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Exacerbations of autoimmune diseases during pregnancy and postpartum

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Autoimmune diseases represent a complex heterogeneous group of disorders that occur as a results of immune homeostasis dysregulation and loss of self-tolerance. Interestingly, more than 80% of the cases are found among women at reproductive age. Normal pregnancy is associated with remarkable changes in the immune and endocrine signaling required to tolerate and support the development and survival of the placenta and the semi-allogenic fetus in the hostile maternal immune system environment. Gravidity and postpartum represent an extremely challenge period, and likewise the general population, women suffering from autoimmune disorders attempt pregnancy. Effective preconception counseling and subsequent gestation and postpartum follow-up are crucial for improving mother and child outcomes. This comprehensive review provides information about the different pathways modulating autoimmune diseases activity and severity, such as the influence hormones, microbiome, infections, vaccines,

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among others, as well as updated recommendations were needed, in order to offer those women better medical care and life quality.

Introduction

Autoimmune diseases (AD) represent a complex heterogeneous group of disorders that occur as a results of immune homeostasis dysregulation and loss of self-tolerance. Their pathogenic mechanisms remain unclear, although an intricate interplay between the immune system and assorted stimuli is well recognized [1]. The concept of the 'Mosaic of Autoimmunity' defines the multifactorial origin in which genetic, environmental, immunological and hormonal factors interact dynamically to engender autoimmune diseases [2]. To date, almost 100 systemic and organ-specific autoimmune/auto-inflammatory conditions have been identified, affecting between 5 and 20% of the Western countries population. Interestingly, more than 80% of the cases are found among women at reproductive age, suggesting a crucial influence of sex hormones in this asymmetry [3,4]. Further, the disease onset or relapse during pregnancy and postpartum, and an amelioration in the postmenopausal years, are some of the points that support this theory [5]. The first explanation could be due to the estrogenic influence, however hormonal variations during pregnancy and postpartum advocate for sophisticated hypothesis [6]. Androgens and progesterone have been reported to carry immunosuppressive properties [7], while estrogen and prolactin play an important role in modulating the immune response, inhibiting the negative selection of autoreactive B lymphocytes, accelerating their maturation and ability to secrete self-reactive antibodies [5,8]. Normal pregnancy is associated with remarkable changes in the immune and endocrine signaling required to tolerate and support the development and survival of the placenta and the semi-allogenic fetus in the hostile maternal immune system environment [9,10]. At the end of pregnancy, immunologic milieu turns into a pro-inflammatory state to promote labor and delivery. Serum levels of estradiol, progesterone and prolactin gradually increase during pregnancy. In contrast, parturition is followed by an abrupt estrogen and progesterone withdrawal, while prolactin levels remain high specially on breastfeeding mothers [11]. Therefore, a growing interest on the immune-modulatory effects of sex hormones and their influence on the development of autoimmune phenomena has emerged in the last years.

Autoimmune diseases during pregnancy and postpartum period

The risk of development an AD is significantly increased during the first year postpartum, but subsequently trended in the opposite direction [12]. Recent studies underscore the importance of delineating time windows in relation to pregnancy, and suggest that the postpartum period warrants special consideration in terms of risk of AD among women, as summarized in Table 1. Until our days, assorted mechanisms have been proposed to clarify this enigmatic leaning.

Plausible mechanisms for autoimmunity during pregnancy and postpartum

Loss of the immunosuppressive state of pregnancy

The fact that immune system allows women to successfully carry a conceptus, which is liken to a semi-allograft, to full term without rejection and protecting, at the same time, against infections is an alluring aspect of pregnancy. One of the important adaptations is the shift, at implantation, from a pro-inflammatory Th1/Th17 response toward a Th2/Treg cell response, which promotes tolerance. Thus, T cells functions exacerbated during pregnancy characterized by a tolerogenic Th2-type profile, could have an influence on AD activity [6,13,14]. Therefore, pregnancy is associated with a protective effect in Th1-dominant immune diseases, like Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA). In contrast, an increased Th2 response and enhanced production of pathogenic autoantibodies have been

Table 1
Influence of pregnancy and postpartum period on autoimmune diseases.

Disease	Influence of Pregnancy	Influence of Postpartum	Comments
Systemic Lupus Erythematosus	Worse	Worse	Reported rate of flares range from 13.5 to 68% among pregnant women [191–202]. Fewer studies have examined postpartum flares [194,203]. Recently, Euly et al. (2018) stated that incidence of disease flare increased during pregnancy (HR 1.59; 95% CI 1.27–1.96) and within the 3 months after delivery (HR 1.48; 95% CI 1.07–1.95), compared with non-pregnant, non-postpartum periods [204].
Rheumatoid Arthritis	Improve	Worse	Approximately 75–90% of patients with Rheumatoid Arthritis will improve during pregnancy and 35–66% will relapse during postpartum [205–210]. The total number of patients in remission increased during pregnancy from 17% in the first trimester to 27% in the third trimester ($P = 0.16$), and decreased to 18% in the 12th week postpartum ($P = 0.07$). The impact of pregnancy on disease activity in the third trimester was most pronounced in patients who had moderate to high disease activity in the first trimester. Postpartum exacerbation was reported in 39.3% of all patients.
Systemic Sclerosis	Inconsistent	Worse	Studies provide inconsistent results regarding the global stability during pregnancy [211–215], although an exacerbation following postpartum period has been demonstrated [215,216].
Autoimmune Thyroid Disease	Improve	Worse	Grave's Disease usually ameliorates during pregnancy [175,218]. Postpartum thyroiditis occurs in 7–10% of postpartum women, although this varies depending on iodine intake and genetic factors [219]. Between 40 and 60% of women with Grave's Disease developed their disease during the postpartum period [220]. Almost 50% of women with anti-thyroid peroxidase antibodies in early pregnancy will develop postpartum thyroiditis [221,222].
Multiple Sclerosis	Improve	Worse	Compared to pre-pregnancy, annualized relapse rate fell by 70% during the third trimester. During the first 3 months postpartum, the relapse rate rebounded to 70% above the pre-pregnancy level, then came down and stayed down at the pre-pregnancy rate [223–229]
Myasthenia gravis	Worse	Worse	During pregnancy, the clinical course is variable, although recent studies report deterioration during pregnancy occurred in 43.3%, and 46.4% occurred at postpartum [230,232].
Inflammatory Bowel Disease	Worse	Worse	Pregnant women with Crohn's Disease had a similar disease course both during pregnancy and after delivery. In contrast, pregnant women with Ulcerative Colitis were at higher risk of relapse during pregnancy (30%) and in the postpartum [233,235].

associated with increment of disease flares in Systemic Lupus Erythematosus (SLE) [15]. For instance, in the postpartum period, when the Th2-type cytokines decreases Th1 and Th17-type inflammatory and autoimmune disorders could get worse and Th2-type could improve (Fig. 1). Postpartum exacerbation of some Th1/Th17 autoimmune conditions may reflect an imbalance in Th2-type cells and T reg cells, which is provoked by the abrupt decline of those lines after delivery [13,16]. The investigation of the dynamic profiles of the Th17/Treg ratio in a natural, physiological condition such as pregnancy and postpartum period, could represent a strong contribution to our knowledge of how to recover homeostasis in the setting of AD [17].

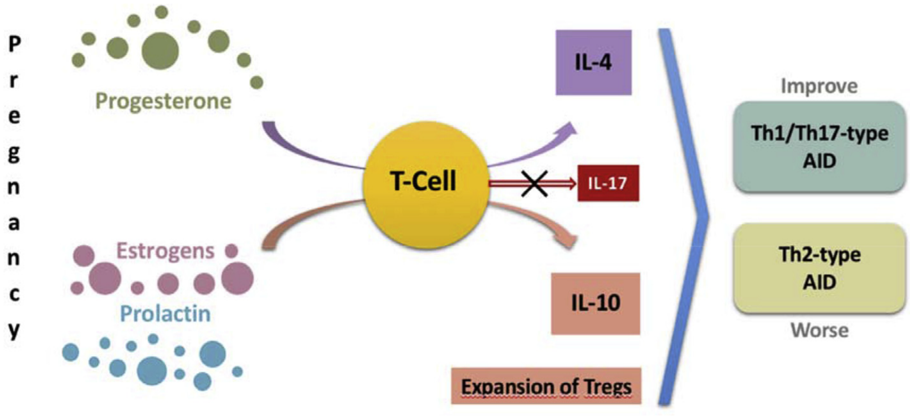

Fig. 1. Influence of hormones on the autoimmune diseases course during pregnancy.

Hormones

Reflecting the influence of sex hormones on the immune system homeostasis, differences in the activity and severity of autoimmune diseases are noticed during pregnancy and postpartum, when cortisol, estrogens, progesterone and prolactin reach high levels [14,18]. Hormones, which influence B cells and T cell cytokine responses involved in the pathogenesis of those disorders, may offer important insights into AD prevention and treatment [19].

Cortisol

Cortisol is a strong natural anti-inflammatory molecule, synthesized in the adrenal cortex and released into circulation after physical and psychological stimuli, such as pain, stress or hypoglycemia [20]. This hormone is a potent immune system modulator [21]. It influences the activity and survival of assorted immune cells and controls circulating levels of pro-inflammatory cytokines, including IFN-γ, TNF-α, IL-2, IL-3 and IL-6 [22]. Among T cells, cortisol is capable of increase the expression of the high affinity IL-2 receptor CD25 on Treg cells, reduce the genetic expression of IL-2, suppress the function of T cell receptor and its downstream molecules [23]. In addition, cortisol binds to glucocorticoid receptor on T cell mitochondria, lowering their function and inducing apoptosis [24]. High levels of cortisol decrease the number of B cells in lymph nodes and spleen, IgG production and circulating B cell activating factor, which influences B lymphocyte survival and maturation, immunoglobulin switching, antibody production and promotes T cell co-stimulation [25]. In addition, cortisol diminishes the ability of dendritic cells to activate T cells, declining proliferation and IFN-production and has immunosuppressive effects on macrophages [26,27]. Across gestation, maternal cortisol levels rise continuously and play an important role in fetal development. Hence, cortisol levels rapidly drop after delivery specially, among breastfeeding women [28,29]. A recent study performed by *Thayer* et al. *(2018)* evaluated the diurnal cortisol profiles among a large cross-sectional sample of healthy Filipino young adult women *(n = 741)* varying in reproductive status and during the postpartum period. Results indicate a marked and progressive elevation in maternal cortisol among gestation. Waking cortisol was significantly lower among breastfeeding women who were either in their first 6 months *(P = 0.001)* or 6–12 months *(P = 0.048)* [30]. In conclusion, the increasing levels of cortisol production during pregnancy, that in turn enhances endogenous immunosuppression, and the abrupt postpartum drop could represent an underlying mechanism for the spontaneous improvement while expecting and the subsequent postpartum flare seen in some AD such as RA [31]. Interestingly, the differences in diseases activity between women who carry of glucocorticoid-sensitive and glucocorticoid-resistant polymorphisms could explain why a beneficial effect of pregnancy does not occur in every patient [32,33].

Estrogens

Estrogens are robust activators of humoral immunity and at the same time seem to play important roles in pathophysiology of autoimmune phenomena [34]. Indeed, menstrual cycle, pregnancy, and menopausal status that are characterized by fluctuations of endogenous estrogens significantly influence the course of AD [35]. Estrogen activity depends of many variables, such as the expression of estrogen receptors (ER) on target cells. In healthy tissues an equilibrium between the concentration of ERα (pro-inflammatory) and ERβ (anti-inflammatory) receptors are found [35]. It is generally accepted that estrogens impact the development of adaptive immunity, with low levels of estrogen promoting pathogenic Th1/Th17 responses and high (as during pregnancy) levels promoting Th2/Treg responses. Despite all, the efficiency of the functional ER expressed in lymphocytes and macrophages might differ under inflammatory conditions or depending on the microenvironment and the type of disease [35,36]. Levels of 17-β-estradiol, which has stimulating effect on IFN-γ T cell production and TNF, follow fluctuating concentrations along women life, from lowest levels during pre-puberal period and menopause, to the highest values while expecting. During gestation, estrogen levels can inhibit TNF, IL-1 and IL-6 production [11,19,37]. *Xiong* et al. *(2017)* demonstrated that Treg cell subsets in peripheral blood are positively correlated with estrogen levels, a relationship that might play an important immunomodulatory role during pregnancy [38]. In accordance, until delivery the expression of Foxp3 was lower within the CD4 and CD25 Treg cells of pregnant women when compared to non-pregnant, probably due to the influence of progesterone and 17-β-estradiol. In the postpartum period, Foxp3 expression increased significantly [39]. Further, at any concentration estrogens shift B cells survival and activation in a B cell-autonomous fashion and thus skews the naive immune system toward autoreactivity and proliferation [37]. Hence, during reproductive years, higher estrogen levels promote immune mediated diseases like IgA nephropathy, SLE and autoimmune thyroid disease (ATD), in contrast with lower estrogen levels founded during postpartum period and menopause, which can trigger T cell or macrophage-driven diseases like MS and RA [11,36,40].

Estriol. Estriol, which is specific from pregnant women, is produced in high concentrations by the feto-placental unit during pregnancy and accounts for almost 90% of all estrogens produced during pregnancy. In female murine models, induction of Experimental Autoimmune Encephalomyelitis causes Dendritic cells (DCs) from Estriol-treated mice to develop a tolerogenic phenotype, in which there is upregulation of activation and costimulatory surface markers, including reduction of pro-inflammatory transcripts as IL-12 and IL-6 mRNA, inhibitory PD-L1, and increased expression of anti-inflammatory transcripts, as TGF-β and IL-10 mRNA. In addition, adoptive transfer of DCs from E3-treated females provides protection against development of disease by causing Th2-biased immune responses [41]. Likewise, effects of estriol on T cell function are mediated by reducing degradation of IκB leading to inhibition of NF-κB activity and decreased concentrations of pro-inflammatory cytokines [42]. Like estradiol, estriol stimulates antibody production against innocuous antigens, which contributes to heightened humoral immunity during pregnancy. A pilot, single-arm, crossover phase IIa trial of estriol treatment showed an 80% reduction in gadolinium-enhancing lesions as compared with pre-treatment on serial monthly brain magnetic resonance imaging among MS patients [43]. Treatment discontinuance showed an enhancing lesion activity [43,44]. Estriol treatment of mice with EAE reduced matrix metalloproteinase-9 (MMP-9) in supernatants from autoantigen-stimulated splenocytes, coinciding with decreased central nervous system infiltration by T cells and monocytes [43]. In conclusion, estriol programs DCs to become tolerogenic, and estriol Tol-DCs protect against autoimmunity, even in the face of inflammatory challenge. Furthermore, it decreases MMP-9 in autoimmune demyelinating disease. The ability to program DCs to induce Th2 or tolerogenic responses has huge therapeutic applications, and targeted generation of stable Tol-DCs to regulate inflammation might represent a promising therapy for AD [41,45,46].

Progesterone

Progesterone is synthesized by the granulosa-theca cells of the ovary, corpus luteum, and placenta during pregnancy. Identically to estrogens, it binds to two different receptors, the glucocorticoid receptor and the progesterone receptor, which are activated depending on serum concentrations [47]. At physiological levels, the hormone binds to progesterone receptor and promotes the reduction of Th1 cells differentiation and stimulates the differentiation of regulatory Treg cells, increasing naive T cells differentiation into FoxP3+T cells that are more stable under inflammatory conditions [48]. Higher hormonal levels, found during pregnancy or contraception, endorse progesterone binding to glucocorticoid receptor. Both seem to have suppressive actions on IFN functions [49]. Hence, progesterone plays a crucial role in gestational tolerance and reduces the activity and severity of some autoimmune diseases by inhibiting immune cell activation and improving immunological status during autoimmunity [50]. After delivery, hormonal levels drop and the anti-inflammatory effect attenuates [51].

Prolactin

Prolactin is a 23kDa polypeptide hormone, mainly secreted by the lactotrophic cells of the pituitary gland, under tonic inhibition of the hypothalamus via dopamine [52]. This hormone can also be secreted in several extra-pituitary locations, including mammary epithelium, ovary, and placenta, although with a different molecular weight and biologic activity [18]. Prolactin exerts a great influence on the innate and adaptive immune response, regulating the maturation of CD4- CD8-thymocytes to CD4+ CD8+ T cells, through IL-2 receptor expression [53]. Interestingly, there is a correlation between prolactin levels and the number of B and CD4+ T lymphocytes [54]. In addition, elevated serum levels of prolactin impair B cell clonal deletion, deregulate receptor editing and decrease the threshold for activation of anergic B cells, promoting aberrant reactivity [55–57]. Prolactin also enhances immunoglobulin production, encourages the development of antigen presenting cells expressing MHC class II and co-stimulatory molecules, including CD40, CD 80 and CD86 [58]. Likewise, it changes Th1 and Th2 type cytokine production, regulates IL-6 and INF-γ production and influences IL-2 levels [59,60]. During pregnancy and the lactation period, assorted autoimmune patients experience disease relapse, suggesting an active influence of prolactin. In contrast with sex hormones (estrogen and progesterone), which abruptly decrease after delivery and slowly recover in the postpartum, prolactin slightly increases during gestation and exponentially rises at delivery and lactation period. Those arguments could explain the postpartum onset or relapses of AD, frequently seen among breastfeeding women [61]. Hyperprolactinemia has been reported in patients with several autoimmune diseases, commonly manipulating disease development and perpetuation [62]. Interestingly, a significant association between prolactin levels and disease flairs was found in SLE and RA [63]. Similar findings were also identified in nursing women, who presented high levels of prolactin and subsequently developed RA, Grave's Disease, dermatomyositis, Sjögren's syndrome and SLE. In this latter group, up to 50% of them had hyperprolactinemia up to 5 years before diagnosis [64,65]. Further, dopamine agonists have been used in the treatment of many AD with great benefits, mainly among SLE patients [66].

Leptin

Leptin is an adipocyte-derived hormone not only with an important role in the central control of energy metabolism, but also as a major influence on the immune system, representing a cornerstone of the new field of immuno-metabolism [67,68]. Increasing evidence demonstrates that leptin has systemic effects apart from those related to energy homeostasis, including regulation of immune, neuroendocrine, reproductive and hematopoietic functions [69]. Leptin is mainly synthesized by adipose cells, and its levels are proportional to the body adipose mass, reflecting the amount of energy stored [70]. Interestingly, white adipocytes have been suggested to share embryonic origin with immune cells, while characterization of adipose tissue-resident lymphocytes led to the notion that this tissue was an ancestral immune organ [71]. Leptin receptor is similar to the class I cytokine receptor superfamily and is widely distributed. It lacks intrinsic tyrosine kinase activity, but requires the activation of JAKs, which initiate downstream signaling, including members of the STAT family of transcription factors [72]. Furthermore, leptin receptor has been shown to have the signaling capabilities of IL-6-type cytokine receptor, activating JAK-STAT, PI3K, and MAPK signaling pathways [73]. Hence, leptin acts as a pro-inflammatory cytokine, influencing both innate and adaptative immune response. Elevated serum levels cause a pro-inflammatory immune response. In monocytes and macrophages, leptin promotes phagocytosis and proliferation together with production of pro-inflammatory cytokines such as IL- 6, IL-12, and TNF-α. It induces chemotaxis of neutrophils and increases cytotoxicity of NK cells. Also, adaptive immunity is shifted to a pro-inflammatory response, decreasing the numbers of

Tregs [68,74]. Growing evidence suggests an important role as a mediator for AID, arousing disease pathogenesis and in some cases relating with disease activity. Recent studies found that leptin can promote autoantibody production, and inhibit immune regulation in SLE patients [75,76]. Consistently, it has been demonstrated that leptin-deficient mice are resistance or less susceptible to develop AD [77]. While expecting, leptin levels rise in accordance to the hypermetabolic state and the changes in the neuroendocrine milieu [78]. Placenta is the second source of leptin and it may play a role in the modulation of mother and fetus immune system. Moreover, it has been found to be an important autocrine signal for trophoblastic growth during pregnancy, promoting anti-apoptotic and trophic effects [79]. Focusing on current evidence, we could hypothesize that leptin might also play a role promoting disease onset or flares during pregnancy and postpartum, although no studies have been made in this direction.

Vitamin D

Vitamin D is a steroid classically recognized for its key role in bone metabolism and calcium homoeostasis. The role for vitamin D as a potential modulator of immune responses during pregnancy was first postulated over 50 years ago [80]. Nowadays, it is known that vitamin D plays a highly versatile role by promoting antibacterial innate immune responses to infection while suppressing adverse inflammatory adaptive immunity, including NK, T, and B cells [81,82]. The mechanisms underlying the assumption that vitamin D is linked with autoimmunity are its anti-inflammatory and immunomodulatory functions, as well as the presence of vitamin D receptors on most immune cells. In addition, epidemiological, genetic, and basic investigations indicate a potential role of vitamin D in the pathogenesis of certain AD [83–85]. Placenta is one of the principal sites for extra-renal synthesis of $1,25(OH)_2D$, with both the maternal and fetal sides of the placenta cooperating to maintain high localized tissue levels of this hormone, probably, in influencing fetal–maternal immune tolerance [86]. Vitamin D influences the phenotype of T cells, in part by promoting a shift from Th1 cytokine profile to Th2. Exposure to $1,25(OH)_2D$ *in vitro* suppresses Th17 cell development and expression of IL17. Further, T cell immune responses to vitamin D are not restricted to Th cells, but also include actions on suppressor Tregs, a group of $CD4^+$ T cells known to inhibit the proliferation of other $CD4^+$ T cells [87]. Treatment of naive $CD4^+$ T cells with $1,25(OH)_2D$ potently induces the development of Tregs and this has been proposed as a mechanism for potential beneficial effects of vitamin D on autoimmune disease [88]. Another mechanism relies on B cells expressing, which proliferation and immunoglobulin production is suppressed by vitamin D [89]. In addition, studies demonstrated that $1,25(OH)_2D$ can inhibit the differentiation of plasma cells and class-switched memory cells, highlighting a potential role for vitamin D in B cell-related disorders such as systemic lupus erythematosus [90]. Pregnant and nursing women appear to be at particular risk of vitamin D deficiency [91]. The implications of vitamin D deficiency during pregnancy and postpartum period yet remains unclear. Nevertheless, it can be seen that low vitamin D appears to be important for autoimmune disease susceptibility, and vitamin D deficiency was associated with an increased presence of autoantibodies. It is possible to speculate that vitamin D deficiency may lead to dysregulation of immune responses, and probably influence the disease progress among mothers with autoimmune diseases [84,92].

Microbiome

The 100 trillion bacteria that reside in the human intestinal tract, referred to as the gut microbiota, are essential to human metabolism and immunity [93]. It is also estimated that the genes contained within the human microbiota, known as the microbiome, are 150-fold greater than those contained within the individual human genome [94]. Microbiome seems to be emerging as the common denominator underlies the strong influence of these dietary bioactive compounds on the immune system. Mounting evidence points towards a potential involvement of immune dysregulation at mucosal sites during the initiation and progression of AD [95]. Probably, in the settings of intestinal inflammation, impairment of the gut barrier results in bacterial translocation, which stimulates immune reactions in distant organs [93,94]. Alternatively, immune cells are abnormally skewed by dysbiosis, as observed for Th17 polarization, the most abundant cells in the *lamina propria*, in charge of maintain the gut barrier integrity and defense against pathogens, secreting pro-inflammatory cytokines as IL-17A, IL-17F and IL-

22 [96]. Molecular mimicry, in which the gut microbiota may serve as a source of cross-reactive antigens that trigger autoimmune reactions, was postulated many years ago and is still being re-assessed and validated in different models [97]. Microbiome undergoes profound changes during gestation. The maternal microbiome remodeling during pregnancy is an active response of the mother, possibly to alter immune system status and to facilitate metabolic and immunological adaptations, which are needed for a successful pregnancy [98]. The exact causality for the pregnancy-induced changes in both the microbiome and the host immune system, remains unclear. The maternal immune system must balance the opposing needs of maintaining robust immune reactivity to protect both mother and fetus from invading pathogens, while at the same time tolerating highly immunogenic paternal alloantigens to sustain fetal integrity. Recent studies reported that significant differences can be found in the microbiome of patients with AD such SLE, RA, diabetes types I and II, psoriasis, Crohn's and Behcet's disease [99,101]. In accordance, patients with new-onset RA manifest a microbiota enriched for the pathobiont *Prevotella copri* [102,103]. Besides, growing evidence points the association between RA and periodontitis, due to the unique peptidylarginine deiminase enzyme expressed by *Porphyromonas gingivalis*, which specifically citrullinates peptides from key autoantigens of RA and thus breaks immune tolerance [104]. These suggest that the dysbiosis of the human microbiome can drive autoimmune disease. In the context of pregnancy, there is an increased concentration of TNF-α that may aid the clearance of bacteria by host innate immunity, which, in turn, may positively influence autoimmune diseases. Such activation of innate immunity may be assisted by the increase in the level of the steroid hormone estradiol, which is capable of enhance the expression of pattern recognition receptors, such as TLR4, on the surface of peritoneal macrophages as well as the production of TNF-α [105]. Hence, estradiol-stimulated TLR4 expression locally in the mucosa together with the expansion of the Enterobacteriaceae in the gut may cumulatively account for increased secretion of TNF-α and improved innate immunity functions [106–108]. Altogether, we can assume a complex interplay between microbiome, sex hormones and immune system during gestation, which could open new avenues of research to identify specific bacteria that could promote immune regulation and improve AD.

Microchiome

The long-term persistence of a small number of cells or DNA, from a genetically disparate individual is referred to as microchimerism [109,110]. Fetal microchimerism is the transfer of intact living fetal cells from the fetal circulation into the maternal circulation, via placenta. Once fetal cells lodge in maternal tissues, they may not be destroyed due to maternal immune system adaptations during pregnancy, allowing them to stablish and survive, even after delivery [111]. Normally, most fetal cells are lost in this period, however studies have shown their presence for decades after birth, probably due a HLA compatibility between mother and fetus [112,113]. The progressively increasing mass and number of fetal cells across maternal tissues during pregnancy correlates with the systemic expansion of immunosuppressive, $CD4^{+}$ and Treg cells [114]. The hypothesis that microchimerism might contribute to AD arose in part from observations of iatrogenic chimerism after transplantation. Fetal microchimeric cells have been demonstrated in skin lesions and labial salivar glands of patients with systemic sclerosis, in affected tissue in localized scleroderma, synovial tissue of patients with RA, among others [112,115]. Several mechanisms have been hypothesized in order to elucidate the link between AD and fetal microchimerism: foreign cells could potentially function as effector cells or as targets of an immune response, presentation of peptides from the fetal cells by one host cell to another host cell and the excess HLA similarity of fetal to maternal cells without complete HLA-identity could hamper recognition of cells as foreign [111,116]. Taken together, these findings suggest fetal cells expressing foreign MHC alleles or other alloantigens that seed maternal tissues may be the target of maternal alloimmunity, which is likely to be clinically indistinguishable from autoimmunity [110,115,117].

Infections

Pregnancy and postpartum period represent a specifically vulnerable physiological state. It is well documented that bacterial and viral infections during pregnancy pose a serious threat to a fetus and mother. Accordingly, an increasing body of evidence pointing to significant associations between certain infectious agents and the development of autoimmunity [118–121]. Most infectious agents, such as viruses, bacteria and parasites, can induce AD via different mechanisms [122,123]. For example, some microbes possess epitopes that are structurally similar to host molecules, thus inducing a self-directed immune response via a mechanism of molecular mimicry. In addition, infection induced inflammation can lead to tissue destruction and paracrine secretion of T cell growth factors and expansion of autoreactive T cells via a process known as 'bystander activation'. *Jara* et al. *(2018)* describe prominent examples of bacterial and viral infections which may be involved in the development of autoimmunity, a repertoire which continues to expand [124]. The most novel member of this brigade of infectious agents is *Zika virus*, which was recently shown to be associated with Guillain–Barré syndrome and idiopathic thrombocytopenic purpura [125]. Further, many bacterial or viral infections are now known to be the cause of various AD, such as RA, antiphospholipid syndrome [118,120,126–128]. Because microorganisms can access the placenta through the uterus, peritoneum and maternal blood, infections represent a significant threat to pregnancy. It is documented that intrauterine infections are commonly connected to preterm labor, primarily through the induction of inflammation processes mediated by TLRs [129].

Vaccines

Nowadays, vaccines are one of the most effective methods for the prevention of infectious diseases. Unfortunately, although vaccines are highly recommended for adults and children, concerns have been raised regarding their safety. Post-vaccination autoimmunity can be subacute and occur quite a long time after the vaccination is given, which leads to difficulties in as certain causality between vaccination and autoimmune phenomena [130]. Indeed, each component of the vaccine might induce autoimmunity via several mechanisms, including molecular mimicry, epitope spreading, bystander activation and polyclonal activation. *Per se*, patients with AD have at least a twofold increased risk of infection compared with healthy individuals [131]. Although studies failed to achieve any strong evidence of AD exacerbation after vaccination, although reports of disease flares induced by vaccines can be found in almost every autoimmune condition [132]. Immunological and physiological changes that occur during pregnancy can alter the susceptibility to assorted infectious diseases. On one hand, the humoral adaptive immunity remains intact with an enhanced Th2 antibody-mediated response. On the other hand, a selective suppression of the Th1 cell-mediated immunity can be observed, which decreases the mother ability to respond to infection [133]. While expecting, most inactivated vaccines and toxoids are not contraindicated. A causal relationship between some vaccines allowed during pregnancy, such as Tetanus-diphtheria-pertussis and Influenza vaccine are known to be related with autoimmune phenomena (arthritis and Guillain-Barré syndrome, respectively) [100]. No worldwide data about any fetal or maternal adverse outcomes attributable to this immunization have been pointed out. Host immunity is typically not therapeutically manipulated in pregnant females and this population is often not enrolled in drug or vaccine efficacy trials [132,134]. Recently, *Pertussis* vaccination during pregnancy has been routinely recommended in both the USA and United Kingdom to prevent pertussis infection in infants. Probably, in the future more information regarding safety of the vaccine among pregnant women will be available. Furthermore, there is no evidence that immunization during lactation can negatively affect the maternal or infant immune response [135]. A note of caution is warranted regarding the safety of vaccination in patients with AD specially, during pregnancy and postpartum period, due to the lack of sufficiently powered studies focusing on harms available in the literature [136].

Stress

The activation of the stress response system influences the close relationships existing between the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system and the immune system. The stress response system results in the release of neurotransmitters, hormones and immune cells which serve to send an efferent message from the brain to the periphery [137]. Stress releases neuroendocrine hormones which effects immune dysregulation or altered and amplified cytokine production resulting in AD [138]. In accordance, many retrospective studies found that up to 80% of patients reported uncommon emotional stress before disease onset or exacerbation [139]. Long-lasting stress may lead to pro-inflammatory effects because no adequate long-term responses of stress axes. Inadequate secretion of cortisol as well as increased sympathetic tone at rest but an inadequate response during stress exposure and a disturbed adrenoceptor intracellular signaling cascade in leukocytes, seem to be the key factors for stress-induced aggravation of these chronic inflammatory rheumatic diseases [4,138,139]. Stress hormones, acting on antigen-presenting immune cells, may influence the differentiation of bi-potential helper T-cells away from a Th1 phenotype and towards a Th2 phenotype [140]. This results in suppression of cellular immunity and in potentiating of humoral immunity. The autonomic nervous system undergoes significant alterations during pregnancy and postpartum. The reactivity of both the hypothalamic-pituitary-adrenal axis and sympatho-adrenal components of the stress response are dampened [141]. The act of breastfeeding itself is associated with decreased neuroendocrine response to stressors, mainly due reactive hyperprolactinemia, promoting emotional and neuroendocrine adaptations [142]. On the other hand, changes on lifestyle due the integration and adaptation to the new member of the family represent an enormous stressor for women life.

Pregnancy-induced gene expression changes

Gene expression studies, more specifically comparison of gene expression profiles (third trimester vs pre-pregnancy baseline) from women followed longitudinally from the pre-pregnancy state to the third trimester, can provide information about biological changes that are induced during pregnancy. Interestingly, a recent a pilot study performed by *Goin* et al. *(2017)* demonstrated an increased pregnancy-induced expression of type I IFN-inducible genes was observed among women with RA [143].

Medication

Equally important is the recognition that untreated disease in pregnancy is associated with risks to the mother and child, and the preponderance of evidence demonstrates the importance of continuing medications that prevent active disease and that do not harm the baby throughout pregnancy. Methotrexate, leflunomide, and mycophenolate mofetil are contraindicated in pregnancy and lactation. It is recommended that therapy with any of these drugs be discontinued prior to conception, and patients be transitioned to a medication that is safe for use, such as azathioprine. Further, drugs considered safe in breastfeeding include NSAIDs, glucocorticoids, cyclosporine, and hydroxychloroquine due to minimal to low exposure in the breast milk [144]. A general recommendation to reduce risk of exposure while nursing is to recommend that mothers avoid feeding at the time of peak levels in the breast milk, which usually occurs several hours after they take their medications. A thorough understanding of the range of therapeutic options available for treatment during pregnancy is therefore essential, and has expanded over recent years to include monoclonal antibody therapy.

Timing of pregnancy

It is increasingly recognized that the risks of pregnancy associated with AD can be minimized if conception is planned and undertaken during a period of minimally active disease. An emphasis on pre-conception counseling and tight disease control in the months leading up to conception are essential components of this new era [13,145,146].

Recommendations

Contraindications to pregnancy

Contraindications to pregnancy for women with AD, include pulmonary hypertension defined by a mean pulmonary artery pressure of $\geq$25 mmHg at rest, measured during right heart catheterization [147], advanced heart failure, severe restrictive lung disease (FVC<1L), chronic renal failure (creatinine > 2.8 mg/dl), previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin, stroke or severe lupus flare within the previous 6 months [148].

Considerations for breastfeeding

Prolactin exerts a great influence in the immune system modulation, mainly inhibiting the negative selection of autoreactive B lymphocytes and has been linked with disease relapses during pregnancy and lactation period [149,150]. The inhibitive effect of placental steroid hormones on prolactin disappears shortly after the separation of the placenta, thereby triggering the onset of milk synthesis [151]. While breastfeeding, plasma levels of prolactin are markedly increased. Suckling stimulates the nerve endings in the nipple-areolar complex and strongly promote hormone release [152,153]. Recently, *Stuebe* et al. *(2015)* performed a large study to evaluate prolactin levels in women who exclusively breastfed their infants, and successfully demonstrated a wide changing baseline values for prolactin (from 9 ng/dL before breastfeeding and 74 ng/dL 10 min after), depending on the feeding frequency [154]. Assorted data demonstrate a positive correlation between prolactin levels and disease activity and severity, such as in SLE, RA, systemic sclerosis and peripartum cardiomyopathy.

Systemic lupus erythematosus

Among SLE patients, recent studies support a significant association between prolactin and neurological, hematological and renal involvement, serositis, low complement and high anti-double stranded DNA antibodies [155,156]. In animal models, prolactin was capable of induce the development of lupus-like phenotype in non-prone mice, and exacerbate the disease in a lupus murine experimental study [157]. On the other hand, the presence of anti-prolactin antibodies was inversely correlated with lupus activity and correlates with better outcomes in pregnant lupus patients [158,159]. During pregnancy, hormones like estrogen and prolactin have crucial interactions with the immune system, amplifying the inflammatory effect that characterizes disease flairs. Hyperprolactinemia during the second and third trimester of pregnancy was associated with lupus anticoagulant, disease activity and poor outcomes for mother and fetus [160].

Rheumatoid arthritis

Clinical trials have demonstrated high levels of prolactin, both in serum and synovial fluid of patients with RA, probably due to an enhanced systemic secretion or increased prolactin production by immune cells, such as macrophages, suggesting a correlation with disease activity [161–163]. While expecting, about 65% of rheumatoid arthritis patients experience disease improvement, likely due to a transient period of hypercortisolism. In the postpartum period, disease relapses are often seen [164]. The risk of developing RA is increased in women who breastfeed after the first pregnancy, suggesting an immune stimulation from prolactin [165–167]. Almost 90% will flare within the first 3 months postpartum and nearly all patients will flare by 9 months. *Jorgensen* et al. *(1996)* performed a large study to evaluate the impact of pregnancy and breastfeeding in women with RA, and successfully found that parity, duration of breastfeeding and number of breast fed children were significantly increased in women with severe disease. Indeed, those with more than 3 children had a 4.8 fold increased risk of developing severe disease, and those with more than 3 breastfed children had a 3.7 fold increased risk for poor disease prognosis. In addition, 46% of patients with severe disease had a history of breastfeeding for a duration greater than 6 months before disease onset, compared with 26% of patients with mild RA ($p < 0.008$) [168].

Systemic sclerosis

Hyperprolactinemia has been described in 13%–59% of patients with systemic sclerosis [169]. In addition, there is significant correlation between the hormone levels and the disease activity and severity of skin sclerosis, cardiovascular and lung involvement [170,171]. Women with systemic

Table 2
Treatment of immune-mediated diseases with bromocriptine during pregnancy and postpartum.

Disease	Study Design	Patients No	Dosage	Main Finding	Adverse Effects	Ref.
Systemic Lupus Erythematosus	Case Control	76 patients (Case: 38; Control 38)	Bromocriptine, 2.5 mg oral, twice a day for 14 days after delivery.	Serum levels of prolactin and estradiol decreased significantly in bromocriptine treatment group at the second week ($P < 0.001$) and second month ($P < 0.05$) after delivery compared to control group. (2) The relapse rate of the treatment group was lower than the control group ($\chi^2 = 4.68$, $P = 0.0305$).	Three patients had mild vertigo and nausea. No severe adverse event was found in this study.	Qian et al. [185]
	Case Control	20 patients (Case 10; Control: 10)	Bromocriptine, 2.5 mg oral, daily, administered from 25 to 35 weeks of gestation.	Lower prolactin levels at week 35 (p 0.002). None patient had flairs. Bromocriptine prevented maternal −fetal complications, such as PRM, preterm birth, and active disease.	Well tolerated.	Jara et al. [183]
	Case Control	68 patients (Case 68; Control 68)	Bromocriptine, 2.5 mg, twice daily, for 14 days started within 12 h of postpartum.	Lower prolactin and estradiol levels. Decreased relapse rate (P = 0,007)	Well tolerated.	Yang et al. [184]
Peripartum Cardiomyopathy	Multicentre Trial	63	Randomly assigned: 32 patients receive 2.5 mg bromocriptine for 1 week (1 W group) and 31 to receive 5 mg bromocriptine for	Bromocriptine treatment was associated with high rate of full left ventricular recovery and low morbidity and	Well tolerated.	Hilfiker-Kleiner et al. [187]

			2 weeks followed by 2.5 mg for 6 weeks (8 W group).	mortality. No significant differences were observed between groups.		
Clinical Trial	20		Group 1: 10 patients receiving standard care. Group 2: 10 patients received standard care plus Bromocriptine (2.5 mg twice daily for 2 weeks followed by 2.5 mg daily for 6 weeks).	Improve left ventricular ejection fraction and a composite clinical outcome.	Well tolerated.	Sliwa et al. [236]

sclerosis can achieve successful pregnancies, although they have higher risk of fetal complications, mainly due to skin fibrosis [172,173]. Patients with disease duration of less than 4 years, with diffuse cutaneous subtype, presence of anti-RNA polymerase III or anti-topoisomerase I antibodies are at higher risk for obstetric complications and should delay pregnancy until the disease is quiescent. The pregnancy per se does not exacerbate the disease, even though women with organ insufficiency mainly pulmonary hypertension should avoid pregnancy due to an elevated risk of hemodynamic complications [174].

Peripartum cardiomyopathy

Several studies successfully demonstrated an active role of prolactin in the pathophysiology of peripartum cardiomyopathy. Increased oxidative stress and subsequent generation of 16kDa prolactin impairs the cardiac vasculature and its metabolism, finally culminating in systolic heart failure [175–177]. In addition, patients demonstrated a heightened level of fetal microchimerism, an abnormal cytokine profile, decreased levels of CD4+ CD25lo regulatory T cells, and a significant reduction in the plasma levels of progesterone, estradiol and relaxin, contributing to aberrant immunologic activities and the inflammatory process [178,179]. The 2010 European position statement advises against breastfeeding based on the concern for propagating the pathogenic prolactin pathway by continual stimulation of prolactin release [180].

Treatment with dopamine agonists

Bromocriptine is an ergot alkaloid that binds to the dopamine receptor and inhibits the pituitary synthesis of prolactin. Despite its effects on prolactin, it may also directly modulate T and B lymphocytes through the dopamine receptor [181,182]. Studies in human models, suggest an immunosuppressive effect, although its mechanisms are not completely elucidated. Bromocriptine has been shown to decrease autoantibodies production, influence lymphocyte function, quantity modulation and expression of surface molecules [182]. A clinical trial performed by *Jara* et al. *(2007)* explored the role of bromocriptine during pregnancy of women with SLE successfully demonstrated a significant decrease in prolactin levels among the group treated with bromocriptine, absence of disease flairs and better outcomes [183]. In accordance, the treatment with bromocriptine for 2 weeks in postpartum patients with lupus showed benefits concerning to the protection against disease flairs and allowed lower steroid and immunosuppressant doses [184–186]. Therefore, treatment with bromocriptine during pregnancy and puerperium has shown clinical and serological benefits, improving maternal–fetal outcomes, as summarized on Table 2 [187–190].

Conclusions

Gravidity and postpartum represent a great challenging period among women life. Physiologic adaptations of the immune system to support such outstanding mission will induce changes on autoimmune diseases onset and progress. Effective preconception counseling and subsequent gestation and postpartum follow-up are crucial for improving mother and child outcomes.

Conflicts of interest

The authors have no potential conflicts of interest in authorship or publication.

Financial declaration

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Practice points

- The risk of development an AD is significantly increased during the first year postpartum, but subsequently trended in the opposite direction.
- Cortisol, androgens and progesterone have been reported to carry immunosuppressive properties, while estrogen and prolactin play an important role in modulating the immune response, inhibiting the negative selection of autoreactive B lymphocytes, accelerating their maturation and ability to secrete self-reactive antibodies. Furthermore, leptin acts as a pro-inflammatory cytokine, influencing both innate and adaptative immune response.
- In addition to the hormonal leverage, several other mechanisms for autoimmunity during pregnancy and postpartum have been proposed: stress, infections, vaccines, medication, lower levels of vitamin D, changes in the microbiome and even microchiome.
- Considerations for breastfeeding should be individualized, measuring the risks and benefits in accordance to each patient condition.

Research agenda

A comprehensive review on the different pathways modulating autoimmune diseases activity and severity, such as the influence hormones, microbiome, vaccines, among others, as well as updated recommendations were needed, in order to offer those women better medical care and life quality.

Abbreviations List

AD	Autoimmune diseases
DC	Dendritic cells
ER	Estrogen Receptors
FVC	Forced Vital Capacity
HLA	Human Leukocyte Antigen
IFN	Interferon
IL	Interleukin
JAK	Receptor-associated Kinases of the Janus Family
MAPK	Mitogen Activated Protein Kinases
MHC	Major Histocompatibility Complex
MMP	Matrix Metalloproteinase
MS	Multiple Sclerosis
NK	Natural Killer Cell
RA	Rheumatoid Arthritis
SLE	Systemic Lupus Erythematosus
STAT	Signal Transducers and Activators of Transcription
TGF	Transforming growth factor
Th	T Helper Cells
TLR	Toll-like Receptors
TNF	Tumor Necrosis Factor
Treg	T Regulatory Cells

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