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The Role of Specialized Pro-resolving Mediators in Maternal-Fetal Health

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SUMMARY

Infants developing in a pro-inflammatory intrauterine environment have a significant risk for severe complications after birth. It has been shown that omega-3 fatty acids reduce inflammation, and also reduce early preterm births and decrease risk of infant admission to the neonatal intensive care unit. However, the mechanism for omega-3 fatty acids exerting these effects was previously unknown. Recent evidence has shown that downstream products of polyunsaturated fatty acids called specialized pro-resolving mediators may mediate inflammatory physiology, thus playing an important role in maternal-fetal health. In this review, current knowledge relating to specialized pro-resolving mediators in pregnancy, delivery, and perinatal disease states will be summarized.

Keywords

pro-resolving lipid mediator; pregnancy; fetal health; omega-3 fatty acid; docosahexaenoic acid; resolvins

1. INTRODUCTION

The inflammatory response is an intricate system that is meant to defend the body from infection or other noxious insults. However, physiology mechanisms exist to limit the extent and duration of the inflammatory response because, without these controls, normal processes

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would be devastated by continued inflammatory cell infiltrates, edema, and tissue damage [1]. This is especially important in pregnancy, when persistent inflammation can result in poor maternal-child outcomes. Studies have shown that preterm infants developing in a pro-inflammatory intrauterine environment are at a significantly higher risk for severe complications of prematurity, such as chronic lung disease, retinopathy of prematurity, intra-ventricular hemorrhage, periventricular leukomalacia, and necrotizing enterocolitis, than infants born equally preterm without these risk factors [2–4]. Each of these complications lead to increased morbidity and mortality, as well as high-cost health care utilization. As such, additional understanding of mechanisms that can modulate this inflammatory environment may lead to clinical interventions that result in improved outcomes.

While not directly covered within the topics of this review, previous reviews have analyzed the importance of LC-PUFA and omega-3 LC-PUFA in maternal-fetal health. In example, in a systematic examination of human studies on the roles of long-chain PUFA (LC-PUFA) in pregnancy, lactation, and infancy by Koletzko et al suggests an important role for LC-PUFA sufficiency in maternal-fetal health [5]. Koletzko et al. also provided summarized recommended average daily intakes of docosahexaenoic acid (DHA) and arachidonic acid (AA) for pregnant and breastfeeding women:

- Pregnant women: 300 mg/day DHA throughout pregnancy (which is 200 mg greater than what is suggested for healthy adults)
- Breastfeeding women: 200 mg/day DHA
- Term infants: 100 mg/day DHA and 140 mg/day AA for the first year of life
- VLBW infants: 55–60 mg/kg/day DHA and 35–45 mg/kg/day AA [5].

In a phase III randomized control trial, women receiving 600–800 mg of omega-3 LC-PUFA during pregnancy delivered infants with larger birth weights, lengths, and head circumferences [6]. In addition, there was a lower risk of early preterm delivery before 34 completed weeks of gestation [6]. Beneficial effects have also been shown for supplementation during pregnancy resulting in decreased immune responses involved in allergic inflammation. For example, decreased incidence of allergic conditions such as asthma [7], atopic eczema [8,9], and food allergy [10] have been associated with increased omega-3 intake/supplementation. Supplementation also enhanced anti-infectious protection and decreased infectious disease risk, as evidenced by increased IgG titers following common childhood vaccines [10] and decreased occurrence of the common cold plus shorter duration of respiratory illnesses in infants younger than 6 months of age [11].

In the face of increasing evidence of the profound positive effects of LC-PUFA on maternal-fetal health and data to indicate their protective role in inflammation, the role LC-PUFA play in modulating inflammation physiology has become a focus of numerous investigations. Recent studies have investigated the role of signaling molecules called specialized pro-resolving lipid mediators (SPM) in this context. Preclinical investigations have shown that SPM are a group of endogenously synthesized chemical mediators that function to limit the extent of inflammation, to promote the termination of inflammation, and to stimulate the immune system to protect against infection [1,12–17]. SPM are derived from omega-3 and

omega-6 LC-PUFA through interaction with lipoxygenases, cyclooxygenases, and cytochrome-P-450 dependent oxygenases. The omega-3 fatty acid DHA produces the Resolvin D [RvD]-, Maresin [MaR]-, and Protectin [PD]-series SPM, the omega-3 fatty acid eicosapentaenoic acid (EPA) produces the Resolvin E [RvE]-series SPM, and the omega-6 fatty acid AA produces the lipoxin [LX]-series SPM [16] (FIGURE 1). The mechanism for the production of these mediators, and their role in resolution of inflammation has been detailed in previous review articles [1,15,16,18,19]. In this review, the role that SPM have in maternal-fetal health will be summarized.

2. METHODS

Articles were selected for inclusion in this review through searches in PubMed and Google Scholar. Strategies for the literature search included various iterations of keywords and phrases such as “specialized pro-resolving lipid mediators,” “resolvins,” “protectins,” “maresins,” “lipidome,” “pregnancy,” “infants,” “placenta,” and “maternal-fetal health”. Peer-reviewed publications including clinical and pre-clinical randomized controlled trials, cohort studies, cross-sectional studies, and review articles were included. No limitations were set regarding time period of publication for inclusion in the review. All material was written in English.

3. LITERATURE REVIEW

3.1 CONCENTRATION OF SPM AND PRECURSORS IN HEALTHY ADULTS AND IN PREGNANCY

Methodology for the determination of SPM levels and multiple pathway precursors has been elucidated by several studies using different techniques, and using different fractions of whole blood [20]. For the purpose of this review, the technique used was liquid chromatography-tandem mass spectrometry (LC-MS/MS) unless stated otherwise. As necessary, it will also be stated if plasma or serum was used. The concentration for various SPM and pathway precursors is typically reported in the picogram per milliliter range, and levels in healthy adults range from not detectable to the low thousands (TABLE 1).

A study by Mas et al. [21] quantified resolvins, protectins, and pathway precursors in human serum and plasma from healthy non-pregnant adults who were supplemented with omega-3 fatty acids, using several common anticoagulants. It was found that RvD2, 17-HDHA, and 18-HEPE were detectable in physiologically relevant quantities in both serum and plasma, while PD1 was not detectable. It was also found that SPM precursors were present in 5–10 fold greater concentrations than their downstream products. The concentration of resolvins did not differ between serum and plasma, while the plasma concentrations of pathway precursors was higher than what was measured in serum [21]. Similarly, Colas et al. [22] compared metabolomes of lipid mediators in commercial human serum, standard reference plasma, and lymphoid tissue. Serum RvD1 and RvD2 concentrations were comparable to those found in the previous study, but plasma RvD1 concentrations were much lower and plasma RvD2 was undetectable. This study also went on to quantify EPA- and AA-derived lipid mediator metabolomes. The application of LC-MS/MS to lymphoid tissue also demonstrated the ability to measure these lipid mediators in target tissues [22]. The

discrepancies in the levels of SPM measured in these two different studies highlight the potential variability of SPM levels in healthy human blood, warranting larger scale investigations to determine typical/reference values of these mediators.

As compared to the studies using LC-MS/MS described above, Croasdell et al. [23] applied an RvD1 enzyme immunoassay to the serum of healthy controls as part of a larger study investigating resolvins in lung inflammation/disease caused by cigarette smoke. Concentrations using this technique were higher than those measured using LC-MS/MS, but no existing studies provide a direct comparison between the two methods. A summary of the findings of several key SPM identified in these three studies is provided in Table 1. Together, these studies provide baseline information regarding potentially normative production of SPM for healthy adults to use as a comparison in future investigations assessing alterations in the production of SPM across pregnancy.

In a study by Mozurkewich et al. [24], pregnant women were supplemented with EPA-rich or DHA-rich fish oil, or a soy oil placebo. Maternal blood was collected at 12–20 weeks gestation, and then again at 34–36 weeks gestation to determine whether fish oil supplementation augments SPM or SPM precursors levels, as well as to determine if differences exist between maternal blood in early and late pregnancy. In initial analyses, D-series resolvins, E-series resolvins, protectins, and maresins were not consistently detected. However, pathway precursors 4-HDHA, 14-HDHA, and 17-HDHA were detected. In addition, maternal serum 17-HDHA, 14-HDHA, and 4-HDHA levels were found to positively correlate with DHA levels. Relating to the time course across pregnancy, 17-HDHA levels were found to increase between early and late pregnancy, while 4-HDHA and 14-HDHA levels did not significantly differ [24]. Further studies are needed to fill gaps in the knowledge of SPM production levels across pregnancy, and during high-risk pregnancy and delivery conditions.

3.2 PLACENTAL PRODUCTION OF SPM AND RECEPTORS

The increase in SPM precursors in umbilical cord blood compared to maternal blood found by Mozurkewich et al. [24] raises questions about the possible production or transfer of SPM and SPM precursors in the placenta, and/or the de novo synthesis of SPM by the fetus. A study by Keelan et al. [25] assessed whether omega-3 supplementation during pregnancy modifies the fatty acid composition in the placenta and inflammatory gene expression, including transcripts for TNF- α , IL-1 β , and IL-6. In placental tissue, it was found that omega-3 and omega-6 LC-PUFA, SPM precursors, and SPM are present in measurable quantities. Supplementation did not alter total omega-3 or omega-6 levels compared to the control group, but did significantly increase DHA levels as well as the tissue omega-3:omega 6-ratio. It was also found that SPM precursors 17-HDHA and 18-HEPE increased with supplementation, while SPM PD1, RvD1, 17R-RvD1, and RvD2 trended upward but did not reach significance. Most inflammatory gene transcripts assayed were not found to be affected by omega-3 PUFA supplementation, although TNF- α mRNA expression was increased in the omega-3 PUFA supplementation group [25]. These findings are potentially counterintuitive to expectation given that SPM regulate inflammation resolution, warranting further investigation.

A study by Jones et al. [26] utilized a rat model to assess the production of SPM in the placenta during pregnancy. In these investigations, rats were fed a standard diet or a diet high in omega-3 PUFA during pregnancy, and the placenta levels of resolvins and protectins and their biosynthetic enzymes were assessed. It was found that maternal supplementation enhanced placental expression of lipoxygenase enzymes (Alox15b and Alox5 transcripts were elevated) along with pathway precursors 18-HEPE and 17-HDHA that were increased in both early and late pregnancy. Placental RvD2 levels increased in mid- and late-pregnancy, whereas PD1, RvD1, and 17R-RvD1 were only increased in late pregnancy [26]. This study corroborates with the findings in human placental tissue described above [25] and supports the hypothesis that maternal omega-3 PUFA supplementation increases placental levels of SPM and SPM precursors, which could result in enhanced ability to modulate or resolve inflammation. Furthermore, while these studies highlight the placenta as a site for production or utilization of SPM, the mechanism for utilization, production, and/or transport of SPM by the placenta is still largely unexplored. It has been previously demonstrated that human placentas contain mRNA from chemR23, a known receptor for RvE1 [27]. This suggests the placenta may be a signaling target for SPM, but the expression and localization of other SPM receptors in the placenta has yet to be demonstrated. There remains a gap of knowledge regarding the functional role of SPM in the placenta.

3.3 INFANT LEVELS OF SPM

Studies assessing infant levels of SPM at the time of delivery and during the neonatal period are limited in the literature. Several investigations have looked at SPM and SPM precursors in cord blood at the time of delivery [24,25], and one study examined lipid mediators in infants supplemented with parenteral lipid emulsions [28]. In the aforementioned study by Mozukewich et al. [24] (see Section 3.2), umbilical cord blood was collected at delivery to examine the relationship between maternal SPM levels and fetal SPM levels. In this study, 14-HDHA levels and 17-HDHA levels were significantly increased in umbilical cord blood compared to maternal blood taken at 12 – 20 weeks or 34 – 36 weeks gestation, while 4-HDHA levels exhibited no differences at these time points [24]. It is noteworthy that no studies to date have assessed SPM levels in mothers or neonates with at-risk pregnancies or deliveries. Further research is needed to explore the relationship between maternal and fetal SPM production, and the regulation of SPM during delivery and times of perinatal stress or inflammation.

3.4 BREAST MILK LEVELS OF SPM

Healthy, mature human milk contains SPM including resolvins, protectins, maresins, and lipoxins at bioactive levels [29]. The breast-fed newborn receives most of its energy from fat in human milk, and the composition of fatty acids in breast milk changes over the lactation period to fit the newborn's needs [30]. In addition, evidence has shown that maternal diet may influence FA composition, and FA composition is different between term and preterm pregnancies [30,31]. The SPM composition of breast milk was defined in a study by Weiss et al. [30], which examined human breast milk over postpartum days 1–30. It was found that 95% of total fatty acids were composed of palmitic acid and stearic acid (saturated FA), oleic acid (monounsaturated FA), and linoleic acid (omega-6 PUFA). Lipoxins and D- and E- series resolvins were also identified in higher concentrations in breast milk than what has

been previously reported in serum of healthy adults, and these concentrations are in the range known to physiologically inhibit inflammatory processes [30]. In addition, the concentrations of FA and SPM changed temporally over the first month following birth. Alpha-linolenic acid (alphaC18:3; a precursor to EPA and DHA) increased over the first 30 days of lactation, and DHA and its metabolite 17-HDHA (a precursor to D-series resolvins) decreased over the same period, while the concentration of total measured resolvins remained stable. The metabolite 17-HDHA was consistently found in higher concentrations than its product RvD1, which authors noted supports the hypothesis that SPM are produced transiently in response to active inflammation [30]. Taken together, these studies identify breast milk as a concentrated source for SPM. These findings suggests maternal SPM provided to an infant via breastmilk could provide the infant protection against infection or assist in immune education. In addition, these findings may offer clues toward the mechanisms of breast milk's superiority to formula during development of the immune system and in incidence of inflammatory disorders. Further studies are warranted to test these hypotheses.

3.5 SPM IN COMPLICATED PREGNANCIES AND INFANT DISEASE STATES

Recent investigations suggest that SPM are differentially regulated in several disease states associated with pregnancy and neonates, and may be key factors in the mechanisms of benefits from LC-PUFA intake (Table 2). Below we have summarized manuscripts identifying differential production or regulatory roles for SPM in various pregnancy or perinatal disease states.

3.5.1 Breast milk SPM levels in complicated pregnancies and infant disease states—As described above, breast milk has been identified as a concentrated source of SPM as compared to other assayed tissues or body fluids. In a study by Arnardottir et al. [29], a lipid mediator isolate from human milk (HLMI), including resolvins, protectins, maresins, and lipoxins, was found to accelerate resolution of peritonitis using *in vivo* and *ex vivo* models. This was demonstrated by a reduction in the maximum neutrophil levels and a reduction in the time necessary to reduce PMN numbers by half. It was also found that macrophages incubated in HLMI had enhanced ability to phagocytosis of bacteria. Interestingly, the milk from inflamed mammary glands (mastitis) had an altered lipid mediator profile, showing increased pro-inflammatory lipid mediators and decreased anti-inflammatory SPM [29]. In addition, the HLMI from mastitis milk did not limit maximum neutrophil numbers in their model of inflammation, as did the HLMI from healthy milk [29].

In addition, a recent study assessed PUFA and SPM levels in human breast milk from 30 women who delivered preterm infants [31]. In this study, authors identified declines in AA and DHA levels over the first month of lactation, while SPM levels remained consistent during this time period. Several SPM, including RvD1 and RvD2, were present at ~4-fold lower concentrations than previous reports in healthy, mature milk, although no side-by-side comparison was performed in this study to rule out differences due to sampling/analysis methods [29–31]. Interestingly, authors also identified significant associations between DHA supplement use and milk DHA and 14-HDHA levels, supporting the use of DHA supplementation for mothers of preterm infants [31]. Together, these studies indicate that

breast milk SPM levels may be dynamically regulated during inflammatory processes. Studies to assess how reduced or altered breast milk SPM levels associated with at-risk deliveries or inflammatory states are warranted.

3.5.2 Preterm Birth—In a study using a mouse model of preterm birth [32], mice with increased tissue levels of omega-3 PUFA had a reduced incidence of LPS-induced preterm birth, reduced uterine gene expression of pro-inflammatory cytokines IL-6 and IL-1 β , and a reduced number of cervical infiltrating macrophages known to be increased in human preterm birth. It was also found that administration of RvE3 to LPS-exposed pregnant mice lowered the incidence of preterm birth, but administration of the SPM precursor 18-HEPE did not [32]. Results from this study suggest increased omega-3 PUFA or SPM production could be protective against preterm birth. However, no studies to date have directly assessed human maternal or fetal SPM levels in preterm births. Although, as described above, breast milk SPM levels following preterm birth have been assessed and found to be potentially reduced compared to breast milk following term births.

3.5.3 Pre-eclampsia—Pre-eclampsia is caused by vascular dysfunction arising from increased inflammation, increased oxidative stress, and endothelial cell dysfunction. Interestingly, LXA₄ has been found to modulate inflammation by regulating the cytokine milieu, inhibiting leukocyte chemotaxis, and limiting generation of reactive oxygen species [33,34]. In a study by Xu et al. [34], it was found that LXA₄, its receptor FPR2/ALX, and the enzymes responsible for synthesizing LXA₄ were decreased in the blood of women with pre-eclampsia. To further define the relationship between LXA₄ and pre-eclampsia, experimental rats were treated with LXA₄. These rats showed an improvement in symptoms of pre-eclampsia, a decrease in LPS-induced pro-inflammatory cytokines, and an increase in anti-inflammatory cytokine IL-10. It was also demonstrated that rats with blocked LXA₄ signaling pathways developed symptoms of pre-eclampsia [34]. Comparatively, Dong et al. [33] demonstrated that LXA₄, TNF- α , and IL-1 β were all significantly increased in women with pre-eclampsia. Although, the ratio of LXA₄ to TNF- α and IL-1 β was significantly decreased, leading to a relative decrease of LXA₄ [33]. Notably, there was no LXA₄ detected in umbilical cord blood of healthy controls or those affected by pre-eclampsia, and this study also found that FPR2/ALX mRNA was increased in placentas affected by pre-eclampsia [33]. Together, these two studies provide seemingly contradictory results regarding the role of lipoxins in modulating pre-eclampsia. Studies assessing lipoxin production over time as well as additional analyses of receptors and enzymatic products may shed light on the dynamic regulation of this pathway in women with pre-eclampsia.

3.5.4 Clinical Chorioamnionitis—Clinical chorioamnionitis is associated with a number of infection-related perinatal complications, and is often characterized by severe maternal and fetal inflammatory responses [35]. A recent study by Maddipati, et al. [36] identified reduced levels of omega-3 FA-derived SPM precursor metabolites in the amniotic fluid in women with clinical chorioamnionitis at term. In this study, no significant changes in prostaglandins or known inflammatory mediators in the amniotic fluid of women with clinical chorioamnionitis compared to women in spontaneous labor were identified [36], suggesting that a reduction in anti-inflammatory/pro-resolution metabolites (as opposed to

an increase in pro-inflammatory mediators) may associate with disease risk. In this study, investigators were unable to detect numerous SPM including RvD1, RvE1, PD1, and LXA₄ in the amniotic fluid [36]. The ability to detect the SPM precursors but not end-product SPM could be attributable to the labile nature of SPM leading to an inability to detect the SPM, or an insufficient production of the SPM physiologically, contributing to the inflammatory state associated with the disease.

3.5.5 Retinopathy of Prematurity—Retinopathy of prematurity is the most common cause of blindness in children, and is the result of oxygen-induced vessel loss followed by pathological neovascularization [37]. The role of omega-3 FA in protection against this retinal damage is well established, and studies have shown that SPM contribute to the mechanism of cyto-protection and point toward potential therapeutic use of SPM in other forms of retinopathy [38]. In a study by Connor et al. [37], a mouse model was used to identify the effect of omega-3 PUFA, omega-6 PUFA, and their downstream lipid mediators on vascular destruction and regrowth in oxygen-induced retinopathy. Mice enriched with omega-3 PUFA were significantly protected from pathologic neovascularization. The SPM PD1 and RvE2 were detected in the retinas of omega-3 supplemented mice, but were not detected in the retinas of mice that received only omega-6 diets. It was also found that a low dose of intraperitoneal RvD1, RvE1, and PD1 to these omega-3 supplemented mice conferred significant protection from vaso-oblivation and neovascularization [37].

Given these preclinical evidences that resolvins and protectins act as potent regulators of angiogenesis, it has been hypothesized that these molecules could be therapeutically useful in the prevention and management of retinopathy of prematurity [39]. Translational studies are warranted to assess the regulation and production of SPM during human cases of retinopathy of prematurity.

3.5.6 Parenteral nutrition-associated liver disease (PNALD)—Lipid emulsions may be co-administered with parenteral nutrition to infants that are unable to tolerate an enteral diet. Commercially available lipid emulsions are either plant-derived or fish-oil based. Plant-derived lipid emulsions are often manufactured from safflower oil or soybean oil (SOLE), and are high in omega-6 PUFA that are precursors for proinflammatory eicosanoids. Fish oil-based lipid emulsions (FOLE), on the other hand, are high in omega-3 PUFA like DHA and EPA that are precursors for anti-inflammatory eicosanoids and SPM [28]. Administration of SOLE is associated with PNALD, which includes a wide range of hepatobiliary pathology such as hepatic steatosis, fibrosis, cirrhosis, and cholestasis, while administration of FOLE is associated with prevention of hepatobiliary dysfunction, and has been shown to speed the reversal of cholestasis in children with short bowel syndrome [40]. In a study by Kalish et al [28], switching infants from SOLE to FOLE resulted in a dramatic increase in blood levels of SPM coincident with reductions in blood levels of pro-inflammatory lipid mediators. Together, these studies suggest a potential mechanism by which omega-3 FA-rich FOLE could contribute a benefit in the management of PNALD, attributable to the increased production of SPM associated with FOLE use. Additional studies are required to further assess these potential benefits.

4. CONCLUSIONS

The role of SPM in modulating inflammation physiology in adults is increasingly recognized. However, additional studies are needed to extend these findings to the unique immune interactions in maternal-fetal biology. Current data suggest SPM precursors are modulated in mothers and infants during pregnancy, and placental and blood SPM levels have been shown to be altered by maternal omega-3 fatty acid intake. Breast milk also contains high levels of SPM, suggestive of a protective effect to the infant. In addition, SPM have been shown to be differentially produced in several high-risk conditions associated with delivery and neonatal health, including pre-eclampsia, pre-term birth, and retinopathy of prematurity. Taken together, these data implicate an important role for SPM in maternal-fetal health. Moving forward, additional studies are warranted to further understand how SPM production impacts health outcomes in the perinatal period.

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HIGHLIGHTS

- This review summarizes recent findings relating to the role of SPM in maternal-fetal health outcomes, including the following findings:
 - Specialized pro-resolving lipid mediators and precursors are modulated in mothers and infants during pregnancy
 - Placental and blood SPM levels can be altered by maternal omega-3 fatty acid intake
 - Breast milk contains high levels of SPM, suggestive of a protective effect to the infant
 - SPM are differentially produced in numerous high-risk conditions associated with delivery and neonatal health

(a) Pathway for the production of representative lipoxins from omega-6 fatty acids **(b) Pathway for the production of representative resolvins, maresins, and protectins from omega-3 fatty acids** **Figure 1**

[11,13,25,33]

(a) Pathway for the production of lipoxins from omega-6 fatty acids

(b) Pathway for the production of resolvins, maresins, and protectins from omega-3 fatty acids

Figure 1 Abbreviations

AA: Arachidonic acid

15-HETE: 15-hydroxyeicosatetraenoic acid

EPA: Eicosapentaenoic acid

DHA: Docosahexaenoic acid

18-HEPE: 18-hydroxyeicosapentaenoic acid

17-H(p)DHA: 17-hydroperoxydocosahexaenoic acid

17-HDHA: 17-hydroperoxydocosahexanoic acid

14-HDHA: 14-hydroperoxydocosahexaenoic acid

4-HDHA: 4-hydroxydocosahexaenoic acid

5-LO: 5-lipoxygenase

12/15-LO: 12/15-lipoxygenases

P450: cytochrome P450

COX2: cyclooxygenase-2

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1 Table 1

Representative blood SPM levels reported in the literature.
Representative SPM levels in healthy adult human blood

Study	Participants	Blood Component	Detection Method	RvD1		RvD2		PD1		RvE1		RvE2	
				Mean (pg/mL)	SE	Mean (pg/mL)	SE	Mean (pg/mL)	SE	Mean (pg/mL)	SE	Mean (pg/mL)	SE
Colas et al., 2014 [22]	NIST human plasma SRM 1950	Plasma (heparin collection)	LC-MS/MS	2.6	0.1	Not detectable	Not detectable	Not detectable	Not detectable	Not detectable	Not detectable	130.6	7.8
	Commercial human serum	Serum	LC-MS/MS	30.9	7.0	42.6	13.9	5.6	3.4	12.5	2.5	2212.6	1587.6
Mas et al., 2012 [21]	Healthy adults after n-3 supplementation	Plasma (heparin collection)	LC-MS/MS	33.0	4.0	29.9	3.8	Not detectable	Not detectable	Not determined	Not determined	Not determined	Not determined
		Serum	LC-MS/MS	24.4	2.5	26.6	4.7	Not detectable	Not detectable	Not determined	Not determined	Not determined	Not determined
Croasdell et al., 2015 [23]	Healthy controls	Serum	EIA	~160	~20	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined	Not determined

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RvD1: resolvin D1
RvD2: resolvin D2
PD1: protectin D1
RvE1: resolvin E1
RvE2: resolvin E2
SE: standard error of the mean
LC-MS/MS: liquid chromatography- tandem mass spectrometry
EIA: enzyme immunoassay

Table 2 2

Publications addressing SPM in complicated pregnancies and infant disease states

Disease State	Authors	Summary of findings	
		Study Type	Outcomes
Preterm birth	Robinson, et al [31]	Prospective cohort of 30 women who delivered preterm infants	Breast milk AA and DHA decreased over the first month of lactation SPM levels remained consistent over first month of lactation, although several mediators were at lower levels than previously published in milk from mothers delivering term infants Milk from mothers taking DHA supplements had significantly higher DHA and 14-HDHA levels than mothers not supplementing with DHA
	Yamashita et al [32]	Preclinical model using fat-1 mice	Increased tissue levels of omega-3 fatty acids were associated with lower incidence of preterm birth induced by LPS Gene expression of IL-6 and IL-1 β were reduced in uteruses of fat-1 mice Cervical infiltrating macrophages were reduced in fat-1 mice Administration of RvE3 to LPS-exposed wild type mice lowered the incidence of preterm birth
Pre-eclampsia	Xu et al. [34]	Preclinical model using Sprague-Dawley rats	Rats treated with an LXA ₄ signaling pathway antagonist had significantly higher systolic blood pressure and urine protein level Rats treated with LXA ₄ showed an improvement in systolic blood pressure and a significant decrease in excretion of urine protein Rats treated with LXA ₄ had down-regulated expressions of IL-6, TNF- α , and IFN- γ and up-regulated expression of IL-10 mRNA when compared to LPS-induced rats who did not received LXA ₄
		Case control study of pregnant women with pre-eclampsia vs. women with normal pregnancies	Serum levels of LXA ₄ were two-fold decreased in women with pre-eclampsia mRNA and protein expressions of 5-LO, 12-LO, and 15-LO were decreased in peripheral blood and placentas of women with pre-eclampsia Placental levels of LXA ₄ were significantly lower in women with pre-eclampsia
	Dong et al. [33]	Case control study of pregnant women with mild and severe pre-eclampsia vs. women with normal pregnancies	Lipoxin A ₄ , TNF α , and IL-1 β were found to be significantly elevated in women with preeclampsia The ratio of LXA ₄ to TNF- α and IL-1 β was significantly decreased in women with pre-eclampsia, indicating a relative deficiency of TNF- α FPR2/ALX mRNA expression was significantly increased in placentas obtained from women with pre-eclampsia No LXA ₄ was detected in umbilical cord blood
Clinical Chorioamnionitis	Maddipati, et al. [36]	Retrospective cross-sectional study	Amniotic fluid samples from women with clinical chorioamnionitis at term contained reduced levels of SPM precursors compared to samples from women undergoing spontaneous labor.
Retinopathy of Prematurity	Connor et al. [37]	Preclinical model using several different knockout mice	Mice enriched with omega-3 PUFA through dietary or genetic means were protected from pathologic neovascularization
Parenteral nutrition-associated liver disease	Kalish et al. [28]	Preclinical model using mice	Administration of SOLE was associated with macro- and microvesicular hepatic steatosis, whereas administration of FOLE reduced the degree of steatosis

Disease State	Authors	Summary of findings	
		Study Type	Outcomes
			Administration of FOLE and SOLE results in unique profiles of lipid mediators that are associated with proresolving and inflammatory properties, respectively
		Observational study of infants following standard clinical care	Switching infants from SOLE to FOLE resulted in a dramatic increase in SPM and decrease in pro-inflammatory mediators

² LPS: lipopolysaccharide

LXA4: Lipoxin A4

RvE3: Resolvin E3

SOLE: soybean oil-based lipid emulsion

FOLE: fish oil-based lipid emulsion

* capable of converting omega-6 to omega-3 fatty acids

^F receptor for Lipoxin A4