

The Role of Vitamin D and Vitamin D Receptor in Placenta Accreta Spectrum: A Literature Review

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Abstract

Objective: This study aims to review the role of vitamin D and vitamin D receptor in Placenta Accreta Spectrum Disorder (PASD)

Method: This review used several databases, namely Google Scholar, Science Direct, Elsevier, Medline, PubMed, Proquest, dan Wiley Online Library to search original and review articles in English about placenta accreta spectrum, placenta accreta, vitamin D, and vitamin D receptor in the last 10 years. Other reference sources used were guidelines and textbooks.

Results: A total of four articles were included in this review.

Discussion: Placenta accreta spectrum disorder is becoming more common around the world, owing to the rise in cesarean deliveries. It is linked to several risk factors, including a lack of vitamin D. Vitamin D and its receptor stimulate endometrial decidualization, which aids implantation. Vitamin D receptors in human placental trophoblasts create and respond to 1,25(OH)₂D₃, which promotes the conversion of endometrial cells to decidual cells. Women with PASD are mostly suffering from vitamin D deficiency.

Conclusion: Vitamin D levels may influence trophoblast invasion in PASD and can be a potential diagnostic marker.

Key words: placenta accreta, vitamin D, vitamin D receptor

Peran Vitamin D dan Reseptor Vitamin D dalam Spektrum Plasenta Akreta: Suatu Tinjauan Pustaka

Abstrak

Tujuan: Penelitian ini bertujuan untuk meninjau peran vitamin D dan reseptor vitamin D dalam Spektrum Plasenta Akreta (SPA)

Metode: Tinjauan pustaka ini menggunakan beberapa sumber data yaitu Google Scholar, Science Direct, Elsevier, Medline, PubMed, Proquest, dan Wiley Online Library untuk mencari artikel penelitian dan tinjauan pustaka dalam Bahasa Inggris mengenai plasenta akreta, vitamin D, dan reseptor vitamin D dalam 10 tahun terakhir. Sumber referensi lain yang digunakan adalah pedoman dan buku teks.

Hasil: Sebanyak empat artikel dimasukkan dalam ulasan ini.

Diskusi: Spektrum Plasenta Akreta terjadi lebih sering di seluruh dunia karena meningkatnya persalinan sesar. Plasenta akreta terkait dengan beberapa faktor risiko termasuk kekurangan vitamin D. Vitamin D dan reseptornya merangsang desidualisasi endometrium dan berperan dalam implantasi. Reseptor vitamin D pada trofoblas plasenta membuat dan merespons 1,25(OH)₂D₃ yang mendorong konversi sel endometrium menjadi sel desidua. Mayoritas wanita dengan SPA mengalami kekurangan vitamin D.

Kesimpulan: Kadar vitamin D dapat mempengaruhi invasi trofoblas pada SPA dan berpotensi menjadi penanda diagnostik.

Kata kunci: spektrum plasenta akreta, reseptor vitamin D, vitamin D

Introduction

Placenta accreta spectrum disorder (PASD) is becoming more common around the world, owing to the rise in cesarean deliveries. Cesarean delivery rates have climbed from less than 10% to over 30% globally over the last 40 years, with a 10-fold increase in the incidence of PASD recorded at the same time.¹ According to a major multicenter US study, the risk of PASD was 3 percent, 11 percent, 40 percent, 61 percent, and 67 percent for the first, second, third, fourth, and fifth or more cesarean deliveries, respectively.² Maternal morbidity and mortality have been documented in up to 60% and 7% of women with placenta accreta, respectively.³ The importance of prenatal diagnosis in improving the outcome of this illness can not be overstated.

The technique of choice for diagnosing and guiding clinical therapy of PASD is antenatal ultrasonography.³ Placenta accreta spectrum disorder is linked to a number of risk factors, including a lack of vitamin D. Vitamin D receptors (VDR) can be found in the woman's reproductive system showing vitamin D involvement in female fertility. Vitamin D along with its receptors stimulates endometrial decidualization, which aids in implantation.⁴ The mean serum vitamin D level was below 20 ng/mL in 37.3 percent among 195 studies conducted in 44 countries with around 168.000 patients involved, indicating that vitamin D deficiency is still a major problem in the world's population. Given that PASD is one of the most common and dangerous conditions for reproductive aged women and is a leading cause of mortality, a study regarding the effect of vitamin D insufficiency on PASD is essential.⁵

Methods

The method used in this writing was literature authors review, which was a systematic,

explicit, and reproducible method for identifying, evaluating, and synthesizing research works, and the ideas that had been produced by researchers and practitioners.

The literature sources used in the preparation of this literature review paper were obtained through national and international journal websites such as Google Scholar, Science Direct, Elsevier, Medline, PubMed, Proquest, and Wiley.

Review Compilation Strategy

The writing of this literature review had several stages or steps: (1) selecting topics to be reviewed and defining the scope of topics to be reviewed, (2) tracking, identifying, and selecting appropriate/relevant article sources, (3) conducting analysis and synthesis of literature, then (4) writing and organizing the writing of the literature review. This literature review was synthesized using the narrative method by grouping similar extracted data according to the results measured to answer the objectives. To further clarify the analysis, journal articles were read and scrutinized, then content analysis was carried out.

Literature Clustering Method

In writing this literature review, the authors used secondary research data obtained from data sources in the form of national and international books and articles that can be obtained through the search engines Google Scholar, Science Direct, Elsevier, PubMed, Proquest, and Wiley. The author used the keywords: placenta accreta spectrum, placenta accreta, vitamin D, and vitamin D receptor, using boolean operators (AND, OR).

Relevant Reference Selection Methods

The authors used several criteria to facilitate the process of selecting relevant references.

Journal articles that matched the established criteria were then taken as references. This literature review used literature published in 2012–2022 which could be accessed full-text in pdf format. Even so, several articles under 2012 were still taken as references if the content and topic of the article was considered important and there were no other articles that review it within the specified timeframe. The selected books and journal articles were in Indonesian and English. Types of article references could be in the form of original articles, meta-analyses, systematic reviews, and literature reviews, with keywords and topics that matched the theme and title of the literature review.

References that matched the established criteria were then collected and a summary of the journal was made including the name of the researcher, year of publication of the journal, title of research, and summary of results or findings.

Results

After rigorous database searching and eliminating duplicates and articles unrelated to the topic, we included 4 articles in this review consisting of: 1 original article on vitamin D and placenta accreta, 1 original article on vitamin D and VDR in missed abortion, 1 original article on vitamin D and VDR in preeclampsia, and 1 systematic review article on vitamin D and endometrium.

Discussion

Metabolism of Vitamin D

Vitamin D (cholecalciferol) is obtained naturally in humans from sunlight, mainly ultraviolet B (UVB) within a specific range of wavelength around 290 to 315 nm, via isomerization reaction that results in 7-dehydrocholesterol converted to vitamin D, which later absorbed to the circulation via the capillary surface and binds to the

binding protein of vitamin D, mostly known as VDBP. Most of the vitamin D metabolites product in serum bind to this binding protein preferentially.⁶

Vitamin D is converted to 25 hydroxyvitamin D [25(OH)D3] and subsequently to 1,25-dihydroxyvitamin D [1,25(OH)2D3], which is a hormone.⁷ VDBP transports vitamin D to the liver through the bloodstream. Vitamin D is hydroxylated at C-25 in the liver, resulting in 25-hydroxyvitamin D [25(OH)D3]. The most common form of vitamin D in circulation is 25(OH)D3 and also one of the most accurate biomarkers of vitamin D status in the blood.⁸

When compared to women who are not pregnant, vitamin D metabolism changes dramatically during pregnancy. Calcitriol levels rise by more than 2–3 times during the first few weeks of pregnancy, while the maternal level of 25(OH)D3 passes the placental barrier and serves as the fetus' main source of vitamin D. Furthermore, the placenta and decidua express vitamin D receptors and regulating metabolic enzymes during pregnancy, suggesting a crucial site in immunomodulating process at the maternal-to-fetal circulation. Because of these consequences, inadequate serum levels of vitamin D has been linked to pregnancy-associated illnesses.⁶

Relationship between the Occurrence of PASD and Serum Levels of Vitamin D

During pregnancy, vitamin D serves three purposes. First, it promotes calcium absorption, which is critical for the fetus's bone mineral accumulation throughout the third trimester of pregnancy. Second, vitamin D acts as an allograft in the fetus' tolerance during pregnancy. Its involvement in several transcriptional controls is the third important role.⁶ Vitamin D improves migration, proliferation, and tube development, which keeps endothelial functions under check.

Table 1 Studies Reporting the Association between Vitamin D and Placental Implantation

First Author (Years)	Title	Type	Findings
Olesya B (2019) ¹⁹	“Expression of Vitamin D and VDR in Chorionic Villous in Missed”	Original Research Article	<ul style="list-style-type: none"> • VDR expression area was proven to exist in trophoblast, chorion villous stroma, and decidual tissue. Trophoblast produces a certain amount of vitamin D, initiating local anti-inflammatory action, and decidual tissue growth. • The relative areas where vitamin D was expressed were found to be considerably lower in people with missed abortion compared to people with no missed abortion. This implies its capability to modulate immune effect and to influence the outcome of pregnancy. • Every pregnant woman with a high risk of termination has an inadequate amount of vitamin D, which simultaneously influences implantation results and pregnancy prolongation. This also suggested immunological modulation as a possible cause of recurrent pregnancy loss.
Jamal A (2019) ⁴	“Effect of Vitamin D on Placenta Accreta”	Original Research Article	<ul style="list-style-type: none"> • Vitamin D acts in the implantation process as cytokines producing agent to initiate CYP27B1 development, a cytochrome required for antiproliferative and pro-differentiation effects of 25(OH)D3. • Researchers discovered the mechanism of vitamin D influencing HOXA10, a gene with a major function in embryo development. Vitamin D has an immunological effect on placental cells influencing oocyte implantation. • This study found that women with placenta accreta are mostly suffering from vitamin D deficiency with serum levels lower than 30 ng/mL.

Martina H (2018) ¹¹	“Impact of Vitamin D and VDR on the Trophoblast Survival Capacity in Preeclampsia”	Original Research Article	<ul style="list-style-type: none"> • This study focuses on defective placentation in preeclampsia caused by vitamin D deficiency, which supposedly serves as a significant biological buffer of pregnant woman homeodynamics. • This study discovered that VDR can be found within nuclei among several locations with receptor including trophoblast nuclei, villous stroma, intervillous space, and fibrin. • Vitamin D as main biological buffer plays a major role in the survival capacity of trophoblast. Therefore, this function wouldn't operate when vitamin D deficiency occurs and this will result in defective placenta implantation.
Greta CC (2018) ²⁰	“Vitamin D and Endometrium: A Systematic Review of a Neglected Area of Research”	Systematic Review	<ul style="list-style-type: none"> • HOXA10 expression has been found to be modulated by 1,25(OH)2D3 in endometrial cells. • In women with defective HOXA10 expression, implantation rate has significantly decreased. • Successful live birth rate can be found lower in the Vitamin D deficient patients compared to Vitamin D repleted patients.

to enhance the synthesis of Interleukin-8, implying that vitamin D can boost neutrophils' ability to respond to invading pathogens by attracting more neutrophils to the infection site. In hyperinflammatory macrophages, vitamin D has also been found to modulate Interleukin-8 secretion. Interleukin-8 has a CXCR2 receptor, and it has been demonstrated that in some circumstances, such as cancer, where there is an increase in Interleukin-8 production and CXCR2 production.¹³

The trophoblastic cells of the placenta accreta penetrate the myometrium in the same way that cancers/tumors do.¹⁴ Interleukin-8 is an angiogenic factor that promotes tumor initiation, migration, and invasion by enhancing neoplastic cell proliferation

and decreasing tumor cell death. In one study, it was found that high Interleukin-8 activity was followed by high CXCR2 expression.¹⁵ Dauletbaev, et al¹⁶ found high concentrations of 25OHD3 and 1,25(OH)2D3 moderately down-regulate Interleukin-8 in hyperinflammatory macrophages. Vitamin D receptors in human placental trophoblasts create and respond to 1,25(OH)2D3, which promotes the conversion of endometrial cells to decidual cells and increases the expression of Homeobox A10 gene (HOXA10), a crucial gene for embryo implantation.¹⁷

In accordance with the previous findings, Guo, et al¹⁸ found that HOXA10 has a significant molecule involved in embryo growth and implantation. Modified

expression of HOXA10 may lead to deteriorated implantation. The Institute of Medicine considers serum levels of 25OHD3 more than 50 nmol/L (20 ng/mL) to be an appropriate level of vitamin D for pregnant women. Vitamin D deficiency is indicated by a serum 25OHD3 level of less than 50 nmol/L. As a result, serum levels of 25–75 nmol/L are considered moderate, whereas values under 25 nmol/L are considered severe.⁴ Several studies reporting the association between Vitamin D and placental implantation are summarized in **Table 1**.

Jamal et al⁴, reported that 97% of people with PASD have low serum levels of vitamin D compared to patients with normal pregnancy. In patients with normal pregnancy, there are only 24% of people with serum levels of vitamin D under 30 ng/mL. There has been no research on the relationship between vitamin D insufficiency and PASD yet. However, research between vitamin D and its effect on female infertility and IVF has shown that women with greater vitamin D levels are found to have more successful implantation, including embryo transfer and IVF.⁴

Olesya, et al¹⁹ discovered that pregnant women with high-risk pregnancies suffer from vitamin D deficiency, which will directly influence the implantation process and prolong the pregnancy period. This also suggested defective immunological regulation as a possible cause of recurrent pregnancy loss.

Conclusion

Vitamin D plays a key role in placental invasion, implantation, angiogenesis, and regulates inflammatory response regarding PASD. High-level maternal vitamin D serum levels are proven to lower the incidence of placenta-mediated complications in pregnancy. The high prevalence of vitamin D insufficiency among pregnant women was

found to have a strong relationship with PASD. Therefore, maintaining adequate vitamin D levels in pregnant women is imperative to reduce and prevent the occurrence of PASD, in order to decrease the number of morbidity, mortality, and surgical complications post-hysterectomy caused by this condition.

Conflict Of Interest

All authors declare no conflict of interest.

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