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Maternal SLE Influence in Fetal Development: Immune and Endocrine Systems

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1. Introduction

Pregnancy markedly alters the normal physiology of the women and immune response mechanisms. During normal pregnancy the immune system is reinforced to maintain the well-being of the mother and fetus by modifying the manner that a mother responds to the environment, in such a way that recognition, communication, trafficking and repair mechanisms are all uniformly regulated. In spite of the fact that the fetus could be considered a stranger to the mother´s immune system, maternal tolerance develops; the latter could be the result of the integration of numerous mechanisms promoted by different cells present in the decidua.

Autoimmunity even in the absence of clinically manifest autoimmune disease can affect each event of pregnancy and can induce fetal and maternal complications as well as adverse outcomes. The effect pregnancy has on the course of systemic lupus erythematosus (SLE) remains speculative. Elevated levels of auto-antibodies are frequently are associated with lost pregnancy, as they can cross placental barrier and make contact with blood vessels. Fetal endothelial cells make the first encounter with maternal cells or molecules that cross the placental barrier and this initial contact induces some primary regulation on endothelial cell activity thereby modifying inflammatory response or vascular tone, amongst others. If maternal antibodies cross the placental barrier, this could induce the expression of proinflammatory molecules, such as TNF-alpha, IL-6 or IL-8 (Yazici et al., 2001), by endothelial cells or could induce the formation of immune complexes that can cause fetal damage. Pregnant lupus patients are susceptible to preeclampsia, especially if they suffer lupus nephritis, and also to steroid-induced hypertension and hyperglycemia. At the same time fetuses are susceptible to placental insufficiency if antiphospholipid antibodies or other procoagulant states are present, and to neonatal lupus in the presence of anti-Ro/La antibodies (Lockshin & Sammaritano, 2003). The study of the physiology and immunology of pregnancy in SLE mothers may enhance our understanding of SLE and the possible consequences on the child development and quality of life.

2. Objective

To describe the effects of maternal SLE on the development of the immune and endocrine systems of the fetus during pregnancy and their postnatal consequences.

3. Immune system deregulation in SLE pregnant women

Systemic lupus erythematosus may remain silent, even undiagnosed, during many years in some women, but in others it may become more aggressive during pregnancy, placing both the mother and the fetus at risk. In general, active inflammation from rheumatic or autoimmune diseases poses a stronger threat to the well-being of both the mother and fetus than many immunosuppressant medications. Therefore, continued immune-suppression could be useful to allow for the most optimal pregnancy outcomes. Autoantibodies are a hallmark in autoimmune diseases but the real problem is the diminishing of their clearance and the subsequent immune complex formation that alters immune responses. Furthermore, the altered production of sexual hormones has an influence on immunity, since sexual dimorphism related to SLE development exists.

3.1 Pro-inflammatory molecules

The placenta serves as an immunologic barrier between the maternal and fetal circulations in normal situations. This barrier prevents the potential damage of maternal immune responses, since the fetus is considered a semiallogeneic graft. The trophoblast is the fetal tissue in most intimate contact with the maternal deciduas and it is crucial to the development of the normal placenta; it participates in the regulation of maternal immune responses but the mechanisms involved are still not clear. The placental barrier is continuously changing during pregnancy but the first hurdle between the invasive trophoblast and the circulating cells of the maternal immune system is the maternal endothelium of local vessels. Therefore, specialized mechanisms may exist regulating leukocyte extravasation into the deciduas, implicating an interaction between trophoblast antigens and maternal leukocytes.

Leukocyte recruitment is mediated by specialized cell adhesion molecules on the surface of circulating cells and their counterreceptors or ligands on the endothelium, especially integrins. The a4b7 integrin, for example, is a lymphocyte homing receptor for the mucosal vascular addressin MAdCAM-1 (mucosal addressin cell adhesion molecule 1), which is expressed by high endothelial venules (HEV) in mucosal lymphoid tissues. Another integrin, a4b1, binds to the vascular cell adhesion molecule 1 (VCAM-1), which can be induced in diverse sites of inflammation (Butcher et al., 1999). The major change in the end-term pregnant uterus is that the decidua basalis contains remarkably few maternal leukocytes in the lumina of the maternal vessels and in the tissue, suggesting decreased recruitment at this stage and it is associated with a loss of selectivity from trophoblast and maternal endothelial cells (Kruse et al., 2002).

Inflammatory cytokines and cell adhesion molecules (CAM) appear to be centrally involved in the pathogenesis of autoimmune diseases. During pregnancy it is possible that placental dysfunction may account for some complications. Hopefully in SLE pregnancy an inflammatory state where TNF-alpha, IL-1 or IL-6 could be elevated, is present. These cytokines can stimulate endothelial cells to express cell adhesion molecules like E-Selectin or P-Selectin, VCAM-1 and/or ICAM-1 to promote leukocyte migration. It has been observed that TNF-alpha may increase the level of IL-6 in human vein endothelial cells (HUVEC) both in SLE and normal mothers, without difference, but E-Selectin, VCAM-1 and ICAM-1 are reduced (Rodriguez et al., 2008). Therefore it is possible that the immune response in the offspring of SLE mothers could be diminished because endothelial cells of corial *villi* might not be activated or be noncompliant to stimulus, or in the SLE mother it could be

diminished because there are increased levels of VCAM-1 and ICAM-1 in maternal serum related with a endothelial cells activation and those may contribute to an increased migration of leukocytes into placenta. Although circulating maternal concentration of soluble cell adhesion molecules showed differences between SLE patients and controls, no differences were observed when placental tissues were immunostained with the same cell adhesion molecule antibodies (Lakasing et al., 2000).

Antiphospholipid antibodies have been associated with thrombosis and endothelial cell activation, so they can enable the increased expression of CAMs and other cytokines by the endothelium, thus enhancing a proinflammatory state. TNF-alpha levels are increased in some diseases related to miscarriage. It is known that TNF-alpha modulates endothelial cells through the activation of NF-kappaB, a transcription factor which activates genes of proinflammatory molecules such as CAMs, but also prothrombotic factors such as tissue factor (TF), thrombomodulin and plasminogen activator inhibitor (PAI-1) (Scarpati & Sadler, 1989). This proinflammatory state would contribute to the malformation of the placenta, miscarriage and fetal circulating system alterations. TF expression on endothelial cells, monocytes and neutrophils is a hallmark of inflammatory conditions, such as sepsis, atherosclerosis, inflammatory bowel disease and systemic lupus erythematosus (Girardi et al., 2008).

3.2 The complement system

This system has a crucial role as an effector mechanism in placental and fetal damage that conduce to ill-fated pregnancy outcomes. In normal pregnancies there are many potential sites where the complement system could be activated as the intervillous space or deciduas, by interaction with the trophoblast. It has been suggested that complement activation during placentation should be highly regulated by locally expressed membrane-bound complement regulators, such as DAF, MCP and CD59, providing protection to the fetus (Girardi et al., 2011).

The complement is part of the innate immune system and can be activated through one of three pathways: the classical, the alternative, or the mannose-binding lectin. Central to each of these pathways is the cleavage of C3, resulting in the production of C3a and C3b. Upon its generation, C3b attaches covalently to cells and has binding affinity for a variety of circulating and cell-bound proteins, meanwhile C3a contributes to inflammatory responses such as leukocyte accumulation and enhancement of vascular permeability occurring in various infectious and noninfectious states. The final stage of complement activation by any pathway, is the formation of C5b by C5-convertase, where C3b is an important component. C5b, together with other complement molecules, form an attack complex bound to the membrane that destroys cells.

Girardi, et al. (2011) have proposed that the activation of complement system during placental and fetal injury is produced by antiphospholipid-autoantibodies, lack of regulatory proteins or activated T-cells. In patients with SLE, recurrent miscarriage, fetal growth restriction and intrauterine fetal death are frequently occurring complications of pregnancy, and it is highly possible that the auto-antibodies produced in SLE form an immune complex recognized by C1, which is the triggering of the complement system classical pathway. C1q, a component of C1, deserves special consideration for its role promoting trophoblast invasion of deciduas, a crucial step in normal placental development (Bulla, 2008). But, in human placenta of women with SLE, immunohistochemically stained for C4d and C1q, the presence of both molecules was observed and the presence of C4d was

strongly related to adverse fetal outcome in the setting of SLE. The excessive deposition of C4d supports the concept of severe autoantibody-mediated injury at the fetal-maternal interface (Cohen et al., 2011).

The role of C3a in the pathogenesis of SLE has not been defined, but it has been found that the inhibition of complement activation at the level of C3-convertases significantly reduced renal disease in MRL/*lpr* mice (Bao et al., 2003). Given that inhibition of C3-convertases prevents generation of C3a (as well as C3b, C5a, and C5b-9), it is conceivable that the use of C3-convertase inhibitors, which limit C3a generation, might be of invaluable therapeutic benefit (Bao et al., 2005). One of the possible mechanisms that damage the developing placenta is through the action of anaphylotoxin C5a, which promotes neutrophil infiltration into the deciduas, leading to fetal death (Girardi et al., 2003). In some, but not in all, mice models of antiphospholipid syndrome (APS), complement activation plays a major role in pregnancy loss, with a massive accumulation of C3 in the placenta. Interestingly, C3 deficient mice do not show fetal reabsorption. Based upon these findings, anti-phospholipid antibodies and complement activation (via C3a, C5a, and MAC) may cooperate in the triggering a local inflammatory process, eventually leading to placental thrombosis, hypoxia, and neutrophil infiltration (Tincani et al., 2010).

3.3 Th1 and Th2 responses

Cytokines secreted by the embryos and cells within the uterus are important for the implantation process, but they can also be responsible for causing miscarriages. The activity of cytokines has been characterized as proinflammatory and anti-inflammatory depending on whether they are secreted by Th1 or Th2 T cells. Prolonged exposure to Th1 cytokines is detrimental to pregnancy, while Th2 cytokines are necessary to stimulate the invasion of the blastocyst and the formation of blood vessels during the implantation period. Trophoblastic cells, as well as uterine epithelium and maternal immune cells, secrete cytokines, which promote immunotolerance. Some of these cytokines are transforming growth factor beta, progesterone-induced blocking factor, and regeneration and tolerance factor. The sources of proinflamatory cytokines, such as interleukins, chemokines and TNF-alpha, are macrophages and NK cells, which infiltrate the implantation sites thus favoring pregnancy loss (Cerkiene et al., 2010).

The immune response is regulated by components of the innate immunity, including antigen-presenting cells (APCs) such as monocyte/macrophage and other phagocytic cells, as well as by components of the acquired immunity such as T helper (Th) cells, subdivided into subclasses Th1 and Th2. Th1 cells produce the cytokines interleukin IL-2, IL-12, interferon (IFN)-γ and tumor necrosis factor-alpha (TNF-alpha) and TNF-beta, whereas Th2 cells produce the cytokines IL-4, IL-6, IL-10 and IL-13. These Th1- and Th2-mediated immune responses are mutually inhibitory, and to some extent opposing (Elenkov & Chouosos, 1999). A strong, maybe deregulated Th1 response is often found in autoimmunity and there is compelling evidence for a third effector Th pathway, so-called Th17 T cells that secrete IL-17A and IL-17F, two cytokines not synthesized by either Th1 or Th2 CD4+ T cells (Saito 2010). Healthy pregnant women have a predominant TH1 response (Lit, 2007; Muñoz-Valle et al., 2003), whereas SLE pregnancy is accompanied by a TH2 response, especially through IL-10, that promote antibody production by B cells. (Viallard et al., 1999). This change could explain protection to the fetus from maternal Th1-cell attack, but a predominant Th2 type immunity in recurrent abortion cases has been observed. So it is not

sufficient to know the Th1/Th2 relationship in order to explain the pathogenesis mechanisms in autoimmune diseases. Treg cells play a central role for induction of tolerance because they inhibit proliferation and cytokine production in both CD4+ and CD8+ T cells. An overstimulation of Th1 or Th2 immunity might be harmful for successful pregnancy. IL-17, a proinflammatory cytokine, has been observed in peripheral blood and deciduas in spontaneous abortion patients; moreover, Treg and Th17 cells can be inversely regulated by IL-6, which blocks the development of Treg cells and induces differentiation of Th17 cells (Saito et al., 2010). Auto-antibodies may induce secretion of IL-6 in mesangial cells (Bobst et al., 2005) and enhance IL-6 concentration in serum (Arslan et al., 2004), therefore they could be related to pregnancy loss.

If auto-antibodies cross the placenta, they would stimulate fetal endothelial cells to produce proinflammatory molecules like IL-6, so the Th1/Th2 immune balance could be modified in the offspring. Indeed, two transcription factors, T-bet (for Th1) and GATA-3 (for Th2), have been found to play an important role in the organogenesis of the immune system of the mice offspring during the perinatal period (Yamamoto et al., 2009). It is possible that autoantibodies of SLE mothers exert some modulation on the above mentioned transcription factors and they may induce some immune suppression on the new born child.

4. Hormonal levels in SLE+ pregnant women

Endocrine and immune systems work very closely to allow and maintain the development of gestation by means of hormones, cytokines and its receptors. These molecules can stimulate or suppress the activity both of them. Therefore, the regulation of autoimmnity by hormones or the alteration of hormone levels by immune responses happen during the reproductive age. The increase of progesterone and estrogens during normal pregnancy allow the regulation of implantation and placentation in order to avoid the rejection of the embryo and fetus.

Serum levels of steroid hormones vary during pregnancy in SLE patients, depending upon disease activity being increased in the second trimester and decreased in the third. However, estradiol and progesterone serum concentrations were found significantly reduced in SLE patients compared with controls (Doria, et al., 2002, 2004). The increase in sexual hormones during normal pregnancy boosts the humoral response and leads to a more efficient clearance of auto-antibodies. But in SLE women there is an increment of circulating auto-antibodies which is associated with a decrease of serum estrogen in the third trimester of pregnancy. Sex hormones are considered as major regulators of the immune response in SLE patients (Doria et al., 2006).

4.1 Estrogens

Estrogens are able to modulate immune response exerting specific effects on T and B cells, dendritic cells (DC) and peripheral blood mononuclear cells (PBMC), enhancing IL-10, IL-2, and IFN-gamma production, inhibiting TNF-alpha secretion by PBMC, stimulating antibody production by B cells, and decreasing apoptosis of DC and macrophages (Zen et al., 2010).

17-beta estradiol induces anti-apoptotic effects in monocyte and macrophage cell lines by interfering with NF-kB activities (Catelo et al., 2005). In consequence, if estrogens are reduced, the activity of NF-kB is augmented; therefore there will be a larger expression of cell adhesion molecules favoring a proinflammatory condition. Estrogen treatment induces an increase in the production of IL-10 and a decrease in that of TNF-alpha by PBMCs of

patients with SLE, but not in healthy subjects (Evans et al., 1997). Because of the TNF-alpha regulatory function on apoptosis, the failure to maintain the production of this cytokine might alter the apoptosis of activated immune cells in SLE patients exposed to high estrogen concentrations, as it occurs in pregnancy.
The serum concentration of soluble adhesion molecules is higher in women with SLE than in normal women, but the placental values are identical (Abd-Elkareem et al., 2010, Lakasing et al., 2000). However, endothelial cells of umbilical cordons of SLE mothers express several times less CAMs (E-Selectin, VCAM-1, ICAM-1) compared with healthy mothers (Rodriguez, 2008). Even if a relationship between diminished serum estrogen and augmented serum CAMs levels exists in SLE patients, maternal estrogen does not exert any deleterious effect on the fetus endothelial cells (FEC). That may be possible if FEC could exhibit immunotolerance or lack estrogen receptors. It is assumed that estrogen regulation upon the immune system uses different pathway in the fetus compared with the SLE mother.

4.2 Androgens

Sexual dimorphism has been shown in SLE diseases since women are more affected than men. In fact, androgens seem to act in counter part to estrogens modulating the immune response; because of that, they have been used as therapy on SLE patients (Gordon et al., 2008). However, it has been shown that androgens can favor adverse effects on circulating lipids increasing the risk of atherosclerosis (Nutall et al., 2003).
Some favorable effects of androgens on immunity are to inhibit Il-1b and IL-6 secretion by PBMC, enhance IL-2 secretion by T cells and inhibit antibody secretion by B cells. Testosterone also exerts pro-apoptotic effects and reduces macrophage proliferation, and inhibits IL-1b and IL-6 secretion by PBMC (Zen et al., 2010).
Testosterone and related steroid hormones have a variety of effects on the immune system. Dehydroepiandrosterone (DHEA), the major product of the adrenal glands in both men and women, whose sulphated (DHEA-S) molecule is its inactivated form, stimulates IL-2 production (Dillon, 2005) and reduces IL-10 (Chang et al., 2004) in normal T cells, therefore favoring the Th1 pathway. But in SLE patients a significant finding is that serum levels of DHEA-S and other adrenal androgens and cortisol are decreased (Zen et al., 2010). Decreased adrenal production, increased conversion or conjugation to downstream hormones are the most likely causes of inadequately low serum levels of adrenal hormones in SLE (Straub 2004). It is believed that lower levels of androgen is a cause of proinflammatory events. In SLE pregnant women, differences in androgen levels compared with normal pregnant women have not been found (Doria, et al., 2002).

4.3 Progesterone

Progesterone is the most important hormone during pregnancy reaching its higher levels at the third trimester of pregnancy. All throughout the sexual cycle, progesterone modulates immune responses generating protection to the female tract against microorganisms. Progesterone can act enhancing IL-4, IL-5, IL-6, and IL-10 production, and inhibiting IFN-gamma secretion by PBMC, stimulating antibody generation by B cells, and decreasing T cell proliferation. Also, it induces the secrection of a 34-kD protein, named "Progesterone-induced blocking factor" (PIBF), which is known to regulate humoral and cell-immune responses in several ways (Beagley & Gockel, 2003), including the induction of a Th2-dominant cytokine profile (Lashley et al., 2011). During pregnancy Th2 polarization occurs

both in the systemic circulation and at the feto-maternal interface, enhancing IL-3, IL-4, IL-5 and IL-10 production. Thus, high progesterone levels might contribute to successful pregnancy, favoring feto-allograft tolerance (Zen et al., 2010).
Disproportional changes of progesterone levels in pregnant women are associated with different manifestations of autoimmune pathologies since Th1-related diseases such as rheumatoid arthritis tend to improve, whereas Th2-related diseases may get worse (Tait 2008). Lower production of progesterone is seen during SLE pregnancy, especially in the third trimester compared with normal pregnancies (Doria eta al., 2004).
Progesterone plays a key important role at many levels including control of neuroendocrine responses to stress, procuring required immune balance and controlling placental and decidual function. A lack of progesterone can explain many unwanted consequences (Douglas 2010). It is possible to speculate that lack of progesterone in SLE mothers could cause damaging effects in the offspring's future development.

4.4 Prolactin

Different to steroids hormones, prolactin is a peptide produced by the adenohypophysis but also by neurons, endothelium, mammary epithelium, leukocytes and thymocytes. Prolactin has pleiotropic effects on the immune system and it appears to stimulate both humoral and cell-mediated immune responses, through enhanced IL-1, IL-2, IL-12, and IFN-gamma secretion by PBMC. It also stimulate antibody secretion, decreases B cell apoptosis, and T cell proliferation (Vera-Lastra et al, 2002), but it specifically promotes the survival of the T-cell-dependent autoreactive follicular B-cell subset, and enhances the development of antigen presenting cells expressing MHC class II and costimulatory molecules CD40, CD80, and CD86 (Matera et al., 2001). The effect of prolactin on antigen presentation and on B-T cells interaction results in increased response to MHC presented auto-antigens, leading to the loss of self tolerance. The interaction between CD40 on B cells and CD40L on T cells up-regulates the expression of the antiapoptotic molecule Bcl-2 leading to autoreactive B cell rescue from negative selection which reduces tolerance to self (Peeva et al., 2003). Thus, hyperprolactinaemia has been found to be a risk factor for the development of autoimmunity by favoring Th1 immunity.
High levels of serum prolactin have been found in a subset of SLE patients associated with active disease, promoting deficiency of dendritic cell functions, suggesting a lack of induction of T and B cell activity (Jara et al., 2008). Hyperprolactinaemia is associated with several autoantibodies involved in SLE such as antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anticardiolipin, and hypocomplementaemia (Zen et al, 2010).

4.5 Hormone receptors

The effects of sexual hormones are mediated through membrane receptors independent of their isoform or the tissue and physiological condition of the host. The relationship between estrogens and its receptor (ER) may play an important role in the pathogenesis of SLE. Results obtained from a mouse model of lupus (NZB/NZW) suggest that ER-alpha activation exerts a stimulatory effect on the endocrine response whereas ER-beta activation appears to induce a slightly immunosuppressive effect on the disease (Li & McMurray, 2007). It has also been reported that ER-alpha mRNA expression is increased and ER-beta mRNA expression decreased in PBMC (Inui et al., 2007) as well as CD4+ T cells (Phiel et al., 2005) of SLE patients.

The presence of estrogen receptors on the cells involved in the immune response, namely thymocytes, macrophages and endothelial cells is well recognized. Estrogens modulate cytokine production by target cells, through interference with their transcriptional activity. The effect of estrogens on the expression of protooncogenes and oncosuppressor genes involved in apoptosis might also be relevant to human autoimmunity (Cutolo et al.,, 1995). It is possible that different polymorphisms of the ER-alpha gene, are involved in SLE development and apparently they are related to sex, age at the onset of the disease, and the appearance of some clinically relevant symptoms, suggesting that these polymorphisms might contribute to SLE susceptibility (Johansson et al., 2005).
Gonadotropin releasing hormone (GnRH) is a hypothalamic and pituitary hormone known to exert immune actions. GnRH administration has been associated with gender-specific alterations in mRNA expression of the GnRH and IL-2 receptors, after 2 weeks of treatment. These differences might be attributable to gender differences in response to gonadectomy. GnRH and GnRH receptor mRNA levels vary dynamically with the estrous cycle in lymphoid organs in the intact female mouse thus contributing to gender differences in the development and activity SLE patients (Jacobson et al., 1999). Interestingly, it has been recently shown that prolactin exerts a regulatory influence on GnRH through dopamine and LH (Hodson et al., 2010).

5. Auto-bodies in SLE pregnant women

Autoimmunity originates after breaking self-tolerance of the immune system, a process that involves many different molecules and yet poorly understood processes. It remains an open question whether bacterial or viral pathogens contribute to the initiation of these diseases as major causative agents (Borchers et al., 2010). The presence of autoantibodies has been mainly associated with pathologic states, probably because they were first described as a hallmark of autoimmune diseases. Indeed, endothelial cell autoantibodies (AECA) are often reported in conditions where pathologic autoantibodies bind to activated or damaged endothelial cells.

5.1 Non active SLE

Although it is increasingly recognized that autoimmunity, even in the absence of clinically manifest autoimmune disease, can affect every aspect of pregnancy (starting with fertilization) and can contribute to maternal complications and adverse fetal outcomes, (Cervera & Balasch, 2008) the risk of lupus flare is not as great as many people used to think and flares, when they do occur, are not necessarily severe. The best prevention of SLE flares during pregnancy is the delay of conception until a woman has had quiescent SLE for at least 6 months. In many situations, however, this is not possible and the continuation of medications for SLE helps to prevent flares.
In the past, patients stopped all their therapy when they discovered that they were pregnant. This may very well have contributed to the increased risk of disease flare during pregnancy, especially in patients with a history of renal involvement and other forms of serious lupus disease. Patients should now be counseled before becoming pregnant, and in early pregnancy, about the use of appropriate drugs. (Gordon, 2004)
Many women with SLE take hydroxychloroquine (HCQ) (Plaquenil) prior to pregnancy. This medication decreases the risk of SLE flare, improves the prognosis of SLE nephritis, and prevents death. (Kasitanon et al., 2006) It is also very well tolerated with arguably the

best side-effect profile of any medication available to treat SLE. An expert panel, comprised of 29 international leaders in research and care of women with SLE, recently recommended the continuation of HCQ during pregnancy. (Ostensen et al., 2006) Among over 300 pregnancies described in the literature that were exposed to HCQ for the treatment of autoimmune disease, no elevation of fetal anomalies was identified. When chloroquine is taken at supratherapeutic doses, there may be ocular or auditory damage. However, no such changes were seen among 133 babies exposed to HCQ *in utero*. (Costedoat-Chalumeau, 2003).

In non-pregnant SLE patients, the cessation of HCQ is associated with a 2-fold risk of SLE flare within the following 6 months. Among pregnant SLE patients, the risk for flare also increases when HCQ is discontinued. In the Hopkins Lupus Pregnancy Cohort, 38 women discontinued HCQ just prior to or early in pregnancy due to concerns about fetal exposure whereas 56 women continued HCQ throughout pregnancy (Clowse et al., 2006) Among those who discontinued the medication, the risk for increased lupus activity, whether measured by the absolute physician's estimate of activity or the SLEDAI scale was significantly increased. More of these women required corticosteroid therapy at higher doses than those who continued HCQ treatment. Within this cohort, as in other reports, there was no increase in fetal abnormalities after HCQ exposure. The pregnancy outcomes among women who continued and discontinued HCQ were similar. This likely reflects the type of SLE activity that women who discontinued HCQ suffered: they did not have increased rates of lupus nephritis, anemia, or thrombocytopenia. Instead, women who discontinued HCQ had increased incidence of fatigue and joint symptoms. Though these symptoms are uncomfortable, they are generally not life-threatening nor require cytotoxic therapy. They may, however, prompt the initiation or the increase of corticosteroid therapy in mid-pregnancy. Again, little data is available about the use of azathioprine in inactive SLE pregnancy. In the Hopkins Lupus Pregnancy Cohort, 31 pregnancies were exposed to azathioprine. (Ostensen et al., 2006) Among the women who conceived while taking azathioprine and continued it through pregnancy, 2 out of 13 ended in pregnancy loss, both women had developed active SLE in pregnancy. Among the 10 women who maintained low lupus activity and azathioprine throughout pregnancy, all gave birth to live newborns at 34 weeks or greater gestations. Based on these data, azathioprine treatment should be continued throughout pregnancy, especially if the woman required it prior to pregnancy to treat her lupus (Clowse, 2007). It is also recommended to switch women from mycophenolate mofetil (MMF) to azathioprine prior to conception to avoid the teratogenic effects of the MMF.

5.2 Active SLE

Mild activity SLE can be treated with low dose prednisone (under 20mg per day) as required. The side effects include increased risk for hypertension and diabetes, just as in a non-pregnant woman. There may be a 2-fold increased risk for cleft lip or palate with systemic corticosteroid use, though the absolute risk for this remains low (about 20 per 10,000 babies with corticosteroid exposure) (Pradat et al. 2003).

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used during the late part of the first trimester and during the second trimester. There is evidence, in a murine model, that COX enzymes are important for embryo implantation, which may explain the increased risk for early miscarriage in women taking NSAIDs around the time of conception. (Clowse, 2007). NSAIDs are considered fairly safe in the second trimester, though they may decrease fetal

renal excretion and therefore promote oligohydramnios. (Holmes and Stone, 2000). NSAIDs should be stopped in the third trimester for 2 reasons: they can prolong labor and may promote premature closure of the ductus arteriosis. (Ostensen et al., 2006).

Moderate lupus activity can also be treated with higher doses of corticosteroids, including pulse-dose steroids. Only a small percentage of each dose of prednisone and prednisolone crosses the materno-fetal barrier. However, fluorinated glucocorticoids, such as dexamethasone and betamethasone, easily transfer to the fetus. These steroids can be helpful in treating the fetus, in particular in promoting fetal lung maturity prior to a preterm delivery. However, they have also been associated with lasting adverse effects on the offspring. Children exposed to these corticosteroids may have increased blood pressure and cognitive deficits. (Velíšek, 2011, Rothenberger et al., 2011) Therefore, dexamethasone and betamethasone should not be used to treat lupus activity during pregnancy.

The commencement of azathioprine in mid-pregnancy for a lupus flare may be risky. There is little data published on the use of azathioprine in lupus pregnancy. However, in the Hopkins Lupus Pregnancy Cohort there was an increase in pregnancy loss among woman who used azathioprine to treat a moderate to severe flare. Of the 8 pregnancies treated with azathioprine, 5 (63%) resulted in pregnancy loss, whereas only 1 out of 9 (11%) without azathioprine had a misscarriage (p=0.02). (Clowse, 2007)

Another option for the treatment of lupus in mid-pregnancy is intravenous immunoglobin (IVIg). IVIg can be particularly helpful in controlling hematologic and renal disease (Friedman et al., 2010). There are no published series of IVIg use in pregnancy for lupus patients, however there are multiple reports of IVIg use to prevent recurrent miscarriage. In these cases, the primary outcome is live birth, and there is no change in this rate with the use of IVIg. Little has been published on the effects of IVIg on the offspring, but cell count levels seem to be stable and no congenital anomalies have been reported. IVIg´s that contain sucrose can prompt renal insufficiency, but this has not held back the treatment of non-pregnant women with lupus nephritis (Micheloud, 2006). Some women will develop headaches, rigors, or fevers with IVIg therapy, but more severe side effects are rare.

Cyclophosphamide (Cytoxan) and mycophenolate mofetil (Cellcept) should be avoided during pregnancy. First trimester exposure to cyclophosphamide causes fetal abnormalities in a significant minority of patients. Exposure in the second and third trimesters does not increase the risk for fetal anomalies among women treated for breast cancer during pregnancy. Of the 3 SLE pregnancies with cyclophosphamide treatment during mid-pregnancy reported in the literature, only one resulted in a live birth. (Clowse et al, 2005b). Cyclophosphamide should only be used when all other options are exhausted and a forthright discussion about the risk for pregnancy loss has been discussed with the mother. The data on the use of mycophenolate mofetil in pregnancy are scarce but worrisome. There appears to be an elevated risk for both fetal anomalies and pregnancy losses especially in SLE mothers.

6. Placental barrier and auto-antibody transfer

During pregnancy the placenta plays a very important role in the mechanism that regulates and maintains a suitable communication between the mother (matro-environment) and the fetus (micro-environment). The placental barrier, mainly constituted by syncytiotrophoblast, cytotrophoblast, mesenchyma and endothelium, is continuously changing while the gestation progresses, in such a way that the placental barrier becomes, at the third trimester,

a thin layer constituted by syncytiotrophoblast and chorionic-vessels endothelium. These morphological changes affect the traffic of cells and molecules through the placenta that could affect fetal development. Endothelial cells control the traffic of molecules and cells across the vessel wall and play an active role in hemostasis, inflammatory reactions, and immunity. The vascular cells dynamically respond to molecular signals, actively regulating many aspects of vascular homeostasis, including metabolic and cellular events, and executing a major role in the modulation of immune–inflammatory responses.

6.1 Maternal auto-antibodies and its effect on the developing fetal immune system

Immunoglobulins with the ability to bind to endothelial cell surface antigens are commonly known as AECA, and are often reported in conditions where potentially pathologic autoantibodies bind to activated or damaged endothelial cells (Salomonsson, 2010). However, natural AECA of both the IgG and IgM classes have been described. These antibodies, present in the serum of healthy individuals, are strictly controlled in terms of antigen specificity, and their expression may be regulated by the idiotypic network (Vazquez-del Mercado, 2006). This control is lost in SLE (Dhar & Sokl, 2006) in which IgG-AECA display quantitative and qualitative modifications and exert proinflammatory effects on cultured endothelial cells (Munther, 2006). So far, little work has been done on AECA expression in pregnant healthy subjects and in pregnant SLE patients.

6.2 Maternal auto-antibodies and its effect on the development of the embryonic and fetal heart

Complete atrioventricular block (AVB), in 91% of affected neonates, results from neonatal lupus erythematosus, a disease associated with transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antibodies (Salomonsson, 2010). The mothers of these neonates are commonly diagnosed with SLE, Sjögren syndrome (SS), or other rheumatic diseases, although many are asymptomatic. Complete fetal AVB, which usually develops during gestational weeks 16 to 24, conveys a significant fetal mortality (15% to 30%) and morbidity rate, where two thirds on the affected offspring will require permanent pacing (Dhar & Sokol, 2006). It has been suggested that complete AVB may result from unresolved wound healing and scarring subsequent to transdifferentiation of cardiac fibroblasts into proliferating myofibroblasts, initiated by the specific maternal antibodies (Buyon et al., 1996). The process that leads to AVB may rarely progress postnatally. Given the high recurrence in neonates of SLE mothers (18% to 25%), complete AVB could be expected to occur in approximately 1-3 of the every 70 newborns whose mothers have anti-SSA/Ro or anti-SSB/Lb antibodies (Rein AJJT, 2009).

Membrane-associated LA protein is required for the in vivo normal maintenance of the inner cell mass (ICM) of the blastocyst, thus demonstrating that nullizygous disruption of the LA gene leads to early embryonic lethality, consistent with the observed critical defect in the ICM of the blastocyst observed during blastocyst outgrowth. (Park JM, 2006). One difficulty in identifying a pathogenic effect of an autoantibody is accounting for the heterogeneity of that effect. Congenital heart block (CHB) is a paradigmatic example in that not only is the injury seemingly rare, but the degree of injury varies along a spectrum from clinically inconsequential first-degree block through third-degree (complete) block and even, in some cases, an associated cardiomyopathy that is often fatal. Identification of a

necessary or essential factor is only part of the challenge in defining the pathology of CHB, since recurrence rates from one pregnancy to the next are 18%, not 100%, and identical twins are, with rare exception, discordant for the disease. Antibodies to the 52-kd SSA/Ro protein (Ro 52) are found in 80% of mothers whose children have CHB (Clansy RM, 2005) and it has been suggested that the core of the problem is that SSA/Ro or SSB/LA antigens translocate and then there is surface binding by maternal autoantibodies, and then through a TGF-beta mediated mechanism, scaring and blockade is initiated.

7. Anomalies in newborns from SLE positive mothers

In addition to causing pregnancy complications and adverse pregnancy outcomes, transplacental passage of maternal autoantibodies of the IgG isotype can result in a variety of neonatal diseases. Among the best known of these is the neonatal lupus syndrome (NLS), which can appear as cutaneous lesions resembling those of SLE (16–50%), life-threatening congenital complete heart blockade (CCHB, 1–2%), and hematological (~26%) and hepatobiliary manifestations (9–24%) (Hoftman et al. 2008). The prevalence of anti-SSA/SSB antibodies varies considerably in different ethnic groups. Overall, ~1–2% of women are thought to have anti-SSA/SSB antibodies, and estimates of the risk of them having a child affected by NLS range between 2% and 52% in prospective studies (Brucato, 2001). Only 1–2% of anti-SSA/SSB antibody positive mothers will give birth to a child with CCHB. The large variation stems from differences in the thoroughness with which the various (and frequently asymptomatic) manifestations of NLS are determined and the length of follow-up since some of the NLS symptoms, including the cutaneous lesions, are not always obvious at birth. The risk that a second child is affected ranges between 15% and 20%. The fact that not all children of women with anti-SSA/SSB antibodies develop NSL indicates that other factors, probably including fetal ones, play a role. NLS is almost invariably associated (in 95% of cases) with maternal antibodies against Ro/SSA alone or in conjunction with anti-La/SSB. Anti-U1-RNP (ribonucleoprotein) antibodies are associated exclusively with the cutaneous manifestations of NLS. All of these antibodies are found primarily in women with SLE. Interestingly, there are some suggestions that infants of mothers with SLE are more rarely affected by CCHB than those of mothers with Sjögren's syndrome or with undifferentiated connective tissue disease (Borchers, 2010). In contrast, there are indications that the presence of hypothyroidism increases the risk of CCHB, but not NLS overall, in infants of anti-SSA-positive mothers regardless of whether they have an underlying autoimmune disease or are asymptomatic. Of particular note, a recent report on the long-term follow-up of 49 children with NSL indicated that definitive autoimmune diseases were already present in 6 of 49 affected children (5 of them female) at a mean age of 14.8 years, but in none of the 45 unaffected siblings or the 53 unrelated controls (Martin et at., 2002) . Similarly, it has been reported that children and adolescents diagnosed with autoimmune thyroid disease had been exposed to maternal thyroid peroxidase antibodies in utero more frequently than randomly selected control children (Svensson, et al 2006). This strongly suggests that, in addition to inheritance of susceptibility genes from an affected mother, transplacental exposure to maternal autoantibodies predisposes one to the development of autoimmune diseases.

7.1 Cardiovascular

A frequent outcome in newborns of SLE mothers is fetal intrauterine growth retardation, which is associated with long-term medical complications such as adult-onset hypertension.

Maternal immune deregulation may play a role in the appearance of diseases such as myocarditis, autoimmnunity and probably atherosclerosis. Cardiac injury is presumed to be dependent on the transplacental passage of maternal IgG autoantibodies via Fc receptor-bearing trophoblasts and the target antigens of the antibodies have been molecularly cloned and identified as three separate proteins: 52 kDa SSA=Ro and 60 kDa SSA=Ro, which share no sequence homology, and 48 kDa SSB=La (Tincani et al, 2010). Sera containing anti-Ro and anti-La antibodies can induce atrioventricular block and inhibit L-type calcium currents in ventricular myocytes in vitro. The developing myocardium appears to be particularly sensitive to the effects of these antibodies because Ro and La are localized in the surface blebs of apoptosing myocytes. (Tseng et al., 1999)

The more severe condition of congenital heart blockade was bradycardia which was observed in 53% of the pregnancies between weeks 16 and 24, in 24% of pregnancies between weeks 25 and 30 weeks and in 23% of pregnancies after week 30. Congenital heart block may be associated with myocarditis, but clinical heart failure is fortunately uncommon. Lesser degrees of heart blockade are sometimes detected prior to the development of congenital third-degree heart blockade and may reverse with fluorinated steroids such as dexamethasone. Heart failure associated with myocarditis and first- and second-degree block may be reversible with steroids. As prednisolone does not cross the placenta, dexamethasone should be used. (Gordon, 2004) There is no evidence to date that established third-degree heart blockade can be reversed with dexamethasone, but in cases where there is strong suspicion that the blockade has developed within the past few days, it may be worth a therapeutic trial. Over half of the children with congenital heart blockade will require a pacemaker by the age of 1 year-old, sadly about one-third will need it within the first month of life. Some of the remaining children will require pacemakers by the age of 12. Up to 20% of children with congenital heart block die in infancy (Gordon, 2004).

In order to identify heart blockade as early as possible, when treatment may be beneficial, mothers with anti-Ro antibodies should have the fetal heart rate assessed weekly from the week 16 onwards by auscultation, and by ultrasound scans monthly, including a detailed scan looking for cardiac abnormalities at 20 weeks of pregnancy. An ECG should be performed after delivery as some neonates develop more severe degrees of blockade after birth. (Askanase et al., 2002). About half the cases of neonatal lupus syndrome will occur in children whose mothers do not have confirmed systemic connective tissue diseases; at least half of these children will develop Sjogren's syndrome or mild lupus over the following 10 years. If a mother has delivered a child with congenital heart blockade, the risk of this recurring in subsequent pregnancies is about one in five (Tseng & Buyon, 1997).

7.2 Immune response

Maternal tolerance of the fetal allograft could be the result of the integration of numerous mechanisms promoted by different cells present in the decidua. Decidual macrophages and dendritic cells, which are found in close association with T lymphocytes are the most potent activators of T lymphocyte responses and could play a sentinel function for the immune system, initiating antigen-specific T cell responses to fetal antigens. T cell cytokines produced in response to fetal molecules could have a role in the maintenance or in the failure of pregnancy. The levels of LIF, IL-4, IL-10 and macrophage colony stimulating factor produced by decidual T cells of women suffering from unexplained spontaneous abortion are lower than those of normal pregnant women indicating that these cytokines may contribute to the maintenance of pregnancy. T cells from the cumulus oophorus

surrounding the blastocyst produce LIF and IL-4. These findings suggest that cytokines produced by maternal T cells create a suitable microenvironment for the proper implantation process and further development of the placenta (Piccinni MP, 2005).

From the early developmental stages onward, the secretory activity of placenta cells clearly contributes to increased local, as well as systemic levels, of cytokines and inflammatory molecules. Two aspects of the progression of the immune response have been thoroughly investigated: the highly regulated process of throphoblast invasion and blastocyst implantation, and the induction of preterm labor associated with infections. With the progression of pregnancy, the physiological role of most placental cytokines is uncertain, since many of them are similar to adipose tissue derived cytokines. It is possible that they contribute to the low grade systemic inflammation that develops during the third trimester of pregnancy.

Maternal transmission of IgG antibodies to the fetus usually occurs between weeks 16 and 32 (Tseng & Buyon 1997), but an autoimmune condition in the neonate may not be diagnosed until after delivery. The best-recognized condition is neonatal lupus syndrome due to the transmission of anti-Ro and/or anti-La antibodies to the fetus from a mother with lupus, primary Sjogren's syndrome or an undifferentiated connective tissue disease. There are three reports of neonatal cutaneous vasculitis in infants born to mothers with cutaneous polyarteritis nodosa (PAN) that appeared early after delivery and resolved with treatment soon after birth, with no neonatal deaths. (Borrego et al., 1997). A case of hypersensitivity vasculitis that deteriorated in pregnancy and postpartum, and that was associated with an identical vasculitis rash in the newborn, has been reported, it was almost certainly associated with the transmission of a maternal autoantibody, although none was identified (Morton, 1998). Neonatal thrombocytopenia is a well recognized consequence of the transmission of anti-platelet antibodies from the mother to the fetus and the transmission of anti-phospholipid antibodies has also been reported. However, most infants born of thrombocytopenic mothers with SLE have normal platelet counts. IgG Coombs' hemolytic antibody may also be transmitted to the fetus and can cause hemolysis in the fetus and newborn. Antiphospholipid antibody causes placental insufficiency, intrauterine growth restriction and fetal death but does not usually cause abnormalities in the infant, although fetal thrombosis has been detected (Tincani et al., 2003). IgG1 and IgG3 antiphospholipid antibodies not only affect the placental barrier but reach the fetus (Sammaritano et al., 1997) and induce the secretion of TF and other inflammatory cytokines by FEC thus favouring a prothrombotic state. Infants do not usually develop APS from maternal antibodies, but exceptions do occur in women with anti-SSA/Ro or anti-SSB/La antibodies, where neonatal lupus development is a risk (Buyon & Clancy, 2003). In all cases of neonatal transmission of autoantibodies, the disease in the neonate usually resolves over 3–6 months as maternal antibodies are gradually destroyed in the infant. But there are many questions to be solved still, such as: What do these maternal antibodies do to the newborn? Do they initiate an early proinflammatory signaling pathway? Do they induce immune complex formations that eventually lead to tissue damage? Do they induce immune tolerance?

The two main determinants of fetal outcome in patients with autoimmune diseases are the degree of active disease at conception and the presence of anti-phospholipid antibodies. The two main outcomes are fetal loss and premature delivery. The term 'fetal loss' includes spontaneous abortions under 10 weeks, miscarriages between 10 and 24 weeks, and stillbirths from 24 weeks onwards. Fetal loss occurs in about 20% of pregnancies in women with lupus (Petri, 2004). Retrospective studies have shown that active disease at conception

and a history of renal disease are associated with a higher risk of fetal loss, but more recent prospective studies do not support this conclusion and show that the main predictor of fetal loss is the presence of high concentrations of anti-phospholipid antibodies. (Meroni et al., 2010). Anti-phospholipid antibodies are also associated with intrauterine growth retardation and pre-eclampsia that may result in premature delivery. These complications are the result of uteroplacental dysfunction, but the mechanisms involved are poorly understood. Early pregnancy loss may result from a failure of placentation owing to the effects of anti-phospholipid antibodies on anionic phospholipids and the co-factor B2-glycoprotein 1 on trophoblasts (Serdiuk, 2008). Second- and third-trimester losses are more likely to result from the damage to the uteroplacental vasculature since histological data reveals massive infarction of the decidual and placental vessels in human and experimental APS. Platelet deposition, prostanoids imbalance and spiral artery vasculopathy may contribute to fetal hypoxia which would lead to fetal death. In stillbirth, the most common predisposing factor to prematurity in SLE mothers, are IgG isotype antibodies (Motta et al. 2009). There is evidence that active SLE at conception, a history of renal disease and maternal high blood pressure increase the risk of a prematurity (Shah et al., 2001). Premature babies, irrespective of the underlying cause, may suffer from complications such as pulmonary immaturity, infection and feeding problems and developmental abnormalities all of which may cause neonatal death. To induce the rapid maturation of the lungs whose hallmark is a shortage of surfactant, a short course of dexamethasone is usually given over 48 hours to the mother if a premature delivery is considered likely because of maternal disease, poor fetal growth or signs of pulmonary distress. Use of antenatal dexamethasone in premature babies to promote lung maturity may significantly diminish the incidence of respiratory distress syndrome and additionally, mortality (5.7% versus 14.8%) and use of the neonatal intensive care unit (12.9% versus 21.1%) were reduced (Nayeri et al., 2005). Therefore, use of corticosteroids during gestation or perinatally could be beneficial to the fetus and SLE mother outcomes.

The most typical feature of neonatal lupus syndrome is a photosensitive rash on the face and scalp, usually erythematous, annular or elliptical (Tseng & Buyon, 1997), that is often precipitated by exposure to sunlight in the first couple of months after delivery or following ultraviolet light exposure if the newborn developed neonatal jaundice. This rash may be accompanied by purpura caused by thrombocytopenia or by haemolytic anaemia. These haematological manifestations may result from the transmission of anti-platelet or anti-erythrocyte antibodies. Other possible manifestations of neonatal lupus include hepatosplenomegaly and abnormal liver function tests without evidence of biliary tract obstruction. Neurological manifestations such as aseptic meningitis and myelopathy are very rare.

7.3 Central nervous system

The central nervous system (CNS) is susceptible to suffer damage during embryo and fetal development. Although in autoimmune diseases, such as SLE, antibodies react with double-stranded DNA forming immune complex that affect several organs including the brain, spinal cord and nerves, the mechanisms involved are not fully understood.

Antibodies and maternal autoantibodies that cross the placental barrier are believed to be responsible of almost all the fetal alterations in NLE, specially the autoantibodies against ribonucleoproteins SSB/La, SSA/Ro and SSA/Ro. Although the most severe and frequent manifestation of neonatal lupus is third-degree heart blockade, which usually begins during the second trimester of gestation, there are other manifestations such as rash, present in 15-

25% of children with NLE, asymptomatic elevation of liver function tests seen in 10-25% of cases, or some neurological manifestations like hydrocephalus, non-specific white matter changes and alterations of brain vessels (Silverman, 2010).

Less evident alterations during development of CNS could be associated to behavior and movement. There are reports that mothers of individuals with autism have antibodies that react with brain proteins and when these antibodies are passively transferred to pregnant non-human primates or rodents the offspring has behavioral and nervous system changes. It is still not clear whether the antibodies found in mothers of individuals with autism actually play a role in the disease. More studies need to be performed to identify the proteins recognized by the antibodies and to determine how these could affect development, behavior and changes within the CNS (Libbey, 2010). Besides, the high incidence of learning disorders in children born to mothers with SLE may be due to the passage of antibodies, mainly IgGs, through the brain barrier. Given that the blood brain barrier is not fully formed in utero, the pathogenic antibodies in maternal circulation represent a risk factor for fetal brain development (Lee, 2009).

Maternal antibodies that pass from the mother to the fetal circulation could interact with proteins or cell receptors to produce organ and tissue damage during gestation. In a murine model of lupus, NP-SLE, it has been shown that nervous system involvement can include seizures, stroke and other cerebrovascular events, psychosis, cognitive dysfunction, and notably a very high incidence of mood disorders, particularly anxiety and depression (Gulinello, 2011). Actually, it has been reported that the involvement of 5-HT4 receptors in congenital heart blockade associated to a systemic autoimmune response in the mother. 5-HT4 receptor isoforms can be expressed in both central and peripheral organs and it is possible that they are important in order to maintain the normal cellular activity (Eftekhari, 2000). Also 5-HT4 receptors have been reported to be involved in memory and learning as well as in gastrointestinal function, although almost nothing is known about its role in embryogenesis. The importance of the embryonic serotoninergic system in central nervous and cardiovascular functions has been largely described [Lambert, 2001; 15-20]. In early mouse embryogenesis, maternal serotonin (5-HT) activates different 5-HT receptors to control gene expression, migration and proliferation of neuronal crest and neuronal-crest derived cells (Kamel, 2007).

When disease manifestations are not so apparent it is too hard to make a diagnostic or an association with a specific pathology, which is the case for SLE. The main alterations could be related with CNS. However, it is not possible to discard environmental factors modulating the interactions of maternal antibodies and autoantibodies with the treatment used. According to Tincani, et. al. (2006), children with complete CHB need permanent pacing, but apparently do not have neuropsychological problems. Nevertheless, their neuropsychological development shows an increased number of learning disabilities, even in children with normal intelligence. The need to consider fetal consequences when the SLE mother is being treated should always be considered thus preferentially choosing non teratogenic drugs, but the withdrawal of medications just because the patient is pregnant should be avoided to protect of SLE flares.

8. Conclusion

Newborns from SLE mothers can have a myriad of silent or openly clear manifestations in several organs, tissues and systems of the newborn, some of which are secondary to the transfer of maternal autoantibodies through the placenta as well as the brain barrier, that

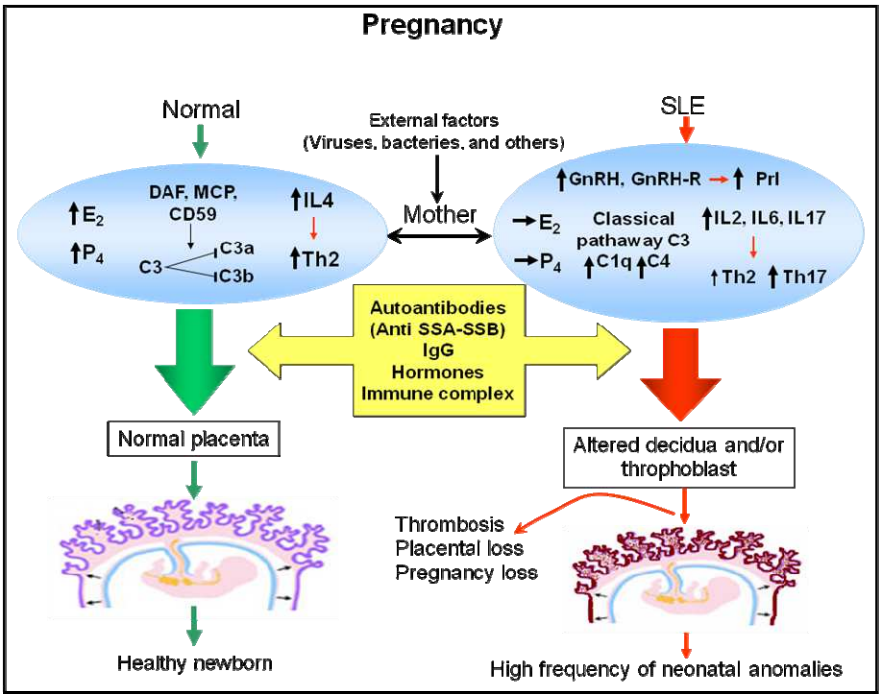

Fig. 1. Represent the two main outcomes of a pregnancy. A normal outcome, shown in the left of the figure, can results even in the presence of maternal autoantibodies the condition being that the quantity and isotype is below a threshold yet to be defined, when there is an excess and the mother has a clear SLE condition, the outcome is shown in the right side of the figure.

react with several fetal proteins (glycoproteins, lipoproteins, or lipids), but there is also the possibility that some of the alterations might be the consequence of drugs used to treat the mother in order to avoid SLE flares. All these should be clearly present within the medical community related to the diagnosis, treatment and follow up of offsprings from SLE mothers, since it is highly possible that these children will manifest some of the pathologies associated with maternal SLE, mainly those of the immune system.

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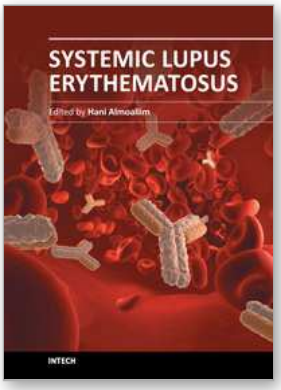

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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