Omega 3 and Preterm Birth

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Preterm birth (PTB) is a major cause of neonatal death and long-term consequences for the newborn. There is not enough available evidence that supports the conclusion that omega 3 supplementation during pregnancy reduces the risk of PTB and ePTB.

Keywords: omega 3 supplementation ; preterm birth

1. Introduction

Preterm birth (PTB), defined as birth <37 weeks of gestational age (GA), has been estimated to affect one in nine infants worldwide and represents the most significant cause of neonatal death [1]. Likewise, early PTB (ePTB, birth <34 weeks of GA) also represents a high risk of heart failure, infections and neonatal mortality [2]. Additionally, women who give birth before 37 weeks of GA have an increased risk of preterm deliveries in their second pregnancies [3]. Many strategies have been used to reduce the risk of PTB, particularly, the use of progesterone and cervical cerclage, which have limitations such as cost, availability and safety [4]. One strategy focused on the prevention of PTB is the administration of long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy, which is accessible and cheap and has minimal side effects.

Omega 3 LCPUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential in metabolic and physiological processes during embryonic and fetal development [5]. Although higher intakes of DHA and EPA's have been recommended worldwide, Dietary Reference Intakes (DRIs) have not been established. The Institute of Medicine (IOM) recommends that the intake of EPA and DHA contributes to 10 percent of the total omega 3 fatty acid intake (160 mg per day approximately) [6]. In the case of the Food and Agriculture Organization (FAO), the recommendation is an intake of 200 mg/day of DHA during pregnancy [7].

Lower plasma levels of omega 3 LCPUFAs during pregnancy have been associated with detrimental perinatal outcomes, such as preterm delivery [8] and preeclampsia [9]. However, until now, there is no consensus on whether omega 3 supplementation during pregnancy reduces the risk of prenatal complications. A significant number of studies have been carried out to address this topic, including randomized controlled trials (RCTs) and meta-analyses. Some of them have shown a significant association between the consumption of fish or DHA supplements in pregnancy and decreased PTB incidence [10][11][12], but others have failed to demonstrate this association [13]. In 2010, Makrides et al. conducted an RCT to evaluate the impact of DHA supplementation during pregnancy on maternal depression and concluded that the consumption of DHA was associated with a decrease in the incidence of ePTB compared to the control group [14]. However, this outcome was secondary, and the analyses were not adjusted for multiplicity, limiting the confidence in the results. Olsen et al. showed in an RCT that fish oil does not prevent PTB in Chinese women; however, it is important to consider that supplementation started at midgestation [15]. Among the mechanisms suggested to explain the effect of omega 3 on PTB are the production of eicosanoids involved in the parturition process [16] and their role in the inflammatory pathway, including an increase in resolving R3 production [17][18]. Besides its tocolytic properties, omega 3 may also have an effect on the electrical activity of the myometrium during the pre-labor period, demonstrating an antiarrhythmic effect that could explain the role of omega 3 in the prevention of PTB [19].

2. Supplementation of Omega 3 during Pregnancy and the Risk of Preterm Birth

Preterm delivery is a leading cause of neonatal and childhood mortality and is associated with cognitive deficiencies and increased risk of cardio-metabolic diseases in adult life [20][21]. LC-PUFA are involved in optimum fetoplacental growth and development through their function associated with oxidative stress, angiogenesis and inflammation [22]. The consumption of oily fish and DHA supplements during pregnancy has been associated with maternal and infant benefits, including decreased maternal blood pressure [23] and infant neurodevelopment and growth [24]. Previous studies have explored the relationship between omega 3 intake during pregnancy and timing of delivery or preterm risk; however, the results are still

inconsistent. Meanwhile, some clinical trials reported an increase in gestational length after DHA and fish oil supplement interventions [25], and others reported no effect in the incidence of ePTB [26] and PTB [15]. A previous meta-analysis also analyzed the effect of omega 3 supplementation on PTB rates; in 2015, Saccone and Berghella reported no effect of omega 3 with only two RCTs analyzed [27]. However, in 2016, Kar et al., following the analyses of nine studies, did find a positive effect of omega 3 supplementation on the prevention of PTB [28]. Besides including a greater number of studies, compared with Kar and Colleagues, our work provides an update of RCTs published until June 2020 as well as the analyses of secondary outcomes, such as preeclampsia, IUGR and fetal and neonatal death.

We conclude that omega 3 supplementation during pregnancy does not reduce the risk of PTB and ePTB. Although preliminary results showed that omega 3 supplementation reduced the risk of PTB and ePTB by 11% and 27%, respectively, after sensitivity analyses were performed and only low risk of bias studies were analyzed, the significance of the effect of omega 3 on PTB and ePTB risk disappears. Concerning the effect of omega 3 supplementation on other perinatal outcomes, such as preeclampsia, IUGR risk and fetal and neonatal death, no differences were found in this study. These results suggest that among the studies analyzed, there is not enough evidence suggesting that omega 3 supplementation during pregnancy decreases the risk of PTB and other perinatal complications.

The form of omega 3 supplementation in the analyzed trials differed and included capsules; liquid fish oil; and enriched food products, such as eggs high in DHA and bars containing DHA. The intake of 600 mg of DHA/day as capsules or bars has shown an increased length of pregnancy by 2.9 days [12] and 4.0–4.5 days [29]; meanwhile, the ingestion of 137 mg of DHA from high-DHA eggs showed a gestation increase of 6 days [25]. It can be hypothesized that food-based DHA (i.e., DHA-rich eggs) might have a more pronounced impact on pregnancy lengths as omega 3 bioavailability is higher when DHA is consumed in a high-fat food matrix [30]. The administration of omega 3 as DHA and EPA by itself or in combination with other nutrients should also be considered at the moment of describing the effect of omega 3 on fetal and maternal outcomes. In this review, considering the number of studies, it was not possible to differentiate between different doses and different components of supplementations. Similarly, nutritional status and omega 3 deficiency should also be considered. Lower levels of plasma EPA and DHA showed a 10-fold increased risk of ePTB compared to the higher plasma levels [8], demonstrating a potential benefit of the supplementation effect during deficiency.

Timing and length of supplementation are important factors determining the effect of omega 3 on preterm delivery risk. Considering the mechanism of action of omega 3 associated with inflammation and electrical activity of myometrium, it can be expected that acute (short-term) and chronic (throughout the pregnancy) supplementation have different effects on outcomes related to preterm delivery. The time of administration, the gestational week when the supplementation started and if the treatment continued through the whole pregnancy or not are characteristics that have to be considered in future studies. The potential adverse effects of omega 3 supplementation are not discussed in this review; however, post-term partition or bleeding have been associated with high omega 3 doses (>2.7 g/day) [31].

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