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Oestrogen and progesterone regulation of inflammatory processes in the human endometrium☆

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ABSTRACT

The human endometrium is a unique tissue that has to undergo cycles of proliferation, differentiation, destruction and repair. This ensures that the endometrium is optimally prepared for potential embryo implantation but in the absence of an embryo, menstruation occurs to allow endometrial regeneration. These cycles of tissue remodelling occur under the sequential influence of the sex steroid hormones, oestrogen and progesterone. The physiological events of implantation and menstruation display features of inflammation, tightly regulated by oestrogen and progesterone. After menstruation cellular proliferation and blood vessel growth is modulated by oestrogen while after ovulation progesterone is the dominant hormone. In preparation for implantation, progesterone regulates decidualization of the endometrium, uterine natural killer cell numbers within the endometrium and chemokine and cytokine expression. Menstruation, in contrast, is preceded by progesterone withdrawal, which results in an influx of leukocytes into the endometrium and increased production of chemokines and matrix metalloproteinases allowing tissue degradation. The aim of this article is to review the current knowledge on the regulation of inflammatory events within the endometrium by oestrogen and progesterone, in relation to two pivotal events for human reproduction, implantation and menstruation.

1. Introduction

Human endometrium is a dynamic steroid-responsive tissue that undergoes repeat cycles involving sequential proliferation, differentiation, breakdown and repair. The function of the endometrium is to allow the implantation of a blastocyst and to support any resultant pregnancy. These cycles of tissue remodelling ensure that the endometrium is in a receptive state for the putative 'implantation window', the few days of each menstrual cycle when an appropriately developed blastocyst may be available in the uterus to implant. If there is no blastocyst or if implantation fails the endometrium degenerates and manifests as menstruation with subsequent regeneration and repair in preparation for the next implantation window. Both implantation and menstruation occur under the control of steroid hormones and are regarded as inflammatory events characterized by leukocyte infiltration and increased inflammatory mediator expression in endometrium [1,2]. This review will focus on the actions of steroid hormones on the human endometrium and particularly their role in regulating the inflammatory processes associated with implantation and menstruation. Steroid hormones and inflammatory pathways also have a crucial role in the uterus in relation to pregnancy and parturition. This has been reviewed elsewhere [3,4].

2. Oestrogen, progesterone and the menstrual cycle

The endometrium is composed of an upper functional and a basal layer (adjacent to the myometrium). The upper functional layer undergoes morphological changes in response to sequential exposure to oestrogen and progesterone, produced by the developing ovarian follicle and corpus luteum, respectively. A developing blastocyst will initially contact the luminal epithelium of the functional layer and it is this layer that is shed as a consequence of progesterone withdrawal at menstruation. Following menses, the endometrium regenerates from the basal layer. Both layers are multicellular and are comprised of epithelial, stromal, endothelial and a dynamic population of immune cells.

The morphological changes in endometrium have been well documented by others [5–7]. In brief, the proliferative phase, with oestrogen the dominant circulating sex steroid, is characterized by endometrial regeneration after menstruation. Narrow, straight glands, a thin surface epithelium and compact stroma are features of the proliferative phase. Growth of the glands and stroma continues and angiogenesis occurs as ovulation approaches.

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After ovulation, the secretory phase commences with cessation of proliferation and the onset of endometrial differentiation. As progesterone levels increase the glands become increasingly tortuous with secretory activity peaking during the implantation window (mid secretory phase). In the late secretory phase the spiral arterioles differentiate and decidual change begins in stromal cells in the perivascular area and immediately below the surface epithelium. In the absence of implantation, the corpus luteum regresses and progesterone levels fall resulting in focal necrosis and the onset of menstruation. In addition to regulation by the ovarian steroid hormones, endometrial function may also be influenced by glucocorticoids and androgens. Although the roles of these steroids are less well understood in the context of the endometrium they will be discussed where appropriate.

3. Local control of intracellular steroid levels: steroid metabolizing enzymes in endometrium

Circulating concentrations of steroid hormones may not always be reflective of the levels found within endometrial cells and several groups of enzymes are likely to be involved in local regulation of steroid levels by the endometrium itself. Steroid metabolizing enzymes that have been documented in endometrium and have functions that are directly relevant to endometrial physiology include 17β-hydroxysteroid dehydrogense (HSD)-2, which inactivates oestrogen and testosterone and activates progesterone; 3α-HSDs (aldo-keto reductases), which metabolize oestrogens, progestins and androgens; 3β-HSD, which synthesises progesterone; and 11β-HSD1 and 2, responsible for the synthesis and inactivation of cortisol, respectively. Data relating to the expression, regulation and potential roles of these steroid metabolizing enzymes in human endometrium are summarized in Table 1.

4. Steroid receptor expression in endometrium

Steroid receptors for oestrogens, progestins, androgens and glucocorticoids are present within the endometrium and their localization has now been well documented in many immunohistochemical studies. Early studies examining oestrogen (ER) and progesterone receptor (PR) expression in endometrium showed both to be maximal in the mid to late proliferative phase and decreased under the influence of progesterone in the secretory phase [27,28]. More recently it has become clear that there are at least two isoforms of both the ER and PR. ERα mRNA expression is highest in the proliferative phase and declines in the secretory phase. In contrast, mRNA levels of the ERb splice variants, ERβ1 and ERβcx/β2, increase in the late secretory phase [29]. Both ERα and ERβ are present in the glandular epithelium and stroma of endometrium from the proliferative phase. ERα shows decreased expression in both compartments in the secretory phase, ERβ1 localization is unaltered across the menstrual cycle while ERβcx/β2 decreases in the glandular epithelium of the functional layer in the mid secretory phase [30–32]. In addition, ERβ1 is expressed in uterine NK cells (uNK [29]) and both ERβ1 and ERβcx/β2 are present in the endometrial endothelium [31]. A recent study has examined expression of the oestrogen receptor related (ERR) NR3B subfamily of proteins in endometrium. ERRs are believed to modulate transcription in part via oestrogen response elements [33]. ERRβ is widely expressed in endometrium and is present in glands, stroma, endothelium and leukocytes including macrophages and uNK cells [34]. The role of ERRβ in endometrium is unknown and the expression of the other ERR family members, ERRα and ERRγ, remains to be determined.

The two isoforms of the PR, PR_A and PR_B are differentially expressed in human endometrium. Immunohistochemical studies suggest that while both isoforms are reduced in the glandular epithelium in the secretory phase, PR_A expression is maintained in the stroma in both the secretory phase and in first trimester decidua indicating a role for PR_A in epithelial–stromal interactions [35–38]. Knock-out mouse studies have illuminated the role of PR_A in the uterus suggesting that in its absence there is failed decidualization and alterations to progesterone mediated gene expression [39]. This is consistent with PR_A localization to the stromal compartment during the latter half of the menstrual cycle. PR is not present in either the endometrial endothelium or uNK cells but both isoforms are present in the perivascular cells suggesting that progesterone actions on the blood vessels and uNK cells are indirect [29,38,40].

GR mRNA expression peaks during menstruation and the protein is predominantly expressed in the stromal compartment in endometrium and is also localized to the endothelium and uNK cells [22,29,41]. GR expression is present in the glandular epithelium of first trimester decidua [22,29]. Most studies agree that AR is present only in the endometrial stroma with maximal expression in the proliferative phase although expression remains detectable throughout the menstrual cycle and in first trimester decidua [12,42–45].

5. Oestrogen and progesterone actions on human endometrium

During each menstrual cycle the endometrium is exposed to three distinct hormonal environments: (a) the oestrogen dominated proliferative phase; (b) the progesterone dominated secretory phase; and (c) progesterone withdrawal immediately prior to and during menstruation.

5.1. The proliferative phase

Regeneration of the endometrium after menstruation is dependent on oestrogen. Endometrial angiogenesis is crucial to the regrowth of the endometrium during the proliferative phase with the endometrial blood vessels subsequently playing a critical role at implantation. Angiogenesis occurs throughout the menstrual cycle and studies in a primate model have indicated that there is a peak in angiogenesis in the proliferative phase, which at least in the Rhesus macaque is oestrogen dependent [46]. Studies in women are less conclusive with some failing to detect any changes to the level of angiogenesis across the menstrual cycle [47] while others have reported that vessel elongation does occur in the proliferative phase [48]. As detailed above endometrial endothelial cells are reported to express ERβ suggesting that oestrogen may have a direct effect on blood vessels [29]. A recent microarray study has confirmed that oestradiol treatment alters gene expression in human endometrial endothelial cells [49] although this study did not detail the functional significance. Oestrogen may also influence endometrial angiogenesis indirectly via actions on other mediators, for example angiopoietin 1 (Ang-1) and vascular endothelial growth factor (VEGF). Vascular smooth muscle cells have been shown to migrate in response to medium conditioned by oestradiol treated endometrial explants from the proliferative phase [50]. This is suggested to show the involvement of oestrogen in modulating early stages in blood vessel remodelling, possibly via Ang-1 [50]. The Rhesus macaque model has provided evidence that the expression of VEGF and its receptors, KDR and Flt-1, in proliferative phase endometrium is dependent on oestrogen [46]. Additionally, blocking the actions of VEGF in this model has been shown to prevent angiogenesis [51]. In women, VEGF has been localized to both endometrial epithelium and stroma [52–56] and oestradiol increases VEGF expression in endometrial cells [52,55,57].

Table 1
Expression, regulation and potential roles of steroid metabolizing enzymes in human endometrium.

Enzyme	mRNA expression	Protein expression	Regulation	Potential role(s) in endometrium
17β-hydroxysteroid dehydrogenase (HSD) family				
17β-HSD1	Low or undetectable [8–10]	Conflicting data [9,11]	Not studied	Synthesis of oestradiol but controversy over expression in normal endometrium
17β-HSD2	Detected in endometrium [8,9,12,13]	Localized to epithelium [9,12]	Peak expression in mid secretory endometrium [8,9,12,13]; activity and mRNA positively regulated by progestins *in vitro* [9,14]	Metabolises oestradiol; may limit the actions of oestrogens and augment those of progesterone in mid secretory phase
17β-HSD4	Detected in endometrium and endometrial epithelial cell lines [9,15]; *in situ* hybridization examining secretory phase endometrium only suggests mRNA present in glandular epithelium [15]	Not studied	Unchanged across menstrual cycle; not regulated by oestrogens or progestins *in vitro*[9]	As for 17β-HSD2
3α-HSD/Aldo-keto reductase (AKR) family				
17β-HSD5/3α-HSD2/AKR1C3	Not studied	Localized to epithelium [16]	Not reported	Variable dependent on availability of substrates and cofactors [16,17]
AKR1C1, 2 and 4	Detected in endometrium [17]	Not studied	Not studied	
3β-HSD	Not studied	Detected in endometrium; localized to epithelium [18,19]	Semi-quantitative immunohistochemistry suggests protein expression highest in secretory phase [18]; isomerase activity highest in secretory phase and regulated by progestins *in vitro*[19]	Progesterone synthesis; data suggests progesterone acts to augment its own production by the endometrium in mid secretory phase
Aromatase cytochrome P450	Not detected [20]	Not studied	No aromatase activity in endometrial stromal cells *in vitro* [20]	Synthesis of oestradiol; not present in normal endometrium; likely role in endometriosis as present in both eutopic and ectopic endometrium [21]
11β-HSD family				
11β-HSD1	Detected in endometrium [22]	Not studied	mRNA expression peaks at menstruation [22]; activity low in endometrium although not adequately examined in menstrual phase [23,24]; increased activity with decidualization of endometrial stromal cell *in vitro* [25]	Synthesis of cortisol; potential role in menstruation and early pregnancy
11β-HSD2	Detected in endometrium [22]	Localized to epithelium [22]	mRNA and protein unchanged across menstrual cycle [22]; activity highest in secretory phase [24]; increased expression in endometrium of women with heavy menstrual bleeding (HMB; menorrhagia) [26]; increased activity with decidualization of endometrial stromal cell *in vitro* [25]	Inactivation of cortisol; potential role in menstruation and early pregnancy [26]

5.2. The implantation window (mid secretory phase)

The implantation window coincides with peak circulating progesterone levels and changes to the endometrium occur as a result of the exposure of an oestrogen-primed endometrium to these increased levels of progesterone. The key endometrial events associated with the implantation window are the increased expression of chemokines and cytokines, the onset of decidualization and the presence of increased numbers of leukocytes including uterine natural killer (uNK) cells (Fig. 1). A number of studies have examined gene expression in endometrium by microarray with the aim of identifying genes that are differentially expressed across the menstrual cycle and specifically, those that may be involved in implantation and/or menstruation [58–63]. There is a lack of consensus between these studies due to various factors including the way comparisons were made between different cycle phases (e.g. proliferative vs. mid secretory or early vs. mid secretory) and the limitations inherent in studies examining a multicellular

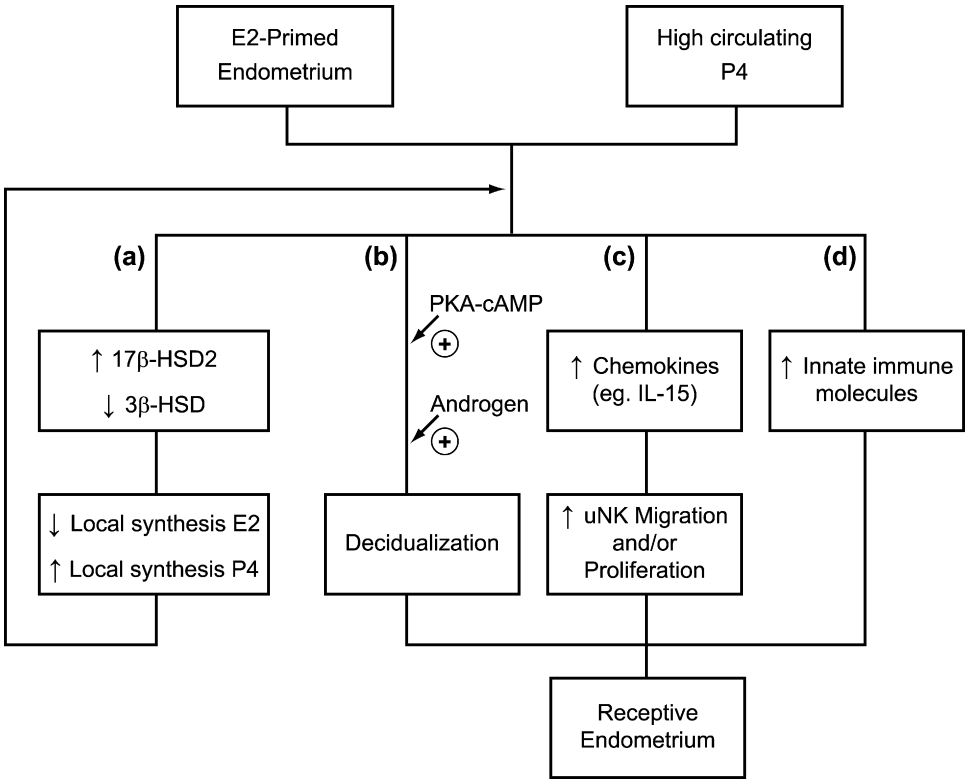

Fig. 1. The implantation window (mid secretory phase): High circulating progesterone concentrations. Progesterone acts on an oestrogen primed endometrium to: (a) alter the expression of steroid metabolizing enzymes resulting in attenuation of the actions of oestrogen and augmentation of those of progesterone; (b) promote decidualization in synergy with androgens and the protein kinase A-cAMP pathway; (c) increase uterine NK cell migration in to and/or proliferation within the endometrium, in part via modulation of chemokine expression; and (d) increase innate immune molecule expression. These actions result in the optimal preparation of the endometrium for embryo implantation.

human tissue, e.g., biological variability between different women [61–64]. However, several of these studies do suggest that there is modulated gene expression of proteins involved in the cell cycle, proliferation and differentiation [59,62,63]; cytokines, chemokines and growth factors [61,63]; and immune mediators [60,63], which is in agreement with the previously published literature.

5.2.1. Decidualization

Decidualization of the human endometrium begins in the mid-late secretory phase of the menstrual cycle irrespective of whether or not a blastocyst is present and continues in the event of pregnancy. It is critical for successful implantation [65]. The stromal compartment shows the most profound changes with the cells becoming plumper, developing a myofibroblast-like phenotype and increasing production of proteins such as prolactin, insulin-like growth factor binding protein-1 and tissue factor [65–69]. Production of extracellular matrix proteins including laminin and fibronectin also increases [70]. Progesterone is necessary for decidualization and the uteri of mice lacking the PR_A fail to exhibit a decidual response [39,71]. In *in vitro* models of stromal cell decidualization there is cross-talk between progesterone signalling and activation of the cAMP-protein kinase A pathway, which is also required to maintain the decidual phenotype [72,73]. cAMP-protein kinase A activity is thought to represent the influence of mediators such as prostaglandins and relaxin *in vivo* [74,75]. A recent study has shown that androgens are also involved in decidualization of endometrial stromal cells at least *in vitro* [76]. Progesterone and androgen-dependent gene expression in decidualizing endometrial stromal cells was examined by utilizing siRNA and microarray technology. This study demonstrated that while PR plays the dominant role in regulation of gene expression during decidualization, AR regulates a smaller group of genes, which are postulated to be involved in organization of the cytoskeleton and the regulation of cell motility and proliferation [76]. Endometrial stromal cells express the GR [29,41] and the influence of cortisol on decidualization and potential interactions between PR, AR and GR-regulated genes remain to be determined.

5.2.2. Uterine NK cells

Decidualization is accompanied by the presence of uNK cells in the endometrium [77]. The uNK cell is a major inflammatory cell type present during the implantation window, with the phenotype $CD56^{bright}CD16^{-}$. This is in contrast to the major peripheral blood (PB) NK cell subtype, which is $CD56^{dim}CD16^{+}$. A minor subgroup of PB NK cells is $CD56^{bright}CD16^{-}$ and it is unresolved whether the increase in the uNK cell population after ovulation results from selective migration of PB $CD56^{bright}$ cells and/or *in situ* proliferation of uNK cells already present in the endometrium. The function of uNK cells is not well understood but may include regulation of trophoblast invasion and placentation and/or angiogenesis [78]. The absolute numbers of uNK cells present in endometrium increases after ovulation although the proportion in relation to other leukocyte subtypes remains constant (30%) across the menstrual cycle [79,80]. It is only when pregnancy occurs that this proportion increases to around 70% of the total leukocyte population [79,81]. It should be noted that recent data have suggested that uNK cells isolated from endometrium differ from those from decidua in their expression of surface activating receptors, chemokine receptors and cytokine and growth factors [80]. Most studies to date have examined uNK cells isolated from first trimester decidua. The increased number of uNK cells present in the secretory phase of the menstrual cycle suggests that uNK cell proliferation and/or migration is regulated by progesterone. However, the lack of PR expression in uNK cells indicates that the

influence of progesterone must be indirect (see below [29]). In contrast, the presence of GR and ERβ indicates that oestrogens and glucocorticoids will alter uNK cell gene expression and function directly. Our group has recently undertaken studies indicating that both oestradiol and cortisol alter uNK cell gene expression with potential functional significance (unpublished data). However, the relevance of these data to endometrial physiology requires further investigation.

5.2.3. Cytokines and chemokines

Many cytokines and chemokines are postulated to have a role in human implantation ([82]). Cytokines from the IL-6 family have been particularly well studied and the potential roles of LIF and a second cytokine (which shares the same receptor), IL-11, in endometrium have been recently reviewed [83]. One mechanism by which progesterone may influence uNK cell function is by modulation of cytokine and/or chemokine expression by other cell types within the endometrium. As stated previously the perivascular cells express PR during the secretory phase and hence, are likely to be a major target of progesterone actions within the uterus [29,38]. Interleukin-15 (IL-15) is present at peak levels during the implantation window when it is expressed by the perivascular cells [84–89] and mRNA for IL-15Rα also shows peak expression in the mid secretory phase [88]. *In vitro* studies have shown IL-15 expression is positively regulated by progestins in endometrial stromal cells [85,90,91] and it has been reported to selectively recruit $CD16^{-}$ NK cells from the peripheral blood [92]. IL-15 has also been shown to increase proliferation of decidual NK cells, which express IL-15Rα [93]. These studies indicate that, at least *in vitro*, IL-15 can modulate uNK cell number via several mechanisms suggesting that IL-15 is a likely mediator of indirect progesterone actions on uNK cells *in vivo*. Interestingly a recent study has reported that the presence of uNK cell conditioned media modulates gene expression in endometrial stromal cells *in vitro*. Expression of several inflammatory genes are upregulated including IL-15, IL-15Rα and adhesion molecules with an implication that uNK cells modulate their local environment to promote migration in to, and proliferation within the endometrium [94].

Chemokines present during the implantation window are also likely to direct the movement of leukocytes (including uNK cells) and trophoblast into endometrium. In the most comprehensive study to date, Jones et al. have reported that macrophage derived chemokine (MDC), monocyte chemotactic protein (MCP)-3, fractalkine (FKN), 6Ckine, hemofiltrate CC chemokine (HCC)-1, HCC-4 and macrophage inflammatory protein (MIP)-1β are upregulated in endometrium during the implantation window, when they may alter leukocyte behaviour [95]. Receptors for FKN, HCC-1 and MIP-1β are present on first trimester trophoblast cells and these chemokines are shown to increase trophoblast migration in *in vitro* migration assays [96]. In addition, endometrial expression of CXCL10 (IP-10), to a lesser extent (trend only), and CXCL11 (IP-9) is highest in the secretory phase suggesting that they may also have a role in implantation [97]. *In vitro* organ cultures have shown that CXCL10 and CXCL11 may be regulated by both oestradiol and progesterone and uNK cells from endometrium express CXCR3 suggesting they can respond to the presence of these chemokines [97]. A further study has shown that both decidual endothelial and stromal cells express MCP-1, IL-8, IP-10, FKN and stromal derived factor (SDF)-1 at the mRNA level and in addition, stromal cells express RANTES and MIP-1β [98]. The $CD56^{+}$ NK cell subtype expresses receptors for all of these chemokines [98]. This study has also indicated that several of these chemokines are steroid regulated: progestin increases expression of IP-10, FKN and MCP-1 in both cell types while oestrogen upregulates IP-10 and FKN in stromal cells [98].

5.2.4. Innate immune molecules

The success of implantation is dependent on the uterus remaining infection-free. In common with other mucosal surfaces the female reproductive tract expresses molecules of the innate immune system, which are likely to be crucial in preventing infection [99,100]. Pattern recognition receptors (PRRs) including the Toll-like receptors (TLRs) and nuclear oligomerization domain proteins (NODs) and effector molecules of the innate immune system such as defensins, secretory leukocyte protease inhibitor (SLPI) and elafin are present in the endometrium [101–108]. Aflatoonian et al. have suggested that TLR2-6, 9 and 10 are expressed at maximal levels in the secretory phase [101] although these data were contradicted by Hirata et al. who reported TLR2-4 and TLR9 to peak perimenstrually [103]. Our unpublished data examining mRNA expression of TLR2, 4 and 5 in well characterized endometrial biopsies from across the menstrual cycle confirms that TLR4 and 5 are maximally expressed in the secretory phase while TLR2 is unaffected by menstrual cycle phase (Fig. 2). Several of the TLRs have been shown to function in response to their ligands in *in vitro* culture models: endometrial epithelial cells respond to a TLR3 ligand and both epithelial and stromal cells respond to LPS, the ligand for TLR4 [109,110]. There are few reports examining the role of steroid hormones in the regulation of TLR expression and/or modulation of their activity in endometrium. However, TLR4 mRNA expression in endometrial stromal cells is reported to be increased by progesterone [103], which would be consistent with increased expression in the secretory phase although progestins have been reported to have no effect on the response of decidual stromal cells to LPS [111]. Oestrogen has been shown to suppress the response of the endometrial epithelial RL95-2 cell line to poly I:C, a mimic of viral infection [112]. Several natural antimicrobial molecules including HBD1, HBD3, HD5 and SLPI are maximally expressed in the secretory phase [102,104,106,108] and SLPI is progesterone regulated [113]. Implantation, and in particular trophoblast invasion of the endometrium, represents a breach of the mucosal barrier and thus, increased expression of the innate immune molecules may be necessary to ensure effective defence against potential infection. In addition, recent data have suggested that TLRs may be activated by endogenous ligands produced as a result of tissue damage and sterile inflammation [114–116]. This is relevant to endometrial physiology as implantation may be considered an example of sterile inflammation and production of endogenous ligands may modulate the inflammatory response via PRRs [107]. This is an area that warrants further investigation.

5.3. Menstruation

Menstruation occurs as a result of progesterone withdrawal (Fig. 3). The endometrial events that precede menstruation have been postulated to fall into two categories [1,2]. Studies in a primate model have shown that the immediate effects of progesterone-withdrawal are reversible if progesterone levels are artificially increased within 24 h [117]. In contrast, around 36 h after progesterone withdrawal (in the rhesus monkey), menstruation becomes inevitable suggesting that later events are progesterone independent [117]. Due to its expression of PR_A during the secretory phase the perivascular cell is likely to be a key site in the initial response to progesterone withdrawal [29,38]. Several groups have used microarray technology to examine changes in gene expression in endometrium from the late secretory phase compared to other menstrual cycle phases [61,63,118]. These studies support the previously published literature indicating that inflammatory mediators and molecules involved in apoptosis, haemostasis and wound healing are involved in the endometrial response to progesterone withdrawal. In addition, one study has used the PR antagonist, RU486, in an *in vivo* model of progesterone withdrawal in women

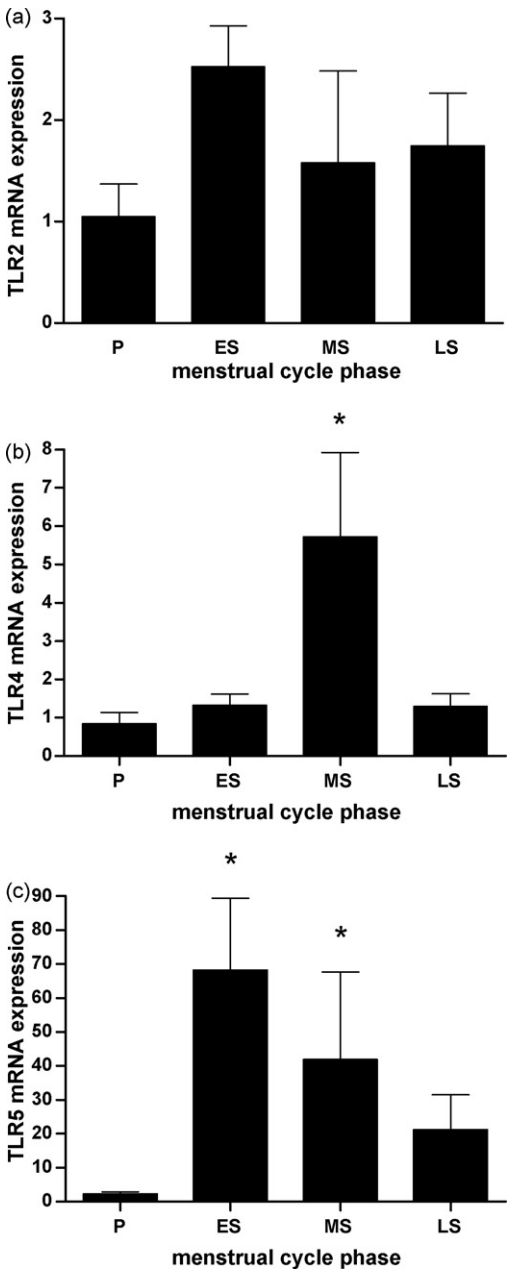

Fig. 2. Differential expression of TLR2, 4 and 5 in endometrium from across the menstrual cycle. P = proliferative phase; E, M and LS = early, mid and late secretory phase. $n = 4$ biopsies in each group. Data were logarithmically transformed prior to statistical analysis by one way ANOVA and Tukey's post hoc analysis. Previous studies are conflicting and have suggested that TLR2, 4 and 5 are maximally expressed in either the secretory phase [101] or in the case of TLR2 and 4 expression menstruation [103]. Our data confirm that TLR4 and 5 are maximally expressed during the secretory phase of the menstrual cycle. This expression pattern may result in increased surveillance for pathogens during the implantation window. (a) TLR2 mRNA expression does not change across the menstrual cycle. (b) TLR4 mRNA expression peaks in the mid secretory phase of the menstrual cycle. $^{*}P < 0.05$; versus all other cycle phases. (c) TLR5 mRNA expression is highest in the early and mid secretory phases of the menstrual cycle. $^{*}P < 0.01$; versus the proliferative phase.

[119]. Endometrial gene expression was examined at 6 and 24 h after RU486 administration. Again this study confirmed previous reports and showed modulation of expression of chemokines, MMPs and molecules involved in prostaglandin synthesis while also indicating that novel pathways may be involved in progesterone withdrawal, e.g., thyroid hormone receptor signalling. A recent study has suggested that dysregulation of glucocorticoid metabolizing enzymes may be involved in heavy menstrual bleeding [26]. This study along with the documented increase in expression of the glucocorticoid synthesizing enzyme, 11β-HSD1, and the GR at menstruation [22,29] indicate that local cortisol generation in the endometrium may play a pivotal role in menstruation.

5.3.1. Endometrial leukocytes, chemokines and prostaglandins

Inflammatory cells, including neutrophils, macrophages and eosinophils, infiltrate the endometrium immediately prior to menstruation [120–122]. Endometrial mast cells are present in constant numbers across the menstrual cycle but there is evidence of increased activation around the onset of menstruation and mast cells are found in association with areas showing evidence of tissue degradation [120,123]. Leukocytes are likely to be involved in the tissue destruction and repair that occurs at menstruation [124] and indeed, neutrophil depletion in a mouse model results in both delayed degradation of the endometrium and its subsequent repair [125]. Although the increased numbers of leukocytes in endometrium perimenstrually suggests regulation by progesterone, data suggest that neutrophils, macrophages, mast cells and eosinophils do not express PR (or ERα) and hence regulation must be indirect [2,126,127]. There are currently no data detailing ERβ, GR or AR expression in these cell types in endometrium. It should be noted that there are studies showing ER and/or PR expression in polymorphonuclear leukocytes and mononuclear cells derived from the peripheral blood and mast cells present at other tissue sites [128,129]. The relevance of these data to endometrial physiology is unclear.

As detailed above in relation to uNK cells, the migration of leukocytes in to endometrium premenstrually is likely to be controlled by chemokines. Jones et al. reported that MDC, 6Ckine, MCP-3 and FKN are present at high levels around the onset of menstruation [95] and this and other studies suggest that IL-8, FKN, eotaxin (chemoattractant for eosinophils) and MDC are upregulated in the vasculature premenstrually [95,130–133]. In addition, leukocytes themselves are a source of chemokines once they have infiltrated the endometrium suggesting the existence of a positive feedback loop [95]. A previous study from our group has also shown that MCP-1 is upregulated in perivascular cells premenstrually [132]. This upregulation of chemokines in perivascular cells at the time of progesterone withdrawal suggests that in the mid secretory phase progesterone inhibits the local production of, for example, IL-8 and MCP-1. This is consistent with *in vitro* culture experiments showing suppression of MCP-1 secretion in human endometrial stromal cells [134] and IL-8 in endometrial explants [135] in the presence of progestin. There are few data relating to progesterone regulation of eotaxin, FKN and MDC.

Prostaglandins have also been implicated in the mechanisms surrounding menstruation [136,137]. Both prostaglandin synthesizing and metabolizing enzymes are regulated by progesterone. Activity of the metabolizing enzyme, prostaglandin dehydrogenase, is highest in endometrium from the secretory phase of the menstrual cycle and mRNA expression is increased by progestin in myometrial smooth muscle cells [138,139]. PGDH is present in the perivascular area in first trimester decidua and expression is reduced in an *in vivo* model of progesterone withdrawal [140]. In contrast, COX-2 (prostaglandin synthesis), which is present throughout the menstrual cycle in the glandular epithelium, is upegulated in the perivascular cells premenstrually [132]. These data suggest that at menstruation there is increased prostaglandin production around the blood vessels. Potential roles include recruitment of neutrophils in synergy with IL-8 [141,142] and regulation of the hypoxic response [143]. These data, along with those relating to chemokine expression, suggest that progesterone and its withdrawal impact endometrial function in part by regulating the local expression of inflammatory mediators.

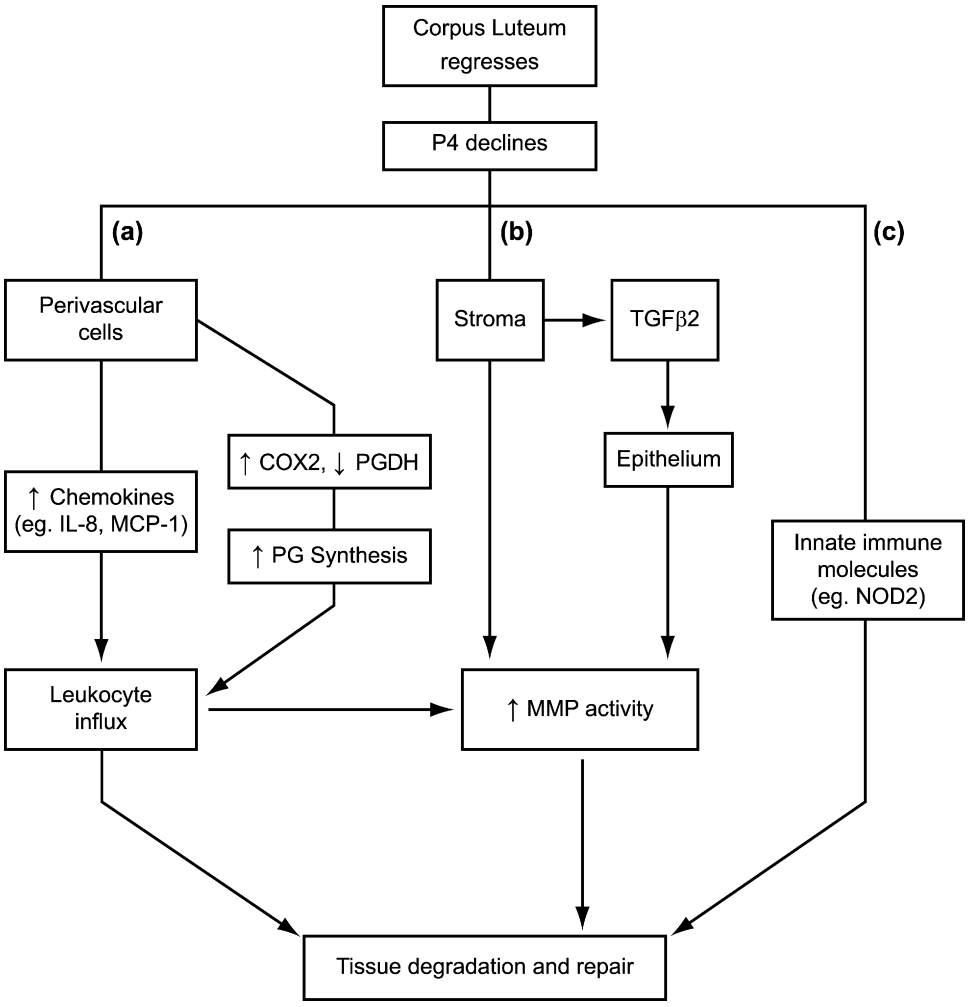

Fig. 3. Menstruation: Progesterone withdrawal. In the absence of implantation the corpus luteum regresses and circulating progesterone concentrations rapidly decline. Progesterone withdrawal causes a local inflammatory response in the endometrium that includes: (a) increased expression of inflammatory mediators resulting in leukocyte influx; (b) increased matrix metalloproteinase activity; and (c) enhanced expression of innate immune molecules, which may modulate factors involved in endometrial repair. The consequences of these actions are breakdown of the endometrium followed by its repair in preparation for the next implantation window.

5.3.2. MMPs

It has been proposed that the later events that trigger menstruation are likely to involve irreversible tissue breakdown mediated by MMPs [reviewed in 2]. Endometrial tissue explant studies have indicated that inhibition of MMPs can prevent the tissue breakdown that results from sex steroid withdrawal [144]. There are several subgroups of MMPs including collagenases, gelatinases and stromelysins. MMPs are either secreted as inactive zymogens or in some cases remain membrane bound. The activity of both MMPs and their endogenous inhibitors, tissue inhibitors of MMPs (TIMPs), must be tightly controlled in both a temporal and spatial manner. It should be noted that TIMP2 has also been implicated in the activation of MMP2 [145]. Many studies have documented increased expression and/or activity of MMPs, including MMP1, 2, 3, 7, 8, 9 and 12, around the time of menstruation [146–153]. Stromal cells are a source of MMPs [149,151,154–156] and leukocytes infiltrating the tissue at menstruation have been shown to express MMP2 and 9 and MT1-MMP and MT2-MMP [154–156]. MMP7 is unusual in that it shows predominantly epithelial expression [151]. The regulated expression of MMPs by progesterone has been well documented in *in vitro* cell and tissue culture models. MMP1, 2, 3 and 9 are reported to increase in response to progesterone withdrawal in endometrial stromal cell and/or endometrial tissue explant studies [157–160]. An epithelial–stromal cell interaction where progesterone acts on the stroma to increase expression of TGFβ2 and subsequently downregulate MMP7 expression in the epithelium has also been reported [161]. These studies along with those showing *in vivo* expression of MMPs at menstruation collectively suggest that the actions of progesterone and its withdrawal premenstrually modulate MMP activity in the endometrium. The focal localization of some MMPs within the endometrium [149,153] indicates a further layer of regulation with *in vitro* culture studies indicating that local expression of cytokines and growth factors may be involved [162,163]. Reports documenting TIMP expression across the menstrual cycle are contradictory. TIMP1 and 2 have been reported to show little variation across the menstrual cycle [154] or to increase at menstruation [152] while two studies have indicated that TIMP3 expression peaks at menstruation [147,152]. Most *in vitro* studies have suggested that TIMP1, 2 and 3 are unaffected by progesterone and its withdrawal [157,160,163] although TIMP3 is upregulated during decidualization [164]. It seems likely that the balance between TIMP and MMP activity is altered at menstruation resulting in highly temporally and spatially controlled tissue degradation.

5.3.3. Innate immune molecules

As at implantation, menstruation involves a breach in the epithelial barrier and hence, increased expression of innate immune molecules may be necessary to limit infection [100,105]. As detailed above contradictory reports regarding expression of

the TLRs in endometrium exist and one group has reported peak expression of TLR 2-4 and TLR9 in perimenstrual endometrium [103]. Our group has recently documented maximal expression of the intracellular PRR, NOD2, in the late secretory phase when NOD2 mRNA expression is inversely correlated with circulating progesterone concentrations [107]. Several antimicrobial effector molecules show maximal expression in endometrium perimenstrually. HBD2 mRNA expression peaks at this time and *in vitro* experiments show that it can be regulated by inflammatory mediators in endometrial epithelial cells, indicating a mechanism by which expression may be upregulated *in vivo* [102,165]. The leukocytes infiltrating endometrium are also a source of antimicrobial molecules. Elafin is present in endometrial neutrophils and peak mRNA expression is observed at menstruation [105]. Similarly, granulysin mRNA peaks in the late secretory phase [102]. This antimicrobial is expressed in peripheral blood NK cells [166] but expression by uNK cells has not yet been reported. The actions of steroid hormones on the local modulation of expression and function of innate immune molecules within the endometrium are not well understood and in addition, the functional consequences of differential expression of innate immune molecules in the endometrium remain unclear.

6. Conclusion

In summary, the actions of oestrogen and progesterone on endometrium are controlled by both the presence of metabolizing enzymes within the tissue and the sites and levels of expression of their respective receptors. The modulation of inflammatory events in endometrium by the sex steroid hormones involves a highly complex network of inflammatory mediators and immune cells, which ultimately prepares the endometrium for embryo implantation. Further elucidation of these networks is critical to our knowledge of normal implantation and menstruation. This in turn will aid our understanding of pathological events such as implantation failure and menstrual dysfunction and will also be highly relevant to the development of future endometrial contraception.

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