



Published in final edited form as:

*J Steroid Biochem Mol Biol.* 2023 May ; 229: 106254. doi:10.1016/j.jsbmb.2023.106254.

## The Effects of Progesterone on Immune Cellular Function at the Maternal-Fetal Interface and Maternal Circulation

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### Abstract

Progesterone is a sex steroid hormone that plays a critical role in the establishment and maintenance of pregnancy. This hormone drives numerous maternal physiological adaptations to ensure the continuation of pregnancy and facilitate fetal growth, including broad and potent

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### DECLARATION OF INTEREST

The authors declare no potential conflicts of interest.

modulation of the maternal immune system to promote maternal-fetal tolerance. In this brief review, we provide an overview of the immunomodulatory functions of progesterone in the decidua, placenta, myometrium, and maternal circulation during pregnancy. Specifically, we summarize current evidence of the regulated functions of innate and adaptive immune cells induced by progesterone and its downstream effector molecules in these compartments, including observations in human pregnancy as well as in animal models. Our review highlights the gaps in knowledge of interactions between progesterone and maternal cellular immunity that may direct future research.

## Keywords

Decidua; Dendritic cell; Macrophage; Neutrophil; NK cell; Pregnancy; T cell

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## 1. INTRODUCTION

Progesterone (pregn-4-ene-3,20-dione or P4) is a hormone classified as a natural sex steroid that plays a key role in the maintenance of pregnancy [1–5]. This hormone is produced by the corpus luteum during the latter half of each menstrual cycle (i.e. secretory phase or luteal phase) to transform and prepare the endometrium for implantation [6, 7]. If implantation does not occur, the corpus luteum spontaneously regresses, resulting in progesterone withdrawal and subsequent menstruation [6, 7]. On the other hand, if the embryo implants in the decidualized endometrium (i.e. decidua), human chorionic gonadotropin (hCG) derived from the developing blastocyst maintains the corpus luteum to promote the production of progesterone [8], which is later produced by the placenta [7, 9]. During pregnancy, progesterone drives multiple maternal physiological changes, including the maintenance of myometrial quiescence [10–16], alteration of the cardiovascular system [17], and preparation of mammary glands for lactation [18], among others [19, 20], via the progesterone receptors (PRs) expressed throughout the body [21].

Besides physiological changes, progesterone also exerts potent immunomodulatory functions throughout pregnancy [22–25]. For example, progesterone promotes the expansion or differentiation of regulatory T cells (Tregs) both systemically [26–30] and at the maternal-fetal interface (i.e. the decidua and placenta) [27, 30–32]. Moreover, this hormone dampens the cytotoxic activity and degranulation of natural killer (NK) cells in these compartments [33–38]. In general, progesterone also drives the polarization of circulating and resident immune cells toward an anti-inflammatory phenotype to promote a tolerogenic microenvironment, a process that involves downregulating the release of pro-inflammatory mediators [39–41]. Moreover, progesterone regulates cellular immune processes in the cervix [42–49]. Together, these progesterone-driven immunological changes foster a homeostatic state that ensures a successful pregnancy.

In this brief review, we summarize the known interactions between progesterone and maternal immune cells during pregnancy. In particular, we highlight the specific changes in cellular immune functions that are driven by progesterone in the decidua, placenta, myometrium, and maternal peripheral blood. Given that this hormone exhibits broad

functions during pregnancy, we have focused on the direct effects of progesterone or its downstream mediators (e.g. progesterone-induced blocking factor, PIBF) on innate and adaptive immune cell subsets. Importantly, this review also reveals gaps in knowledge of the mechanisms of progesterone-cellular immune interactions that require further investigation.

## 2.1 DECIDUA

The decidua and its non-pregnant counterpart, the endometrium, are indispensable for successful implantation and pregnancy [50, 51]. During the latter half of the menstrual cycle (i.e. secretory phase or luteal phase), progesterone regulates decidualization, which is the dramatic remodeling of the endometrial tissue in preparation for implantation [7, 52, 53]. This process includes the transformation of glands to the secretory state, leukocyte recruitment, angiogenesis, and mesenchymal-epithelial transition of endometrial stromal cells [54–56]. Once transformation has completed, a constant supply of progesterone is required to maintain the decidua [57, 58]. Furthermore, the decidua hosts a diverse array of immune cells that play a key role in the establishment and maintenance of pregnancy [59, 60]: decidual NK cells promote spiral artery remodeling in early pregnancy [61, 62], homeostatic macrophages act as tissue sentinels and control the decidual microenvironment [63], and Tregs facilitate and maintain maternal tolerance of the semi-allogeneic fetus [64, 65], among others. Given the importance of decidual immune cells in maintaining effective maternal-fetal crosstalk, a large number of studies have focused on the immunological effects of progesterone in this compartment, which are summarized in Figure 1.

### 2.1.1 Decidual effector T cells

Several studies have demonstrated the effects of progesterone on decidual effector T cells. The administration of the PR antagonist RU486 to pregnant mice on 15.5 days *post coitum* (dpc) led to withdrawal of progesterone action and preterm birth without inducing major changes in the immune cell composition of the decidua [66]. However, progesterone prevented preterm birth induced by activated maternal T cells, and reduced the gene expression of inflammation-associated molecules (*Casp11*, *Ccl22*, *Icam1*, *Ctla4*, *Nod1*, and *Ccl5*) in the decidua, suggesting anti-inflammatory effects of this hormone on T cell-mediated inflammatory processes in this maternal-fetal interface [66]. The alteration of decidual T-cell functions by progesterone is further supported by *in vitro* studies [35, 67]. Progesterone reduced the perforin production of first-trimester human decidual lymphocytes either directly or indirectly (co-culture of these immune cells with decidual adherent cells), which was potentially mediated by PIBF [35], an immunomodulatory protein produced by activated lymphocytes in the presence of progesterone [68–70]. Moreover, progesterone treatment of CD4<sup>+</sup> or CD8<sup>+</sup> T cells isolated from the mid-luteal phase human endometrium increased the expression of RANTES [67], a chemokine that has been associated with the induction of immune tolerance at the maternal-fetal interface [67, 71]. Therefore, progesterone appears to preclude excessive T-cell activity in the decidua.

### 2.1.2 Decidual $\gamma\delta$ T cells

Other T-cell subsets are also affected by progesterone.  $\gamma\delta$  T cells, expressing a T-cell receptor (TCR) composed of a  $\gamma$  chain and  $\delta$  chain [72], can express PRs [73]. Such cells

may participate in the immunomodulatory effects of progesterone in the decidua, mediated in part by their release of PIBF as observed *in vitro* [74]. Indeed, the frequency of  $\gamma\delta$  T cells among total T cells was increased in the secretory phase endometrium (high progesterone levels) of non-pregnant women compared to the proliferative phase endometrium (low progesterone levels), and progesterone treatment increased the frequency of  $\gamma\delta$  T cells during the latter phase [75]. The observed increase in the proportion of  $\gamma\delta$  T cells was maintained in the early pregnancy decidua [75], supporting the regulation of this T-cell subset by progesterone.

### 2.1.3 Decidual Tregs

The effects of progestogens on decidual Tregs were also investigated using a clinically-relevant murine model [31]. The vaginal administration of progesterone, which is utilized to treat women who undergo preterm labor with short cervix [76–84], in late pregnancy (days 13 to 17 of gestation) increased the frequency of decidual CD4<sup>+</sup> Tregs in mice [31]. By contrast, the systemic administration of 17-alpha-hydroxyprogesterone caproate (17OHP-C) to pregnant mice did not alter Treg proportions in the decidua [31]. Similarly, the systemic administration of progesterone in early pregnancy (days 0, 2, 4, and 6 of gestation) increased the frequency of decidual Tregs by mid-gestation [30]. Therefore, the type of progestogen as well as the timing of administration may be important factors. In addition, progesterone can indirectly modulate the migration of induced Tregs (iTregs) by upregulating RANTES production in endometrial stromal cells under inflammatory conditions, a process mediated by vasoactive intestinal peptide (VIP) [85]. These studies suggest that progesterone exhibits immunosuppressive functions not only through direct effects on decidual immune cells but also by the promotion of Treg expansion or differentiation at the maternal-fetal interface.

### 2.1.4 Decidual B cells

Although few studies have explored the effects of progesterone on decidual B cells, the treatment of pregnant mice with an anti-PIBF antibody depleted decidual B cells and increased fetal resorption in mice [86]. In this context, a previous study reported that PIBF increased the production of asymmetric antibodies [87], which have a protective role during pregnancy [88]. The above evidence suggests a role for progesterone and PIBF in the maintenance and function of decidual B cells; yet, this concept requires further research.

### 2.1.5 Decidual NK cells

*In vivo* studies have explored the relationship between progesterone and uterine and decidual NK cells. The systemic administration of progesterone increased the number of dolichos biflorus agglutinin (DBA) lectin<sup>+</sup> uterine NK cells in the endometrium of non-pregnant ovariectomized mice, and this effect was blocked by RU486 [89]. By contrast, treatment with RU486 alone did not decrease the number of decidual NK cells in human first trimester decidua [90]. Serum concentrations of progesterone are also associated with the maintenance of decidual NK cells, as the number of these innate immune cells was retained if progesterone withdrawal was prevented by the systemic administration of this hormone in mice [91]. Consistently, the relationship between the serum concentration of progesterone and frequency of decidual NK cells was also observed after the administration of high doses of dexamethasone in early pregnancy in mice, which decreased both factors [92]. These

results suggest the importance of progesterone in the expansion and maintenance of uterine and decidual NK cells.

Despite the known effects of progesterone on uterine and decidual NK cells, the expression of PRs by such cells is still under debate. One study demonstrated PR expression on a subset of uterine NK cells from pregnant mice, although the PR<sup>+</sup> population of this innate immune subset was small [93]. On the other hand, a lack of PRs was reported on NK cells from the non-pregnant human endometrium [94–96], first trimester human decidua [94–96], and rat decidua (days 8 – 12 and 14 – 21 of gestation) [97]. Moreover, progesterone had no direct effects on the *in vitro* proliferation, cytolytic activity, or cytokine secretion of CD16<sup>-</sup>CD56<sup>bright</sup> NK cells isolated from human endometrium [98]. Therefore, it is plausible that progesterone influences uterine NK cells through indirect mechanisms [99], although a possible role for the glucocorticoid receptor in mediating the direct effects of progesterone on NK cells has been reported [100]. Indeed, the co-culture of endometrial stromal cells and lymphocyte fraction from non-pregnant human endometrium with progesterone induced the expansion of CD56<sup>+</sup> NK cells [101]. Further, since co-localization of PR-expressing cells and DBA lectin-expressing decidual NK cells in the murine decidua throughout pregnancy was not observed [102], the progesterone-induced effects of decidual or endometrial stromal cells on uterine NK cells may also be mediated by soluble factors.

One of the most important cytokines produced by endometrial or decidual stromal cells in response to progesterone is interleukin (IL)-15, which is essential for NK-cell development and proliferation [103]. IL-15 was detected in human endometrium and decidua, where its expression is increased in the secretory phase endometrium [104, 105] and first trimester decidua [105]. In addition, progesterone increased the production of IL-15 by human first trimester decidual cells [105] and endometrial stromal cells *in vitro* [104, 106], suggesting that progesterone controls the release of this cytokine in these tissues. Moreover, NK cells isolated from human first trimester decidua expressed the IL-15 receptor [107], which is expected given the key role of this cytokine in the proliferation, chemoattraction, and differentiation of these innate immune cells [98, 107–110]. Other mediators produced by endometrial or decidual stromal cells with progesterone stimulation are also implicated in the chemoattraction and differentiation of uterine NK cells, such as CXCL12, CX3CL1, CXCL10, CXCL14, and osteopontin, among others [111–113]. Progesterone also upregulated the expression of KLRK1 by murine trophoblasts, resulting in increased production of IFN $\gamma$  by uterine NK cells [114].

Other factors that can mediate the effects of progesterone on uterine NK cells include PIBF. This factor can inhibit the degranulation of NK cells derived from human peripheral blood [36] and reduce the cytotoxicity of NK cells isolated from human first trimester decidua *in vitro* [115]. In addition, the inhibition of PIBF by a monoclonal anti-PIBF antibody in mice during early pregnancy (on 1.5 and 4.5 dpc) increased the cytotoxicity of decidual NK cells, leading to implantation failure and resorption [86]. Of note, decidual NK cells are not only affected by PIBF, but also may produce this immunomodulatory molecule in mice [86, 116]; yet, the mechanisms by which progesterone induces PIBF production in decidual NK cells remain unclear. Together, these results suggest that progesterone can indirectly regulate

decidual and uterine NK cells, thereby modulating the immune milieu of the endometrium and decidua during implantation and gestation.

### 2.1.6 Decidual macrophages

Animal and human studies have suggested that macrophages in the endometrium, the non-pregnant counterpart of the decidua, are responsive towards progesterone. In the murine endometrium, the number of F4/80<sup>+</sup> macrophages increased during estrus [117], and ovariectomy resulted in a significant decrease of this cell population [118]. Using the same ovariectomy model, another study reported that progesterone inhibited the estrogen-induced infiltration of macrophages into the endometrium, a phenomenon that was mediated by PRs as determined using PR-deficient mice [119]. In addition, progesterone withdrawal during the menstrual cycle also increased the number of macrophages in the human endometrium [120], whereas women who received progesterone treatment during the secretory phase (i.e. hormone replacement therapy) showed increased endometrial expression of macrophage chemoattractant protein (MCP)-1 [121]. These studies suggest that endometrial macrophages are at least partially regulated by progesterone and estrogen in the non-pregnant state.

A role for progesterone in regulating decidual macrophages has also been reported. The blockade of PR by RU486 during the first trimester increased the number of macrophages present in the human decidua [90]. Moreover, a clinically-relevant murine model showed that vaginal progesterone decreased the frequency of decidual macrophages, whereas the systemic administration of 17OHP-C did not [31]. In line with this concept, a murine study suggested that the anti-inflammatory effects of progesterone were at least partially due to inhibited production of macrophage chemoattractants [e.g. colony stimulating factor (CSF)-1 and MCP-1] in decidual stromal cells via the nuclear protein high-mobility group box-1 (HMGB-1) [122]. By contrast, the decidual infiltration of macrophages was not increased during RU486-induced preterm birth in mice [66, 123].

Direct effects of progesterone on monocytes/macrophages have been described using *in vitro* models. Medroxyprogesterone acetate (MPA; a synthetic progesterone analog), but not natural progesterone, triggered the differentiation of the monocyte cell line THP-1 towards a homeostatic (M2-like) phenotype [124]. These MPA-treated THP-1 cells could promote the decidualization of a human endometrial stromal cell line and the invasion of the trophoblast cell line (HTR8/SVneo), suggesting that MPA facilitates the differentiation of peripheral blood monocytes into homeostatic decidual macrophages [124]. Of note, despite the direct effects of MPA on THP-1 cells, there is currently no evidence of PR expression by decidual or endometrial macrophages [94, 95]. Therefore, the indirect effects of progesterone on decidual macrophages should also be considered.

### 2.1.7 Decidual DCs

Mature dendritic cells (DCs), defined by the maturation markers CD83 and HLA-DR, were present in human first trimester decidua [125]. Progesterone facilitated the differentiation of human peripheral blood mononuclear cell (PBMC)-derived monocytes into CD83<sup>+</sup>HLA-DR<sup>+</sup> mature DCs *in vitro*, indicating a potential role for this hormone in the maturation of

decidual DCs [125]. Moreover, transcriptome analysis of decidual DCs from human term placentas identified higher upregulation of estrogen- and progesterone-modulated genes as well as genes encoding immunomodulatory cytokines compared to monocyte-derived DCs from PBMCs [126], suggesting that such cells undergo additional differentiation within the decidual microenvironment. This concept is further evidenced by the observation that the maturation of decidual DCs in response to bacterial pathogen-associated molecular patterns (PAMPs) or bacteria known for their placental tropism (*Coxiella burnetii* and *Brucella abortus*) was lower compared to that of monocyte-derived DCs [126]. However, a causal link between the effects of progesterone and decidual DCs has not been shown, given that progesterone administration in pregnant CBA/J × DBA/2J abortion-prone mice did not increase the number of total or mature DCs in the decidua [30]. Therefore, future studies are needed to clarify the involvement of progesterone in the maturation and differentiation of decidual DCs.

### 2.1.8 Decidual neutrophils

The effects of progesterone on decidual neutrophils have also been investigated. The administration of RU486 and a prostaglandin E analog increased the number of neutrophils in human first trimester decidua [127], suggesting that blockade of PR promotes the infiltration of neutrophils into this compartment. In line with this concept, progesterone was reported to reduce the expression of IL-8, which is a strong chemoattractant for neutrophils, in human endometrial explants [128] and term decidual tissues *in vitro* [129]. Progesterone also inhibited the increased expression of IL-8 and neutrophil chemotaxis induced by mechanical stretch in human decidual cells *in vitro* [130]. Consistently, the withdrawal or inhibition of progesterone increased the expression of IL-8 in the human endometrium during the menstrual cycle and in human first trimester decidual explants [90, 131]. However, the blockade of PR by RU486 in the first trimester did not change the proportion of human decidual neutrophils [90], and the decidual infiltration of neutrophils was not increased during RU486-induced preterm birth in mice [66, 123]. In addition, several studies reported the upregulation of IL-8 by progesterone in the secretory phase human endometrium [121] and by MPA in IL-1 $\alpha$ -stimulated human endometrial stromal cells *in vitro* [132]. Together, these results suggest that progesterone plays a role in the regulation of neutrophil migration in the decidua; yet, further studies are needed to confirm the precise effects and mechanisms that underlie this phenomenon.

## 2.2 PLACENTA

The placenta is a unique organ that carries out multiple functions. First, the placenta, together with the extraplacental chorioamniotic membranes, acts as a physical barrier to protect the fetus from exposure to harmful microbes acquired by the mother [133–136]. Importantly, the placenta also acts as the lungs, gut, kidneys, and liver of the developing fetus [137, 138]. Besides its role in fetal physiology, the placenta releases numerous mediators, such as hormones, cytokines, and exosomes/microparticles [137, 139–141], that can modulate maternal physiological systems, including the immune response. Indeed, the placenta is a major producer of progesterone during pregnancy [9], and thus multiple studies

have investigated how this hormone can affect the immune cells residing in this central organ.

### 2.2.1 Placental T cells

Several reports have suggested that progesterone influences the activity of placental T cells. The administration of 17OHP-C significantly increased placental T helper 2 (Th2) cells in a rat model of reduced uterine perfusion pressure (RUPP) [37]. Moreover, the administration of progesterone-dependent PIBF resulted in decreased total CD4<sup>+</sup> T cells in the placenta while simultaneously elevating circulating Th2 cells and plasma IL-4 concentrations [38]. Such mechanisms could be at least partially driven by the reduced expression of CXCL9 and CXCL10 reported after pretreatment with 17OHP-C in mice with lipopolysaccharide (LPS)-induced intrauterine inflammation [142]. However, micronized progesterone failed to replicate this effect [142]. Regardless, these reports indicate progesterone-dependent mechanisms controlling placental T-cell activity, and highlight the varying immunological effects caused by progestins.

### 2.2.2 Placental Tregs

Progesterone has been suggested to maintain an immunosuppressive microenvironment in the placenta by promoting Treg development and activity [27, 32]. Foxp3 expression is highest in the murine placenta during midterm pregnancy (10 dpc), and RU486 treatment significantly decreased such expression [27]. As estrogen has previously been shown to induce Treg expansion *in vivo* [143], both hormones may play a role in the maintenance of placental Tregs throughout pregnancy. Several mechanisms have been suggested whereby progesterone may promote placental Treg functions. The expression of the immunoregulatory glycan-binding protein Galectin-1 (Gal-1) by extravillous cytotrophoblasts in the human first trimester and term placenta appeared to be driven by progesterone [32]. Furthermore, the expression of Gal-1 by the JEG-3 trophoblast cell line promoted the *in vitro* expansion of Tregs [32]. Progesterone-stimulated Gal-1 may also promote a tolerogenic placental microenvironment by inducing IL-10 secretion from placental cells [27, 32]. Placental Gal-1 expression was unaffected by the selective knockout of PRs on DCs [144], reinforcing the proposed mechanism that tolerogenic DCs function downstream of Gal-1 [144]. Collectively, these studies provide evidence that progesterone encourages pregnancy maintenance by promoting an immunosuppressive environment in the placenta through local expansion of Tregs and stimulation of the Gal-1 pathway.

### 2.2.3 Placental NK cells

Several studies have demonstrated immunomodulatory effects of progesterone on placental NK cells [37, 38]. The intraperitoneal administration of 17OHP-C to RUPP rats on day 15 of pregnancy significantly decreased both total and cytolytic placental NK cells as well as placental levels of perforin and granzyme B [37]. Similar findings were observed after supplementation with PIBF in RUPP rats also decreased total and cytolytic placental NK cells [38]. These results are consistent with a previous report showing reduced peripheral NK-cell perforin release upon treatment with this factor *in vitro* [36]. Thus, progesterone and its induced factor PIBF exert specific immunoregulatory effects on placental NK cells.



#### 2.2.4 Placental neutrophils

Progesterone differentially influences the activity of two distinct populations of neutrophils that are found in the placenta [145, 146]. The administration of RU486 at advanced gestation (>160 days) in pregnant cynomolgus monkeys caused a neutrophilic invasion of the placenta, resulting in damage to this organ [145]. In addition, molecular studies noted markedly depressed the levels of serum and placental pregnancy associated plasma protein A (PAPP-A) [145]. Thus, as a consequence of progesterone withdrawal, the loss of human granulocyte elastase inhibition increases neutrophilic infiltration of the placenta, destroying the villous structures and ultimately leading to fetal demise [145].

Progesterone also impacts a more recently described population of homeostatic neutrophils that are functionally dissimilar to polymorphonuclear neutrophils [146]. Possessing anti-inflammatory and quiescent properties, these cells are induced by estrogen and progesterone from immature neutrophils and are proposed to function in placental development and maternal-fetal immune tolerance [146]. Indeed, the co-culture of estrogen- and progesterone-treated neutrophils and T cells resulted in the differentiation of CD4<sup>+</sup> T cells displaying a regulatory-like phenotype, termed neutrophil-induced T (niT) cells, which may participate in the process of placentation [146]. The induction of niT cells was shown to rely on the transfer of neutrophil-derived molecules, such as FOXO1, to T cells, and the neutrophil-specific knockdown of FOXO1 resulted in defective placentation and fetal development [146]. Altogether, progesterone plays a dual role in preventing the invasion of peripheral neutrophils to the placenta while inducing pro-angiogenic neutrophils that promote homeostatic placental T cells and thus facilitating proper placental and fetal development.

#### 2.2.5 Placental macrophages

The anti-inflammatory effects of progesterone may also be attributed to its effects on placental macrophage populations [147]. Human placental mesenchymal stem cells (pMSCs) induced a homeostatic M2-like polarization of monocyte-derived macrophages *in vitro*, which was at least partially driven by progesterone and glucocorticoid receptors expressed by such cells [147]. This mechanism was evidenced by treatment with RU486, which resulted in a shift towards a pro-inflammatory cytokine profile in macrophages [147]. Yet, changes in gene expression were not observed in bone marrow-derived macrophages exposed to progesterone *in vitro* [148], suggesting that other aspects of the placental microenvironment may also contribute to macrophage phenotypes and activity in this organ. In contrast with the above-mentioned beneficial effects of progesterone on placental macrophages, this hormone has been suggested to increase low-density lipoprotein (LDL) oxidation and cytotoxicity of macrophages and trophoblasts *in vitro* [149]. Thus, under specific conditions, progesterone could exacerbate placental macrophage-mediated LDL oxidation and acute atherosclerosis; however, this concept requires further investigation.

#### 2.2.6 Placental DCs

Similar to placental macrophages, progesterone signaling of DCs appears to be beneficial for placental development, as impairment of this process resulted in a decreased ratio of placental labyrinth zone area to junctional zone area in mice at 13.5 dpc and 18.5 dpc,

although the latter time point was not significantly different from controls [144]. Moreover, loss of progesterone signaling in DCs resulted in decreased placental mRNA expression of *Egf* and *Igf1* [144], both of which have been implicated in placental and fetal development [150, 151]. In addition to enhancing placentation, progesterone may indirectly promote DC-mediated local immune tolerance, as pretreatment of female mice with syngeneic immature DCs prior to allogeneic abortion-prone mating (CBA/J × DBA/2J) resulted in increased numbers of PIBF<sup>+</sup> cells in the mid-pregnancy placenta and a reduced rate of abortion [152]. Moreover, *in vitro* progesterone treatment of pregnant rat-derived placental and embryonic cells reduced indoleamine-2,3-dioxygenase (IDO) expression by DCs [153]. Despite the seemingly counterintuitive nature of this observation, it was speculated that progesterone maintains IDO expression at basal levels to ensure an adequate immune response in the case of infection or other insults [153].

### 2.2.7 Placental myeloid cells

Lastly, progesterone not only affects the differentiation of myeloid cells in the placenta but can also influence their precursor cells [154], termed immature myeloid cells (IMCs), which are found in this compartment [154, 155]. Murine placental tissues were enriched for granulocytic IMCs, while monocytic IMCs in this tissue were lower compared to subcutaneous murine tumors [154]. In addition, progesterone treatment of bone marrow-derived CD11b<sup>+</sup> cells *ex vivo* resulted in a similar composition of granulocytic and monocytic IMCs [154]. Notably, intraperitoneal LPS injection of pregnant mice (on day 15 and 16) decreased the placental IMC population, and this effect was prevented by progesterone pretreatment [154]. Thus, progesterone may participate in the maintenance of IMCs, and subsequently of mature myeloid cell subsets, in the placenta.

## 2.3 MYOMETRIUM

The uterus is a primary reproductive organ that undergoes dramatic changes to accommodate the growing fetus and placenta as pregnancy progresses [156]. Such modifications include an increase in uterine size, remodeling of myometrial thickness, and enlargement of the blood vessels, among others [157–161]. The uterus is by nature a contractile organ, which transitions from a state of non-contractility (termed myometrial quiescence) to a state of activation and stimulation that results in myometrial contractions required to effectively deliver the fetus during parturition [16, 162, 163]. This transformation is tightly regulated by complex mechanisms that are still under investigation [10, 12, 164]. Regardless, it is well known that progesterone induces myometrial quiescence through several mechanisms [10–16]. However, the cellular immune responses triggered by this hormone have been less characterized. Indeed, most research has focused on the administration of exogenous progestogens to evaluate such immune responses.

### 2.3.1 Myometrial T cells

Several reports have indicated effects of progestogens on myometrial T cells. Progesterone receptors were present in pooled CD4<sup>+</sup> T cells from the embryo, placenta, and uterus of pregnant rats on 6 dpc [153]. Moreover, the expression of IDO by CD4<sup>+</sup> T cells was reduced when cultured with progesterone, which recovered after exposure to RU486 due to its

antagonizing effect [153]. In a murine model of abortion induced by stress, treatment with dydrogesterone (a synthetic progestogen [165]) reduced the rate of abortion [166, 167] and restored the physiological proportions of CD8<sup>+</sup> T cells in the uterine tissues [167]. However, such an effect was suppressed when CD8<sup>+</sup> T cells were depleted by using an anti-CD8 mAb [167]. Furthermore, the injection of dydrogesterone significantly decreased the proportions of TNF- and IFN $\gamma$ -producing cells while simultaneously increasing the proportion of IL-4-producing cells in the uterus [167]. Importantly, the dydrogesterone-induced downregulation of Th1 cytokines in uterine cells was abolished after CD8<sup>+</sup> T-cell depletion [167], suggesting that the protective effects of progestogens against abortion are at least partially CD8<sup>+</sup> T cell-dependent. Progesterone also reduced the rate of preterm birth in a model of maternal T-cell activation-induced preterm birth and caused the downregulated myometrial expression of the inflammation associated molecule *I/33* [66]. On the other hand, the administration of vaginal progesterone to mice during mid-pregnancy did not alter the proportions of myometrial CD4<sup>+</sup> Tregs or CD8<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T cells [31], suggesting differential effects of progesterone on myometrial T-cell subsets.

### 2.3.2 Myometrial NK cells

Hormonal replacement with estradiol and/or progesterone in ovariectomized mice induced a marked increase in human CD56<sup>bright</sup> NK cell adhesion to murine uterine tissues compared to controls, a process that was mediated by L-selectin and  $\alpha_4$  integrin [168]. Yet, the proportion of NK cells in the myometrium was reduced in superovulated mice, which have increased serum concentrations of both estradiol and progesterone, suggesting an inverse correlation between myometrial NK cells and systemic concentrations of steroidal hormones [169]. Therefore, further investigation is required to clarify the relationship between myometrial NK cells and both local and systemic progesterone concentrations.

### 2.3.3 Myometrial neutrophils and macrophages

The proportions of total neutrophils and macrophages in the pregnant murine myometrium were shown to be unaffected by administration of vaginal progesterone [31], potentially due to the capacity of progesterone to block the migration of these innate immune cells to the myometrial tissues [119, 170, 171]. However, vaginal progesterone treatment caused a decrease in the proportions of IFN $\gamma$ <sup>+</sup> neutrophils in the myometrium, highlighting the specific effects of this hormone on inflammatory immune cell subsets [31]. Progesterone signaling of myometrial innate immune cells may differ with gestational age and between species, as the blockade of the PR by RU486 on 15.5 dpc in mice did not increase the infiltration of neutrophils and macrophages into the myometrium [66, 172]. Yet, the sudden blockade of PR by RU486 during late gestation (19.5 dpc) in rats induced an increase in CCL2 gene and protein expression, which was associated with enhanced macrophage infiltration in the myometrial tissues [173]. This is consistent with the evidence showing that there is a reduction in the density of myometrial macrophages after progesterone treatment during late gestation in mice [174]. The cellular composition of the myometrial microenvironment may also drive the effects of progesterone signaling, as this hormone inhibited LPS-induced cytokine secretion in a co-culture of human pregnant myometrial cells and monocytes, but did not demonstrate this effect on each cell type alone [175]. Indeed, one study suggested that myometrial macrophages are dispensable for regulating

the proliferative events induced by progesterone during early pregnancy [176]; however, this concept requires further investigation. In contrast with the above study, DCs appear to be responsive to progesterone signaling, given that they expressed PRs [153], and the selective deletion of such receptors on these cells resulted in enhanced DC expression of co-stimulatory molecules, decreased proportions of myometrial Tregs and CD8<sup>+</sup>CD122<sup>+</sup> cells, and reduced fetal weight [144]. Moreover, dydrogesterone-induced Gal-1 promoted the generation of tolerogenic myometrial DCs that could rescue stress-driven fetal loss in mice [177]. Progesterone can therefore exert immunomodulatory effects on DCs that indirectly promote tolerogenic processes in the myometrium during pregnancy.

#### 2.3.4 Myometrial mast cells

Several studies have also reported interactions between progesterone and myometrial mast cells. A pioneer study using rat myometrium demonstrated that the number of mast cells is decreased upon treatment with estrogen, but was unchanged upon treatment with progesterone. Yet, myometrial mast cells significantly increased after treatment with both estrogen and progesterone together, showing a synergistic effect of these hormones [178] that was also demonstrated by the increased expression of iNOS by uterine mast cells [117]. In contrast with this early report, later studies indicated that the number of mast cells in the myometrium of virgin ovariectomized mice was increased after treatment with progesterone [179, 180], as was the maturation and degranulation of such cells [180]. Thus, the impact of progesterone signaling on uterine mast cells requires further research.

### 2.4 MATERNAL PERIPHERAL BLOOD

Progesterone exhibits strong regulation of the local microenvironment by controlling the infiltration, differentiation, and activity of innate and adaptive immune cells in the decidual, placental, and myometrial tissues. Yet, a large body of evidence supports a role for this hormone in the modulation of systemic maternal immunity as well. Such mechanisms require a state of balance: peripheral tolerance must be maintained to protect the developing fetus while also allowing for a sufficient immune response to protect the mother from any potential insults during pregnancy [181–188]. Consistently, progesterone seems to promote the necessary homeostatic immune profile without completely compromising maternal immune functions.

#### 2.4.1 Peripheral T cells

Adult peripheral T cells have been shown to express the membrane PR (mPR)- $\alpha$ , - $\beta$ , and - $\gamma$  [189], which expression can be further modulated by external factors such as vitamin D supplementation [190]. On the other hand, one study reported that glucocorticoid receptors, rather than PRs, mediated progesterone-induced T-cell apoptosis of murine splenocytes [191]. Notwithstanding, progesterone has been reported to diminish the overall activation [189, 192, 193], proliferation [193–196], and cytotoxic activity [197, 198] of peripheral T cells; yet, *in vitro* treatment with progesterone causes increased intracellular Ca<sup>2+</sup> levels [189, 195, 199, 200], suggesting that specific signaling pathways are activated by this hormone. Yet, one study indicated that progesterone may block K<sup>+</sup> channels and thus decrease Ca<sup>2+</sup> signaling in peripheral T cells, which may promote progesterone-induced T-

cell suppression [201]. Progesterone treatment can also regulate peripheral T-cell phenotypes by increasing the expression of immune checkpoint molecules such as CTLA-4 and TIM-3 in patients with a history of recurrent spontaneous abortion [202]. Together with the demonstrated modulation of peripheral T-cell cytokine profiles [195, 196, 203], progesterone seems to exert strong immunoregulatory effects on circulating T-cell responses in the mother.

Several *in vitro* reports have documented the progesterone-induced release of a blocking factor (PIBF) that may mediate some of the suppressive effects of this hormone. Like progesterone, PIBF prevents the *in vitro* cytotoxic activity of peripheral T cells [33, 204], and this effect can be blocked by RU486 treatment [33]. PIBF may also carry out some of the immunomodulatory functions of progesterone by preventing the release of pro-inflammatory cytokines such as IL-12 from peripheral lymphocytes [205]. Several animal studies have provided further mechanistic demonstration of PIBF functions in pregnancy [38, 86, 206]. PIBF may be derived from the embryo in response to maternal progesterone signaling, subsequently entering the maternal circulation contained in embryo-derived extracellular vesicles and promoting the production of IL-10 by CD8<sup>+</sup> T cells [206]. Indeed, the blockade of this factor in early pregnancy led to impaired implantation and increase resorption rates as well as dysregulation of gene expression in maternal CD4<sup>+</sup> and CD8<sup>+</sup> T cells [86]. Consistently, the administration of PIBF during late pregnancy in a rat RUPP model increased maternal plasma levels of IL-4 as well as circulating Th2 cells together with reduced IL-6 and IL-17 levels [38]. The above-mentioned studies demonstrate the immunoregulatory effects of progesterone and PIBF on peripheral T-cell activity.

It is worth mentioning that one study specifically investigated the potential interaction between progesterone and peripheral  $\gamma\delta$  T cells during pregnancy [73]. The authors noted that a substantial proportion of  $\gamma\delta$  T cells expressed the PR, and that the incubation of peripheral lymphocytes with an anti- $\gamma\delta$  TCR antibody decreased their production of PIBF [73]. Thus, peripheral  $\gamma\delta$  T cells may participate in progesterone-mediated mechanisms of immunoregulation during pregnancy.

#### 2.4.2 Peripheral Tregs

Similar to conventional T cells, peripheral Tregs from pregnant women have also been reported to express PRs, such as mPR $\alpha$  [207], that likely mediate the increased expression of CTLA-4, TIM-3, and PD-1 observed on Tregs treated with this hormone *in vitro* [202]. Indeed, the culture of murine splenic CD4<sup>+</sup> T cells with progesterone induced their differentiation into Tregs, which was driven in part by nuclear PR (nPR)-A and nPR-B, and can be blocked by RU486 [27]. Several studies using murine models indicated that systemic progesterone treatment results in at least a modest increase in systemic Treg proportions [26, 27, 30], although it has been suggested that physiological changes in systemic progesterone levels during pregnancy are not directly correlated with the expansion of Tregs that takes place in early gestation [208]. Nonetheless, clinical studies have reported that pregnant women with cervical incompetence [28] or preterm labor [29] that received vaginal progesterone displayed higher peripheral Treg counts after treatment [28, 29], providing further evidence of a relationship between progesterone and the development

of immunoregulatory T cell subsets during pregnancy. Of note, one study reported that progesterone expanded murine splenocyte-derived Tregs via the glucocorticoid receptor [209].

### 2.4.3 Peripheral NK cells

Expression of both PR isoforms has been noted on peripheral NK cells from non-pregnant adults [210]. The expression of PR-A and PR-B seems to be limited to mature KIR<sup>+</sup> NK cells, and treatment of such cells with progesterone suppressed IFN $\gamma$  secretion and caused apoptosis *in vitro* that could be reversed by anti-progestins such as ZK98.299 or RU486 [210]. Progesterone seemingly induced the expansion of local endometrial CD56<sup>+</sup> NK cells, but not those derived from the circulation [101]; yet, this hormone may also promote the migration of peripheral NK cells to the myometrium and decidua tissues in early pregnancy by upregulating the expression of integrins in these tissues, thereby enhancing NK-cell adhesion [168]. Yet, *in vivo* and *in vitro* observations suggest that luteinizing hormone (LH) and estradiol may also exert some influence on NK-cell adhesion/migration [211]. Consistent with the elevated expression of integrins at the maternal-fetal interface, peripheral NK cells derived from pregnant women show higher migratory capacity compared to non-pregnant or male-derived cells, and progesterone upregulated decidual stromal cell chemokine expression that facilitated NK cell migration [111]. After cell-cell contact with decidual stromal cells, peripheral NK cells acquired a chemokine receptor profile that is described on decidual NK cells, providing further evidence that peripheral NK cells are recruited to the decidua as part of their accumulation in early pregnancy [111].

Progesterone was indicated to prevent NK-cell cytotoxicity promoted by RU486 [34]. This hormone can also modulate the functions of peripheral NK cells by blocking perforin action [35], likely through PIBF-mediated inhibition of degranulation-related processes as observed *in vitro* [33, 36]. Dysregulation of this mechanism may have translational implications, as PIBF<sup>+</sup> lymphocytes were found to be more prevalent in women with healthy pregnancies compared to those at risk of preterm birth [69]. The blockade of PIBF in early pregnancy resulted in reduced numbers of decidual PIBF<sup>+</sup> NK cells, increased peripheral NK cell activity, and pregnancy loss, emphasizing the importance of this progesterone-induced factor [86]. Indeed, the administration of PIBF to a rat RUPP model resulted in reduction of circulating NK cell numbers as well as reduced plasma IL-17 and IL-6 levels [38].

More recently, the expression of the inhibitory checkpoint marker Tim3 was also described on a subset of peripheral NK cells during pregnancy [212]. The expression of Tim3 was upregulated by physiological progesterone concentrations, and peripheral Tim3<sup>+</sup> NK cells were induced by progesterone treatment in an abortion-prone mouse model [212]. Interestingly, such Tim3<sup>+</sup> NK cells may also exert immunosuppressive functions and displayed potential to induce Tregs [212]. Thus, progesterone modulates peripheral NK-cell phenotypes and function to promote systemic immune regulation during pregnancy.

### 2.4.4 Peripheral neutrophils

Neutrophils represent a major component of circulating leukocytes, and thus any potential effects of progesterone on these immune cells could have major implications on maternal

systemic immunity. A clinical study of women with twin pregnancies revealed that vaginal progesterone treatment between 24 – 34 weeks of gestation resulted in increased numbers of peripheral neutrophils [213]. Such neutrophils displayed reduced CD11b and total peripheral leukocytes tended to have lower mRNA expression of pro-inflammatory cytokines together with higher IL-10 [213]; moreover, progesterone was shown to prevent NETosis (i.e. the release of neutrophil extracellular traps or NETs) of peripheral neutrophils [214]. Such findings are consistent with *in vitro* observations that peripheral neutrophils from male donors display an anti-inflammatory/quiescent phenotype after culture with progesterone [146], and such cells induced the differentiation of T cells to a regulatory-like phenotype *in vitro* that may further promote pregnancy-specific immune tolerance [146]. Thus, progesterone exerts immunoregulatory effects on peripheral neutrophils that can indirectly impact other immune cell subsets as well as placental and fetal development.

#### 2.4.5 Peripheral DCs and monocytes

Several investigations have pointed to DCs and monocytes as being receptive to progesterone signaling. Peripheral monocytes derived from non-pregnant adults showed reduced mRNA and/or protein expression of several key molecules such as TLR2, CD14, and COX2 in response to *in vitro* progesterone treatment [215]. Moreover, progesterone inhibited LPS-induced NF- $\kappa$ B signaling by upregulating I $\kappa$ B $\alpha$  expression in peripheral monocytes [215] and reduced the mRNA expression of IL-1 $\beta$  [216]. Such functions may rely on the regulation of monocyte miRNAs, as progesterone suppressed TLR-driven monocyte responses by inhibiting miR-155 and thereby reducing IL-6 and IFN- $\beta$  [217]. Bone marrow-derived DCs also showed increased *in vitro* differentiation in response to progesterone, and expressed higher levels of co-stimulatory and activation markers such as MHC-II, CD40, CD54, and CD86 [218]. Notably, progesterone seems to promote a DC cytokine profile that favors production of IL-10 [218–220] and other homeostatic cytokines [220] together with downregulation of pro-inflammatory mediators such as TNF [218]. Yet, *in vitro* progesterone treatment did not alter mature DC phenotype or capacity for stimulating T-cell proliferation [221], potentially indicating a diminished effect of progesterone on fully matured DCs. Progesterone may have differential effects on distinct DC subsets, as peripheral plasmacytoid DCs were negatively correlated with the increasing progesterone concentrations observed in normal pregnancy [222]. However, this observation has not been supported mechanistically, and may not indicate a causal relationship.

## 2.5 PROGESTERONE RECEPTORS

The progesterone receptor (PR) belongs to the nuclear receptor superfamily of transcription factors, and was the first receptor to be characterized as having multiple true isoforms [15, 223]. The two best-characterized isoforms are termed PR-A and PR-B, which despite their high similarity (PR-A is simply a truncated PR-B) regulated different target genes [223]. Important for reproductive immunology, the anti-inflammatory effects of progesterone signaling are thus at least partially reliant on the relative expression levels of PR-A and PR-B within a specific tissue or cell type [15, 224]. A subsequent investigation reported that the PR-C isoform [225] is upregulated in the laboring myometrium resulting from activation of the NF- $\kappa$ B pathway [226], favoring the withdrawal of progesterone action.

While multiple other isoforms and splice variants have been reported in the literature [223], few follow-up investigations have been carried out and thus their relevance for pregnancy remains unclear. A mitochondrial PR (PR-M) was also described [227], which regulates cellular respiration [228]. In addition, animal studies have led to the discovery of multiple membrane progesterone receptors (mPRs) and progesterone receptor membrane components (PGRMCs), which were subsequently identified in humans [229–231]. Furthermore, it has also been demonstrated that progesterone can bind the nuclear glucocorticoid receptor (nGR), whereby it may exert some of its anti-inflammatory effects [25, 209]. Thus, given the potential signaling pathways by which progesterone can influence immune function, it is unsurprising that there remains a significant gap in knowledge of this area, particularly in regards to pregnancy and maternal-fetal tolerance. There is accumulating evidence that maternal peripheral T cells express mPRs and PGRMCs during pregnancy [25, 196, 207], and studies of other disease contexts have shown that progesterone signaling modulates the TCR as well as transcription factors such as NF- $\kappa$ B, AP-1, and NFAT [25, 196, 201, 232–234]; yet, the expression of PRs and GRs by other immune cells is less firmly established. Nonetheless, herein we have summarized the current data supporting the presence or absence of PR and/or GR by individual immune cell subsets during pregnancy, a topic that requires continued investigation.

### 3. CONCLUSION

Herein, we have summarized the importance of progesterone signaling for regulating cellular immune functions in the maternal periphery as well as in the decidual, placental, and myometrial tissues. Current evidence indicates specific interactions between progesterone and individual immune cell subsets that depend on the localization of these cells in addition to other pregnancy-specific variables such as gestational age. Despite a strong body of evidence for such progesterone-driven mechanisms, additional investigation is required to further unravel the specific immunomodulatory functions of this important hormone throughout pregnancy.

### ACKNOWLEDGEMENTS

We regret our inability to cite all relevant studies due to the length of this brief review.

This research was supported, in part, by the Perinatology Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services (NICHD/NIH/DHHS); and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C. Dr. Romero has contributed to this work as part of his official duties as an employee of the United States Federal Government. This research was also supported by the Wayne State University Perinatal Initiative in Maternal, Perinatal and Child Health. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Abbreviations:

<b>17OHP-C</b>	17-alpha-hydroxyprogesterone caproate
<b>CSF-1</b>	colony stimulating factor-1
<b>DBA</b>	dolichos biflorus agglutinin



<b>DC</b>	dendritic cell
<b>dpc</b>	days post coitum
<b>Gal-1</b>	Galectin-1
<b>GR</b>	glucocorticoid receptor
<b>hCG</b>	human chorionic gonadotropin
<b>HMGB1</b>	nuclear protein high-mobility group box-1
<b>IDO</b>	indoleamine-2,3-dioxygenase
<b>IL</b>	interleukin
<b>IMC</b>	immature myeloid cell
<b>iTreg</b>	induced regulatory T cell
<b>LDL</b>	low-density lipoprotein
<b>LH</b>	luteinizing hormone
<b>LPS</b>	lipopolysaccharide
<b>MCP-1</b>	macrophage chemoattractant protein-1
<b>MPA</b>	medroxyprogesterone acetate
<b>mPR</b>	membrane progesterone receptor
<b>NET</b>	neutrophil extracellular trap
<b>niT cell</b>	neutrophil-induced T cell
<b>NK cell</b>	natural killer cell
<b>nPR</b>	nuclear progesterone receptor
<b>P4</b>	progesterone
<b>PAMP</b>	pathogen-associated molecular pattern
<b>PAPP-A</b>	pregnancy associated plasma protein A
<b>PBMC</b>	peripheral blood mononuclear cell
<b>PIBF</b>	progesterone-induced blocking factor
<b>PGRMC</b>	progesterone receptor membrane component
<b>pMSC</b>	placental mesenchymal stem cell
<b>PR</b>	progesterone receptor
<b>RUPP</b>	reduced uterine perfusion pressure

<b>TCR</b>	T-cell receptor
<b>Th</b>	T helper cell
<b>Treg</b>	regulatory T cell
<b>VIP</b>	vasoactive intestinal peptide

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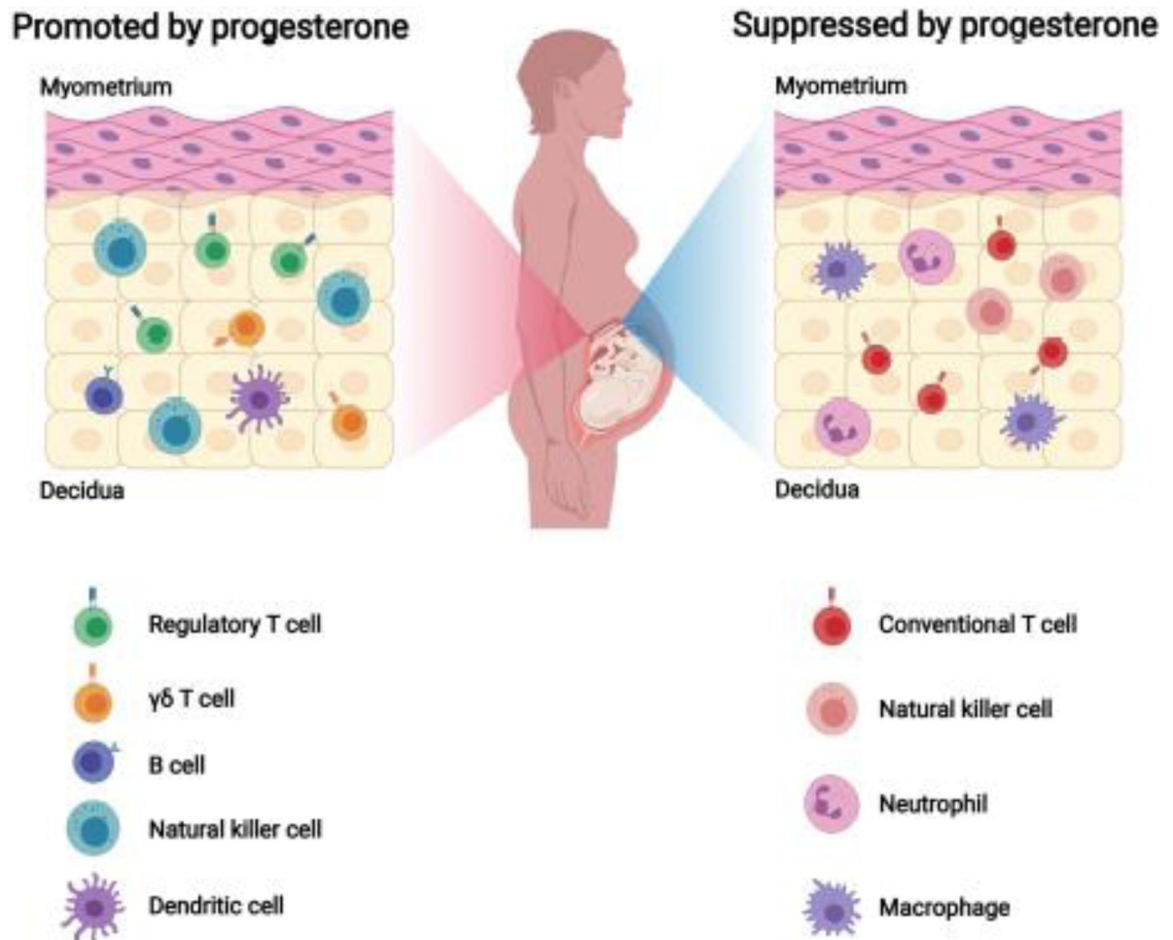
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### HIGHLIGHTS

- Progesterone has specific effects on local and systemic cellular immunity
- Progesterone promotes maternal-fetal tolerance by expanding regulatory T cells
- Progesterone regulates the infiltration and activity of inflammatory immune cells



**Figure 1.** Cellular immune responses altered by progesterone signaling in the decidua. During pregnancy, progesterone favors natural killer (NK)-cell activity that is necessary for successful remodeling and angiogenesis in this tissue. This hormone then fosters a local tolerogenic microenvironment by promoting regulatory T cells,  $\gamma\delta$  T cells, and B cells as well as controlling the maturation of decidual dendritic cells (DCs). On the other hand, progesterone limits the migration and functions of conventional T cells, cytotoxic NK cells, neutrophils, and macrophages to further maintain decidual homeostasis. Created with [BioRender.com](https://www.biorender.com).