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Hormones, immune response, and pregnancy in healthy women and SLE patients

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Summary

During pregnancy the maternal immune system is modified in order to achieve immune tolerance toward paternal antigen expressed on foetal cells. These modifications, which occur both at the foeto-maternal interface and in the systemic circulation, are driven by oestrogens and progesterone whose blood concentrations increase during pregnancy. The cytokine profile is also modified. Th2 cytokines are enhanced while the Th1 response is inhibited. This could explain why Th1-mediated autoimmune diseases tend to improve and Th2-mediated diseases, such as systemic lupus erythematosus (SLE), tend to worsen during pregnancy.

However, whether or not SLE relapses more frequently during pregnancy is still a matter of debate.

Steroid hormone and cytokine profiles differ in SLE patients compared with healthy subjects during pregnancy leading to a dysregulation of the balance between cell-mediated and humoral immune response, which, in turn, could explain the variability of the SLE course during gestation.

This review focuses on hormonal-related cytokine changes observed during pregnancy in healthy subjects and SLE patients.

Key words: pregnancy; sex-hormones; cytokines; autoimmunity; systemic lupus erythematosus

Endocrine and immune systems are closely related and in their mutual interactions steroid hormones and cytokines act as mediators and messengers.

Immune and endocrine cells can synthesize and express receptors for both cytokines and hormones [1] and these molecules can stimulate or suppress the activity of immune and endocrine cells by binding to their receptors [2]. For example, glucocorticoids (GCs) released as a consequence of hypothalamic-pituitary-adrenal axis (HPA) stimulation are among the most powerful endogenous mechanisms for suppressing inflammatory response genes [3, 4]. Moreover, the receptor for the component C3a (C3aR) of the complement pathway is expressed on adrenal gland and pituitary cells [5].

Sex steroids and gonadotrophin-releasing hormone (GnRH) have binding sites in primary lymphoid organs and peripheral immune cells, suggesting that they can both influence immune system by hypothalamic-pituitary-gonadal axis (HPG) activation. GnRH is involved in thymus maturation and exerts a potent immune-stimulatory effect, leading to increased levels of interleukine (IL)-2 receptor (IL-2R) and serum interferon-gamma (IFN-γ), and activation of helper T (Th) cells [6].

The mutual influence between the endocrine and immune systems could also explain why both of them may be affected by autoimmune diseases. In fact, the altered immune response may lead to altered hormone levels leading to endocrine abnormalities; by contrast, physiological hormonal variations may affect immune responses and, in turn, autoimmune diseases.

As far as systemic lupus erythematosus (SLE) is concerned, the serum levels of oestrogens, androgens, prolactin and other adrenal hormones are different in SLE patients compared to healthy subjects [7] and, conversely, changes in disease activity have been observed in physiological conditions, such as pregnancy, characterised by fluctuations of hormone levels [8–11].

In this review we first summarise the main immunological effects of sex hormones and, thereafter, we analyse the immunological changes induced by pregnancy in healthy subjects and SLE patients.

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Oestrogens

Oestrogens are considered immunomodulating hormones because they are able to "modulate" the immune response [12, 13].

Oestrogens have specific effects on the maturation of T and B cells, dendritic cells (DC) and peripheral blood mononuclear cells (PBMC) [6] (fig. 1).

Oestrogens reduce the number of immature thymic lymphocytes (CD4+/CD8+) and thymic stromal tissue, the so-called thymic involution, whereas they enhance hepatic T cell lymphopoiesis, where maturing T cells do not undergo negative selection and induction of tolerance [1, 6, 12, 14]. Oestrogens also alter the ratio of CD4+/CD8+ T cells, promoting CD4+/CD8-(T-helper)-cell phenotype [6, 15]. High levels of oestrogens can increase IFN-γ and IL-2 production by activated Th1 cells.

Oestrogens are important stimulators of humoral immunity and they have binding sites in both bone-marrow and peripheral B cells. By reducing the number of stromal cells, oestrogens cause a rapid maturation of B cells in the bone marrow, whereby they make auto-reactive B cell deletion less efficient [16–20].

Oestrogens also enhance extramedullar B cell lymphopoiesis, allowing potential autoreactive cells to completely bypass negative selection and tolerance induction [21].

These hormones also stimulate antibody production by increasing IL-10 secretion [16, 17]. During puberty and reproductive age, females have higher immunoglobulin levels compared with age-matched males at baseline and in response to immunisation or infections [12, 22].

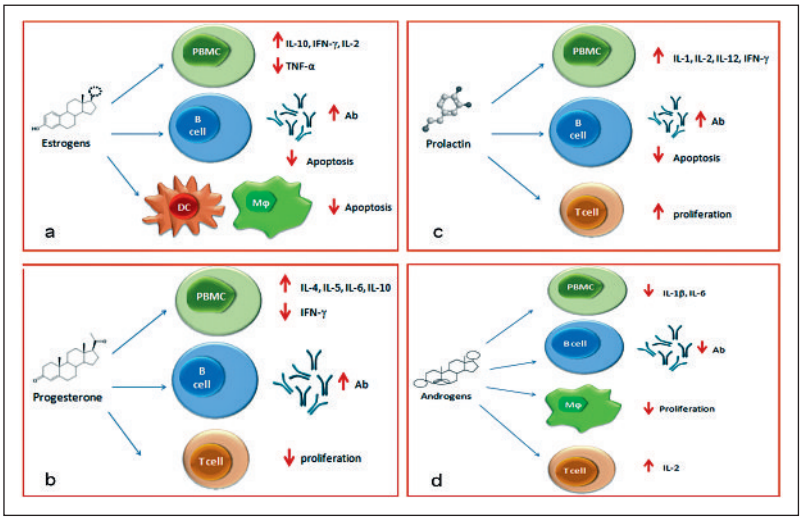

Figure 1

Main effects of steroid hormones on immune cells.
a Oestrogens enhance interleukin (IL)10, IL-2, and interferon gamma (IFN-γ) production, and inhibit TNF-α secretion by peripheral blood mononuclear cells (PBMC); stimulate antibody (Ab) production by B cells, and decrease apoptosis of dendritic cells (DC) and macrophages (Mφ).
b Progesterone enhances IL-4, IL-5, IL-6, and IL-10 production, and inhibits IFN-γ production by PBMC; stimulates Ab secretion by B cells, and decreases T cell proliferation.
c Prolactin enhances IL-1, IL-2, IL-12, and IFN-γ secretion by PBMC; stimulates Ab secretion, decreases B cell apoptosis, and T cell proliferation.
d Androgens inhibit Il-1β and IL-6 secretion by PBMC and enhance IL-2 secretion by T cells; inhibit Ab secretion by B cells and Mφ proliferation.

Oestrogens also play a role in the regulation of DC [23, 24]. Siracusa et al. [25] demonstrated that 17β oestradiol may promote innate immunity by enhancing IFN-γ production by CD11+ DC. In addition 17β oestradiol induces anti-apoptotic effects in monocyte and macrophage cell lines by interfering with NF-kB activities [26].

Noteworthy, oestrogenic effects are mediated by two different oestrogen receptors (ER), ERα and ERβ [27, 28]; it has been suggested that different oestrogen effects may be due to a preponderance of one ER subtype over the other, in different situations or tissues [29]. An inflammatory-dependent up-regulation of ERα compared to ERβ has been observed, meaning that acute and chronic inflammation can influence oestrogen effects [29].

Oestrogens in SLE

SLE patients have alterations in steroid hormone metabolism [7, 30]. An altered peripheral metabolic conversion of upstream steroid precursors to oestrogens and antioestrogens has been observed in both males and females. In SLE patients renal excretion ratio of urinary 16-alpha-hydroxyoestrone/2-hydroxyoestrogens is more than 20 times higher, so that in SLE a large shift to mitogenic oestrogens (i.e., 16-alpha-hydroxyoestrone) in relation to endogenous antioestrogens (2-hydroxyoestrogens) occurs, suggesting that abnormalities in metabolic pathways may lead to increased oestrogenic activity [31].

Whether or not the use of exogenous oestrogens is associated with higher risk of inducing the onset or exacerbation of SLE is still a matter of debate. Some clinical studies reported an association between exogenous oestrogen administration and disease flare-ups [32–36], in contrast others did not show any significant relationship [37–43].

As far as the risk of SLE induction is concerned, two large epidemiological studies with the use of oral contraceptive pills (OCP) [32, 33], and two other studies, one epidemiological [34] and the other case-controlled [35], with the use of hormonal replacement therapy (HRT) have been published. In these studies an increased risk of developing SLE was reported, with a relative risk (RR) of 1.54 and 1.9 for OCP, and a RR of 2.1 and 2.8 for HRT.

Three retrospective studies on the risk of SLE exacerbation due to the use of OCP have been published. Two of them [37, 38] found that the frequency of disease exacerbations was not different in users and non-users, being in both cases 13%; in the third study [36], OCP were administered to patients with glomerulonephritis, and the frequency of disease flare-ups in this group was high, and higher in users compared with non-users.

Three studies on the risk of SLE exacerbation due to HRT have been published [39–41], and they found a frequency of disease flare-ups similar in users and non-users.

A study, named "Safety of Oestrogens in Lupus Erythematosus: National Assessment" (SE-

LENA), was carried out in order to prospectively investigate the safety of exogenous oestrogen therapies (HRT and OCP).

One arm of the SELENA trial was a double-blind placebo-controlled randomised clinical trial (RCT) of HRT [44]. Hormonal therapy consisted of conjugated oestrogens 0.625 μg die, and 5 mg of medroxyprogesterone for twelve days each month. An increased frequency of mild to moderate disease flare-ups in users compared to non-users was observed, while the frequency of severe exacerbations was not different in users and non-users.

The second arm of the SELENA trial [42] was a double-blind placebo-controlled RCT of OCP (triphasic 35 μg ethinyloestradiol/norethindine) vs placebo for one year. No differences in the rate of mild, moderate and severe flare-ups, which was low in both groups, were reported.

It has to be pointed out that the OCP arm of SELENA trial considered only patients with stable or inactive disease, without major organ involvement, without thrombotic risk factors, including antiphospholipid antibodies, and without disease flare-up for several months before the enrollment into the study. Conversely, the patients enrolled in the HRT arm had a stable disease after menopause, which increased the eligibility of those with an oestrogen responsive disease. Thus, these results may not be extended to all women with SLE.

In 2005 a study on the safety of HRT in SLE patients was published [43]. It was an RCT which compared the use of an oestroprogestinic pill (30 μg etiniloestradiol plus 150 μg levonorgestrel), a progestinic pill (30 μg levonorgestrel) and an intrauterin device containing copper (TCu 380). The study did not show any substantial differences regarding disease activity, incidence of disease flare-ups and drug dose needed to control the disease among the three groups.

As far as the effects of oestrogens on the immune system of patients with SLE is concerned, several studies support a direct effect of 17β oestradiol on the production of IgG anti-double stranded DNA (dsDNA) antibodies as well as total immunoglobulins (Ig)G in PBMCs from SLE patients [45, 46] and it has been shown that an increase in oestrogens or prolactin can induce B cell hyperactivity leading to a break of tolerance for high-affinity DNA-reactive B cells [17].

Thus, oestrogens may facilitate the maturation of pathogenic naïve autoreactive B cells, whereas hampering a potentially protective autoreactive B-cell repertoire [47].

In a mouse model of oestrogen-induced lupus, oestrogens promote the survival and activation of the T-independent marginal zone B-cell subset [48]. Tamoxifen, in this murine model, blocks the development of autoreactive B cells by blocking the expansion of the marginal zone B cells [49].

Oestrogens have a stimulatory effects on SLE T cells; for example, they have been proven to exert an anti-apoptotic effect, increasing the expression of the anti-apoptotic molecule Bcl-2, which blocks tolerance induction of T cells [50].

Oestrogen treatment induces an increase in the production of IL-10 and a decrease in that of tumour necrosis factor alpha (TNF-α) by PBMCs of patients with SLE, but not in healthy subjects [51]. Because of TNF-α 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 oestrogen concentrations, as occurs in pregnancy.

The relationship between oestrogens and ER may play a role in the pathogenesis of SLE. One study in New Zealand Black & New Zealand white (NZB/NZW) F1 mouse model of lupus-like disease suggests that ERα activation exerts a stimulatory effect on endocrine response in lupus, while ERβ activation appears to have a slightly immunosuppressive effect on the disease [52].

It has also been shown that ERα may promote lupus, at least in part, by inducing IFN-γ in NZB/NZW F1 mice [53].

Some Authors [54] reported that ERα mRNA expression is increased and ERβ mRNA expression decreased in PBMC from SLE patients compared to normal controls. In contrast, Rider V et al. [55] demonstrated that ERβ and ERα mRNA expression is similar in T cells from SLE patients and healthy controls. Finally, Phiel KL et al. [56] showed that in SLE the expression of ERα mRNA was higher compared to that of ERβ mRNA in CD4+ T cells, but the former was lower than the latter in B cells, and the expression of both receptors was similar in CD8+ T cells and monocytes.

Different polymorphisms of ERα gene have been reported in SLE patients where they seem to be related to sex, age at disease onset, and some clinical disease symptoms [57–60], suggesting that these polymorphisms might contribute to SLE susceptibility.

It is noteworthy that a recent study [61] which analysed the association between ERα gene polymorphisms and Th1 and Th2 cytokine expression found that there were some differences in cytokine mRNA expression among SLE patients with different ERα genotype: for example, the level of IL-10 mRNA was higher in SLE patients with the ERα PpXx genotype than in healthy controls. In a recent study it has been shown that ERα activation coincidentally increased prolactin serum levels which, in turn, may accelerate disease activity [62].

Progesterone

Progesterone is a potent immune modulator as demonstrated by the observation that the course and symptoms of autoimmune diseases change during the menstrual cycle and pregnancy [63–65].

Progesterone acts in a number of immunological pathways (fig. 1), e.g., it blocks mitogen-stimulated T cell proliferation [66], alters cytokine se-

cretion of T-cell clones enhancing IL-10 production [67], modulates antibody production [68], decreases the oxidative burst of monocytes [69], and reduces the production of pro-inflammatory cytokines by macrophages in response to bacterial products [67].

As far as its effect on Th1/Th2 immune profile is concerned, progesterone promotes a Th2 polarisation stimulating the production of IL-4, IL-5 and the anti-inflammatory cytokine IL-10 [67]. Moreover, IFN-related genes are down regulated in peripheral blood leukocytes (PBLs) in women in the luteal phase, when progesterone reaches its peak levels, compared with the follicular phase of the cycle [70]. In addition, progesterone has been reported to induce a 34-kD protein, named "Progesterone-induced blocking factor" (PIBF), which is known to regulate humoral and cell-immune responses in several ways [71], including the induction of a Th2-dominant cytokine profile [72].

During pregnancy Th2 polarisation occurs both in the systemic circulation and at the foeto-maternal interface. At pharmacological levels, such as those observed in the second part of gestation, progesterone inhibits Th1 type cytokine production from T cells and induces Th2 cytokines and IL-10 production, leading to a stimulation of humoral immune response [73]. Thus, high progesterone levels at the feto-maternal interface might contribute to successful pregnancy [69].

This hypothesis is supported by the observation that progesterone and IL-4 up-regulate leukaemia inhibitory factor (LIF) [74], which is essential for embryo implantation and for pregnancy maintenance [75]. A defect of LIF, IL-4, and IL-10 production was observed in decidual T cells of women suffering from unexplained recurrent abortion [74].

At the foeto–maternal interface, progesterone in part contributes to support IL-3, IL-4, IL-5 and IL-10 production [76], inhibiting Th1 responses and favouring foeto-allograft tolerance in women.

Progesterone also modulates the IL-6 signal transduction pathway [77].

Three homologous genes of membrane progesterone receptor (mPR) have been recently identified in humans, mPRα, mPRβ, and mPRγ [78]; mPRα and mPRβ are expressed by PBMCs and T cells [79]. The expression of mPRα in CD8+T cells appears to be modulated by progesterone. At high levels, like those observed in the mid-luteal phase of the cycle, progesterone up-regulates mPRα [79]. This observation is particularly interesting, since these cells seem to mediate a protective effect of progesterone derivatives against stress-induced abortion in mice by favouring Th2 polarisation [80].

Progesterone in SLE

Inadequate or lower production of progesterone in early follicular phase and in the luteal phase of menstrual cycle has been found both in adult SLE and in juvenile SLE [81–83] compared to healthy women, supporting a possible luteal dysfunction in this disease.

Prolactin

Prolactin is a 23 kD polypeptide hormone produced mainly by the anterior pituitary gland that stimulates mammary growth and differentiation.

This hormone is produced also in extrapituitary sites, including neurons, mammary epithelium, prostate, endothelium, skin, and immune cells including thymocytes and PBMCs, mainly lymphocytes. Extrapituitary prolactin has a different molecular weight and biological activity [17].

Prolactin is thought to be important in maintaining immune competence and seems to have a role in the pathogenesis of autoimmune rheumatic diseases (ARD) [84].

All activities of prolactin are mediated by the prolactin-receptor (PRL-R), a member of the haematopoietin cytokine receptor superfamily [2]. PRL-Rs are expressed on monocytes, macrophages, T and mainly B cells, natural killer (NK) cells, granulocytes, spleen and thymic epithelial cells [17, 85].

Prolactin has pleiotropic effects on the immune system and it appears to stimulate both humoral and cell-mediated immune response (fig. 1).

Prolactin stimulates inducible nitric oxide (iNO) synthesis production, immunoglobulin release and cytokine expression in human leukocytes [86, 87]; it acts as a mitogen for T cell [88], significantly enhances the expression of CD69, CD25 and CD154 on DC [89], and modulates B cells development [90–92].

Prolactin 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 co-stimulatory molecules CD40, CD80, and CD86 [93]. The effect of prolactin on antigen presentation and on B-T cells interaction results in increased response to MHC presented auto-antigens, leading to 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 [94].

Thus, hyperprolactinaemia has been found to be a risk factor for the development of autoimmunity and ARD [29].

Prolactin up-regulates Th1 type cytokines including IL-12, IL-1, IL-6, and IFN-γ [17, 95], and increases the effect of IL-2 on lymphocytes [96].

Physiological concentrations of prolactin have an inhibitory effect on GM-CSF-driven differentiation of DC, whereas higher concentrations (i.e., 80 ng/mL) have a stimulatory effect [89]. These observations suggest that prolactin participates in DC maturation and provides further evidence of

the role of prolactin in the T cell activation process.

Prolactin induces a decrease in apoptosis of transitional B cells and may be important in the breakdown of B cell tolerance to self antigens and, in turn, in the development of autoimmunity [84].

Therefore, prolactin can modulate immune and inflammatory responses.

The production of prolactin by T cells is regulated by cytokines. Both IL-2 and IL-4 reduce prolactin mRNA levels in T cells [97].

Prolactin progressively increases during pregnancy, reaching at term serum levels which are about 10 times pre-pregnancy levels, and in post partum (during breastfeeding) serum levels which are about 30 times pre-pregnancy levels.

Prolactin in SLE

Prolactin has some immune effects that mirror oestrogens and others which antagonise them [98].

In mice prolactin stimulates immune response and it has been demonstrated to play a role in murine lupus and other autoimmune diseases. In murine SLE models, hyperprolactinaemic mice have elevated albuminuria, regardless of oestrogen levels [99].

Mild to moderate hyperprolactinaemia has been demonstrated in 15–33% of SLE patients of both genders [100].

The exact origin of hyperprolactinaemia in SLE patients is unknown but some studies suggest that active SLE lymphocytes from patients with active disease may be the source of prolactin [100–102]. However, it is not known if lymphocytes can produce enough prolactin to cause an increase in serum prolactin levels.

Human studies have suggested that high levels of prolactin are associated with major and minor organ involvements such as joint and cutaneous manifestations, nephritis, and neuropsychiatric involvement [103].

Moreover, association between increased levels of prolactin and clinical or laboratory indices of disease activity has been observed [96, 100, 104–107] and a significant correlation between bioactive or immunoreactive prolactin levels and SLE activity [106], suggesting an immune-stimulatory contribution of this hormone to the pathogenesis of the disease, has been found.

Hyperprolactinaemia is associated with several autoantibodies involved in SLE such as antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anticardiolipin, and hypocomplementaemia [100].

Anti-prolactin antibodies were reported in the serum of lupus patients where they were associated with decreased disease activity. This effect could be due to a lowering of the biological activity of prolactin, by interfering with the binding to its receptor (PRL-Rs) on lymphocytes. Moreover, anti-prolactin antibodies may deregulate prolactin secretion and induce hyperprolactinaemia [107].

Prolactin may also interact with DCs, skewing their function from antigen presentation to a pro-inflammatory phenotype characterised by high interferon-α production [108]. The relationships between prolactin and DCs may have a role in the pathogenesis of SLE.

Androgens

Androgens seem to act as oestrogens counterbalance in their immunological effects [6] (fig. 1). Androgens influence the size and the composition of the thymus and seem to reduce antibody production [6]. Testosterone influences the subsets of mature T-cell, inducing the CD4-/CD8+(T-suppressor)-cell phenotype [6].

Androgen administration in hypogonadal males with Klinefelter Syndrome reduces immunoglobulin levels from a higher and female-like level to a lower and healthy male-like one [109].

Testosterone also exerts pro-apoptotic effects and reduces macrophage proliferation [26], and inhibits IL-1β and IL-6 secretion by PBMC [6].

Dehydroepiandrosterone (DHEA), the major product of the adrenal glands in both men and women, dehydroepiandrosterone-sulphate (DHEAS), and related steroid hormones have a variety of effects on the immune system in vitro, experimental models, and humans. DHEA, for example, upregulates IL-2 production in normal T cells [110, 111].

Androgens in SLE

In autoimmune diseases such as SLE, there is a shift from DHEAS to cortisol or androstenedione [112]. In men with lupus, lower testosterone levels and higher oestrogens levels have been reported [113]. In women with SLE, there are lower levels of both testosterone and the mild androgen DHEA [113].

Clinical trials carried out in women with SLE showed that women taking DHEA 200 mg/day were more likely to have stable or improved disease [114], low daily prednisone maintenance dose [115], or fewer SLE flares over one year [116].

Cytokines

Although it represents an over simplification, cytokines can be schematically subdivided into two functional groups: Th1 type cytokines, produced by Th1 cells, which are involved in cell-mediated immunity, and Th2 type cytokines, produced by Th2 committed cells, which enhance humoral immunity.

Th1 cells produce IL-2, INF-γ, TNF-α, and

IL-12 and are thought to drive tissue damage in some chronic inflammatory autoimmune diseases such as rheumatoid arthritis. Th2 cells secrete IL-4, IL-5, IL-13 which mediate B cell activation and antibody production, driving other autoimmune diseases such as SLE.

It is well known that these two pathways reciprocally inhibit each other [117, 118].

During T cell activation, the cytokine secretion pattern drives the differentiation of precursor CD4+ T cells into Th1 or Th2 cells: IL-12, IL-18, and IFN-γ drive a Th1 differentiation while IL-4 and/or IL-6 lead to a Th2 differentiation [119, 120].

IFN-γ is a major contributor to a Th1 immune response because it strongly inhibits Th2 cell development.

By contrast, IL-10 is an anti-inflammatory cytokine produced by both Th1 and Th2 cells, which down-regulates the production of pro-inflammatory cytokines by Th1 cells and macrophages, thus favouring a Th2 cytokine mediated response [118].

It has to be noted that IL-6 exerts a double effect in Th2 polarisation: on the one hand it stimulates Th2 differentiation through a IL-4 mediated mechanism, on the other hand it inhibits Th1 differentiation with a different and independent mechanism, interfering with IFNγ signalling [121].

In the last few years a new interest in the Th17 cell family has emerged [122–127] (fig. 2). Most studies have focused on murine Th cells which mainly produce IL-17 and indicated that IL-17 is predominantly produced by a Th cell subset that is distinct from Th1 and Th2 cells [128].

IL-17 cytokine family has gained prominence due to its involvement in both human and mouse autoimmune diseases. The IL-17 family consists of six members including IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F [129].

IL-17 is expressed by CD4+ T cells, CD8+ T cells, NK T cells, γδ T cells, and neutrophils under certain conditions [130].

Studies on IL-17 receptor (IL-17R)-deficient mice showed that the IL-17/ IL-17R system is essential for host defense against infections, particularly with gram-negative bacteria; these infections require the production of IL-17 to generate an appropriate host response and abscess formation [131, 132].

In Mycobacterium tuberculosis pulmonary infection an early pathogen-specific response from these cells infiltrating the lung triggers the induction of chemokines that attract IFN-γ-producing Th1 cells which eventually control infection [133].

IL-17A and IL-17F are also key cytokines for the recruitment, activation and migration of neutrophils [133].

Th17 cells also play an important role in protection from systemic fungal infections [134].

Some studies have recently shown that IL-21 is an important cytokine produced by Th17 cells and exerts an important role in promoting Th17 differentiation [135–138]. In the presence of Tumour Growth Factor beta (TGFβ), IL-21 promotes Th17 differentiation and inhibits generation of regulatory T cells (Treg) [139].

IL-21- and IL-21R-deficient mice exhibit deficiency of Th17 cells in vivo [137].

IL-6 or IL-21 can induce Th17 cells to produce more IL-21 and disruption of the IL-21 pathway results in reduced Th17 differentiation [140]. In addition, it was found that IL-23 could drive the expansion of the IL-17-producing T cell population [141].

Several studies indicate that IL-1β, in combination with IL-6 and/or IL-23, is required for human Th17 differentiation, and its production determines the ability of APCs to promote Th17 differentiation [140].

The optimum condition for human Th17 differentiation is the presence of TGFβ-1, IL-1β, and IL-2 in combination with IL-6, IL-21 or IL-23 [142].

Altogether, current data suggest that IL-6 can induce IL-21 production from IL-17-producing T cells which, in turn, functions in an autocrine self-amplification loop to increase Th17 response. Furthermore, both IL-6 and IL-21 can up-regulate the expression of IL-23 receptor on Th17 cells.

Therefore, there are three distinct steps in the development of Th17 cells: induction, amplification and stabilization, in which three distinct cytokines, IL-6, IL-21 and IL-23 are crucially involved.

Th1 and Th2 cells cross-inhibit each other's differentiation. Similarly, the hallmark cytokines

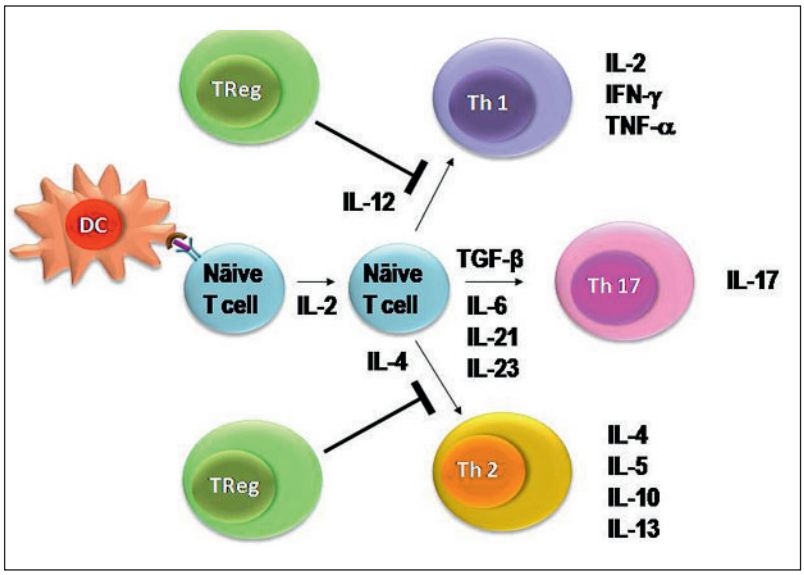

Figure 2

Näive T cell differentiation into Th1, Th2, or Th17 cells and cytokine prevalently produced by these cells.
The presence of interleukin (IL) 12 drives Th1 differentiation; IL-4 induces the Th2 phenotype, while TGF-β, IL-6, IL-21, and IL-23 stimulate Th17 differentiation. Regulatory T cells (TReg) inhibit IL-12 and IL-4-mediated Th1 and Th2 differentiation.
IL: Interleukin; IFN: Interferon; TNF: Tumour necrosis factor; TGF: Tumour growth factor; DC: Dendritic cell; Th: T helper cell.

of Th1 and Th2 cells, IFN-γ and IL-4, inhibit the IL-23-driven expansion of Th17 cells [143].

IL-27 has also been demonstrated to be a negative regulator of Th17 cell development. IL-27 belongs to the IL-12 family and it is produced by DC and macrophages [144].

Cytokines in SLE

SLE patients exhibit a Th2-type cytokine enhanced profile: IFN-γ production, in vitro IL-2 secretion by T cells, IL-12 synthesis by B cells, macrophages, and dendritic cells were reduced, whereas an enhanced IL-10 spontaneous production by B cells and PBMC, and an increase of IL-4 secretion were observed [11, 26, 113].

The number of IFN-γ-secreting PBMC is lower in SLE patients than in healthy subjects, and the decrease in IFN-γ-secreting cells is greater in patients with active disease [113]. This study did not find any difference in the number of IL-10, IL-6 and TNF-α-secreting cells.

Th17 cells are increasingly recognised as important mediators of autoimmune diseases [125, 145–147]. They are observed in human inflamed tissues from patients suffering from a variety of inflammatory [148–150] and autoimmune disorders [151–154].

Studies of several mouse models of lupus-like disease support the idea that IL-17 is involved in the development of SLE [155]. Interestingly, it has been suggested that IL-17 can promote SLE development by inducing the formation of spontaneous germinal centers [155].

High IL-17 serum levels have been reported in patients with SLE [156–160]. However only one study [160] found correlations between IL-17 serum levels and SLE disease activity, whereas in the others no associations between IL-17 serum levels and clinical or laboratory features, including glomerulonephritis, were found [159]. Doreau et al. [160] found a correlation between IL-17 serum levels and anti-dsDNA antibody levels, but not with total immunoglobulin serum levels.

A relationship between Th17 cell number and SLE disease activity, especially vasculitic manifestations, was reported [158]. Vasculitis is one of the hallmarks of SLE and is characterised by lymphocyte infiltration in small vessel walls. Th17 cells might contribute to SLE vascular inflammation.

IL-17 might have an important role in the pathogenesis of lupus nephritis through IL-6 overexpression by PBMC and the induction of IgG, including anti-dsDNA antibodies. In addition, IL-17-producing double-negative T-cell infiltration in kidney biopsy from patients with SLE nephritis was found [161].

These findings are in keeping with the abnormal cytokine profile which characterises SLE patients in which low IL-2 concentration, high IL-6 secretion, and an over-expression of other pro-inflammatory cytokines could promote Th17 differentiation.

Hormone variations during pregnancy in healthy subjects

During pregnancy, hormonal changes are driven by the foeto-placental unit [162]: oestrogens, progesterone and prolactin increase, while androgens decrease (table 1).

Progesterone is secreted by the corpus luteum during the first 6–8 weeks of gestation and, thereafter, it is mainly produced by the placenta. It is the key hormone in the first part of pregnancy and is the precursor of some foetal hormones. During pregnancy, progesterone serum levels are 4–6 times higher than those observed in non-pregnant women. One of its metabolites, deoxycorticosterone, reaches concentrations 1000 times higher than those observed outside pregnancy, but its physiological role remains unknown [162].

Also oestrogen concentrations greatly increase during pregnancy, reaching levels 3–8 times higher than those observed at baseline [162]. This increase is the result of a mutual exchange between mother and foetus. The foetus uses pregnenolone, produced by the placenta, to produce DHEA and DHEAS in the adrenal gland. These hormones are metabolised to androstenedione and testosterone by the placenta, then they are

Table 1

Steroid hormone levels in healthy and SLE pregnant women in the third trimester of pregnancy compared to healthy non pregnant levels. The data refer to Doria et al. [9], Branch et al. [162], Shabanova et al. [7].

	Healthy pregnant women	SLE pregnant women	Difference between SLE and healthy pregnant women
17β oestradiol	↑↑	↑ =	Significantly lower
Progesterone	↑↑	↑ =	Significantly lower
Testosterone	↑	↑	Same
DHEAS	↑	↑	Significantly lower
Cortisol	↑↑	↑	Same

↑↑: Highly increased
↑: Increased
↑ =: Slightly increased

rapidly converted to oestrone and oestradiol entering maternal circulation [162]. The metabolite of DHEA, hydroxylated in position 16-α by foetal liver, is converted to oestriol in the same way.

Hormone variations during pregnancy in SLE patients

In SLE patients serum levels of all steroids vary significantly during pregnancy and the postpartum period.

In SLE pregnant patients 17-β oestradiol, progesterone, and DHEAS concentrations have been found to be significantly reduced compared with those observed in healthy pregnant women in the same trimester of gestation [9, 163, 164]. Interestingly, during the second and to a further extent during the third trimester of gestation a lack of 17-β oestradiol serum level increase, and, to a lesser extent, of progesterone serum level increase have been observed in SLE patients compared to healthy subjects [9].

Immunological changes induced by pregnancy

During pregnancy there is a physiological adaptation of the maternal immune system to prevent the rejection of the foetus which in the mother's perspective is a sort of semi-allogeneic transplant. Tolerance to foetal antigens of paternal origin should occur without compromising maternal immune system, since it is crucial for the mother and the foetus to maintain immune competence.

Trophoblast cells play a decisive role in the development of maternal tolerance to paternal antigens, by using four main mechanisms:

1. Trophoblast cells do not express MHC class I and class II molecules preventing maternal T cells to mount a classical cytotoxic-mediated rejection against alloantigens expressed on foetal cells [165].
2. Placental extravillous cytotrophoblast cells express the non-classic MHC class I b gene encoding HLA-G, HLA-E and HLA-F [166]. Whereas the role of HLA-F still needs some elucidation, HLA-G and HLA-E seem to act as immunotolerogenic agents in two ways: first, they might play a role in the down regulation of NK cell activity, since trophoblast cells expressing HLA-G can not be killed by NK cells; secondly, they might induce the activation of some CD8+ T cells with suppressor function [167–170];
3. The trophoblast expresses FAS ligand (FASL) thereby protecting itself from immune-cell attack; in fact, the interaction between maternal FAS+ T cells and FASL expressing foetal cells leads to programmed cell death or apoptosis of immune cells thus contributing to immune specific tolerance to paternal antigens [171].
4. The trophoblast express CD46, CD55 and CD59 which are complement regulatory proteins that can prevent complement activation via the classic and the alternative pathways. CD46 and CD55 inhibit C3 convertase activity while CD59 inhibits Membrane Attack Complex (MAC) formation, thus protecting the foetus from complement mediated maternal reactions [172].

In addition to these protective mechanisms which involve the expression of membrane molecules on the trophoblast cell surface, other soluble factors such as cytokines, which are produced in large quantities by the placenta, can play an important immunoregulatory role at the foeto-maternal interface.

Variations in cytokine profile during pregnancy in healthy women

A central role in immunological adaptation to pregnancy is played by cytokines, whose production undergoes considerable changes during pregnancy.

Many studies have shown that the increase in cortisol, progesterone, oestradiol and testosterone concentrations during pregnancy is associated with an increased production of Th2 cytokines and a reduced expression of Th1 cytokines, resulting in a Th2 polarisation of immune response which was observed at systemic level as well as at the maternal-foetal interface [173, 174] (table 2).

As a consequence of Th2 polarisation, cell-mediated immunity and Th1 cytokines are inhibited, while Th2-mediated humoral response is enhanced [10].

Th1-Th2 shift could explain why Th2-mediated autoimmune diseases, such as SLE, tend to develop or worsen during pregnancy [11], while Th1-mediated diseases, such as rheumatoid arthritis, tend to improve. In both cases a disease flare may occurs in the postpartum period [174].

Th2 cytokines deviation seems to be important for the trophoblast to invade and anchor to the deciduas, favoring pregnancy maintenance [175]. In this process cytokines act in a coordinated fashion either at the maternal-foetal interface or systemically [176, 177]. In fact, an adequate

Table 2

Cytokine levels in healthy pregnant women, SLE patients, and SLE pregnant patients compared with those observed in healthy non pregnant women.

	Healthy pregnant women	SLE patients	SLE pregnant patients
IL-6	↑	↑	=
IA–10	↑↑	↑	↑
TNF-α	= or ↓	↓	n.d.
sTNFR I	↑↑	↑	=
sTNFR II	=	=	=

↑↑: Highly increased
↑: Increased
↓: Decreased
=: Unchanged
n.d.: Not done
The data derive from the following studies: Doria et al. [10, 11], Verthelyi et al. [113], Halonen et al. [185], Østensen et al. [186], Kupferminc et al. [187], Richard-Patin et al. [213].
IL: Interleukin; TNF: Tumour necrosis factor; sTNFR: soluble TNF receptor

cytokine profile is crucial in order to orchestrate the early stage of embryo implantation and the late stage of trophoblast invasion by maternal uterine vessels [178].

At the foeto-maternal interface cytokines are produced by local T cells, however Th2 cytokines seem to be mostly produced in non-lymphoid tissues including placental/decidual tissues, particularly the trophoblast [175].

Th1-type cytokines such as TNF-α, IFN-γ, IFN type 1, IL-1, and IL-2, and Th2-type cytokines such as IL-4, IL-5, IL-6, TGF-β, and other cytokines such as colony stimulating factors (CSF) and IL-10, have been detected in placental tissues [179, 180]; however, Th2-type cytokines and IL-10 were found to be highly expressed [181], whereas Th1-type cytokines were only marginally expressed [182].

The expression of a panel of cytokines, including IL-17, in the uterus, the peri-implantation embryo, and later on decidual and placental tissues in murine pregnancy was evaluated [183]. In this study IL-17 was expressed at the feto-maternal interface during pregnancy.

It has been shown that IL-17 is expressed on trophoblast cells as well as on invasive HLA-G+ extravillous trophoblast, on villous cyto- and syncytiotrophoblasts, and on placental macrophages (Hofbauer cells) in at term human placenta [184].

The precise role of IL-17 in placental development is unclear. IL-17 has been detected with an identical pattern in placental tissues of successful pregnancy, spontaneous miscarriage and molar pregnancy. This suggests that IL-17 does not exert an inhibitory effect on placental development although it may regulate the production of other cytokines normally expressed at the foeto-maternal interface [184].

Cytokine and soluble cytokine receptor serum levels change throughout the different trimesters of pregnancy.

In the systemic circulation of pregnant healthy women, IL-10, IL-4, IL-6, and IL-13 production progressively increases, while serum levels of most Th1-type cytokines (IL-1α, IL-1β, IL-2, IL-12, IFN-γ) significantly decrease in the third trimester compared with those observed in the first trimester of pregnancy [44, 72, 185].

TNF-α serum levels do not seem to vary during pregnancy, while those of sTNF-αR increase [10, 186, 187], probably in order to protect the foetus from the deleterious effects of TNF-α, which has been associated with preeclampsia, intrauterine growth retardation, and pathologic labor [188, 189].

Therefore, Th1 cell immune response decreases and Th2-type cytokines enhance as a result of these immunological changes induced by pregnancy.

Four recent studies investigated the levels of IL-17 in the sera from pregnant women: three of them [190–192] found no significant differences in IL-17 serum levels between pregnant women with and without preeclampsia; one found detectable levels of IL-17 both in serum and in amniotic fluid of pregnant women without evidence of infection [180].

In the last few years a great interest on the relationship between inflammation and pregnancy outcome has emerged. A deregulation of cytokine networks can lead to adverse pregnancy outcomes including spontaneous abortion, preterm labour, pre-eclampsia, and intrauterine growth restriction [175, 193, 194]. For example, high-secretor genotypes of IFN-γ and IL-10 genes have been associated with an increased risk of recurrent early pregnancy loss [195], while an altered endometrial IL-1α and IL-6 production at the implantation site has been implicated in recurrent miscarriage [196]. Higher levels of IL-6, IL-8, and soluble IL-4 receptor in the sera of women with preeclampsia compared to women with normal pregnancies were observed [190].

Variations in cytokine profile during pregnancy in SLE patients

The immune regulatory changes induced by pregnancy in patients with rheumatic diseases have been recently evaluated [10, 11, 197, 198].

SLE patients show a lower than expected increase in IL-6 serum concentration in the third trimester of pregnancy [11] (table 2). This is probably due to the lower than expected oestrogen and progesterone levels observed in SLE pregnancies [30] (table 1).

SLE patients show persistently high IL-10 serum levels without any changes during gestation and the postpartum period, thus suggesting a constitutional rather than steroid-induced hyperproduction of this cytokine [10, 11] (table 2). Interestingly, SLE pregnant women have higher IL-10 serum levels compared to healthy pregnant women within each trimester of pregnancy [11].

It is noteworthy that a significantly decreased level of IL-4 mRNA expression during all trimesters of gestation and in postpartum period was observed in SLE pregnant patients compared with healthy pregnant women [199].

sTNFR I serum levels were higher in SLE patients than in controls before and after pregnancy, but not during gestation [11]. No differences were observed in sTNFR II serum levels in SLE patients compared with controls before, during and after pregnancy [11].

Unfortunately, no data on Th17 response in SLE pregnant women are available to date.

Pregnancy outcome in SLE

Pregnancy and the postpartum period represent a paradigmatic example of how changes in steroid hormone concentrations affect immune and inflammatory responses in healthy women and how they can modify the expression of autoimmune diseases.

The greatest risk for SLE mothers during pregnancy is the occurrence of a disease relapse.

SLE flare-ups during pregnancy and post partum are usually mild to moderate, with a predominance of cutaneous and articular manifestations [10, 11, 200–202]. Severe relapses with major organ involvement, such as glomerulonephritis or central nervous system involvement are reported with a frequency ranging between 5% and 46% [203, 204].

Observational studies show higher disease activity during pregnancy and post partum, with the highest rate of flare-ups among women with active disease at the time of conception and, conversely, lower frequency among patients with inactive disease for a long time [10, 202, 205, 206]. This suggests that maternal disease activity in 6–12 months before conception represent a risk factor for SLE relapse during pregnancy.

It is noteworthy that a relapse of glomerulonephritis is common during pregnancy even in patients with inactive disease [205, 207].

Whether or not SLE tends to flare-up more during pregnancy is still a matter of debate.

Up to now seven prospective control studies, using SLE non-pregnant patients as controls, have been published, but they did not allow a definitive conclusion: in fact, according to three of them SLE flares up more during pregnancy [205, 206, 208], whereas according to the other four there are no differences in the relapse frequency between pregnant and non-pregnant patients [209–212].

According to some recent prospective studies, the incidence of flare-ups is higher in the second trimester of gestation and lower in the third trimester [10, 11, 213, 214].

This might be related to the fact that in SLE pregnant women oestrogen, progesterone, testosterone and DHEAS serum levels do not show a peak in the third trimester as expected in healthy women [10, 164]. The mechanism underlying these hormonal abnormalities in SLE patients might be placental damage [10]. Indeed, vascular changes and/or coagulation abnormalities including infarctions, oedema/swelling, and villous thrombosis have been observed in placental histological examination [215, 216].

Since the disease prognosis has greatly improved in the last few decades [217–222], it is quite common to observe SLE patients who are pregnant or are eager to become pregnant. Thus, it is very important to study the reciprocal relationship between pregnancy and the disease in order to plan pregnancy when it is more appropriate.

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