Effects of Supplements as Nutritional Additives on the Reproductive and Digestive System Metabolism of Vitamin A and Effects on Reproduction

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Abstract

In recent years, studies have frequently emphasized the effects of vitamin A on metabolism and the reproductive system in both animals and humans. Although research on its role in reproduction reports no conflicting results, it is evident that there are still aspects that require further clarification. Vitamin A and its precursor β-carotene play a special role in the reproductive system through various systematic events such as epithelial production and differentiation, RNA synthesis, glycoprotein synthesis and resistance to infections. In addition, it improves sperm quality by regulating the internal environment of the uterus and improving sperm quality by affecting steroid production in the ovaries and testes due to its antioxidant activity. It has also been reported that vitamin A is one of the factors controlling the development of follicles and the growth of the dominant follicle, especially in females. It is known that vitamin A has a primary effect on the release of progesterone from the ovaries in the sexual cycle and that progesterone released from the uterus provides the secretion of proteins important for the continuation of pregnancy and fetal development. Vitamin A deficiency causes structural and compartmental changes in placental glycosaminoglycan and embryonic deaths are observed accordingly. This chapter will discuss research findings on the impact of vitamin A supplementation on oocyte growth, ovulation, pregnancy, and both embryonic and fetal development in females. It will also cover the effects of vitamin A on steroidogenesis, spermatogenesis, and sperm motility in the male reproductive system, based on the results of various studies.

Keywords: Vitamin A, Metabolism, Reproductive system, Dominant follicle, Glycosaminoglycan, Embryonic deaths.

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Introduction

The use of antioxidants in livestock enterprises is effective in improving animal welfare and reducing environmental impacts, as well as contributing to animal health, protecting maternal-offspring health, and achieving high meat yield. Additionally, it is known that strict legal regulations regarding supplement strategies for animals generally have a positive outlook on natural products and vitamins. This indicates significant potential for carotenoids, tocopherols, botanical extracts, and vitamins (Boyko et al., 2021).

Feed additives and supplements for animals are used worldwide for various reasons. Some meet basic nutritional needs, while others help enhance growth performance, improve feed palatability, increase feed intake, and regulate feed utilization. Some feed additives, such as antibiotics, have been banned in animal diets due to risks that negatively affect human health. To reduce these negative effects and provide healthy products for consumption, there has been a growing trend towards risk-free feed additives. The main ones include probiotics, prebiotics, enzymes, and products derived from minerals, vitamins, and plant sources (Karásková et al., 2015).

Vitamins and minerals are essential elements that organisms must intake in small amounts to carry out normal body functions. It is known that vitamins function as coenzymes in many metabolic pathways, supporting immune functions, gene regulation, reproduction, and digestive system functions (Pond, 2004).

If potential spoilage occurs in the feed given to animals, and if this continues without interruption in the feed or even in a single component, both the animal's feed intake may decrease, and there may be a significant deficiency in the nutrients obtained from the feed. Methods have been developed to address the challenges posed by uncontrolled oxidation in feeds and to control these oxidation processes. The use of feed antioxidants is one of these methods. These antioxidants extend the shelf life of the product by preventing or delaying the oxidation of lipids, proteins, and other sensitive components in the feed, ensuring that animals receive the best possible nutrition. Additionally, antioxidants in animal nutrition can reduce oxidative stress by neutralizing free radicals and protecting the animal's cells. This can improve the animal's immune system, fertility, and overall health (Celi & Gabai, 2015).

For an antioxidant to be beneficial, it must meet the following criteria:

- It should be effective in protecting tissues and cellular functions that may be exposed to oxidative damage.
- It must not be toxic to humans and livestock.
- It should be effective at very low concentrations.

- Its cost should be sufficiently low (Celi & Gabai, 2015).

When the term "Vitamin," meaning "vital amines," was first proposed, there was no definitive definition to express it fully (Seigler et al., 2021).Vitamins are organic compounds present in trace amounts in natural foods, and they are essential for normal metabolic processes. A lack or insufficient intake of these compounds in the diet can result in various diseases (Rucker & Morris, 1997). The use of vitamins has gained significant importance in recent years, particularly for protecting animal health and enhancing the expected productivity from livestock. The importance of nutrition and supplementation strategies for reproductive health is also increasingly recognized. However, among the fundamental approaches to optimizing reproductive performance in both males and females, vitamins A and E hold a particularly distinct place (Clagett-Dame & Knutson, 2011).

In males, retinol and retinoic acids play a critical role in activating molecular pathways that regulate spermatogenesis. These pathways oversee the differentiation of spermatogonia into fully mature spermatozoa. In females, carotenoids and their derivatives precursors of vitamin A are involved in regulating essential reproductive processes, including folliculogenesis, oogenesis, and steroidogenesis. Additionally, carotenoids and vitamin A derivatives enhance fertility by lowering the risk of embryonic loss. A deficiency in vitamin A has been linked to the degeneration of testicular parenchyma, which leads to the absence of mature sperm cells.(Kumar et al., 2010). Besides, carotenoids and retinol also refer to as antioxidants since they reduce the harmful effects of free radicals. Vitamin A is an unsaturated cyclic alcohol containing 20 carbon atoms. It is mainly synthesized in the intestines, which converts carotene from both animal and plant sources into retinol. This formed retinol then travels to the liver as retinyl palmitate with chylomicrons. The conversion process of β-carotene into retinol includes the mediation by copper-dependent dioxygenase and zinc-dependent retinene reductase enzymes (Kumar et al., 2010). The produced retinol, being lipophilic, is transported by the bloodstream and bound with a specific transport protein called RPB. Its intracellular levels would be taken cared of at cellular membrane and certain mechanisms related to its excretion. The process is further complemented intracellularly by cytosolic retinol-binding proteins, which facilitate the transport of retinol into the nucleus, interacting with specific nuclear receptors to execute its biological function. These further elaborate on the complex mechanisms involving vitamin A, both in reproductive function and cellular regulation. In female reproduction and embryonic development, molecular mechanisms have placed vitamin A in major functional roles both in fertilization and implantation. It has also been determined that through the milk, vitamin A is transferred from mother to the offspring and affects the survival and development of the latter (Kamiloglu et al., 2006).

This chapter provides an overview of the results of studies associated with the metabolism of supplemental vitamin A and its effects on the female and male reproductive systems.

1. Vitamin A

Vitamin A is typically consumed in its inactive form as carotene or provitamin A. Carotenoids are present in plant-based feed sources predominantly as β-carotene, constituting approximately 90%. However, the actual percentage of β-carotene may vary depending on the timing of plant harvest, duration, and conditions of storage. β-Carotene is converted into vitamin A by the enzyme β-carotene dioxygenase in the intestinal mucosa. This enzyme cleaves β-carotene to form two molecules of retinaldehyde, which are subsequently reduced by the pancreatic enzyme retinaldehyde reductase to form retinol. Consequently, one mole of β-carotene yields two moles of vitamin A. This conversion process requires bile salts.(Meléndez-Martínez et al., 2022).

During the initial phase, dietary vitamin A is absorbed in the proximal jejunal mucosa. Within the intestinal lumen, fat micelles facilitate the transport of dietary vitamin A into intestinal mucosal epithelial cells. In the intestinal mucosal cells, vitamin A undergoes esterification and complexation with long-chain fatty acids, forming retinyl palmitate. The resultant retinyl palmitate subsequently exits the mucosal cells and enters lymphatic circulation. Upon entering lymphatic circulation, it is transported via chylomicrons and low-density lipoproteins (LDL).

Retinyl esters in chylomicrons are absorbed by the liver and stored as retinyl palmitate. As required, stored retinyl palmitate in the liver is reconverted to retinol and subsequently released into blood circulation. In the bloodstream, retinol forms a complex with a specific carrier molecule, namely, retinol-binding protein (RBP), which is synthesized in hepatic parenchymal cells. This retinol-RBP complex interacts with cellular retinol-binding proteins located on cell membranes, allowing the transport of retinol into the cell nucleus. This mechanism of action is similar to that observed in steroid hormones.(Kamiloğlu et al., 2006)

Among the various forms of vitamin A, retinol and retinal are the primary forms responsible for the vitamin's biological activity. Retinoic acid, another derivative, serves regulatory functions but lacks the complete vitamin A activity seen in retinol and retinal. Some derivatives of vitamin A are excreted into the intestine via bile as retinol glucuronide. These compounds can be reabsorbed and participate in the enterohepatic circulation of vitamin A metabolites.(Kamiloğlu et al., 2006)

Provitamin A, an inactive precursor obtained from dietary sources, is converted into active vitamin A in the small intestine. The bioactive form of vitamin A is subsequently stored in various organs, including the liver, muscles, eggs, and milk, for utilization in future physiological processes, particularly reproductive functions (Kamiloğlu et al., 2005). Vitamin availability is augmented by retinyl esters, derived from both animal and plant sources. Vitamin A aldehyde, a significant derivative, is involved in the synthesis of ocular pigments, and through oxidation, it is metabolized to form vitamin A acid, contributing to growth and tissue maintenance (Kamİloğlu et al., 2005).

Lecithin retinol acyltransferase (LRAT) is a crucial enzyme involved in the conversion of retinol to retinyl esters, the form in which vitamin A is stored. There are several isomers of retinol, including retinoic acid (RA), all-trans-RA, 9-cis-RA, and 13-cis-RA. Retinoic acid, a retinol derivative, functions as a ligand for nuclear retinoic acid receptors (RARs) and plays a pivotal role in regulating essential developmental processes (Napoli, 2016).

Retinoic acid production is initiated by the enzyme retinol dehydrogenase-10 (RDH10), which is responsible for converting retinol to retinaldehyde. This intermediate is then irreversibly oxidized to retinoic acid by retinaldehyde dehydrogenases (ALDH1A1, ALDH1A2, and ALDH1A3). Although the conversion to retinoic acid is permanent, retinoic acid is rapidly metabolized by cytochrome P450 enzymes (CYP26A1, CYP26B1, and CYP26C1), resulting in a short biological half-life of approximately one hour (Vasiliou & Nebert, 2005).

Retinoic acid regulates gene expression by binding to nuclear retinoic acid receptors (RARs), which form heterodimers with retinoid X receptors (RXR). These RAR-RXR complexes interact with specific DNA sequences known as retinoic acid response elements (RAREs). The complex, upon binding to RAREs, regulates gene expression through the recruitment of either nuclear receptor coactivators, NCOA, to stimulate transcription or corepressors, NCOR, to repress transcription (Cunningham et al., 2015; Napoli, 2016).

In summary, the absorption, storage, metabolism, and regulation of vitamin A involve highly complex processes that ensure its availability for physiological functions such as growth, reproduction, and cellular maintenance.

1.1. Effects of Vitamin A on the Reproductive System

1.1.1. Effects of Vitamin A on the Female Reproductive System and Offspring Production

Vitamin A significantly contributes to the growth of bones, development and maintenance of epithelial tissues, skin, and mucous membranes, enhancing the immune system's functions, including the proper functioning of reproductive organs (Carazo et al., 2021). Furthermore, vitamin A plays a crucial role in the normal development of the embryo. Nutritional requirements during pregnancy are considered elevated due to the necessity of meeting the additional demands of a developing fetus in addition to those of the mother. During the later stages of pregnancy, the demand for vitamin A increases due to the high rate of fetal growth (Meyers et al., 2006).

In the early 20th century, vitamin A was discovered to play a role in reproduction, particularly in the development of eyes in embryos. More recently, research into nutritional deficiencies in rat embryos and genetic studies in mice have provided substantial information about the numerous developmental processes dependent on vitamin A. Vitamin A plays a critical role in the development and maintenance of normal function in the reproductive systems and gametes of males and females, and also supports spermatogenesis and the integrity of the male reproductive system. Recent reports also suggest that active vitamin A participates in initiating meiotic signals both in developing female gonads and, in males, postnatally within the gonads. Insights into these vitamin A-dependent mechanisms have been provided by both nutritional studies and genetic research (Quadro et al., 2005).

Research into the molecular mechanisms of vitamin A in female reproduction and fetal development has established that all-trans retinoic acid is the bioactive form of vitamin A for these critical functions. This suggests that during pregnancy, in particular, vitamin A is essential in both the mother and the fetus. Conversely, inadequate intake of vitamin A can impact the proper development of the fetus and decrease the likelihood of survival and growth of the offspring postnatally. Vitamin A deficiency of sufficient severity is believed to lead to reproductive failure even before implantation, whereas in moderate deficiencies, although fertilization and implantation can occur, embryonic death has frequently been observed in the later stages of pregnancy. One of the critical factors that influence reproductive outcomes is vitamin A deficiency in females at the time of mating. It may result in complications such as pre-implantation failure, fetal resorption, embryonic death, or prolonged pregnancy without successful fetal development.The effects of vitamin A deficiency on the female reproductive system depend on the severity and timing of the deficiency (Clagett-Dame & DeLuca, 2002).

Research by Warkany and Schraffenberger (1946) demonstrated that female rats with severe vitamin A deficiency could achieve fertilization and implantation after receiving a small amount of provitamin A carotenoid prior to mating. However, the resulting mild deficiency caused embryonic death during mid-pregnancy. Similarly, vitamin A was shown to be essential for embryonic development in studies by Hale (1933, 1935), where female pigs deprived of vitamin A gave birth to offspring with severe abnormalities, such as defective eye development or complete absence of eyes. Additionally, female pigs on a vitamin A-deficient diet failed to exhibit signs of estrus (Warkany & Roth, 1948; Warkany et al., 1948).

Retinol plays a key role in promoting the differentiation of theca cells, which are essential for estrogen production. Therefore, maintaining adequate levels of vitamin A in the diet is crucial for supporting reproductive health and fertility (Yang et al., 2018). Research by Shaw et al. (1995) found that administering vitamin A (retinol palmitate) to cattle during superovulation positively influenced embryo quality, significantly increasing the number of high-quality embryos in vitamin A-supplemented cows (Yang et al., 2018). The reproductive disorders observed in female livestock due to vitamin A deficiency can be summarized as follows (Yang et al., 2018)

- Delayed puberty
- Low fertilization rates
- High embryo mortality
- Increased perinatal mortality due to weak and blind offspring

The demand for vitamin A and β-carotene increases significantly during pregnancy and lactation. During pregnancy, vitamin A is transferred from the mother to the fetus through the placenta, while during lactation, it is provided to the offspring via breast milk. The placenta plays a pivotal role in mediating the transfer of retinol from the maternal to the fetal compartment, ensuring a continuous supply throughout pregnancy. Studies have shown that when pregnant animals receive high doses of retinol, retinaldehyde, or retinoic acid, these compounds are transported to the embryo through maternal circulation. Although both retinol and retinoic acid are transferred to the fetus, the necessity of retinoic acid transfer under normal physiological conditions remains uncertain. Retinol-binding protein (RBP) is indispensable for the efficient transport of retinol (Spiegler et al., 2012)

Research also indicates that high-dose vitamin A supplementation elevates serum retinol levels in maternal plasma and breast milk. However, the duration of this elevation is not fully understood. In breast milk, vitamin A is predominantly stored as retinyl esters, with retinyl palmitate being the most significant. Following supplementation, vitamin A accumulates in the mammary epithelial tissue in the form of retinyl palmitate, leading to elevated vitamin A concentrations in breast milk during the initial days postpartum. During this time, some of the supplemented vitamin A is preferentially directed to the mammary glands rather than the liver, which underscores the importance of postpartum supplementation for addressing the offspring's nutritional requirements. However, there appears to be a limit to the increase in vitamin A concentration in breast milk. This limitation is attributed to the saturation of transfer proteins, such as lipoproteins and RBPs, that facilitate the movement of retinol from the bloodstream to the mammary glands (Bahl et al., 2002; Bezerra et al., 2010). Colostrum, the initial

breast milk secreted immediately after birth, is rich in fat-soluble vitamins, including vitamin A. Transitional milk, which is produced during the first 7 to 21 days postpartum, also contains elevated vitamin A concentrations. In contrast, mature milk maintains a consistent vitamin A concentration throughout the lactation period, providing a steady source of essential nutrients and vitamins for the offspring. Due to this phenomenon, mature milk serves as a primary medium for assessing vitamin A deficiency in mothers and their infants (Grilo et al., 2015; Y. de Vries et al., 2018).

1.1.2. Effects of Vitamin A on the Male Reproductive System

Fertilization represents the most critical stage in the conception of new offspring, wherein sperm released from the male reproductive system fertilizes oocytes formed in the ampulla region of the fallopian tube within the female reproductive system. However, abnormal spermatogenesis and sperm production can lead to infertility and reproductive problems because they prevent sperm from reaching the oocyte and achieving fertilization. Since retinol and retinoic acids activate molecular pathways related to spermatogenesis, vitamin A is an important vitamin for the male reproductive system(Clagett-Dame & Knutson, 2011).

Spermatogenesis is a highly intricate biological process involving the division and differentiation of cells, leading to the production of spermatozoa within the seminiferous tubules of the testes. The efficiency of spermatogenesis is often measured by the number of spermatozoa generated per gram of testicular tissue daily. The seminiferous tubules consist of a mix of somatic cells, such as myoid cells and Sertoli cells, as well as germ cells, which include spermatogonia, spermatocytes, and spermatids. The activities and division of these germ cells divide spermatogenesis into three major stages: spermatocytogenesis, meiosis, and spermiogenesis. Vitamin A deficiency disrupts normal spermatogenesis and affects the reproductive system. Historical studies have shown that in cases of deficiency, the epithelial lining of the epididymis, prostate, and seminal vesicles becomes squamous and keratinized, leading to the cessation of sperm production (Clagett-Dame & DeLuca, 2002). Further research revealed that in mice, spermatogonia fail to differentiate, leaving only Sertoli cells and a limited number of spermatocytes in the testes. Similarly, in mice, spermatogenesis is arrested at the spermatogonia stage (Boucheron-Houston et al., 2013; Li et al., 2011).

Sertoli cells host three types of spermatogonia, each with a specific function:

- **Stem cells**, responsible for renewing the germ cell population.
- **Undifferentiated spermatogonia**, also referred to as "A aligned," which expand the pool of progenitor cells.
- **Differentiating the spermatogonia**, distinguishing the spermatogonia, which advance towards spermatogenesis, commencing with the A1 spermatogonia (Hai et al., 2014)

Retinoik asit is a crucial regulator of spermatogenesis. It facilitates the transition of A aligned spermatogonia into A1 spermatogonia, the initial step necessary for the progression of spermatogenesis. Additionally, it plays a vital role in the early stages of mature spermatid release. Sertoli cells produce RA, which initiates the initial A aligned to A1 transition. Consequently, a protective mechanism mediated by the CYP26 enzymes prevents any premature activation of this transition from occurring via externally administered RA unless given at high concentrations (Endo et al., 2019; Khanehzad et al., 2021).

While Sertoli cells are generally considered the primary source of retinoic acid (RA), spermatocytes synthesize RA through the enzyme ALDH1A. RA from both spermatocytes and Sertoli cells serves a redundant function in supporting spermatogenesis. Current evidence indicates that RA originating from the spermatocytes themselves is essential for maintaining periodic releases of spermatozoa or sperm waves, facilitating the release of mature spermatids. Concurrently, RA from Sertoli cells is sufficient to support both processes (Chung & Wolgemuth, 2004; Teletin et al., 2019). RA also plays a significant role in regulating meiosis and spermiogenesis. It coordinates meiotic initiation shortly after the A aligned to A1 transition in spermatogonia and is central to the onset of spermiogenesis and release of mature spermatids (Evans et al., 2014; Endo et al., 2017). Furthermore, RARs expressed on the RA ligand in Sertoli cells regulate spermiogenesis and sperm maturation.

A deficiency of vitamin-A in livestock results in various disorders of male reproduction:

- Impairments in spermatocytogenesis, meiosis, and spermiogenesis.
- Reduced libido.

Carotenoids, recognized for their antioxidant properties, protect testicular cells by neutralizing free radicals. Studies have demonstrated that carotenoid supplementation can enhance critical semen parameters, such as sperm motility, membrane integrity, and DNA integrity (Pasquariello et al., 2022).

Conclusion

It has been observed that supplementation of vitamin A may play a crucial role in the male and female reproductive systems for the development and health of offspring. The administration of vitamin A as an exogenous supplement was hypothesized to enhance performance on farms by improving productivity in livestock. Furthermore, as vitamin A is a potent antioxidant, it was postulated to contribute to enhanced reproductive performance through the elimination of free radicals generated due to stress in both males and females during the reproductive period.

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