



An Innovative Approach of Escalating Maternal Fetal Outcomes in Pregnancies associated with Obesity: Overcoming Deficiency of Resolvins associated with Obesity: A Systematic Review

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Abstract

In view of pregnancy possessing the properties of mild however considerable significant inflammatory action under physiological circumstances, on getting complicated by obesity the chances of a continuous inflammatory state enhances with subsequent numerous consequences with additional complications correlated with acute inflammation. Regarding this the part of resolvins alias Specialized proresolving mediators (SPM) obtained from Omega3 essential fatty acids might be key. Actually differential generation of multiple high risk situations is correlated with child birth along with neonatal health, the association amongst, maternal omega 3 fatty acids consumption as well as resolvins amounts in maternal blood along with placental level in addition to greater amounts observed in breast milk at the time of first month of breast feeding, represent certain of the maximum significant cornerstone concerning these autacoids. In addition to that escalation of scientific corroboration proves the absence of SPM at the immuno metabolic tissue level regarding obesity. Moreover, the obesity correlated absence of SPMs apparently is the deciding factor even regarding the recent Coronavirus disease (COVID19) pandemic since apparently it is amongst the reasons correlated with greater complications in addition to the negative results of SARS-CoV2 infection. The utilization of metabolomics in this speciality has been clarified, with the information that via metabolome it is feasible to watch the multiple along with complicated crosstalk amongst mother, placenta along with fetus, regarding the Identification of particular biomarker regarding the anticipation, diagnosis besides supervision of different obstetric situations. Nevertheless, greater evaluation is required for part of resolving as biomarkers of Maternal –Fetal outcomes besides generation of enough values regarding integration in pregnant women with Omega3 fatty acids or with greater derivatives for ensuring ideal SPM generation under high risk situations.

Keywords: resolvins, obesity, Omega essential fatty acids, breast milk, maternal-fetal outcomes

Introduction

Pregnancy offer a greater chance for acquisition of future maternal besides fetal health ^[1]. Actually, negative influence on the offspring of certain maternal metabolic changes like obesity along with type2 Diabetes mellitus (T2DM) is believed to be mainly due to the teratogenic action at the embryonic level besides secondary to the greater chances of preterm along with still births. Moreover, till date abundant scientific proof corroborated regarding probably metabolic programming of the fetus with longer term actions inclusive of escalated risk of generation of metabolic pathologies in addition to cardiovascular issues ^[2].

Regarding the pregnant patients, the woman has to tackle physical along with metabolic alterations with the objective of conferring protection as well as ensuring precise fetal formation that is intricately associated with the nutritional status prior to pregnancy along with weight accrual that takes place, at the time of gestation ^[1]. Hence enhanced apprehension exists regarding the escalation of body mass index (BMI) $\geq 30 \text{ kg/m}^2$ ^[3]. Actually from the consideration of maternal health, gestational obesity is correlated with an enhancement of maternal mortality along with morbidity both for fetus along with mother. The robust complications in the obese pregnant woman are inclusive of preeclampsia, thromboembolism besides an escalated uptill 3.8 fold greater incidence of Gestational Diabetes mellitus (GDM) ^[2].

Obesity in pregnancy is further implicated regarding maternal sequelae in longer term as well with an escalated incidence of cardiovascular along with metabolic issues. Additionally the negative influence of the SARS-CoV2 pandemic on eating behaviour exists. The maximum recent publications ^[4] corroborated regarding deleterious diet quality along with decreased physical activity in the population at the time of the lockdown that made weight management tough. These issues were considerably more significant in patients presenting with greater BMI who were possessing the properties of minimum amounts of physical activity, the maximum deleterious diet quality along with maximum diet intake of enhanced amounts of food ^[4]. These results were in corroboration with the negative impact of the SARS-CoV2 emergency regarding the glycemic regulation of pregnant women ^[5]. Additionally, Coronavirus disease (COVID19) correlated reduction in the mental health further was associated with robust consequences regarding eating behaviour anticipating over eating along with lesser motion ^[4]. In particular the observation was that emotional eating influenced numerous pregnant women at the time of COVID19 pandemic lockdown that led to escalated weight accrual at pregnancy time ^[6].

Furthermore obesity at the time of pregnancy along with GDM are in general correlated with a chronic low grade inflammation, that by definition is a meta-inflammation whose influence on the probable initiation of maternal fetal complications is well known ^[7]. The changed reaction to pathogenesis secondary, to meta-inflammation was established prior to the SARS-CoV2 COVID19 pandemic ^[8], along with recent scientific proof corroborated that this chronic low grade inflammation apparently accelerated the pathogenic modes behind COVID19 via different modes, inclusive of dysfunctional innate along with adaptive immune responses besides an enhancement of chronic inflammation along with oxidative stress (OS) ^[9]. Furthermore, data reveals greater chances of complications in the premature newborn undergoing development in a proinflammatory intrauterine milieu inclusive of necrotizing enterocolitis, paraventricular leukomalacia along with intraventricular haemorrhage, pulmonary complications as well as retinopathy ^[10].

Recently it has been emphasized the manner by which specific modes of lipids inflammation modulators labeled as specialized pro resolving mediators (SPM) obtained from omega3 LC polyunsaturated fatty acids (PUFA's), are generated in variable methods under multiple high risk situations correlated with both child birth along with neonatal health.

The association of these results with the considerable aid of omega3 LC PUFA's regarding maternal-fetal health ^[11],

inclusive of the decrease of risk of preterm birth prior to 34 wks along with their part as modulators of chronic low grade inflammation ^[12] highlights the central origin of the substances obtained from omega3 FA's. Moreover considerable experimental corroboration *in vivo*, *in vitro* to prove that the escalation of SPM subsequent to dietary supplementation with omega3 FA's might be at the time of initiation of the advantages seen ^[7, 13-16]. Earlier we had reviewed the role of omega 3, besides 6 polyunsaturated fatty acids (PUFA's), resolvins regarding obesity, NPD with obesity along with gut microbiome alterations besides numerous articles on obesity etiopathogenesis ^[17-19]. Here thus we reviewed the part of SPM's, resolvins in relation to obese pregnant women n maternal-fetal health.

Methods

Here we conducted a systematic review utilizing search engine pubmed, google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like Obesity; specialized proresolving mediators (SPM); omega3 LC polyunsaturated fatty acids (PUFA's); resolvins; maternal- fetal outcomes; preeclampsia (PE); COVID19; supplementation effect of omega3 FA's from 1990's till date in 2022.

Results

We found a total of 300 articles out of which we selected 91 articles for this review. No meta-analysis was done.

2. Acute along with Chronic Inflammation

The inflammatory responses are necessary regarding the body's capacity of fighting pathogenic infection or an inimical injury ^[7, 20]. In particular a local response of the vascular system occurs following changes in homeostasis inclusive of escalated permeability besides perfusion of the blood vessels. This mode whose activation takes place within minutes is essential for aiding the extravasation of the circulating leukocyte besides certain plasma proteins implicated in the disinfection of tissues along with controlling of the inflammatory events by themselves along with antigen particular immune reaction. Regarding this specifically eicosanoids or lipids mediators of inflammation possess a crucial part of which the major ones are obtained from arachidonic acid (ARA, 20:4), like leukotrienes (LTs), along with prostaglandins ^[7, 13]. LTs basically possess chemotactic characteristic for neutrophils along with controlling of vascular permeability, whereas prostaglandins are the major players implicated in alterations in blood flow (that facilitates leukocyte migration as well as plasma exudation towards injured tissues). Nevertheless, the inflammatory reaction self restricts itself at the time of acute type ^[14]. Actually, this phase that is totally proinflammatory gets followed by a subsequent one. Normally this results in tissue besides homeostasis getting restored, in view of certain foundational physiological events which restrict both the expansion besides time period of the inflammatory reaction ^[15]. During the initiation phase, both the control of granulocyte enrollment, along with the regulation of their activation status, whereas in the subsequent phase of restoration, elimination of granulocyte infiltrate takes place in view of recovery of the normal function of the injured tissues ^[7, 13]. The regulation of this phase takes place at 2 steps i) systemic ii) local ^[19]. The level implicates circulating glucocorticoids in addition to acute phase reaction ^[7] along

with certain anti inflammatory efferent cholinergic neuronal pathways^[16]. In this latter part the control of tissue particular responses is essential for restriction of the inflammatory injuries along with homeostasis restored.

Despite multiple constituents of the canonical inflammatory reaction are implicated like systemic escalation of proinflammatory cytokines along with acute phase proteins (C Reactive Protein(CRP), leukocyte enrollment to in flamed tissues as well as activation of tissues in toto with healing reaction of the tissues on their own, the inflammation properties of obesity display individual besides distinctive traits [21]. Firstly it is chronic^[22], getting stimulated by nutrients along with energy excess^[22]. Furthermore in this particular situation the inflammatory molecules along with metabolic pathways implicated have a double part in the form of inflammatory mediators along with controllers of metabolic pathways besides energy storage^[23]. Additionally, the typical chronic kind decides a low grade activation of innate immune system tonically implicated in the changes in the metabolic homeostasis gradually in time^[21]. This basically influences adipose tissue (AT), where there is escalated generation of adipokines, inclusive of Tumor necrosis factor alpha(TNF α), interleukin-1 β (IL1 β), IL-6, along with leptin as well as resistin^[22, 24]. Evans *et al.*^[25], further observed an escalated generation along with liberation of inflammatory adipokines was parallel to the quantity of AT existent. Simultaneously, a reduction in the formation of antiinflammatory factors was documented like adiponectin^[26, 8], besides an inherent incapacity of resolution of inflammation along with restoration of homeostasis besides tissue function^[23]. Secondly the multi organ involvement of obesity correlated inflammation possess their unique characteristics in view of them not normally correlated with chronic inflammatory diseases however with temporary inflammatory states like in sepsis. Actually it influences the working of different organs inclusive of heart liver, AT, pancreas, brain skeletal muscle that results in systemic situations like insulin resistance (IR)^[21]. These changes apparently influence the leptin sensitivity at arcuate nucleus of the mid basal hypothalamus with consequences on the mode of controlling of satiety^[26]. Regarding this the complicated along with distinctive endogenous modes behind the inflammation resolution apparently is of considerable significance of obesity correlated inflammation. Actually recently, the significance of certain autoacids of lipids kinds obtained from omega3 PUFA's has been revealed in this delicate events of restriction along with resolution of inflammatory reaction^[15, 27]. These SPM's are the lipoxins derived from the AA, the resolvins (Rvs) D along with E series obtained from docosahexaenoic acid (DHA, 22:6). Along with eicosapentaenoic acid (EPA, respectively as well as protectins along with maresins, other metabolites of DHA. They are generated in specific temporary windows in view of the particular heterotypic crosstalk of inflammatory leukocytes with the cells of the inflamed tissue like endothelial cells, epithelial cells, macrophages as well as platelets. Moreover they control the rhythm along with the degree of inflammatory reaction^[7]. Actually SPM's work in the form of endogenous receptor agonist at low concentrations (pM along with low nM) at the level of particular trans membrane G- proteins where they decide a down regulation of inflammatory events along with stimulation regarding resolution of exudates^[27]. The different publications by Chiang *et al.*^[7], revealed

multiple literature dedicated to autacoids in the inflammatory events that was inclusive of down regulation of cell adhesion molecule at endothelial cells along with leukocyte level, a decrease in chemo taxis besides transendothelial migration, lesser neutrophil activation, hampering of generation of along with effectiveness of proinflammatory mediators, non inflammatory phagocytosis of neutrophils as well as apoptotic macrophages along with active liberation of inflammatory leukocytes. Specifically it was demonstrated in a recent review that Rv's might possess greater anti inflammatory along with pro resolving characteristic in contrast to (EPA in addition to DHA precursors [7], The fragile part of these pro resolution molecules acquires further considerable significance at the time of pregnancy when continuous inflammation is implicated in maternal fetal complications^[21].

Actually apparently meta-inflammation might possess a key part in maternal obesity along with GDM that results in modifications of the generational programming in utero, by impacting placental function.

3. Resolvins

3.1. Kinds along with Biogenesis

The invention of pro resolution lipids mediators obtained from omega 3 fatty acids is comparatively recent. As per the review by Bannenberg & Serhan^[29] cyclooxygenase enzyme implicated for effective oxygenation of AA which is the generator of prostaglandin -H₂ (PGH₂), further forms oxygenated products obtained from EPA in addition to DHA, however at a comparatively lesser rates. Moreover these metabolites have demonstrated a weak affinity for well-illustrated prostaglandin receptors. Nevertheless, it has been observed that both cyclooxygenase (COX) along with lipoxygenase (LOX) possess the capacity of oxygenation of omega 3 fatty acids for generating intermediate oxygenated products that can further undergo bioconversion. In particular, Resolvins in humans vary based on their precursors, like (RvD1-6) or (RvE1-3) take origin from DHA or EPA respectively. Their are probably 2 bio generational pathway for (RvD1-6) group, one being the aspirin COX 2 based along with forms the epimeric type which is activated by aspirin epimeric (AT- RvD1- AT- RvD6), whereas the crucial major bio generational pathway is attained via the crosstalk amongst 15 LOX besides the 5 LOX. A crucial part gets played by 17 hydroxyperoxy DHA an intermediate product of 15 LOX which works in the form of a restricting metabolite for the generation of resolvins for the D series, whose pathway marker gets determined by its 17 hydroxyperoxy DHA(17HDHA) [30] This mode is apparently to be developed for the generation of resolving RvD1 as well as RvD2 along with is existent within the mononuclear cells like macrophages besides neutrophils along with between cells (endothelial cells-leukocyte, neutrophils- macrophages)^[31, 32].

Furthermore, regarding resolvins obtained from EPA, or E series 2 unique bio generational pathway are feasible that initiate from a common precursor-18- hydroxy eicosapentaenoic acid (18HEPE). Of these one pathway gets catalyzed by aspirin - COX 2 besides 5 LOX via the crosstalk amongst endothelial cells- leukocyte, whereas the second one is aspirin independent along with gets initiated with the oxygenation of EPA driven by the cytochrome p450^[33].

Both the pathways result in the generation of RvE1 as well as RvE2 basically in reaction to escalated 5 LOX amounts at the

time of inflammation^[32]. Maximum RvE2 generation takes place in the eosinophils via the 12/15 LOX pathways, always initiating from the common precursor 18HEPE^[34]. A simplistic bio generation pathways are depicted in fig1 [rev in 35].

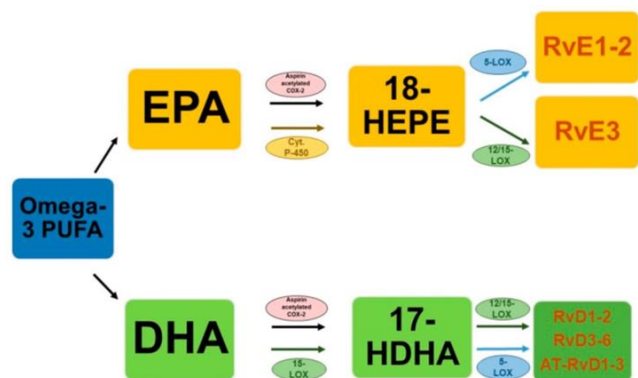


Fig 1: Courtesy ref 35- Simplified scheme of the biosynthesis of resolvins.

Valdes *et al.*^[36], illustrated the way these metabolic pathways develop for the maximum part molecules which are unstable, hence broken down fast /metabolized *in vivo* with resultant short biological half-life. Furthermore, the study by Mas *et al.*^[37], observed that in healthy adults the amounts of SPM precursors in serum along with plasma were 5-10 fold greater in contrast to metabolites by themselves.

3.2. Maternal Fetal Amounts

Elliot *et al.*^[7], performed a review of literature regarding assessment of amounts of SPM in pregnant women emphasized the basic amounts observed in healthy adults be utilized for contrasting, inspite of the existence of variables in view of the both the variable methodologies utilized (LC-MS/ MS), liquid chromatography which is coupled with tandem mass spectrometry [MS]- enzyme immune assay), as well as the probability of variability of SPM results in healthy adults. Mozurkewicz *et al.*^[30] performed assessment of secondary blood samples from 60 secondary mothers, Omega3 along with mental Health study subsequent to dietary supplementation with EPA in addition to DHA rich fish oil versus soya bean oil as placebo, imparted certain knowledge regarding amounts of SPM in pregnant women [30]. From these assessments it was observed that contrasted to placebo fish oil supplementation escalated the precursors 17HDHA (alias metabolic marker of the resolvins D series) in maternal besides cord blood along with this metabolite enhanced with considerable significance amongst recruitment along with the culmination of gestation. 17HDHA amounts were observed to be significantly greater in the umbilical cord blood contrasted to maternal blood. As per the placental amounts, Keelan *et al.*^[38], corroborated the beneficial results from murine studies^[39]. Actually this research pointed to supplementation with Omega3 rich fish oil at the time of gestation escalated the existence at the placental level of DHA (however not EPA) of the SPM precursors 17HDHA as well as 18HEPE despite the assessments of resolvins it did not reveal statistically significant escalation of DHA. 17HDHA actually the outcomes as per the probable actions on gene expression apparently did not point to any kind of stimulatory action on inflammation. The assessment of all these outcomes by Elliot

et al.^[7], emphasized the fragile part of SPMs at the placental level pointing to a particular formation besides utilization of these mediators despite outcomes on these modes of utilization along with receptor expression are occasional. Nevertheless, certain *in vitro* as well as animal model studies performed on microglial cells^[40] as well as microglial cells cardiac fibroblast^[41] respectively have demonstrated with clarity the anti inflammatory modes. Detailed description- in these tissues, the modes of resolvins in the anti inflammatory events vary from avoidance of the enhanced intercellular cell adhesion molecule [ICAM]-1 along with vascular cell adhesion molecule [VCAM]-1 protein amounts, IL-6, TNF α , along with IL-10 in cardiac fibroblasts to the controlling of nuclear factor κ B (NF κ B) signaling pathway as well as mi RNA expression in the microglial cells.

Studies in the SPM amounts in the newborn are further scanty, with maximum concentrating on cord blood amounts at the time of delivery^[7].

In reference to the results on SPM amounts in the breast milk, Weiss *et al.*^[42], evaluated the fatty acids content of 94 human milk samples from 30 mothers during the first mth of lactation with the utilization of gas chromatography(GS-MS) evaluation besides the quantification of lipid mediators via a HPLC-MS/MS (high performance liquid chromatography mass spectrometry). They observed the existence of RvD1 as well as RvE1 in the breast milk besides in greater amounts in contrast to healthy volunteers in amounts that are physiologically understood to hamper inflammatory events. They are observed at the time of the 1st mth of breast feeding, despite the amounts of SPM persist to be the same, the amounts of α -linolenic acid (precursor of EPA as well as DHA) escalate whereas reduction of the amounts of DHA along with 17HDHA^[42]. Thus Weiss *et al.*^[42], posited that these amounts are responsive to the requirements just subsequent to birth along with greater amounts of SPM observed might point to a innate considerably significant part in the immune system which could illustrate the probable advantages correlated with breast milk. Armardottir *et al.*^[43], corroborated the existence of robust lipid mediators of inflammation in breast milk, inclusive of D series of resolvins (RvD1-4), aspirin activated epimeric form (AT- RvD3) as well as E series of resolvins (RvE1-3). Nevertheless, during mastitis, the amounts of SPM in the milk were lesser probably in view of the rapid utilization secondary to the hyperinflammatory state that corroborated with the considerable dynamism associated with their generation.

3.3. Part in situations in changes in Maternal -Fetal Health

Despite, apparently the illustration that amounts of SPM in the breast milk get controlled dynamically at the time of inflammatory events^[7], subsequent assessment is required regarding the manner these changes of amounts of SPM in the breast milk are associated with inflammatory states besides deliveries that are at risk. Prior studies on the breast milk of women in case of preterm births have illustrated that certain SPMs inclusive of Rvd1 as well as Rvd2 were existent in that amounts that were 4 fold lesser in contrast to the amounts observed in case of milk of mothers with full term deliveries. Nevertheless outcomes obtained from this study did not take into account the variations in view of the sampling along with/or assessment approaches.

Elliot *et al.*^[7] review yields clarity regarding the formation of certain SPM's get controlled as per the existence of

pregnancy or perinatal pathological states. In a murine study it was found that the delivery of RvE3 to pregnant mice having exposure to LPS decreased the incidence of preterm labour conversely to the delivery of the precursor 18HEPE having no action. Furthermore, the significance of SPM's was further illustrated in a study that had assessment of amniotic fluid of full term birth patients along with clinical chorioamnionitis. Their observation was that apparently this clinical situation would possess the properties of comparative deficiency of SPM's. Actually certain resolvins like RvE1 along with RvD1 were not observed. Nevertheless, their precursors were seen. Thus these actions might be in view of the active deficiency of these mediators at the term chorioamnionitis, along with secondary to the lability of SPM's [7]. Preclinical animal studies [45], emphasized the probability of utilization of resolvins as modulators of angiogenesis, thus a probable therapeutic utilization regarding avoidance of retinopathy generation in preterm infants was posited [45].

Furthermore Nordgren *et al.* [47], analysed the probable part of SPM's in conferring protection against, maternal –fetal complications. In this evaluation acquisition of outcomes regarding the consumption of omega 3 fatty acids from 135 mothers that were admitted in the delivery room with a food frequency questionnaire. The amounts of RvD1 as well as RvD2 in maternal plasma besides cord blood were further determined with the observation that SPM's amounts were enhanced in maternal plasma in contrast to cord blood. Furthermore it was found that the enhanced amounts were correlated with greater complications. Corroborating the probability of utilization of resolvins as biomarkers a study by Aung *et al.* [48], that concentrated regarding pregnancy outcomes, the single meta bolome study in this particular area. It concentrated on the isolation as well as correlation besides anticipative ability regarding premature birth of a big panel of metabolites (eicosanoids, immune biomarkers, Oxidative stress (OS) markers along with growth factors). A cross sectional study was performed in the pregnant women in the LIFECODES birth cohort that was inclusive of 58 preterm patients delivery, with 31 spontaneous preterm deliveries, besides premature rupture of membranes (PROM), 25 patients correlated with placental abnormalities (PE, intrauterine growth retardation [IUGR]) with 2 patients with no classification was feasible contrasted to 115 controls. Maximum of correlations seen were regarding spontaneous premature births, besides in particular certain lipid biomarkers, inclusive of RvD1 that was apparently the biggest anticipator of metabolites. Moreover, the complicated statistical evaluation of these outcomes illustrated that lipid biomarkers corroborated as being maximum efficacious regarding separation of patients from controls contrasted to other metabolites evaluated. Furthermore of the variable eicosanoids those obtained from lipooxygenase pathway illustrated the maximum robust correlation with preterm birth, thus drawing conclusions of a probable combination of lipid biomarkers utilization might aid in anticipation of preterm birth. Regarding this greater outcomes were revealed by Perucci *et al.* [49], who performed a longitudinal study with the objective of contrasting certain lipid metabolites (leukotriene B4 (LTB4), lipoxin A4 (LXA4) along with resolvin D1 (RvD1) In pregnant women at risk for preeclampsia (PE) with those with generated (n=11) or those not generated (n=17) PE. It was illustrated that pregnant women with PE possessed lesser amounts of RvD1 along

with RvD1/ LTB4 ratio of <30-34wks contrasted to controls. On the other hand an escalation of RvD1 numerous amounts at 12-19wks in those generating PE later. Noticeably amounts of RvD1 were greater at 30-34wks contrasted to 20-29wks taking into account both groups of pregnant women. With these outcomes, Perucci *et al.* [49], drew conclusions that a probable association amongst pregnancy outcomes as well as gestation duration regarding RvD1 existed. Human studies that evaluated utilization of resolvins as clinical biomarkers in anticipating pregnancy outcomes of the studies utilized the probable utilization of resolvins has to be evaluated till now. Actually, the probable clinical importance anticipates probable part in form of biomarkers regarding high risk pregnancy/delivery situations or negative neonatal outcomes, like as PE, preterm birth, for RvD1. Nevertheless, no conclusions have been feasible in view of the dosages as well as determination time standardization have not been done as per a single pathological situation.

3.4. Part in Obesity

The accounting along with therapeutic probability of resolvins in facilitation of resolution of inflammation is apparently of considerable significance in pathologies with the properties of greater problems in resolving inflammatory events as well as restoration of homeostasis [50, 51]. This takes place in obesity, regarding which enhanced scientific corroboration prove the absence at the level of immuno metabolic tissues of SPM's [52], despite no development of inflammatory metabolic situations in each obese person [53]. In case of preclinical studies on mouse model along with cell culture exogenous delivery of resolvins has illustrated an attractive resolving effect at AT level along with reduction in correlated complications like Nonalcoholic steatohepatitis (NASH) along with insulin resistance (IR) [54, 55].

However, regarding this part of resolvins has numerous facets that need definition. At the initiation tissue hypoxia at adipocytes level is implicated in the escalation of inflammatory adipocytokines that subsequently gets followed by macrophages infiltration that results in generation of chronic low grade inflammation. At the time period tissues pro resolution mediators aid in the problems encountered in resolving inflammatory events [54]. Actually the resolvins RvD1 as well as RvD2 have been illustrated to be implicated in macrophages switch towards a proresolving phenotype along with lesser migration besides adhesion of monocytes to adipose tissue [54]. They impact the decrease in the liberation of proinflammatory cytokines, like leptin, TNF α , IL-1 β along with IL-6 was further illustrated besides an escalation of along with expression as well as liberation of adiponectin [62]. Akin outcomes were illustrated in a study per by Neuhofer *et al.* [56], who illustrated that obese mice revealed a fast decrease contrasted to control of SPM along with precursors obtained from DHA in white adipose tissue (WAT) within 4 days of consumption of HFD. Moreover treatment with 17HDHA resulted in reduction in expression in proinflammatory cytokines, escalated expression of adiponectin besides enhancement of glucose tolerance in conjunction with insulin sensitivity in obese mice. These outcomes emphasized the fragile part of resolvins in the inflammation of AT in obesity.

In the complicated situations of changed generation of obesity correlated SPMs at variable immuno metabolic tissues there is addition of sequelae in the central nervous system (CNS) level with consequences regarding energy

storage. Regarding this diet induced hypothalamic inflammation is of considerable significance which results in impairment of the neurons implicated in the regulation of body mass. In particular the study by Pascoal *et al.* [57], demonstrated a decrease in RvD2 at the hypothalamic level in obese mice.

As pregnancy possesses beforehand mild albeit considerably significant inflammatory action physiological situations [58], on association with obesity the chances of a continuous inflammatory state escalates with subsequent numerous consequences which give additional weightage regarding the complications correlated with acute inflammation [58], as demonstrated in fig2. Actually there is existent information regarding enhanced CRP, a systemic marker of inflammation are associated with PE, preterm delivery, pregnancy loss besides IUGR [59]. Other systemic pointers of inflammation inclusive of IL-1 β have been recently correlated with dysfunctional *et al* growth besides poor birth outcomes. Moreover Hanetal. [61], illustrated that a maternal

inflammatory state, chronic as well as acute is correlated with neurodevelopment which might result in development of Autistic spectrum disorders (ASD)"; besides attention deficit hyperactivity disorder syndrome (ADHD). Additionally, in obesity the proinflammatory cytokines imbalance with repercussions on escalated circulating leptin amounts associated with leptin resistance [62], by itself can further impact birth [68]. Actually, the physiological hampering action of leptin on uterine contractility can aid in the greater chances of impaired labour, thus greater LSCS rates as a consequence [63]. Moreover the repercussions on changed inflammatory state might further influence the fragile glycemic regulation at the time of pregnancy. Actually RvD2 is implicated in the regulation of insulin sensitivity in view of the impact on insulin signaling pathway along with correlated inflammatory pathways [64], a situation that might explain the greater incidence of GDM in pregnancies in associated maternal obesity.

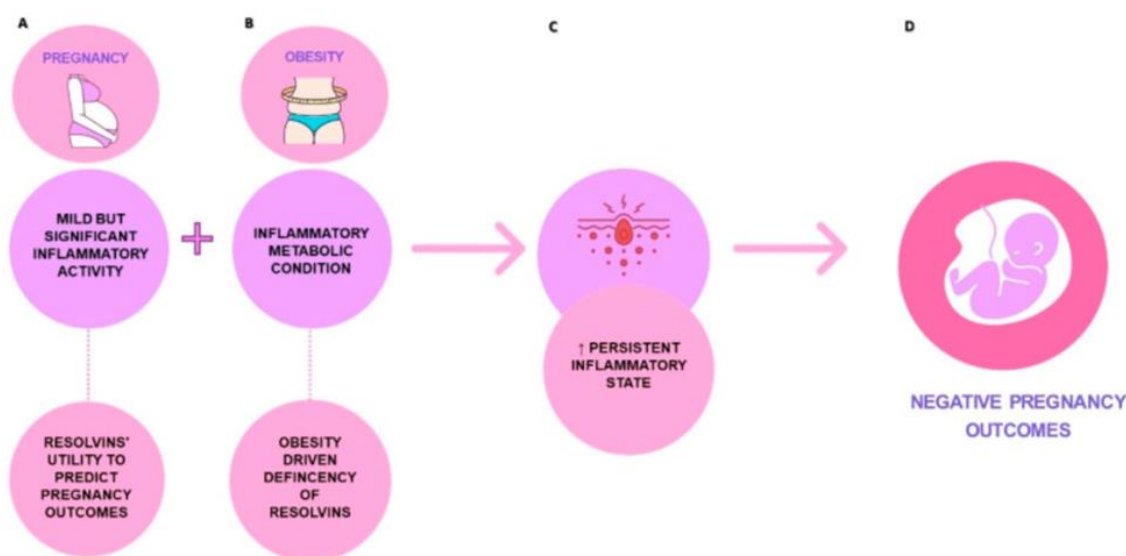


Fig 2: Courtesy ref 35- Pregnancy and obesity involvement in inflammatory state and resolvins' correlation: (A) mild but significant inflammatory activity in physiological pregnancy where resolvins could be useful biomarkers for pregnancy and neonatal outcomes (B) in pregnancies complicated by obesity the probability of a persistent inflammatory state increases also due to the resolvins' deficiency, (C) consequences are a persistent inflammatory state and multiple repercussions that add up to the complications associated with acute inflammation and (D) subsequent negative pregnancy outcomes.

Regarding the explanation for SPM deficiency in the AT there might be variable causes with no clarity till now. Prior studies have demonstrated an up regulation of certain crucial enzymes implicated in the inactivation of SPM like PG dehydrogenase/ eicosanoid oxidoreductase [54] along with ineffective bio generation [65]. Moreover noticeably this deficiency in obesity apparently impacts other immuno metabolic tissues besides AT inclusive of skeletal muscle [65]. Conversely Echeverria *et al.* [66], demonstrated unanticipated outcomes demonstrating that despite hepatic EPA along with DHA amounts were low in obese mice contrasted to controls, the amounts of resolvins inclusive of RvE1, RvE2, RvD1 along with RvD2 were preescalated in the form of a reaction to the priorexistent chronic low grade inflammation. However more recent studies have corroborated the changed balance amongst resolvins of the D series along with proinflammatory mediators favouring the latter as well in the peripheral blood leukocyte of obese individuals corroborating multiorgan inflammatory situation of obesity

[67]. Bashir *et al.* [68], corroborated the total reduction of resolvins in the AT of the mouse model resolvins inclusive of RvE1, RvE2, RvD2, RvD3 along with RvD5 with only RvD6 not implicated. Additionally the *in vitro* evaluation conducted by Lopez Vicario *et al.* [67], apparently corroborated the in capacity of resolution of inflammation estimated in the peripheral blood leukocytes in obese individuals needs to be secondary to inefficient bio generation instead of dysfunctional breakdown metabolism [62]. Actually, a reduction in the expression of 15LOX enzymes has been demonstrated along with supplementation of 17HDHA, that is a byproduct of this enzyme has proved effectiveness. These outcomes pointed to an alternate utilization of Omega3 fatty acids regarding nutrition antiinflammatory nutritional treatment in future.

3.5 Association with SARS-CoV2 infection

Obesity seems to be associated with greater proneness to infection [69, 70]. The publications mainly documented an

escalated generation of inflammatory cytokines as well as chemokines that apparently results in reduction in cells of immune system that impact innate along with acquired reaction to both bacterial in addition to viral infections. The imbalance of microbiome/virome in the intestines further has sequelae on the changes of effectiveness of the immune system^[81]. Regarding this the state of FA has previously demonstrated to be deciding in the manner found to be impacting the humoral immunity with the probability of mode modulated by SPM^[69].

Despite, obesity was not appreciated commonly amongst the risk factors for SARS-CoV2 infection, numerous new publications have appeared regarding this issue^[70]. Simonnet *et al.*^[71], demonstrated a greater degree of obesity amongst patients admitted in ICU regarding SARS-CoV2 further documenting an escalation of robustness of the disease with an escalation of BMI. Liu *et al.*^[72], emphasized the no correlation amongst escalated BMI along with robustness of the infection in COVID19 positive patients. The association of escalated BMI with poor survival rates was further stressed on evaluation by Peng *et al.*^[73]. Furthermore Lighter *et al.*^[74], observed that in younger patients as well an association amongst the obesity with negative COVID19 prognosis emphasizing the manner by which patients <60 with a BMI amongst 30-34 possessed greater chances of getting admitted in ICU contrasted to lesser chances for patients with a BMI <30. The obesity correlated absence of SPM apparently decides in this aspect also in view of it being correlated with the maximum complications as well as negative results of SARS-CoV2 infection^[47, 70]. This pointed that SPMs are implicated as crucial modes via which infection results in generation of cytokine storm along with changed deregulated lung reaction^[57]. Actually, Costela –Ruiz *et al.*^[86], basically illustrated over generation of proinflammatory cytokines inclusive of IL1, IL6, IL12, IFN γ as well as TNF α in particular in the lung tissue, with most inimical prognosis in robust SARS-CoV2 infection cases. Regarding this part of RvD1 as well as RvD2 in decreasing the liberation of proinflammatory cytokines inclusive of IL6 along with TNF α ^[54], has been detailed earlier^[54]. The over generation of proinflammatory cytokines IL6 along with TNF α has further been correlated with deregulation of some fat resident regulatory T cells (Treg) along with specifically with the generation of Th17 immunity (Tcell sublineage) that in turn is associated with the modes implicated in the greater incidence along with mortality correlated with COVID19 in obese patients^[70].

This gets further complicated at the time of pregnancy possibly in view of numerous factors. Of these the specific cardiopulmonary situations (acute cardiopulmonary situations) existent in 2nd along with 3rd trimester of pregnancy^[76], as well as the particular immune phenotype of the pregnant women^[67, 68]. The latter possesses the properties of a changed Th1/ Th2 ratio^[78] along with variable immune predilection, with strength provision regarding innate immune barriers along with simultaneous decrease in adaptive/ inflammatory immunity in the later pregnancy stages^[77]. The higher mortality along with morbidity during pregnancy from variable infections has been appreciated in literature^[70], inclusive of all influenza infection pandemics revealed till date^[79] along with SARS-CoV2^[80], in over weight prior to pregnancy obesity as well as obesity. Till date outcomes accessible regarding SARS-CoV2 infection apparently corroborate this pattern. Actually from the meta-analysis conducted by Khalil *et al.*^[81], 38.2% of 2567 pregnant women

with SARS-CoV2 symptoms possessed obesity. Moreover outcomes have been procured by 8 United States care centres which demonstrated that prior to pregnancy obesity along with GDM had prevalence in pregnant women that got hospital admitted regarding COVID19 contrast to total pregnant women testing positive during delivery^[82]. Furthermore, Lapolla *et al.*^[96] on evaluation of literature documented outcomes by the Vaccine safety Datalink correlated with surveillance of COVID19 hospitals from 1/3/20 to 30/5/20 emphasized, situations like prior to pregnancy obesity along with GDM possessed greater prevalence amongst pregnant women who were hospital admitted for COVID19 contrasted to pregnant women admitted for obstetrical causes.

4. Benefits of Dietary/Supplement Manipulation of Resolvin Amounts

Probability exists regarding eating behaviour alterations might represent the 1st step to make sure adequate resolvin amounts are there despite this strategy might show certain key problems. Firstly it guides regarding the vehicle of precursors (EPA along with DHA) that possess activity contrasted to resolvins^[22]. Secondly no chance exist regarding attempting compensation for any enzymatic changes regarding biogenesis (15LOX)^[65, 67] as well as /or breakdown kind (PG-dehydrogenase/ eicosanoid oxidoreductase or^[54] implicated in Resolvin deficiency in certain particular situations like obesity. Actually till date the outcomes accessible in literature pointed that placental along with blood SPM amounts can get modulated at the time of pregnancy via consumption of Omega3 fatty acids along with SPM play a crucial part regarding the advantages correlated with LC-PUFA^[7, 34]. In maternal obesity there are changes in the generation of resolvins. In spite of that the role of an appropriate along with balanced diet seems necessary for numerous causes. Basically the negative actions of a HFD on the generation of SPM along with precursors have been emphasized earlier in the animal model^[56]. Furthermore, the outcomes regarding western diet pointed that the amounts of Omega3 fatty acids was lesser^[84], whereas the consumption of Omega 6 fatty acids was escalated considerably with probability of sequelae of enzymes competing^[85, 86]. Lastly these eating behaviours were included as environmental factors aiding in morbidity correlated with lung diseases regarding obesity^[87].

Moreover probability exists on aiding the generation of enough resolvins via supplementing food that has apparently been efficacious in some situations. Actually the utility of this has been illustrated in the prior detailed Keelan *et al.*^[38] the study that emphasized on supplementation with Omega3 rich oil at the time of pregnancy in association with escalated DHA, 17H DHA along with 18HEPA at the placental level. Additionally, recently study conducted by Souza *et al.*^[88], who evaluated correlation amongst Omega3 supplementation as well as peripheral SPM amounts who illustrated the manner by which an enriched marine oil resulted in escalation of SPM amounts in peripheral blood in a time based manner with considerably significant consequences at the immune system. In case of pregnant women attaining 300mg/day consumption of DHA (triple amounts contrasted to healthy adults) an avoidance amounts recently posited by Koletzko *et al.*^[12] These are the proper rates as per the Guidelines of European Food Safety Authority (EFSA) that has advocated an enough consumption of EPA of 250mg as well as

DHA(adult need dependent on cardiovascular (CVS) requirement as well as an extra 100-200mg of pregnane rated DHA(regarding compensation for Oxidative elimination of maternal dietary DHA in fetal newborn body fat ^[12]. This constitutes the minimum amounts regarding avoidance point of view. Actually greater consumption of DHA (600-800mgdaily) might ensure more protection contrasted to lesser dosages, however direct contrasting of dose - action evaluation are not accessible ^[12]. Nevertheless, the association with appropriate diet behaviour is necessary in view of the probable enzymatic competition that might impact the efficacy of the supplement per se in the existence of unbalanced dietary consumption ^[84-86]. With regards to targeted as well as individualize dietary supplementation via the direct delivery of resolvins has been observed to be efficacious in reduction of obesity correlated complications in variable preclinical studies on animal models detailed earlier ^[54, 55]. The effectiveness of RvE3 was further evaluated in pregnant mice that had been exposed to LPS for avoidance of preterm birth regarding the study performed by Yamashita *et al.* ^[43]. Furthermore, Lopez Vicario *et al.* ^[67], emphasized regarding the efficacy of supplementation with 17H DHA subsequent to the observation of changed bio generation of resolvins in leukocytes of obese individuals. Moreover in a study performed by Quiros *et al.* ^[89], it was illustrated that RvE3 delivery in the form of a synthetic polymer nanoparticles promoted wound healing in a model comprising of human intestines. Additionally, regarding requirement for novel as well as escalatingly individualized nutritional therapy Pal *et al.* ^[90], emphasized on the need of individualized delivery of RvE1 as per the particular metabolic requirements. Actually they found regarding the advantageous actions of EPA for hyperinsulinemia along with hyperglycemia are secondary partly to activation based on the host genetic way of the G- protein coupled receptor ERV1/ChemR23 or RvE1. However for this feasible therapeutic strategy, the mode of delivery is still required to get assessed ^[57], further in view of the short biological half-life of certain agents ^[40].

5. Conclusions

Apparently the various scientific publications accessible till date pointed that the maternal dietary Omega3 fatty acids consumption impacts the existence of resolvins in maternal blood besides placental level. Moreover a modulation of generation of Resolvins at the time of full course of pregnancy along with association with maternal -fetal complications along with the concentration of these molecules. Regarding this obesity, a situation of comparative resolvins deficiency at the time of pregnancy escalates the potential of continuous inflammatory state, the consequences of which are numerous along with cause additional complications correlated with acute inflammation ^[65]. Depending on these, the utilization of metabolomics in this issue is clarified, a strategy possessing the capacity of provision of an individual phenotype portrait regarding an organism in view of its capacity of direct determination of numerous metabolites within the complicated biological systems. Actually via the metabolome it is feasible to watch the multiple besides the complicated crosstalk amongst mother, the placenta, the fetus, regarding the Identification of particular biomarkers of utility in anticipation, diagnosis as well as super vision of various obstetric situations ^[91]. Furthermore, metabolomics estimates the global sets of low

molecular weight metabolites with provision of a snapshot of the metabolic status of an organism in association of the genetic variability as well as external stimuli ^[92]. This characteristic aids in getting over the short half-life of resolvins products, that till now Apparently is the major issue regarding clinical scenario.

Future examination is the requirement with the Objective of preventive medicine for assessment of probability of utilization of certain resolvins in form of biomarkers regarding maternal-fetal results, besides demonstration of enough integration amounts in pregnant women with omega 3 fatty acids or with greater active derivatives which ensure ideal SPM formation in situations considered risky.

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