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Deficiency of vitamin D is associated with antenatal depression: A cross-sectional study

Short Title: Deficiency of vit D and antenatal depression

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Abstract

Objective: Approximately 6 to 13% of women suffer from antenatal depression (AD) around the world. AD can lead to several health problems for mother-baby. Vitamin D is a molecule that appears to have great preventive/therapeutic potential against neuropsychiatric disorders. The present study aimed to analyze the association between deficiency of vitamin D and AD in pregnant women in a city in the south of Brazil (Pelotas, RS). We hypothesize that pregnant women with a positive AD diagnosis have deficient levels of 25-hydroxyvitamin D (25(OH)D).

Methods: This cross-sectional study was conducted in a cohort study (CEP/UCPEL 47807915.4.0000.5339). From this cohort, 180 pregnant women at up to 24 weeks gestation were selected (130 non-depressed and 50 depressed), and the diagnosis of depression was made using the MINI-Plus. Blood was collected and stored for the later analysis of vitamin D (25(OH)D) by chemiluminescence method. The SPSS program was used for data analysis, and *p<0.05* was considered statistically significant.

Results: In our study, we showed a significant association between Major Depressive Episode current in the antenatal period and vitamin D deficiency (OR: 0.9; CI 95%: 0.9;1.0, *p=0.003*).

Conclusion: Our results demonstrate that vitamin D deficiency may be involved in major depressive disorder in the antenatal period, in this way it advised a follow-up of vitamin D levels in the pregnancy-puerperal cycle to minimize mental health problems in women and prevent developmental deficits in children.

Keywords: Antenatal Depression; Pregnant Women; Vitamin D; Major Depressive Episode; 25-hydroxyvitamin D.

Introduction

With the strong biological, physical, and social changes it causes, major depressive disorder (MDD) is considered the most frequent mood disorder that occurs during pregnancy and after childbirth.[1,2] In Brazil, the prevalence of antenatal depression (AD) varies according to the location where the study was carried out. In a study developed in the city of Pelotas that used the Edinburgh Postnatal Depression Scale (EPDS) as an instrument, it was found that 21.1% of women had a depressive disorder during pregnancy.[3] Another study executed in two capitals of Brazil, Recife,

and Campinas, used the same instrument (EPDS) and found an AD prevalence of 24.3%.[4] Depression during and after childbirth is associated with maternal factors and unfavorable foetal outcomes, including low birth weight, premature birth,[5] poor mother-infant interactions,[6] and has a negative influence on the cognitive and emotional development of children.[7]

The psychological, biological, and environmental theories of MDD are advancing; however, the underlying pathophysiology of AD remains unknown, and it is plausible that several mechanisms are involved.[8] Recent studies have proposed different study targets related to AD pathophysiology, such as the monoamine hypothesis, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, genetic and environmental factors, increased inflammatory cytokine secretion (immunological factors), elevated levels of corticotrophin-releasing factor (CRF), and abnormalities of second messenger systems.[9-13]

Vitamin D is a molecule that appears to have great preventive/therapeutic potential in combating MDD. In a recent study in which serum vitamin D was evaluated, 85% of pregnant women and 80.5% of newborns were shown to have deficient/insufficient levels of vitamin D.[14] Vitamin D is a steroid hormone, and its concentration in the body depends on diet and sun exposure. Vitamin D can be obtained through the diet as ergocalciferol (D2) from plant sources or cholecalciferol (D3) from animal sources. Except for fish oil, other foods are not rich in vitamin D. Synthesis in the epidermis is one of the major sources of vitamin D that depends on ultraviolet (UV) radiation from sunlight.[15] Vitamin D intake and status are low in many countries due to seasonal variations in UVB exposure.[16]

The serum 25-hydroxyvitamin D (25(OH)D) concentration is the classical marker of vitamin D status. Holick,[17] in your literature review proposed that adults with (25(OH)D) concentrations below 20 ng/mL are considered with vitamin D deficiency, while adults with (25(OH)D) concentrations between 20 and 30 ng/mL indicate an insufficiency of vitamin D. In our study we will follow the vitamin D deficiency/insufficiency criteria proposed by Holick.[17] A systematic review and meta-analysis found potentially significant roles of vitamin D deficiency in depression in the general population, indicating that low concentrations of vitamin D may be causative or predictive of depression during pregnancy and after childbirth.[18]

The present study aimed to analyze the association between the serum concentration of 25(OH)D and AD in pregnant women in the urban region of Pelotas, Brazil. In our work, we hypothesized that deficiency of vitamin D during the gestational period results in a reduction of VDR activation in all cells, particularly brain cells, which induces less production of neurotransmitters and favors the major depression episode.

Methods and Materials

Design

This cross-sectional study was conducted in a cohort study in a city in southern Brazil. The project to which this study is linked was approved by the Research Ethics Committee of the Catholic University of Pelotas under protocol number 47807915.4.0000.5339, process number 1.729.653. The central project (cohort study) began in 2016 and was carried out in multiple stages, with census tracts restricted by the Brazilian Institute of Statistics (IBGE) as initial sampling units. Census tracts are territorial units relatively homogeneous in terms of population characteristics, economic status, living conditions and number of inhabitants. First, the 488 census tracts of the urban area of Pelotas, a city in southern Brazil, were listed, according to the 2010 Census (IBGE 2010) for random sampling selection of 244 tracts (50.0% of the total of the urban area). Subsequently, each of the tracts drawn received a visit from the capture team, and all pregnant women were identified. Those who were up to 24 weeks pregnant were invited to participate in the study. All pregnant women signed an informed consent form agreeing to participate in the research. For more details on sample capturing, the publications of Pinheiro et al.,[19,20] can be referenced.

First, the pregnant women were paired by maternal variables during pregnancy from the central project: maternal age in years, education level (completed years of study), gestational weeks, and socioeconomic level according to the classification of the Brazilian Association of Research Companies (ABEP) (Figure 1). Second, we assessed the presence or absence of depression in paired pregnant women (N=180). Third, we separate the women in two groups: non-depressed (N=130) and depressed (N=50). Lastly, we evaluated the vitamin D status (serum of 25(OH)D levels) in all pregnant women. All pregnant women identified with a current major depressive episode were referred to a treatment using a brief cognitive-behavioral psychotherapy model offered by the university.[20]

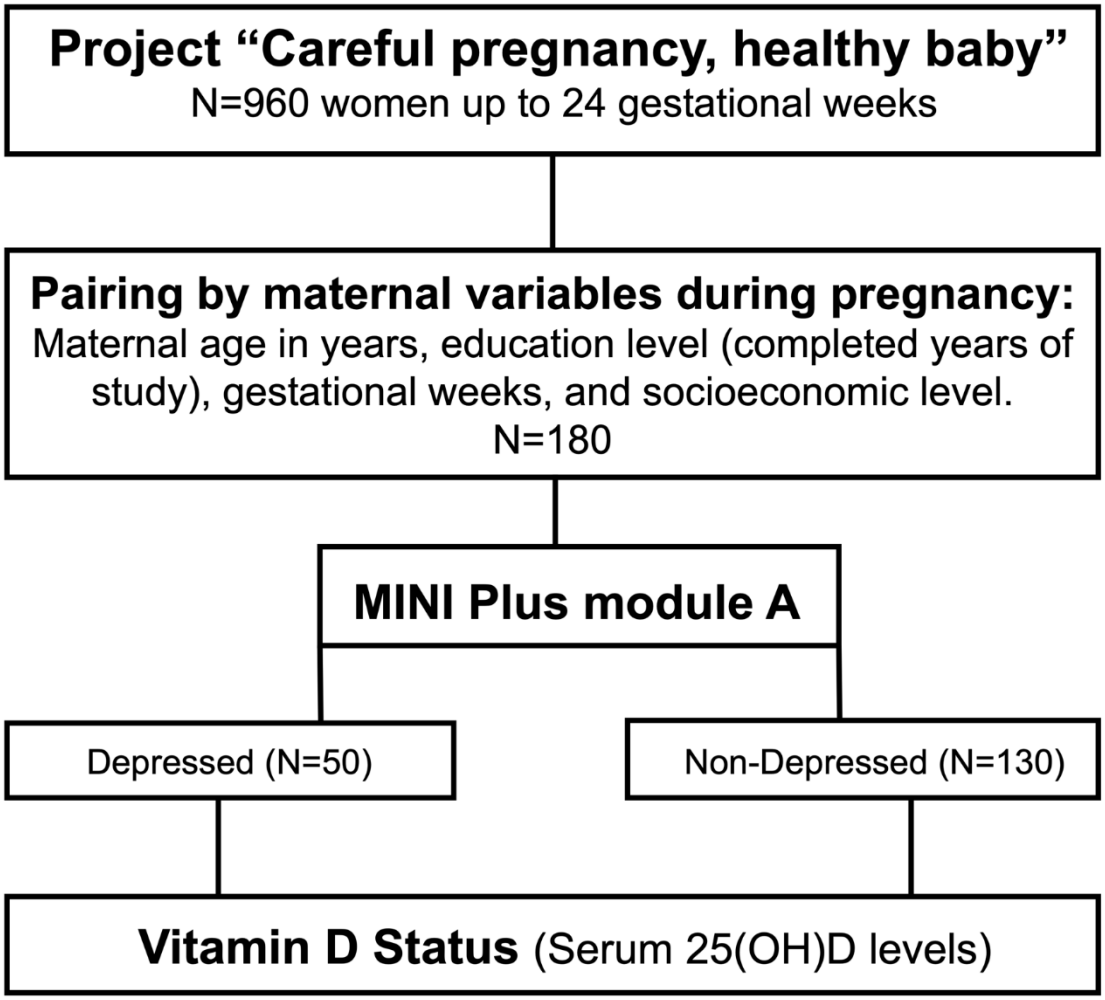

Figure 1. Study organization chart. Pregnant women in the urban region of Pelotas, Brazil, up to 24 gestational weeks (N = 180, Depressed and Non-depressed) were selected from the cohort entitled "Careful pregnancy, healthy baby" for the analysis of association of serum 25(OH)D levels and antenatal depression. For the diagnosis of MDD, the Mini International Neuropsychiatric Interview (MINI) Plus Module A was used.

Instruments

MDD was evaluated with the "A" module of the Mini International Neuropsychiatric Interview (Mini Plus 5.0.0 Brazilian Version). The economic assessment of participants was performed through the ABEP classification, with levels

being categorized as follows: A+B (high levels), C (average levels), and D+E (low levels) (www.abep.org).[20]

Maternal variables, including age, ethnic group (white or other), vitamin since becoming pregnant (yes/no), gestational age in weeks, were collected via a structured general questionnaire.

The assessment of the nutritional status of pregnant women was carried out according to Atalah et al.,[21] which takes into account the gestational age and the pregnant woman's current Body Mass Index (BMI), showing, based on this information, the ideal weight gain for the period. The classification is given through the curve, BMI X gestational age, which allows the classification of nutritional status into low weight, normal weight, overweight, and obesity. For our study, the continuous BMI score was used.[22] The body mass index (BMI) was evaluated by weight/height^2 (kg/m2), with weight measured with an anthropometric scale and height measured with a stadiometer.

Blood sample collection and processing

Blood samples were obtained from all pregnant women (n=180) by venipuncture (10 mL). The serum blood sample was immediately centrifuged at 3000 × g for 10 min, and the supernatant was transferred to tubes and stored at –80 °C for further analysis of vitamin D (25(OH)D) at the Laboratory of Clinical Analysis. Participants were asked to fast 8-10 hours before blood collection, and 20 mL of peripheral venous blood was collected from each participant.[23]

Measurement of serum 25(OH)D by chemiluminescence

Serum 25(OH)D concentrations (ng/mL) were measured using the microparticle chemiluminescence method according to the manufacturer's instructions using Atellica® IM (Siemens, Erlangen, BV, Germany). Atellica® IM is an accurate and precise assay with a functional sensitivity of ≤ 3.0 ng/mL and inter-assay imprecision of ≤ 20%.[24] Since 2018, it has received certification for the total 25-hydroxyvitamin D assays from the Vitamin D Standardization Certification Program by the Center for Disease Control and Prevention (CDC).[25] Serum 25(OH)D concentrations were classified with cut-off values into sufficient (>30 ng/mL), insufficient (20–30 ng/mL), and deficient (<20 ng/mL).[17]

Statistical analyses

Data on independent variables were collected through questionnaires later coded and double-entered in EpiData 3.1 to check for inconsistencies. To describe the characteristics of the sample, simple and relative frequencies are used for the categorical variables and means and standard deviations are used to describe the outcomes. Covariant analysis was performed using Student's t-test and analysis of variance (ANOVA), with variables $p<0.20$ in the crude analysis included in the multivariate analysis by logistic regression (backward method), presented as OR (Odds Ratio) and 95% confidence intervals (CIs). Associations with $p<0.05$ were considered statistically significant.

Results

Table 1 presents the sample characteristics and the covariant analysis results. Of the 180 pregnant women analyzed, the average vitamin D level was 20.1 ± 6.1 ng/mL. Regarding the characteristics of the sample by univariate analysis, most pregnant women were between 24 and 29 years old (n=77, 42.8%), more than half (n=110, 61.1%) were overweight or obese, the vast majority had white ethnicity (n=114, 73.5%), of the total sample (71.1%) were in the second trimester, and belonged to economic class C (n=119, 67.2%). Regarding the current major depressive episode, 50 (27.8%) participants were diagnosed with depression. Concerning the use of vitamins since becoming pregnant, only 53 (29.4%) women reported taking vitamins. Additionally, in Table 1, the covariant analysis (ANOVA) showed a statistical difference between serum vitamin D concentration, ethnic group and psychological/psychiatric treatment with Major Depressive Episode current (*p<0.05)*. The other variables, including age, nutritional status, economic class, gestational trimester, and use of vitamins since becoming pregnant, were not different in relation to the outcome (*p>0.05).*

Table 1. Sample characteristics and covariant analysis of pregnant women in the urban region of Pelotas, Brazil.

Variables	Total N=180 N (%)	Depressed N=50 N (%)	Non-depressed N=130 N (%)	p-value [2]
Age				0.478
Up to 23	41 (22.8)	10 (20.0)	31 (23.8)	
Between 24 to 29	77 (42.8)	25 (50.0)	52 (40.0)	
30 or more	62 (34.4)	15 (30.0)	47 (36.2)	
Ethnic group *				0.045
White	114 (73.5)	26 (61.9)	88 (79.9)	
No-white	41 (26.5)	16 (38.1)	25 (22.1)	
Nutritional status				0.965
Low weight	16 (8.9)	04 (8.0)	12 (9.2)	
Eutrophic	54 (30.0)	15 (30.0)	39 (30.0)	
Overweight/obesity	110 (61.1)	31 (62.0)	79 (60.8)	
Economic class *				0.933
High classes (A/B)	35 (19.8)	10 (20.4)	25 (19.5)	
Middle class (C)	119 (67.2)	32 (65.3)	87 (68.0)	
Lower classes (D/E)	23 (13.0)	07 (14.3)	16 (12.5)	
Gestational trimester				0.295
First	51 (28.3)	17 (34.0)	34 (26.2)	
Second	129 (71.7)	33 (66.0)	96 (73.8)	
MDE past				0.012
No	166 (92.2)	50 (100.0)	116 (89.2)	
Yes	14 (7.8)	00 (0.0)	14 (10.8)	
Psychological/psychiatric treatment				0.066
No	176 (97.8)	47 (94.0)	129 (99.2)	
Yes	04 (2.2)	03 (6.0)	01 (0.8)	
Vitamins since becoming pregnant				0.174
No	127 (70.6)	39 (78.0)	88 (67.7)	
Yes	53 (29.4)	11 (22.0)	42 (32.3)	
Serum Vitamin D Concentration	20.1 (6.1) [1, #]	17.7 (5.2) [1, #]	21.1 (6.1)	0.001

MDE = Major Depressive Episode

 # Mean (SD)

*** Variables with missing data**

[1] ng/mL

[2] Student's t-test and analysis of variance (ANOVA)

Table 2 shows the analysis, adjusted by linear regression, of the variables that presented a *p<0.20* in the covariant analysis: serum vitamin D concentration, ethnic group and psychological/psychiatric treatment. Of these, only serum vitamin D is associated with the Major Depressive Episode current (OR: 0.9; CI 95%: 0.9;1.0, *p=0.003*).

Table 2: **Serum Vitamin D concentration are associated with Major Depressive Episode (Current) outcome.** Multivariate analysis by logistic regression (95% confidence intervals (CIs)) in independent variables that presented p<0.20 using Major Depressive Episode (Current) as the outcome in pregnant women in the urban region of Pelotas, Brazil.

Variables	OR [1]	CI [2] (95%)	p-value
Serum Vitamin D concentration	0.9	0.9;1.0	0.003 [3]
Ethnic group (white*)	2.0	0.9;4.3	0.100
Psychological/psychiatric treatment (no*)	4.1	0.3;51.9	0.270

[1] OR = odds ratio.
[2] CI = Confidence Interval.
[3] Associations with p<0.05 were considered statistically significant.
*** Reference category**

In Figure 2A, it was found that depressed pregnant women had significantly lower serum vitamin D levels compared to non-depressed pregnant women. The non-depressed group had an average of 21.1 ± 6.1 ng/mL serum vitamin D, whereas the depressed group had an average of 17.7 ± 5.2 ng/mL serum vitamin D. This difference was statistically significant (*p=0.001*). In Figure 2B, the non-depressed and depressed pregnant women were categorized according to the cut-off values of serum 25(OH)D proposed by Holick [17]. Although no statistical difference was found in this comparison, it was observed that the majority of depressed pregnant women (N=34, 68%) had 25(OH)D levels lower than 20 ng/mL. Conversely, the majority of non-depressed pregnant women (N=72, 55,4%) had serum 25(OH)D levels ranging from 20 to 30 ng/mL.

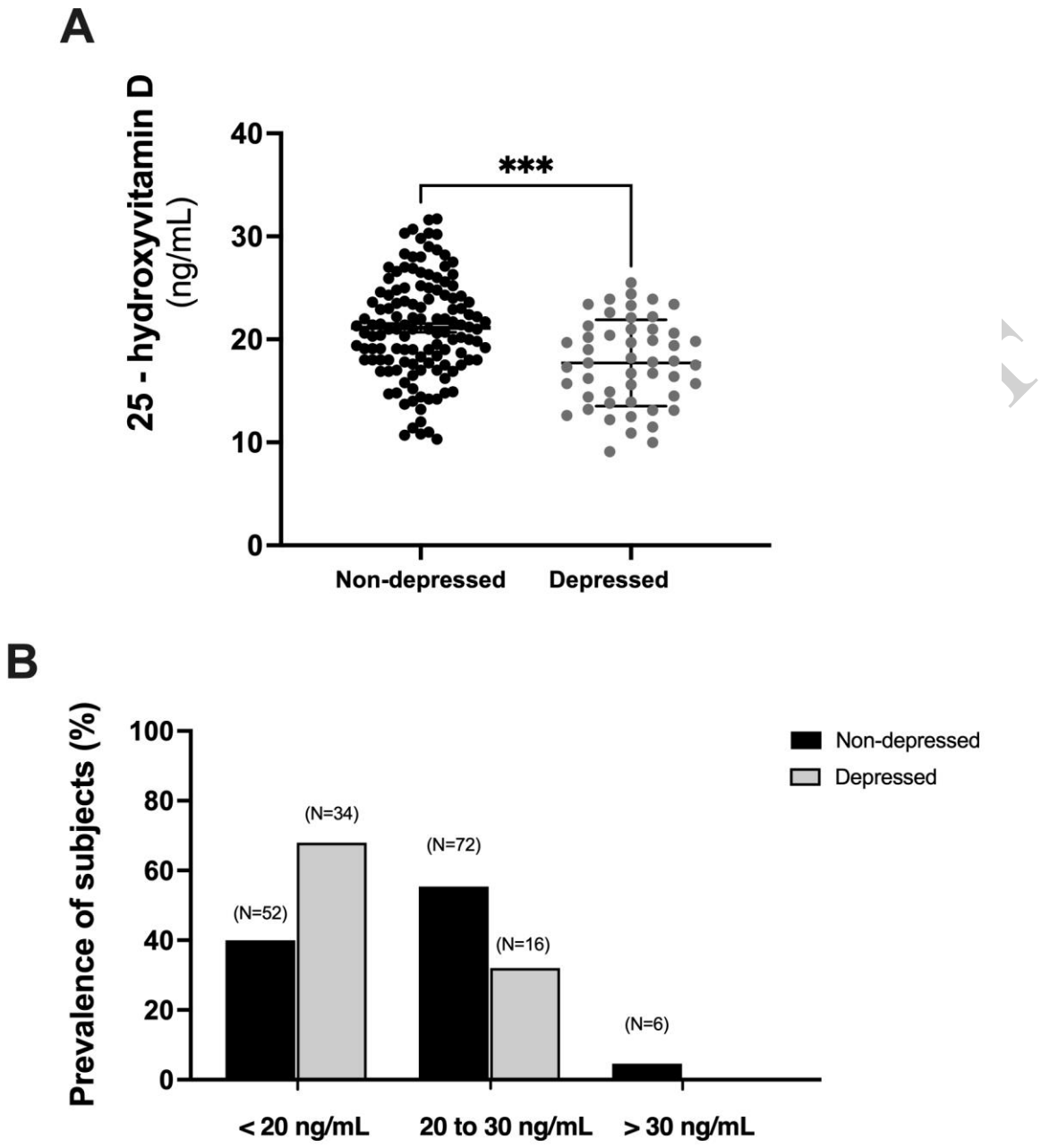

Figure 2. Depressed pregnant women in the urban region of Pelotas, Brazil, showed a deficiency of vitamin D. **(A)** Covariant analysis by Student's t-test of the serum 25(OH)D levels in pregnant women (Depressed, N=50 and Non-depressed, N=130). *** *p<0.001*. **(B)** Prevalence of depressed and non-depressed pregnant women were allocated by cut-off values of serum 25(OH)D: sufficient (>30 ng/mL), insufficient (20–30 ng/mL), and deficient (<20 ng/mL).

In our study, the sample of pregnant women was between a gestational week interval of 5 to 24 weeks. Supplementary Table 1 contains the vitamin D concentration per gestational week of the pregnant women included in the study. Statistical analysis demonstrated no difference in vitamin D concentration between gestational weeks.

Discussion

Pregnancy is a life event accompanied by numerous psychological and physiological changes that increase vulnerability to the onset or recurrence of mental disorders, with antenatal depression being one of the most prevalent psychiatric disorders that has adverse impacts on the health of both the mother and baby.[26] Vitamin D deficiency is one of the most prevalent micronutrient deficiencies in pregnant women. In our cross-sectional study, we confirmed the working hypothesis, since pregnant women with antenatal depression had a deficiency of vitamin D. In addition, we observed that increasing age of pregnant women was significantly related to higher vitamin D. Together, our results have clinical importance, since vitamin D is associated with numerous important physiological functions, especially during the pregnancy-puerperal cycle, and its deficiency is directly associated with neuropsychiatric disorders such as antenatal depression.

High rates of insufficient/deficient serum vitamin D have been reported in several countries around the world. Some studies report that 88% of the population has serum vitamin D less than 30 ng/mL, 37% have vitamin D less than 20 ng/mL, and up to 7% have vitamin D under 10 ng/mL.[27,28] Various societies in several countries determine different cut-offs to the definition of deficient, insufficient, and sufficient vitamin D. In our work we consider deficient, insufficient, and sufficient serum vitamin D levels, respectively: below 20 ng/mL as deficient; between 20 to 30 ng/mL as insufficient; and above 30 to 50 ng/mL as sufficient for health benefits.[29,30] Our study demonstrated that depressed pregnant women have lower vitamin D levels compared to non-depressed pregnant women (Depressed, 21.1 ± 6.1 ng/mL vs Non-depressed, 17.7 ± 5.2 ng/mL, Figure 2). When we represent the results of vitamin D levels according to the 25(OH)D cutoff values proposed by Holick,[17] (Figure 2B) we can observe that the majority of depressed pregnant women have 25(OH)D levels below 20 ng/mL (Depressed, 15.49 ± 2.99 ng/mL: 68%), which represents deficient levels of this vitamin. However, we can see that most non-depressed pregnant women have

25(OH)D levels between 20 and 30 ng/mL (23.63 ± 2.66 ng/mL: 55,4%), representing insufficient levels of vitamin D. Our data demonstrate that in addition to an association between antenatal depression and decreased levels of vitamin D, most depressed pregnant women have deficient levels of vitamin D. We believe that these results are linked, in part, to the fact that Pelotas, RS, is located in the extremely southern region of Brazil and therefore has a more rigorous and long-lasting winter; thus, the population of this region has less exposure to the sun.

Studies indicate that pregnant women are more likely to have low concentrations of vitamin D when compared to nonpregnant women,[31] and the 25(OH)D can vary between trimesters, with lower levels in the first and third trimesters than in the second trimester.[32] Physiological vitamin D metabolism during pregnancy differs from that of a non-pregnant woman.[33] Heaney et al.,[34] showed the conversion of vitamin D to 25(OH)D unchanged during pregnancy, therefore, the conversion of 25(OH)D to 1,25$(OH)_2$D is significantly altered in this period. This change that occurs in the metabolism of vitamin D (conversion of 25(OH)D to 1,25$(OH)_2$D) is unique and is not seen at any other stage of life. Hollis et al.,[35] in their work, demonstrated that at 12 weeks of gestation, the serum concentration of 1,25(OH)2D is increased more than twice compared to a non-pregnant woman and this increase continues in the following gestational weeks. In Supplementary Table 1 we compare 25(OH)D concentrations by gestational week of all women included in the study. We can observe that despite there being fluctuations in vitamin D concentrations throughout the gestational weeks, there was no significant difference.

A recent study that examined the association between vitamin D and perinatal depression in Chinese pregnant and lactating women suggested a significant association between vitamin D status and PPD; however, the association between vitamin D status and AD was not significant.[36] In another study, the researchers found a potential role of vitamin D deficiency in depression in the general population, indicating that low vitamin D may be causative or predictive of depression during pregnancy and after childbirth.[18] In a recent systematic review that analyzed seven studies measuring vitamin D during pregnancy or 24 hours after delivery, six studies showed conclusive results that lower 25(OH)D levels were related to PPD.[37] On the other hand, several randomized clinical trials have been carried out to propose a safe dosage of vitamin D supplementation to minimize the effects of vitamin D deficiency.

These studies demonstrated that a 4000 IU dose of vitamin D3/day safely elevates circulating 25(OH)D to a level that, regardless of race, fully restores vitamin D metabolism in pregnant women.[35,38,39]

Numerous biological mechanisms may explain the observed association between 25(OH)D concentrations and antenatal depression. Depression is classically associated with dysregulated hypothalamic–pituitary–adrenal axis function, increased inflammatory markers, oxidative stress, and overactivity of the sympathoadrenal system.[40] Vitamin D may beneficially act in three (3) proposed pathways responsible for the development of perinatal depression: 1) by reducing the production of pro-inflammatory cytokines via inhibition of the NF-κB gene through the binding of vitamin D with its nuclear receptor (nVDR); 2) by inhibiting the release of corticotropin-releasing hormone (CRH) from the hypothalamus, thus decreasing the secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, resulting in a lower synthesis of cortisol by the adrenal gland; and 3) by increasing calcium metabolism, which stimulates the secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus. GnRH stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland, which act on the gonads by stimulating the production of estriol.[41-43]

Our study had some limitations, including the small sample size, the lack of information about the previous use of vitamin D or calcium, diet composition, skin tone, or the amount of sun exposure that could alter vitamin D levels. However, our results have translational importance, as we demonstrated a significant association between vitamin D deficiency and antenatal depression in pregnant women (Figure 2). MDE current during pregnancy results in several health risks for a pregnant woman and her child after birth.[44] Based on our work, we propose that new studies evaluate pregnant women for longer periods through longitudinal studies or perform vitamin D supplementation through randomized clinical trials. Thus, guidelines and public policy protocols should be created to control vitamin D status during pregnancy in developing countries.

Conflict of interest declaration: All authors declare no conflicts of interest to disclose.

CRediT authorship contribution statement: Helena Garcia dos Santos: Conceptualization, Methodology, Investigation, Writing- Original draft preparation; **Aline Longoni:** Conceptualization, Methodology, Investigation; **Isabela Thurow Lemes:** Methodology, Investigation**; Jéssica Puchalski Trettim:** Methodology, Data Curation; **Júlia de Castro Menchaca:** Methodology, Investigation**; Cainá Correa do Amaral:** Methodology, Investigation**; Mariana Bonati de Matos:** Methodology, Data Curation, Visualization; **Luciana de Ávila Quevedo:** Methodology, Investigation**,** Visualization; **Fernanda Nedel:** Methodology, Investigation**,** Visualization; **Gabriele Ghisleni:** Methodology, Investigation**,** Visualization; **Diogo Onofre Souza:** Writing - Review & Editing, Visualization, Funding acquisition; **Ricardo Tavares Pinheiro:** Writing - Review & Editing, Project administration, Funding acquisition; **Adriano M. de Assis:** Conceptualization, Methodology, Visualization, Writing- Original draft preparation, Project administration, Supervision.

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