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SPECIALIZED PRO-RESOLVING LIPID MEDIATORS AND ANTI-INFLAMMATORY PROPERTIES: BENEFITS IN PREGNANCY

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Juntos, conseguimos.

“O que dá o verdadeiro sentido ao encontro é a busca,

e é preciso andar muito para se alcançar o que está perto.”

José Saramago, Todos os nomes

INDEX

ACRONIMS

BMI - body mass index

CCT - clinical chorioamnionitis at term

COX - cyclooxygenases

CYP-450 - cytochrome P-450 dependent oxygenases

DHA - docosahexaenoic acid

EPA - eicosapentaenoic acid

GPCRs - G protein-coupled receptors

LOX - lipoxygenases

Lxs - lipoxins

MaRs - maresins

n-3 PUFA - omega-3 fatty acid

n-6 PUFA - omega- 6 fatty acid

NF-kB - nuclear factor kappa-light-chain-enhancer of activated B cells

PDs - proctetins

PE - preeclampsia

PTL - preterm labor

PUFA - long-chain polyunsaturated fatty acids

RvDs - D-series resolvins

RvEs - E-series resolvins

Rvs - resolvins

SPMs - *specialized pro-resolving lipid mediators*

ABSTRACT

Inflammation plays a critical role in pregnancy. A successful obstetric outcome is inextricably linked to an adequate maternal inflammatory response at the appropriate time, and this dysregulated response can lead to adverse obstetric outcomes. Modern women have undergone numerous changes that could threaten this balance. The profile of the contemporary pregnant woman is conducive to a pro-inflammatory state. It is therefore important to monitor and promote an appropriate maternal inflammatory response during the reproductive period and pregnancy.

Specialized pro-resolving lipid mediators or SPMs are a group of endogenously synthesised chemical mediators that limit the extent of inflammation, promote its resolution, and stimulate the immune system to protect against infection.

Supplementation of pregnant women with SPMs precursor shows a positive effect on fetal development and pregnancy management, as well as benefits in childhood. Studies of SPMs behaviour in pregnant women have also shown an association between specific profile mediators and poor obstetric outcomes. This association suggests the potential applicability of SPMs as biomarkers of adverse neonatal outcomes, allowing early detection and intervention in specific clinical contexts.

Despite the potential impact on obstetrics, there are still many inherent limitations. Due to its recent discovery, most results are based on animal models. Furthermore, only two classes of SPMs have established relationships with pregnancy and most results are referent to supplementation with mediator precursors, such as omega-3 fatty acids. Therefore, further studies are needed to clarify the true impact of SPMs during pregnancy.

This review describes the benefits of the anti-inflammatory properties of SPMs in pregnancy. Our aim is to review how SPMs can control the maternal inflammatory response to promote healthy pregnancies and successful pregnancy outcomes. We analysed articles published in the last ten years, attempting to integrate all the information described to date.

KEYWORDS

Anti-inflammatory**;** inflammation; pregnancy; specialized pro-resolving lipid mediator.

1. INTRODUCTION

Inflammation is a fundamental component of the innate immune system that plays a critical role in protection and survival against injury and/or infection; however, it is not always harmless (1). If the inflammatory response is inappropriate and/or the event is not resolved and persists over time, it can become pathological and have devastating consequences (1). The ideal inflammatory response involves two phases: activation of the innate immune system against the pathogen or tissue damage – the initiation phase; and the development of mechanisms to control inflammation and promote its resolution – the resolution phase (2).

The resolution phase maintains homeostasis (1). It is a biosynthetically active process coordinated by endogenous chemical mediators responsible for inhibiting pro-inflammatory signalling and increasing the production of anti-inflammatory cytokines (2). Researchers identified inflammatory lipid compounds and molecules with anti-inflammatory properties at inflammation sites (3). Among these mediators we highlight SPMs: a superfamily of mediators produced from endogenous or dietary long-chain polyunsaturated fatty acids (PUFA), present in biological fluids, cells, and tissues, and recognised for their anti-inflammatory and immunostimulatory properties (4).

Pregnancy is a challenging time for women, as their bodies undergo physiological and psychological changes. These adaptations are essential for fetal and mother well-being (5). Inflammation plays a critical role in pregnancy (6). A successful obstetric outcome is inextricably linked to an appropriate maternal inflammatory response at an exact time (7). However, if there is deficit or excessive activation of inflammatory response, or if it persists over time, it can be catastrophic. Inflammatory dysregulation is associated with poor obstetric outcomes and infertility (7). Control of maternal inflammatory response is therefore crucial.

The utility and benefits of SPMs in pregnancy will be the subject of our study. Throughout the article, we aim to identify the anti-inflammatory properties of SPMs that can control the appropriate maternal inflammatory response to promote healthy pregnancies and successful obstetric outcomes.

2. METHODS

A narrative review concerning the effects of anti-inflammatory properties of SPMs in pregnancy was performed by conducting a thorough search in PubMed and Embase databases. Strategies for literature search included various interactions of keywords and phrases such as “specialized pro-resolving lipid mediators”, “lipoxins”, “resolvins”, “protectins”, “maresins”, “inflammation”, “pregnancy” and “maternal-fetal health”. The last search was conducted on 27th of December 2023. Peer-reviewed publications including randomized controlled trials, cohort studies, cross-sectional studies, and review articles were included. Case series and case reports were excluded. Both animal and human studies were included. The temporal inclusion criteria were articles from the last ten years with publication dates between Jan 2013 and Dec 2023. All material was written in English. To look for any missing articles, all the citations included were cross-referenced, as well as the references of review articles and editorials.

The work carried out did not involve the use of human data and did not require any type of clinical laboratory evaluation and therefore did not require approval from the Ethics Committee.

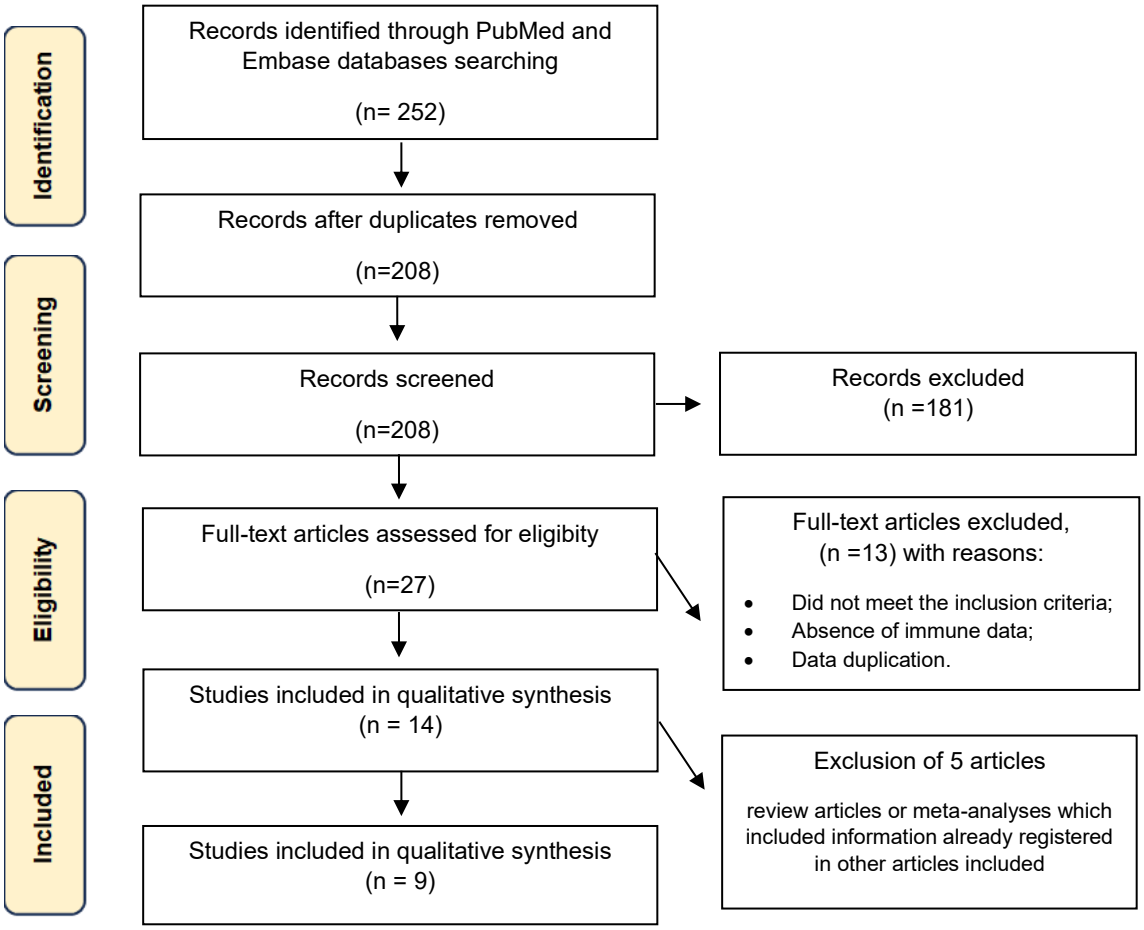

Figure 1. Prisma Flow-chart—data collection and study protocol

3. SPECIALIZED PRO-RESOLVING LIPID MEDIATORS

Specialized pro-resolving lipid mediators or SPMs are a family of small lipid molecules described for the first time in 1984 by pioneering studies in Dr Serhan's laboratory (4). Lipoxins (Lxs) were the first class of SPMs to be identified. Four main classes have been extensively studied: Lxs (LXA_4 and LXB_4), resolvins (RvD_1- RvD_6 and RvE_1- RvE_2), protectins (PD_1 and NPD_1) and maresins (MaR_1 and MaR_2) (8). However, the 'SPMs family' is not complete. Recent studies have shown that precursors of these classes can form conjugates, for example, with peptides derived from glutathione, giving rise to molecules with biological activity in tissue damage repair (9).

Endogenous or dietary PUFA are the substrate for the synthesis of SPMs through enzymatic and non-enzymatic reactions (10). Most SPMs are generated from dietary omega-3 fatty acids (n-3 PUFA) (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA)), while Lxs are generated from dietary omega-6 fatty acids (n-6 PUFA) (arachidonic acid) (10,11). These precursors undergo stereoselective conversion, whereby non-esterified fatty acids are enzymatically modified by cyclooxygenases (COX), lipoxygenases (LOX), cytochrome P-450 dependent oxygenases (CYP-450) and other enzymes to create bioactive lipid metabolites (10). Figure 2 shows the branching diagram of SPMs production.

In healthy adults, SPMs concentrations and other pathway precursors are typically reported in picogram per millilitre, with levels ranging from 20 to 2000 pg/mL (11). SPMs exist in tissues, cells, and biological fluids, such as plasma, breast milk, urine, and cerebrospinal fluid (12).

The profile of SPMs is age, sex and race-specific (11). Several biological mechanisms also can be linked to changes in SPMs levels. For example, the concentration of SPMs increases during the inflammatory process (11). However, the ratio of increase is unpredictable and depends on organ, stimulus, and the levels of other classes of mediators (13). The large discrepancies in the levels of SPMs measured in different studies, highlight the potential variability of SPMs levels in healthy human (11).

These mediators exert anti-inflammatory and immunostimulatory effects through the activation of various cell surface G protein-coupled receptors (GPCRs), which rapidly transduce signals and activate intracellular pathways to control a range of biological functions (14).

At the cellular level, SPMs limit polymorphonuclear neutrophils (PMN) recruitment and activity; enhance macrophage phagocytosis and efferocytosis; counter-regulate production of pro-inflammatory mediators, including prostaglandins (PG); leukotrienes (LTs); chemokines; cytokines; growth factors and reactive oxygen species; and stimulating the production of anti-inflammatory mediators, including nitric oxide (NO) and PGI1 by endothelial cells (10,14). However, each class of SPMs has a specific role in the resolution phase (14). The main biological functions of the different classes are explored in Figure 2.

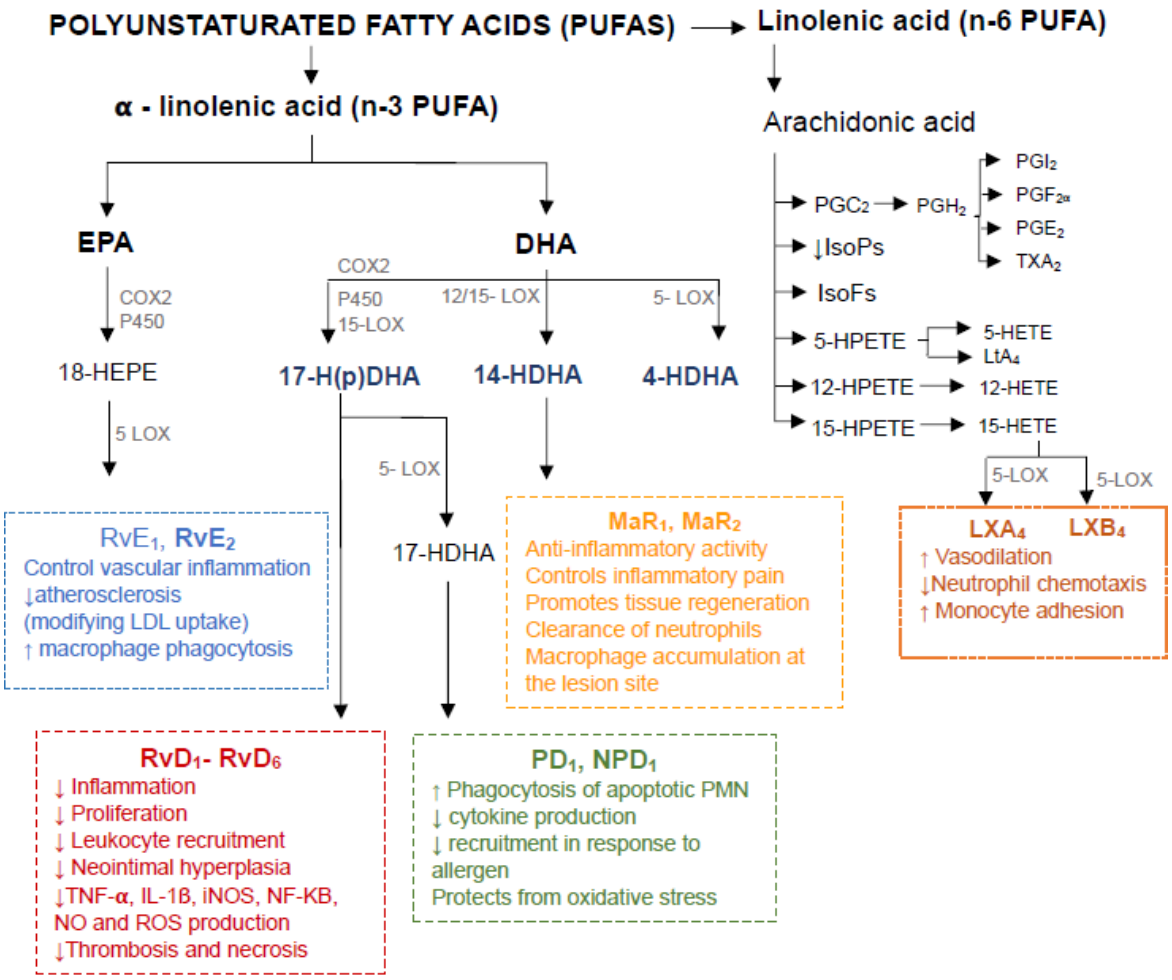

Figure 2. Branching diagram showing derivatives of linoleic acid (18:2, n-6 PUFA) and α-linolenic acid (18:3, n-3 PUFA) with indication of the main biological functions described for the separate classes. COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDHA, hydroxydocosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetrenoic acid; IsoF, isofurans; IsoP, isoprostanes; LOX, lipo-oxygenase; Lt, leukotrienes; Lx, lipoxins; MaR, maresin; PD, protectins; PG, prostaglandins; Rvs, resolvins; Tx, thromboxanes; LDL, low-density lipoprotein; TNF-α, tumour necrosis factor alpha; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, Nitric oxide; ROS, reactive oxygen species; ↑, increase; ↓, decrease.

Behind this effects, recent studies suggest a promising role for SPMs. Indeed, SPMs have shown to enhance bacterial containment and improve antibiotic efficacy (12); reduce pain by acting on specific receptors expressed by immune cells as silencing nociceptors (15); and promote tissue regeneration of wounds (9).

4. INFLAMMATION AND PREGNANCY

Pregnancy is categorized by endocrine, immunological, inflammatory, and metabolic changes. These adaptations occur to ensure that the developmental and energy requirements of the placenta and fetus are met throughout pregnancy (16).

Research has concluded that inflammation plays a physiological role in pregnancy (6). Successful obstetric outcomes are achieved by the presence of an adequate inflammatory state (pro/ anti-inflammatory) at an appropriate time (7). This suitable maternal inflammatory response will be associated with maintenance of an adequate uterine environment for fetal development, allowing the establishment of implantation, placentation, decidualization, fetus development and parturition (5,13). Thus, the regulation of inflammatory uterine environment is key for mother and fetus well-being.

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is a transcription factor responsible for the synthesis of inflammatory mediators that regulate maternal inflammatory response (17). The activation of nuclear factors promotes the increase of pro-inflammatory factors, cytokines and prostaglandins at the maternal-fetal interface, and increase in secretory molecules, acute phase reactants and immune cells at a systemic level (17). Conversely, the downregulation of nuclear factors promotes an anti-inflammatory environment as so, levels of NF-kB change according to the stage of pregnancy and maternal-fetal needs (17).

During pregnancy, two critical changes in inflammatory molecules profile are described (7). In the first phase, implantation and placentation occur, and the presence of a pro-inflammatory phenotype enhances uterine receptivity, placental cell invasion and the establishment of maternal-fetal blood flow (5). The second phase aligns with fetal development, where an anti-inflammatory phenotype is necessary for an uncomplicated pregnancy (7). As the fetus develops, the production of anti-inflammatory molecules decreases, and the expression of pro-inflammatory molecules is triggered. The development of an inflammatory environment is essential for labour, being responsible for the initiation of regular uterine contractions and fetal membranes rupture (18). These variations are explored in figure 3.

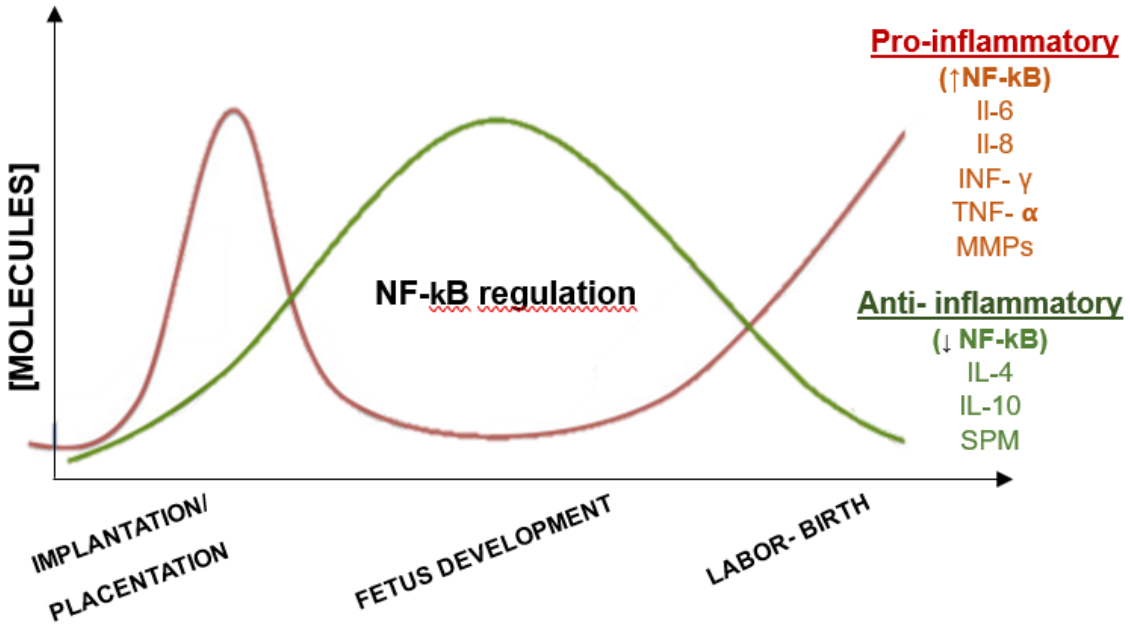

Figure 3. NF-kB regulation during pregnancy. Three inflammatory phases are described. The first and third phases are pro-inflammatory, and the second phase is anti-inflammatory. This response acts accordingly to immune system activity and is regulated by the NF-kB. NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; Il-6, interleukin-6; Il-8, interleukin-8; INF- γ, interferon γ; TNF- **α**, tumoral necrose factor alpha; MMPs, matrix metalloproteinases; IL-4, interleukin-4; IL-10, interleukin-10; SPM, specialized pro-resolving lipid mediators.

Inflammatory processes are critical for several pregnancy events. However, this response must be controlled. Failure or amplification of an appropriate inflammatory response at specific times leads to dysregulation of the uterine environment with obstetric consequences (19). Changes in the uterine environment are a typical feature of pregnancy complications such as preterm labour (PTL), preeclampsia (PE) and fetal growth restriction. In addition to adverse outcomes, neonates are known to be at risk of serious complications after birth, with significantly increased morbidity and mortality (7,19).

For example, endometriosis is a chronic inflammatory condition of the uterus that is associated with high rates of miscarriage or pregnancy loss (7).

5. MODERN PREGNANT WOMEN

Humans are the source and the object of their own change. The changing role of women in society, lifestyle adoption and the development of a polluted planet are all results of evolution that affect pregnancy. Indeed, the pregnant woman has undergone numerous changes in terms of age at first pregnancy, weight, levels of stress and concomitant diseases.

Today, most women's main concern is to build a successful career. As a result of this ambition, women are exposed to high levels of stress and motherhood has been postponed (20). In high-income countries, the proportion of women giving birth over the age of 35 has increased over time (21). This situation raises concerns about the impact of advanced maternal age on pregnancy outcomes, and it is important to highlight that aging is additionally associated with progressive modifications in the immune reactivity and pro-inflammatory status (22).

Modern society's diet and body image (under- and over-weight) have also been changing. In fact, the prevalence of maternal obesity is rising rapidly worldwide, and the number of women who become pregnant with a body mass index (BMI) ≥30 kg/m^2 is increasing (23). Studies in the non-pregnant state described that obesity is associated with a chronic low-grade inflammatory state, termed 'meta-inflammation' or metabolically induced inflammation (24).

Long-term exposure to inflammatory triggers and stressors, such as chemical irritants and dietary habits, with the contribution of systemic dysregulation and prolonged insults induced by ageing, synergistically increase the inflammatory status during the reproductive period and pregnancy (22). Thus, the impact of these elements is particularly relevant in the reproductive capacities of women and may constitute a major obstetric problem (19).

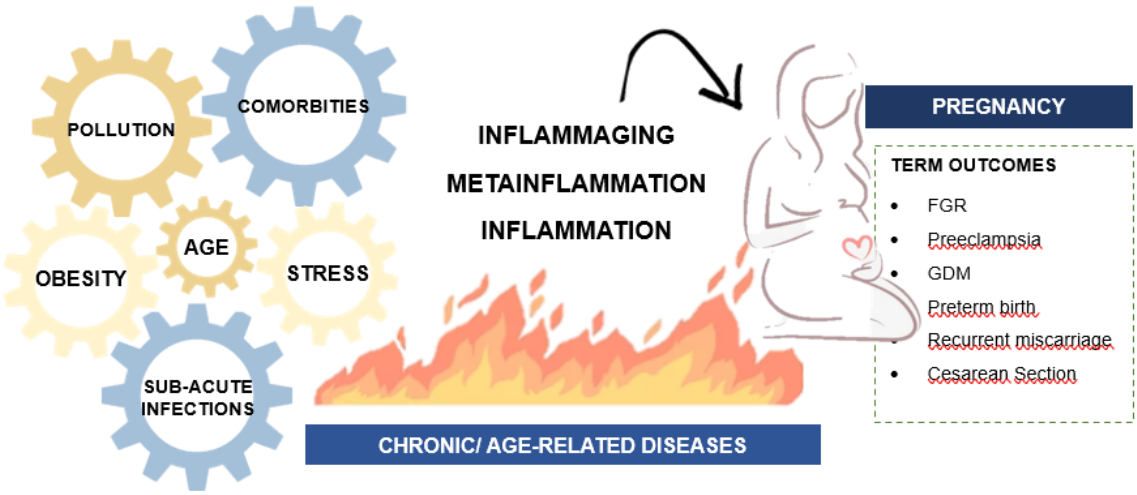

Figure 4. Inflammation effects on pregnancy and mother. On the left etiological factors contributing to the pathogenesis of pro-inflammatory states; on the right effects of pro-inflammatory states on pregnancy, outcomes and potential feedback loop of pregnancy and effects on inflammaging and chronic age-related diseases onset; FGR, fetal growth restriction; GDM, gestational diabetes mellitus.

6. THE IMPACT OF *SPECIALIZED PRO- RESOLVING LIPID MEDIATORS* IN PREGNANCY

6.1 STATE OF THE ART

Studies, both in vitro and in vivo, have been carried out to clarify the usefulness of SPMs as a diagnostic, therapeutic and prognostic tool in pregnancy (25). Due to the recent discovery of SPMs, most results to date have been based on animal models and most information relates to mediator precursors, such as n-3 PUFA, because of the potential instability of SPMs levels in human tissues (11).

To determine the behaviour of SPMs and their precursors in pregnant women, *Mozurkewich et al.* studied the blood samples from 118 pregnant women randomised to supplementation with EPA- and DHA-rich fish oil supplementation versus soya oil placebo. Maternal serum analysis detected the pathway precursors 4-HDHA, 14-HDHA and 17-HDHA, but not consistently D-series resolvins (RvDs), E-series resolvins (RvEs) and PDs (26). The precursors levels were found to positively correlate with DHA levels. Regarding the time course during pregnancy, a significant increase in the precursor 17-HDHA (a metabolic marker of RvDs) was observed between enrolment (12-20 weeks) and the end of pregnancy (34-36 weeks), whereas 4-HDHA and 14-HDHA levels did not differ significantly (26). The increase in 17-HDHA was seen in both maternal blood and cord blood, but was significantly higher in cord blood, raising questions about the possible production or transfer of SPMs and SPMs precursors across the placenta (26).

A study by *Keelan et al.* looked at how supplementation with SPMs precursors modified the composition of the placenta and of the inflammatory genes, including transcripts for TNF-α, IL-1β, and IL-6. In placental tissue, SPMs precursors and SPMs were found to be present in measurable amounts. Research shows that n-3 PUFA rich fish oil supplementation during pregnancy is associated with increased levels of 17-HDHA, 18-HEPE and DHA (but not EPA). Analysed Rvs did not show a statistically significant increase (27). Although the n-3 PUFA supplemented group showed an increase in TNF-α mRNA expression, the placental inflammatory genes tested were also found to be unaffected by SPMs concentrations (27). These findings may be counterintuitive and do not support an anti-inflammatory role for SPMs and their precursors in the placenta in normal pregnancy.

These data were supported by *Jones et al.* study. In a pregnant rat model fed on a diet high in n-3 PUFA, placental levels of Rvs, PDs and their biosynthetic enzymes were assessed (26). Maternal supplementation was found to increase placental expression of lipoxygenase enzymes. The pathway precursors, 17-HDHA and 18-HEPE were increased in both early (day 1) and late (day 17-22) pregnancy. Placental RvD_2 levels were increased in mid- and late pregnancy, whereas RvD_1, 17R-RvD_1, and PD_1 were increased only in late pregnancy (26).

Regarding different classes of SPMs, LXA_4 has been reported to be present in pregnant women circulation at higher levels than in non-pregnant women at 24 weeks' gestation but has not been detected in umbilical cord blood (28). Also, it was verified that LXA_4 receptor, FPR2/ALX receptor levels increase in human placenta after the third trimester, but no effects on the fetus have been reported (28).

RvD_1 and RvD_2 were detected in both maternal plasma and cord blood. RvDs levels were higher in maternal plasma than in cord blood (29). In human placenta RvDs act through formyl peptide receptor 2 (ALX/FPR2), and lysopho- sphatidic acid receptor 4 (GPR32), whereas RvEs act through the G-protein-coupled receptors chemerin receptor 23 (ChemR23) and leukotriene B4 receptor (BLT1). ALX/FPR2 has been shown to be present and active in the placenta, while ChemR23 and BLT1 have only been shown to be expressed in the human placenta. Low levels of GPR32 mRNA expression have also been reported in human placenta, although its functionality remains unknown (29).

This suggests that the placenta may be a signalling target for SPMs, but the expression and localization of other SPM receptors in the placenta have yet to be demonstrated (28). There remains a knowledge gap regarding the functional role of SPMs in the placenta.

SPMs were also identified in human milk -including RvDs, RvEs, PDs, MaR_1. Their presence was associated with accelerated resolution of acute inflammation in vivo and may be therapeutically relevant in the treatment of pregnancy-related disorders (24).

Nonetheless, no relationship was found between PDs or MaRs and pregnancy.

The role of these mediators in pregnancy is still being characterized, but some properties have already been well proved. These are outlined in Table 1.

Table 1. SPMs actions and target in pregnancy

SPM	Target	Bioaction	Reference
LXA_4	PMN	↓ Migration ↓ Penetration	(2)
	Monocytes	↑ Recruitment ↑ Phagocytosis of apoptotic PMN	(8)
	Mast Cells	Control migration ↓ iNOS, CCL2, IFN-γ and IL-6 ↑ IL-10 expression in the placenta.	(8)
	FPR2/ALX	↑ proliferation, differentiation, invasion, and angiogenesis. Regulate ILK.	(8)
	Mesenchymal Epithelium	↓ secretory activity ↓ MMP9, β-catenin, vimentin, Akt, Gsk-3β and NF-κB	(28)
	Endometrial cell lines	Compete with estrogen and progesterone Regulate GABAAπ throughout HOXA10 Control LIF and CT	(28)
	HUVEC	↓ oxidative stress induced by LPS ↑ NQO1 and HO-1 ↑ expression Nrf2	(28)
RvEs	ChemR23/ BLT-1	↓ iNOS, CCL2, IFN-γ and IL-6 Control placentation	(29)
RvDs	GPR32	↓ Inflammation Proper vascular function Placentation	(10)
	Placental cell lines	Regulate inflammation Placentation	(29)

Table 1. LXA_4, Lipoxin A_4; RvD, D-series resolvins; RvE, E-series resolvins; HUVEC, Human umbilical vein endothelial cells; ChemR23, Chemerin receptor 23; GPR32, BLT-1, Leukotriene B_4 receptor; lysophosphatidic acid receptor 4; PMN, polymorphonuclear neutrophils; iNOS, Nitric oxide synthase; CCL2, monocyte chemoattractant protein-1; IFN-γ, interferon gama; MMP9, matrix metalloproteinases; Protein kinase B, Akt; Glycogen synthase kinase-3 beta, Gsk-3β; ILK, integrin linked kinase; GABAAπ, γ-aminobutyric acid; HOXA10, homeobox A10; LIF, leukemia inhibitory factors; CT, cardiotrophin; LPS, lipopolysaccharides; NQO1, nicotinamide adenine dinucleotide quinone oxidoreductase; HO-1, heme oxidase 1; Nrf2, factor 2 protein; ↑, increase; ↓, decrease.

6.2 APPLICABILITY OF *SPECIALIZED PRO-RESOLVING LIPID MEDIATORS* IN PREGNANCY

Given the anti-inflammatory and immunostimulatory properties of SPMs and SPMs precursors, their use may result in an enhanced ability to modulate or resolve inflammation (16).

Koletzko et al. suggest a possible relationship between maternal intake of n-3 PUFA and maternal-fetal health through control of blood and placental levels of SPMs precursors and SPMs (30). Prenatal supplementation has been shown to increase the number of full-term births, reduce immune responses involved in allergic inflammation, increase protection against infections, and reduce infectious diseases' risk (30). There are also benefits for the fetus: prenatal supplementation with n-3 PUFA increases SPMs precursors in offspring at birth plays a protective role in neonatal maturation, especially in neurodevelopment (3). Therefore, it is recommended that pregnant women should aim for an additional minimum average daily intake of 200 mg DHA over and above the recommended intake for general adult health (26).

These findings suggest that increased SPMs precursors, for example with n-3 PUFA intake, may provide increased substrate to produce SPMs during high-risk pregnancy, reinforcing the protective association SPMs/ better pregnancy outcomes.

Nevertheless, high levels of SPMs can also be associated with adverse obstetric outcomes. *Nordgren et al.* reported that maternal RvD_1 and RvD_2 were increased in cases where babies were admitted to newborn intensive care units, compared to those who were not admitted (31).

In an analysis of SPMs and other clinical outcomes in mother-infant pairs, its changes have been associated with several high-risk conditions. In the clinical setting, SPMs also show many associations between the profile of SPMs and the subjacent condition. SPMs changes in different precursors were detected in PTL, PE and clinical chorioamnionitis at term (CCT) (26). Besides these conditions, there are also neonatal conditions associated with abnormal levels of SPMs, such as prematurity retinopathy and parenteral nutrition associated liver disease (26).

These results suggest another potential applicability of SPMs. Maternal plasma SPM levels can be used in pregnancy monitoring as a biomarker for adverse neonatal outcomes (32).

To evaluate SPMs as a predictive factor, *Aung et al.* focused on identifying the associations and predictive capacity of a large panel of metabolites in relation to preterm birth. Research has identified several lipid biomarkers, including RvD_1, which proved to be one of the most predictive metabolites (32).

6.2.1 *SPECIALIZED PRO-RESOLVING LIPID MEDIATORS* AND POOR OBSTETRIC OUTCOMES

Preterm labour

In the setting of PTL (defined as delivery before 37 weeks gestational age), SPMs levels of DHA-derived RvD_1 and RvD_2 in maternal plasma and RvD_2 in cord blood were significantly higher compared to mothers delivering at term (31). However, a recent Taiwanese report has identified that RvD_1 levels are reduced in maternal circulation of preterm compared to term birth (33). Nevertheless, in a systematic review, *Koletzko et al.* suggest a general protective effect of n–3 PUFA supplementation during pregnancy in reducing the incidence of early preterm birth (30).

Preeclampsia

In pregnant women with PE, *Xu et al.* described that LXA_4 levels are much lower than in healthy pregnant women (28). *Perucci et al.* also demonstrated increased levels of RvD_1 in early (12-19 weeks) and late (30-34 weeks) pregnancy, with decreased levels in mid-pregnancy (20-29 weeks) in pregnant women with PE (34). The introduction of SPMs as a treatment has also been tested (35). Now, in pregnant women with history of previous PE early administration of low-dose aspirin in pregnancy (before the 16^{th} week of gestation) is recommended. However, a recent study concluded that supplementation with LXA_4, to ensure adequate fetal levels, may also be a novel method for PE treatment without adverse effects on the fetus (35).

Clinical chorioamnionitis at term

Maddipati et al. were unable to detect many SPMs, including RvD_1, RvE_1, PD_1 and LXA_4, in the amniotic fluid of women with CCT, either driven by intra-amniotic infection or idiopathic. However, their precursors were observed, albeit at low levels (36). This report suggests that CCT in the absence of microbial invasion of the amniotic cavity may be due to insufficient anti-inflammatory and pro-resolution lipid mediator. Elucidating the mechanisms of pro-resolution insufficiency could identify valuable biomarkers of impending clinical CCT (36).

The relationship between SPMs changes and poor obstetric outcomes are described in Table 2.

Table 2. SPMs and poor obstetric outcomes

Authors, Year	Patients	Sample	Main Results	Clinical Significance
Nordgren et al.(31) , 2019	136 mothers and 138 infants at the time of delivery	Maternal and cord plasma samples	↑ SPMs in maternal versus cord plasma ↑ SPMs levels associated with at-risk outcomes ↑ maternal DHA intake associated with ↑ maternal plasma RvD1 e RvD_2	↑ n-3 fatty acid intake may provide ↑ substrate for the production of SPMs during high-risk pregnancy/delivery conditions ↑ maternal plasma SPM could serve as a biomarker for negative neonatal outcomes
Perucci et al. (34), 2021	28 pregnant women, 11 women developed PE and 17 remained normotensive	Blood samples	↓ RvD_1 levels and ↓ RvD_1/LTB_4 ratio at 30–34 weeks in pregnant women with PE ↑RvD1 levels at weeks 12–19 and ↑ LXA_4 and RvD1 levels at 30–34 weeks than those at 20–29 weeks	Potential use of lipid mediators (RvD_1) as clinical markers for PE development
Maddipati et al. (36) , 2016	35 pregnant women, 24 women with CCT (12 CCT- MIAC and 2 CCT-noMIAC)	Amniotic fluid samples	↓ 11-HEPE, 8-HETE,11-HETE levels in pregnant in pregnant women with TCC noMIAC ↑ concentrations of inflammatory cytokines (IL-1, IL-6, TNF-**α**) Undetachable RvD_1, RvE_1, PD_1 and LXA_4	Potential use of lipid mediators (RvD_1, RvE_1, PD_1 and LXA_4) as clinical markers for CTT development

Table 2. SPMs, specialized pro-resolving lipid mediator; DHA, docosahexaenoic acid; RvDs, D-series-resolvins; PE, preeclampsia; CCT, clinical chorioamnionitis at term; IL, interleukin; PD_1, proctetins; CCT-MIAC, clinical chorioamnionitis at term with microbial invasion of the amniotic cavity; CCT-noMIAC; n-3 fatty acid, omega-3 fatty acid, HEPE, hydroxy eicosapentaenoic acid, HETE, hydroxyeicosatrienoic acid; ↑, increase; ↓, decrease.

7. COMMMENT

A successful obstetric outcome is inextricably linked to an adequate maternal inflammatory response at the appropriate time and this dysregulated response can lead to adverse obstetric outcomes. The profile of the modern woman has undergone numerous changes, in lifestyle and environment, that are conducive to pro-inflammatory states in modern pregnant woman. Thus, maintenance of adequate maternal inflammatory response during the reproductive period and pregnancy may be at risk. In this sense, there is an urgent need to develop a tool to ensure that an appropriate maternal inflammatory response is maintained during pregnancy.

The delicate role of SPMs as modulators of chronic low-grade inflammation has become a device of potential interest in the control of appropriate inflammatory response in pregnancy. SPMs have been shown to have a range of properties, including inflammatory resolution without immunosuppression, tissue regeneration and pain relief. These properties can be used as a preventive, diagnostic and therapeutic tool in pregnancy.

At the obstetric level, SPMs are promising. Their anti-inflammatory properties could be used as a powerful control and therapeutic weapon in pregnancy, allowing the inflammatory or anti-inflammatory states of the specific period of pregnancy to be maintained. Studies have shown benefits from SPMs, not only in healthy pregnant women, but also in pregnant women with associated problems. Indeed, research has concluded that supplementation of pregnant women with SPMs precursors, particularly n-3 PUFA, and SPMs can influence poor obstetric outcomes and improve adverse obstetric conditions such as PTL and PE. At diagnosis, certain poor obstetric outcomes have also been shown to be associated with the dysregulation of SPMs levels. Therefore, SPMs monitoring could serve as a biomarker for adverse neonatal outcomes, allowing early detection and intervention in specific clinical contexts.

Despite the possible impact in obstetrics, there are still many inherent limitations. The studies that have been carried out are still few and most have been in animal models. Given that diet is the main source, the difference in dietary n-3 PUFA content and duration of supplementation in the animal versus human studies may be responsible for erroneous conclusions. There are large discrepancies in SPMs levels measured in different studies, highlighting their potential variability in healthy human tissues, and warranting larger scale investigations to establish reference levels of these mediators. It has not yet been possible to accurately characterise SPMs specific levels and assess their behaviour.

Unfortunately, most information is still controversial, and more studies are needed to clarify it. Therefore, supplementary studies are required to fill the gaps in knowledge about SPMs production levels throughout pregnancy and during high-risk pregnancy and labour. Moreover, forthcoming studies may also examine other SPM properties such as analgesic and tissue resurfacing.

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