CPQ Women and Child Health (2019) 1:4
Review Article

An Update on Cytokines in Pregnancy: Implications on Mothers and Newborns

Obeagu Emmanuel Ifeanyi[1*] & Obeagu Getrude Uzoma[2]

[1]*Department of Medical Laboratory Science, Imo State University, Owerri, Nigeria*

[2]*Department of Nursing Science, Ebonyi State University, Abakaliki, Nigeria*

[*]**Correspondence to:** Obeagu Emmanuel Ifeanyi, Department of Medical Laboratory Science, Imo State University, Owerri, Nigeria.

Copyright

Received: 18 March 2019
Published: 20 March 2019

Keywords: *Cytokines; Pregnancy; Implications on Mothers and Newborns*

Abstract

Cytokines are a broad and loose category of small proteins secreted by cells of the immune system that act as chemical messengers. Cytokines are produced by a broad range of cells; a given cytokine may be produced by more than one type of cell. Maternal and, thereby, fetal cytokine pattern can be modulated by exogenous or endogenous exposures during pregnancy. It is well established that pregnancy-related dysfunctions such as preeclampsia or maternal stress are able to modulate maternal cytokines. Pregnancy presents differently and causes so many changes in the mothers and the babies. Some of the cytokines are growth hormones that are needed in differentiations of many cells. This paper is written to update the world on cytokines in pregnancy.

Cytokines

Cytokines are a broad and loose category of small proteins (~5-20 kDa) secreted by cells of the immune system that act as chemical messengers. Their release has an effect on the behavior of cells around them. It can be said that cytokines are involved in autocrine signalling, paracrine signalling and endocrine signalling as immunomodulating agents. Their definite distinction from hormones is still part of ongoing research.

Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell.

They act through receptors, and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways [1].

Impact of Pregnancy on Cytokines

Up to now, maternal allergic health outcomes represent the most reliable markers for later allergy of neonates, reflecting the strong genetic background and the respective maternal immunological environment in which the concept is embedded. Under the sign of the worldwide atopic epidemic with growing incidences even in non risk families, the challenge arises how to predict the risk of allergy development in these newborns.

As there is growing evidence that the course toward tolerance or allergy is set already in utero, maternal immune responses during pregnancy got in focus of research [2]. Based on the close relationship between maternal immune responses and neonatal maturation of the immune system, maternal and neonatal cytokines profiles were suggested as candidates for allergy prediction. A conclusive marker of T-cell maturation and differentiation represents the cytokinesIL-4, IFN-c, and IL-10 reflecting the balance between key T-cell subsets. Maternal cytokine profiles might provide an elegant insight into the conditions that shape the maturation of the fetal immune system during pregnancy. However, their impact of maternal cytokines on the maturation of the fetal immune system and thereby on the development of disease phenotypes is currently discussed contradictory. While some studies present associations between maternal inflammatory (IL-6, IL-8, IL-10 or TNF-a) and Th1/Th2 (IL-4, IL-5, IL-13, IFN-c or IL-10) cytokines during pregnancy and the later risk of allergic disease, others do not suggest such influences [3,4]. The inconsistent picture is not surprising as the basic mechanisms that shape the prenatal cytokine network and its relevance for immunological programming in the fetus are not even fully understood. According to the Th2 bias paradigm, initially postulated by Wegmann *et al.* (1993) [5], the maturing immune system of the fetus is mainly exposed to a Th2-dominated uterine milieu that protects the allograft from abortion and promoting survival of the fetus. As the concept of an allograft protecting compartment arose, this hypothesis was revised by three major lines of investigation:

First, studies on the course of pregnancy demonstrated that maternal cytokine production during pregnancy is rather a dynamic than a static process adapted to the requirements of the different stages of gestation. The implantation of the embryo, the development of the placenta, the maintenance and development of the fetus and, finally, the initiation of the partition and term of birth implicate a modulation of this milieu. A study conducted by Aris *et al.* (2008) [6] clearly demonstrates that levels of circulating maternal Th1/Th2 cytokines change within the progress of pregnancy indicated by increasing and decreasing IFN-c and IL-6 production. Maternal peripheral cytokine profiles during implantation and initiation of gestation seemed to

be characterized by a low Th2 bias that increases within the second trimester. In the third trimester, maternal cytokine expression is characterized by the upcoming process of birth. To promote the initiation of labor and the detachment of the placenta, TNF-a is increasingly released by the placental cells [6].

Second, cytokine profiles in the peripheral system of the pregnant mother may neither reflect the cytokine network at the fetal-maternal interface nor the placental or fetal cytokine milieu (Dealry *et al.,* 2000).

Third, maternal and, thereby, fetal cytokine pattern can be modulated by exogenous or endogenous exposures during pregnancy. It is well established that pregnancy-related dysfunctions such as preeclampsia or maternal stress are able to modulate maternal cytokines (Wood *et al.,* 2011). The health status of the mother especially of those suffering from allergies may favor a Th2-skewed cytokine milieu in the mother's circulation [4].

Exogenous environmental exposures for example 'season of pregnancy' may also modify cytokine expression in the mother [7]. Recently, we could demonstrate that exposures from allergo-protective settings are capable to influence the level of cytokines produced during the perinatal phase. Although we have not investigated maternal blood samples, we could clearly describe different cytokine patterns in cord blood from newborns born to farmer and non farmer families. We observed a significantly higher production of Th1 cytokines and TNF-a in cord blood of children born to mothers that were exposed to environmental and lifestyle factors that are characterized by a diverse microbial world [8].

In sum, the formation of maternal cytokines during pregnancy is influenced by factors closely related to changing functional conditions during pregnancy and modulated by exogenous and endogenous maternal exposures. These exposures might modulate the direction of maternal cytokine expression in the course of pregnancy and thereby act as stimuli for the developing fetal immune repertoire.

A study by Herberth *et al.* [9] published in this issue added new evidence to this field of research. Within the Lifestyle and Environmental factors and their Influence on Newborns Allergy risk (LINA) study, the group examined the influence of maternal immune responses in pregnancy on children's immune competence and the development of pediatric atopic dermatitis (AD) in the first year of life. The unselected study population of this prospective birth cohort study allowed new insights into potential maternal effects on the development of the early immune system and the resulting risks for allergic diseases in the offspring. The analyses of samples from mother and child pairs indeed confirmed astrong correlation between maternal and neonatal inflammatory cytokines production during pregnancy but without showing any associations with disease phenotypes of atopy in the offspring at the age of one year. Compared with maternal cytokines levels measured postpartum, maternal Th1/Th2cytokines during pregnancy were significantly lower expressed. In line with Halonen *et al.* (2009) [10], the group observed a bias in favor of Th1 responses at week 34 of gestation.

In contrast, the analyses of cord blood samples displayeda strong Th1/Th2 bias at birth supporting a Th2milieu in utero. Although elevated maternal IL-10, TNFa, and IFN-c/IL-10 production was associated with a high level of children's corresponding cytokine production at one year, only maternal production of TNFa was predictive for a protection against inhalant allergens. These finding are in line with our data from the PASTURE study as we found aninverse association between elevated levels TNFa production in cord blood

and IgE to inhalant allergens. Nevertheless, on the risk site, the LINA study team clearly showed that AD in the child was only predicted by the disease in the mother.

As expected, maternal AD was found to be the strongest predictor for AD in the progeny in the LINA study. Among allergic health conditions, AD seems to have the strongest genetic background codetermined by susceptibility loci responsible for the functional loss of filaggrin, a component that is responsible for the integrity of epithelial barrier [11]. Currently, it seems that allergic disease of the mother is still the best predictor for child's illness. But this picture may change when allergic health outcomes will appear within the LINA study, which are predominantly determined by immune parameters.

Conclusion

Pregnancy is associate with many physiological, haematological and biochemical changes which are attributable to changes in cytokines levels which are critical to the stages of the pregnancy. Cytokines should be monitored because over expression can be dangerous to both mother and child as seen in pre elampsia, eclampsia and allergy.

Bibliography

1. Horst, I. (2013). *Cytokines in Cytokines & Cells Online Pathfinder Encyclopedia*, Version 4th Edition.

2. Ege, M. J., Bieli, C., Frei, R., van Strien, R. T., Riedler, J., *et al.* (2006). Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. *J Allergy Clin Immunol., 117*(4), 817-823.

3. Breckler, L. A., Hale, J., Jung, W., Westcott, L., Dunstan, J. A. & Thornton, C. A. (2010). Modulation of *in vivo* and *in vitro* cytokine production over the course of pregnancy in allergic and non-allergic mothers. *Pediatr Allergy Immunol., 21*(1 Pt 1), 14-21.

4. Kim, J. H., Kim, K., Woo, H. Y. & Shim, J. Y. (2008). Maternal cytokine production during pregnancy and the development of childhood wheezing and allergic disease in offspring three years of age. *Journal of Asthma, 45*(10), 948-952.

5. Wegmann, T. G., Lin, H., Guilbert, L. & Mosmann, T. R. (1993). Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon. *Immunol Today, 14*(7), 353-356.

6. Aris, A., Lambert, F., Bessette, P. & Moutquin, J. (2008). Maternal circulating interferon-gamma and interleukin-6 as biomarkers of Th1/Th2 immune status throughout pregnancy. *Journal Obstet Gynaecol Res., 34*(1), 7-11.

7. Sullivan Dillie, K. T., Tisler, C. J., Dasilva, D. F., Pappas, T. E., Roberg, K. A., *et al.* (2008). The influence of processing factors and non-atopy-related maternal and neonate characteristics on yield and cytokine responses of cord blood mononuclear cells. *Clin Exp Allergy., 38*(2), 298-304.

8. Pfefferle, P. I., Buchele, G., Blumer, N., Roponen, M., Ege, M. J. & Krauss-Etschmann, S. (2010). Cord blood cytokines are modulated by maternal farming activities and consumption of farm dairy products during pregnancy. the PASTURE Study. *J Allergy Clin Immunol., 125*(1), 108-115.

9. Herberth, G., Hinz, D., Roder, S., Schlink, U., Sack, U. & Diez, U. (2011). Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk. *Allergy, 66*(8), 1065-1074.

10. Halonen, M., Lohman, I. C., Stern, D. A., Spangenberg, A., Anderson, D. & Mobley, S. (2009). Th1/Th2 patterns and balance in cytokine production in the parents and infants of a large birth cohort. *J Immunol., 182*(5), 3285-3293.

11. Bussmann, C., Weidinger, S. & Novak, N. (2011). Genetics of atopic dermatitis. *J Dtsch Dermatol Ges., 9*(9), 670-676.