the presence of 1α-hydroxylase and CYP24A1 in neurons and glial cells. 57 VDR is highly
expressed in different areas of the mesencephalon during embryonic development as well as in the hippocampus, thalamus, hypothalamus, cortex and substantia nigra, suggesting that VD can modulate brain development and maturation. 57–59

During brain development, VD inhibits proliferation and potentiates neuronal cell differentiation and apoptosis. In accordance with these observations, it has been demonstrated that VDD in embryonic rats induced an increase in brain cell proliferation and a decrease in apoptosis with a dysregulation of pro-apoptotic genes such as Bak (BCL2 Antagonist/Killer 1). 12,60 From a morphological point of view, maternal VDD in rats induced longer and larger brain, a longer and thinner cortex and enlarged lateral ventricles 12,60 that persists into adulthood. 61 However, the brain of maternal VDD mice was reduced in length with reduced lateral ventricle volume. 62 The absence of VD during foetal development also appears to affect brain development in C57BL/6j female mice at P0 with a reduction in their hippocampal volume that did not persist in adulthood. 63 Altogether, these observations strongly suggest the involvement of VD in the release of many neurotransmitters. In the context of a role for VD in the onset of neurotransmitter systems, it has been shown in a Sprague–Dawley rat maternal VDD model that VD depletion during development reduced factors essential for the onset of dopaminergic phenotype such as Nurr1 (nuclear receptor-related 1) and p57ki2p (p57kinase inhibitory protein2). 64 The tyrosine hydroxylase (TH) gene expression was reduced in the foetal brain of female offspring from a mice model of maternal VDD with a decrease of TH protein in the substantia nigra. 65 Regarding the GABAergic system, it has been shown that maternal VD deficiency is associated with a decrease in the expression of GABA-A alpha4 (gamma-Aminobutyric acid alpha-Aa4), a gene involved in GABA neurotransmission, in the male offspring brains. 61 This micronutrient also promotes the release and expression of neurotrophic factors such as nerve growth factor (NGF) 12,65, glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) 12,66 in different neuronal and glial cell models. Interestingly, a decrease in the synthesis of NGF as well as the expression of genes involved in neuronal structure such as MAP-2 (microtubule associated protein-2) was observed in 10 weeks-old male rats born from VDD dams. 65 Maternal VDD affects brain development during foetal life and causes alterations that may persist into adulthood, which can lead to the onset of many neurological disorders and diseases.

4.2. Maternal vitamin D deficiency and brain pathologies

4.2.1. Behavioural defects

In a behavioural context, rats exposed to a maternal VDD appeared to have cognitive impairment that was reflected in a more impulsive behaviour and decreased inhibitory control in adulthood. 67 Hawes et al. 68 showed that maternal VDD in BALB/c mice altered the expression of BDNF and TGF-ß1 (Transforming growth factor beta 1) which are involved in neuronal survival as well as FoxP2 (Forkhead box protein P2) which is known to be involved in speech and language. Maternal VDD also induced spontaneous locomotor hyperactivity in mice and rat offspring 6,68 and similar results were observed in maternal VDD rat offspring exposed to MK-801 (a hyperactivity-inducing agent). 55,69 Interestingly, this hyperactivity was observed in rats exposed to maternal VDD during advanced stages of gestation; however, it was not observed when exposure to the deficiency occurred only at early stages of gestation emphasizing the importance of critical developmental windows. 55 In a rat model of maternal VDD, adult male rats exhibited alterations in learning and memory, decreased social behaviour and increased grooming behaviour correlated with decreased levels of FoxP2. 70 Impaired learning was also observed in the adult progeny of VDD female mice (Table 1).

Some behavioural defects were also observed in humans as it has been reported in an Australian cohort that there was a 2-fold increase in the risk of language disorder at age of 5 and 10 years in the offspring of mothers with rates of 25(OH)D ≤ 46 nmol/L during the second trimester. 72 The Spanish INMA cohort also showed that there was a positive association between maternal VD levels and social competence in 5 years old offspring. 73

4.2.2. Autism

Autism spectrum disorder (ASD) is a complex neurodevelopmental disease with repetitive behaviour and difficulties in social interaction, communication and learning. 74 Several murine studies and cohorts have demonstrated that early exposure to low levels of VD during pregnancy could be a risk factor for ASD. 75,76 In 2019, Ali et al. 77 aimed to find out the impact of a maternal VDD on early postnatal, adolescent and adult offspring. By assessing righting reflex and negative geotaxis, they found out that the pups from deficient dams showed a delay in their motor development. 77 P12 rats from deficient females also exhibited increased ultrasound vocalization indicating an alteration in their vocal communication. Adolescent and young adult rats displayed an altered stereotyped repetitive behaviour as they had a reduced digging behaviour. Adolescent rats had less social interaction with longer latency to interact, which was not found in adult rats; however, adults were more hyperactive but showed no anxiety like behaviour. 77 In another animal study, maternal VDD induced an increase in the vocalizations of the pups accompanied with a decrease in cortical FoxP2, decrease in social behaviour and impaired learning and memory were observed in adult males (Table 1).

Using data from the Stockholm youth cohort, Magnusson et al. 78 examined a population of 4–17-year-old children exposed to low levels of VD during gestation and was able to report a positive association between maternal VDD and ASD. 78 Analysing the same cohort, Lee et al. 79 suggested that high
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BDNF: Brain-Derived Growth Factor; DVD: Developmental Vitamin D deficiency; Foxp2: Forkhead box protein P2; GABA-Aα4: Gamma-Amino Butyric Acid alpha 4; GDNF: Glial-Derived Neurotrophic Factor; MAP-2: Microtubule Associated Protein-2; NGF: Nerve Growth Factor; Nur1: Nuclear receptor-related 1; p57Kip2: p57Kinase inhibitory protein2; p75NTR: p75 Neurotrophin Receptor; TgfB1: Transforming growth factor beta 1; TH: Tyrosine Hydroxylase.
levels of VD during pregnancy were associated with a moderate decrease in risk of ASD in the offspring. 79 A prospective study of a multi-ethnic cohort in the Netherlands (generation R study) has also shown an association between maternal mid-gestation VDD and a two-fold increase in the risk of autism in children 80 (Table 2). Interestingly, VD supplementation seems to clinically improve ASD symptoms of affected children. 81,82

4.2.3. Schizophrenia

Schizophrenia is a neurodevelopmental disorder that affects a person’s way of thinking, feeling and behaving. Many risk factors are associated with the onset of this disease such as the season of birth 83, dark skin 84, malnutrition 85 and VDD. 86 Schizophrenia manifests itself in both cognitive, positive and negative symptoms. Positive symptoms reflect psychosis (hallucinations, delusions) while negative and cognitive symptoms refer to emotional, social and intellectual disabilities. 87 Although not all aspects of schizophrenia are observed in the murine model of maternal VDD, some features of this disease can be noticed such as enlarged lateral ventricles and increased behavioral sensitivity to antagonists of NMDA (N-methyl-D-aspartate) receptors as well as altered dopamine system development. 64,89-92 The assessment of positive symptoms in the maternal VDD murine model is done by measuring locomotor activity, which often reflects psychomotor agitation and behavioral disruption. As mentioned earlier, rats and mice from VD deficient dams are characterized by spontaneous locomotor hyperactivity 55,68,69 (Table 1). A recent study on Balb/c mice examined the impact of VD on prefrontal cortex (PFC) which is involved in the pathophysiology of schizophrenia. This study showed that optimal levels of 1,25(OH)2D significantly increased Ca2+ influx through L-VGCCs (L-type Voltage-Gated Calcium Channels) consequently increasing intracellular Ca2+ levels in a subset of prefrontal cortex neurons. Thus suggesting that inadequate levels of VD during foetal growth may modulate the function of L-VGCCs and alter neuronal maturation and excitability. 93 In humans, the neonatal status of 25(OH)D from dried blood spots showed that children born from mothers with VDD had their short moods and feelings questionnaire (SMFQ) assessed at least once, indicated that a maternal VDD during pregnancy did not increase the risk of developing childhood/adolescence depression 105 (Table 2). Several studies have explored the link between VDD and depression as well as the impact of a VD supplementation in reducing depressive symptoms. 107,108 However, the exact mechanism on how VD contributes to the aetiology and treatment of depression needs further study.

4.2.5. Multiple sclerosis

Multiple sclerosis (MS) is a neurodegenerative and inflammatory disease that affects the brain and the spinal cord. Genetic and environmental factors play a major role in the incidence of this pathology. A growing body of evidence suggests that low VD levels can contribute to the risk of developing or worsening MS. 109 In an animal model of maternal VDD, 10 weeks old progeny exhibited a dysregulation of many prefrontal cortex and hippocampus genes and proteins involved in MS 110,111 (Table 1).

Similar observations were assessed in many human studies. A Finnish study reported an increased risk of developing MS in the offspring of VD deficient mothers with 25(OH)D levels <30 nmol/L early in their pregnancy. 112 Another study assessing the diet of 35,794 pregnant mothers and the follow up of their daughters found that the offspring of mothers with higher VD dietary intake and higher 25(OH)D predicted levels during pregnancy had a lower risk of developing MS during adulthood. 113 Since MS patients with low VD levels have been associated with higher disease activity, 114,115 Many studies on time and region of birth have found associations between low maternal exposure to ultraviolet rays (UV) 116, the month of birth 117 and the risk of MS in offspring (Table 2). As VD seems to be a risk factor for MS, several studies tried to investigate the potential therapeutic role of VD supplementation in MS. To address this question, a rodent model of MS was used to explore the impact of a VD supplementation during different development stages including a supplementation prior and during gestation and lactation, after weaning and throughout juvenile/adolescence period and during adulthood. 118 This study highlighted that VD supplementation was associated with a decrease in central nervous system inflammation and demyelination. However, these results were dependent on the developmental stage.
### Table 2 Maternal VDD and neurological disorders in humans

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ASD: Autism Spectrum Disorder; VD: Vitamin D; VDD: Vitamin D Deficiency; MS: Multiple Sclerosis; UV: Ultra Violet.
During which this supplementation occurred. However, the benefits of a VD supplementation on the disease course of MS have yet to be established as many clinical studies have shown mixed results as for the effectiveness of a VD supplementation in MS and appropriate dosing still remains undetermined.

Conclusions and perspectives

Many animal and epidemiological studies have been conducted to explore the implication of VDD during foetal life on the developing brain and many have found associations between low gestational VD levels and the onset of many neurological diseases in adulthood. Different animal studies described changes in the expression of many genes related to overall brain development and functions but the molecular mechanisms by which maternal VDD alters brain development remain poorly understood (Fig. 2).

However, recent research has generated interesting data on the role of epigenetic modifications during gestational VD restriction. For instance, the group of Eyles observed an upregulation of miR-181c-5p that suppressed neurite outgrowth of DA neurons from the ventral mesencephalon. This data suggested that miRNAs can be involved in the onset of psychological disorders such as schizophrenia.

In addition, it has been shown that VD plays a role in the DNA methylation state in the germline and soma cells suggesting a role of this mechanism in the brain development. In their preclinical study, Liang et al. showed that VDD potentiates maternal diabetes induced autism-related phenotypes in offspring by epigenetic mechanisms. In the same way, epigenetic modifications were observed in a population-based mother-offspring cohort in which a negative association between free maternal 25(OH)D index and RXR Alpha (retinoic X receptor) methylation at a specific site has been detected. Altogether, these data indicate that maternal VDD induces epigenetic modifications in the offspring. However, more studies are needed to identify the exact mechanisms underlying the changes and outcomes that a developmental VDD has on the brain. Many clinical studies show that supplementation with VD during pregnancy has beneficial effects on both the mother and the offspring. These studies suggest that maintaining optimal VD levels might reduce the risk of developing a wide range of disorders. Additional rigorous and larger randomised trials are required to evaluate the effects of VD supplementation in pregnancy, particularly in relation to the onset of brain disorders.
ARTICLE


68 T. H. J. Burne, A. Becker, J. Brown, D. W. Eyles, A. Mackay-Sim and J. J. McGrath, Transient prenatal Vitamin D deficiency is associated with hyperlocomotion in adult rats, *Behavioural Brain
84 E. Cantor-Graae and J.-P. Selten, Schizophrenia and Migration: A


