Turkish Journal of Immunology - Open Access
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Turk J Immunol 2019; 7(1):S108–S118

Role of Cytokines on Fetal Immune Programming

Cenin Bağışıklığının Programlanmasında Sitokinlerin Rolü

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Abstract

Fetal Immune Programming (FIP) is the reset of the normal fetal development due to the changes in the metabolic environment during critical period in the intrauterine life. Barker's hypothesis states that, uterus is the first environment which the developing fetal immune system encounters. Several reports revealed that intrauterine growth retardation is the cause for increased risk of several non-communicable diseases to the fetus. FIP is connected with maternal immune milieu and hence has a significant impact on the fetal immune system. T-lymphocytes (T-cells) are important for coordinating the immune response and can be characterized into subsets according to their phenotypic characteristics as type-1, type-2 and regulatory T-cells. Each T-cell subset has an exclusive functional role, including their capacity to produce pro- and anti-inflammatory cytokines in response to an immune challenge. Type 1 T cells produce, interferon-γ, interleukin-2 and tumour necrosis factor-α, which promote cellular immune responses, whereas type 2 T cells produce IL-4, IL-5, IL-9, IL10 and IL-13 that provide optimal help for humoral immune responses. Although it is known that T cell cytokines produced in response to fetal molecules could have a role in fetal programming and fetal immune outcomes, the molecular mechanisms underlying the regulation of the immune components at various levels are yet to be elucidated. The present review outlines the role of cytokines on fetal immune programming which would aid in understanding alarmingly increasing incidence of diseases associated with immune dysregulation in the fetus.

Keywords: Fetal immune programming, cytokines, interleukin-6, tumour necrosis factor-alpha, interleukin-10

Öz

Cenin bağışıklık sisteminin düzenlenmesi (CBİ), intrauterin hayatta kritik dönem sürecinde metabolik çevredeki değişikliklerden dolayı normal cenin gelişiminin yenilenmesidir. Barker'ın hipotezine göre, uterus, tüm bağışıklık sisteminin ilk geliştiği ortamdır. Bir dizi çalışma, uterus içindeki gelişme yavaşlığının, ceninde bulaşıcı olmayan bazı hastalıkların gelişme olasılığı artırdığını göstermiştir. CBİ, annenin bağışıklık ortamı ile ilişkilidir ve ceninin bağışıklık sistemi üzerinde çok önemli etkisi vardır. T hücreleri, bağışıklık yanıtını düzenlemede etkin hücrelerdir ve tip 1, tip 2 ve düzenleyici T hücreleri olarak ayrı fenotipik gruplara ayrılır. Her bir T hücresi alt grubu yangıyı artıran veya engelleyen sitokinler salgılayarak bağışıklığı etkiler. Tip 1 T hücreleri interferon-γ, interlökin-2 and tümör nekroze edici faktör-α, salınımı ile hücresel bağışıklık yanıtını artırır iken, tip 2 T hücreleri IL-4, IL-5, IL-9, IL10 ve IL-13 salınımı ile sıvısal bağışıklık yanıtını düzenlemede önemli göreve sahiptir. Her ne kadar ceninde üretilen bazı moleküllere yanıt olarak T hücresinden salınan sitokinlerin cenindeki bağışıklık oluşumunda etkili olduğu bilinse de, bu etkinin moleküler mekanizmaları henüz tam olarak ortaya çıkarılamamıştır. Bu derlemede, sitokinlerin ceninin bağışıklığının gelişimindeki rolü ve bu rolün bozulması nedeni ile ortaya çıkan, son yıllarda çok dikkat çekici şekilde artan hastalıklar hakkında açıklayıcı bilgiler bulunmaktadır.

Anahtar Kelimeler: Cenin bağışıklığının düzenlenmesi, sitokinler, interlökin-6, tümörü nekroze eden faktör-α, interlökin-10

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Received: Jan 08, 2019
Accepted: May 22, 2019

https://doi.org/10.25002/tji.2019.1017

Introduction

Fetal programming is observed during the embryonic development, which is a crucial phase as the development of tissue and organs occurs.[1] During implantation, the maternal and fetal milieu is separated from maternal tissues by placental and fetal membranes which interact physiologically as well as metabolically.[2] As the fetus grow, it starts developing its own immune system which is influenced by maternal immune system.[3] According to Barker's, organs structure and function undergo programming during the development of the embryo that acts as the start point for the metabolic and physiological changes in the adulthood.[4] The changes that occur during this phase lead to an irreversible alteration to

the structural as well as metabolic functions of the embryo and may affect the individual in the adult life, leaving them prone to cardiovascular, metabolic and endocrine diseases.[5] Interestingly, maternal cytokine levels (MCP-1, TNF-α, IL-10) during pregnancy correlate with the offspring's cytokine levels at 1 year of age.[6] In gestational environment significant elevation of immune-regulatory cytokines such as IL-10, TGF-β[7] and pro-inflammatory cytokines such as IL-6 and IFN-γ[8] has been observed. This review, focuses on the potential role of various cytokines and their adverse effects leading to fetal immune programming.

Factors Affecting Fetal Immune Programming

Disturbances in the uterine environment result in fetal programming.[9] Factors such as psychosocial stress, neurological disorders, infections, depression, anxiety, oxidative stress, cytokine stress, hormones such as glucocorticoids, serotonin, plays a major role in fetal programming.[10] Various factors that could trigger fetal programming are depicted in Figure 1.

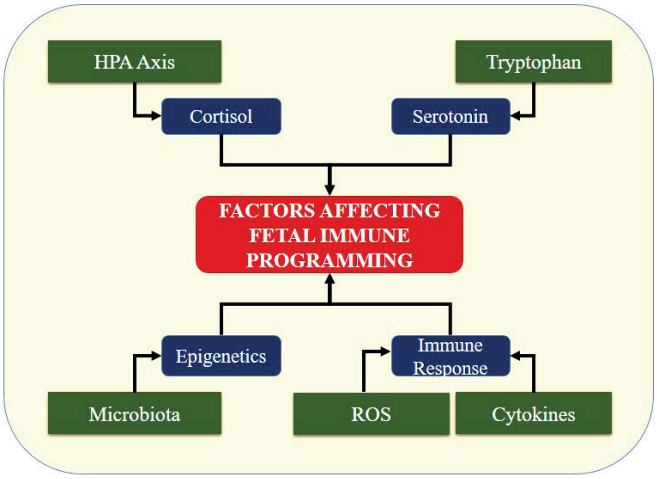

Figure 1. Factors affecting fetal immune programming. Several mechanisms have been reported to be responsible for fetal immune programming. Maternal exposure to exogenous glucocorticoids can lead to permanent modification of hypothalamo-pituitary-adrenal (HPA) function which leads to the modification of behavior, brain and organ morphology, as well as altered regulation of other endocrine systems of the fetus. The placenta is involved in the synthesis of serotonin from maternally derived tryptophan. The genetic and environmental perturbations directly affecting placental tryptophan metabolism may contribute to the fetal immune programming. Exposure to microorganisms is suggested to play a pivotal role in the maturation of the immune system, and thereby improving the protection against infections. Aberrations in the communication between the innate immune system and the gut microbiota might contribute to fetal immune programming. Elevated levels of cytokines and Reactive Oxygen Species (ROS) can traverse the placental barrier and initiate a fetal immune response leading to neuroinflammation.

Glucocorticoids are steroid hormones stimulate maturation of the lungs[11] and also plays a role in the regulation of immunomodulatory effects.[12] They also support development of the brain by initiating terminal maturation of the fetus.[13,14] Sudden elevation in levels of glucocorticoids in blood during late gestation helps in maturation of fetal tissues and organs.[15,16] Studies showed that Hypothalamic-pituitary-adrenal (HPA) axis directs changes in maternal environment during fetal growth and is regulated by adrenal glucocorticoids.[17] Exposure to glucocorticoids during the prenatal stages reduces HPA axis influence in fetus but there is no evidence of increased glucocorticoid levels in postnatal stage.[18] Experiments offspring in the rats showed that prenatal exposure of glucocorticoids permanently elevate basal plasma corticosterone levels in adults.[19,20] This is due to reduction in the levels of glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) levels in hippocampus are constantly reduced leading to diminished HPA axis feedback sensitivity.[21] Increased intracellular levels of glucocorticoid results in hypertension and hyperglycaemia, affective disorders, cognitive deficits, immunosuppression and cardio-metabolic disease.[22]

Prenatal dexamethasone exposure to male offspring resulted in elevated hypothalamic and medullary serotonin but decreased levels of hippocampal serotonin.[23] Antenatal GC stimuli promote development of the serotonin transporter and also results in the elevated activity of the transporter in the brain stem.[24] Experimental evidences on adult rats shown that serotonin helps in upregulation of hippocampal GR.[25] Further thyroid activity has been shown to increase in the neonates.[25,26] Administration of thyroid hormone in the neonates mirrors the effect of GR binding in adults and subsequently results in elevated serotonin levels in the hippocampus.[26,27] It has been suggested that increasing levels of serotonin results in the production of thyroid hormone which increases the hippocampal serotonin followed by GR expression.[26]

Gut microbiome plays a major role in epigenetic changes inside the host which eventually leads to various diseases.[28,29] Evidence suggests that in utero environment can either activate or silence by changing DNA methylation, histone acetylation and methylation and chromatin structure.[30] Studies have shown that unsuitable epigenetic reprogramming results in more developmental syndromes.[31] The mechanism by which epigenetic changes occur due to gut microbiome is still unknown,

but a significant correlation between gut microbiota composition and epigenetic changes has been reported in few human diseases.[32] Bioactive metabolites such as acetate, butyrate, biotin, folate and acetyl-CoA produced by gut microbiome also help in epigenetic modifications.[33] For example, butyrate is one of the essential metabolite to maintain balance in the colon environment, which is regulated by beneficial site specific bacteria such as *Bifidobacterium, Anaerostipes, Eubacterium*and *Roseburia* species.[33] Also, butyrate is a histone deacetylase (HDAC) inhibitor which affects histone modification.[34] Further, butyrate can alter DNA methylation changing the levels of methyl donor and the regulation of folate production.[35] Decreased production and folate bioavailability lead to dysregulation of epigenetic profiles in offspring.[36]

Oxidative stress induces production of free radicals, when nitric oxide and ROS react in cellular compartments resulting in the formation of peroxynitrate, which is a powerful oxidising agent leading to nitrative stress and affects the signal transduction pathways like p38 MAPK.[37] This kinase is activated in response to environmental stress as well as cytokines, its modification can have adverse effects on cellular functions.[38] In complications associated with fetal programming a marked increase in kinase has been observed leading placental oxidative stress and altered expression of eNOS.[39]

The levels of maternal cytokines are important for the pre-implantation embryo development and minor changes in the cytokine levels to the fetal environment would lead to changes in gene expression leads to FIP.[40] Cytokines fluctuations in the genome have been reported due to epigenetic factors.[41, 42] Bain et al., showed that periodontitis in rats results in higher local and systemic concentration of pro-inflammatory cytokines.[43] Changes in the levels of pro-inflammatory cytokine during pregnancy affects fetal birth weight which leads to complications in later life.[44, 45]

Cytokines

Cytokines secreted by the epithelial cells and the uterine wall helps in the development of the blastocyst, protects the blastocysts from various stresses and shields them from apoptosis, as well as promotes its implantation.[46] Insulin-like growth factors (IGF), Interleukin-6 (IL-6), Granulocyte-macrophage colony stimulating factor (GM-CSF) and Interleukin-10 (IL-10) have shown to be embryotrophic factors.[47, 48] On the other hand, there are cytokines that contribute to the cell stress and bring about inhibitory effects on the embryo, elucidating the destructive capabilities of the maternally-derived agents.[49] Pro-inflammatory cytokines secreted by the uterine cells exert negative effects on the viability and development of the fetus.[50] Tumour Necrosis Factor alpha (TNF-α) and Interferon Gamma (IFN-γ) are among some of the cytokines that suppress the development of the embryo, induce cell death at high concentrations.[50-52]

Tumour Necrosis Factor alpha (TNF-α)

TNF-α is a pleiotropic cytokines involved in systemic inflammation and is also associated with apoptosis-inducing activity.[53] It is initially synthesised as a 26kDa cell surface precursor and is later cleaved to form a 17kDa protein.[54, 55] The primary source of TNF-alpha (TNF-α) has been identified as the uterine natural killer cells and uterine macrophages in the reproductive tract and oviductal epithelial cells in humans.[56] TNF-α is associated to its receptors such as TNFR1 or TNFR2, which promotes nuclear factor kappa B (NFκB) transcription factors translocation into the nucleus, which triggers inflammatory mediators (IL-6 and IL-1A) transcription, based on certain factors that determine the cell survival or cell death of the cells.[53] TNF-α has been found in the oviduct and uterus all through the pre-implantation phase in mice and humans.[56, 57] Pre-implantation embryo of mouse expresses the receptor TNFR1 and can show a response to elevated levels of TNF-α.[51, 58, 59] TNF-α exposure resulted in the increase in the apoptotic activity in blastomeres in species like mouse[60, 61] and inner cell mass of rat as demonstrated by *in vitro* study.[51] The mouse blastocysts culture when treated with high concentration of TNF-α showed an increase in cell apoptosis and also results in the retarded development in a time and dose-dependent manner.[61] The administration of TNF-α to the mice in the early pregnancy period was found to reduce litter size and impair implantation.[62] Bovine embryos after fertilization when treated with TNF-α showed reduced development of blastocyst and accelerated cell death due to the caspase-9 mediated apoptosis.[63, 64] TNF-α is shown to reduce the effectiveness towards other cytokines.[65] Direct effects of TNF-α on embryo or indirect effects via immune response suggest that the contribution of TNF-α exposure during the pre-implantation period, impairs implantation and reduces the litter size in rats and mice.[66] Embryotrophic factors were found to have an influence on the TNF-α

exposure; co-culture of TNF-α with the stem cell factor, IGF-1, IGF-2 have been found to act as protective agents against the inhibitory effects of TNF-α.[67, 68]

Glucose is the vital energy source for the fetus and placenta.[69] Glucose transporter 1 (GLUT1), a major placental glucose transporter in humans, is the only isoform which is shown more in early pregnancy[70] and mainly found in syncytiotrophoblast (SCTB), along with cytotrophoblasts and fetal endothelial cells.[71] Low oxygen usage in females is observed when TNF-α acts on SCTB, but this is not observed in male counterparts.[72, 73] Amino acids have a major role in the development of fetal tissue and are required for the formation of nucleic acids and proteins in the fetus and placenta.[74] The amino acid level is more in the circulation in fetus than in the circulation in mother[75] indicating active transport of amino acids through SCTB .[76] Two systems are involved in amino acid transport systems.[76] System A is a sodium-dependent accumulative transport system which assists the progress of the transport of small neutral amino acids (SNAT) like alanine into the cell and its activity is seen in both SCTB and microvillous plasma membrane (MVM), but more revealed in the latter.[77] System A activity is accelerated by insulin, leptin, IGF-1, TNF-α and IL-6.[78-80] *In-vitro* supplementation of TNF-α to trophoblast cells resulted in the regulation of amino acid uptake and transport by MAPK dependent mechanism.[79]

Interferon gamma (IFN-γ)

IFN-γ is a pro-inflammatory cytokine, secreted by the uterine cells during the pre-implantation phase. IFN-γ plays a crucial role in various cellular processes, such as activation of the innate, adaptive responses, inhibition of cell proliferation and induction of apoptosis.[81] IFN-γ is essential for angiogenesis at implantation sites, remodelling of endometrial vasculature and maintenance of the maternal component of the placenta in rodent pregnancies[82], but increased levels have resulted in retardation in growth and development of the embryo. Also, the presence of IFN-γ has been reported to inhibit the GM-CSF secretion that assists in the growth and differentiation of the blastocyst in mice and humans.[83] IFN-γ receptor is expressed in mouse oocytes and pre-implantation embryo.[84] Earlier experiments have demonstrated that IFN-γ is inhibitory to the culture of mouse embryo.[85, 86] A study involving cattle showed that the levels of the IFN-γ were elevated in the inner epithelial cells of the uterus of cattle with failed pregnancy or delayed development of embryo.[87]

Interleukin-6 (IL-6)

IL-6 is a 26kDa cytokine having multiple functions such as regulation of different events in the immune system and has dual role of action such as pro-inflammatory and anti-inflammatory.[88,89] It also has a vital role in acute and chronic inflammation as well as autoimmunity.[90] IL-6 is a protein that binds to Interleukin-6 receptor (IL-6R) and glycoprotein-130.[91,92] IL-6 is secreted by the endometrial epithelium and reported to have a positive influence on the blastocyst development and rate of implantation.[93] In recent studies using mice model, addition of IL-6 to the culture medium showed an increase in the number of blastocyst and a significant reduction in the apoptotic activity.[94] Also the stimulation of the ovary reduced the IL-6 secretion in the mice and human pre-implantation blastocyst.[95] Levels of IL-6 were reported to be elevated in women with recurrent abortions.[96] In response to the administration of lipopolysaccharide, the serum, uterine and conceptus cells showed elevated levels of TNF-α and IL-6 in the IL-10 -/- mice as compared to the wild type, this resulted in fetal loss.[97] Thus, a relationship between pro-inflammatory cytokines and fetal loss exists.[98]

Interleukin-10 (IL-10)

IL-10 is an anti-inflammatory cytokine secreted by the leukocytes and somatic cells.[99] It is primarily produced by the Th2 cells and involved in a negative feedback loop to reduce inflammation.[100] IL-10 ceases the inflammatory responses and limits the inflammation induced pathology by inhibiting synthesis of TNF-α and other pro-inflammatory cytokines.[101] IL-10 also inhibits proliferation of Th1 cells and thus the cytokine synthesis. It has been reported to modulate the resistance to the inflammatory stimuli by down regulating pro-inflammatory cytokine levels in the uterus.[98] In the milieu of the reproductive tract, a balance of the cytokine is required for the proper development of the embryo. Increase in the expression of pro-inflammatory cytokines results in abortion of the fetus.[102] Whereas, elevated levels of anti-inflammatory cytokines promotes implantation. Thus, the balance in the anti-inflammatory IL-10 and pro-inflammatory TNF-α appears to regulate the immune response in gestation period.[103] IL-10 has been reported to suppress the endometrial inflammatory responses during the pregnancy. In the experiments conducted, it has been reported that the IL-10-/- (knockout) mice were more susceptible to fetal loss and other complications during the pregnancy and also exhibited a different placental structure and function as compared to the wild type mice.[98, 104]

Transforming Growth Factor – beta (TGF-β)

Transforming growth factor beta (TGF-β) is a multifunctional cytokine that belongs to the TGF-β superfamily. TGF-β family consists of three isoforms, namely TGF-β1, TGF-β2, and TGF-β3 along with their high affinity receptors, TGF-β-RI and TGF-β-RII.[105] These factors have been shown to act as regulators of the ovarian function and hence play an important role in the mammalian fertility.[106, 107] They are also associated with the remodelling of male and female reproductive tissues, promotion of the pre and post implantation development of the embryo and mediation of the trophoblast invasion into the endometrium during implantation.[105, 108, 109] Recent studies have shown that TGF-β1 is expressed in the bovine oviduct[110] and has shown to have higher transcriptional levels during the postovulatory stage.[111] *In vitro* studies have reported that TGF-β in combination with other growth factors and cytokines or alone assists in the development of the bovine embryo.[112-114] Further transcriptomic data has demonstrated the changes in the dynamics of the TGF-β signalling pathway in various species including humans.[115, 116]

It has been observed that TGF-β upregulates IGF (Insulin-like Growth Factor).[117] In knockout studies, it was observed that the IGF-1, IGF-2 or IGF-1R decreased the birth weight resulting in the neonatal lethality.[118] IGF1 knockout mice also showed infertility and retardation in growth.[119] The study using the transgenic mice carrying in an IGF1 null background demonstrated that IGF1 plays a vital role in sustaining the postnatal development and reproductive function in both sexes.[120] On the other hand, it was reported that IGF2 acts as modulator to the fetal and placental growth.[121] *In vitro* studies, wherein the addition of IGF1 to the culture medium, showed an improvement in the cleavage rate of the bovine oocytes.[122]

In human developmental embryo cells, IGF-1 increases GLUT1 expression and stimulates glucose and amino acid uptake.[123] Report indicate that the expression of GLUT and the embryo translocation[124] is regulated by IGF receptors in granulosa cells human and mouse oocytes[125], also by insulin and IGF-1. In experimental study oocytes obtained from IGF-1-/- (knockout) mice showed a reduction in the expression of GLUT1 which is renewed with exogenous IGF-1. Also it was observed that estradiol treatment increased GLUT1 mRNA in wild type and IGF-/- oocytes which indicates steroid management of GLUT in the oocytes.[126] The reduction in the levels of IGF-1 in the mother has been related to the retarded growth of the baby.

Granulocyte-macrophage colony stimulating factor (GM-CSF):

GM-CSF also known as the colony stimulating factor 2 (CSF2) is a monomeric glycoprotein of 23 kDa a product of activated T-lymphocytes, macrophages and natural killer cells responsible for the regulation of activation, proliferation and differentiation of the myeloid haematopoietic cells.[127] GM-CSF functions as a cytokine with its receptors consisting of a GM-CSF specific alpha subunit (GM-Rα) and beta subunit.[128] GM-CSF shows a low affinity for the alpha subunit and high affinity for beta subunit. The beta subunit does not directly bind to the GM-CSF, but rather forms a complex with the alpha subunit and this alpha-beta subunit complex binds to GM-CSF.[129, 130] During the pre-implantation period, GM-CSF is secreted by the epithelial cells lining the uterus.[131,132] Exposure to the seminal fluid in the uterus at the time of coitus upregulates the expression of GM-CSF mRNA.[133] Of the two subunits present, human embryo express the alpha subunit is expressed in most of the pre-implantation embryo developmental stages, which indicates that the GM-CSF was secreted in the paracrine manner by the mother from the uterine epithelial cells during the pre-implantation of the embryo.[134] Mice having null mutation in the CSF2 gene, produced 25% smaller litter size with impaired blastocyst development, while CSF2-/- embryos were found to have fewer cells in the inner cell mass and the trophoectoderm.[134] *In vitro* experiments demonstrated that the GM-CSF acts as an embrytrophic factor which affects the inner cell mass of the mouse and human embryo that promotes the survival of the blastocyst. The most apparent effect of GM-CSF was the increase in the total number of blastomeres.[135, 134] In humans, GM-CSF triggered a rise in the percentage of embryo reaching the blastocyst stage along with the increase in the pace of development and implantation.[136] Studies have shown a significant improvement in clinical pregnancy and the survival rate in human assisted reproductive technology programs when GM-CSF was used as a culture medium supplement.[137]

Cytokines offer important paracrine, autocrine and systemic signals for immune cells.[138] The chapter outline the role of the cytokines in fetal programming. In order to understand this, the evidence for the effect of cytokine on leptin, amino

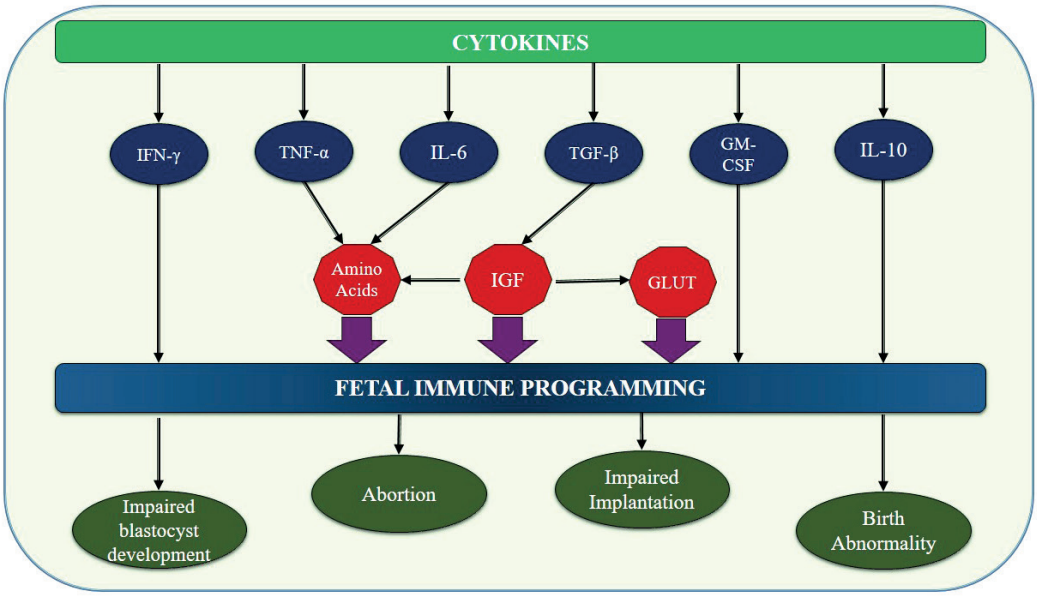

Figure 2. Effect of cytokines in fetal immune programming. Cytokines play an important role in stimulating or suppressing inflammation as well as also being closely linked to oxidative stress. Cytokines can pass through the placenta and enter fetal circulation where they can then directly interact with cells of the fetal immune system. There is a possible role for cytokines on glucose transport (GLUT) and aminoacid metabolism by direct or indirect co-relation with the cytokines such as Interferon-gamma (IFN-γ), Tumor necrosis factor alpha (TNF-α), Interleukin 6 (IL-6), Transforming growth factor β (TGF-β), Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Interleukin 10 (IL-10) which results in changes in the developing fetal immune system. TGF-β family signaling integrates with Insulin like growth factor 1 (IGF-1), a major regulator of fetal growth and development of most organs especially the central nervous system and also involved in the regulation of protein synthesis via amino acids and glucose uptake and mobilization via GLUT.

acid metabolism and glucose transporter programming in fetal programming is discussed (Figure 2).

Conclusion

Over the past decade, compelling epidemiological studies highlighted a clear association between low birth weight and an increased risk of a subsequent occurrence of diseases such as hypertension, type II diabetes, metabolic syndrome, insulin resistance, and obesity. However there is insufficient knowledge about the mechanism and tools to identify the factors underlying the susceptibility of fetus to certain diseases. Hence research on programming in the intrauterine environment influences the possibility of the fetus is therefore required. Cytokines are crucial factors of healthy pregnancy, for their role to significantly modify cellular function, migration, cell-cell communication, proliferation, and gene expression. However, when inappropriately expressed, these possibly act as teratogens and disrupt offspring through fetal programming mechanisms. Understanding the biological processes of cytokines on preimplantation development and to influence the phenotype of offspring will offer supportive tools in the management of fertility and protecting reproductive health. Further, studying the role of cytokines in embryo loss and fetal programming will not only ensure optimal fetal development, but will also help in developing therapeutic strategies for reducing the risk of chronic diseases in adults.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: Study design/planning: KMR; Data collection/entry: NUD, MSN,AS, JR; Data analysis/statistics: DU; Data interpretation: DU, KMR; Manuscript preparation: NUD, MSA, AS, JR; Literature search/analysis: NUD, MSN,AS, JR.

Acknowledgment: We thank Ms. Teena Rajan (Ph.D scholar) and Mr.Karan Naresh Amin (Ph.D scholar) for their valuable help.

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