

Editorial

Immune response in pregnancy: An evolutionary challenge against external and internal stimuli

La respuesta inmunitaria en el embarazo: Un desafío evolutivo contra los estímulos externos e internos

Raquel Cariño-Cortés ^{a*}

Several studies from the 1990s found that adverse effects on the fetal environment, such as poor maternal nutrition, can lead to an increased risk of developing chronic diseases in adulthood.

These findings led to the fetal origins of disease hypothesis, commonly known as the Barker hypothesis, which proposes that exposures to insults during critical or sensitive windows of development can permanently reprogram physiological responses, thereby giving rise to metabolic and hormonal diseases and disorders later in life.^{1,2}

Pregnancy remains one of the most vulnerable periods in terms of morbidity and mortality, certainly for the fetus, but also for the mother. According to the INEGI, in 2020 there were 22,637 fetal deaths, which corresponds to a national rate of 6.7 per 10,000 women of childbearing age. 82.9% of fetal deaths occurred before delivery, 15.6% during delivery, and in 1.5% of cases was not specified.³

The main complications, which cause 75% of maternal deaths, are: severe bleeding (mostly after childbirth); infections (usually after childbirth); gestational hypertension (preeclampsia and eclampsia); childbirth complications; unsafe abortions (performed clandestinely, in unsuitable conditions, and by untrained personnel).⁴

Interactions between the product of conception and the mother are bidirectional: the fetoplacental tissues need nutrition and a suitable environment under homeostatic conditions, while the mother, influenced by placental factors, adapts her metabolism and immune system to ensure tolerance, which include embryonic and fetal, placental and maternal elements.⁵ At the maternal-fetal interface, the placenta contains cells of the immune system and mediators, such as uterine NK cells (uNK, 70%), macrophages (20%), T cells (including CD4+, CD8+, $\gamma\delta$ T cells, and regulatory T cells) (10 %), dendritic cells, and few B cells. The numbers of these cells and the roles they play vary at different stages of pregnancy. It has been suggested that there may be several local and systemic modifications related to the protection of the developing fetus against attack by the maternal immune system, mainly the expression of unique human leukocyte antigens (HLA) by trophoblasts, the influence of female sex hormones and the bias of cytokines.⁶

As soon as the embryo makes contact with the maternal endometrium, trophoblast cells fuse with the attachment site, forming a syncytium called a syncytiotrophoblast.⁷ This tissue and the cytotrophoblast do not express major histocompatibility complex (MHC) class I or class II molecules. In contrast, the extravillous cytotrophoblast does express non-classical MHC molecules (HLA-G or HLA-E), which inhibit the activation of uNK cells, favoring immunological tolerance.⁸

During the first trimester, uNK cells represent up to 50–70% of decidua lymphocytes. Differently from peripheral-blood NK, these are poorly cytolytic, and they release cytokines/chemokines that induce trophoblast invasion, tissue remodeling, embryonic development, and placentation. NK cells can also shift to a cytotoxic identity and carry out immune defense if infected *in utero* by pathogens. At late gestation, premature activation of NK cells can lead to a breakdown of tolerance of the maternal–fetal interface and, subsequently, can result in preterm birth.⁹ HLA-G interacts with receptors ILT2 and KIR2DL4 on macrophages and NK cells to enhance the production of proangiogenic cytokines and enhance trophoblast integrity, invasion of decidua, thereby promoting spiral artery remodeling. In addition, HLA-G binds to ILT2, ILT4, and KIR2DL4 on NK cells, T cells and macrophages, inhibits the

^a Academic Area of Medicine, Institute of Health Sciences, Universidad Autónoma del Estado de Hidalgo, <https://orcid.org/0000-0003-4776-3534>, Email: raquelcortesc@gmail.com



cytotoxicity of NK cells and CD8+ T cells, and causes an increase in the percentage of Treg cells in the population, and thereby contributes to immune tolerance.

The abnormal expression and polymorphisms of HLA-G are related to adverse pregnancy outcomes such as preeclampsia (PE) and recurrent spontaneous abortion (RSA).¹⁰

Cytokine bias is associated with the predominance of Th2-type immunity, while Th1-type responses are considered potentially dangerous for the continuation of the pregnancy.¹¹ Sex hormones have profound effects on the immune system and play a critical role in shaping Th cell immunity throughout stages of pregnancy. Androgens are considered to promote anti-inflammatory responses whereas estrogens can exhibit both pro- and anti-inflammatory roles depending on the relative expression of estrogen receptor isoforms.¹² However, significantly high doses of estrogens such as those observed in pregnancy typically suppress immune responses. Pregnancy levels of estradiol also influence CD4+ T cell polarization through enhanced expression of Th2 associated (GATA3, IL-4) and Treg associated genes (Foxp3, PD-1, IL-10, and TGF- β) while suppressing the expression of Th1 associated (T-bet, IL-2, TNF- α , IFN- γ) and Th17 associated genes (ROR- γ t, IL-6, IL-17, IL-23).^{12,13} During pregnancy progesterone induces anti-inflammatory responses and promotes tolerance through the selectively inducing differentiation of naive CD4 T cells into Tregs, while suppressing their differentiation into inflammatory Th17 cells, potentially through suppression of the IL-6 receptor expression, and a systemic decline in its concentration prior to the onset of labor in most animal models.¹⁴ In conclusion, both allogeneic and hormonal stimulation are responsible for a harmonious regulation of the immune system leading to a successful pregnancy.

References

- [1] Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*. 1991;303(6809):1019–22.
- [2] Mandy M, Nyirenda M. Developmental Origins of Health and Disease: the relevance to developing nations. *Int. Health*. 2018;10(2):66–70.
- [3] Instituto Nacional de Estadística y Geografía (INEGI). Censo de Población y Vivienda 2020 [Internet]. Org.mx. Disponible en: <https://www.inegi.org.mx/programas/ccpv/2020/>
- [4] World Health Organisation. Maternal Mortality. [Accessed on 21th October 2022 at who.int: <https://www.who.int/news-room/fact-sheets/detail/maternal-mortality>].
- [5] Bowman CE, Arany Z, Wolfgang MJ. Regulation of maternal–fetal metabolic communication. *Cell Mol. Life Sci*. 2021;78(4):1455–86.
- [6] Li X, Zhou J, Fang M, Yu B. Pregnancy immune tolerance at the maternal-fetal interface. *Int. Rev. Immunol*. 2020;39(6):247–63.
- [7] Chen S-J, Liu Y-L, Sytwu H-K. Immunologic regulation in pregnancy: From mechanism to therapeutic strategy for immunomodulation. *Clin. Dev. Immunol*. 2012; 2012:1–10.
- [8] Zhuang B, Shang J, Yao Y. HLA-G: An important mediator of maternal-fetal immune-tolerance. *Front. Immunol*. 2021; 12:744324.
- [9] Zhang X, Wei H. Role of decidual natural killer cells in human pregnancy and related pregnancy complications. *Front. Immunol*. 2021; 12:728291.
- [10] Xu X, Zhou Y, Wei H. Roles of HLA-G in the maternal-fetal immune microenvironment. *Front. Immunol*. 2020;11:592010.
- [11] Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today*. 1993;14(7):353–6.
- [12] Graham JJ, Longhi MS, Heneghan MA. T helper cell immunity in pregnancy and influence on autoimmune disease progression. *J. Autoimmun*. 2021;121(102651):102651.
- [13] Polese B, Grیدهlet V, Araklioti E, Martens H, Perrier d'Hauterive S, Geenen V. The endocrine milieu and CD4 T-lymphocyte polarization during pregnancy. *Front Endocrinol (Lausanne)*. 2014;5:106
- [14] Shah NM, Lai PF, Imami N, Johnson MR. Progesterone-related immune modulation of pregnancy and labor. *Front Endocrinol (Lausanne)*. 2019; 10:198.