Chapter

Role of Vitamin E in Pregnancy

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Abstract

Vitamins play important roles in female health. They are essential for many functions, including menstruation and ovulation, oocyte (egg) quality and maturation. Vitamin E was first discovered in 1922 as a substance necessary for reproduction. It has become widely known as a powerful lipid-soluble antioxidant. There are various reports on the benefits of vitamin E on health in general. Vitamin E helps your body create and maintain red blood cells, healthy skin, eyes and strengthens your natural immune system. However, despite it being initially discovered as a vitamin necessary for reproduction, to date studies relating to its effects in this area are lacking. Vitamin E supplementation may help reduce the risk of pregnancy complications involving oxidative stress, such as pre-eclampsia. This chapter is written to provide a review of the known roles of vitamin E in pregnancy.

Keywords: Vitamin E, Pregnancy, Oxidative stress, Tocopherol

1. Introduction

Vitamin E is an important micronutrient in the human body. Vitamin E maintains various body functions. It plays a very important role in maternal health and child development [1]. Vitamin E is an essential fat-soluble micronutrient for higher mammals and functions as an antioxidant for lipids [2]. American scientists Herbert McLean Evans and Katherine Scott Bishop discovered vitamin E in 1922. Vitamin E is an essential lipid-soluble vitamin. It was initially denoted as an "anti-sterility factor X" that was necessary for reproduction. The vital role of vitamin E in reproduction was first investigated 80 years ago [3]. It was named according to a consecutive alphabetical order preceded by the discovery of vitamins A to D. Later vitamin E was called alpha-tocopherol, according to the Greek term "tokos" childbirth, "phero" to bear, and -ol indicating alcohol. Vitamin E is also called the "protecting vitamin" [4]. The amount of vitamin E is determined by age. For adults, the safest dose of vitamin E supplements is 1,500 IU/day for natural forms and 1,000 IU/day for man-made (synthetic) forms. **Table 1** shows the average daily prescribed doses as determined by the Food and Nutrition Board of the Institute of Medicine [5–7].

Some vitamin E containing foods include wheat, rice bran, barley, oat, coconut, palm, and annatto [8–9]. Other sources include rye, amaranth, walnut, hazelnut, poppy, sunflower, maize and the seeds of grape and pumpkins [10]. The richest sources are nuts, spinach, whole grains, olive oil, and sunflower oil [11]. Vitamin E now refers to eight different isoforms that belong to two categories, four saturated analogues (α, β, γ, and δ) called tocopherols and four unsaturated analogues

Life stage	Recommended Amount
Birth to 6 months	4 mg/day
Infants 7 to 12 months	5 mg/day
Children 1 to 3 years	6 mg/day
Children 4 to 8 years	7 mg/day
Children 9 to 13 years	11 mg/day
Teens 14–18 years	15 mg/day
Adults	15 mg/day
Pregnant women	15 mg/day
Breastfeeding women	19 mg/day

Table 1.
Recommended Dietary Allowances (RDAs) for Vitamin E.

(α, β, γ, and δ) referred to as tocotrienols [12]. α-, β-, γ- and δ-homologues contain three, two, two and one methyl groups, respectively. These structural differences and isomerism determine the biological activity [13]. Tocotrienols differ in the presence of 3 double bonds in their side chain from tocopherols. The position of the methyl groups on the chromanol ring varies between the tocopherol and tocotrienol isomers. Tocopherols can form 8 stereoisomers due to the presence of 3 asymmetrical carbons in their side chains (RRR, RRS, RSR, RSS, SRR, SRS, SSR, SSS) [14]. Among these isomers, α-tocopherol (**Figure 1**) has the highest biologically active form [15]. α-tocopherol is the most abundant in plasma, cell membranes, other human tissues, and nutritional supplements, whereas γ-tocopherol is the primary form found in the human diet [16]. Tocopherols and tocotrienols, collectively known as tocols, are phenolic compounds. Although phenolic and polyphenolic compounds such as phenolic acids, flavonoids, anthocyanins, proanthocyanidins, and ellagitannins have received much attention due to their antioxidant activities and potential health benefits [17, 18].

Natural and synthetic forms of the tocopherols and tocotrienols are equally absorbed from the intestinal lumen in the form of mixed micelles. After the passage of the micelles into the intestinal mucosa, chylomicrons are synthesized to transport vitamin E from the intestinal mucosa through the lymphatic system to the circulatory system [19]. In plasma, alpha-tocopherol is found in all lipoprotein fractions but mostly is associated with apo B-containing lipoproteins. Via the action of lipoprotein lipase (LPL), extrahepatic tissues pick up parts of the tocopherols transported in chylomicrons, and the remaining chylomicrons transport the remaining tocopherols to the liver. Here, a large proportion of alpha-tocopherol is incorporated into nascent very-low-density lipoproteins by the operation of the "alpha-tocopherol transfer protein" (VLDL), whereas the excess of alpha-tocopherol plus the other forms of vitamin E is excreted in bile. When VLDL is secreted into circulation, the action of LPL transforms VLDL into IDL and LDL, and the excess surface components, including alpha-tocopherol, are transferred to HDL. In addition to the LPL action, alpha-tocopherol is transmitted to tissues via the absorption of lipoproteins by different tissues through their corresponding receptors [20–24].

Metabolism of vitamin E begins with one cycle of CYP4F2/CYP3A4-dependent ω-hydroxylation followed by five cycles of subsequent β-oxidation and forms the water-soluble end-product carboxyethyl hydroxy chroman. α-Tocopherol can be oxidized to the tocopheroxyl radical. Further oxidation of the tocopheroxyl radical forms tocopheryl quinone. Other Metabolites of vitamin E include

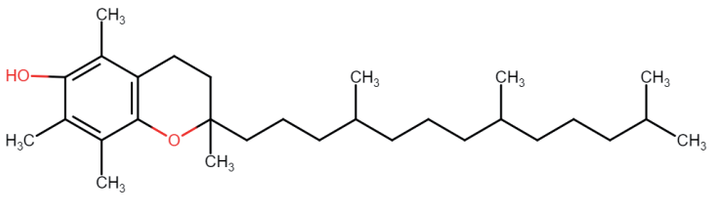

Figure 1.
Chemical Structure of alpha-Tocopherol.

2,5,7,8-tetramethyl-2-(2′-carboxyethyl)-6-hydroxychroman (α-CEHC) derived from α-tocopherol and 2,7,8-trimethyl-2- (2′-carboxyethyl)-6-hydroxychroman (γ-CEHC) derived from γ-tocopherol. There are two primary pathways for the excretion of vitamin E. Bile, which is then excreted in the urine, is the primary path of excretion. The second path is in the urine to make it more water-soluble after vitamin E is chain-shortened in a process similar to beta-oxidation. The major route of excretion of ingested vitamin E is fecal elimination because of its relatively low intestinal absorption [25, 26].

Because of its antioxidant function, it has several significant functions within the body. Numerous potential complications and disorders, including cancer, diabetes, arthritis and cataracts, have been related to oxidation; vitamin E is beneficial against these conditions. Vitamin E may also prevent platelet hyper aggregation, which can lead to atherosclerosis; it also helps to reduce the development of prostaglandins, such as thromboxane, that cause platelet clumping [27].

2. Role of vitamin E in pregnancy

Vitamin E supplementation may help reduce the risk of pregnancy complications involving oxidative stress. There is a need to evaluate the efficacy and safety of vitamin E supplementation in pregnancy [28]. A lack of vitamin E can lead to female infertility, miscarriage, premature delivery, eclampsia, fetal intrauterine growth restriction and other diseases associated with pregnancy [29–31]. Here some conditions in which vitamin E role are being described:

2.1 Infertility

Due to excessive production of ROS and/or insufficient consumption of antioxidants, oxidative stress arises. When the generation of reactive oxygen species (ROS) and other radical species exceeds then scavenging ability of antioxidants fail, injury to cells can occur. The mitochondrial respiratory chain produces the majority of ROS, although they may also be generated through exogenous exposures such as alcohol, cigarette smoke, and environmental pollutants. Antioxidants (such as vitamins C and E) and antioxidant cofactors (such as selenium, zinc, and copper) can dispose of, scavenge, or suppress the formation of reactive oxygen species (ROS). Reduced sperm motility, sperm number, and sperm–oocyte fusion have all been linked to oxidative stress in male infertility. In women, several animal and in-vitro studies suggest that oxidative stress may affect female fertility. Adequate intake of vitamin E protects from free radical generation [32].

According to Cooper et al., vitamin E deficiency impaired both male and female rats' germ cells. Vitamin E deficiency has a significant impact on secondary spermatocytes and spermatids [33]. According to several studies, vitamin E deficiency has been linked to reduced fertility in both humans and lab animals. Rengaraj et al.

discovered that a moderate amount of vitamin E in poultry diet preserves semen/sperm quality in male birds and egg quality in female birds by reducing lipid peroxidation in semen/sperms and eggs [34]. The effects of vitamin E on sperm motility were studied by Suleiman et al. A total of 11 out of 52 treated patients (21%) were pregnant, and 31 subjects experienced increased sperm motility [35]. In a systematic review of the effect of oral antioxidants (vitamins C and E, zinc, Se, carnitine) on male infertility by Ross et al., 17 randomized trials, including a total of 1665 men, were identified. Of the 17 trials, 14(82%) showed an improvement in either sperm quality or pregnancy rate after antioxidant therapy [36]. Cicek et al., studied the impact of vitamin E on the treatment results of women who were going through intrauterine insemination and controlled ovarian stimulation and had an unknown cause of infertility. Two groups A and B had 53 and 50 volunteers respectively. Group A received 400 IU/day of vitamin E and clomiphene citrate. This combination was used for producing controlled ovarian stimulations. Group B (control) also received controlled ovarian stimulation but without vitamin E. Outcome of the study demonstrated that both the groups had a significant difference in the thickness of endometrium on the day which human chorionic gonadotropin (hCG) was administered. Nevertheless, implantation and pregnancy rates had no connection with the administration of vitamin E. Based on the study it can be concluded that vitamin E possesses antioxidant effect and its administration could enhance the response of endometrium in females with unknown cause of infertility [37]. Das et al. performed a study in which female rats (30 days age) were maintained on a vitamin E-deficient diet for 70 days. At 100 days of age, the vitamin E-deficient and control animals were sacrificed. A group of animals was supplemented with a normal diet for the last 25 days following a 45-day deficient diet, or vice versa. The most notable findings were (i) a significant decrease in uterine weight in the deficient group, (ii) a significant decrease in estrogen, LH, and estrogen-induced uterine enzymes alkaline phosphatase and peroxidase, and (iii) ovarian dysfunction as shown by degenerating graffian follicles [38].

2.2 Endometriosis

Endometriosis is a condition characterized by the presence of endometrial tissue outside the uterine cavity [39]. Endometriosis is a condition that affects mostly women of reproductive age. The peak incidence is between 35 and 45 years old [40]. Endometriosis is found in 25 to 40% of women with infertility and 40–87% of women with chronic pelvic pain have endometriosis [41–43]. Endometriosis is associated with oxidative stress, even though the pathogenesis of the condition is currently unknown. Patient with endometriosis have an altered balance of prooxidant and antioxidant molecules [44–46].

Santanam et al. performed a randomized, placebo-controlled trial of antioxidant vitamins (vitamin E and C) in women with pelvic pain and endometriosis. This study included 59 women between the ages of 19 and 41 who had pelvic pain and had a history of endometriosis or infertility. Before surgery, patients were randomly assigned to one of two groups: vitamin E (1200 IU) and vitamin C (1000 mg) or placebo for eight weeks. Results indicated that after treatment with antioxidants, chronic pain ("everyday pain") improved in 43 percent of patients in the antioxidant treatment group ($P = 0.0055$) compared with the placebo group. The results of this clinical trial show that administration of antioxidants reduces chronic pelvic pain in women with endometriosis and inflammatory markers [47]. East-Powell et al. performed a randomized, placebo-controlled trial of antioxidant vitamins (vitamin E and C) in women with pelvic pain and endometriosis and/or infertility. A total of 59 women were included in the trial. Patients were randomly assigned to

2 groups: vitamin E 1200 IU (3 capsules of 400 mg each) and vitamin C 1000 mg (2 tablets of 500 mg each) daily for eight weeks before surgery. The results of this clinical trial show that administration of antioxidants (vitamin E and C) reduces chronic pelvic pain in women with endometriosis and inflammatory markers [48]. Hashemi et al. performed a randomized clinical trial in 40 women with implantation failure aged 18–37 years old. Participants were randomly divided into two groups: group A received 400-IU vitamin E supplements and group B received a placebo for 12 weeks. Vitamin E supplements were shown to dramatically improve serum vitamin E levels and endometrial thickness in women with implantation failure [49]. Kavtaradze et al. performed a clinical trial in 59 patients age 19–41 years with pelvic pain and history of endometriosis and/or infertility. Patients were randomly assigned to 2 groups: vitamin E (1200 IU) and vitamin C (1000 mg) combination or placebo daily for two months before surgery. This clinical trial's preliminary findings indicate that antioxidants (vitamins E and C) improve pelvic pain in women with endometriosis. According to this report, antioxidant vitamins are effective in reducing chronic pelvic pain in women with endometriosis. This research supports the development of a new class of medicines for the treatment of endometriosis-related pelvic pain. This information further supports our overall conclusion that endometriosis is an oxidative stress-related condition [50].

2.3 Miscarriage

Miscarriage is a serious pregnancy complication that can be brought about by a variety of causes. Vitamin deficiency has been linked to an increased risk of miscarriage, so supplementing women with vitamins before or during pregnancy can help prevent miscarriage [51]. Vitamin E deficiency's effects on human health have yet to be thoroughly reported and investigated. Low plasma vitamin E, on the other hand, has been linked to miscarriage in the first trimester of a woman's pregnancy. Furthermore, vitamin E supplementation in the diet reduced the rate of miscarriage in pregnant women by around 50% [52].

Pregnant women have quicker metabolism, increased production of free radicals, and increased lipid peroxidation. Thus, low levels of vitamin E can lead to the production of excessive free radicals, leading to placental aging, endothelial vascular damage, which increases the incidence of high-risk infections in pregnancy [53, 54]. It can also damage the lining of the fetal cell membranes, increasing the risk of premature rupture of the embryo [55]. Increased reactive oxygen species and decreased antioxidant levels in men are associated with recurrent miscarriage (RM). Antioxidant therapy has recently been recognized as a way to improve sperm parameters. Pourmasumi et al. evaluate the effect of paternal factor and antioxidant therapy on sperm parameters in couples with RM. Sixty samples with RM patients were analyzed before and after 3 months of vitamin E and selenium therapy. Results of this study show that antioxidants can improve sperm parameters and chromatin condensation in recurrent miscarriage male partners [56].

Vitamin E has anticoagulant activity; excessive vitamin E can have an impact on blood clotting in the fetus, increasing the risks of high levels of bilirubin and nuclear jaundice for newborn babies. Also, excessive vitamin E has an antagonistic effect on other fat-soluble vitamins in the blood of pregnant women, preventing the absorption and functions of other vitamins. As a result, clinicians should pay careful attention to changes in vitamin E levels during pregnancy and offer appropriate dietary advice, with an emphasis on reasonable vitamin E supplementation [57].

Kurmacheva et al. conduct a pharmacoeconomic analysis of two schemes of vitamin-mineral drugs in the peri-gestation period in women. In two classes of women, the cost-effectiveness of vitamin-mineral formulations was calculated. Patients in

the first group (n = 60) were given a vitamin-mineral complex before and during pregnancy that included metafolin, other B vitamins, vitamins C, E, PP, and iodine (150 mcg) in physiological doses, as well as 200 mg of docosahexaenoic acid in a capsule intended for use from the 13th week until the end of pregnancy. During pregravid preparation and the gestational period, women in the second group (n = 54) took high doses of synthetic folic acid, vitamins B6 and B12 as part of two vitamin and mineral preparations. The use of vitamin-mineral complex containing physiological dosages of vitamins of group B, vitamins C, E, PP and iodine in the peri-gestation period in women with habitual miscarriages has tangible clinical and economic advantages in comparison with the administration of high doses of synthetic folic acid, vitamins B6 and B12 [58].

Shamim et al. studied the contribution of deficiencies of vitamin E to human pregnancy loss (pregnancy losses <24 wk. of gestation) in rural Bangladesh. A trial was done in 1605 pregnant Bangladeshi women, gestational age: 8–13 weeks. Of the 1,605 women in the study, 141, or 8.8%, miscarried. About 5.2% of women with adequate alpha-tocopherol miscarried in the first or second trimester, compared with 10.2 percent of women with low levels. It was found that low plasma α-tocopherol was associated with an increased risk of miscarriage. Maternal vitamin E status in the first trimester may influence the risk of early pregnancy loss [59].

Junovich et al. investigate the fertility properties of Vitamin E. Pregnant females from CBA/J × DBA/2 miscarriage model (creates an immune type miscarriage) were orally supplemented with Vitamin E (15 mg/day). It was found that Vitamin E has able to decrease the miscarriage rate [60]. Şimşek et al. investigated plasma levels of vitamin E in 40 women with habitual abortion (HA) at the Department of Obstetrics and Gynaecology, Medical Faculty of Firat University, ElazigÏ, Turkey. The mean age of the patients was 28.5 years (21 ± 38 years). The levels of vitamin E were significantly lower in women with HA than in controls. According to the results of this study, it was found that a level of vitamin E was significantly decreased ($P < 0.01$) in HA. The decrease of this antioxidant may play a significant role in women with habitual abortion [61]. Vural et al. performed a clinical trial to determine the relationship between changes in some parameters of the antioxidant system like vitamin E and recurrent abortion. For the study 120 women with recurrent abortions, 25 non-pregnant healthy women in the productive era and 25 normotensive pregnant women within their first trimester were taken into the study in Istanbul Medical Faculty, Gynecology and Obstetric Department. According to the etiology, women with chronic miscarriage were classified into four subgroups: autoimmune, luteal phase defect, anatomical disease, and unexplained. Vitamin E levels in the autoimmune, unexplained, and luteal phase defect subgroups were slightly lower than in the two control groups and the anatomical defect group. It was found that decreased concentrations of plasma vitamin E reflect the increased oxidative stress. In a conclusion, recurrent miscarriages may also result in oxidative stress and depletion and weakness of antioxidant defence [62].

Von Mandach et al. studied that whether there is an association between reduced vitamin E levels and abnormal pregnancy. Abnormal pregnancies were compared with normals. In normal pregnancies, mean vitamin E levels rose from 12.9 +/− 1.1 micrograms/ml in early pregnancy to 22.5 +/− 1.5 micrograms/ml at term ($p < 0.05$, $n = 11$). In pregnancies with fetal complications or maternal risks, vitamin E levels were lower than in normal at corresponding gestational age. The results show lower maternal levels of vitamin E in abnormal pregnancies [63].

Oladimeji et al. performed a clinical trial to examine the relationship between serum vitamin E levels and unexplained infertility and recurrent miscarriages. Eighty-two healthy Nigerian Women volunteers were recruited for this study.

The mean serum vitamin E concentration in pregnant women was found to be insignificantly higher (10.36 ± 3.52 mg/ml) than the reported values in women with unexplained infertility and persistent miscarriage (8.97 ± 3.56 mg/ml). It was concluded from this study that there is no relationship between recurrent miscarriages and unexplained infertility and vitamin E levels [64].

Miscarriage risk is significantly reduced by taking supplementary vitamin E (at least 200 IU and perhaps 400 IU daily). There were already results of medical reports confirming this by the end of WW II [65].

2.4 Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome is a common birth defect in women during childbearing age. According to the Endocrine Society released training strategies for PCOS, in adolescents with PCOS, metformin and hormonal contraceptives are the treatment options [66].

Vitamin E is not a hormone but acts as a hormone. It works by impersonating the effects of progesterone on the body, as well as by reducing the side effects of high levels of androgens (testosterone and estrogen). In a study after 12 weeks, the amount of serum testosterone decreased which provides evidence against it. The study also found that lifestyle changes and the use of supplements including omega-3 and/or Vitamin E will improve inflammation and insulin sensitivity thus remaining an effective treatment approach for PCOS subjects. Vitamin E may serve as a necessary supplement included in the current treatment guide to improve PCOS parameters, which will also improve the quality of life in PCOS and reduce overall medical costs, often unaffordable for most people with PCOS in India [67]. Vitamin E reacts often with lipid peroxyl radicals which leads to the elimination of peroxidation chain reactions and thus reduces oxidative damage. The serum concentration of vitamin E in the study was significantly lower in PCOS patients compared with controls. Similar reports of reduced vitamin E concentration in PCOS patients were stated in various studies [68]. The prospect of a fast response of vitamin E to cellular oxygen and free radicals may be the cause of a significant decrease in vitamin E concentration. Therefore, it is proposed that vitamin E through its natural scavenging method protects polyunsaturated fatty acids from peroxidation reactions [69]. Mohan et al. 2009 estimated plasma vitamin E level in fifty-six Polycystic Ovary Syndrome patients. It was observed that there was a significant decrease in plasma vitamin E levels in patients with polycystic ovary syndrome when compared to controls [70]. Hamad et al. studied the effect of vitamin E and selenium on ovulation in PCOS patients. The participants in this sample included 25 PCOS patients who were untreated and 26 PCOS patients who were treated, as well as 42 healthy controls. From the results of this study, it was found that vitamin E has a significant role in the ovulation of PCOS patients [71]. Angiogenesis disturbances are common in women with polycystic ovary syndrome (PCOS). Shirazi et al. performed a randomized, double-blind, placebo-controlled trial on 43 women, ages 20–40 years, with PCOS to evaluate antiangiogenic properties of Vitamin E. Patients were randomly assigned into two groups: group A received vitamin E 400 IU/day and group B received placebo for 8 weeks. At the start and end of the analysis, anthropometric and angiogenic parameters such as body weight, fat mass, and fat-free mass, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) were calculated using standard methods. Vitamin E supplementation for eight weeks had beneficial effects on body weight, Ang-1, Ang-1/Ang-2 ratio, and VEGF level in PCOS women [72]. Carotid intima-media thickness (CIMT) artery in women with PCOS was significantly higher than healthy women. CIMT has been widely

used as a surrogate index of atherosclerosis and CVD events. Talari et al. performed a randomized, double-blind, placebo-controlled trial in 60 women with PCOS to evaluate the beneficial effects of omega-3 and vitamin E co-supplementation on carotid intima-media thickness (CIMT). Participants were randomly assigned into two groups and assigned to take either 1000 mg omega-3 plus 400 IU vitamin E supplements or a placebo for 12 weeks. It was found a significant reduction in maximum and mean levels of the left and right CIMT in patients with PCOS compared with placebo. Antioxidant and anti-inflammatory effects of Vitamin E may improve CIMT [73].

PCOS is a heterogeneous syndrome characterized by hyperandrogenism symptoms. Izadi et al. performed a randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of CoQ10 and/or vitamin E on glucose homeostasis parameters and reproductive hormones in women with PCOS. In this study, it was found that CoQ10 with or without vitamin E supplementation for 8 weeks among patients with PCOS significantly decreased serum total testosterone levels ($P < 0.001$) compared with those of the placebo group. CoQ10 supplementation in combination with vitamin E significantly improved sex hormone-binding globulin (SHBG) levels compared with other groups ($P = 0.008$) [74].

2.5 Embryonic development

Human embryonic development refers to the development and formation of the human embryo. It is characterized by the processes of cell division and cellular differentiation of the embryo that occurs during the early stages of development [75].

ROS are highly reactive molecules, their accumulation can lead to damage and breakage of DNA strands. Many pieces of evidence have been found that ROS compromises embryo development in many species [76–78].

Selenium and Vitamin E are the important antioxidants that protect mammalian cells against lipid peroxidation. Tsujii et al. conducted a study to investigate whether Selenium or Vitamin E and Selenium + Vitamin E overcome the undesirable oxidative stress produced by hydrogen peroxide (H_2O_2) and enhance the development of pre implanted mice embryo. Co-incubating the embryos with 60 nM Selenium and/or 100 nM Vitamin E were increased ($P < 0.05$) the blastocyst development rate. The addition of H_2O_2 reduced the development of mouse embryos, but the addition of Vitamin E, Se and Selenium+Vitamin E reduced the detrimental effect of H_2O_2 and influenced the higher rate of development to blastocysts, compared to CZB alone ($P < 0.05$). The incorporation and oxidation of 14C-glucose in the blastocysts developed by the medium supplemented with Se and/or Vitamin E in the presence or absence of H_2O_2 were significantly higher ($P < 0.05$) than that of the control. Moreover, Vitamin E is more effective than Selenium and Selenium + Vitamin E in reversing ROS-induced mouse embryotoxicity [79]. McDougall et al. studied the long-term effects of Vitamin E deficiency on embryonic development and improvement effect after feeding Vitamin E-adequate diets by using a zebrafish model. Adult zebrafish maintained on Vitamin E-deficient (E-) or sufficient (E+) diets up to 12 days post-fertilization (dpf) to obtained E- and E+ embryos. The E- group suffered significantly increased morbidity and mortality as well as altered DNA methylation status through 5 dpf when compared to E+ larvae, but upon feeding with a Vitamin E -adequate diet from 5 to 12 dpf both the E- and E+ groups survived and grew normally; the DNA methylation profile also was similar between groups by 12 dpf. However, 12 dpf E- larvae still had behavioral defects. Outcomes suggest that embryonic Vitamin E deficiency causes behavioral impairments due to persistent lipid peroxidation and metabolic perturbations that are not resolved via later dietary vitamin E supplementation [80].

2.6 Pre-mature delivery

Every year, about 15 million babies (1 in 10) are delivered prematurely around the world. Prematurity is the second leading cause of death among newborns after pneumonia. Pre-mature babies struggle with visual, auditory and learning disabilities. Over 60% of pre-mature delivery worldwide occurs in Sub-Saharan Africa and South Asia [81].

Cruz et al. studied the effect of vitamin E supplementation on mothers with threatened premature delivery and premature infants. It was found that maternal vitamin E treatment did not prevent either erythrocyte hemolysis or lipid peroxide formation in premature infants after birth. On the other hand, intramuscular vitamins E to infants after birth prevent erythrocyte hemolysis and low lipid peroxide formation when serum vitamin E increased above 2 mg/100 ml [82]. Hittner et al. performed a double-blind study in 101 preterm infants to evaluate the efficacy of oral vitamin E in preventing the development of retrolental fibroplasia. 50 infants received vitamin E 100 mg/Kg/ day and 51 infants received 5 mg mg/Kg/ day (controls). The severity of retrolental fibroplasia was found to be significantly reduced in infants given 100 mg of vitamin E ($P = 0.012$) [83]. The link between vitamin E deficiency and hemolytic anemia in small premature infants prompted researchers to look into vitamin E absorption in infants of different gestational and developmental ages. Premature infants' capacity to sustain vitamin E sufficiency during the first three months of life was shown to be directly related to their gestational age; infants with the lowest gestational age were the least likely to attain vitamin E sufficiency, even when given a vitamin E supplement. In infants with a gestational age of fewer than 32 weeks, there was a gradual increase in vitamin absorption in the intestine. Oral iron administration has been linked to a reduction in vitamin E absorption in the intestine. Since maintenance of vitamin E sufficiency appears to be nutritionally important in the premature infant, the efficacy of other routes of administration of the vitamin should be explored [84]. Vitamin E has been linked to several positive outcomes in premature newborn infants. Vitamin E deficiency is believed to be at least partially responsible for the anemia that happens often 4 to 6 weeks after premature birth, and regular vitamin E supplementation is often recommended. However, a review of published controlled trials of vitamin E supplementation shows that the extent, if any, of this preventive effect against anemia is debated. According to research, the dietary ratio of alpha-tocopherol to polyunsaturated fatty acids is normally sufficient to avoid symptoms of vitamin E deficiency without the use of supplements. Premature infants exposed to oxygen-rich conditions and artificial ventilation are protected from the risks of retrolental fibroplasia and bronchopulmonary dysplasia by receiving large parenteral doses of vitamin E. However, subsequent research has yet to verify these positive early findings of preventive effects. At this time, there does not seem to be any clear evidence that supplementing a premature infant's usual vitamin E intake is essential [85].

2.7 Uterine fibroids

Uterine fibroids or myomas are benign tumours of the human uterus. The main symptoms are prolonged or heavy menstrual bleeding, pelvic pressure or pain, and reproductive dysfunction [86]. Fibroids have an effect on a woman's pregnancy as well as her quality of life. Fibroids affect approximately 35–77% of reproductive-age women. Fibroids may cause infertility by obstructing the fallopian tubes and impairing gamete transport [87].

A total of 49 patients were enrolled in a double-blind, randomized, placebo-controlled trial conducted by Harrison et al. in 2003. For six months, all patients were

given either vitamins E (1000 IU) and C (1000 mg) or a placebo. Results show that a statistically significant improvement in fibrosis score ($p = 0.002$) [88]. Fruscella et al. studied the effect of vitamin E (300 mg per day) in a group of 25 women, aged between 25 and 41 years old, suffering from uterine myomas in pregnancy. All the pregnancies continued to term. The neonatal outcome was satisfactory in all cases and no collateral effects were observed in either mothers or fetuses [89]. Tocopherol can stop cancer cells from growing in culture by trapping free radicals and other mechanisms [90]. Young et al. discovered that vitamin E succinate (a vitamin E analogue) decreased the number of UF cells and caused cell death [91]. In addition, Zhang et al. discovered that vitamin E succinate ester could suppress steroid hormone signalling [92].

2.8 Preeclampsia

Preeclampsia is a major cause of both maternal and fetal neonatal morbidity. Endothelial damage in the arteries is believed to play a role. The simple clinical definition [gestational hypertension (>90 mmHg diastolic) occurring after the 20th week of gestation with superimposed proteinuria (>300 mg/day) belies the complexity of preeclampsia, which is often accompanied by multi-organ dysfunction. Free radical-mediated lipid peroxidation may be involved in endothelial damage in preeclampsia. Complications such as endothelial cell dysfunction of blood vessels in women with preeclampsia and other hypertensive conditions are linked with oxidative stress and lipid peroxidation.

Antioxidants may be essential for lipid peroxidation prevention and, hypothetically, pre-eclampsia prevention. Vitamin E, which is a free radical scavenger and thus inhibits the development of lipid peroxides, opposes the toxic acts of lipid peroxides. It acts as in-vivo antioxidant that protects tissue lipids from free radical attack and thus stabilizes cell membranes. Compared to non-pregnancy, maternal levels of vitamin E are elevated in pregnancy, which is consistent with previous studies. In women with preeclampsia, the antioxidant function is decreased relative to women who have normal pregnancies. Antioxidant activity increases throughout normal gestation, but not with preeclampsia. It has been suggested that evidence of vitamin E consumption is an alerting mechanism for the development of preeclampsia [93, 94]. Some preclinical studies show that vitamin E plays a role in preeclampsia [95]. But some clinical studies suggest that there is no role of vitamin E in preeclampsia [96, 97]. A study has found that level of vitamin E in preeclampsia was low, but no preventive role was found in preeclampsia [98].

2.9 Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is the inability of fetuses to achieve their genetically defined growth rate resulting in offspring with low birth weight (LBW) and is a problem for both human and veterinary medicine. IUGR has significant consequences for the mortality and morbidity of LBW newborns and has long-term effects on their development and health. The presence of IUGR is directly linked to an insufficient supply of nutrients and oxygen to the fetus due to maternal malnutrition and/or placental insufficiency [99, 100].

In the study, Sales et al. found that combined maternal administration of vitamin C and E in sheep was associated with increased levels of both vitamins in the fetal cord, enhanced antioxidant status, and increased fetal development in singleton and twin pregnancies, but with a greater impact on twin pregnancies. These findings demonstrate the ability of supplementation of vitamin C and E to reduce the effects of IUGRR [101]. Since the transplacental transmission of

alpha-tocopherol is minimal, newborns are considered an at-risk category for vitamin E deficiency. Low serum levels of alpha-tocopherol are associated with the development of edemas, thrombocytosis, and hemolytic anemia, which can result in cardiomyopathy and the possible consequence of this vitamin deficiency is its restriction on the intrauterine growth of fetuses [102].

Atherosclerosis is one of the main factor of intrauterine growth restriction. Busso et al. [103] studied LDL KO mice diet-induced maternal hypercholesterolemia and atherosclerosis during pregnancy can negatively impact fetal growth. Vitamin E dietary supplementation has a beneficial effect, preventing growth restriction in a significant proportion of fetuses from HC-fed mice [103].

2.10 Premature rupture of membranes

Preterm, premature rupture of the membranes (PPROM) is defined as membrane rupture before 37 weeks' gestation in the absence of labour.

PPROM occurs in 1–2% of all deliveries and results in a major portion of preterm deliveries with the regular mortality rate in neonates [104]. Infection, cigarette smoke, and inflammation have all been linked to preterm premature rupture of fetal membranes. Since hypochlorous acid (a reactive oxygen species) is essential to the body's reaction to infection, it may cause tissue damage when destroying pathogens. Plessinger et al. found that antioxidant therapy (vitamins C and E) has a protective effect against hypochlorous acid-induced damage [105].

Preterm infants have a higher risk of oxidative stress and free-radical-mediated diseases, which is partially due to their low antioxidant levels. Bolisetty et al. studied the effect of maternal supplementation of antioxidant vitamins before delivery to reduce the oxidative stress in the mothers and their infants. Five mothers between the ages of 30 and 36 weeks who were at risk of preterm delivery were given a daily oral dosage of betacarotene 20 mg, vitamin E 167.8 mg, and vitamin C 1000 mg until delivery. There was a trend of lower plasma MDA and higher vitamin E at birth in infants born to supplemented mothers. Finally, it has been concluded that short supplementation of antioxidant vitamins to preterm pregnant women reduced the oxidative stress at delivery in mothers and probably in their neonates [106].

The fetal membranes (amnion and chorion) derive their strength principally from collagen. Collagen provides fetal membranes with both tensile strength and elasticity. Reactive oxygen species (ROS) generated by the body's response to infection, cigarette smoking, bleeding, or cocaine use can activate collagen lytic enzymes and impair fetal membrane integrity. Vitamin E, a lipid-soluble antioxidant, inhibits its membrane-damaging effects of reactive oxygen species induced lipid peroxidation [107]. Hauth et al., studied that maternal supplementation with vitamin C and E did not reduce the occurrence of spontaneous preterm birth [108].

3. Discussion

Several risk factors contributing to reproductive- and pregnancy-related disorders have been reported. Environmental and lifestyle factors are the two main types factors. Examples of major environmental pollutants include hazardous man-made chemicals, industrial discharge, agricultural run-off, human and animal waste, municipal and domestic effluents, and spillage of vessels and oil spills [109]. Lifestyle factors represent another category of major risk factors for reproductive and pregnancy-related disorders. Unhealthy lifestyle behaviors, including cigarette smoking, alcohol consumption, and/or drug abuse,

have negative impacts, particularly on female fertility [110, 111]. Furthermore, exposure to multiple environmental pollutants may also result in reactive oxygen species (ROS)-induced oxidative stress (OS). High levels of OS can be linked to a variety of pregnancy-related issues, including embryonic death, early spontaneous abortion, IUGR, fetal death, preterm births, and low birth weight [112, 113]. ROS are highly reactive and unstable. They acquire electrons from nucleic acids, lipids, proteins, carbohydrates, or any other nearby molecule causing a string of chain reactions to become stable. These chain reactions result in cellular damage and diseases [114]. The human body produces reactive compounds known as free radicals which exert a positive as well as a negative impact on the body. To minimize the harmful effect, a complex protection system is required which is known as the antioxidant system. When there is an imbalance between the production of free radicals and the defense mechanism of the antioxidant system it leads to a condition known as oxidative stress [115]. Oxidative stress affects the interaction of gametes and their quality. Spermatozoa, embryos, and oocyte and their environment are affected by free radicals such as reactive oxygen species (ROS). The quality of sperm-mediated oocyte activation, early embryo development, implantation, sperm oocyte interaction is dependent on the microenvironment associated with peritoneal fluid, follicular fluid, and hydrosalpingeal fluid. Implantation and early embryo development are adversely affected by oxidative stress leading to a negative effect on the rate of pregnancy. One of the causative factors for infertility and endometriosis is oxidative stress [116]. ROS or prooxidant or free radicals production have a connection with aerobic metabolism [117, 118], and also the hormones, cytokines, and other stressors are associated with its production. Hydroxyl radical, superoxide anion and hydrogen peroxide are examples of reactive oxygen species (ROS) and they act by modulating the gene expression and transcription factor. A broad range of antioxidants is available which hold the capability to repair cell damage caused by ROS and can neutralize them as well [119, 120].

Some studies suggested that there is a direct relationship between the outcome of the pregnancy and the level of ROS. The placental mitochondrion is the place that has been identified for the production of superoxide in a great amount [121, 122]. Antioxidants such as vitamin C and vitamin E have been reported to be efficient, and their uses in reproductive- and pregnancy-related disorders have been the subject of significant clinical trials [123]. Vitamin E is a chain-breaking antioxidant that helps to inhibit lipid peroxidation [124, 125].

All of these studies show that vitamin E is essential for a natural and stable pregnancy and that vitamin E supplementation has no negative effects on pregnancy outcomes. As discussed above, vitamin E has been proven to be beneficial in pregnancy and neonatal health.

4. Conclusion

Vitamin E has antioxidant properties that may support pregnancy, but more research is needed to determine its effectiveness. There is a need to evaluate the efficacy and safety of vitamin E supplementation in pregnancy. More research is needed to accurately quantify antioxidant-like vitamin E levels in pregnancy and how they change throughout the pregnancy. It is necessary to investigate the effects of antioxidants on maternal, fetal, and placental health. Prenatal advice should be clear to ensure that women and physicians understand the dietary conditions during pregnancy and how a balanced diet contains antioxidant micronutrients like vitamin E will help avoid pregnancy-related diseases.

Conflict of interest

The authors declare no conflict of interest.

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