Journal of Nutrition & Intermediary Metabolism 5 (2016) 23–33

Contents lists available at ScienceDirect

Journal of Nutrition & Intermediary Metabolism

journal homepage: http://www.jnimonline.com/

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

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ARTICLE INFO

Article history:
Received 15 December 2015
Accepted 28 April 2016
Available online 4 May 2016

Keywords:
Cytokines
Pregnancy
Implantation
Labour
Polyunsaturated fatty acids
Birth outcomes

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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http://dx.doi.org/10.1016/j.jnim.2016.04.008

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

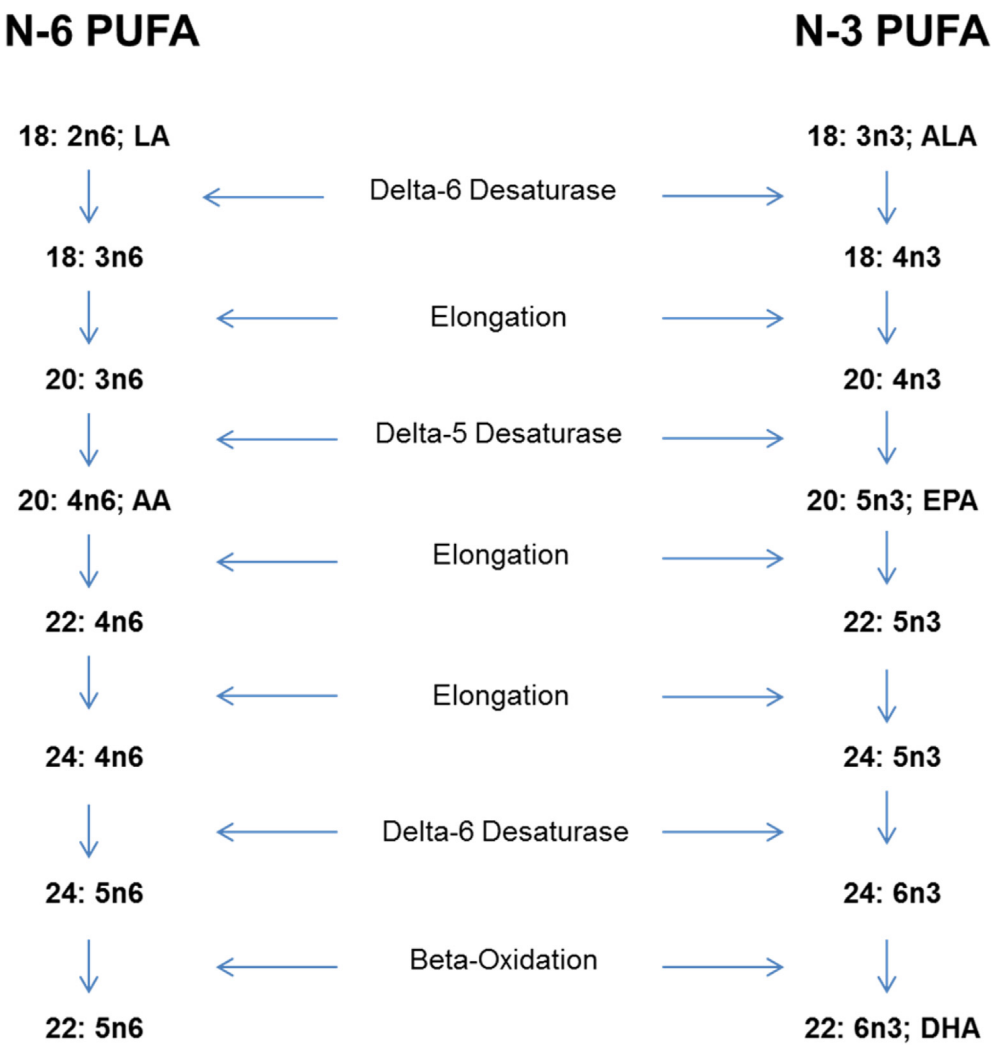

Fig. 1. Elongation and desaturation of essential polyunsaturated fatty acids. AA: Arachidonic acid; ALA: Alpha linolenic acid; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; LA: Linoleic acid; PUFA: Polyunsaturated fatty acid.

with DHA during pregnancy. A recent study conducted in women undergoing frozen embryo transfer reported an increase in the mobilization of maternal DHA at early stage of pregnancy prior to neural tube closure [61], and the concentration of DHA in maternal plasma doubles in twin pregnancies compared to singleton pregnancies. These studies emphasize the importance of maternal metabolic response during pregnancy on fetal development, especially in the closure of neural tube. As such, DHA intake of women before and during pregnancy may have a great impact on the amount of DHA available for fetal use. In addition to the increased maternal metabolic capacity for DHA synthesis during pregnancy, the rate of transfer across the placenta also plays a critical role in regulating the amount of DHA in fetal tissues [62]. Pre-formed longer chain PUFA such as DHA and AA from maternal circulation are selectively and preferentially transferred across the placenta to the fetus during pregnancy [57,62]. Fetal accumulation of *n-3* PUFA *in utero* is predominantly regulated by maternal *n-3* PUFA status and the placental function [62].

Development of the placenta is a remarkably coordinated physiological adaptation required for materno-fetal interaction during pregnancy. The placental functions are precisely regulated to ensure efficient and timely exchange of nutrient, oxygen, and waste between maternal circulation and the growing fetus. Nutrients and oxygen transfer during pregnancy is further enhanced by increased blood flow to the placenta via dilated blood vessels [63]. In addition, the functional characteristics of the placenta changes in order to accommodate the metabolic requirement of the developing fetus, and this include preferential transfer of essential fatty acids during the last trimester of pregnancy [62,63]. Translocation of essential fatty acids across the placenta occur via passive diffusion or through membrane protein-mediated mechanism [62,64] (Fig. 2). Physiologically, the protein-mediated transportation of fatty acids has been shown to be quantitatively more important than passive diffusion [62]. Several membrane located proteins have been identified to be involved in the transport of longer chain *n*-3 PUFA across the placenta, and these include the highly glycosylated fatty acid translocase (FAT), also referred to as cluster of differentiation-36 (CD36); placental membrane fatty acid binding protein (p-FABPpm); and the fatty acid transport proteins (FATP) [62]. Furthermore, transfer of long chain PUFA to the fetus is amplified by the activity of placental lipoprotein lipase (LPL), phospholipase A2 (PLA2), intracellular lipases, and triacylglycerol hydroxylase [65,66]. LPL and PLA2 hydrolyse maternal plasma lipoproteins and phospholipids, resulting in the liberation of PUFA, which are subsequently transported to the fetus. Lipolytic activity increases dramatically during the third trimester [67], and

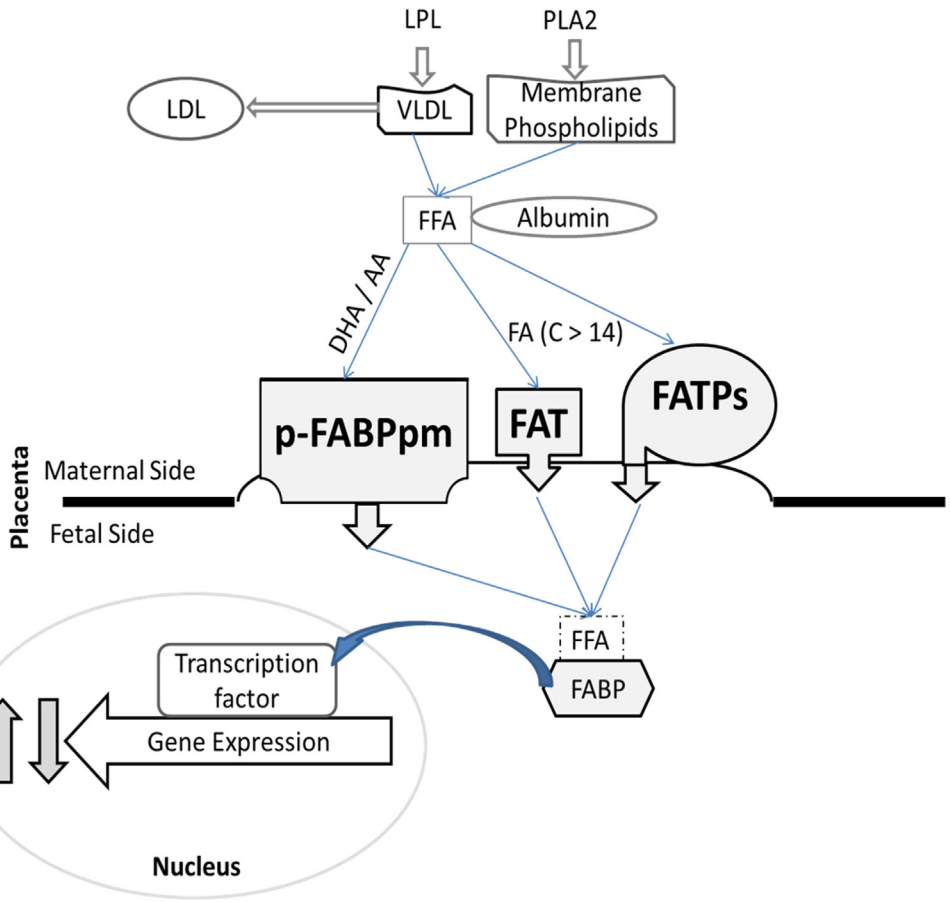

Fig. 2. Transport of essential PUFA during fetal development (Adapted from Duttaroy, 2009) [62]. AA: Arachidonic acid; DHA: Docosahexaenoic acid; FAT: Fatty acid translocase; FABP: Fatty acid binding proteins; FATP: Fatty acid transport protein; LDL: Low density lipoprotein; LPL: Lipoprotein lipase; PLA2: Phospholipase A2; p-FABPpm: Placental plasma-membrane fatty acid binding protein; VLDL: Very low density lipoprotein.

this is perhaps necessary to promote healthy fetal growth through adequate delivery of essential longer chain PUFA via the placenta. A deficit in essential longer chain PUFA supply due to placental dysfunction or inadequate perinatal consumption has been attributed to specific adverse pregnancy outcomes [68].

3. Omega-3 PUFA intake and pregnancy outcomes

3.1. Effect of omega-3 PUFA intake on the risk of pre-term birth (PTB)

PTB is a major recurrent problem in obstetrics which accounted for about 35% of all infant deaths in the United States in 2010 [69]. PTB is currently the leading cause of developmental disabilities [70], as well as neonatal morbidity and mortality in Canada and worldwide [71]. Data from World Health Organization (WHO, 2015) [72] revealed that an estimated 15 million babies are born premature every year across the globe. PTB constitutes an economic burden of about $587.1 million per year in Canada [71]. The pathophysiology of PTB is yet to be completely understood, however, several studies have reported a significant positive association between maternal *n*-3 PUFA intake and PTB. Earliest population-wide study reported that women in Faroe Island consuming high amounts of marine foods (rich source of *n*-3 PUFA) had a very low risk of birth before 37th week of pregnancy [73]. Subsequent studies further confirmed the positive effect of consuming *n*-3 PUFA on PTB (Table 1).

A prospective cohort study conducted in Denmark revealed that a low intake of *n*-3 PUFA is a risk factor for PTB; the incidence of PTB was higher in women who never ate fish compared to those who consumed fish at least once per week [21]. Furthermore, data from a 50-year-old controlled fish supplementation trial conducted in London showed a 20.4% reduction in PTB [75]. More recent intervention studies show that the hazard risk of spontaneous PTB reduced by about 39% in women who consume moderate amount of fish [76,77]. Fish oil intake was also observed to reduce the recurrence of PTB from about 33% to 21% in women who received fish oil supplementation (2.7 g/d of EPA and DHA) at 20 weeks gestation, or 6.1 g/d of EPA and DHA at about 33 weeks gestation [27]. The beneficial effects of consuming *n*-3 PUFA, relating to reduction in the risk of PTB during pregnancy, has been attributed to its involvement in gestation length modulation [78].

3.2. Effects of n-3 PUFA on gestation length and infant size at birth

Studies have suggested that the intake of longer chain *n-3* PUFA can improve pregnancy outcomes [20,22,24,28,31]. Data from intervention trials and observational studies have suggested a positive association between intake of *n*-3 PUFA during pregnancy and the gestation length, and consequently the weight of infants at birth [73,75,78]. Of interest is the observation that about 1% relative increase in cord serum phospholipid DHA in Faroe Island women was associated with approximately 1.5 days increase in gestation length [79]. Likewise, high intake of marine fat slightly reduced the

Table 1
Omega-3 polyunsaturated fatty acids and pre-term delivery.

Intervention	Outcome(s) in the treatment group	Reference(s)
Fish oil 2.7 g and 6.1 g EPA + DHA (20 weeks gestation until delivery until delivery)	Fish oil reduced recurrence risk of pre-term delivery from 33% to 21%.	[27]
Fish and fish oil intake (at least once per week)	Reduced incidence of preterm delivery from 7.1% to 1.9%	[21]
DHA capsules, 600 mg/day (<20 weeks until delivery)	Lower risk of PTB	[30]
DHA supplementation; up to 600 mg/day (16–20 weeks of gestation)	Reduced the rate of early PTB significantly	[74]
Fish oil consumption (week 20 until delivery)	20.4% reduction in risk of early delivery	[75]
Fish oil capsule containing 2.7 g *n*-3 PUFA at week 20 or 6.3 g *n*-3 PUFA at week 33 until delivery	44% reduction in the hazard rate of spontaneous delivery	[76]

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acis; PUFA: Polyunsaturated fatty acid; PTB: Pre-term birth.

incidence of low weight infants among Faroese women when compared with Danish women [73,78]. A randomized controlled trial suggested that fish oil supplementation may alter pregnancy duration by inhibiting the production of prostaglandins which play key roles in labour induction at term, thereby increasing the gestation period [26].

Randomized controlled clinical trials on the effects of *n*-3 PUFA on pregnancy duration and birth weight have produced consistent results over years (Table 2). These intervention studies showed that marine oil supplementation increases the risk of prolonged pregnancy and high birth dimensions such as head circumference, birth length and birth weight. Women supplemented with longer chain *n*-3 PUFA from fish oil had a significantly longer gestation period; average of 4 days for most pregnancy and higher in high risk pregnancies [22,25,26,28–30]. Danish women who received fish oil supplements during third trimester of pregnancy (1.13 g DHA/day and 1.57 g EPA/day) had higher birth weight and increased gestation period (about 4 days) compared to the control group [25]. Similar outcomes have also been observed in epidemiological and cohort studies where mothers consumed *n*-3 PUFA before pregnancy establishment and throughout the gestation period [24,32,73]. A randomized, double-blind, controlled study has also revealed that dietary supplementation with DHA-enriched eggs (about 133 mg/egg/day) during the last trimester increases gestation length by approximately 6 days [34]; This was a population-based study (n = 350), in which 83% of subjects completed the study. Also, pregnant women who received fish oil (about 323 mg/day containing approx. 100 mg DHA) or sunflower oil, from 15 weeks gestation until delivery, showed a slightly increased gestation length in infants with higher umbilical cord plasma DHA in the DHA-supplemented group compared to the placebo group; however, this observation did not reach statistical significance [81]. It appears that fish oil containing 2.7 g omega-3 fatty acids (EPA + DHA)/day from 30th week of pregnancy until parturition produced the most significant increase in infant weight at birth by 107 g, while consuming DHA (33 or 133 mg) from eggs at 24th and 28th week of pregnancy until parturition increased gestation length the most by 6.0 ± 2.3 days (P = 0.009) in the higher DHA group. The observed variations in the gestation length, as well as the weight of the infants at birth can clearly be attributed to varying doses of *n*-3 PUFA during intervention, timing of the intervention, as well as the duration of the treatment. However, the findings published to date do not provide evidence towards an appropriate dose of *n*-3 PUFA and/or the time of intervention to cause an increase in gestation time period or birth weight.

Of keen interest in the intervention studies is the observation that *n*-3 PUFA treatment were generally administered after the pregnancy had been established (Table 2). Data from observational studies, where mothers consumed high amount of *n*-3 PUFA prior to conception, revealed a significantly higher infant weight at birth. Corrected average birth weight among Faroese woman was 3610 ± 603 g, and the frequency of having new born infants heavier than 4.5 kg was 3 (three) times higher than Denmark where *n*-3 PUFA consumption was very low [73]. It can therefore be argued that *n-3* PUFA supplementation at the early stage of pregnancy may have a significant influence on gestation length and other pregnancy outcomes; perhaps by regulating pregnancy establishment activities, leading to gestation length prolongation and consequently high infant weight at birth. On the other hand, a few studies have shown that *n*-3 PUFA has neither beneficial nor harmful effects on gestation length, infant weight at birth and other pregnancy outcomes [82,83]. In general, it appears that a diet high in *n*-3 PUFA may influence various activities involved in successful and timely pregnancy establishment, and requires a more robust and mechanistic investigation. The mechanism through which *n*-3 PUFA influences gestation length is perhaps associated with their effect on regulating the balance of pro- and anti-inflammatory cytokines.

Table 2
Effects of omega-3 polyunsaturated fatty acids on gestation length and birth weight.

Intervention	Outcome(s) in the treatment group	Reference(s)
Fish oil containing 2.7 g *n*-3 fatty acids (EPA + DHA)/day (30 weeks gestation until delivery)	Prolonged gestation by about an average of 4 days. Increased birthweight by 107 g	[25,26]
DHA-enriched eggs, 133 mg per day (24–28 weeks gestation until delivery)	Prolonged gestation by 6 days. Birth weight also increased but did not reach statistical significance (P = 0.06)	[34]
Seafood intake during pregnancy	Increase in gestational length of 0.02 week (95%CI: 0.002 to 0.035). No association was observed with birthweight.	[80]
Maternal DHA intake (<16 weeks until delivery)	Higher birth weight and head circumference Gestation length was not determined	[31]
323 mg fish oil containing about 100 mg DHA per day from 15 weeks gestation until delivery	Increased gestation length in infants with higher umbilical cord plasma DHA No significant effect on birth weight, length and head circumference	[81]
Maternal fatty fish consumption (about 3.8 g day)	Reduction in the risk of having babies with low birth weight	[32]
DHA supplementation; up to 600 mg per day (16–20 weeks of gestation)	1.6 days increase in gestational length. No significant effects on birth weight, birth length, or head circumference.	[74]

DHA: Docosahexaenoic acid; EPA: Eicosapantaenoic acid; PTB: Pre-term birth.

4. Role of cytokines during pregnancy

Pregnancy has been clearly divided into three (3) distinct stages (trimesters), and each of these stages is characterized by different proportions of pro- and anti-inflammatory molecules [43]. It has been shown that the first trimester of pregnancy is primarily characterised by increased production of pro-inflammatory biomolecules such as the cytokines as they are required for embryo reception, successful implantation, and co-ordination of fetal-maternal cross-talk [43,44,84]. Likewise, activities involving cervical ripening and uterine contraction regulation at term are mediated by local pro-inflammatory signals in the maternal uterine tissues [43,85]. In contrast, the second stage of pregnancy requires high levels of anti-inflammatory molecules necessary for uterine quiescence and optimum fetal development. Implantation is a critical stage in pregnancy establishment involving complex sequence of signalling cascades required for a harmonized dialogue between a functional blastocyst and the endometrium, and it is largely mediated by pro-inflammatory cytokines [43,86].

Embryonic implantation occurs about 9 days after fertilization in human and this process involves several cytokines such as interleukins (IL), leukemia inhibitory factor (LIF), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and migration inhibitory factor (MIF). TNFα regulates the synthesis and activity of matrix metalloproteinase (MMP-2 and MMP-9) which is associated with the invasive phase of blastocysts implantation [87,88]. IFNγ is involved in the initiation of endometrial vasculature remodelling, maintenance of implantation sites, and the decidua (maternal component of the placenta) [89]. Prior to embryo implantation, activities involving endometrial function and embryo reception regulation has been shown to be mediated by cytokines such as TNF-α [87,88], IL-1 [43,44,90,91], IL-6 [43,44,92], IL-15 [90,93,94], IL-18 [94,95], LIF [44,96,97], IFN-γ and MIF [97–100] (Table 3).

LIF was the first cytokine shown to be very critical for implantation in mice as it was found to be very abundant at the implantation site [101]. Hence, blastocyst implantation was suggested to be strictly dependent on maternal expression of LIF. However, several other studies argued that MIF plays a major role as a pro-inflammatory cytokine mediator during pregnancy establishment as it can either directly or indirectly regulate the synthesis of several other pro-inflammatory cytokines including TNF-α, IL-10 and IL-12 [102]. MIF has been found to be highly expressed in the oviduct, ovaries and uterus of mouse at early pregnancy [100]. Protein and mRNA expression of MIF was reported to be higher at early stages of gestation in the placenta, amniotic fluid and maternal serum [103,104]. The concentration of MIF declines as the pregnancy progresses, with most significant changes in the late first trimester [105]. This evidence further supports the roles of MIF in important cellular functions leading to endometrial receptivity, successful embryonic implantation and timely placental formation. As expected, mice treated with MIF were shown to have enhanced embryo implantation compared to the untreated mice [98]. Likewise, intraperitoneal injection of IL-1 receptor antagonist into pregnant mice few days before implantation was observed to interfere with embryonic interaction with the endometrial tissue, thereby causing implantation failure [106]. IL-1 has also been shown to be involved in the stimulation of several other cytokines such as TNF-α, LIF, IL-6, and IL-8 [90]. IL-1 has been found in human trophoblast, fallopian tube, and endometrium [107,108], and the presence of its bioactive ligands (IL-1α and IL-1β) in human embryo culture medium has been shown to correlate with the implantation rates of patients undergoing *in vitro* fertilization-embryo transfer [109]. Other molecular mediators involved in the embryo implantation and pregnancy establishment are growth factors, adhesion molecules, prostaglandins, hormones and lipids [43–45,86].

As pregnancy progresses towards the second trimester, the profile of cytokines shifts towards less inflammatory/anti-inflammatory cytokines [43]. Studies have shown that the expression of anti-inflammatory cytokines such as IL-4 and IL-10 plays an important role in the resolution of inflammation during pregnancy, especially at the second trimester [43,110]. Optimally functioning inflammation resolution system during pregnancy is essentially required to regulate series of complex processes that could degenerate into persistent inflammation and hence, complications during pregnancy. PTB has been associated with the induction of prostaglandin synthesis before term via excessive production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β which triggers pre-term labour [111]. Also, infusion of IL-6 and TNF-α has been shown to produce symptoms of pre-eclampsia in rat [112,113]. However, other studies have associated IL-10 deficiency with the onset of hypoxia-induced pre-eclampsia features such as proteinuria, hypertension and renal pathology in mice [114]. As such, administration of recombinant IL-10 was observed to reverse features of pre-eclampsia in IL-10 knock out pregnant mice [114]. IL-10 has been shown to peak on gestation day 12 in mice, which represent second trimester [115]. Inhibition of IL-10 during pregnancy has been shown to result in neonatal growth retardation [116], while administration of exogenous IL-10 has been shown to

Table 3
Roles of pro-inflammatory cytokines in pregnancy establishment.

Cytokines	Production site	Roles in implantation	Reference(s)
TNFα	Peri-implantation endometrium	Regulates the synthesis and activity of matrix metalloproteinase (MMP-2 and MMP-9)	[87 – Human endometrial cells, *in vitro*]
IFNγ	Uterus NK cells and trophoblasts	Initiates endometrial vasculature remodelling, angiogenesis at implantation sites, maintenance of the decidua	[89 – Mice]
LIF	Stroma cells and endometrial epithelium	Regulate the adhesion and invasion of uterus by embryo	[96 – Human endometrial cells, *in vitro*]
IL-1	Endometrium and blastocyst	Stimulate the secretion of other cytokines (IL-6, LIF, and TNFα), regulates uterine receptivity, play important role in embryo implantation and decidualization	[43,44,90,91 – Human endometrial cells, *in vitro*]
IL-6	Embryo and uterus (stroma cells and endometrial epithelium)	Regulates endometrial function and synthesis of MMP-2 and MMP-6, involved in viability of implantation sites and decidua formation	[43,44,92 – Mice]
IL-15	Decidua and endometrium	Involved in implantation and decidualization, regulates the growth of NK cells in the uterus	[90,93,94 – Mice]
IL-18	Stroma cells and endometrial epithelium	Regulate the growth of NK cells in the uterus, and stimulate the production of IFNγ and IL-1β	[94,95 – Human endometrial cells]
MIF	Endometrial tissues and decidua	Induces the expression of other cytokines (TNFα, IFNγ, IL-1 and IL-6), regulates the synthesis and activity of MMPs, and reduces the cytolytic activity of purified uNK cells in a dose-dependent manner	[98,100 – Mice] [99 – Human decidual tissue]

IFNγ: Interferon gamma; IL: Interleukine; MIF: Macrophage Migration Inhibitory Factor; MMP: Matrix metalloproteinase; TNFα: Tumor necrosis factor alpha; uNK cells: Uterine natural killer cells.

prevent fetal resorption in pregnant CBA/J × DBA/2 mice [117]. Although IL-4 and IL-10 has been suggested not to be involved in fetal or neonatal survival in mice [118], the roles of anti-inflammatory cytokines in inflammation resolution during pregnancy cannot be overemphasized.

At near term, cytokine profile has been characterized to align towards increased production of pro-inflammatory cytokines [43]. Pro-inflammatory cytokines have been suggested to play vital roles in the coordination of several processes leading to labour; these include cervical ripening, and uterine contraction [43]. The exact mechanism through which labour is regulated by pro-inflammatory cytokines is vaguely understood. An increased production of major pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 in the uterus has been implicated in the stimulation of phospholipid metabolism pathways, release of arachidonic acid, as well as serving as precursors for the production of prostaglandins which play key role in cervical dilation and myometrial contraction during labour [119]. Furthermore, IL-1β and IL-8 have been found at increased levels in the myometrium and choriodecidua at last trimester of pregnancy [120]. Clearly, cytokine balance during pregnancy is very important for successful pregnancy establishment, and maintenance. As such, dysregulation in pro- and anti-inflammatory cytokines could result in detrimental pregnancy outcomes. Plethora of evidence have shown that longer chain *n*-3 PUFA could alter the production, as well as the activities of pro- and anti-inflammatory cytokines [121], which may have a profound effect on pregnancy establishment and outcomes.

5. Omega-3 PUFA and cytokine regulation during pregnancy

Metabolism of *n-3* PUFA gives rise to anti-inflammatory molecules [122]. Interestingly, the same group of enzymes are required for the metabolism of *n*-3 and *n*-6 PUFA (Fig. 1), and as such, the anti-inflammatory properties of *n*-3 PUFA is partly mediated by suppressing or inhibiting the downstream production of pro-inflammatory molecules from *n*-6 PUFA metabolism [123]. An established mechanism for the anti-inflammatory effect of *n-3* PUFA is by inhibiting the production of nuclear factor-kappaB (NF-κB), which is a transcription factor for a number of pro-inflammatory cytokines such as TNF-α, and IL [122]. Likewise, it has been shown that *n-3* PUFA could directly reduce the gene expression of IL-6, and IL-1β [124]. Studies have shown that supplementing maternal diet with *n*-3 PUFA (2 g EPA + DHA per day) results in significant reduction in the production of IL-1, IL-6, and TNF-α by mononuclear cells [125]. Also, fish oil feeding reduces *ex vivo* production of IL-1β, IL-6, and TNF-α by macrophages in rodents [126]. Similar results were also obtained in cell culture studies as EPA and DHA was observed to supress the production of pro-inflammatory cytokines by macrophages and endothelial cells [127,128]. However, DHA has been shown to be more effective than EPA in reducing plasma TNF-α concentrations, 35% and 20% for DHA and EPA respectively [129].

As explained earlier, the complexity of pregnancy establishment, maintenance and labour is exemplified by a number of cytokines and other factors playing specific roles in this process as the pregnancy progresses [43,84]. As such, *n*-3 PUFA as a potent precursor for inflammation resolving biomolecules may be influencing gestation length by disturbing the normal expression and activities of pro-inflammatory cytokines that are required at different stages of pregnancy as depicted in Fig. 3. However, there are no studies to date to show the effect of *n*-3 PUFA at each stage of pregnancy on the outcome of pregnancy establishment and outcome. Consuming high amounts of *n*-3 PUFA prior to embryo implantation may downregulate the expression, and the activities of key pro-inflammatory cytokines [130], such as IL-1, IL-6, MIF, LIF, and TNF-α that play key regulatory roles in the receptivity of the endometrium, as well as the apposition, adhesion and invasion of the uterine wall by the blastocyst. This may result in the elongation of time required for pregnancy establishment. Thus, understanding the effect of *n*-3 PUFA at this stage of pregnancy may provide additional plausible insight into the mechanism/s through which *n*-3 PUFA elongates gestation length.

Available data only suggest that *n*-3 PUFA prolongs pregnancy duration by suppressing the synthesis of prostaglandins required for the induction of labour. The effects of prolonged gestation on both maternal and fetal health has been well documented [131–133]. From a paediatric perspective, increased gestational period and birth weight could be viewed as a positive outcome. However, prolonged gestation is a predisposing factor for a number of obstetrical complications [132]. Maternal peri-partum complications has been shown to increase as pregnancy progresses beyond 40 weeks of gestation [133]. The risk of perinatal death also increases from 39th week of pregnancy with a more dramatic increase after week 40 of pregnancy [131]. Major reason for increased risk of perinatal death in post-term pregnancy has been attributed to reduced placental function [41]. Thus, prolonged pregnancy is a major challenge in obstetrics as it is difficult to know when to induce labour [134]. It is also challenging to distinguish between those that will respond to labour induction and those that require caesarean section [134]. More so, high infant weight at birth as a consequence of prolonged gestation has been linked to childhood obesity, as well as several metabolic and cardiovascular disorders in the offspring. Higher birth weight was associated with higher risk of child obesity (a risk of cardivascular diseases) in Australia in boys and girls before and after adjusting for several socio-demographic factors [37]. Likewise, it has been shown that metabolic syndrome was more prevalent in children born with larger birth weight, thereby suggesting that hypertension and hypertriglyceridemia as better components for diagonising metabolic syndrome in obese children [135]. As such, it is highly pertinent to determine the dose of *n*-3 PUFA at different stages of pregnancy to prevent detrimental pregnancy outcomes.

6. Conclusions

Supplementation of maternal diet with *n-3* PUFA has been shown to have a positive effect on fetal brain development and reduction in the recurrence of PTB, especially in women with history of pre-term or low baseline *n-3* PUFA intake (high risk population). However, supplementation of maternal diet with high *n*-3 PUFA has been linked to prolonged gestation length and consequently, high infant birth weight. The variation in gestation length and birth weight of infants in mothers supplemented with *n*-3 PUFA during pregnancy can be attributed to dosage of the *n*-3 enriched diet as well as the timing and duration of intervention during pregnancy. Plethora of adverse pregnancy outcomes relating to maternal and perinatal health have been associated with prolonged gestation. Increased birth weights also have prognostic potential for development of diseases at adult life. Most *n*-3 PUFA intervention studies started at the second trimester of pregnancy, thus the available data can only suggest that *n*-3 PUFA prolong pregnancy by influencing the production of prostaglandins involved in labour induction. There is paucity of evidence on the effects of different dosage of *n*-3 and *n*-6 PUFA on the profiles of local cytokines in the uterus at embryo reception, and pregnancy establishment. Although a recent prospective, observational study of human pregnancy by Meyer et al. [61] highlights the effect of metabolic response in women undergoing frozen embryo transfer at early pregnancy, more evidence is required to establish the precise function of *n*-3 and *n*-6 PUFA at different stages of

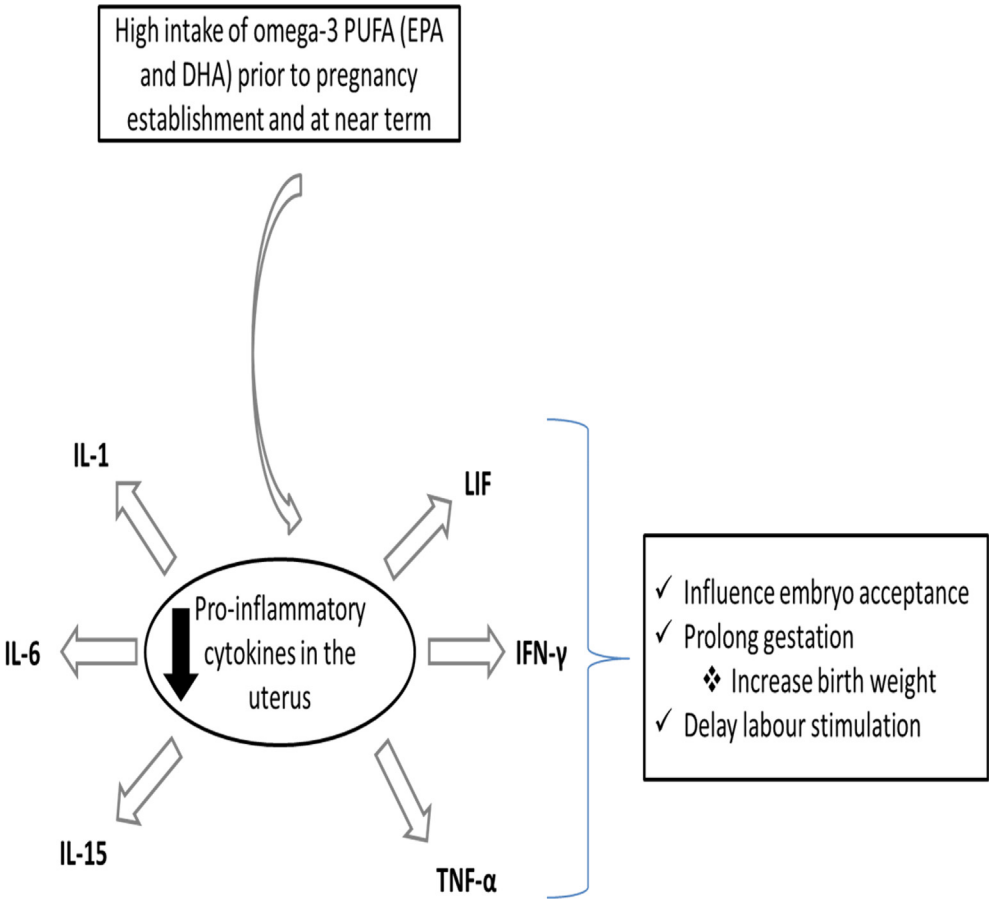

Fig. 3. Possible effects of omega-3 PUFA on pregnancy establishment and outcomes. DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; IFN-γ: Interferon gamma; IL: Interleukin; LIF: Leukaemia inhibition factor; PUFA: Polyunsaturated fatty acids; TNF-α: Tumor necrosis factor alpha.

pregnancy with respect to pregnancy duration and birth dimensions. This review concludes that investigating the effect of feeding different amount of *n*-3 and *n*-6 PUFA diet in animal model on the local profiles (gene and protein expression) of inflammatory cytokines in the uterine *milieu* at different stages of pregnancy may provide a better insight unto the mechanism/s through which *n*-3 PUFA modifies gestation length and consequently, the weight of infants at birth.

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