

# Neutrophils in Pregnancy, Term and Preterm Labour

Subjects: Immunology

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Neutrophils are surveillance cells, and the first to react and migrate to sites of inflammation and infection following a chemotactic gradient. Neutrophils play a key role in both sterile inflammation and infection, performing a wide variety of effector functions such as degranulation, phagocytosis, ROS production and release of neutrophil extracellular traps (NETs). Healthy term labour requires a sterile pro-inflammatory process, whereas one of the most common causes of spontaneous preterm birth is microbial driven. Peripheral neutrophilia has long been described during pregnancy, and evidence exists demonstrating neutrophils infiltrating the cervix, uterus and foetal membranes during both term and preterm deliveries. Their presence supports a role in tissue remodelling via their effector functions.

Keywords: neutrophils ; pregnancy ; term labour ; premature labour ; inflammation

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## 1. Neutrophils and Their Effector Functions

Neutrophils, also known as granulocytes, are a type of polymorphonuclear innate immune cell, and comprise 50–70% of circulating leukocytes. As part of the innate immune system, they are the first line of defence during infection, however they also play a role in sterile inflammation and tumorigenesis <sup>[1]</sup>. Neutrophils are typically characterized by a distinctive multi-lobulated nucleus and the presence of granules in their cytoplasm. They originate from the myeloid progenitor cells located within the bone marrow and extramedullary sites including the spleen. The process that leads to the production of neutrophils is known as granulopoiesis, with differentiation mainly driven by IL-17, G-CSF, and IL-1 $\beta$ . Neutrophils are also characterised as a heterogeneous cell type, with various subpopulations depending on temporal and anatomical factors <sup>[2]</sup>. They express different markers on their surfaces that change according to the maturation status, allowing them to exhibit high plasticity to respond depending on conditions of health and disease <sup>[3][4][5]</sup>.

There are two major distinct subpopulations: normal density and low-density neutrophils, that can be differentiated and retrieved via density gradient separation. Normal density neutrophils will precipitate with other polymorphonuclear cells, whereas low-density neutrophils (low density granulocytes (LDGs) co-purify with PBMCs (peripheral blood mononuclear cells). Less is understood on the functions of LDGs, however they are known to exhibit both immunosuppressive and pro-inflammatory properties, and are abundant in inflammatory conditions that are associated with relative immunosuppression such as HIV <sup>[6]</sup>, tuberculosis <sup>[7]</sup>, visceral leishmaniasis <sup>[8]</sup> and systemic lupus erythematosus (SLE) <sup>[9]</sup>. Pregnancy and labour, both term and preterm are associated with an increase in circulating normal density and low-density neutrophils <sup>[10][11][12]</sup>, suggesting they play a functional role. Circulating neutrophils migrate into tissue in response to certain triggers.

## 2. Neutrophils during Healthy Pregnancy

Pregnancy involves a complex immunological state that requires a balance between tolerance and immunosuppression to allow growth of the semi-allogeneic foetus, whilst maintaining an effective defence mechanism that can protect against infection <sup>[13]</sup>. There is acknowledgement of a highly active and regulated immune response with shifts between predominance of an anti-inflammatory and pro-inflammatory immune milieu, depending on gestational timepoint and anatomical location <sup>[14][15]</sup>. In the most simplistic description, the first trimester is described as a pro-inflammatory phase, to enable implantation. The second phase resembles an anti-inflammatory phase, where a shift in cytokine bias towards T helper 2 phenotype is thought to contribute to foetal growth. Thirdly, a pro-inflammatory switch is seen in preparation for labour, with influx of immune cells into gestational tissue. Recent signatures from peripheral blood immune cells also support a systemic immune clock for human pregnancy <sup>[16]</sup>.

### 2.1. Peripheral Blood Neutrophils in Healthy Pregnancy

There is an increase in white blood cell counts in pregnancy, especially towards the end; and a further increase at the time of labour <sup>[17]</sup>. This increase in leukocyte counts is mainly driven by an increase in peripheral granulocyte numbers <sup>[18]</sup>, with

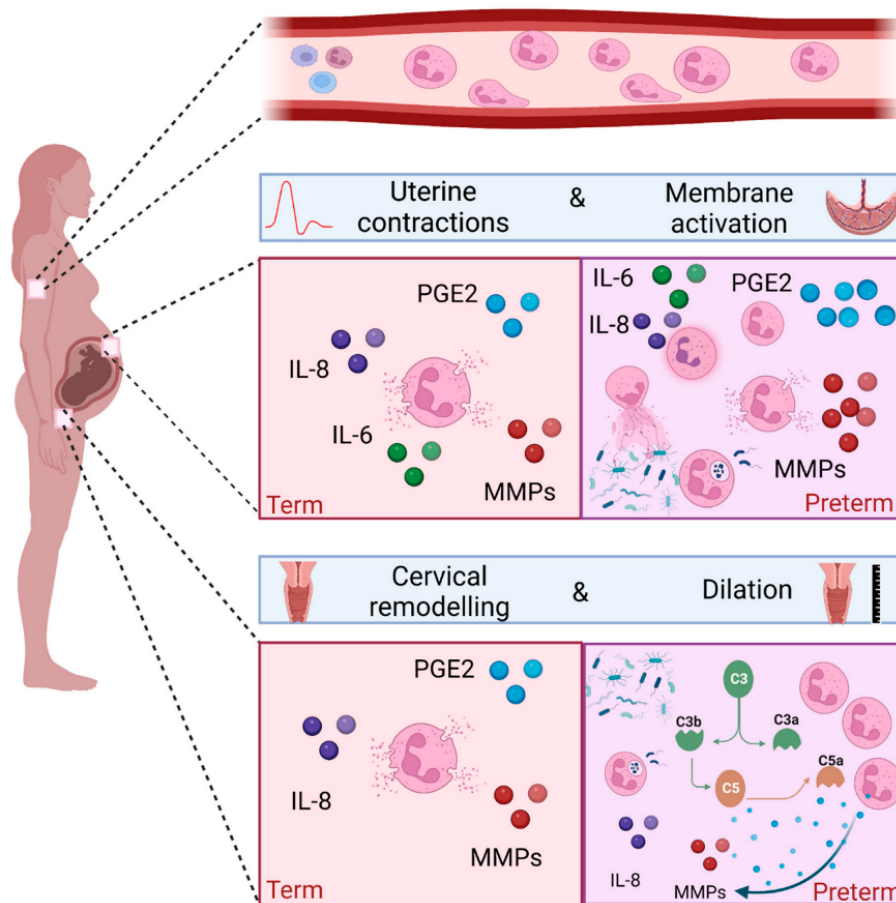
several studies confirming that pregnancy is associated with a mild neutrophilia [19]. The immunophenotype of maternal peripheral neutrophils has been shown to reflect increased activation during pregnancy compared to non-pregnant women. Increased capacity for phagocytosis [20][21], increased ROS production [4][22][23], and arginase metabolism [24] have all been demonstrated in peripheral blood neutrophils of pregnant women compared to non-pregnant controls. Furthermore, response to common pathogens associated with an infectious aetiology of preterm birth is heightened in neutrophils taken from pregnant women compared to non-pregnant controls [25].

## 2.2. Neutrophils at the Maternal–Foetal Interface in Healthy Pregnancy

Neutrophils are detected in the decidua of healthy human pregnancy from as early as the first trimester. It is thought that decidual neutrophils play a key role in tissue remodelling and placental vascularization-like spiral artery remodelling [26]. Detection of neutrophils in amniotic fluid is also seen and increases with advancing gestational age [27]. Their presence is likely to ensure protection against any invading pathogens in a highly sterile environment, to protect the growing foetus. In contrast, there is sparse distribution of neutrophils in myometrium and the cervix prior to the onset of labour [28][29].

## 3. The Role of Neutrophils in Human Term Labour

Successful pregnancy requires uterine quiescence, the foetus to be contained in the amniotic sac, and the cervix to remain long and closed [30][31]. The process of parturition requires the onset of uterine contractions, rupture of the foetal membranes, and dilatation of the cervix. This ultimately leads to delivery of the foetus and the placenta, and subsequent involution of the uterus and tissue repair of the cervix. These events are driven by mechanical, inflammatory, and endocrine processes, whose regulation are complex and interlinked [32][33]. These key processes depend on pro-labour mediators such as COX-2, prostaglandins, matrix metalloproteinases and pro-inflammatory cytokines such as IL-8 [34][35][36], all of which can be produced by neutrophils [37][38][39][40]. Despite the triggers of term labour being poorly understood, it is associated with both systemic and local sterile inflammation, with much evidence to support a functional role for neutrophils. **Figure 1** illustrates the physiological processes and their anatomical locations where neutrophils are considered to play a key role in term birth.



**Figure 1.** The role of neutrophils in term birth and microbial-driven preterm birth. The number of circulating peripheral blood neutrophils increase during healthy pregnancy. Neutrophils can migrate into tissue following a chemotactic gradient. Term labour (left) is associated with infiltration of neutrophils in the lower uterine segment, foetal membranes and cervix. Their detection is accompanied by an increase in cytokines such as IL-8 and MMPs participating in the degradation of the extracellular matrix, therefore contributing to tissue remodelling. Neutrophils are also a source of COX-2 and PGE2,

therefore can contribute to uterine contractility membrane activation and cervical dilation. In cases of infection (right), neutrophils are detected in foetal membranes and amniotic fluid, along with an increase in pro-inflammatory mediators. Ex vivo experiments using neutrophils demonstrate their capacity to perform phagocytosis, NETosis and release of pro-inflammatory mediators. Finally, an adverse vaginal microbial composition is associated with an increase in cervical neutrophils, inflammatory mediators and complement activation. Image created with Biorender.com.

### 3.1. Peripheral Blood Neutrophils and Term Labour

The onset of labour is consistently associated with neutrophilia <sup>[12][41]</sup>. Furthermore, peripheral blood neutrophils taken from women in labour show signs of increased activation compared to women not in established labour <sup>[41]</sup>. In addition, an increase in markers of migration such as CD11a/b and CD62L is seen in vivo, and in vitro studies have confirmed the increased migratory capacity of neutrophils taken from women in labour <sup>[12][41]</sup>.

### 3.2. Neutrophils and the Uterus in Term Labour

Neutrophil infiltration of the myometrium is seen during labour <sup>[29][38]</sup> and unsurprisingly this coincides with an increase in cell adhesion molecule expression to aid transmigration <sup>[12]</sup>. Expression of the chemoattractant *CXCL8* mRNA was found to be higher in myometrium of women at term during labour compared to term not in labour, which may explain in part the increased abundance of neutrophils during labour <sup>[42]</sup>. Consistent with this, a parallel increase in IL-8 concentrations and neutrophil counts are seen in the lower uterine segment in women who are in active labour. This is also associated with increased concentrations of matrix metalloproteinases 8 and 9 <sup>[43]</sup>.

### 3.3. Neutrophils and the Foetal Membranes in Term Labour

Leukocytes, including neutrophils, are known to infiltrate foetal membranes at the time of term labour <sup>[38][39]</sup>, and this is accompanied by an increase in the concentrations of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-8 <sup>[38][39]</sup>, and pro-labour mediators such as COX-2 and PGE2 synthases <sup>[44][45]</sup>.

### 3.4. Neutrophils and Cervical Remodelling in Term Labour

To facilitate vaginal delivery, cervical dilation is one of the processes that occurs during labour. It is a complex process involving softening, effacement and ripening of the cervix. Biochemical changes are required, including a decline in collagen synthesis, an increase in collagenase activity, local immune cell infiltration, and increased concentrations of cytokines and prostaglandins <sup>[46]</sup>. Several studies have demonstrated cervical infiltration of neutrophils from biopsies taken at the time of labour <sup>[29][38][43][47]</sup>. Furthermore, the content of the cervical mucous plug is rich in neutrophils <sup>[48]</sup>. There are conflicting opinions about the importance of cervical neutrophils in causing the cervical changes required for labour, since not all human and murine studies have demonstrated increased neutrophil density in the presence of cervical ripening <sup>[29][49]</sup>.

## 4. The Role of Neutrophils in Preterm Labour

Preterm birth (PTB) is defined as a birth occurring before 37 completed weeks of pregnancy and can be further classified as extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate to late preterm (32–36 weeks). There are 15 million babies born preterm each year, with global rates averaging 10%, although significant variations (5–18%) exist depending on geographical location <sup>[50]</sup>. PTB is the biggest cause of childhood mortality under the age of 5, with morbidity and mortality increasing with decreasing gestational age at delivery <sup>[51]</sup>. Roughly two thirds of births are spontaneous, with women presenting either with preterm prelabour rupture of membranes (PPROM), or with uterine contractions and cervical dilation. The causes of preterm birth are multifactorial, but the most common causal factors are infection and/or inflammation. Extreme and very preterm birth are most likely to have evidence of infection and/or inflammation, and babies born with evidence of foetal inflammatory response have a worse prognosis for any given gestational age.

Since neutrophils play a major role in infection and inflammation, they are also likely to play a key role in infection and inflammation in the context of preterm birth. The most common source of intrauterine infection is ascending pathogenic microbes from the cervical-vaginal interface <sup>[52]</sup>. The presence of intrauterine infection is associated with neutrophil infiltration and pro-inflammatory cytokine production <sup>[53]</sup>. PPROM often presents with or leads to clinical signs of chorioamnionitis, with neutrophil invasion of the chorioamnion being the hallmark of histological chorioamnionitis <sup>[54]</sup>. Evidence also exists to support the role of neutrophils in driving local inflammation at the cervical-vaginal interface in women who deliver preterm <sup>[7][55][56][57]</sup>.

Inflammation in the absence of infection, also referred to as sterile inflammation, has also been widely reported in the context of preterm birth [58][59][60]. DAMPs, also known as alarmins, are endogenous molecules that send a danger message as part of a response to inflammation. Alarmins that have been commonly associated with preterm labour include high mobility group box 1 (HMGB1), IL-1 $\alpha$ , and cell free DNA. HMGB1 [61][62] and IL-1  $\alpha$  [63][64] concentrations are higher in amniotic fluid of women who have evidence of sterile inflammation and deliver preterm. Cell free DNA activates Toll-like receptor 9 (TLR-9), and animal models support the concept of cell free DNA leading to preterm delivery via leukocyte migration and inflammation at the maternal–foetal interface [65][66].

Products of the microbiota can be translocated into the circulation, priming and enhancing neutrophil's function [67]. The use of peripheral blood neutrophil concentrations as a predictor of preterm birth has been explored in women presenting in threatened preterm labour and PPRM, using the neutrophil-to-lymphocyte ratio (NLR) and total neutrophil counts [68][69]. Several studies show an increase in neutrophil counts and the NLR in women who subsequently deliver preterm [12][70]. Peripheral blood neutrophils exhibit a more activated immunophenotype in women who deliver preterm. Gervasi et al. collected peripheral blood from women who had a healthy pregnancy and subsequent term labour and compared the granulocyte phenotype with women who delivered preterm. Using flow cytometry, they identified that granulocytes expressed higher levels of CD11b, CD15 and CD66 in women who delivered preterm [71].

The neutrophils migrate towards a chemotactic gradient, with in vitro evidence demonstrating the chemotactic effect of both unstimulated and LPS stimulated foetal membranes [72]. Conditioned media from LPS stimulated foetal membranes leads to the release of cytokines, chemokines, and reactive oxygen species from neutrophils, as well as neutrophil degranulation and NET release [72].

No significant differences were seen in neutrophil concentrations between women who delivered at term compared to preterm, however the study was likely to be underpowered for this outcome as only six women delivered preterm. RNA-seq was performed on cervical neutrophils from a subset of the cohort (n = 9). Despite small numbers, the expression of genes involved in neutrophil activation and degranulation negatively correlated with the presence of *G. vaginalis* and positively correlated with the presence of *L. iners* in matched vaginal swabs. It has shown that in women at high risk of preterm birth, neutrophils are more likely to be present at the cervical-vaginal interface if the microbial composition is one of high risk of preterm birth (CST III/L. *iners*, or CST IV, diverse), compared to low risk (CST I/L. *crispatus*, CST II/L. *gasseri*, CST VI/L. *jensenii*) [73]. Furthermore, in women that have detectable live cervical neutrophils, there are higher concentrations of pro-inflammatory mediators such as C3b, C1q and C4b in the cervical-vaginal fluid. Taken together, these data suggest a plausible role for cervical neutrophils in microbial driven cervical shortening and PTB [73].

## 5. Conclusions

Neutrophils are polymorphonuclear cells and are the most predominant circulating innate immune cells. They play a key role in both inflammation and infection, with effector functions that lead to direct and indirect cell death and microbial clearance. Activated neutrophils secrete pro-inflammatory mediators such as cytokines, proteases and collagenases, and pro-labour mediators such as COX-2 and PGE2. These mediators are required for the physiological processes of healthy term labour; cervical remodelling, uterine contractility, and foetal membrane rupture. However, in cases of microbial driven preterm birth, the premature recruitment of neutrophils into the cervix, uterus and foetal membranes, combined with increased activation, are likely to play a key role in triggering PPRM and PTB.

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