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The relationship between vitamin D intake with umbilical cord serum interleukin-6 levels

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Abstract

Background: During pregnancy, vitamin D is associated with the growth and development of the fetus, especially in the third trimester. Vitamin D also plays a role in regulating the body's immune system and the placenta. This study aimed to determine the relationship between vitamin D intake and interleukin-6 levels in umbilical cord serum.

Methods and study design: This research was an observational analytic study with a cross-sectional design, at Hermina Hospital, BMC, Reksodiwiryo Hospital, and Unand Biomedical Laboratory on June-December 2022. The samples were 40 pregnant women at term. The sampling technique was consecutive sampling. Data was collected by taking maternal blood, umbilical cord, and birth weight and filling out the FFQ questionnaire. Examination of serum IL-6 by ELISA method. Bivariate analysis used Pearson correlation tests.

Result: The mean intake of vitamin D, umbilical cord serum IL-6 levels was 16.54 ± 2.92 μg, 98.75±16.58 ng/L. Intake of vitamin D with umbilical cord serum IL-6 levels showed a weak relationship but not significantly ($r = -0.243; p = 0.131$).

Conclusion: There is no relationship between vitamin D intake and IL-6 levels in umbilical cord serum. It is expected that pregnant women can consume foods that contain vitamin D.

Keywords: Vitamin D Intake; Umbilical cord; Interleukin-6; Pregnancy

1. Introduction

Vitamin D regulates bone health and calcium metabolism. Vitamin D plays a significant role in almost all life cycles, starting from the cellular level, toddlers, children, and adults. Vitamin D is associated with fetal growth and development during pregnancy through increased calcium requirements for bone formation, especially in the third trimester [1].

Vitamin D not only plays a role in bone growth, but also in regulating the body's immune system, placenta, pancreas, testes, endometrium, pituitary gland, and ovaries [2]. Inside the cell, vitamin D binds to the core vitamin D receptor (VDR) and the activated VDR then dimerizes with itself or with the retinoid X receptor (RXR) and translocates to the nucleus to engage the vitamin D receptor element (VDRE). VDRE regulates the expression of many host genes such as beta-defensins and cathelicidins (antimicrobials). In addition, vitamin D levels can affect the expression of toll-like receptors that drive innate immune responses when they recognize pathogenic proteins. Other important genes regulated by vitamin D include beta-defensins which can directly cleave viral membranes and cathelicidins which are involved in the activation of macrophages, dendritic cells, and neutrophils. For example, an activated VDR can bind to the VDRE of the cathelicidin gene promoter and can lead to the initiation of host defense against some infections [3].

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Vitamin D also plays an immune regulatory role by suppressing adaptive immune responses in epithelial cells. This is manifested mainly through the dampening of T cell proliferation and the resulting shift from T helper type 1 (Th1) to T helper type 2 (Th2) cells. Reduced Th1 proliferation can be said to result in lower pro-inflammatory cytokine levels and reduced acquired immune response, and this may be counterproductive in eliciting a successful immune response against viruses. Vitamin D also influences T-cell maturation and may divert growing masses of inflammatory T helper type 17 (Th17) cells towards a population of anti-inflammatory regulatory T cells (reg T cells). In this way, vitamin D can reduce levels of pro-inflammatory cytokines including Interleukin (IL)-1, IL-6, IL-12, TNF alpha, and IL-17 while increasing anti-inflammatory IL-10. Reduced expression of pro-inflammatory cytokines restrains the differentiation and activation of various types of immune cells and may prevent immune-mediated injury [3].

Vitamin D in the umbilical cord is associated with the production of antimicrobial substances and inflammatory responses induced by Toll-Like Receptors (TLRs). Escalation in vitamin D levels will modulate and reduce TLR 2, TLR 4, and TLR 9 levels, thereby reducing IL-6 secretion as a marker of inflammation in circulation [8]. In line with the research by Lisnawati, Marianna, and Rohsiswatmo [4] it was stated that vitamin D plays a role in inhibiting the production of IL-6 cytokines and found a tendency for cord IL-6 levels and serum C-reactive protein (CRP) babies to be higher in the group of mothers who are deficient vitamin D.

The synthesis of proinflammatory cytokines is closely related to the immune response in the body. One of the factors that play a role in modulating the immune response is nutrition, such as vitamin D (25-dihydroxy vitamin D3). Vitamin D in pregnancy in its active form 1,25-dihydroxy vitamin D3 [1,25(OH)D] will affect the innate immune response via the trophoblast, reducing inflammation and markers of oxidative stress. It will also induce cathelicidin in various tissues to reduce bacterial infection, including in the placenta [5].The results of Liu and Hewison's [2] study found that lower maternal vitamin D levels have been reported to stimulate an acute phase response, and increase CRP, hemostatic factors, and proinflammatory concentrations in mothers and newborns. Another study in healthy women aged 25 to 82 years reported that there appeared to be a slight trend toward an inverse relationship between serum 25(OH)D and IL-6 levels ($p = 0.0909$). These results indicate that the higher the mother's vitamin D level, the lower the expected level of IL-6 and CRP [4].

The role of vitamin D during pregnancy is evidenced by several studies that found a relationship between vitamin D status and pregnancy outcomes. Morgan et al. [6] reported that vitamin D affects the birth size, namely low birth weight babies (LBW). Gernand et al. [7] reported that vitamin D deficiency during pregnancy has a relationship with bone mineralization associated with Small Gestational Age (SGA) births.

Sources of vitamin D come from exposure to sunlight and food intake. Exposure to sunlight on the skin will form vitamin D3 (cholecalciferol) which is the main source of vitamin D in the body, but vitamin D intake is also necessary because vitamin D from food is mostly obtained in the form of vitamin D3 (animal source) and some in the form of D2 (ergocalciferol).) which is present in plants and is only obtained from the intake of foods containing vitamin D [9]. The main food sources are fish such as salmon, mackerel, tuna, sardines, and cod liver oil, but traces can also be found in mushrooms. Vitamin D-fortified foods or dietary supplements may be optimal sources of additional vitamin D [10].

Vitamin D deficiency is a major public health problem, especially in age groups at risk for vitamin D deficiency statuses such as children, toddlers, pregnant women, and breastfeeding mothers [11]. Several studies have shown that vitamin D deficiency in pregnancy can cause complications for the mother, such as gestational diabetes mellitus (GDM), preeclampsia, cesarean section, and postpartum depression. Meanwhile, a deficiency of vitamin D in the fetus can cause complications such as low birth weight (LBW), premature birth, Intra Uterine Growth Restriction (IUGR), respiratory infections, effects on anthropometry, risk of autism, and impact on lung maturation [12].

Vitamin D deficiency rates are quite high in many parts of the world. The prevalence of vitamin D deficiency in Europe is 40.4% [13]. A study in China stated that 6.69% of children in China had vitamin D deficiency and 15.92% had vitamin D insufficiency [14]. In Indonesia, vitamin D deficiency is common in pregnant women. Based on Bardosono's research [15] it was found that there was a 90.2% prevalence of vitamin D deficiency in pregnant women. Lifestyle and culture are determining factors for the availability of vitamin D due to their influence on sun exposure and food intake [13]. In West Java, 75% of pregnant women experience vitamin D deficiency [16]. In West Sumatra, 82.8% of pregnant women experienced vitamin D deficiency, and 17.2% experienced vitamin D insufficiency [17]. Vitamin D deficiency often occurs in Minangkabau pregnant women because the increase in body surface area exposed to sunlight may not be culturally acceptable, especially in clothing [18].

2. Material and methods

The type of research used in this research is observational analytic with cross sectional design. This research starts from June to December 2022 with no. Ethics 2937/UN.16.02.D/PP/2022. The subjects of this study were 40 term pregnant women with inclusion criteria of normal term pregnant women who were willing to be research subjects. Exclusion criteria for pregnant women who have chronic diseases (hypertension, DM, liver, kidney, etc.). The research location is Hermia Hospital, Bunda BMC Padang Hospital, Dr. Reksodiwiryo. Intake of vitamin D using the Food Frequency Questionnaire (FFQ) questionnaire conducted by enumerators [19]. Umbilical cord serum was examined using the ELISA (Bioassay Technology Laboratory/BTLab) method at the Andalas University Padang Biomedical Laboratory. The test used in this study is the Pearson correlation test.

3. Results and discussion

The research subjects were of healthy reproductive age, highly educated, not working, and multiparous can be seen in table 1. The average maternal vitamin D intake was in the adequate category, and the mean umbilical cord IL-6 levels were within normal limits can be seen in table 2.

The relationship between vitamin D intake and umbilical cord serum 25(OH)D levels was not significantly correlated.

Table 1 Maternal Characteristics

Characteristics	**n**	**%**
Age		
20-35	36	90
>35	4	10
Education		
Junior High School	1	2.5
Senior High School	13	32.5
PT	26	65.5
Occupation		
Unemployed	26	65
Employed	14	35
Parity		
Primipara	11	27.5
Multipara	28	70.0
Grandemultipara	1	2.5
Total	40	100

Table 2 Vitamin D intake and umbilical cord serum IL-6 levels

Variabel	**n**	**Mean ± SD**
Vitamin D Intake (μg)	40	16.54±2.92
Umbilical cord serum IL-6 levels (ng/L)	40	98.75±16.58

Table 3 The relationship between vitamin D intake and umbilical cord serum IL-6 levels

		Vitamin D Intake
Umbilical cord serum IL-6 levels	r	-0.243
	p	0.131

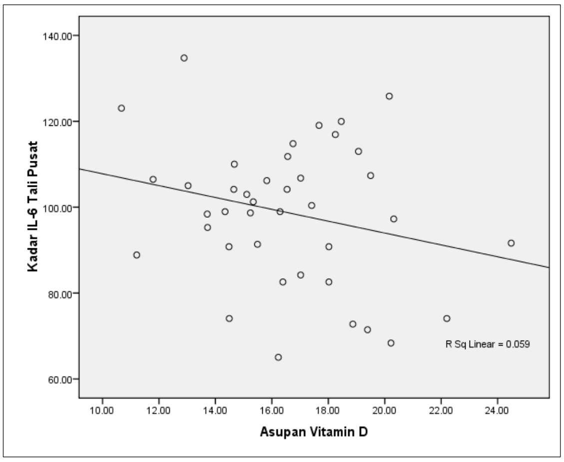

Figure 1 The relationship between vitamin D intake and umbilical cord serum IL-6 levels

The results of this study found that vitamin D intake and cord serum IL-6 levels showed a weak relationship (r = 0.243) and had a negative pattern, meaning that the higher the intake of vitamin D, the lower the cord serum IL-6 levels. Statistical test results showed that there was no significant relationship between vitamin D intake and cord serum IL-6 levels (p = 0.131).

Research conducted by Mazidi et al. [8] found that vitamin D in the umbilical cord is associated with the production of antimicrobial substances and the inflammatory response induced by Toll-Like Receptors (TLRs). Escalation in vitamin D levels will modulate and decrease levels of TLR 2, TLR 4, and TLR 9, thereby reducing IL-6 secretion as a marker of inflammation in circulation. In line with the research of Lisnawati et al [4] stated that vitamin D plays a role in inhibiting the production of IL-6 cytokines and found a tendency for infant cord IL-6 levels and serum C-reactive protein (CRP) to be higher in groups of mothers who lack vitamin D.

The synthesis of proinflammatory cytokines is closely related to the immune response in the body. One of the factors that play a role in modulating the immune response is nutrition, such as vitamin D (25-dihydroxy vitamin D3). Vitamin D in pregnancy in its active form 1,25-dihydroxy vitamin D3 [1,25(OH)D] will affect the innate immune response via the trophoblast, reducing inflammation and markers of oxidative stress. It will also induce cathelicidin in various tissues to reduce bacterial infection, including in the placenta [5]. The results of Liu and Hewison's [2] study found that lower maternal vitamin D levels have been reported to stimulate an acute phase response, and increase CRP, hemostatic factors, and proinflammatory concentrations in mothers and newborns. Another study in healthy women aged 25 to 82 years reported that there appeared to be a slight trend toward an inverse relationship between serum 25(OH)D and IL-6 levels (p = 0.0909). These results indicate that the higher the mother's vitamin D level, the lower the expected level of IL-6 and CRP [4].

Vitamin D plays an important role from early fetal development through implantation and the inflammatory response of the placenta. Placenta functions to process the transfer of blood, and oxygen, disposal of waste products, and exchange of gases and nutrients that connect mother and fetus. The formation of the placenta is initiated by the process of adaptation and receptivity of the fetus to the mother which will later determine the success of the formation of the spiral arteries [20]. If the process of implantation and development of the placenta in early pregnancy is not normal, it will interfere with the growth and development of the fetus while in the womb. This has a big influence on the outcome of pregnancy which is seen based on indicators of fetal growth such as body weight, body length, and head circumference of the baby born.

It was found that pregnant women with a sufficient average intake of vitamin D had cord IL-6 levels of 98.75 ± 16.58 ng/L which were within normal limits. This could be due to vitamin D intake only representing a small portion of 25(OH)D so it does not reflect 25(OH)D levels and their correlation in the subjects of this study.

4. Conclusion

There is no relationship between vitamin D intake and IL-6 levels in umbilical cord serum.

Compliance with ethical standards

Acknowledgements

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Disclosure Conflict of interest

The authors have no financial or another potential conflict of interest to disclose.

Statement of ethical approval

This research was conducted after conducting an ethical test on the Ethics Committee at the Faculty of Medicine, Andalas University. Certificate of Passing Ethics Review has been obtained with number 794/UN.16.2/KEP-FK/2022.

Statement of informed consent

In this study, all respondents had agreed and signed the informed consent voluntarily.

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