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Review article

The role of innate immunity in spontaneous preterm labor: A systematic review

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ABSTRACT

Background: Immunoinflammatory response by innate immunity components is a field with increasing interest in understanding the mechanisms behind preterm labor (PTL).
Objectives: Systematic review of the role of innate immunity in spontaneous PTL.
Study design: PubMed, Scopus, ClinicalTrials.gov and Web of Science were searched using pregnancy AND innate OR toll-like OR natural-killer OR dendritic AND delivery OR premature OR rupture of membranes.
Main outcome measures: All article titles and abstracts were evaluated by two individuals, based in strict predefined inclusion criteria. For relevant studies, title, abstract, and full text were assessed to identify PTL and innate immunity studies, excluding multiple pregnancies, cervical insufficiency and indicated PTL.
Results: From **894** articles evaluated, **101** full texts articles were assessed independently. For this systematic review 44 studies were finally included.

Toll-like receptors 2 and 4 mediated immune dysfunction and inflammation can result in PTL. Moreover, PTL is linked to high levels of $CD14^+$ monocytes; neutrophils seem important in inflammation-associated PTL and in pathological preterm premature rupture of membranes. Besides, decidual natural-killer cells and premature activation of dendritic cells may also participate in the etiology of PTL. Finally, dysregulation of maternal complement might increase the risk of PTL, characterized by high levels of innate lymphoid cells 2 and 3.
Conclusions: Further research is warranted to ascertain the precise role of innate immunity in PTL. Nonetheless, our results indicate that Toll-like receptors, monocytes, natural-killer cells, dendritic cells and complement have significant roles in PTL.

1. Introduction

The maternal innate immune system plays a pivotal role in all phases of human pregnancy; moreover, innate immune cells actively participate in the labor process by producing pro-inflammatory cytokines that lead to uterine contractility (Cappelletti et al., 2016).

It is scientifically accepted that the act of giving birth is the final step of a proinflammatory cascade that is coordinated by an intrauterine environment connected with hormonal signals. Consequently, the inflammatory process plays a fundamental role during the pathogenesis of human labor, both term and preterm (Kalagiri et al., 2016).

Preterm labor (PTL) is defined as labor that begins before 37 completed weeks of pregnancy, accounting for almost 12% of all live births (Dunn et al., 2017). Unfortunately, very likely, it is the immune response of the host that presumably leads to an inflammatory reaction and PTL (Kalagiri et al., 2016).

Inflammation is how the human body responds physiologically to injury and external agents. Parturition and the inflammatory response are inseparable, although the magnitude of the inflammatory response in PTL is believed to be higher than during term labor. Moreover, recent reports implicate pathological inflammation in the majority of PTL (Riley and Nelson, 2010; Kalagiri et al., 2016).

The first line of defence during bacterial or other pathogenic infections is the activation of the innate immune system, which is equipped with several levels of surveillance against infectious agents. Besides, accumulating scientific evidence suggests that innate immune cells mediate the process of labor by releasing pro-inflammatory factors (Cappelletti et al., 2016). As so, the issue of how innate immunity components influence the inflammatory response that prompts PTL is

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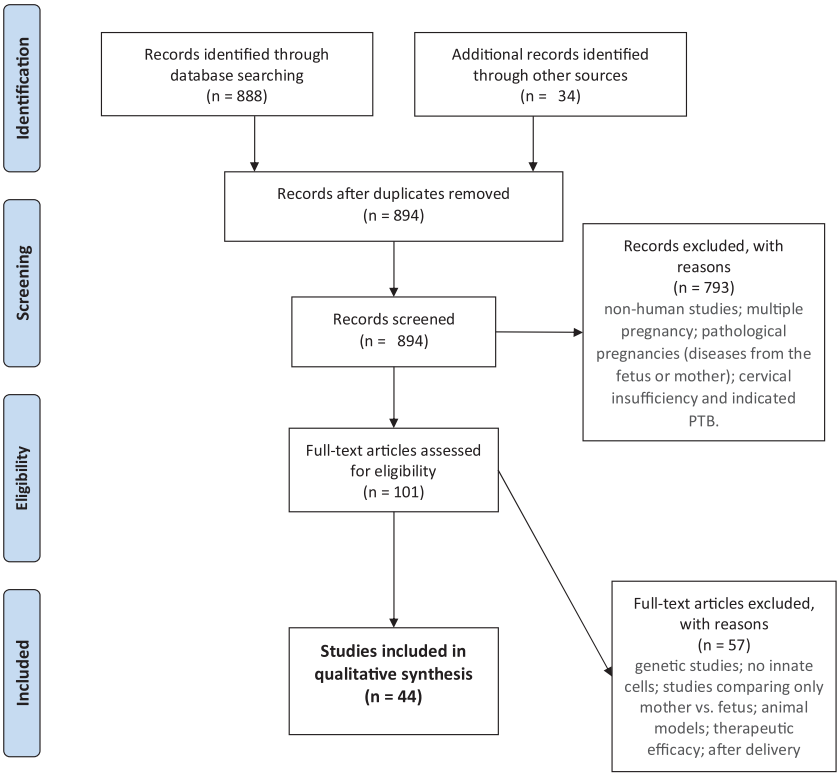

Fig. 1. PRISMA 2009 Flow Diagram.

pertinent.

In this sense, the most described innate immune components are toll-like receptors (TLR); monocytes / macrophages; neutrophils; dendritic cells (DCs); the complement system (C') and innate lymphoid cells (ILCs).

TLR respond to external and to internal ligands and are present in numerous cells initiating a cascade of immune responses. Although localized intrauterine infection is often subclinical, it can cause recruitment and activation of monocytes and result in the production of pro-inflammatory cytokines, with subsequent deleterious effects in pregnancy (Cappelletti et al., 2016).

Macrophages have two phenotypes: M_1, that produce pro-inflammatory cytokines and promote Th_1 responses and M_2 with immunoregulatory functions. In this way, M_1- M_2 phenotypes mirror Th_1-Th_2 polarization of T cells, being able to switch their phenotype in response to microenvironmental signals (Tang et al., 2015; Cappelletti et al., 2016). Neutrophils are central effectors of acute inflammation. Neutrophil's numbers are higher in circulation of women who undergo labor, term or preterm, with an increased ability to migrate, even without the presence of infection (Cappelletti et al., 2016).

DCs are antigen presenting cells that bridge innate and adaptive immunity, with different subtypes capable of eliciting either a Th_1 response (lymphoid DCs) or a Th_2 response (myeloid DCs) (Cappelletti et al., 2016). NOD-like receptors are cytoplasmatic receptors that respond to infectious components (Cappelletti et al., 2016; Kalagiri et al., 2016). Pregnancy is associated with C' activation that promotes an exaggerated inflammatory response (Dunn et al., 2017). ILCs are classified as ILC_1 (like Th_1 cells), ILC_2 (Th_2-like) and ILC_3 (produce Th_{17}-like cytokines, pro-inflammatory), having varied functions (Mjosberg and Spits, 2016).

As so, the immunoinflammatory response, namely by innate immunity components, is a field with increasing interest in the understanding of the mechanisms behind PTL. Accordingly, our objective was to evaluate the role of innate immunity in spontaneous PTL by conducting a systematic review of studies published on this issue.

2. Materials and methods

2.1. Type of study and selection of manuscripts

A systematic review of innate immunity and PTL studies was performed by conducting a thorough search in several databases: PubMed, Scopus and Web of Science. The last search was conducted on June 1st, 2018. This systematic review only includes studies on humans but does not involve patients by itself.

Preterm labor is defined as labor occurring before 37 weeks of pregnancy. The protocol keywords used to perform the search were chosen to obtain spontaneous PTL and innate immunity studies, intentionally excluding indicated PTL (for maternal or fetal conditions) and cervical insufficiency (defined as the inability of the uterine cervix to retain a pregnancy in the second trimester in the absence of clinical contractions, labor, or both). The keywords used were pregnancy AND (innate OR toll-like OR natural-killer OR dendritic) AND (delivery OR premature OR rupture of membranes).

The following options were used to define the type of entry in each database: "Title/abstract/keywords" in PubMed; "Title/abstract/keywords" in Scopus; and "Topic" in Web of Science. The filters and restrictions used were language (English, Portuguese, French), type of study (journal articles or abstracts, excluding letters and conferences) and human studies. Reviews and editorials were evaluated just for eventual missing references. An example of a full strategy search for PubMed is depicted in Appendix S1.

This systematic review was registered in PROSPERO, with the number CRD4-2018089859.

2.2. Study selection

All article titles and abstracts retrieved from the query in the databases were independently evaluated by two individuals, based in strict inclusion criteria (PTL as topic), excluding all other nonrelevant articles (nonmedical and nonhuman articles). For all studies considered

relevant, title, abstract, and full text were assessed to identify PTL and innate immunity studies, excluding multiple pregnancies, cervical insufficiency and indicated PTL. To search for any missing article at this stage, all included citations were cross-referenced, as well as references from review articles and editorials. In all these steps, consensus meetings were held to resolve disagreements, and a record of reasons for exclusion was kept (Fig. 1).

2.3. Data extraction

For each study retrieved, the final full report was assessed for a list of predefined items such as: type of study, population involved, type of innate component studied, and actions in PTL. In accordance, the results of each investigation were reported as variations of each of the studied innate cellular component in women with PTL. Finally, suitable conclusions were recorded and future applications in clinical practice were recognized.

Results are presented in accordance to the PRISMA statement recommendations.

Due to the nature of this type of studies no data combining was performed as there is no statistical methodology to aggregate results of these types of studies.

2.3.1. Description of the Studies

The initial search returned **894** articles. From that list, after the exclusion of duplicates, 793 articles were further excluded for the following reasons: non-human studies; multiple pregnancy; pathological pregnancies (diseases from the fetus or mother); cervical insufficiency and indicated PTL.

The remaining **101** articles were assessed independently as full texts, to identify only studies concerning PTL and toll-like receptors, natural-killer cells, dendritic cells, neutrophils, and complement. Of these, 57 full-text articles were excluded due to: genetic studies; no innate cells; studies comparing only mother *vs.* postnatal fetal evaluation; animal models; therapeutic efficacy; after delivery.

Finally, 44 studies were included in this systematic review for qualitative analysis (Gervasi et al., 2001; Lorenz et al., 2002a, b; Xu et al., 2002; Miyazaki et al., 2003; Kim et al., 2004; Kumazaki et al., 2004; Esplin et al., 2005; Steel et al., 2005; Zariffard et al., 2005; Costello et al., 2007; Krediet et al., 2007; Lynch et al., 2008; Rey et al., 2008; Patni et al., 2009; Soto et al., 2009; Timmons et al., 2009; Youssef et al., 2009; Koga and Mor, 2010; Li et al., 2010; Pawelczyk et al., 2010a, b; Vaisbuch et al., 2010; Abrahams, 2011; Cardenas et al., 2011a, b; Lynch et al., 2011; Hamilton et al., 2012; Kacerovsky et al., 2012; Kim et al., 2012b; Kim et al., 2012a; Lappas et al., 2012; Andrys et al., 2013; Lappas, 2013; Gomez-Lopez et al., 2014; Hoang et al., 2014; Romero et al., 2014; Alamrani et al., 2015; Giugliano et al., 2015; Lynch et al., 2016; St Louis et al., 2016; Walsh et al., 2017; Prearo Moço et al., 2018; Xu et al., 2018).

3. Results

44 articles were considered, some of them studying more than one population, regarding: TLR and PTL; multiple innate immune cells; complement system; monocytes/macrophages; NOD-like receptors; soluble TLR; neutrophils; and innate lymphoid cells.

The main characteristics of the articles included in the systematic review are depicted in Table 1.

3.1. Main findings

Concerning TLR, our results indicate that TLR signalling might be the trigger through which PTL is initiated and even maintained. Specifically, activation of TLR 2 and 4 may result in PTL, since studies showed an increased expression of both receptors in the decidua, amnion, and myometrium during PTL (Lorenz et al., 2002a; Miyazaki et al., 2003; Kim et al., 2004; Kumazaki et al., 2004; Zariffard et al., 2005; Krediet et al., 2007; Rey et al., 2008; Patni et al., 2009; Youssef et al., 2009; Pawelczyk et al., 2010a; Cardenas et al., 2011a; Kacerovsky et al., 2012; Kim et al., 2012a; Andrys et al., 2013; Hoang et al., 2014; Romero et al., 2014; Alamrani et al., 2015; Walsh et al., 2017, Prearo Moço et al. 2018). Moreover, TLR-4 is directly implicated in the pathophysiology of PTL in humans, with its expression peaking at labor (Prearo Moço et al., 2018).

Nevertheless, not only infection induced innate immune responses lead to PTL. In fact, this can be inferred as recent research found that sterile intra amniotic inflammation was more common in women with PTL and intact membranes, than in those with microbial-associated intra-amniotic infection (Andrys et al., 2013). Degradation of extracellular matrix proteins (such as fibronectin and proteoglycans) activates TLR-4 offering a suggestion of how sterile inflammation can lead to parturition (Pawelczyk et al., 2010b; Andrys et al., 2013; Walsh et al., 2017). Furthermore, our research revealed that sTLR-4 is high in infection driven PTL (Kacerovsky et al., 2012) and sTLR-2 can even be used as a predictor of infection (Andrys et al., 2013).

Regarding monocytes and macrophages, high levels of $CD14^+$ monocytes may also be the trigger for maternal proinflammatory response secondary to infectious stimuli, which prompts PTL (Gervasi et al., 2001; Timmons et al., 2009; Li et al., 2010; Pawelczyk et al., 2010b; Hamilton et al., 2012; Kim et al., 2012b). Moreover, PTL is preceded by the selective accumulation of decidual macrophages and some chemokines are elevated in those women, in the presence of infection (Hamilton et al., 2012; Giugliano et al., 2015).

Regarding neutrophils, all available data suggest that they not only are increased in inflammation-associated PTL, but also that they contribute to preterm premature rupture of membranes during PTL (Xu et al., 2002; Esplin et al., 2005; Steel et al., 2005; Hamilton et al., 2012; Gomez-Lopez et al., 2014; Giugliano et al., 2015; St Louis et al., 2016). Moreover, TLR-4 expression on the surface of maternal neutrophils is associated with spontaneous PTL (Prearo Moço et al., 2018).

Besides, NK cells are increased in PTL and through phenotype shifting may participate in the etiology of PTL (Gomez-Lopez et al., 2014; St Louis et al., 2016).

As for DCs, authors defend that the premature activation might elicit inflammatory responses that culminate in PTL (Gomez-Lopez et al., 2014).

About NOD receptors, NOD1 activation induces PTL, which is associated with altered cytokine expression at the maternal-fetal interface (Costello et al., 2007; Abrahams, 2011; Cardenas et al., 2011b; Lappas, 2013).

Furthermore, complement dysregulation increases the risk of PTL; specifically, C5a and C3a may have a causal role in PTL. As so, authors defend that complement activation in early gestation might be predictor of spontaneous PTL (Lynch et al., 2008; Soto et al., 2009; Vaisbuch et al., 2010; Lynch et al., 2011; Lappas et al., 2012; Lynch et al., 2016; Xu et al., 2018).

Finally, PTL can be characterized by high levels of ILC_2 and ILC_3 (Xu et al., 2018).

3.2. Quality assessment

Risk of bias of individual studies was assessed by evaluating the fulfilling or not of each of five items chosen, as suggested by PROSPERO (Anon, 2019). The items chosen encompassed: the correct/objective explanation of the research question; the completeness of outcome data (participant exclusions, attrition and incomplete outcome data adequately addressed in the published report); the existence of selective outcome reporting (that could affect study results); the potential other sources of bias (problems that could produce a high risk of bias); and publication bias. A summary of our analysis is shown in Fig. 2.

Table 1
Risk of Bias amongst included studies.

Studies included First author, year	Population involved	Innate Immune cells
(Lorenz et al., 2002b; Kim et al., 2004; Kumazaki et al., 2004; Zariffard et al., 2005; Patni et al., 2009; Koga and Mor, 2010; Abrahams, 2011; Cardenas et al., 2011a; Romero et al., 2014; Alamrani et al., 2015; Walsh et al., 2017)	Infection-associated preterm labor (PTL)[a] TLR and PTL	Toll-like receptors (TLR)[b]
(Kacerovsky et al., 2012)	Rupture of membranes	sTLR-4
(Andrys et al., 2013)	Rupture of membranes	sTLR-2
(Prearo Moço et al., 2018)	TLR-2 and TLR-4 in PTL	TLR and Neutrophils
(Pawelczyk et al., 2010a)	TLR-4 expression	TLR and Monocytes
(Kim et al., 2012a)	PTL	TLR-4 and Monocytes
(Lorenz et al., 2002a; Kim et al., 2004; Youssef et al., 2009; Hoang et al., 2014)	Infection-associated PTL	TLR and Macrophages
(Gervasi et al., 2001; Timmons et al., 2009; Li et al., 2010; Pawelczyk et al., 2010b; Hamilton et al., 2012; Kim et al., 2012b; Gomez-Lopez et al., 2014)	PTL	Monocytes / Macrophages
(Xu et al., 2002; Esplin et al., 2005; Steel et al., 2005; Hamilton et al., 2012; Gomez-Lopez et al., 2014; St Louis et al., 2016)	Inflammation and PTL	Multiple
(Miyazaki et al., 2003; Krediet et al., 2007; Rey et al., 2008; Gomez-Lopez et al., 2014; Giugliano et al., 2015)	Inflammation and PTL	Multiple
(Costello et al., 2007; Abrahams, 2011; Cardenas et al., 2011b; Lappas, 2013)	Inflammation and PTL	Nod-like receptors
(Lynch et al., 2008; Soto et al., 2009; Vaisbuch et al., 2010; Lynch et al., 2011; Lappas et al., 2012; Lynch et al., 2016)	Complement (C')[c] in pregnancy	C'
(Xu et al., 2018)	Inflammation and PTL	Innate lymphoid cells (ILCs)[d]

[a] Preterm labor (PTL).
[b] Toll-like receptors (TLR).
[c] Complement (C').
[d] Innate lymphoid cells (ILCs).

4. Discussion

4.1. Specific innate system components

4.1.1. Toll-like receptors (TLR)

TLR-2 and TLR-4 are innate immune receptors that recognize the microorganisms most frequently involved in amniotic cavity infection, that are highly expressed in labor, no matter if it is term or preterm. Indeed, studies have found an **increased expression** of both receptors in the decidua, amnion, and myometrium during term and **PTL** (Kim et al., 2004; Alamrani et al., 2015). Moreover, TLR-4 is directly implicated in the pathophysiology of PTL in humans, with its expression peaking at labor (Alamrani et al., 2015). In fact, intrauterine inflammation leads to higher expression of TLR-4 in amniotic endothelium even without infection (Kacerovsky et al., 2012).

The discovery in animals of a cooperation during combined stimulation of TLR-2 or TLR-4, and TLR-3, has led to the development of a two-hit concept to explain the pathophysiology of PTL. A two-hit trigger and that interaction could tend to blunt maternal responses to mild insults, while providing for rapid and efficient amplification of labor responses in cases of superimposed severe infection (Agrawal and Hirsch, 2012).

But TLR mediated responses have to be tightly regulated in order to avoid the potentially deleterious consequences of uncontrolled TLR

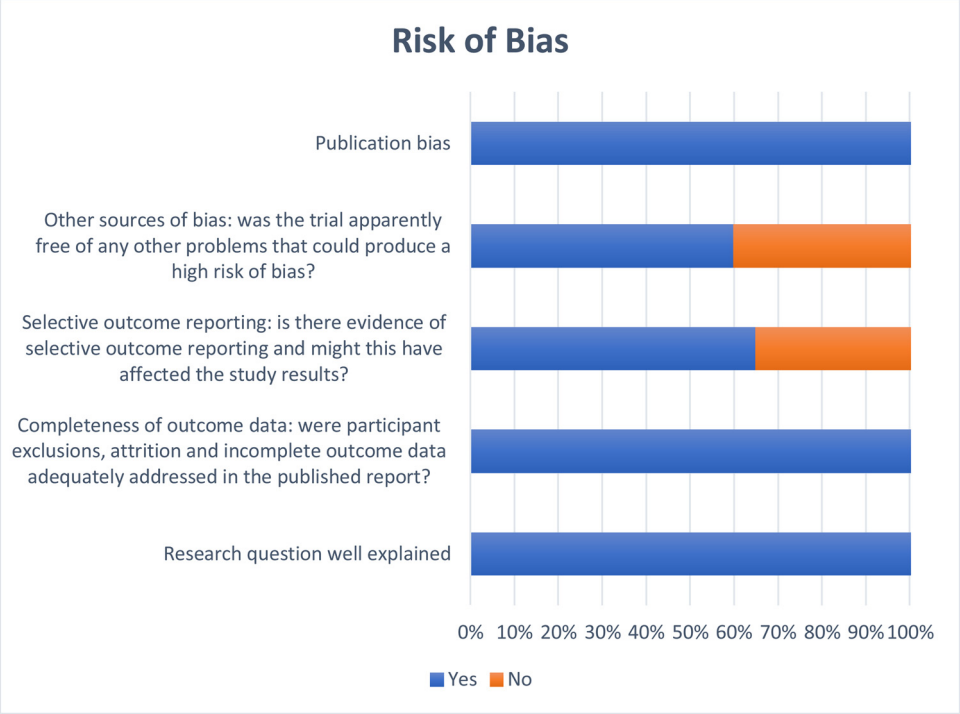

Fig. 2. Risk of Bias amongst included studies.

triggering (Andrys et al., 2013). Accordingly, soluble TLR-2 is such a mechanism, reducing TLR-2 expression and function. It is a natural constituent of human amniotic fluid, which levels increase until 30 weeks of gestational age, with a subsequent reduction from therein (Andrys et al., 2013). Unfortunately, there is no consensus regarding levels of soluble TLR-2 in PTL. Some authors claim that these are higher only in the presence of microbial invasion of the amniotic cavity, with high specificity in the prediction of chorioamnionitis (Andrys et al., 2013), while others defend that soluble TLR-2 are constantly higher than normal in PTL (Dulay et al., 2009). Similarly, research found that **soluble TLR-4 is increased** when there is microbial invasion of the amniotic cavity after preterm premature rupture of membranes (Kacerovsky et al., 2012).

The role of Progesterone in human labor has been questioned for decades as it maintains uterine quiescence, although its exact role in impeding an inflammatory response is unclear. Progesterone immunomodulatory actions may be explained not only by the increase in IL-10 (an anti-inflammatory cytokine), but also by the diminution of TLR-2 and 4 stimulation, in response to intrauterine infection (inhibiting TLR-mediated activation of NF-kB) (Alamrani et al., 2015; Kalagiri et al., 2016).

Also, progesterone beneficial role in PTL may be attained by the reduction of TLR-2 and 4 stimulation (Alamrani et al., 2015). Nevertheless, there is conflicting evidence supporting the role of other TLR in preterm parturition (Cappelletti et al., 2016).

4.1.2. Monocytes/macrophages

Research has revealed that women with PTL have **higher CD16^{+} monocytes with higher expression of CD14** (characterized by a proinflammatory profile) producing higher pro-inflammatory cytokines, particularly during preterm labor. Thus, monocyte activation in PTL may indicate the trigger for maternal proinflammatory response secondary to inflammation, which prompts PTL (Kim et al., 2012a).

Even more, increased expression of TLR-4 in monocytes of PTL women most likely represents a host response that occurs when maternal immune cells are stimulated by inflammation (Kim et al., 2012a). This higher expression could be a useful marker associated with PTL (Pawelczyk et al., 2010a) or even be used to prevent PTL (Kim et al., 2012a).

Decidual macrophages are primary immune cells that contribute to parturition as they secrete pro-inflammatory cytokines and accumulate rapidly in human cervix preceding delivery. Thus, these cells exhibit a pro-inflammatory phenotype reflected in the production of pro-inflammatory mediators such as TNF-α and IL-1 β (Tang et al., 2015). Indeed, PTL is preceded by the selective accumulation of decidual macrophages (Cappelletti et al., 2016) with even an elevation of some chemokines (such as MCP-1 and MIF) in women with infectiondriven PTL (Tang et al., 2015). Additionally, CCL2 concentration is increased in the amniotic fluid of women delivering preterm, both in the presence and in the absence of infection (Gomez-Lopez et al., 2014). More studies are needed to ascertain the exact role of Macrophages in PTL triggering.

4.1.3. Neutrophils

The mechanisms regulating neutrophils recruitment to mucosal sites, myometrium and fetal membranes and their role in the promotion of PTL are not well understood (Cappelletti et al., 2016), but have been thoroughly investigated in human PTL (Prearo Moço et al., 2018). The number of neutrophils is higher in human decidual tissues not only in normal labor but also in PTL, with or without chorioamnionitis, reflecting once more the importance of inflammation in PTL triggering. Also, all available data suggests that decidual neutrophils contribute to the physiological rupture of membranes and pathological preterm premature rupture of membranes during term and PTL, respectively (Gomez-Lopez et al., 2014). Furthermore, higher TLR-2 and 4 expression on the surface of maternal neutrophils is associated with spontaneous PTL, probably by eliciting inflammatory responses (Prearo Moço et al., 2018). This goes also in accordance to the findings of high TLR-4 expression in monocytes in women with PTL (Pawelczyk et al., 2010a).

4.1.4. Natural-killer (NK) cells

NK cells bridge between the innate and adaptive immune systems in term and PTL through the secretion of a variety of cytokines and chemokines (Gomez-Lopez et al., 2014; Cappelletti et al., 2016). Decidual NK cells are mostly noncytotoxic, immature CD56^{bright}/CD16^{neg}; their role seems important to promote adequate placentation. But decidual NK cells can switch their phenotype in case of infection (to a pro-inflammatory profile) and this may explain the possible involvement of these cells in the pathogenesis of PTL (Gomez-Lopez et al., 2014; Cappelletti et al., 2016).

4.1.5. Dendritic Cells (DC)

In human decidua, DCs mainly belong to myeloid DC and they seem to regulate Th_1/Th_2 balance to maintain Th_2 polarization, with an increase in the production of IL10 (Cappelletti et al., 2016). This anti-inflammatory cytokine could therefore be a potential early biomarker for PTL (Gomez-Lopez et al., 2014). However, specific studies demonstrating clearly DCs' function have not been reported.

4.1.6. NOD-like receptors

The NOD-like receptors most studied, NOD_1 and NOD_2, recognize peptides derived from degradation of bacterial peptidoglycan that engenders an inflammatory response characterized by the production of cytokines. As so, NOD-like receptors behave as a second line of defence, should TLR signalling be evaded, reduced or absent (Abrahams, 2011). *In vivo* studies demonstrate that NOD_1 activation induces PTL, which is associated with altered cytokine expression at the maternal-fetal interface (Costello et al., 2007; Abrahams, 2011; Cardenas et al., 2011b; Lappas, 2013).

4.1.7. Complement (C')

Excessive C' activation in early gestation (< 20 weeks) has been suggested as a predictor of later spontaneous preterm birth (Lynch et al., 2008, 2016). Such C' activation may be a response to subclinical inflammation; however, it may be possible that C' behaves merely as a marker of placental tissue necrosis, tissue ischemia or abnormal placentation. In addition, recent evidence supports the hypothesis that the interactions of C_{5a} with its receptor can elicit PTL, *via* NF-kB activation (Lynch et al., 2011, 2016).

But PTL has a multiplicity of causes, so it remains likely that in some obstetric populations, elevations in plasmatic or amniotic fluid C' levels may be a consequence of, rather than a primary contributor to premature delivery (Lynch et al., 2016).

4.1.8. Innate lymphoid cells (ILCs)

Published research showed an increase in ILC_s number in spontaneous PTL. More specifically, ILC_2 and ILC_3 subsets are augmented in the decidua of women delivering preterm (Xu et al., 2018). Additionally, decidual ILC_3 express high levels of IL-13 during the process of PTL (anti-inflammatory cytokine usually produced by ILC_2) (Xu et al., 2018).

4.2. Strengths and limitations

To the best of our knowledge, this study presents the first systematic review ever made evaluating the role of innate immunity in preterm labor. A strength of this review is that we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, thus providing a comprehensive basis that objectively assesses quality indicators and risk of bias in the studies included.

Moreover, we included solely articles that specifically assessed

spontaneous preterm labor and innate immunity, which brings consistency in the inclusion criteria, enables some conclusions, and conveys future investigation.

Our review also presents some limitations that need to be noted. The systematic review could have been improved by refining the query used, searching in other databases, making personal contact with authors, searching in grey literature, and manual searching medical journals. But not a single new article was detected in a new query held in the month of June (the first query had been on February 2018).

Another limitation arises from the quantification of article quality by the fulfilment of items when they quite certainly do not have the same importance in terms of quality, but without an alternative (bias evaluation of review articles is not consensual), this seemed to us a possible methodology. Finally, due to the lack of a statistical method to aggregate these type of results, conclusions can only be labelled in general.

4.3. Interpretation

According to our findings, not only TLR 2 and 4 are important in PTL ensue, but also, in the presence of inflammation, the combination of TLR 2, 3 and 4 elicits too early the mechanism of parturition, leading to PTL.

Some authors defend that soluble TLR-2 are constantly higher than normal in PTL; this would lead to a reduction in TLR-2 function, with dampening of the inflammatory responses known to elicit PTL. This is contradictory to the findings cited before of higher TLR 2 in PTL. As so, more investigation is needed to ascertain the specific role of soluble TLR-2 in PTL.

Nevertheless, data point out that it might be through adjustments on TLR 2 and 4 that the beneficial roles of progesterone in PTL are attained.

Moreover, monocyte CD16+ activation in PTL, characterized by higher TLR 4 expression, may indicate the trigger for maternal pro-inflammatory response secondary to inflammation, which prompts PTL. Also, decidual NK cells phenotype switch to a pro-inflammatory profile contributes to PTL.

Due to the role played by DCs in maternal immune adaptation to pregnancy and fetal health, an incoming premature/inadequate activation of proinflammatory DCs may likely participate in the etiology of PTL (Cappelletti et al., 2016). Likewise, NOD_1 activation seems to induce PTL by engendering also an inflammatory response to infectious components that have gained access to the cell's intracellular space or that have evaded recognition by the TLRs.

Similarly, dysregulation of maternal complement activation at any point across gestation (from implantation until term), might increase the risk of PTL.

Finally, published research showed an increase in ILC_2 and ILC_3 number in spontaneous PTL although these results seem inconsistent due to their antagonist effects. However, decidual ILC_3 paradoxically express high levels of IL-13, probably to down-regulate the normal inflammatory responses exhibited by such cells.

5. Conclusions

This research revealed that the innate immune system has a role in PTL triggering.

Indeed, not only some of its components are characteristically high in PTL (TLR-2,4; sTLR-2,4; NK cells; monocytes and macrophages; ILC 2 and ILC3), but also the premature activation of other innate components might be used as a predictor of PTL (complement, sTLR-2, NK cells).

As so, it seems that there is a redundancy in the innate immune system when it is activated in response to an insult, which may trigger preterm delivery.

This disentangles future investigation in creating antagonists for each of these innate immune components, to discover novel PTL treatments.

Contribution to authorship

ALA and PM were responsible for article evaluation; ALA made data collection, evaluation and manuscript preparation.

All the authors were responsible for data evaluation and manuscript revision.

Details of ethics approval

Non-applicable.

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Declaration of Competing Interest

The authors report NO conflict of interest.

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