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Vitamin A and pregnancy: myths and reality; prospects for the use in patients with endometriosis. A review

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BACKGROUND: Retinol in its various forms, being a powerful antioxidant, has a multifaceted effect on the functioning of body systems. Replenishment of the daily requirement for the vitamin is possible only when it is supplied from outside sources. Both excess intake and deficiency of retinol are associated with adverse effects.

AIM: The aim of this study was to assess the role of vitamin A in the functioning of the female reproductive system, its effect on pregnancy, and the prospects of using it as a pathogenically justified therapy for endometriosis.

MATERIALS AND METHODS: We performed this review, analyzing articles from such electronic databases as PubMed, ScienceDirect, and Cyberleninka, published in the period from 2000 to 2020.

RESULTS AND CONCLUSIONS: Vitamin A plays an important role in pregnancy; its deficiency is associated with a number of malformations, the risk of respiratory distress syndrome and disorders of the immune system development in the fetus. Despite the alleged risk of using vitamin A in pregnant women, it can be prescribed both at the planning stage and during pregnancy in safe therapeutic doses, up to 10,000 IU / day, in order to reduce the number of congenital malformations, to give birth to children with higher Apgar scores, and to prevent anemia. Retinol has antiproliferative and antitumor effects and affects the biosynthesis of estrogens, which justifies the possibility of its involvement in the pathogenesis of genital endometriosis. Given the ability of vitamin A to inhibit the proliferation of endometrioid ovarian cysts, to reduce the size of endometrioid heterotopias, and to modulate the synthesis of proinflammatory cytokines, it can be considered as a perspective therapy in the combined treatment of genital endometriosis.

Keywords: vitamin A; endometriosis; all-trans-retinoic acid; pregnancy.

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Витамин А и беременность — мифы и реальность, перспективы применения при эндометриозе (обзор литературы)

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Обоснование. Ретинол в виде различных его форм, являясь мощным антиоксидантом, оказывает многогранное влияние на функционирование различных систем организма. Восполнение суточной потребности в витамине возможно только при его поступлении извне. Как избыточное потребление, так и дефицит ретинола ассоциированы с неблагоприятными последствиями.

Цель — оценить роль витамина А в функционировании репродуктивной системы, его влияние на течение беременности, перспективы применения в качестве патогенетически обоснованной терапии эндометриоза.

Материалы и методы. Для проведения обзора литературных данных были проанализированы статьи, находящиеся в таких электронных базах, как PubMed, ScienceDirect, Cyberleninka, в период с 2000 по 2020 г.

Результаты и заключение. Витамин А имеет большое значение при беременности, его дефицит связан с формированием ряда пороков развития, возникновением респираторного дистресс-синдрома и нарушений иммунной системы у плода. Несмотря на то что существует мнение об опасности применения витамина А у беременных, он может быть назначен как на этапе планирования, так и во время беременности в безопасных терапевтических дозах (до 10 000 МЕ/сут) с целью снижения риска врожденных пороков развития, рождения детей с более высокой оценкой по шкале Апгар, профилактики анемии. Ретинол обладает антипролиферативным, противоопухолевым эффектами, влияет на биосинтез эстрогенов, что обосновывает возможность его участия в патогенезе генитального эндометриоза. С учетом способности витамина А ингибировать пролиферацию эндометриоидных кист яичников, уменьшать размеры эндометриоидных гетеротопий, модулировать синтез провоспалительных цитокинов его можно рассматривать в качестве перспективного направления в составе терапии для комплексного лечения генитального эндометриоза.

Ключевые слова: витамин А; эндометриоз; полностью транс-ретиноевая кислота; беременность.

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BACKGROUND

Vitamins are low molecular weight organic compounds that are necessary for minimal amounts to implement various metabolic body processes. Water-soluble vitamin derivatives are part of enzyme systems that catalyze the metabolism of carbohydrates, proteins, and fats and are involved in energy conversion and synthesis of precursors of complex macromolecules from simple molecules [1].

Liposoluble vitamins A and D are known to have a hormone-like effect by binding to intracellular receptors in target tissues [1].

The first experimental studies, which later discovered vitamin A, were conducted by W. Stepp (1909). He revealed that food, which is quite sufficient to ensure the normal growth and development of mice (bread and milk), loses its nutritional values after being treated with alcohol and ether by studying the ability of the animal organism to synthesize the necessary components. The obtained extract was added to the extracted food making it suitable for nutrition. W. Stepp believed that, with such processing, those lipids are removed from the food, of which synthesis is impossible in mammals.

This problem was further developed by E. Maccollum and M. Davis (1913), who conducted a study on young, growing rats. Feeding the animals with a food mixture of specially processed foods (protein [casein], carbohydrates, and a mixture of salts) led to growth arrest, which resumed after adding butter or egg yolk essential extract.

E. Maccollum (1967), when reporting more than half a century later on the individual stages of vitamins A and D discovery, pointed out the significance of the work by N.I. Lunin back in 1880. In 1931, Swiss scientist Paul Karrer described the chemical properties and structural formula of vitamin A. Additionally, unsaturated alcohol with the empirical formula $C_{20}H_{30}O$, with five double bonds, one in the beta-ionone ring and four in the side aliphatic chain was established. In 1937, crystalline preparations of vitamin A were obtained.

At present, the possibilities of using vitamin A in various fields of medicine, namely gynecology, ophthalmology, and oncology, are being considered.

The study aimed to evaluate the role of vitamin A in the reproductive system functioning, its effect on the pregnancy course, and its prospects as a pathogenetically substantiated therapy for endometriosis.

MATERIALS AND METHODS

Articles were analyzed and included in electronic databases, such as PubMed, ScienceDirect, and Cyberleninka, from 2000 to 2020 for the literature review.

RESULTS AND DISCUSSION

Vitamin A metabolism

Vitamin A is a cyclic unsaturated monohydric alcohol that is soluble in most organic solvents [2]. Liposoluble vitamin A belongs to the retinoid group. Vitamin A in the human body can exist in various forms, such as alcohol (retinol), aldehyde (retinal), and acid (retinoic acid). Additionally, esters of these compounds and their spatial isomers are known [3].

Vitamin A is most often called retinol; however, its variability leads to the emergence of various names, such as retinol (vitamin A alcohol and vitamin A_1), dehydroretinol (vitamin A_2), retinal (retinene and vitamin A aldehyde), and retinoic acid (vitamin A acid). These vitamers are quite unstable, thus vitamin A composes vitamin-mineral complexes, and food supplements are used in more chemically stable forms, namely retinol esters (usually retinol acetate or palmitate) [3]. Retinol acetate and other retinol esters represent the so-called "sealed," "conserved" forms of the vitamin [4]. Vitamin A precursors in the human body include carotenoids. The biological value of carotenoids is determined by their ability to convert into vitamin A in the body. Examples of such provitamins are the structural isomers of carotene, alpha-, beta-, and gamma-carotenes. The most common structural isomer is beta-carotene. Its molecule consists of two beta-ionone rings that are connected by an aliphatic chain with 9 unsaturated double bonds. One such bond is found in each ionic ring. Alpha-carotene with the same structure of the aliphatic chain contains only one beta-ionone cycle, while the second cycle is replaced by an alpha-ionone one. Gamma-carotene contains 12 unsaturated double bonds, one beta-ionone cycle, and an open ring at the other end of the molecule [2]. Along with other carotenoids, beta-carotene functions as antioxidants that influence carcinogenesis by reducing the free radical level that causes deoxyribonucleic acid damage [5]. The biological activity of vitamin A is usually expressed in international units (IU), wherein 1 IU corresponds to the activity of 0.3 μg of retinol or retinal, 0.344 μg of retinyl acetate, 0.55 μg of retinyl palmitate, and 1.8 μg of beta-carotene [6].

Group A vitamins are found in products of animal origin. Their largest amount is revealed in the liver of cod and sharks, where retinol A_1 is in the esterified form, whereas retinol A_2 is found in the liver of freshwater fish. Group A provitamins, carotenoids (alpha, beta, and gamma), are exclusively found in plants and undergo several changes when they enter the body of animals and humans [7]. Two retinol molecules are formed from symmetrical beta-carotene, and only one molecule is formed from alpha- and gamma-carotene. Retinol molecules are less effective than beta-carotene when taken with food. Vitamin A cannot be synthesized by vertebrates in the animal

kingdom, including humans, who obtain it from food. The liver creates an adequate vitamin A supply (>20 μg/g), which is expressed in retinol activity equivalents (RAE), wherein 1 μg of RAE is defined as the biological activity associated with 1 μg of trans-retinol and is equivalent to 12 μg of beta-carotene and 24 μg of alpha-carotene (or beta-cryptoxanthin) based on the efficiency of absorption and conversion to vitamin A. Other dietary carotenoids, such as lycopene, lutein, and zeaxanthin, are not metabolic precursors of vitamin A [7]. Vitamin A is found in food mainly in ester forms. Therefore, along with food, mainly vitamin A esters enter the body, and in most cases, in palmitate form. Hydrolysis of vitamin A esters in the intestine occurs with the involvement of pancreatic enzymes and epithelial cells of the small intestine mucosa. Bile acids are very significant in vitamin A absorption. They are involved in emulsification, hydrolytic cleavage of retinol esters, solubilization of hydrolysis products, and their transport to the intestinal epithelial cells [8]. As suggested, they are involved in retinol reesterification within the epithelial cells of the mucosa due to the role of bile acids in preventing the oxidation of vitamin A and its esters, as well as carotene in the intestine [8]. These esters are completely hydrolyzed when absorbed in the intestine, and free retinol enters the epithelial cells of the mucous membrane.

The next stage in vitamin A metabolism is the retinol reesterification in the epitheliocytes with the formation of its higher esters, mainly retinol palmitate. After absorption, the vitamin enters other organs through the thoracic lymphatic duct. Based on vitamin A detection in the thoracic lymphatic duct in the form of its higher esters after A-vitaminization, the intestinal epithelial cells can be the site of retinol reesterification [8]. Thus, retinol reesterification occurs in the mucous membrane epithelial cells of the small intestine, which is formed due to the hydrolysis of alimentary ester forms of vitamin A with the participation of retinyl ether hydrolases of the pancreas, as well as the intestine. These resynthesized retinol esters (not all) are attached to specific monoproteins and enter the liver through the lymphatic vessels as part of chylomicrons. Notably, a certain amount of retinol and its esters received from outside is also absorbed through the portal vein. Retinyl esters are released and hydrolyzed in the liver to form free retinol. Subsequently, free retinol in the liver is secondarily reesterified and converted to retinyl palmitate, binding with liver proteins and forming a reserve form of vitamin A [9].

Vitamin A functions as a hormone through retinoic acid receptors. Vitamin A level in the pancreas is critical for retinoid signaling and maintaining physiological glucose levels in the pancreas [10]. Vitamin A is transported in the blood as a complex with retinol-binding protein (RBP), but the molecular mechanism by which vitamin A is absorbed by cells from the vitamin A-RBP complex is not fully understood. In studies, the multitransmembrane domain protein STRA6 was identified in bovine retinal pigment epithelial cells as a specific membrane RBP receptor. STRA6 binds to RBP with high affinity and absorbs vitamin A from the vitamin A-RBP complex with high activity. The binding of vitamin A to these receptors is of great physiological importance in solubilizing water-insoluble retinol, thereby preventing it from rapid chemical degradation and elimination in the urine, as well as delivering retinol from the depot to the target organs and transferring it to specific receptor molecules of cells, which is required for the manifestation of specific metabolic functions of vitamin A in these organs and tissues. Vitamin A-transporting protein concentration in the blood plasma under normal conditions correlates with the provision of the body with the vitamin. The possibility of such a correlation is to a certain extent since vitamin A is one of the regulators of its transport protein metabolism [11]. Information regarding the content of endogenous vitamin A is transmitted by two retinoid receptors, namely the retinoic acid receptor (RAR) and the retinoid X receptor (RXR). Both RAR and RXR are members of the nuclear receptor superfamily of ligand-activated transcription factors and primarily act as heterodimers, which activate target gene transcription with their all-trans retinoic acid ligand [12]. RAR-α, RAR-β, RAR-γ, and peroxisome proliferator-activated receptor (PPAR)-β/δ, which regulates the target gene transcription, are also known among retinoic acid receptors [2].

The biological role of vitamin A in the body

Vitamin A plays an important role in the cell differentiation of the visual system organs and xerophthalmia prevention. Vitamin A deficiency is the major cause of preventable blindness worldwide [13]. Vitamin A, being an antioxidant, affects the barrier function of the skin and mucous membranes and cell membrane permeability and plays a vital role in preventing reproductive system diseases (endometriosis, mastopathy, and carcinogenesis of various localizations) by neutralizing the excess amount of free radicals induced by oxidative stress [13]. The relationship between serum vitamin A levels or dietary intake and cancer risk is unclear. Several prospective and retrospective observational studies in current and former smokers, as well as in people who have never smoked, have revealed a reduced risk of lung cancer when eating foods containing vitamin A and carotenoids [14]. Some authors point to the efficient use of vitamin A for the topical treatment of acne, which, by promoting the opening of comedones, provides regeneration and prevents new lesion formation. The effect usually develops within 2–3 months and is dose-independent [15, 16].

Hypercarotenemia is characterized by keratoderma resulting in skin yellowing, especially the palms and soles.

Hypercarotenemia occurs in people who consume foods rich in carotenoids (>30 mg/day) for several months. The use of carotenoids in physiological or lesser amounts leads very rarely to carotene jaundice due to genetic defects in enzyme 15-15'-carotenoid dioxygenase. Additionally, in people with hypothyroidism and diabetes mellitus, hypercarotenemia develops with the normal consumption of foods rich in carotenoids [17].

The use of vitamin A during pregnancy and the postpartum period

Vitamin A is essential for the normal development of the embryo [18]. The molecular and clinical effects of physiological doses of vitamin A in a pregnant woman and fetus depend on the availability of other vitamins and microelements, thus vitamin A supplementation in combination with other micronutrients contributes to 1) reduced risk of cleft palate, diaphragmatic hernia, neural tube defects, hypertrophic pyloric stenosis, and other vitamin-A-dependent malformations; 2) gene expression of lung surfactant proteins, prevention of bronchopulmonary dysplasia and chronic lung diseases (bronchiolitis, bronchitis, bronchial asthma, and pneumonia) at an early age; 3) reduced mortality from measles; 4) better fetal growth rates and a higher Apgar score; 5) prevention of the development of allergies in children; 6) prevention of anemia; and 7) cognitive and behavioral development improvement of children at an early age [18].

Vitamin A in high doses (>7.5 mg or 24750 IU per day) can have a teratogenic effect (impaired facial skeleton and aorta formation, microphthalmia, gastric atresia, and other malformations), as well as intrauterine fetal growth retardation and early epiphyseal growth zone closure. With hypervitaminosis A, blood coagulation factor synthesis can slow down due to impaired liver function, as well as increased cerebrospinal fluid secretion with increased intracranial pressure. According to the international recommendations, the maximum daily dose of vitamin A for pregnant women should not exceed 10,000 IU (3 mg) [1]. The resolution of the Council of Experts in 2020 noted that the routine intake of vitamin A as a single drug is not recommended but can be included in specially designed vitamin and mineral complexes for pregnant women [19, 20]. Retinol toxicity depends on the dose and duration of use, as well as the person's age. In rare cases, mild symptoms of chronic intoxication in adults can develop even when taking 10 mg/day of retinol for 6 months. A single dose of retinol at >500 mg leads to acute poisoning. The teratogenic effect of high retinol doses persists even after its discontinuation; therefore, pregnancy should be planned after using the drug at a therapeutic dose only after 6–12 months [1]. Vitamin A doses of 700–1000 μg of retinol equivalents correspond to the norms of its daily demand during pregnancy [19, 20].

Unlike vitamin A, beta-carotene is not teratogenic or toxic. Additionally, even large supplemental doses (20–30 mg/day) of beta-carotene or a long-term diet high in food rich in carotenoids are not associated with toxicity. The most significant effect of long-term or excessive beta-carotene intake is carotenoderma, in which the skin becomes yellow. This condition is leveled by plant pigment intake cessation [14].

K. Ribeiro et al. compared mothers who received 200,000 IU of vitamin A and a control group (who did not receive vitamin A) to analyze its effect on breast milk and concluded that megadoses of vitamin A in the first days of the postpartum period increased retinol levels in the first 24 h after supplementation, but this increase was more effective in women with low vitamin A levels in the colostrum [21].

D. Bezerra et al. also investigated the effect of retinyl palmitate supplementation and compared it with the control group (not treated with vitamin A) but considered two periods, the first week of postpartum and thirty days after dose administration. The retinol concentration assessment in the colostrum in two periods revealed its higher levels in patients receiving vitamin A. Further follow-up revealed a decreased retinol concentration in the colostrum 30 days after delivery [22].

The importance of vitamin A in the pathogenesis of genital endometriosis

Decreased vitamin A and retinoic acid metabolite levels may contribute to the pathogenesis of endometriosis. All-trans-retinoic acid (or tretinoin) simultaneously prevents endometrioid cyst proliferation with a locally decreased estradiol production [23]. Following the steroid level fluctuations during the menstrual cycle, retinoid receptor expression and tretinoin synthesis change. Local trans-retinoic acid modulates the endometrial synthesis of many immunological factors altered in endometriosis, including interleukin-6, tumor necrosis factor-alpha, vascular endothelial growth factor, monocytic chemoattractant protein-1, connexin-43, and integrins [23]. Tretinoin biosynthesis is impaired in tissues that are affected by endometriosis, which is associated with a decreased RBP type 1 level [23]. Vitamin A metabolite regulation, including trans-retinoic acid, is mediated by endogenous enzymes induced by histone deacetylase inhibitors, suggesting the modulation of intestinal butyrate and other endogenous deacetylase inhibitors [24].

Retinoic acid acts in a paracrine manner, stimulating differentiation and counteracting estradiol (E2)-dependent endometrial epithelial cell proliferation. Additionally, retinoic acid induces the production of the enzyme 17β-hydroxysteroid dehydrogenase 2 (HSD17B2), which converts biologically active E2 into weak estrone (E1). A lower progesterone receptor level that leads to a reduced retinoic acid formation

was revealed in the endometrioid stromal cells [25]. Thus, paracrine signaling to neighboring epithelial cells is lost, and these cells do not differentiate and do not express HSD17B2, which in turn leads to excess E2 synthesis [25].

Vitamin A metabolite level may decrease due to an increased level of the CYP26 enzyme. Elevated levels of transforming growth factor-beta in serum and peritoneal fluid in endometriosis decrease CYP26 and thereby increase the availability of vitamin A metabolites. An increased regulatory T cell count has been associated with high vitamin A metabolite availability [26]. However, the retinoic acid catabolic enzyme CYP26A1 is a progesterone-dependent gene that is overexpressed in women with endometriosis. Through retinoic acid inactivation, CYP26A1 promotes endometrial lesion formation [27, 28]. Decreased intrauterine vitamin A levels significantly alter the gut development after birth and act as a prenatal pathoetiological factor in various digestive disorders due to the effects of reduced vitamin A levels on mitochondria and cellular regulatory functions [26].

Retinoic acid performs various cellular functions and is a biological modulator by participating in the metabolism of cells affected by endometriosis. The transcriptome was analyzed and the estradiol level was measured in cultured endometrioid cells and tissues to assess the therapeutic effect of tretinoin (all-trans-retinoic acid). HSD17B2 mRNA expression was studied in endometrioid stromal cells derived from ovarian endometriomas. In an isolated culture of endometrioid stromal cells treated with all-trans-retinoic acid for four days, the total RNA was isolated followed by transcriptome analysis using the GeneChip. The expression of 49 genes was upregulated and that of four genes was downregulated by all-trans-retinoic acid. Increased gene expression was associated with cell proliferation suppression [24].

H. Lu et al. revealed that retinoic acid treatment induces autophagy in endometrioid stromal cells derived from women with endometriosis with previous hysterectomy. The authors reported that vitamin A induces Beclin1, a major protein involved in autophagosome formation, and noted an inverse correlation between Beclin1 expression and more severe endometriosis. Additionally, retinoic acid reduces the volume of endometrioid heterotopias. Moreover, the authors hypothesized that retinoic acid may have different efficacy in the treatment of peritoneal endometriosis, ovarian endometriomas, or deep infiltrative endometriosis by inducing endometrioid cell apoptosis. Researchers believe that foci of deep infiltrative endometriosis, consisting of fibromuscular tissue, are more sensitive to retinoic acid, which has not only an anti-fibrotic effect but also the ability to change collagen metabolism. The main limiting factors of retinoic acid usage include minor side effects, such as skin and mucous membranes changes, myalgia, and increased transaminase activity. The efficiency of continuous retinoic acid usage has not been proven; thus, course therapy is recommended in women with endometriosis to improve the quality of life [29, 30].

CONCLUSION

Vitamin A is of great importance during pregnancy; its deficiency is associated with several malformations, the risk of respiratory distress syndrome, and impaired fetal immune system development. Various forms of retinol have a comprehensive effect on various body system functions. Vitamin A has antiproliferative and antitumor effects, affects the biosynthesis of estrogen, and is a powerful antioxidant, which justifies its involvement in the pathogenesis of genital endometriosis. Given its ability to inhibit endometrioid ovarian cyst proliferation, reduce the endometrioid heterotopia size, and modulate the pro-inflammatory cytokine synthesis, vitamin A can be considered a promising factor in complex genital endometriosis treatment.

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