Harmful and beneficial effects of inflammatory response on reproduction: sterile and pathogen-associated inflammation

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ABSTRACT

In reproduction, inflammatory processes play important roles in the development of many pregnancy complications such as preterm labor/birth, recurrent pregnancy loss, recurrent implantation failure, and preeclampsia. Inflammation can be initiated by both microbial and non-microbial causes. Bacterial infection in the feto-maternal interface and uterus can provoke preterm labor/birth, miscarriage, and chronic endometritis. By contrast, inflammation without infection, or ‘sterile inflammation,’ can also lead to many kinds of complications, such as preterm labor/birth, miscarriage, or preeclampsia. Aberrant inflammation is facilitated by immune cells such as macrophages, dendritic cells, natural killer cells, and invariant natural killer T cells. In addition, cytokines, chemokines, and several kinds of inflammatory mediators are involved. On the other hand, appropriate inflammation is required for a successful offspring during the progression of the entire pregnancy. Herein, we discuss the relation between pregnancy and inflammation with immunological alterations. Understanding the role of inflammation in complications during pregnancy may establish new perspectives of the progress of normal pregnancy as well as treatments during pregnancy complications.

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1. Introduction

Inflammation is part of the host defensive response against microbial infection. It encompasses the phagocytic function of macrophages and neutrophils during bacterial infection; recognition, activation, and cytotoxic activity of T cells and B cells for viral infection; and the critical roles of these immune cells to eliminate microbes. However, the concept of inflammation has been widely recognized as an immune response regardless of pathogen infection. Aberrant, excessive, or suppressive inflammation is observed in many pathologies such as cancer, autoimmune diseases, and metabolic disease. Inflammation in the absence of infection is known as ‘sterile inflammation,’ [1] and immune cells (innate and acquired immune cells) and their interactions are responsible for this inflammation.

In reproduction, many complications during pregnancy are associated with inadequate inflammation. Microbial infection is an important agent for the development of complications during pregnancy; however, sometimes no obvious pathogens are detected in these complications. These findings indicate that the development of complications during pregnancy can be induced by either microbial or non-microbial causes [2,3]. Acute chorioamnionitis (aCAM) is thought to be of particular importance for the development of preterm labor/birth; however, recent studies have reported that many clinical cases of preterm labor/birth occur without obvious infection. Indeed, antibiotics do not always provide benefits in treating preterm labor/birth [4]. Preeclampsia, which is characterized by hypertension, proteinuria, and edema during pregnancy, is associated with an excessive maternal inflammatory response without microbial infection [5]. In addition, chronic endometritis is sometimes diagnosed in patients with infertility, and antibiotics can improve the implantation rate [6–8]. Interestingly, inflammation can conversely have beneficial effects on pregnancy progress. Adequate inflammation is thought to be required during the entire pregnancy progress, such as for ovulation [9], implantation of the embryo to the maternal endometrium [10,11]. In addition, inflammatory mediators have a critical role in human parturition [12].

In this review, we focus on pregnancy complications and characteristic features in terms of inflammation induced by both microbial and non-
microbial causes with a delicate balance of immune function.

1.1. Acute chorioamnionitis

Preterm labor/birth is considered the most common complication during pregnancy, which sometimes determines neonatal morbidity and mortality [13]. The presence of acute chorioamnionitis (aCAM), which is characterized by neutrophil infiltration into the chorioamniotic membranes, is usually considered related to bacterial infection and is often observed in the placenta with preterm birth. Previous studies reported that bacterial infection provokes the production of pro-inflammatory cytokines (e.g., interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-8), inflammatory mediators (e.g., platelet-activating factor, prostaglandins, leukotrienes, reactive oxygen species, and nitric oxide, NO), and chemokines from macrophages and other host cells during pregnancy [14]. IL-1 production of the decidua can facilitate prostaglandin production from the decidua and amnion and is an important factor for triggering labor during intrauterine infection [15]. In addition, IL-1 can induce myometrial contractions leading to preterm labor [16]. TNF-α produced from the decidua in response to bacterial infection also can facilitate prostaglandin production from the decidua, amnion, and myometrium [17]. TNF-α and IL-8 can induce the production of matrix metalloproteinases (MMPs), which facilitate cervical ripening and rupture of the membranes (amniorrhexis) in human pregnancy [18–24]. Thus, aCAM related to bacterial infection is an important finding for the initiation of preterm cervical ripening, labor, and rupture of the membranes.

Preterm birth is classified into the following three categories according to gestational age at delivery: extremely preterm birth (less than 28°0 weeks), moderately preterm birth (28°0–33°6 weeks), and late preterm birth (34°0–36°6 weeks) [13]. The histological findings of aCAM are involved in about 20%–60% of placenta with preterm birth [25]. In particular, the prevalence of aCAM becomes higher with earlier gestational ages [25], and the onset of extremely preterm birth is mainly caused by aCAM [26,27]. Ascending or hematogenous bacterial infection can initiate the onset of preterm birth and rupture of the membranes [3,28,29]. The major microorganisms that result in intrauterine infection are Ureaplasma urealyticum [30,31], Mycoplasma hominis [32], Streptococcus agalactiae, Escherichia coli, Fusobacterium, and Gardnerella vaginalis [31]. Thus, infection with one or more of these microorganisms are related to histological aCAM. However, recent studies have revealed that many clinical cases of aCAM in the placenta and excessive cytokines in the amniotic fluid do not always involve apparent microorganism infection [33–35]. Thus, aCAM, which presents as excessive inflammation with neutrophil accumulation, can be induced by microbial or non-microbial causes (see 'Sterile inflammation' section); bacterial infection is not always associated with aCAM [35].

More importantly, excessive progression of infection or inflammation in uterine fluid can provoke neonatal problems such as respiratory distress, necrotizing enterocolitis, neurodevelopmental disorder, and psychiatric disorders [36–39]. Indeed, histological aCAM is diagnosed after, not before, delivery. Therefore, assessment of the excessive cytokine milieu and the level of aCAM during pregnancy is strongly required for determination of the appropriate delivery mode and timing. Recent studies have suggested that the level of IL-8 in the amniotic fluid is a useful marker for the prediction of histological aCAM [40], and the accurate detection of intra-amniotic microbes by amniocentesis and highly sensitive PCR can be helpful to determine appropriate antibiotic therapy for the patient with preterm labor [41]. Collectively, aCAM and excessive intrauterine inflammation induced by microbial or non-microbial causes sometimes increases the incidence of serious disorders in neonates.

1.2. Chronic chorioamnionitis

Chorioamnionitis (CAM) is divided into two categories: aCAM and chronic CAM (cCAM). The former is associated with neutrophil infiltration into the chorioamniotic membranes as mentioned above and is traditionally called simply ‘CAM’ [32,42,43]. The latter is characterized by the infiltration of lymphocytes, plasma cells, and macrophages, and it has been defined only in the last decade [44]. A recent report suggested that aCAM is the most common cause of extremely preterm birth, whereas cCAM is the most common cause of late preterm birth [45]. Another report showed that 39% of cCAM cases were observed in preterm labor/birth [46]. In general, aCAM is mainly caused by infection; however, the etiology of cCAM not only involves infection but also other factors. Previous reports indicated the presence of intrauterine viral infections such as adenovirus, cytomegalovirus, parvovirus, and enterovirus [47,48]; nevertheless, specific infectious etiology was not detected in cCAM [49]. In addition, another report suggested that cCAM may be have non-infectious, immunologic causes [50]. Arenas-Hernandez et al. suggested that effector and activated T cells elicit pathological inflammation on the feto-maternal interface without neutrophil
infiltration, and this inflammation causes preterm birth [51].

Recently, the relationship between cCAM and preterm labor/birth related to sterile inflammation has been discussed [44–46]. In addition, innate immune cells such as invariant natural killer (iNKT) and dendritic cells (DCs) have been studied in the context of inflammation at the feto-maternal interface. The iNKT cell is a subset of innate lymphocytes that recognizes lipid or glycosphingolipid antigens on nonpolymorphic CD1 molecules [52–54]. The population of iNKT cells in human peripheral blood is very low [55]; however, iNKT cells have multiple effector functions and can rapidly produce large numbers of many types of cytokines [56,57]. Indeed, iNKT cells are present in the decidua in a small but robust proportion in humans and mice [58–61]. DCs are one of the key players for antigen recognition and presentation to T cells, and they are involved in maintaining healthy pregnancy in mice and humans [11,62]. After recognition of antigens by pattern recognition receptors (PRRs) on DCs, DCs regulate T cells via direct interaction between the T-cell receptor (TCR) and the major histocompatibility complex (MHC) or via indirect pathways of cytokine networks. In our recent study, accumulation of iNKT cells and DCs were observed in the decidua of late preterm births without aCAM in humans, and there were functional differences between the DCs obtained from decidua with aCAM and those obtained from decidua without aCAM [63]. Another study described that activated iNKT-like cells are more abundant in the decidua basalis during late preterm birth, where the aCAM abundance is low, than in those of term birth [58].

Collectively, it is possible that these innate cells play important roles in the onset of preterm labor/birth with cCAM or sterile inflammation (see the ‘Sterile inflammation’ section). Accurate assessment of aCAM and cCAM, including the kinetics of innate and effector cells, may be required for understanding their mechanistic involvement in preterm labor/birth.

1.3. Sterile inflammation

1.3.1. Alarmins and PRRs

Inflammation processes are essential for pregnancy: in particular, implantation, protection against exogenous pathogens, and parturition. However, excessive inflammation can trigger many kinds of complications related to pregnancy such as infertility [64], recurrent pregnancy loss [65,66], premature delivery [33,34], and preeclampsia [5]. Recently, ‘sterile inflammation’, or inflammation without apparent pathogenic infection, has been implicated in many kinds of diseases such as cancer [67], diabetic kidney disease [68], cardiovascular disease [69,70], pulmonary disorders [71], and environmental microparticles [1,72,73]. Sterile inflammation is induced by endogenous molecules such as high mobility group box 1 (HMGB1), IL-1α, IL-33, heat shock protein (HSP), and S100 protein that are released by tissue and cellular damage in the absence of infection. These molecules are collectively called alarmins. PRRs recognize these alarmins by TLRs, NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and receptors for advanced glycation end-products (RAGEs) on antigen presenting cells (APCs), macrophages, and DCs [74,75]. After the immunostimulatory activities of APCs are upregulated by alarmins, these cells can directly and indirectly stimulate other immune cells, T cells, neutrophils, NK cells, and iNKT cells, leading to the production of pro-inflammatory cytokines and chemokines [1]. Sterile inflammation can contribute to the onset of parturition and other obstetric complications: implantation failure, miscarriage, preterm labor/birth, fetal growth restriction, and preeclampsia during pregnancy (reviewed in [2]). Indeed, we often experience many clinical cases of preeclampsia, fetal growth restriction, and preterm labor/birth without apparent pathogen infection. The TLRs NLRs, and CLRs are expressed on not only APCs but also in the decidua, placenta, membranes, and myometrium [74–76]. Therefore, the feto-maternal interface can also be a direct target for the alarmins.

1.3.2. Preterm labor/birth

Recently, several studies have been reported for preterm labor/birth associated with sterile inflammation. Yoneda et al. reported that about 70% of patients with preterm labor contained microbe-negative amniotic fluid [41]. In addition, sterile inflammation in the amniotic fluid is more frequent than microbial-associated inflammation in patients with preterm labor [35]. In this study, patients with high concentrations of HMGB1 in their amniotic fluid delivered earlier than those with low concentrations of HMGB1. HMGB1 ubiquitously exists in the nucleus to maintain nucleosome stability and is released extracellularly in response to tissue damage and cell death. Extracellular HMGB1 binds to multiple receptors including toll-like receptor (TLR)2, TLR4, TLR9, RAGE, and CD24 [77], and leads to the activation of nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinase1/2, p38 mitogen-activated protein kinase, and Src-family kinases [78]. Eventually, excessive inflammation is provoked. Another study revealed that HMGB1 level increased in patients with preterm labor [79]. In our
study for preterm birth without aCAM, we observed that the production of HMGB1 in viable APCs in the patients with preterm labor and/or rupture of membranes were significantly higher than in those without preterm labor and/or rupture of membrane (manuscript submitted). These results indicate that HMGB1 is a trigger or inducer of preterm birth without aCAM. In a murine model, intra-amniotic injection of HMGB1 facilitated preterm labor and birth [80]. Thus, it is possible that HMGB1 prompts the onset of preterm labor/birth to some extent.

Cell-free fetal DNA (cffDNA) from placenta that migrates into the maternal system has also been studied for preterm labor/birth as an alarmin. This cffDNA was observed in maternal plasma and could be a predictive marker and a risk factor for preterm birth [81–83].

IL-1 has critical roles in inflammation and infection and includes IL-1α and IL-1β [84]. The production of IL-1β is strictly controlled via the inflammasome in response to endogenous and exogenous antigens (see the ‘Inflammasome’ section). By contrast, IL-1α is ubiquitously expressed in the cytoplasm, but during necrosis or apoptosis it is released extracellularly, where it functions as an alarmin [85,86]. Several studies have shown an increased level of IL-1α during preterm labor/birth.

Levels of IL-1α in amniotic fluid with sterile intra-amniotic inflammation was significantly higher than in that without sterile intra-amniotic inflammation [87]. Figueroa et al. showed that among patients undergoing amniocentesis who showed negative amniotic fluid culture, a statistical difference arose in IL-1α (and IL-6 and IL-8) concentrations but not IL-1β concentrations between patients who delivered within seven days compared with those that delivered after seven days of amniocentesis [88]. These results indicate that IL-1α in the amniotic fluid may affect the development of inflammation leading to the onset of preterm labor/birth.

As mentioned above, alarmins may have critical roles in excessive inflammation and the onset of preterm birth; however, the mechanisms leading to their release is unclear. In fact, placental tissues including trophoblasts contain numerous alarmins, HMGB1, cffDNA, IL-1α, and uric acid, which can provoke the sterile inflammatory response [2,89–91]. Therefore, hypoxia from placental dysfunction, trauma, and abnormal maternal metabolism may facilitate the alarmins, and can then promote sterile inflammation (reviewed in [2]).

Interestingly, some studies have pointed out that iNKT cells may contribute to the onset of preterm labor/birth in the absence of microbial-associated inflammation. iNKT cells can be activated indirectly or directly by APCs via IL-12 secretion and CD1d-invariant TCR interaction and exist at the fetomaternal interface [92–94]. Louis et al. suggested that the amounts of iNKT-like cells in the decidua obtained from patients with late preterm birth are abundant compared with those undergoing term birth [58]. In addition, rosiglitazone, a peroxisome proliferator-activated receptor γ agonist, prevents murine preterm birth induced by β-galactosylceramide (β-GalCer), which is one of the glycolipid antigens originally identified in marine sponges and known to be specific activator of iNKT cells [58]. In our previous study for patients with preterm birth, we observed that the number of iNKT cells in decidua without aCAM was higher than in those with aCAM [63]. In addition, Rinaldi et al. observed no statistical differences in the number of iNKT cells between preterm birth with labor and preterm birth without labor; however, CD1d expression, which is recognized by iNKT cells, is increased in preterm birth with labor [95]. In our recent study for preterm birth without aCAM, expression of CD1d, TLR4, and RAGE in preterm birth with signs of parturition (labor and/or rupture of the membranes) were higher than those in preterm birth without parturition signs (manuscript submitted). Collectively, alarmins, innate immune cells such as APCs and iNKT cells, and the interaction of these cells may be involved in inducing preterm labor/birth related to sterile inflammation.

1.3.3. Miscarriage and infertility
Sterile inflammation and innate immune cells also have important roles in the onset of miscarriage and infertility. In particular, these complications are thought to be linked to the function of DCs. In humans, DCs consist of plasmacytoid DCs, monocyte-derived DC, and conventional (classical) DC (cDC) subtypes [96–98]. The cDC type can be further divided into two major subsets: cDC1 and cDC2. The cDC1 subset has the capacity to establish Th1 polarization [99], and the cDC2 subset can induce Th2 polarization [100–102]. In mice, cDCs are also divided into cDC1 and cDC2 subsets [100,103]. Similarly to humans, mouse cDC1s can activate Th1 cells, and cDC2 cells can induce Th2 dominance. DCs contribute to successful pregnancy in both mice and humans [11,62]. In mice, depletion of uterine DCs induced implantation failure and embryo resorption [104]. DCs entrapped in the decidua can establish tolerance for the embryo [105]. Our study showed that the depletion of the cDC2 subset during pregnancy induced murine miscarriage without infection [106]. We also examined the murine pregnancy in mice treated with β-GalCer, which is a specific activator of iNKT cells, as an abortion model induced by sterile
inflammation. The administration of α-GalCer provoked murine miscarriage with the accumulation of cDC1 as well as activated iNKT cells [107]. Furthermore, adoptive transfer of DCs co-cultured with α-GalCer into pregnant mice, and the adoptive transfer of iNKT cells after intraperitoneal administration of α-GalCer into iNKT-deficient mice also induced miscarriage [108]. These results indicate the activated innate immune cells DCs and iNKT cells directly lead to miscarriage without microbial-associated inflammation. Interestingly, miscarriage and preterm birth induced by α-GalCer were ameliorated by treatment with rosiglitazone [58] and Tokishakuyakusan, a traditional Japanese medicine [109]. Innate immune cells, DCs, and iNKT cells are therefore associated with not only preterm but also miscarriage in the absence of infection.

Alarmins are also implicated in miscarriage and implantation failure. HMGB1 level decreased on the day of implantation in pregnant rats, and administration of HMGB1 on day 3 post-coitum induced pregnancy loss [110]. In humans, the interaction between HMGB1 and its receptor RAGE facilitated inflammation where monocyte migration occurred via elevated production of cytokines and chemokines such as IL-6, IL-8, and CCL2 in the first trimester [111]. Recent observations revealed a relation between S100 protein and pregnancy loss. Nair et al. reported that the systemic level of S100A8 protein was elevated in patients with early pregnancy loss [112]. This indicates that the S100A8 protein may be useful as a prediction marker for early pregnancy loss. For inflammation processes in early pregnancy, levels of IL-12, IL-18, IFN-γ, intracellular adhesion molecule-1, leukemic inhibitory factor, and migratory inhibitory factor were abundant in endometrial cells and blood samples during the mid-secretory phase in patients with recurrent pregnancy loss compared with those in fertility; therefore, the inflammatory response is associated with recurrent pregnancy loss [113]. Namely, inflammation related to alarmins may be associated with the onset of miscarriage and implantation failure without microbial-associated infection.

Aspirin, low-molecular weight heparin (LMWH), and the combination of these drugs are considered to be beneficial therapies for recurrent pregnancy loss and recurrent implantation failure. It has been reported that these treatments have not both an anticoagulant effect and also an anti-inflammatory effect [114]. In addition, LMWH blocks HMGB1-RAGE interaction and demonstrates the anti-inflammatory effects on the placenta (see 'Preeclampsia' section) [115,116]. Recently, immunomodulatory drugs including steroids [117,118], intravenous immunoglobulins [119], TNF-α antagonist [120], granulocyte colony-stimulating factor (G-CSF) agonist [121], and intravenous intralipids [122] also have been attempted for treatment of recurrent pregnancy loss and recurrent implantation failure (reviewed in [123]). The effects of these treatments are controversial [124].

Elevated levels of alarmins released before pregnancy increase the risk for infertility and recurrent pregnancy loss; the latter can be caused by HMGB1 gene polymorphisms affecting gene expression in chorionic villi [125]. Our recent findings also show that HMGB1 levels are higher in non-immune cells and APCs obtained from endometrial cysts than those obtained from non-endometrial cysts (manuscript in preparation). A recent report suggested IL-33 is found in cystic fluid of ovarian tumors and is linked to the pathogenesis of endometriosis and infertility [126]. These findings indicate that the increased level of alarmin releasing in pre-pregnancy might be the risk of infertility and recurrent pregnancy loss.

### 1.3.4. Preeclampsia

Preeclampsia is characterized by hypertension, proteinuria, and edema during pregnancy and sometimes determines maternal and fetal mortality. Preeclampsia is associated with an excessive maternal inflammatory response [5]. Although the pathogenesis of preeclampsia had been unknown for a long time, the two-stage model for the onset of preeclampsia has recently been proposed [127,128]. In the first trimester, extravillous trophoblast invasion to the maternal tissue is impaired, resulting in the restriction of placental vessel remodeling and insufficient placentaion (first stage). In the insufficient placenta, oxidative stress, suppression of autophagy, and aberrant placental perfusion are induced. Subsequently, excessive inflammatory responses including endothelial disorders, apoptosis of trophoblasts, upregulation of soluble endoglin, soluble fms-like tyrosine kinase-1, and pro-inflammatory cytokines (e.g., IL-1β, IL-6, IL-12, and TNF-α) as well as downregulation of anti-inflammatory cytokines (e.g., IL-10) and placental growth factors occur (second stage) [129–133]. Eventually, these abnormalities cause maternal hypertension and sometimes interfere the intrauterine fetal growth restriction associated with placental hypoplasia and dysfunction [134,135]. These inflammatory responses occur without apparent microbial infection, and preeclampsia is considered a disease associated with sterile inflammation. The inflammatory milieu in the feto-maternal interface initiates the release of micro particles form trophoblasts and placental tissues into the maternal systemic circulation. Indeed, many kinds of alarmins, uric acid, HMGB1, cFFDNA, S100
protein, HSP, and adenosine triphosphate exist in the placenta [89]. Pradavet al. reported that serum HMGB1 levels of patients with preeclampsia were significantly higher than those of non-pregnant women and healthy pregnant women [136]. RAGEs, TLR2, and TLR4 are the major recognition receptors for HMGB1. HMGB1-RAGE signaling has been implicated in the pathogenesis of preeclampsia [137], and the expression of TLR4 is increased in trophoblasts of patients with preeclampsia [138]. Interestingly, a recent study has suggested that LMWH, which has been used for the treatment of patients with recurrent pregnancy loss, blocks the HMGB1-RAGE interaction, and LMWH may exert anti-inflammatory effects on the placenta under preeclampsia [116]. Indeed, heparin can modulate the conformation of HMGB1 and reduce the affinity of HMGB1 toward RAGE [115]. Thus, alarmins may be significantly involved in the development of preeclampsia, and investigating the function of alarmins may provide new therapeutic approaches for the prevention of preeclampsia.

1.3.5. Endometriosis

Endometriosis affects more than 10% of women of reproductive age and causes dysmenorrhea, dyspareunia, and infertility [139]. Endometrial tissues grow ectopically outside the uterine endometrium, leading to the adhesion of ectopic endometrial tissues to the other organs, the peritoneum, ovaries, and the myometrium. The clinical features of endometriosis are characterized by intraperitoneal adhesion, endometriotic cysts, and uterine adenomyosis. Endometriosis is also associated with inflammation of the intrauterine tissue, peritoneum, and ovaries. A recent review highlighted that non-specific bacterial infection and subsequent sterile inflammation and oxidative stress are essential for the development of endometriosis [140]. Chronic inflammation related to danger signals, HSP, S100 protein, fibropectin, oxidized low density lipoprotein, neutrophil elastase, and hyaluronan promotes the development of endometriosis via TLRs and NF-κB signaling [141]. Together, these data indicate that the pathogenesis of endometriosis consists of excessive inflammation. By contrast, other studies suggest that insufficient removal of retrograde menstrual tissue in the pelvic cavity is responsible for the development of endometriosis [142]. Elevation of regulatory T cells and the decrease of Th17 cells were observed in patients with endometriosis [143]. This indicates that the anti-inflammatory milieu enables ectopic endometrial lesions to survive in the pelvic cavity. IL-33, a known alarmin and a number of the IL-1 family that induces cytokines of the Th2 subtype, was expressed on endometriosis lesions [126,144]. Ono et al. showed that IL-33 polarizes peritoneal macrophages to the M2 immunosuppressive phenotype with the elevation of IL-1β mRNA levels; furthermore, IL-1β induces IL-33 in endometriotic stromal cells [126]. In general, macrophages consist of two plastic subsets, M1 and M2 [145,146]. The M1 phenotype can produce pro-inflammatory cytokines and promote Th1 responses [147,148]. By contrast, the M2 phenotype promotes the Th2 response and has immunosuppressive effects responsible for tissue remodeling, resolution of chronic inflammation, and tumor progression [148,149]. Therefore, IL-33 polarization of macrophages to the M2 phenotype in endometriosis lesions would preclude the removal of menstrual tissue or debris. Moreover, the cycle of IL-1β and IL-33 production may further exacerbate the symptoms of endometriosis.

The pathogenesis of endometriosis is also linked to NK cell function. The cell number and the cytotoxic activity of NK cells were diminished in patients with endometriosis [150–153]. A recent study reported that the expression of NKp46, which is an activation marker, on NK cells in the peritoneal fluid of severe endometriosis was significantly lower than that of controls [154]. These results indicate that NK cells promote defective clearance of retrograde menstrual tissue.

Collectively, these data show that excessive inflammation occurs in endometriosis and that appropriate inflammation by macrophages and NK cells to eliminate menstrual tissue may be required for the prevention of endometriosis.

1.4. Chronic endometritis

The concept of chronic endometritis has been established for decades, and it was initially thought to have few significant clinical symptoms [155]. However, recent studies have revealed that chronic endometritis promotes implantation failure and pregnancy loss [8,156–158]. The pathological feature of chronic endometritis is the infiltration of CD138 (Syndecan-1)-positive plasma cells into the endometrium [156,159–161]. Hysteroscopic observation showed stromal edema and thickening, micro polyps, and focal or diffuse hyperemia in patients with chronic endometritis [6,156,162]. Aberrant inflammatory responses are expected in the uterine lumen; indeed, pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α increased in menstrual effluents of women with chronic endometritis [163]. Pathogenesis of chronic endometritis is thought to be caused by infection with bacteria such as *Escherichia coli*, *Streptococcus* spp., *Staphylococcus* spp., *Enterococcus faecalis*, *Corynebacterium*, *Mycoplasma*, and *Ureaplasma* [156,162]. Chronic
endometritis is a frequent finding in patients with recurrent pregnancy loss and repeated, unexplained implantation failure [6,8]. Importantly, antibiotics for patients with chronic endometritis can improve the pregnancy rate and live birth rate in these patients [6–8]. This clinical indication confirms that chronic endometritis is caused by microbial infection. However, cases have arisen for which antibiotics did not improve chronic endometritis [6]. Therefore, chronic endometritis is caused not only by microbial infections but also by other factors, intrauterine leiomyomas, endometrial biopsy, and endometriosis [161,164]. Further investigation into the etiology and more appropriate treatments for chronic endometritis are required.

1.5. Inflammasomes

Inflammasomes are composed of a protein complex including inflammasome sensor molecules such as NLRs, the adaptor protein, apoptosis-associated speck-like protein containing a caspase recruitment domain, and the caspase-1 precursor [165]. In particular, NOD-, LRP-, and pyrin domain-containing protein 3 (NLRP3) among the NLRs has been widely investigated as a sensor of endogenous and exogenous danger signals [166]. In response to stimulation of these danger signals in the cytoplasm, the NLRP3 inflammasome is assembled to induce cleavage of pro-caspase-1 into its activate form. Subsequently, active caspase-1 converts pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18 as well as converting gasdermin D (GSDMD) to the N-terminal fragment, which forms GSDMD pores in the plasma membrane [167]. These pro-inflammatory cytokines are secreted extracellularly through GSDMD pores, thus inducing the inflammatory cell death pathway of pyroptosis and provoking inflammation in organs and tissues. Therefore, the NLRP3 inflammasome is considered to be the intracellular innate sensor of alarmins and strictly modulates the production of IL-1β and IL-18. The NLRP3 inflammasome has been implicated in many inflammatory diseases, metabolic disorders, cancer, atherosclerosis, ischemic brain injury, and type 2 diabetes [1,168–170]. In reproduction, several studies of inflammasomes have been performed for many pregnancy complications. Mulla et al. reported that inflammasomes in trophoblast cells are stimulated by uric acid, an alarmin that increases in patients with preeclampsia [171]. Uric acid also facilitates placental inflammation and fetal growth restriction [172]. Kohli et al. showed that the injection of maternal extracellular vesicles released from the placenta induces a preeclampsia-like phenotype in pregnant mice via inflammasome activation in trophoblasts [173]. In women with spontaneous term labor, a higher concentration of NLRP3 and NOD1 as well as an increase in the active form of caspase-1 and caspase-4 were observed with higher amounts of IL-1β but not IL-18 [174]. In addition, increased levels of NLRP3 were observed in human myometrial cells with spontaneous labor [175]. In patients with recurrent pregnancy loss, endometrial NLRP3, caspase-1, and IL-1β expression were upregulated by lipopolysaccharide (LPS) invading maternal circulation via leakage of the gut [176]. Exogenous and endogenous particles also stimulate NLRP3 activity [177]. Nanoparticles, silica, and titanium dioxide, can induce fetal growth restriction and placental dysfunction [178]. Therefore, investigating inflammasomes during reproduction may enable establishment of new prediction tools and new therapeutic targets for complications during pregnancy.

1.6. Beneficial effects of inflammation

1.6.1. Ovulation

The hypothesis that ovulation is considered to be an inflammatory response was presented by Espey [9] and is now widely accepted (reviewed in [179]). Ovulation is initiated by the luteinizing hormone (LH) surge. The invasion of vessels into the granulosa cell region with the disruption of granulosa basal lamina allows the infiltration of theca cells and leukocytes into this region. After dilatation and permeability of the vessels occur, the cumulus oocyte complex is detached from the surrounding granulosa cells and enlarged (cumulus expansion). The cumulus-enclosed oocyte is released after the follicle deteriorates and ruptures; afterwards, the ruptured tissue is repaired.

Thus, ovulation is a complex interaction of the oocyte, granulosa cells, theca cells, endothelial cells, and resident and infiltrated immune cells with the secretion of inflammatory mediators, prostaglandins, reproductive hormones, matrix metalloproteinases, cytokines, and chemokines. In fact, the preovulatory follicle contains inflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) [180–185]. The LH surge produces chemokines that can attract various immune cells, such as neutrophils, monocytes, macrophages, NK cells, B cells, and T cells [186–191]. Neutrophils produce cytotoxic peptides and proteases, which can degrade the follicular wall [192,193]. Neutrophils are recruited by bone morphogenetic protein 6, which also suppresses the function of protease inhibitors [194]. Macrophages are crucial for follicular growth and rupture, and
they secrete cytokines and chemokines that facilitate the migration of other immune cells [195–197]. NK cells and their chemokine receptors are involved in ovulation and angiogenesis [191,198]. Ovarian DCs are essential for cumulus expansion and ovulation and for restricting ovulatory-associated inflammation [199].

Luteinized unruptured follicle (LUF) is frequent among patients with infertility [200–202] and is defined as the absence of follicular rupture that then results in ovulatory dysfunction. LUF formation could be related to the dysregulation of ovulation-associated inflammation in the ovary. Systemic depletion of neutrophils results in the decrease of the ovulation rate in an animal model [203]. In humans, G-CSF concentration increases in peripheral blood in the late follicular phase of the normal ovulatory cycle [204], and LUF can be improved by administration of G-CSF in the clomiphene citrate stimulation [205,206]. These results suggest that insufficient inflammatory response by granulocytes may cause the pathogenesis of LUF.

Polycystic ovary syndrome (PCOS) is a major cause of infertility and is characterized by endocrine disorder, polycystic ovarian morphology, and ovulatory dysfunction [207]. PCOS is also characterized by systemic low-grade inflammation [208,209]. Some studies show that PCOS patients had an elevated C-reactive protein [210] and inflammatory cytokines [211,212]. HMGB1 increases in adolescents with PCOS, and levels of HMGB1 can be decreased by the administration of myo-inositol and alpha-lipoic acid, both considered to be anti-inflammatory [213]. Ovulatory dysfunction related to PCOS may result from an excessive inflammatory response. The inflammation involved in the ovulation process is considered sterile, but infection by pathogens can reduce follicular growth. Granulosa cells express LPS receptors TLR4, CD14, and MD-2, and exposure of granulosa cells to LPS causes disturbance of estradiol production and follicular growth failure in an animal model [214,215].

**1.6.2. Early pregnancy**

Excessive inflammation in reproduction is associated with the onset of preterm labor/birth, miscarriage, preeclampsia, fetal growth restriction, and neonatal disorders. However, appropriate inflammation is necessary for successful pregnancy outcomes. In humans, pro-inflammatory responses including the secretion of IL-6, IL-8, and TNF-α are required for the acquisition of uterine receptivity [10,216,217]. Moreover, elevation of IL-12, IL-1β, TNF-α, IL-6, and NO promote embryo attachment to the decidua [218]. Endometrial biopsy with mechanical injury induces the production of macrophage inflammatory protein 3 beta, TNF-α, CXCL1, osteopontin, and IL-15 with the abundance of macrophages and DCs [219]. Implantation rates, *in vitro* fertilization, and clinical pregnancy rates in patients with unexpected infertility were improved by inducing DC and macrophage accumulation *via* pro-inflammatory cytokine upregulation [219–223]. Indeed, DCs are recruited to the uterus prior to implantation and modulate the cytokine profile at the feto-maternal interface [62,104,224,225], and the adequate inflammation induced by DCs is required for ensuring successful implantation and preventing miscarriage in the first trimester [11]. In our recent study, we observed a low level of DC1s (CD141<sup>+</sup> DCs), which establish Th1 polarization, at the region of the uterine septum in patients with septate uterus [226]. In general, the septate uterus is considered a major risk factor of recurrent pregnancy loss [227]. Hence, we concluded that the low CD141<sup>+</sup> DC accumulation in uterine sepatate may establish a hostile immune environment in early pregnancy.

Macrophages with flexible plasticity also play an important role in early pregnancy [218]. The M2 phenotype has important roles for the establishment of folliculogenesis [228]. During the implantation period, macrophages are skewed to the M1 type, which produces pro-inflammatory cytokines [10]. After implantation, macrophages switch to the M1/M2 mixed type and the M2 type to suppress maternal rejection of the fetus as the pregnancy progresses [218,229]. At the end of pregnancy, M1 macrophages secreting pro-inflammatory cytokines are again required for parturition [218,230]. Moreover, IFN-γ, a representative pro-inflammatory cytokine that is mainly produced by uterine NK cells at the feto-maternal interface, has crucial roles in uterine arterial remodeling during early pregnancy (reviewed in [231]). Thus, temporally appropriate inflammation is necessary; however, excessive or insufficient inflammation may induce complications, particularly during early pregnancy.

**1.6.3. Parturition**

The mechanism of labor onset is controversial at the end of pregnancy; however, inflammation processes are involved in parturition [12]. Prior to term labor, pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α were upregulated in human fetal membranes, decidua, cervix, and myometrium with the accumulation of leukocytes (mainly neutrophils and macrophages) [232]. Bacterial infections can certainly induce labor as shown during preterm labor with aCAM (see the ‘aCAM’ section); nevertheless, at term labor/birth with normal pregnancy progress, pathogenic microbes are often irrelevant, and the baby is born without infectious signs. These clinical
findings imply the existence of sterile inflammation during term delivery. The cfDNA, an alarmin, is increased with pregnancy progress [233], and it is considered that a high level of cfDNA is associated with preterm birth [83]. In addition, the NLRP3 inflammasome is associated with spontaneous term labor [174] as described above (see the 'Inflammasome' section). HMGB1 and its receptors TLR2, TLR4, and RAGE are expressed in the human cervix, and HMGB1 may contribute to cervical ripening [234]. Macrophages also have crucial roles in parturition, as they accumulate to the decidua prior to labor in humans and rats [230,232]. Another study showed that macrophages are recruited into the human cervix and contribute to cervical ripening for vaginal delivery [235]. Thus, it is expected that various inflammatory and immune responses occur at the end of pregnancy for successful parturition.

Sterile inflammation may facilitate the parturition; although, the initial trigger of this inflammation is unclear. In the onset of parturition, there are changes in progesterone levels, sensitivity of progesterone receptors, and expression of oxytocin receptors [236,237]. We recently showed in a pregnant murine model that progesterone suppressed the immunostimulatory activity of APCs and recognition of alarmins on PRRs (manuscript under preparation). Thus, we suppose that progesterone may regulate APCs as they act to induce inflammation in the feto-maternal interface. In a study of dental stress, mechanical stresses were shown to induce inflammation and upregulation of IL-8 secretion via IL-1β [238]. We suspect that mechanical stresses during pregnancy, such as uterine construction and stretching of the uterine wall, may trigger the release of alarmins and induce inflammation in the feto-maternal interface. We are currently planning experiments to induce inflammation with mechanical stresses to uterine tissues.

1.7. Reception and rejection roles of sterile inflammation

As mentioned above, sterile inflammation is critical for a successful pregnancy, but pregnancy complications can be caused by excessive or insufficient inflammation. In the same way, sterile inflammation can have both reception and rejection roles for the semi-allogeneic fetus. Increased production of IFN-γ, an important Th1 type cytokine, is associated with infertility and the antiphospholipid syndrome (APS) [239–241]. IFN-γ production, upregulated by excessive inflammation, can cause fetal rejection. However, it has been reported that IFN-γ contributes to uterine vascular modification [231,242], and the proportion of IFN-γ and TNF-α positive cells decreased in the endometrium of patients with recurrent pregnancy loss [243]. These findings indicate that IFN-γ secretion can also have a positive role in maintaining a successful pregnancy. Human chorionic gonadotropin (hCG) is a placental
glycoprotein hormone that increases significantly in early pregnancy. It induces IL-8 secretion from monocytes [244] and contributes to the differentiation of the endometrium and the implantation via the modulation of immune cell activity [245–248]. By contrast, overexpression of hCG provokes an excessive inflammatory state and pregnancy failures. In clinical cases, elevation of hCG production is observed in patients with ovarian hyperstimulation syndrome (OHSS). It has been reported that the pro-inflammatory cytokines in plasma and ascitic fluid can lead to reproductive failure and other adverse pathologies in the patients with OHSS [249]. In addition, excessive hCG stimulation can cause multiple defects in the differentiation of the fetal gonad [250,251]. HMGB1 has dual roles in sterile inflammation. It can act as a trigger of excessive inflammation and is associated with infertility [77,110]. However, HMGB1 is also known to induce immunological tolerance that leads to tumor progression [252,253] and vascular remodeling [254]. Thus, sterile inflammation can be associated with both immunogenic and tolerogenic milieu.

Collectively, reception and rejection of semi-allogeneic fetus in the maternal system may depend on the delicate balance of sterile inflammation, and controlled inflammatory responses may be required for the progression of a successful pregnancy.

2. Conclusions

Inflammation is needed throughout a normal pregnancy. A controlled inflammatory response is required for successful ovulation, implantation and placental formation, retention of the semi-allogeneic fetus, protection against external pathogens for the fetus, and, finally, for parturition. However, these reproductive events can also be associated with harmful inflammation and microbial infection, which can provoke various reproductive disorders, such as endometriosis, implantation failure, recurrent pregnancy loss, preterm labor/birth, and preeclampsia. The inflammatory milieu in each disease is complex and involves the function of various immune cells; consequently, it is difficult to determine strictly whether each disorder is induced by microbial or non-microbial causes (Figure 1). Further investigation of these diseases in terms of inflammation may lead to new etiological perspectives of pregnancy complications. Inflammation during reproductive disorders involve complex dynamics of immune responses related to the kinetics of immune cells, the secretion of cytokines and chemokines, and the activation of inflammasomes. A deeper understanding of inflammation during reproduction may allow us to establish new therapeutic approaches for these complications and the proper control of pregnancy progression.

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No potential conflict of interest was reported by the author(s).

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