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Diet Induced Inflammation and Potential Consequences on Fetal Development

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Abstract

The significance of diet induced inflammation in gestational tissues (chorioamnionitis) on fetal growth and development is emerging as an important area of research. Role of infection and intrauterine inflammation in preterm deliveries has been extensively explored, but, implication of sterile inflammation (not associated with infection) on fetal development has received little attention. Inflammation is generally thought to be the result of a local or systemic infection or products of infection; conversely, inflammation may result from high calorie intake or from diets low in micronutrients. While systemic inflammation is widely proposed as the predisposing factor for the increasing incidence of non-communicable diseases such as diabetes mellitus and cardiovascular diseases in adults, accumulating evidences now suggest that low grade intrauterine inflammation might impair linear growth and adversely affect myogenesis and adipogenesis that might have lasting effects on offspring. Given that intrauterine inflammation is frequently present, its origin and impact on fetal development needs attention. The public health implications of nutrition-mediated inflammation is of particular importance in India, which is burdened with problem of over-nutrition coupled with undernutrition and micronutrient malnutrition. Studies to unearth the link between nutrition and inflammation and its impact on fetal growth and development are needed. This review explores the potential consequences of intrauterine inflammation on fetal growth and development.

Keywords: Inflammation; Chorioamnionitis; Nutrition; Fetal growth; Diabetes; Insulin resistance; Myogenesis; Adipogenesis

Introduction

The immune system is a complex array of organs, tissues and specialized cells that protects the body from outside invaders, such as bacteria, viruses, parasites and from other harmful invaders [1]. Inflammation is a nonspecific protective action of the immune system, a response that defends the host from bacteria and other infectious agents [2]. Typically, inflammation is the result of a highly nuanced interaction between pro- and anti-inflammatory cytokines, thought to originate only during infections [3,4]. Conversely, inflammation may result from high calorie intake or from diets low in micronutrients as well. High calorie diet is associated with exaggerated post-prandial spikes in glucose and lipids that generate excess free radicals that stimulate chronic low-grade systemic inflammation [5,6].

High calorie and the ensuing chronic inflammatory state induce insulin resistance and is the underlying cause of many chronic diseases such as obesity, diabetes, atherosclerosis, cancer and arthritis [6-10]. Many age related diseases such as cataract and Alzheimer's disease are also attributed at least partially to inflammation.

Even as chronic low grade systemic inflammation is proposed as the predisposing factor in the increasing incidence of non-communicable diseases such as diabetes mellitus and cardiovascular diseases in adults [11,12], recent observations have revealed that intrauterine inflammation, due to high calorie diet during pregnancy, may predispose the offspring to the adult chronic diseases. Inflammation due to high calorie diet during pregnancy has been shown to adversely influence myogenesis and triglyceridemia and adipose tissue deposition in muscle and liver of offspring [13-15]. Exposures, during critical periods of development are highly vulnerable to insults such as faulty diet, which may permanently alter myogenesis and adipogenesis potential in the offspring. In this connection, the role of nutrition and intrauterine inflammation in a particularly vulnerable subset of the population, that of undernourished women in the reproductive age, deserves to be critically examined [16-18].

Nutrition and Systemic Inflammation

It is now well accepted that low-grade chronic systemic inflammation also called sterile inflammation is associated with high calorie diet in the absence of any systemic or local infection and that inflammation contributes to risk of insulin resistance and related disorders [19-23]. High fat or high calorie diet associated with exaggerated post-prandial spikes in glucose and lipids generate excess free radicals that can trigger low-grade systemic inflammation [5,24]. Numerous studies have shown elevated concentration of adipose tissue derived cytokines in obese humans, suggesting a concept that inflammation may be derived from the accumulation of activated macrophages surrounding enlarged adipocytes in obese subjects [19-23]. Other studies have shown that circulating free fatty acids (FFA) can directly trigger inflammatory responses by activating toll like receptors (TLR)-4 or nuclear factor kappa b (NF-κB) [24-26]. Furthermore, accumulating pyruvate in mitochondria may favour free radical generation and inflammation during glucose metabolism [22]. Taken together, these studies suggest that inflammation can possibly occur after every high calorie meal, and that obesity is not a prerequisite.

In addition to the direct effect of FFA on inflammatory cascade, intake of a high calorie diet can alter gut bacteria and affect intestinal barrier function and favour endotoxemia and inflammation by a mechanism that increases intestinal permeability [26,27]. Thus indicating gastrointestinal tract as a potential source of inflammation associated with high calorie diet. High calorie diet is followed by

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reduction in gram positive bifidobacteria and increase in gram negative bacteria. With reduction in gram positive bacteria, the intestinal membrane integrity is impaired, which becomes more permeable to endotoxin (cell wall component of gram negative bacteria) resulting in increasing endotoxin (lipopolysaccharide (LPS) in the blood, which stimulates TLR-4 on immune cells and triggers systemic inflammation [26,27]. Alternatively, gut microbiota on a high-fat diet may convert dietary choline into methylamines, reducing choline bioavailability, which is necessary for the secretion of VLDLs. This may eventually promote fatty liver, insulin resistance and lipid peroxidation and inflammation [28].

In India, a large proportion of population is insulin resistant and the prevalence of diabetes and chronic heart disease (CHD) is high [29-31]. Though, it may be presumed that increasing prevalence of diabetes in Indians is due to lack of physical activity and excess calorie intake, the role of inflammation is not known. Excess calorie intake stimulates inflammatory cytokines, leading to insulin resistance and eventually to diabetes; consequently, it is plausible to believe that it is overnutrition or faulty nutrition (diet that is poor in micronutrients) that are responsible for inflammation, insulin resistance and associated disorders, rather than high fat or high carbohydrate diets [29-31]. A link between obesity and insulin resistance is well known, but a significant proportion of population with insulin resistance in India are not obese, but are centrally adipose [32-34]. Indians are susceptible to diabetes at a younger age and at a relatively lower BMI compared to the whites, but the thin Indians have higher body fat percent, especially visceral adiposity [33,34]. Though, evidence linking thin fat babies and susceptibility to metabolic syndrome like characteristics is overwhelming, inflammation as the cause for adipogenesis in foetal life is inconclusive [33,34].

Inflammation in Gestational Membranes (chorioamnionitis) and Offspring Phenotype

Studies on Indian neonates showed higher insulin levels and greater adiposity even at birth compared to Caucasians [33,34]. They also showed low birth weight as contributing factor to insulin resistance among Indians [33]. The hypothesis is that, small Indian babies have smaller abdominal viscera and low muscle mass, but preserve body fat during their intrauterine development, which may predispose to an insulin-resistant state [34]. Though mechanism for thin-fat Indian body composition related to fat and muscle components is not known, it may be presumed that intrauterine epigenetic regulation perhaps mediated by intrauterine inflammation could contribute to less skeletal muscle and more fat mass formation; however, we need to confirm this hypothesis as also the burden and origin of intrauterine inflammation in India.

The foetal stage is critical for skeletal muscle and adipose tissue development. Skeletal muscle forms 40 to 50% of total body mass composition [35]. Fetal stage contains a large number of mesenchymal stem cells (MSC) that differentiate into the myogenic cells, adipogenic cells and fibrogenic cells around mid-gestation. Differentiation of MSC is controlled by a set of transcription factors, which Include wingless and int (WNT), paired box gene 3 (PAX3), (PAX7) and myogenic regulatory factors [35-37]. Activation of the WNT signaling pathway leads to the transformation of nonmyogenic cells into the myogenic lineage and suppression of MSC commitment to the adipogenic lineage [38,39]. MSC committed to become myogenic progenitor cells express PAX 3 and PAX7, which then induce MRF [40]. Under the control of MRFs myogenic precursors cells differentiate into myoblasts and then myotubes; however, proinflammatory cytokines in the gestational tissues inhibits skeletal myogenesis through transcriptional silencing of myofibrillar genes [14,13]. Skeletal muscle develops during embryonic, fetal and postnatal period. Most muscle fibres develop during fetal stage and therefore this stage is critial for skeletal muscle formation [34-36].

Foetal inflammation has been shown to impair foetal skeletal muscle development while promoting adipogenesis [40,13,41]. Inflammation due to any stress might influence myogenesis through activation of NF-κB, which is upregulated during adipogenesis and fat cell differentiation [42]. In contrast, inhibition of NF-κB and TNFα are associated with expression of myogenic genes. The potential role of inflammation in MSC differentiation was further evidenced by c-Jun N-terminal kinases (JNK) signaling. The absence of JNK has been reported to decrease adipogenesis [43,44]. Accordingly, inflammation increases intramuscular fat and connective tissue deposition and reduces number of muscle fiber and/or diameter with adverse consequences in adult life [45-48]. Adipocytes arise from MSCs during mid to late gestation. Thus, any insult such as maternal undernutrition, overnutrition or infection, occurring during mid-gestation, can induce inflammation and may shift MSC from myogenesis to adipogenesis or fibrogenesis [45-47].

Skeletal muscle and liver are the organs critical for glucose metabolism [49]. Skeletal muscle is the key organ for glucose and fatty acid utilization [50]. Poor skeletal muscle development impairs glucose and fatty acid metabolism and predisposes offspring to diabetes and obesity. Linkage between maternal intake or nutritional status and chronic noncommunicable diseases in the offspring through an inflammatory path way is still under exploratory stage. Nevertheless, it is important to understand the source (diet and infection) and the role of inflammation on fetal muscle and fat development and higher diabetes and cardiovascular risk of thin fat Indian babies. Especially, when, higher diabetes and cardiovascular risk in thin fat Indian babies, who are overweight/obese at later stage has been suggested to be an inevitable consequence of socioeconomic development [51].

Maternal Nutrition and Inflammation in Gestational Membranes (Chorioamnionitis)

It is rather well established that perinatal undernutrition and reduced birth weight result in offspring phenotype that has increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood [48]. But, overnutrition associated with Inflammation in gestational membranes can promote a similar phenotype that has increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood is a relatively recent concept. Studies have demonstrated the relation between maternal over nutrition and increased risk of cardiovascular or diabetes type 2 phenotype of the offspring [35,52]. A cohort study from Scotland suggested programming of blood pressure and glucose metabolism in adult offspring of women who consumed high carbohydrate diet [52,53]. Similarly, children born to mothers on high fat diet (HFD) had accelerated development of fatty streaks in aorta [54,55].

The adverse effects of maternal overnutrition have been shown to be mediated through chronic low grade inflammation in gestational tissues (intrauterine inflammation) (Figure 1). Consumption of a HFD increases placental inflammatory cytokines and the expression of toll-like receptor [56]. The extent to which maternal undernutrition (particularly micronutrient malnutrition), which is widely prevalent in India, could influence immuno-modulatory functions and then induce inflammation in gestational membranes is not known [57]. Earlier,

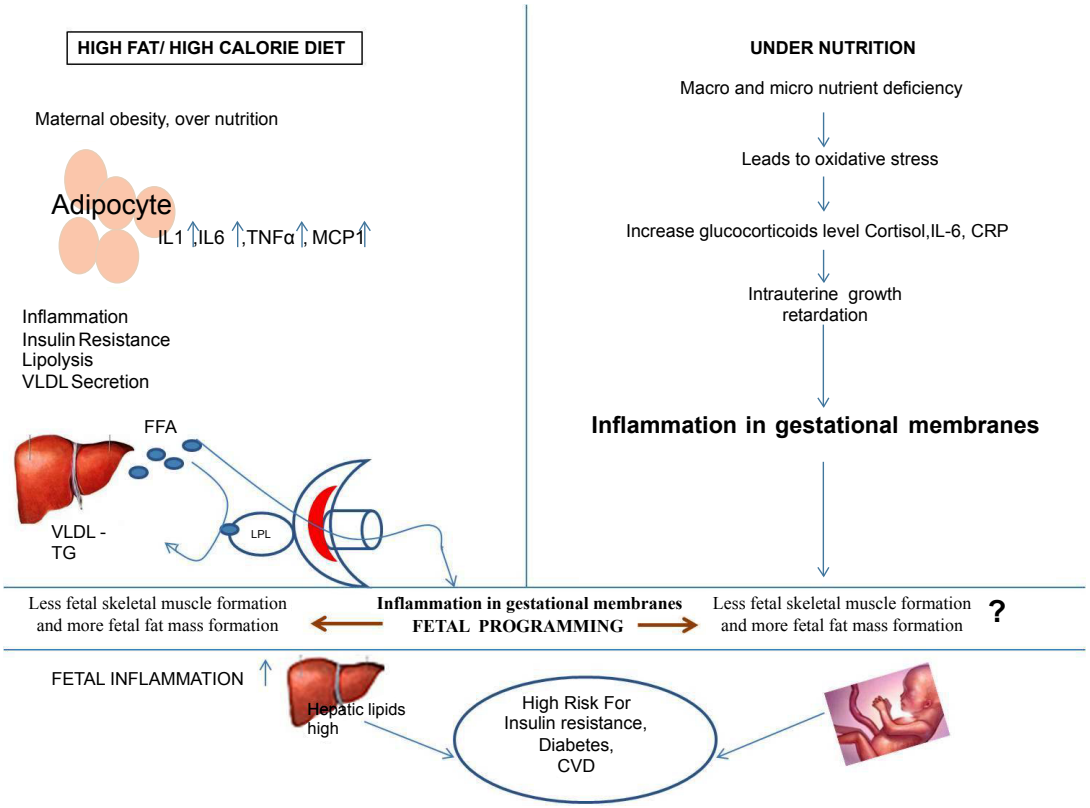

Figure 1: Suboptimal or excess nutrition in pregnancy induce inflammatory responses in the gestational (fetal) membranes that may promote less skeletal mass and more fat mass formation in the offspring; eventually predisposing the offspring to high risk for insulin resistance, diabetes, cardiovascular diseases (CVD) at later stage in life.

LPL (Placental Lipoprotein Lipase); MCP1 (Monocyte Chemoatractant Protein 1)

a study at National Institute of Nutrition (NIN) found histologic chorioamnionitis (intrauterine inflammation) associated with high concentration of interleukin 8 (IL-8) and interleukin 6 (IL-6) in chorioamnion membranes of twenty nine percent of apparently normal women who were undernourished. Most of the women with histologic chorioamnionitis had foetal growth restriction [16]. Studies conducted at NIN, suggest that nearly 29% and 30% of randomly selected, apparently normal, free living pregnant or nonpregnant population in India, have intrauterine or cervico vaginal inflammation respectively [16,17]. Importantly, 30% of both pregnant and nonpregnant population were undernourished and Vitamin A deficiency was significantly associated with cervico vaginal inflammation. Heightened local inflammation is often associated with abnormal local (vaginal) flora as well [17]. It is evident from these observations that any form of malnutrition such as overnutrition or undernutrition, micronutrient deficiency may potentially induce intrauterine inflammation in gestational membranes (Figure 1). Additionally, infections during pregnancy, which stimulate inflammation, may also have a role. It is seemingly possible that maternal malnutrition and infections may share many of the same adverse consequences and reflect two sides of the same coin (Figure 1). In both cases, alterations in physiological functions can be induced and may lead to the development of a phenotype that increases the susceptibility to non-communicable conditions.

In summary, exposure to high-fat diets or to undernutrition in utero might program the offspring to intrinsic enhanced lipogenesis and adipocyte proliferation. This is attributed to inflammation and early induction of adipogenic transcription factor peroxisome proliferator-activated receptor (PPAR) γ, whose activity is enhanced with excess nutriton or undernutrition. Induction of adipogenic transcription factor peroxisome proliferator-activated receptor (PPAR) γ activity is enhanced under limited or excess nutrient availability. Nonetheless, this occurs via different mechanisms involving PPARγ coregulators: in undernutrition, it is upregulation of coactivators, whereas in excess nutriton, it is downregulation of corepressors [58-60].

Though, evidence of diet induced inflammation and altered foetal phenotype is overwhelming, the data are inconclusive. How far, the association between nutrition and inflammation can be extended to thin fat phenotype of Indians, needs to be investigated. In Indian context, where both overnutrition and undernutrition are widely prevalent, it becomes that much more important to address the issue of causal relationship of diet and intrauterine inflammation.

Other Well Known Complications of Inflammation (Chorioamnionitis)

Reproductive tract inflammation has been widely implicated in preterm delivery (PTD), intrauterine growth restriction (IUGR), increased HIV and sexually transmissible infections (STIs) and HIV replication [61-64]. Evidence for fetal involvement with funisitis and chorionic vasculitis has been reported in chorioamnionitis [65,66]. Histologic chorioamnionitis (HCA) and fetal inflammatory response (FIR) have been reported to be associated with IUGR, with extremely

low gestational age at birth [62]. Around 90% of all LBW infants are born in developing countries, which are caused by IUGR rather than PTD, most of which, may be mediated by inflammation [67,68].

In our study, babies born to mothers with histologic chorioamnionitis (HCA), also called intrauterine inflammation, weighed 140 g lesser and were 1.2 cm shorter [16]. The birth weight, crown-heel length and head circumference of these babies were consistently lower than babies born to mothers without HCA. Furthermore, it was interesting to note that higher proportion of mothers who delivered babies with symmetrical growth restriction (SGR) had histologic chorioamnionitis, suggesting the possibility of histologic chorioamnionitis right from early pregnancy [16,68]. Moreover, concentration of IL8 in our women was considerably higher than that reported elsewhere [69].

Similar results were reported by Williams et al. who defined histologic chorioamnionitis as marked leukocyte infiltrate of placenta and showed association of HCA with markers of fetal growth restriction (birth weight, length, head circumference, weight/length ratio and Ponderal index in the lowest 5th percentile) [16,63]. Taken together, these results suggest that evidence linking role of inflammation (chorioamnionitis) and foetal growth restriction and development is scanty, though its link with preterm delivery is relatively well established. In India, foetal growth restriction and preterm delivery contribute to 20 and 10% of low birth weight (LBW) respectively. Yet, role of inflammation (chorioamnionitis) on LBW is scant [16]. Understanding burden of inflammation and its role on foetal growth and development could be very important in India to prevent immediate (preterm and LBW) as well as long term complications (NCD)

Inflammation in the Gestational Membranes (Chorioamnionitis) due to Infections

Intrauterine inflammation is defined as the presence of inflammatory infiltrates in the chorion, amnion, or decidua and has been suggested as a good marker for intrauterine infection [70-72]. Chorioamnionitis or intra-amniotic infection is an inflammation of placenta membranes, typically caused by bacteria ascending from lower genital tract.

Extension of inflammation to the chorionic plate and umbilical cord and to the fetal vessels is termed foetal inflammatory response (FIR) [65,66]. Chorioamnionitis is often due to a polymicrobial infection caused by organisms ascending from lower genital tract [70,71]. *Ureaplasma urealyticum* and *Mycoplasma hominis*, which are commonly found in the lower genital tract, constitute the most frequently isolated organisms from chorioamnion inflammation [62,64,71]. Anaerobes such as *Gardnerella vaginalis* (25%) and bacteroides (30%), as well as aerobes such as Group B streptococcus (15%) and gram-negative rods including *Escherichia coli* (8%) [72,73] are also isolated frequently from chorioamnion inflammation. Chorioamnionitis due to hematogenous spread is relatively rare, but may occur in women with perionditis or some viral infections. Human case-control studies have demonstrated that women who have low-birth-weight infants as a consequence of either preterm labor or premature rupture of membranes tend to have more severe periodontal disease than mothers with normal-birth-weight infants [74], suggesting that a remote infection such as periodontal disease may have the potential to affect pregnancy outcome by triggering inflammation in placental membranes with histologically proven chorioamnionitis in the absence of any bacterial infection in the vagina or cervical area [74]. It is well known that local or remote infection may induce inflammation, but, it would be important to investigate the consequences of infection induced inflammation and influence on myogenensis and adipogenesis in the offspring.

Conclusions

In summary, faulty maternal nutrition stimulates inflammation and promotes a phenotype that is more susceptible to metabolic syndrome like characteristics. Though, evidence pointing to the association between inflammation and genes regulating fetal myogenesis and adipogenesis is overwhelming; evidence is lacking with respect to type of maternal nutrition and inflammation, barring a few studies linking maternal obesity and high fat diet and intrauterine inflammation. Subclinical intrauterine inflammation appears to be more common than anticipated in pregnant women. Detailed investigations as to the type of diet (high/low calorie/micronutrient malnutrition) in pregnancy that induces chronic local inflammation are required to fill the gaps in our knowledge to enable us to move closer towards providing meaningful diet advice to pregnant women. Given the prevalence of adolescent female undernutrition in India, such studies take on more relevance.

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