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Review

Immunology and the menstrual cycle

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ABSTRACT

Sex and gender differences in disease prevalence, pathogenesis and modulation have been frequently reported. The menstrual cycle represents the opportunity to study the physiological effect of hormonal fluctuations *in vivo* on the immune function and chronic disease modulation. Reports on the effect of the cycle on immune cell numbers and activity fluctuations are scarce, but recent publications demonstrate an increasing interest in the subject. The menstrual cycle might affect immune cell numbers and modulate their activity throughout the 4-week cycle, as demonstrated in the case of regulatory T cells. The implications of these fluctuations are particularly relevant in the field of chronic diseases affecting women of reproductive age. In fact, baseline inflammation and immune cell activation in association with other mechanisms, such as regulation of receptor expression, modulation of muscular contraction and behavioral aspects might explain the menstrual-associated fluctuations described in chronic and acute diseases. In the following review the current knowledge about the modulatory effects of the menstrual cycle on both immune cells and systemic diseases, such as autoimmune diseases, asthma, diabetes, cardiac arrhythmia and schizophrenia, is reported. Most of these diseases display worsening of symptoms premenstrually or during menses due to physiologic effects on the target tissue mediated by progesterone and estrogen fluctuations and, thus, display paradigmatic changes potentially relevant to numerous other conditions.

Contents

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1. Introduction

The menstrual cycle punctuates the life of most women of fertile age. Every month the cyclic fluctuation of sex hormones prepares the uterus for the potential implantation of a fertilized ovum and induces the shedding of the myometrium if this implantation did not take place.

Cycling is conventionally divided into two phases, the follicular and luteal phase, which are then followed by the menstrual bleeding [1]. During the follicular phase estrogen levels progressively rise until LH (luteinizing hormone) secretion from the pituitary gland induces ovulation and within 24 hours—if no fertilization occurred—these levels will sharply drop. LH also induces the transformation of granulosa cells from androgen-converting into progesterone-producing cells, leading to elevated progesterone levels throughout the luteal phase. If no implantation has occurred progesterone levels will drop after 14 days and menstrual bleeding will occur [1]. This standardized succession of a 2-week estrogen-driven environment—at progressively increasing concentrations—followed by a 2-week progesterone-preponderant environment throughout the female reproductive years, should allow for the analysis of the physiological role of these hormones in cellular homeostasis in an *in-vivo* environment.

Referring to the Th1/Th2 scheme elevated levels of estrogen and progesterone are supposed to induce Th2 type responses, while low estrogen and prolactin concentrations have been reported to enhance Th1 type responses [2]. In addition, progesterone appears to suppress Th1 responses and enhance Th2 cytokine production [3]. Thus, the menstrual and early follicular, as well as the early post-ovulatory phase should be characterized by a Th1-predominant cellular and cytokine milieu and the late follicular and mid- to late luteal phase by a Th2 milieu. However, this should only be considered a simplification for explanatory purposes; immune responses are regulated by multiple stimulatory and inhibitory pathways and hormones act on several of the target cells.

In addition to cellular differences, systemic effects are also relevant. Most healthy women experience some degree of physiological changes throughout the menstrual cycle, e.g. weight fluctuations, fluid retention or mood swings, which recur every month in a similar fashion [4].

The combination of these patterns has prompted the investigation of the effect of the menstrual cycle on disease in fertile women, which will be detailed in the following review. First, changes in immune cells will be briefly described, followed by several examples of cycle-modulated chronic diseases. As immune modulation appears causative only in few of these conditions, several other putative mechanisms will be presented as well.

2. Cellular modulation by the menstrual cycle

While much interest and effort has been invested in the analysis of immunologic changes during pregnancy, surprisingly little is known about the fluctuations of immune cell numbers and function during the menstrual cycle. Only in recent years, possibly due to an increased interest towards sex differences in disease, publications investigating this phenomenon are increasing. Nonetheless, investigation of small sample sizes and different timing of sampling throughout the menstrual cycle frequently complicate the comparison of research results. Furthermore, some authors chose to investigate the same cohort at different times during the cycle while others investigated different study populations at different timing points. Several results have yet to be unequivocally confirmed, however, some general patterns appear (Fig. 1) and will be briefly described.

2.1. Receptors

Estrogen and progesterone exert their function through linkage to specific receptors, which are present within most cell types and, specifically, on several immune cells.

Estrogens act through binding to two receptors, estrogen receptor (ER) α and β, as well as through direct effects on the nucleus [5]. ERs have been described on most immune cells [6] and the relative ratio of the two receptors might modulate their effect [7].

Progesterone has two nuclear receptors and three membrane receptors [8]. Progesterone receptor (PR) expression on lymphocytes has been initially described in pregnant women [9]. Next, membrane PR alpha has been detected in T cells, and appears to be upregulated in the luteal phase in CD8+ but not CD4+ lymphocytes [8]. Receptors are also present in lymphoid organs [10]. Discussion of these receptors goes beyond the scope of this review, but interested readers could consult the following reviews [11,12].

2.2. T lymphocytes

The distinctive role that female sex hormones play in T lymphocyte homeostasis has been identified studying cell number modifications during menopause. In fact, in postmenopausal women numbers

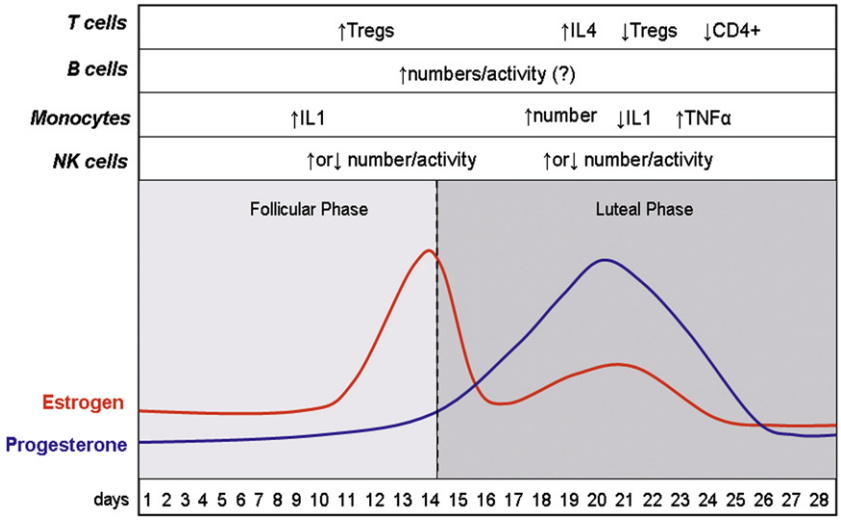

Fig. 1. Sex differences in immune cell numbers and activity. Results concerning immune cell modulation throughout the menstrual cycle are limited. Most agreement exists on the fluctuation of regulatory T cells throughout the menstrual cycle. B cell numbers and activity might increase in the periovulatory period. Monocyte numbers increase during the luteal phase, while their IL-1 and TNFα production develop in opposing fashion. Results on NK cell number and activity have been conflicting, with reports of increase/decrease in both phases of the menstrual cycle.

of CD4+ and B lymphocytes decrease, while absolute CD8+ numbers appear increased compared to fertile women. Hormone replacement therapy appears to potentially revert this phenomenon [13].

The effects that cycling hormones have on T lymphocyte number and function are still debated. In a recent publication, with the largest examined cohort to date, Lee and colleagues identified a reduction of CD4+ cells in the luteal phase compared to the early follicular one [14]—a behavior in accordance with the expected hormonal effects. In contrast, in a previous study Lopez-Karpovitchs et al. detected no difference in peripheral blood cells during the menstrual cycle; however, this study was conducted on a smaller cohort and at different sampling times [15].

At the cytokine level, Lee et al. identified no variation in Th1/Th2 ratios throughout cycle [14]. A stimulatory effect of estrogens at periovulatory levels on IL-10 and IFNγ production has been described, while the effect on TNFα appears biphasic, with lower concentrations stimulating its release and elevated concentrations inhibiting it. Progesterone induced IL-4 secretion [16]. A finding supported also by results from other groups, who described an increased IL-4 production in the luteal phase of the cycle compared to the follicular one [17].

2.2.1. Regulatory T cells

Regulatory T cells (Tregs), represent a specific subset of T lymphocytes that play a relevant role in the maintenance of immunologic tolerance during pregnancy and prevention of autoimmunity [18]. In fact, circulating and decidual Tregs increase in the first trimesters of pregnancy [19,20]. Estrogen's ability to expand the CD4+CD25+ compartment and induce Treg proliferation has been described [21], however no differences in the cell population during the menstrual cycle were identified. In a following study, Arruvito and colleagues have described how the Treg population expands during the follicular phase of the menstrual cycle to reach its peak preovulatorily, while significantly decreasing in the following luteal phase [22].

2.3. B lymphocytes

Scarce information is available about the effect of the menstrual cycle on B lymphocytes. It is generally accepted that estrogen at pregnancy levels—which are similar to preovulatory levels—can prevent B cell apoptosis and enhance survival of autoreactive cells [23]. However, whether this phenomenon is of relevance in the monthly cycle is not known. Circulating numbers do not vary throughout the menstrual cycle in women not using oral contraceptives (OCs), while OCs might enhance the potential for fluctuations due to estrogen activity [24]. The levels of circulating antibodies, an expression of B cell activity, have been investigated through the menstrual cycle. While levels of circulating immonuglobulins appear to be stable [15], localized differences have been reported. For instance, in cycling women the largest amount of immunoglobulin levels in cervical mucus have been identified right before ovulation, which would confirm data on enhanced B cell activity with elevated estrogen levels. In addition, women taking OCs displayed an even further increase in IgA and IgG levels in association with hormonal fluctuations [25].

2.4. Monocytes

Little is known about the modulation of monocyte numbers and activity throughout the menstrual cycle. Some reports identified increased total monocyte numbers in the luteal phase compared to the follicular phase [26,27]. Increased TNFα secretion from this cell population has been reported in the luteal phase compared to the follicular one [28]. Estrogen and progesterone appear to have a biphasic effect on IL-1 secretion by this cell population with low levels increasing secretion and high levels inhibiting it [29]. Data about variations of IL-6 production during the menstrual cycle have been inconclusive; some authors have reported increased production during the follicular phase [30], others could not confirm this finding and identified an increase during the luteal phase [31].

2.5. NK cells

Reports about natural killer (NK) number and activity fluctuations due to the menstrual cycle are conflicting. Some authors identified an increase in NK cell numbers during the luteal phase, compared to the follicular one [14,32]. However, other authors identified a periovulatory increase [33] or no changes at all [27].

No consensus exists on NK cell activity modifications, either. Increased activity during the luteal phase has been described [14], as well as increased activity during the follicular phase and no correlation with progesterone activity [34] and a decrease in activity limited to the periovulatory phase [35].

3. Disease modulation by the menstrual cycle

Disease modulation throughout the menstrual cycle has been reported in several conditions; among others migraine, epilepsy, asthma, rheumatoid arthritis, depression [36]. Although this research could offer much insight into disease modulation and investigators have frequently focused on aspects of female biology in former years, little recent data are available. The mechanisms responsible for these fluctuations are often disease-specific and exemplify how hormonal fluctuations affect chronic disease in many distinct ways.

3.1. Autoimmune diseases

In this group of diseases correlation of immune cell fluctuations and disease severity throughout the menstrual cycle appears most predictable, however, additional mechanisms have been identified.

3.1.1. Systemic lupus erythematosus

Much research on systemic lupus erythematosus (SLE) has focused on pregnancy and its impact on the disease; surprisingly little is known about the impact of the menstrual cycle. Early reports have documented worsening of symptoms during the luteal phase [37]. More recently, Colangelo and colleagues have identified self-reported differences between SLE and rheumatoid arthritis (RA) flares. Patients with SLE reported significantly more premenstrual flares and pain increase compared to patients with RA; interestingly, patients with fibromyalgia displayed even more significant premenstrual flares than patients with lupus [38].

Rather than studying the effects of the menstrual cycle on SLE, several authors have documented the endocrinological effects of the disease. Menstrual alterations are common, especially in juvenile SLE [39], nonetheless these alterations are relevant in adults as well, especially before initiation of therapy [40].

3.1.2. Multiple sclerosis

Zorgdrager et al. have documented a worsening of multiple sclerosis (MS) symptoms premenstrually in several clinical cohorts [41,42]; the use of oral contraceptives appears protective in some subgroups but not in others. The potential explanation of these phenomena might not be limited to the cyclic hormonal fluctuations, but lie in modified baseline levels. In support of this, Tomassini and colleagues demonstrated how women with MS have lower estradiol, but normal progesterone levels during the luteal phase and lower plasma testosterone concentrations than normal subjects [43]. Lower testosterone levels in these patients appeared to correlate with more active disease; the pathophysiologic mechanism is, however, elusive.

Lesion size and numbers, documented by imaging techniques, can also be influenced by hormonal variations. A correlation between the size of lesions and a high progesterone/estrogen ratio in the luteal phase has been described [44], as well as a correlation of active lesion

numbers with a high estrogen/progesterone ratio [45]. In conclusion, both estrogen and progesterone have been identified as potential disease modulators, especially during the luteal phase, with no definite result to date.

3.1.3. Rheumatoid arthritis

Overall, women with RA display higher disease activity scores than men with the disease [46]. Data about the influence of menses on disease progression and severity are scarce and no recent investigation has been performed. Two aspects concerning the effect of the menstrual cycle on RA have been investigated and are frequently cited. Latman and colleagues have reported a subjective increase in morning stiffness and pain during menstruation and in the early follicular phase [47], in addition, Rudge et al. have demonstrated an objectively measured decline in mean grip strength at start of menstruation [48].

In addition to these few reports, McDonagh described a case of "Menstrual Arthritis"—a patient with inflammatory polyarthritis occurring only during menstruation [49]. Unfortunately, no recent studies have been performed.

3.2. Asthma

In the case of asthma a combination of immune factors, muscle tone modifications and respiratory rate variations appear to modulate menstrual cycle related fluctuations.

An increased frequency of asthma, as well as cystic fibrosis and chronic obstructive pulmonary disease has been reported in women compared to men [50], in addition to reports of the expression of estrogen receptors on lung tissue [6,51]. The first reports of premenstrual and menstrual exacerbations of asthma date back to the early 1980s [52]—in a cohort of 100 women 36% reported these flares. Premenstrual exacerbations have been confirmed by several subsequent reports [53,54]. In addition to premenstrual exacerbation of disease, an increase in hospitalization rates for complications and respiratory failure has been documented at the same time during the hormonal cycle [55-57].

The causes for these cyclic modifications have been associated with different aspects of bronchial physiology. Progesterone acts as a smooth muscle relaxant within the human body and affects the bronchial muscles as well [58]. In addition, progesterone appears to increase respiratory rates [59]. Estrogens have been analyzed for their ability to modulate the immune function. A combination of rapid reduction of progesterone levels before menses in association with reducing estrogen levels from midcycle to menses appear to cause these exacerbations (reviewed in [60]). In fact, reduced premenstrual peak expiratory flow rates [54], as well as low FEV1 (forced expiration volume in the first second) and FVC (forced vital capacity) after ovulation [61] have been reported. However, these changes appear relevant to a subgroup of the asthmatic patient population and not apply to all female asthma patients [52,62].

A role of immune fluctuations has also been postulated. Female mice challenged with allergens mount increased airway inflammation compared to males [63]. The authors of the study suggested that testosterone levels rather than estrogen fluctuations might be at the origin of the process. A following report, however, identified estradiol as a modulator of bronchial inflammation in rats; with effects that could be abolished by ovariectomy and tamoxifen injection [64].

Last, heightened awareness of premenstrual symptoms has also been indicated as a possible cause [54], as women with premenstrual flares appear to suffer more frequently from a variety of other premenstrual symptoms [65].

3.3. Diabetes

Cycle-related alterations in diabetes control appear due to fluctuations in glycemic control, eating behavior and baseline inflammatory changes, which associate with insulin resistance. Several authors have described alterations of glycemic control in the premenstrual and luteal phase. These changes include improvement, but mostly worsening, of glycemic levels, including an increased incidence of ketoacidosis and hypoglycemic episodes [66-68]. While fluctuations could imply better or worse control perimenstrually in the whole study population, the type of fluctuation was constant in a single subject throughout different menstrual cycles [69]. A role for estrogens in glycemic control has been identified by hormone replacement therapy (HRT) trials, which demonstrated how HRT reduced the incidence of diabetes in women at risk [70].

Different pathophysiologic mechanisms have been identified. Menstrual-related glucose tolerance fluctuations in healthy women have been reported as early as 1968 [71]. In this study, glucose tolerance appears increased during menstruation, in line with reports of premenstrual tolerance improvement. The authors point out that estrogens might have different effects on glucose tolerance in healthy and diabetic women. These data, however, are contradicted by a more recent report. Brennan and colleagues identified slower gastric emptying times and lower glycemic levels during the follicular phase compared to the luteal one in healthy women [72]. While in accordance with reports of perimenstrual worsening of glycemic control, one might have expected slower gastric emptying in the luteal phase due to the myorelaxant effect of progesterone [73].

Food craving and poor premenstrual eating behavior have also been credited for worsening of glycemic control [74], as well as a direct role of premenstrual syndrome [75].

Inflammatory status and a direct interaction of insulin with immune cells might also play a role. Analyzing highly sensitive-CRP fluctuations during the menstrual cycle, Blum and colleagues identified a relation with insulin resistance [76]. The protective effect of estrogens against insulin resistance and their modulation of body mass is widely accepted and has been reported in animal and human studies [77]. Given the effects of hormonal fluctuations on glycemic control and conversely on insulin levels and the need for insulin therapy in diabetic patients, the potential effects of such treatment on regulatory T cells in patients with type 1 diabetes [78] might also be an interesting aspect to investigate.

Finally, as identified in the case of other autoimmune conditions, type 1 diabetes represents a risk factor for menstrual alterations [79].

3.4. Cardiac arrhythmia

Modulation of cardiac rhythm throughout the menstrual cycle differs from the previously illustrated chronic diseases. Although immunogenic factors play no role in its variation, the different expression of transporter molecules and ion channels throughout the cycle represent another form of hormonal disease modulation [80]. Women have a higher resting heart beat than men and a shorter sinus cycle [81]. At birth, corrected QT intervals between males and females are similar [82], while in males they shorten during puberty. Over time, male QT intervals progressively elongate until the age of about 50 years of age, when they match the ones of women. This is directly related to the slow decrease in testosterone levels occurring in males upon ageing [83]. Depending on these differences arrhythmic disease differs in incidence in women and men based on their mechanism of origin.

One relevant arrhythmic disease that could lead to fatal consequences is torsade de pointes (TdP). TdP is much more frequent in women and should be taken into consideration as it represents a relevant side effect of several cardiac and non-cardiac medications [84]. In this review only menstrual variations of TdP risk and incidences will be described.

While heart rate appears predominantly regulated by androgens, estrogens and specifically progesterone are relevant in this context. One study has documented no variation of QTc (corrected QT) over the duration of the menstrual cycle in baseline conditions, but a

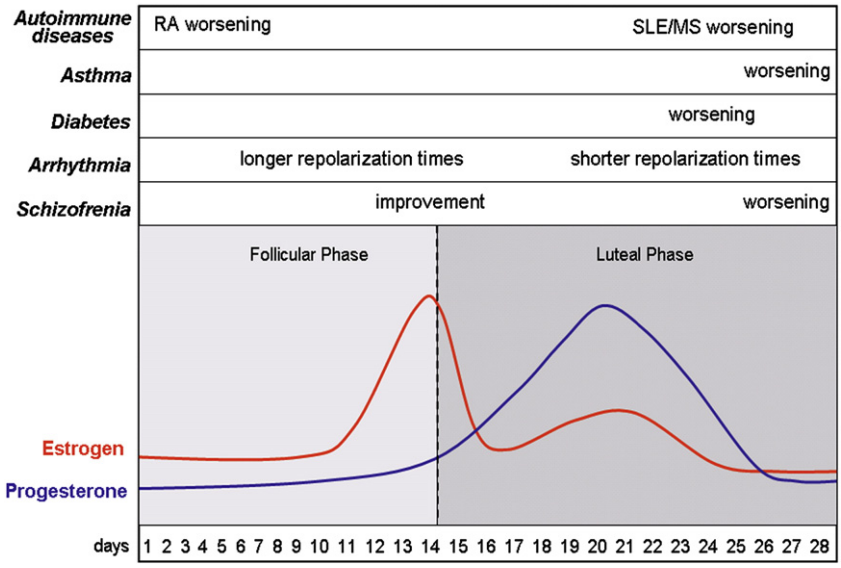

Fig. 2. Sex and gender differences in disease activity. Premenstrual worsening of all cited conditions, but cardiac arrhythmia, has been demonstrated. In the case of autoimmune conditions, SLE and MS appear to worsen premenstrually, while RA worsens during menstruation. Due to a different mechanism (see text), the risk of cardiac arrhythmia decreases during the luteal phase compared to the follicular one.

reduction during the luteal phase after autonomic blockade [85]. Ibutilide, a class III antyarrhythmic drug, prolonged QT intervals most during menstruation and least in the luteal phase, providing evidence for a protective role of progesterone [86]. In fact, repolarization times appear much shorter in the luteal phase compared to the follicular one [87]. While these differences might be of limited importance in the overall pathogenesis of arrhythmic disease, they should be taken into account when cardiac arrhythmia appears as a side effect of medication, especially at more vulnerable times during the menstrual cycle. A recent review offers a detailed description of gender differences in cardiac electrophysiology and the associated pathophysiologic mechanisms [88] (Fig. 2).

3.5. Schizophrenia

Gender differences in the symptoms of schizophrenia have been extensively described. Male patients tend to isolate themselves and suffer more frequently from inability to function, whereas female patients display more of the "characteristic" traits, such as paranoia, impulsive and erratic behavior and hallucinations. Attempted suicide and relational problems are also more frequent in women [89]. These traits vary in a cyclic fashion, with relevant increase of hallucinations, paranoia and hyperactivity in the premenstrual phase [90]. Moreover, as reported for asthma, hospitalization for acute symptoms is most common premenstrually [91].

Estrogens appear to have a protective role; in fact, the disease appears later in women compared to men and tends to recur postmenopausally. Elevated estrogen levels have been reported to reduce symptoms while low levels have been found to enhance them [92]. Several authors have identified decreased estrogen levels in schizophrenic patients compared to healthy controls at the same phase of the menstrual cycle [91,92].

In support of this hypothesis Gattaz and colleagues reported that women admitted during the luteal phase of the menstrual cycle needed progressively lower doses of neuroleptics to obtain the same therapeutic effects as controls, suggesting a possible adjuvant effect of raising estrogen levels in the following follicular phase [93].

As a possible explanatory mechanism, the influence of estrogens on the sensitivity of dopaminergic receptors has been postulated. Indeed, estrogens could downregulate dopaminergic receptor sensitivity exerting an analogous effect as neuroleptics [94]. Accordingly, different studies identified an increased number of dopaminergic receptors and modified neurotransmitter uptake in schizophrenia patients [95-97] after estrogen administration.

4. Conclusion

Several lines of evidence indicate the fluctuation of disease severity of specific medical conditions during the menstrual cycle. Although more research and clinical studies are exploring this topic, perhaps prompted by the general awareness of the critical role of gender differences in disease and therapy, many aspects of disease modulation remain obscure. Research into the modulation of the immune system by the menstrual cycle is much needed, especially in the light of a possible application of the results towards etiopathogenetic investigation. A better understanding of the underlying mechanisms is auspicial not only to predict and possibly avoid unwanted exacerbations in women, but also to gain a more profound knowledge of disease pathogenesis and, thus, improve the overall outcome in both female and male patients.

Conflicts of interest statement

None to declare

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References

[1] Channing CP, Schaerf FW, Anderson LD, Tsafriri A. Ovarian follicular and luteal physiology. Int Rev Physiol 1980;22:117–201.
[2] Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Science 1999;283:1277–8.
[3] Miyaura H, Iwata M. Direct and indirect inhibition of Th1 development by progesterone and glucocorticoids. J Immunol 2002;168:1087–94.
[4] Mortola JF. Premenstrual syndrome—pathophysiologic considerations. N Engl J Med 1998;338:256–7.
[5] Cunningham M, Gilkeson G. Estrogen receptors in immunity and autoimmunity. Clin Rev Allergy Immunol 2011;40:66–73.
[6] Couse JF, Lindzey J, Grandien K, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptor-alpha (ERalpha) and estrogen receptor-

beta (ERbeta) messenger ribonucleic acid in the wild-type and ERalpha-knockout mouse. Endocrinology 1997;138:4613–21.
[7] Hall JM, McDonnell DP. The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ERalpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinology 1999;140:5566–78.
[8] Dosiou C, Hamilton AE, Pang Y, Overgaard MT, Tulac S, Dong J, et al. Expression of membrane progesterone receptors on human T lymphocytes and Jurkat cells and activation of G-proteins by progesterone. J Endocrinol 2008;196:67–77.
[9] Szekeres-Bartho J, Szekeres G, Debre P, Autran B, Chaouat G. Reactivity of lymphocytes to a progesterone receptor-specific monoclonal antibody. Cell Immunol 1990;125:273–83.
[10] Tanriverdi F, Silveira LF, MacColl GS, Bouloux PM. The hypothalamic–pituitary–gonadal axis: immune function and autoimmunity. J Endocrinol 2003;176: 293–304.
[11] Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, et al. Estrogen receptors: how do they signal and what are their targets. Physiol Rev 2007;87: 905–31.
[12] Scarpin KM, Graham JD, Mote PA, Clarke CL. Progesterone action in human tissues: regulation by progesterone receptor (PR) isoform expression, nuclear positioning and coregulator expression. Nucl Recept Signal 2009;7:e009.
[13] Gameiro CM, Romao F, Castelo-Branco C. Menopause and aging: changes in the immune system—a review. Maturitas 2010;67:316–20.
[14] Lee S, Kim J, Jang B, Hur S, Jung U, Kil K, et al. Fluctuation of peripheral blood T, B, and NK cells during a menstrual cycle of normal healthy women. J Immunol 2010;185:756–62.
[15] Lopez-Karpovitchs X, Larrea F, Cardenas R, Valencia X, Piedras J, Diaz-Sanchez V, et al. Peripheral blood lymphocyte subsets and serum immunoglobulins in Sheehan's syndrome and in normal women during the menstrual cycle. Rev Invest Clin 1993;45:247–53.
[16] Correale J, Arias M, Gilmore W. Steroid hormone regulation of cytokine secretion by proteolipid protein-specific CD4+ T cell clones isolated from multiple sclerosis patients and normal control subjects. J Immunol 1998;161:3365–74.
[17] Faas M, Bouman A, Moesa H, Heineman MJ, de Leij L, Schuiling G. The immune response during the luteal phase of the ovarian cycle: a Th2-type response? Fertil Steril 2000;74:1008–13.
[18] Campbell DJ, Koch MA. Phenotypical and functional specialization of FOXP3+ regulatory T cells. Nat Rev Immunol 2011;11:119–30.
[19] Heikkinen J, Mottonen M, Alanen A, Lassila O. Phenotypic characterization of regulatory T cells in the human decidua. Clin Exp Immunol 2004;136:373–8.
[20] Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. Immunology 2004;112:38–43.
[21] Prieto GA, Rosenstein Y. Oestradiol potentiates the suppressive function of human CD4 CD25 regulatory T cells by promoting their proliferation. Immunology 2006;118:58–65.
[22] Arruvito L, Sanz M, Banham AH, Fainboim L. Expansion of CD4+CD25+and FOXP3+ regulatory T cells during the follicular phase of the menstrual cycle: implications for human reproduction. J Immunol 2007;178:2572–8.
[23] Peeva E, Venkatesh J, Diamond B. Tamoxifen blocks estrogen-induced B cell maturation but not survival. J Immunol 2005;175:1415–23.
[24] Auerbach L, Hafner T, Huber JC, Panzer S. Influence of low-dose oral contraception on peripheral blood lymphocyte subsets at particular phases of the hormonal cycle. Fertil Steril 2002;78:83–9.
[25] Franklin RD, Kutteh WH. Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones. J Reprod Immunol 1999;42:93–106.
[26] Mathur S, Mathur RS, Goust JM, Williamson HO, Fudenberg HH. Cyclic variations in white cell subpopulations in the human menstrual cycle: correlations with progesterone and estradiol. Clin Immunol Immunopathol 1979;13:246–53.
[27] Northern AL, Rutter SM, Peterson CM. Cyclic changes in the concentrations of peripheral blood immune cells during the normal menstrual cycle. Proc Soc Exp Biol Med 1994;207:81–8.
[28] Brannstrom M, Friden BE, Jasper M, Norman RJ. Variations in peripheral blood levels of immunoreactive tumor necrosis factor alpha (TNFalpha) throughout the menstrual cycle and secretion of TNFalpha from the human corpus luteum. Eur J Obstet Gynecol Reprod Biol 1999;83:213–7.
[29] Polan ML, Daniele A, Kuo A. Gonadal steroids modulate human monocyte interleukin-1 (IL-1) activity. Fertil Steril 1988;49:964–8.
[30] Angstwurm MW, Gartner R, Ziegler-Heitbrock HW. Cyclic plasma IL-6 levels during normal menstrual cycle. Cytokine 1997;9:370–4.
[31] Konecna L, Yan MS, Miller LE, Scholmerich J, Falk W, Straub RH. Modulation of IL-6 production during the menstrual cycle in vivo and in vitro. Brain Behav Immun 2000;14:49–61.
[32] Bouman A, Moes H, Heineman MJ, de Leij LF, Faas MM. Cytokine production by natural killer lymphocytes in follicular and luteal phase of the ovarian cycle in humans. Am J Reprod Immunol 2001;45:130–4.
[33] Yovel G, Shakhar K, Ben-Eliyahu S. The effects of sex, menstrual cycle, and oral contraceptives on the number and activity of natural killer cells. Gynecol Oncol 2001;81:254–62.
[34] Souza SS, Castro FA, Mendonca HC, Palma PV, Morais FR, Ferriani RA, et al. Influence of menstrual cycle on NK activity. J Reprod Immunol 2001;50:151–9.
[35] Sulke AN, Jones DB, Wood PJ. Variation in natural killer activity in peripheral blood during the menstrual cycle. Br Med J (Clin Res Ed) 1985;290:884–6.
[36] Case AM, Reid RL. Effects of the menstrual cycle on medical disorders. Arch Intern Med 1998;158:1405–12.
[37] Steinberg AD, Steinberg BJ. Lupus disease activity associated with menstrual cycle. J Rheumatol 1985;12:816–7.
[38] Colangelo K, Haig S, Bonner A, Zelenietz C, Pope J. Self-reported flaring varies during the menstrual cycle in systemic lupus erythematosus compared with rheumatoid arthritis and fibromyalgia. Rheumatology (Oxford) 2011;50:703–8.
[39] Medeiros PB, Febronio MV, Bonfa E, Borba EF, Takiuti AD, Silva CA. Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. Lupus 2009;18: 38–43.
[40] Shabanova SS, Ananieva LP, Alekberova ZS, Guzov II. Ovarian function and disease activity in patients with systemic lupus erythematosus. Clin Exp Rheumatol 2008;26:436–41.
[41] Zorgdrager A, De Keyser J. Menstrually related worsening of symptoms in multiple sclerosis. J Neurol Sci 1997;149:95–7.
[42] Zorgdrager A, De Keyser J. The premenstrual period and exacerbations in multiple sclerosis. Eur Neurol 2002;48:204–6.
[43] Tomassini V, Onesti E, Mainero C, Giugni E, Paolillo A, Salvetti M, et al. Sex hormones modulate brain damage in multiple sclerosis: MRI evidence. J Neurol Neurosurg Psychiatry 2005;76:272–5.
[44] Pozzilli C, Falaschi P, Mainero C, Martocchia A, D'Urso R, Proietti A, et al. MRI in multiple sclerosis during the menstrual cycle: relationship with sex hormone patterns. Neurology 1999;53:622–4.
[45] Bansil S, Lee HJ, Jindal S, Holtz CR, Cook SD. Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. Acta Neurol Scand 1999;99:91–4.
[46] Tengstrand B, Ahlmen M, Hafstrom I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31: 214–22.
[47] Latman NS. Relation of menstrual cycle phase to symptoms of rheumatoid arthritis. Am J Med 1983;74:957–60.
[48] Rudge SR, Kowanko IC, Drury PL. Menstrual cyclicity of finger joint size and grip strength in patients with rheumatoid arthritis. Ann Rheum Dis 1983;42:425–30.
[49] McDonagh JE, Singh MM, Griffiths ID. Menstrual arthritis. Ann Rheum Dis 1993;52:65–6.
[50] Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SF, Sin DD. The role of female hormones on lung function in chronic lung diseases. BMC Womens Health 2011;11:24.
[51] Fasco MJ, Hurteau GJ, Spivack SD. Gender-dependent expression of alpha and beta estrogen receptors in human nontumor and tumor lung tissue. Mol Cell Endocrinol 2002;188:125–40.
[52] Hanley SP. Asthma variation with menstruation. Br J Dis Chest 1981;75:306–8.
[53] Chandler MH, Schuldheisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function, and beta 2-receptors. Pharmacotherapy 1997;17:224–34.
[54] Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. Thorax 1984;39:833–6.
[55] Eliasson O, Scherzer HH, DeGraff Jr AC. Morbidity in asthma in relation to the menstrual cycle. J Allergy Clin Immunol 1986;77:87–94.
[56] Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. Arch Intern Med 1996;156:1837–40.
[57] Zimmerman JL, Woodruff PG, Clark S, Camargo CA. Relation between phase of menstrual cycle and emergency department visits for acute asthma. Am J Respir Crit Care Med 2000;162:512–5.
[58] Boggess KA, Williamson HO, Homm RJ. Influence of the menstrual cycle on systemic diseases. Obstet Gynecol Clin North Am 1990;17:321–42.
[59] Schoene RB, Robertson HT, Pierson DJ, Peterson AP. Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. J Appl Physiol 1981;50:1300–5.
[60] Haggerty CL, Ness RB, Kelsey S, Waterer GW. The impact of estrogen and progesterone on asthma. Ann Allergy Asthma Immunol 2003;90:284–91 quiz 91–3, 347.
[61] Farha S, Asosingh K, Laskowski D, Hammel J, Dweik RA, Wiedemann HP, et al. Effects of the menstrual cycle on lung function variables in women with asthma. Am J Respir Crit Care Med 2009;180:304–10.
[62] Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. Am Rev Respir Dis 1989;140:358–62.
[63] Hayashi T, Adachi Y, Hasegawa K, Morimoto M. Less sensitivity for late airway inflammation in males than females in BALB/c mice. Scand J Immunol 2003;57: 562–7.
[64] Ligeiro de Oliveira AP, Oliveira-Filho RM, da Silva ZL, Borelli P, Tavares de Lima W. Regulation of allergic lung inflammation in rats: interaction between estradiol and corticosterone. Neuroimmunomodulation 2004;11:20–7.
[65] Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, Adelman DC. Clinical differences among women with and without self-reported perimenstrual asthma. Ann Allergy Asthma Immunol 1998;81:65–72.
[66] Letterie GS, Fredlund PN. Catamenial insulin reactions treated with a long-acting gonadotropin releasing hormone agonist. Arch Intern Med 1994;154:1868–70.
[67] Ovalle F, Vaughan III TB, Sohn JE, Gower B. Catamenial diabetic ketoacidosis and catamenial hyperglycemia: case report and review of the literature. Am J Med Sci 2008;335:298–303.
[68] Walsh CH, Malins JM. Menstruation and control of diabetes. Br Med J 1977;2: 177–9.
[69] Goldner WS, Kraus VL, Sivitz WI, Hunter SK, Dillon JS. Cyclic changes in glycemia assessed by continuous glucose monitoring system during multiple complete menstrual cycles in women with type 1 diabetes. Diabetes Technol Ther 2004;6: 473–80.

[70] Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2003;138:1–9.
[71] Jarrett RJ, Graver HJ. Changes in oral glucose tolerance during the menstrual cycle. Br Med J 1968;2:528–9.
[72] Brennan IM, Feltrin KL, Nair NS, Hausken T, Little TJ, Gentilcore D, et al. Effects of the phases of the menstrual cycle on gastric emptying, glycemia, plasma GLP-1 and insulin, and energy intake in healthy lean women. Am J Physiol Gastrointest Liver Physiol 2009;297:G602–10.
[73] Wald A, Van Thiel DH, Hoechstetter L, Gavaler JS, Egler KM, Verm R, et al. Gastrointestinal transit: the effect of the menstrual cycle. Gastroenterology 1981;80: 1497–500.
[74] Cawood EH, Bancroft J, Steel JM. Perimenstrual symptoms in women with diabetes mellitus and the relationship to diabetic control. Diabet Med 1993;10:444–8.
[75] Trout KK, Teff KL. Insulin sensitivity and premenstrual syndrome. Curr Diab Rep 2004;4:273–80.
[76] Blum CA, Muller B, Huber P, Kraenzlin M, Schindler C, De Geyter C, et al. Low-grade inflammation and estimates of insulin resistance during the menstrual cycle in lean and overweight women. J Clin Endocrinol Metab 2005;90:3230–5.
[77] Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med 2009;6(Suppl 1):60–75.
[78] Tiittanen M, Huupponen JT, Knip M, Vaarala O. Insulin treatment in patients with type 1 diabetes induces upregulation of regulatory T-cell markers in peripheral blood mononuclear cells stimulated with insulin in vitro. Diabetes 2006;55: 3446–54.
[79] Strotmeyer ES, Steenkiste AR, Foley Jr TP, Berga SL, Dorman JS. Menstrual cycle differences between women with type 1 diabetes and women without diabetes. Diabetes Care 2003;26:1016–21.
[80] Gaborit N, Varro A, Le Bouter S, Szuts V, Escande D, Nattel S, et al. Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. J Mol Cell Cardiol 2010;49:639–46.
[81] Kuch B, Hense HW, Sinnreich R, Kark JD, von Eckardstein A, Sapoznikov D, et al. Determinants of short-period heart rate variability in the general population. Cardiology 2001;95:131–8.
[82] Stramba-Badiale M, Spagnolo D, Bosi G, Schwartz PJ. Are gender differences in QTc present at birth? MISNES Investigators. Multicenter Italian Study on Neonatal Electrocardiography and Sudden Infant Death Syndrome. Am J Cardiol 1995;75: 1277–8.
[83] Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. Eur Heart J 1997;18:1000–6.
[84] Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993;270:2590–7.
[85] Burke JH, Ehlert FA, Kruse JT, Parker MA, Goldberger JJ, Kadish AH. Gender-specific differences in the QT interval and the effect of autonomic tone and menstrual cycle in healthy adults. Am J Cardiol 1997;79:178–81.
[86] Rodriguez I, Kilborn MJ, Liu XK, Pezzullo JC, Woosley RL. Drug-induced QT prolongation in women during the menstrual cycle. JAMA 2001;285:1322–6.
[87] Nakagawa M, Ooie T, Takahashi N, Taniguchi Y, Anan F, Yonemochi H, et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol 2006;29:607–13.
[88] Jonsson MK, Vos MA, Duker G, Demolombe S, van Veen TA. Gender disparity in cardiac electrophysiology: implications for cardiac safety pharmacology. Pharmacol Ther 2010;127:9–18.
[89] Goldstein JM, Link BG. Gender and the expression of schizophrenia. J Psychiatr Res 1988;22:141–55.
[90] Glick ID, Stewart D. A new drug treatment for premenstrual exacerbation of schizophrenia. Compr Psychiatry 1980;21:281–7.
[91] Huber TJ, Borsutzky M, Schneider U, Emrich HM. Psychotic disorders and gonadal function: evidence supporting the oestrogen hypothesis. Acta Psychiatr Scand 2004;109:269–74.
[92] Riecher-Rossler A, Hafner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull 1994;20:203–14.
[93] Gattaz WF, Vogel P, Riecher-Rossler A, Soddu G. Influence of the menstrual cycle phase on the therapeutic response in schizophrenia. Biol Psychiatry 1994;36: 137–9.
[94] Hafner H, Behrens S, De Vry J, Gattaz WF. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Evidence from an epidemiological study and from animal experiments. Eur Arch Psychiatry Clin Neurosci 1991;241:65–8.
[95] Di Paolo T, Poyet P, Labrie F. Effect of prolactin and estradiol on rat striatal dopamine receptors. Life Sci 1982;31:2921–9.
[96] Disshon KA, Boja JW, Dluzen DE. Inhibition of striatal dopamine transporter activity by 17beta-estradiol. Eur J Pharmacol 1998;345:207–11.
[97] Hruska RE. Elevation of striatal dopamine receptors by estrogen: dose and time studies. J Neurochem 1986;47:1908–15.