Mini Review Paper

Maternal Nutrition and Fetal Programming of the Immune system: Epidemiological and Experimental Evidences

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Maternal nutrition will not only affects pregnancy outcomes (such as birth weight) but will also affect the state of the fetus in their adult life in terms of diseases occurrence and also immune system development. Inadequate nutrition particularly will have a negative impact on the proliferation of the various cell populations responsible for the immune functions as well as the accumulation of high concentrations of inflammatory components. Maternal nutrition affects immunity 'programming' during the period of pre-natal and post-natal life. Over the last decade, epidemiological and experimental studies have helped to expedite more understanding of immunity 'programming.' External exposures such as smoking, alcohol and drugs during fetal life have also shown to have an impact on immunity 'programming.' In this review, the relationship between fetal programming and the immune system, such as effects on the various immune-cellular components through some evidence from epidemiological and experimental models will be discussed.

Keywords: Maternal nutrition, fetal programming, immune system, thymus

1. INTRODUCTION

Programming is the term used to represent the effect of the condition in the womb to the development imprint of the fetus in the adult life [1, 2]. Major programming outcome is the greatest during the particular critical period of development of the organs [3]. The theory of 'fetal programming' in relation to the outcome of the adult diseases was first described by Dr David Barker [4]. During pregnancy, the condition of the maternal nutrition, will not only affect pregnancy outcomes (such as birth weight) but will also affect the state of the fetus in their adult life in terms of diseases occurrence and also immune system development [2]. Fetal programming has been linked to the incidence of various adult diseases such as hypertension, obesity, cardiovascular diseases and diabetes [2, 5]. In this review, the relationship between fetal programming and the immune system, such as effects on the various immune-cellular components through some evidence from epidemiological and experimental models will be discussed.

The mechanism of how programming occurs is still not entirely understood. Over the last decades, however, several underlying theories have been identified. One of the main theories of fetal programming showed that it was due to epigenetic alteration such as DNA methylation by certain nutrients, which consequently affects gene expression and phenotype [6-12]. DNA methylation affects cell proliferation, thus has an impact on the development of body organs and its functions [8, 9]. This will, in turn, cause some developmental changes or adaptations. As a result, long term effects on the immune system will be seen as a result

of this growth alteration. Interest on epigenetic nutritional programming effect has led to the study of various types of nutrients to determine their effect on gene expression and subsequently fetal outcome. For instance, in one of an earlier study, reported that amino acids played a very important role in the modulation of the initiation phase of mRNA translation, therefore affecting protein synthesis and tissues growth [13]. Another study has also identified that glucose intake affects the transcription of enzyme fatty synthase which is responsible for converting glucose to fatty acids [14].

In the intrauterine, fetal normally develops in a low oxygen environment and has low antioxidants capacity to eliminates Reactive Oxygen Species (ROS) [15]. Oxidative stress, which is the accumulation of ROS was also believed to be one of the underlying theory behind fetal programming [15, 16]. Oxidative stress in the intrauterine environment can occur as a consequence from prenatal hypoxia (high oxygen exposures due to smoking), undernourishment or overnutrition and exposures to metabolites such as glucocorticoid [15]. High levels of ROS have been associated with an increased incidence of hypertension in adult life which was first reported in rat studies [17]. Free radical species in the intrauterine environment may subsequently disrupt the endothelial cell lining of the blood vessels as well as other organs such as the heart, therefore, contributing to heart diseases [18, 19].

Tissues proliferation and organs development take place at different rates and stages during fetal life [10]. Therefore, one of the main challenges in understanding the theory of fetal programming of the immune system is to identify the critical period of development by which any insults during that period will lead to permanent changes or effect. The ‘programming' of the immune system was believed to occur particularly during early gestation periods and during the post-natal life [10]. The main reason for this claim was that, during the early and late gestation period, demands for nutrients for various organs growth, including the thymus are significantly important [20].

The fetus entirely depends on the mother's nutrition supply for growth [12, 21]. Maternal nutrition has ‘programming' effect on the development of the immune system in adult life [22, 23]. The hypothesis of maternal nutrition on epigenetic alteration leading to the development of various organs such as thymus and its implication to some adult diseases [24]. The production of methyl groups occurred with the help of various nutrients such as Vitamin B6, folate, selenium and histones (the activation of suppression of gene expression) [24, 25]. In addition, the availability of methyl groups for methylation processes on various locus positions leads to alteration of the gene expression for cell proliferation, differentiation and many other vital processes. Maternal nutrition affects the size and composition of the fetus at birth which in turn reflects the condition of their health in the future [25].

2.1 Evidences from epidemiological and experimental studies

Majority of the experimental studies on fetal programming involves the use of animal models such as rats or sheep. Animal studies provide useful background information on the biochemical processes as well as the consequences of nutrition on fetal programming. Furthermore, experimental evidence of fetal programming in humans is a very challenging task. This is because it is ethically unacceptable to manipulate the diet of pregnant women for a purpose of experimental studies. Despite the study limitation, however, there was a lot of evidence from epidemiological evidence to summarize the effect of maternal nutrition during pre-natal and post-natal on fetal programming of the immune cellular components. One important point that needs to be well understood is that the programming effect is not entirely produced by a single known nutrient. Programming effect is produced as a result of a combination of various types of macronutrients and micronutrients supplied from the mother to the fetus. The effect of these nutrients on the development of various components

of the immune system such as lymphoid organs particularly thymus will also be discussed here.

Inadequate nutrition particularly will have a negative impact on the proliferation of the various cell populations responsible for the immune functions as well as the accumulation of high concentrations of inflammatory components [15, 16, 20]. In the context of immune function, the organ which plays a very important role is the thymus (which is responsible for maturation of the T cells and others). The thymus is important for releasing T-cells which circulates in the body to monitor the presence of harmful antigens [10, 20]. Therefore, the proper development in the thymus during fetal life is important in order to achieve good immune system integrity.

The outcome of prenatal exposures to undernutrition was observed in infants who were born during Dutch Famine from 1944 to 1945 in the Netherlands [26, 27]. In the follow-up, it was found that babies who were exposed to maternal undernutrition during early, mid or late gestation of the pregnancy produced different programming outcomes. This is because based on the observations, a different type of diseases was developed in their adult life. For example, higher incidences of heart diseases and obesity cases for those that have been exposed to famine in earlier gestation periods compared those not exposed to the famine periods [26]. The exposure of famine during the mid-gestation was found to be highly associated with the incidence of respiratory problems [26]. Therefore, this earlier evidence has shown that various period of maternal undernutrition during pregnancy is critical to the development of different types of organs in the growing fetus.

In another epidemiological study, the effect of maternal nutrition during the hungry and harvest period was investigated in Gambian infants study [28]. In this study, the thymus size of the infants was compared between the hungry and harvest periods. It was found that babies born during the hungry period had smaller sized thymus compared to those born during the harvest season. Those born during the hungry season were also found to be more likely to develop infections and have higher mortality. Therefore, this particular study showed that the ‘programming' period of the immune system may occur during early post-natal life. However, there are many other confounding factors need to be considered, such as breast milk quality because it will also affect the immune system development against infections in an infant during early post-natal life [29]. Therefore, maternal undernutrition at any stages of pregnancy has a very large impact on the programming of the immune system. It has been shown that fetal development is highly responsive particularly to the period of undernourishment as observed in the fetal exposure study during the Dutch Famine [26, 27].
However, there are some drawbacks from the epidemiological studies as it may vary in terms of the type of participants (race, ethnicity, regions), type of nutrients exposure and exposures time which may affect the study outcome. Despite the growing evidence, the debate on the relationship between nutrition and immune system development is still ongoing. The evidence of fetal programming from the epidemiological studies can be supported scientifically via experimental studies. Generally, most of the epidemiological evidence showed that the most sensitive period to undernutrition is during post-natal life. However, in experimental studies, it was shown that maternal undernutrition not only sensitive during post-natal life but also during pre-natal life.

One of the significant findings was evidence that maternal nutrition affects the size of the thymus, which is one of the important components of the immune system. The size of the thymus is associated with the strength of the immune system function. The fundamental evidence is that as we get older, the thymic activity tends to decline which is subsequent to a reduction in the immune system competence to fight diseases or infections [30]. A study

attempted to demonstrate the effect on the immune system of male rats exposed to inadequate and adequate maternal nutrition during their fetal life in response to endotoxin during weaning. The outcome of the study showed that a pup, which has been exposed to low maternal nutrition has poor immune response towards endotoxin. This study showed that maternal undernutrition leads to reduced integrity of the immune system. More specific studies were carried out using various types of nutrients. In the following section, various types of nutrients with its impact on certain components of the immune system will be discussed.

2.1.1 Protein-energy malnutrition

One of the most studied nutrients in this area of fetal programming is the protein-energy malnutrition. Protein malnutrition was shown to have detrimental effects on the thymus development. A study has shown that protein-energy malnutrition exposure to pregnant rats led to massive decrease to the thymus and spleen level proliferation in the offspring compared to rats with adequate protein diet [31]. A study has also shown that human patients with protein-energy malnutrition were also found to be more vulnerable to parasites infection in the stomach [32]. These studies showed that protein nourishment from the mother produced a programming effect on thymus development. Similarly, in a sheep study has shown that protein malnutrition reduced the ability of the sheep to fight against nematode infection compared to those exposed with adequate protein [33]. In human, protein-energy malnutrition has been associated with increased risks of various diseases in children such as marasmus or Kwashiorkor which is one of the major health problems in many developing countries [34].

Therefore, based on the studies described above, there is a very strong link between protein-energy malnutrition and the integrity of the immune system. Adequate protein nourishment is required to ensure the ideal environment for the thymus to develop during fetal life in order to survive better after birth. It was also believed that protein helps to increase the proliferation of goblet lymphocytes of the mucosal which plays a very important role in elimination harmful agents such as bacteria or viruses that can cause diseases [35].

2.1.2 Micronutrients: Selenium

Apart from the major macronutrients such as proteins, micronutrients such as selenium also play a very important role in the programming effect of the immune system components. Poor intake of selenium by the female rats that breastfed disrupt the proliferation of natural killer cells and cytotoxic T-cells in the offspring [36]. Selenium has an antioxidant capacity to eliminate ROS in the body [37]. Therefore, adequate intake of selenium may, in turn, produce a preferable programming effect by preventing the action of ROS. Furthermore, as mentioned earlier, free radicals may complicate development during neonatal life [16]. Inadequate supply of selenium to the offspring from the mother's breast milk leads to increased chances of getting infections. This particular study was another example to show that programming of the immune system not only occurs during gestation periods but also takes place during post-natal life of the infant. In the earlier study, selenium may help to reduce the level of ROS, but this does not affect the survival of those babies with lungs oxidative complications (Barlow et al., 2006). However, the latest study in mice has shown that selenium does have protective effects against free radicals in the lungs and liver, as a result of oxidative stress exposures such as smoking [38]. Therefore, the role of selenium in relation to the immune system programming is still not fully understood and calls for more studies in this field.

2.1.3 Alcohol exposure

There are also growing interested in the study of alcohol exposure to fetal development in the uterus [39, 40]. In the US, up to 3% of the babies born shown impact from alcohol exposures during fetal life [41]. Studies in fetal sheep have shown that prenatal exposures during the second trimester have led to a major detrimental effect on the brain development of the fetus [42, 43]. It is reported that children commonly have poor brain functions as a result of the alcohol exposure (Taylor et al, 2006). The affected children were found to have very low scores in their IQ test due to impaired cognitive performance. Due to the affected brain functions, the immune system will be affected as well because these two systems worked closely together. Therefore, disturbances to the brain functions due to alcohol exposures will, in turn, affect the integrity of the immune system as well (due to the hypothalamic-pituitary axis relationship).

2.1.4 Smoking and drug exposures

Several studies have attempted to identify the effect of smoking on the various immune system components. In a study, post-natal rats were injected with nicotine, were found to have reduced T-cells response ability towards exposure to a mutagenic compound called Calvonolin A (Misra, 2006). This experiment proved that smoking will impair the proper development of the immune system which affects one of the important components, the T-cells. Studies have shown that smoking exposures during early post-natal life, affect the programming of the immune system via the impairment of the interferon 1, which makes babies more susceptible to infection and allergic reactions [44]. Exposures to smoking in the womb were also believed to affect the proper function of Natural Killer Cells which may lead to premature birth or spontaneous abortion [45]. It was also observed that maternal smoking has resulted in significantly reduced birth weights of their babies compared to non-smoking mothers [46]. Therefore, due to these observations, pregnant mothers need to abstain from smoking not just for the health of the mother but also affects the susceptibility to infections and allergic reactions of the developing fetus.

Drugs are sometimes administered during pregnancy in case of certain health issues or complications. Drugs may also result in adverse effects on fetal organ development such as kidneys. In particular, it was stated that the use of high doses of a steroidal type of drugs may lead to impairment of brain development as shown in animal studies. Thymus, as part of the brain, therefore may also be affected. Due to the growing concern of drugs towards fetal development, safer treatment alternative is suggested for pregnant women. There is also a need to educate pregnant women on the effects of drugs during pregnancy because as reported in India, only about 30% of the women are aware that drugs may have detrimental effects on pregnancy

3. CONCLUSIONS

Maternal nutrition impacts the development of the immune system including other important biochemical components [31]. In particular, many studies relates to maternal undernutrition with poor thymus development [20, 28]. Thymus development is important because it affects the integrity of the immune system. Poor thymus development increases vulnerability to bacterial infection and allergic reactions development such as asthma [20, 44]. Therefore, adequate nourishment during fetal life is very crucial because, in turn, this will affect immunity against various types of viral and bacterial infection.

Despite the ongoing investigations, to identify the relationship between nutrition and the immune system, many questions remain unanswered. Much of the reports were from epidemiological studies, a lot of confounding factors needed to be considered. For example,

different human subjects have been exposed to different living environment and culture, therefore, their eating habits will differ a lot. Another factor that affects the mother's nutrients intake is also their socio-economic status, which also needed to be considered. In terms of animal studies, there are a lot of similarities in the thymus and spleen development in human and animals such as rats and sheep, which makes them suitable as a comparison to human studies. In general, most of the animal studies focused mainly on a single nutrients effect on fetal programming of the immune system functions. In the real world, organ development requires various types of nutrients. Such single nutrient study may be inconclusive or adequate as evidence. A more effective nutrition based studies, such as a complete controlled diet with adequate large samples or models may be useful to support the evidence. In human epidemiological studies, combined nutrient studies might be difficult to implement, but may be more feasible in animal models such as mice, rats or sheep. Combination of both studies, experimental and epidemiological studies, however, so far has established more understanding on the topic of fetal programming, not just the immune system but also various types of adult diseases such as obesity and hypertension. A future suggestion is to conduct long term epidemiologic studies by involving large sample numbers with stringent records of their nutrition and medicines exposures. Another research that could be done is to observe the effect of maternal overnutrition on the development of the immune system. This is because overfeeding has also proven to show an impact on the programming of certain diseases such as obesity. Therefore, it is possible that overnutrition may also have an impact on the development of the cellular components of the immune system.

Epidemiological and experimental studies have helped to develop a much better understanding on the subject of fetal programming of the immune system. Conclusively, the knowledge on fetal programming not only benefits human but also major interests in the field of agricultural sciences to ensure a healthy breed of animals. By understanding this theory further, health standards can be improved through diet and nutrition intervention at a much early stage via maternal nutrition. This is important particularly in the third world countries where medical intervention may not be easily accessible and expensive.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

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