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A balance of omega-3 and omega-6 polyunsaturated fatty acids is important in pregnancy

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ABSTRACT

Emerging evidence suggests that omega (n)-3 PUFA and their metabolites improve maternal and neonatal health outcomes by modifying gestation length, and reducing the recurrence of pre-term delivery. N-3 PUFA has been associated with prolonged gestation and increased birth dimensions such as birth weight and head circumference. However, mothers giving birth to larger babies are at an increased risk of having dysfunctional labour, genital tract laceration, and delivery via caesarean section. Likewise, high infant weight at birth has been linked to several metabolic and cardiovascular disorders in the offspring. Prolonged gestation also leads to reduced placental function which has been implicated in fetal distress, and perinatal death. Till date, the mechanism through which high *n*-3 PUFA intake during pregnancy increases gestation length and birth weight is vaguely understood. Early and later stages of pregnancy is characterised by increased production of pro-inflammatory cytokines which are required for pregnancy establishment and labour regulation respectively. Conversely, mid-stage of pregnancy requires anti-inflammatory cytokines necessary for uterine quiescence, pregnancy maintenance and optimal fetal growth. Apparently, changes in the profiles of local cytokines in the uterus during different stages of pregnancy have a profound effect on pregnancy progression. This review focuses on the intake of *n*-3 and *n*-6 PUFA during pregnancy and the impact it has on gestation length and infant weight at birth, with a particular emphasis on the expression of inflammatory cytokines required for timely pregnancy establishment (embryo reception and implantation) and labour induction. It is concluded that an appropriate dose of *n*-3 and *n*-6 PUFA needs to be established during different stages of pregnancy.

Contents

1. Background

Maternal diet is critical for a successful pregnancy establishment, as well as fetal health outcomes [1,2]. Nutrition during pregnancy programs set points for metabolic and physiological

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responses in the offspring which manifest at either childhood or at adult life [3–5]. The hypothesis that early life dietary insults *in utero* increases the vulnerability of the offspring to developing several pathological conditions is now unequivocally accepted [3,6]. Several studies have now established that the quantity and quality of dietary fats consumed during pregnancy have profound health implication during and after pregnancy [7,8]. Omega (*n*)-6 and *n*-3 polyunsaturated fatty acids (PUFA), the essential fatty acids [9], play critical roles during fetal growth and development [8,10–12]. However, the mean *n*-3 PUFA intake of about 90% of Canadian women is only 82 mg per day, which is far below the recommendation of the International Society for the Study of Fatty Acids and Lipids for North Americans (300 mg/day) [13]. Dietary shift over the years to Western diet has caused a drastic change in the ratio of *n*-6 to *n*-3 fatty acids from about 1–2:1 in the Paleolithic diet (hunter gatherer's diet) to about 20–30:1 [14]. This transition has been found to promote the pathogenesis of several diseases [15]. Metabolism of *n*-3 PUFA such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) produce anti-inflammatory lipids mediators which have been shown to reduce the risks of specific clinical endpoints [16,17], while *n*-6 PUFA are generally considered inflammatory in nature [18].

DHA is important in the overall fetal growth, as well as the development of vital organs such as the brain and eyes [11,12]. As such, an inadequate intake of DHA during pregnancy has been associated with impaired cognitive functions and visual acuity in the offspring [19]. Besides, other spectrum of evidence has shown that *n-3* PUFA supplementation during pregnancy reduces the risk of pre-term birth (PTB), especially in high risk pregnancies [20–23]. Women consuming diets high in *n*-3 PUFA during pregnancy were observed to have longer gestational length, and consequently, high birth dimensions such as birth length, birth weight and head circumference [22–33]. To identify appropriate studies on the effect of *n*-3 PUFA on pregnancy establishments and outcomes, MEDLINE (PubMed) and Web of Science databases were searched thoroughly using the following keywords; pregnancy, implantation, labour, cytokines, polyunsaturated fatty acids, and birth outcomes. Adequately controlled studies (Randomized controlled clinical trials), as well as prospective cohort studies assessing the effect of *n*-3 PUFA intake during pregnancy on pregnancy duration and outcomes in women of reproductive age were considered for this review. Studies limited by subject number (<50 subjects) were excluded, while studies published in English language, between 1985 and 2015 were included.

Women supplemented with high *n*-3 PUFA had their gestation length extended by 6 days [34] and 8.3 days longer in high risk pregnancies [35]. Prolonged gestation and high birth weight, however, has been associated with several maternal, fetal and neonatal health risks. Mothers giving birth to larger babies are at an increased risk of having prolong labour, excessive bleeding, and genital tract laceration due to baby having head or shoulder too big to pass through the mother's pelvis, thereby resulting in instrument-assisted delivery, or caesarean delivery [36]. High birth weight has also been associated with childhood obesity [37], diabetes [38], and metabolic syndrome [39]. Equally, prolonged pregnancy (post-term) increases emotional stress in mothers [40]. Prolonged pregnancy also result in reduced placental function, and this increases the risk of fetal distress and ultimately perinatal death due to low supply of nutrients and oxygen to the developing fetus [41]. These observations emphasize on the possible negative impact of consuming high *n*-3 PUFA diet during pregnancy due to gestational length modification, however, the dosage and mechanism/s through which *n*-3 PUFA increases gestation length and birth weight is yet to be clearly elucidated. Pregnancy was initially thought to be a single event characterised by either pro-inflammatory or anti-inflammatory molecules [42]. However, subsequent studies disapproved the pro- or anti-inflammatory molecules dichotomy during pregnancy.

Pregnancy is made up of three (3) distinct biological phases with each phase having different classes of predominating pro- or anti-inflammatory mediators [43]. Early and later stages of pregnancy are characterised by an increased production of pro-inflammatory cytokines which are required for timely pregnancy establishment [44,45] and labour stimulation respectively [43,46]. In contrast, the mid-stage requires anti-inflammatory cytokines necessary for uterine quiescence, and optimum fetal growth [43]. This review explores the properties of *n*-3 PUFA on the regulation of uterine expression of cytokines required for timely and successful pregnancy establishment and labour stimulation. The focus will be on the plausible consequences of altering pro-inflammatory cytokines signalling on gestation length and infant weight at birth.

2. Metabolism and transport of essential PUFA during pregnancy

Humans lack the enzyme required for the insertion of a cis double bond at 3rd and 6th carbon of *n*-3 and *n*-6 PUFA respectively, thus making these fatty acids essential [47]. The simplest form of *n*-3 (alpha-linolenic acid; ALA) and *n*-6 PUFA (linoleic acid; LA) must therefore be obtained from the diet. Once consumed, longer chain PUFA, such as arachidonic acid (AA), can be synthesized endogenously from LA, while EPA and DHA are produced from ALA through series of desaturation and elongation processes [48] (Fig. 1). Studies using stable radiolabelled fatty acids have shown that the rate of metabolism of essential PUFA is sex specific; sex hormones may influence the enzymatic synthesis of longer chain fatty acids as the metabolism of ALA to DHA was observed to be higher and faster in women than men [49,50]. In men, the conversion rate of ALA to EPA is about 8%, while ALA to DHA is between 0 and 4%. On the other hand, about 21% and 9% ALA is converted to EPA and DHA respectively in women [49].

DHA is very important for healthy brain and eyes (retina) development, as well as overall fetal growth during pregnancy [11,12]. Brain has the largest amount of lipids (60% dry weight), compared to other organs in the body [51]. DHA constitute about 10–15% of total fatty acids in the brain, and this represents more than 97% of total *n-3* PUFA [52,53]. It has been shown that there is acceleration of fetal brain growth during the second trimester [8]; perhaps, this is the most critical stage for DHA supplementation. However, it has been shown that the accumulation of DHA in the brain is most rapid during the third trimester of pregnancy and the first year after birth [54,55]. Fetus accrues up to 70 mg DHA per day during the last trimester, specifically in the brain, and white adipose tissues [56], demonstrating the significance of maternal DHA status on fetal health. Interestingly, studies have shown that maternal DHA level is usually low during the last trimester, which explains a higher rate of transfer of DHA to the fetus [57]. At the same time, low maternal *n*-3 PUFA levels at the last trimester could be an in-built regulatory mechanism to enhance the synthesis of the pro-inflammatory molecules required for labour induction. Nonetheless, a deficit of *n-3* PUFA during pregnancy results in impaired cognitive and physiological functions in rats [58], which has been suggested to be irreversible by postnatal supplementation [59].

Evidence suggests that the pathway for the synthesis of longer chain PUFA becomes upregulated and highly efficient during pregnancy so as to meet both maternal and fetal requirement [60]. The ALA to DHA conversion pathway is complimented by increased mobilization of accumulated DHA reserves in the maternal tissues prior to conception [50], and also by supplementing maternal diet