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The Relationship between Endocrine System and Immune System In The Pregnancy and Lactation in the Female Human

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Abstract
Pregnancy is an active and highly regulated immunological process: for 9 months, the mother's body must bear a fetus of which half of the genetic capital is that of its father. It is a state of semi-allogeneic transplant. It should therefore be recognized as a foreign body by the maternal immune system, but this is not the case: many changes take place so that it can tolerate the fetus, and that it is protected during the 9 months of gestation. The placenta and the maternal immune system are closely linked to create a tolerant environment for the unborn child. The backbone of all of these changes is the trophoblast, which is the main cell that makes up the placenta. The innate immune system is at the forefront: Natural Killer (NK) cells, macrophages, and dendritic cells. Sucking leads to stimulation of the areolo-mammary complex, this in turn leads to action of the hypothalamo-hypophyseal complex. Under the influence of prolactin production, lactocytes ensure the synthesis and storage of milk. Under the effect of the secretion of oxytocin, the myoepithelial cells surrounding the lactocytes contract and allow the milk to be ejected outwards, via the milk ducts.

Keywords*: endocrine, immune, pregnancy, lactation, female*

I. Introduction

The phenomenon of decidualization, which corresponds to numerous structural changes in the endometrium, will then be set up. It is partly initiated by the increase in the level of progesterone at the level of the feto-maternal interface. All the stages of implantation are orchestrated by phenomena of apoptosis of the surrounding cells (endometrial cells, endothelial cells, etc.) which are crucial for the proper establishment of a tolerant environment for the fetus. The feto-maternal interface is made up of 2 distinct parts: the placental part (fetal) and the endometrial / decidual and myometrial part (maternal). Deciduous tissues (maternal tissues in contact with the fetoplacental unit) have an important nutritional and **endocrine role** during pregnancy. (Morelli, 2015) They produce cytokines, help implantation and embryonic and fetal growth, and help maintain pregnancy. The placental part, for its part, is made up of a cellular contingent that is at the heart of all exchanges and interactions at the level of the feto-maternal interface: the trophoblasts. (Csaba, 2014)

II. Literature review

1. The endocrine system and immune system in the pregnant woman

A. The endocrine system in the pregnant woman

- **The pituitary gland**

*Anatomical changes***:** During pregnancy, there are significant variations in pituitary cells. The pituitary gland goes from 0.4 to 0.8 g at the end of pregnancy. After lactation finished, the pituitary gland will regain nearly its size. (Karaca, 2009)

Functional modifications: Plasma Thyroid Stimulating Hormone (TSH) decreases when there is a surge in placental Human Chorionic Gonadotropin (HCG) and then increases while remaining normal. The serum prolactin level gradually rises to be 5 to 10 times higher at the end of pregnancy. The more its production increases, the more those of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (which are low during pregnancy) decrease. (Harold, 2011) Oxytocin increases during pregnancy, reaching 165 µg / ml. Its role in the physiological induction of labor is discussed, its secretion during labor is periodic and brief, and the frequency of peaks increases as labor progresses. Oxytocin is thought to have a regulatory role, but not an inducer in the induction of labor. The level of circulating vasopressin does not vary but there is a lowering of the osmotic threshold of vasopressin secretion, resulting in a possible increase in water retention at the end of pregnancy. (Laway, 2013)

- **The thyroid gland**

There is a possibility of maternal iodine deficiency goiter because: (a) There is an increase in glomerular filtration and renal iodine excretion, (b) There is loss of iodine from the fetal-placental complex at the end of pregnancy. Enlarged thyroid gland is a compensatory mechanism to maintain hormone production. Circulating levels of the major thyroxin transport protein, Thyroxin-Binding Globulin, increase. This causes an

increase in the level of total T4 and triiodothyronine which makes their dosages unnecessary. (Olatinwo, 2009).There is a slight decrease in the concentrations of free hormones (free T3 and T4) as well as TSH in late pregnancy, reaching lower limits of normal with no clinical impact. The resulting medical implications are: (a) On clinical examination, a slight palpable goiter is found in 50% of pregnant women; (b) As the iodine requirements are increased, nutritional advice should be given focusing on the essential sources of iodine (milk, fish, eggs, salt enriched with iodine); (c) In situations at risk of deficiency (mountainous regions, sub-Saharan zone), supplementation of 100 to 150 μg/day of iodine is recommended. (Korevaar, 2017)

- **The parathyroid glands**

Maternal changes in phosphocalcic metabolism during pregnancy are significant. They are mainly linked to the rapid mineralization of the fetal skeleton. Fetal calcium needs increase especially in the 3rd trimester where they can reach 300 mg/day. For this, the mother responds to this request by: (a) Increased intestinal absorption of calcium, (b) Decreased renal excretion of calcium, (c) Increased skeletal calcium stores. Phosphoremia decreases for up to 30 Weeks of Amenorrhea, then it increases until term. (McMullen, 2010) Parathyroid hormone (PTH) increases around the 28th week. This hyperparathyroidism is accompanied by an increase in calcitonin (by compensatory effect). This increase meets the increased need for calcium during pregnancy. These two hormones do not cross the placental barrier. The fetus responds to hypercalcemia by increasing its calcitonin and decreasing PTH, which is favorable to its bone growth. (Seki, 1994)

- **Adrenal glands**

Catecholamines (produced by the adrenal medulla) are little modified except adrenaline and noradrenaline which decrease. Plasma cortisol (glucocorticoids) doubles in early pregnancy. But, the free fraction remaining stable, there is no clinical disturbance. Aldosterone (mineralocorticoids) also increases because the renin-angiotensin-aldosterone system is stimulated during pregnancy. This system is regulated by blood volume, natremia and serum potassium. Androgens as testosterone and androstenedione increase in maternal blood while dehydroepiandrosterone decreases. (Yuen, 2013)

B. **The immune system in the pregnant woman**

- **Trophoblasts**

These are the cells of the developing feto-placental unit. Due to their significant production of cytokines and chemokines, they are in a way the "*orchestra conductor*" of the establishment of immune tolerance. We must differentiate between villous and extravillous trophoblasts.

– Villous trophoblasts are those which make up the cytotrophoblast (CTB), a pool of mononuclear cells, which continually proliferate to form the syncitiotrophoblast, a polynucleated cell pool, which is in direct contact with the maternal circulation. (Staun-Ram, 2005).

– Extravillous trophoblasts (EVT) are a specific cell population, with the ability to invade decidua and remodel uterine arteries, in order to ensure the fetus has an adequate blood supply. (Tanya, 1996)

EVT (differentiated from migrating CTB) is therefore a pool of invasive cells which will play a key regulatory role in angiogenesis through its modulation of the expression of vasoactive proteins in adjacent decidual cells. Indeed, these cells express large amounts of Vascular-Endothelial Growth Factor (VEGF) and Placenta Growth Factor (PlGF) in early pregnancy. Placental tissues thus express numerous cytokines and chemokines which will induce the production of homeostatic macrophages and regulatory T lymphocytes. The main molecules inducing these phenotypes are IL-10 and M-CSF, produced by trophoblasts. The latter therefore play a major role in creating a homeostatic and tolerant environment for the fetus. There are Toll-Like receptors (TLR) on trophoblasts which detect foreign antigens, and modulate the recruitment of monocytes and their production of cytokines. (Weiss, 2016)

- **The HLA-G complex**

The trophoblasts express a molecule of the non-classical class I Human Leukocyte Antigen (HLA) family: HLA-G. It interacts with macrophages and NK cells, among others. The HLA-G molecule is called un-classical because of its limited tissue distribution and selective expression on trophoblast cells at IFM. Highly polymorphic HLA molecules (HLA-A and HLA-B among others) are not expressed on trophoblasts. HLA-G is involved in embryonic development and the maintenance of pregnancy, by inhibiting the maternal cytotoxic immune response. The fetus thus escapes recognition as an element of the Non-Self by the maternal immune system. (Hunt, 2005) Mention may be made, for example, of the inhibitory role of HLA-G on the migration, proliferation and production of gamma interferon (IFNγ) by NK cells, its participation in the induction of regulatory T cells (defined below), and its effect on reducing the proliferation of CD4 and CD8 T lymphocytes, which will lead to a direct decrease in the immune response by the T cells. The HLA-G molecule also modulates the production of cytokines: it increases the production of anti-inflammatory cytokines and decreases that of

pro-inflammatory cytokines. The HLA-G molecule therefore participates directly and indirectly in immune tolerance: it is involved in the process of vascularization and increase in blood volume brought to the fetus, in the phenomenon of trophoblastic invasion of the spiral arteries, and in the maintenance of immunosuppression at the fetal-maternal interface. (Hunt, 2006)

- **Natural Killer (NK) cells**

These are the most abundant immunity cells to IFM: they represent about 70% of decidual lymphocytes. They are present in the endometrium before implantation, but are also recruited from peripheral blood, by the secretion of chemokines and their receptors by trophoblasts. Once in the endometrium, they will adapt their chemokine secretion thanks to the microenvironment of the pre-implantation endometrium (set up by trophoblasts and decidual stromal cells) to become decidual NK cells (dNK). The numerous NK cells recruited at the start do not contain cytotoxic granules, and will mature due to the combined action of progesterone and IL15, to become granular uterine NK. (Rodrigues, 2013). These cells basically have innate cytotoxic capacities: they directly induce the death of infected cells. There are 2 populations in peripheral blood: CD56dimCD16 + NK cells (90-95% of NK cells, they are cytotoxic) and CD56brightCD16- NK cells (5%). And in the uterus, there are also 2 types of NK cells: endometrial and decidual. Decidual NK cells therefore represent 70% of decidual lymphocytes, and they express the CD56brightCD16- phenotype. They have various origins: distant (cells from other organs such as the spinal cord) or local (proliferation and conversion of endometrial NK cells under the influence of TGF β). They will proliferate until the end of the 1st trimester, and then decrease in number. (Moffett, 2002)

Cytotoxicity of decidual NK cells: They are perfectly equipped to fight infection. They contain perforin in their granules (which, when released, will lyse target cells), and express receptors that recognize stress signals. They are activated when they are confronted with a cytotoxic signal. Their overall cytotoxicity is reduced: they are not very cytotoxic towards trophoblasts, which implement several strategies to protect themselves. (Sojka, 2019) This results in functional abnormalities of the NK cells, such as an inability to form synapses with their target, or a blockage of perforin degranulation. In addition to this, the decidual stromal cells will secrete substances inhibiting the cytotoxicity of these NK cells (TGFβ and VEGF). There are also receptors on their surface that activate or inhibit their cytotoxic response. The more inhibitory receptors there are, the more the NK cell will allow the recognition of the molecules of the Non-Self, and the disappearance of foreign cells while too few inhibitory receptors will cause strong mobilization of NK cells in response to infection. (Sharma, 2014)

Initiation of immune-surveillance: Trophoblasts protect themselves from NK cytotoxicity by the expression on their surface of molecules of the HLA complex: HLA-C, HLA-E and HLA-. Indeed, HLA-G inhibits the cytotoxic activity of NK cells by binding to their inhibitory receptors. The HLA-E molecule, on the other hand, stabilizes HLA-G expression and facilitates its interaction with the receptors of NK cells. The expression of non-classical HLA complexes and the secretion of suppressive molecules by trophoblasts make it possible to locally suppress the immune response and prevent rejection of the fetus. (Moffett, 2002)

Different cytokine profiles will define several types of NK cells: - NK1 cells, which are NK cells in the peripheral blood of a non-pregnant woman. - Nkr1 cells, which are NK cells in the peripheral blood of a woman in early pregnancy - NK3 cells, which are NK cells in the decidua of a woman in early pregnancy. (Jabrane, 2019) There are 2 hypotheses as to their origin: they come either from a distinct hematopoietic precursor, or from the maturation of peripheral blood NK cells under the effect of the decidual microenvironment. NK cells are therefore cells of a transient nature during pregnancy. They play a crucial role in immune tolerance: they participate in placental angiogenesis establish immune-surveillance at the feto-maternal interface, and their reduced cytotoxicity allows them to detect and fight infection without risk to the development of the unborn child. (Chong, 2016)

- **Macrophages**

These are the most abundant immune cells at IFM after NK cells; they represent 20% of the immune cells present in decidua. They participate in the establishment of immune tolerance and tissue remodeling at the level of the IFM. They also have a role in the recognition and elimination of infectious agents, in the adaptation of the inflammatory response to placental aggression, and finally in the elimination of apoptotic cell. Their origins are diverse: they are either endometrial macrophages which differentiate and proliferate, or macrophages recruited from the peripheral blood and which will mature in the decidua under the control of the local microenvironment. Recruitment, proliferation and differentiation into decidual macrophages take place through molecules secreted by stromal cells, NK cells, and trophoblasts. These are highly plastic cells, which will polarize differently depending on the microenvironment. (Mao-Xing, 2015)

Tolerance and immune-modulatory activity of macrophages: Macrophages have immunosuppressive activity through the production of anti-inflammatory molecules, such as IL-10 or prostaglandins E2. They also have an enzymatic activity of the indolamine 2,3-dioxygenase (IDO) type, promoter of tolerance, which will

inhibit the activation of T lymphocytes and the cytotoxicity of NK cells. (Jena, 2019) They also participate in the establishment of homeostasis at the feto-maternal interface, by creating part of the overall homeostatic environment, by regulating the inflammatory response and by maintaining the tolerogenic environment (Xuezi, 2020).

Production of cytokines, chemokines and growth factors: There is a phenomenon of transient inflammation of the decidua at the very beginning of pregnancy, to allow implantation, then, during the fetal-placental growth phase, the environment becomes immunosuppressive. The genes encoding the anti-inflammatory phenotype M2 are overexpressed while those encoding the pro-inflammatory phenotype M1 (expressed at the time of implantation) have become silent. Decidual macrophages will therefore have an anti-inflammatory cytokine profile throughout this period (IDO pathway, IL-10 secretion, etc.). During childbirth, a further increase in the expression of pro-inflammatory cytokines (IL-1β, IL-6, IL-8 ...) is observed, as well as the accumulation of leukocytes in the cervix, decidua and myometrium (Zhang, 2017). There is therefore again a context of inflammation and a significant influx of macrophages into the myometrium and the decidua, in order to initiate labor. Finally, the production of cytokines and chemokines by macrophages allows them to interact with NK cells and to decrease their cytotoxic properties. Decidual macrophages are therefore potential mediators and regulators of NK cells. Macrophages are therefore also transient immune cells with multiple roles. They participate in the establishment of immune tolerance, tissue remodeling and placental development, while protecting the fetus against infections. (Yockey, 2018)

- **Dendritic cells (DC)**

Dendritic cells are the sentinels of the adaptive immune response; they are rare at IFM. These are antigen-presenting cells: following their exposure to a pathogen, they will migrate into the lymph nodes in order to present the antigen present on their surface to naive T cells. This will cause the activation, expansion and polarization of T cells. Dendritic cells (DC) can be myeloid or plasmacytoid in peripheral blood. Peripheral myeloid DCs play a role in building tolerance during pregnancy by activating regulatory T lymphocytes (through the secretion of IDO), which will produce IL-10 and TGFβ. (Blois, 2007) Regulatory T lymphocytes are cells with an immunosuppressive function, which participate in maintaining specific tolerance towards auto-antigens, and tolerance towards alloantigens. They represent 20% T cells in decidua, and express the Foxp3 + surface receptor. Their number increases from the start of pregnancy, and reaches its maximum in the 2nd trimester, then gradually decreases. They are also induced by decidual macrophages (which also have a role in their proliferation, with the secretion of IDO or TGFβ) and by trophoblasts (Wei, 2021). There are 2 types of myeloid DC in the 1st trimester: type I and type II myeloid DC. The latter are induced by the secretion of IL-10, and do not recognize fetal antigens on trophoblasts, hence an increase in the tolerogenic climate. Dendritic cells are retained in the endometrium at an immature stage: decidualization is associated with an increase in immature DC (iDC) and a decrease in mature DC. The danger lies in the contact with a fetal antigen: there would then be transformation of the iDCs into mature DCs, which would migrate secondarily in the lymphatic organs to present the antigen to the T cells, and activate an adaptive response. (Lucy, 2003) This immaturity is maintained thanks to trophoblasts, progesterone, and molecules produced by decidual cells. Immature dendritic cells (iDC) are tolerogenic cells, which can be generated in the absence of stimuli, or under the effect of an anti-inflammatory medium (IL-10, progesterone, HCG, estradiol, etc.). They will subsequently produce anti-inflammatory cytokines and develop an inhibitory phenotype, which will prevent the activation of T cells. Certain DCs produce IL-10, and therefore participate in the establishment of tolerance and maintenance of pregnancy. (Wei, 2021)

- **Other players: cytokines and chemokines**

They are multifunctional molecules, which intervene in the migration, the differentiation, or the traffic of leukocytes. Binding to their receptor plays a role in almost all cellular interactions at the feto-maternal interface. Chemokines are part of the small chemotactic cytokine superfamily, and are subdivided into 4 subfamilies (CXCs, CCs, CXC3s and Cs). Their primary function is the directional stimulation of the adhesion and migration of cells of the immune system. (Chatterjee, 2014) They are expressed, as well as their receptors, by a large majority of cells at the feto-maternal interface (trophoblasts, stromal, endothelial, immune decidual cells, etc.). It is therefore a transient innate immunity that is set up at the start of pregnancy. It will allow, in addition to its protective role against infections, to establish a climate of tolerance at the fetal-maternal interface, necessary for the proper development of the unborn child. (Veenstra, 2003)

The endocrine system and immune system in the lactating woman

A. The endocrine system in the lactating woman

- **Prolactin**

Prolactin is the main hormone which will allow the synthesis of the constituents of milk. This prolactin is secreted by lactotropic cells in the anterior pituitary. Its secretion is pulsatile. You can have 7 to 20 peaks per

day, added to the basal serum level for the duration of breastfeeding. Its secretion is permitted by mechanical areolar simulation. The magnitude of its secretion will depend on the intensity of the stimulation, but it decreases over time. An increase in receptor sensitivity is mentioned, without certainty, to explain this decrease. The secretion of this hormone will experience circadian variations, that is to say variations during the day: higher at the end of the night and reduced during the day. (Al-Chalabi, 2020) In association with cortisol, prolactin will exert a positive or negative feedback on the manufacture of its own receptors:

– *Positive effect*: an increase in the concentration of prolactin and an increase in the duration of exposure of lactocytes to this same hormone will lead to an increase in the number of receptors on the membrane of the lactocytes;

– *Negative effect*: a decrease in the prolactin concentration and a reduction in the duration of exposure of lactocytes will lead to a decrease in the number of receptors on the membrane of the lactocytes. (Mennella, 2010).

- **Oxytocin**

Oxytocin is the hormone that causes milk ejection. It is synthesized in the hypothalamus, but storage is located in the post-pituitary. Oxytocin secretion is pulsatile; there are 4 to 10 peaks per 10 minutes. Stimulation of the areola-nipple complex via the stretch receptors located on the areola will allow the synthesis of this hormone. Its secretion is also dependent on the emotional state of the mother. A situation of stress or maternal annoyance can lead to a decrease or even a disappearance of oxytocin synthesis and secretion. There is sometimes a lag time between the moment of breast stimulation and the start of oxytocin synthesis, that is, the start of milk ejection. This latency time varies from woman to woman from 0 to 15 minutes. It is important to avoid short latching less than 10 minutes in patients with a long latency time. (Drewett, 1982)

B. The immune system in the lactating woman

C. Impacts of the transition period on the immune system

During the transition period, there is an increase in the incidence of metabolic and infectious diseases: milk fever, retained placenta, ketosis, clinical mastitis, etc. At the start of lactation, most women undergo immunosuppression. It is commonly accepted that this immunosuppression is correlated with the negative energy balance at the start of lactation. Indeed, there is a complex relationship between metabolic status and immune functions and these complex interactions increase the risk of disease in early lactation. At the level of carbohydrate metabolism, glucose is necessary for phagocytic cells (macrophages and PMNL) for their proliferation, survival and differentiation. Glucose has been shown to be the preferred metabolic fuel for activated PMNLs, macrophages and lymphocytes during inflammation rather than fatty acids, amino acids or ketones. (Hassiotou, 2015) An increase in serum glucose after an intra-mammary infection may be associated with either an increase in hepatic gluconeogenesis or a reduction in glucose consumption by peripheral tissues, thus making it possible to increase the glucose available for phagocytic cells during infection. Sufficient supply of glucose by immune cells is essential for maintaining cellular function and for eliciting a host response to invading microorganisms. Glucose concentration is lower at the start of lactation and low glucose availability can limit immune function and therefore increase the risk of infections. Myeloperoxidase is an enzyme very abundant in the granulocytes of neutrophils and allows the production of hypochlorous acid (HOCl) which gives it its antimicrobial activity. It is active during the oxidative outbreak. There is a relationship between energy status and PMN dysfunction during the peripartum period. Previous studies had demonstrated the relationship between the energy status after parturition and immune dysfunction. BHBA abolishes the formation of Neutrophil Extracellular Traps (NETs) and their bactericidal activity. NETs are extracellular structures produced by polymorphonuclear neutrophils after activation and composed of de-condensed chromatin fibers associated with different proteins. (Palmeira, 2016). These NETs can deactivate and kill bacteria. They observed a negative correlation between the concentration of BHBA and the formation of NETs and their bactericidal activity. Normally the level of oxygenated reagents (OR) is maintained on a very narrow physiological scale thanks to a network of antioxidant defense mechanisms in order to optimize cell performance and prevent tissue damage. During the peripartum period, the production of RO increases due to lipid mobilization resulting in an accumulation of RO which can cause cell and tissue damage. This condition is recognized as oxidative stress. It has been found that oxidative stress is an underlying factor leading to immune and inflammatory dysfunctions and more particularly in times of high metabolic stress (Cacho, 2017). Indeed, mature neutrophils respond to a high concentration of cortisol via glucocorticoid receptors (GRα). The response leads to an alteration in the functions and signaling pathway of the neutrophils. The increase in cortisol concentration helps to decrease leukocyte functions, in particular by reducing chemotactic activity. There is a negative correlation between the expression of glucocorticoid receptors in mononuclear cells and the concentration of cortisol in serum. The results suggested that glucocorticoid receptors are down regulated for mononuclear leukocytes in association

with increased cortisol secretion. They also play an immunosuppressive and anti-inflammatory role through an inhibitory action on the synthesis, release and efficiency of cytokines. (Elizabeth, 2011)

III. Conclusion

The main molecules inducing these phenotypes are IL-10 and M-CSF, produced by trophoblasts. The latter therefore play a major role in creating a homeostatic and tolerant environment for the fetus. There are Toll-Like receptors (TLR) on trophoblasts which detect foreign antigens, and modulate the recruitment of monocytes and their production of cytokines.

There is a phenomenon of transient inflammation of the decidua at the very beginning of pregnancy, to allow implantation, then, during the fetal-placental growth phase, the environment becomes immunosuppressive. The genes encoding the anti-inflammatory phenotype M2 are overexpressed while those encoding the pro-inflammatory phenotype M1 (expressed at the time of implantation) have become silent. Decidual macrophages will therefore have an anti-inflammatory cytokine profile throughout this period (IDO pathway, IL-10 secretion, etc.).

In the light of these various studies, it is increasingly evident that the metabolic imbalances present in the peripartum period are, at least in part, responsible for the natural immunosuppression experienced at the start of lactation.

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