Myometrial cytokines and their role in the onset of labour

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Abstract

Human labour is an inflammatory event, physiologically driven by an interaction between hormonal and mechanical factors and pathologically associated with infection, bleeding and excessive uterine stretch. The initiation and communicators of inflammation is still not completely understood; however, a key role for cytokines has been implicated. We summarise the current understanding of the nature and role of cytokines, chemokines and hormones and their involvement in signalling within the myometrium particularly during labour.

Key Words
- inflammatory diseases
- labour
- cytokines
- reproduction

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Introduction

Human labour is an inflammatory event, physiologically driven by an interaction between hormonal and mechanical factors and pathologically associated with infection, bleeding and excessive uterine stretch (Golightly *et al.* 2011). However, the processes involved are not fully understood, especially the triggers/activators of labour. Local pro-inflammatory cytokine and chemokines have been implicated in the pathophysiology of human labour since the 1980s; with more recent data strongly linking increased intrauterine cytokine and chemokine production with both term (TL) and preterm labour (PTL) (Keelan *et al.* 2003).

Various inflammatory mediators have been studied in reproductive tissues obtained at the time of TL and PTL showing the involvement of a range of cytokines and chemokines in the choriodecidua (Hamilton *et al.* 2013), amnion (Gomez-Lopez *et al.* 2010) and placenta (Haugueldemouzon & Guerremillo 2006). This review will be focused on recent work and current understanding of the nature and role of cytokines, chemokines, and hormones and their involvement in signalling within the myometrium particularly during labour.

Myometrial inflammation

Inflammation typically involves white cell infiltration and the production of cytokines that induce changes in cell function through the modulation of gene expression. It is a highly coordinated process designed to protect the organism from infection (Meeusen *et al.* 2001, Martinon *et al.* 2009), but can be induced by other stimuli including chemicals and damaged cells. Generally, the inflammatory response is beneficial to the host, but when it is directed against components of the body as in joints in rheumatoid arthritis for example, or when it is excessive, such as in septic shock, inflammation can be harmful. In the myometrium, with the onset of labour at term, inflammation is thought to play a physiological role transforming the myometrium from a quiescent to a contractile state. In contrast, in PTL, inflammation takes on a pathological role, precipitating early delivery in response to a variety of triggers including infection, overdistension and haemorrhage.

The first reports of myometrial inflammation in association with labour appeared in the later 1980s. Azziz and coworkers reported the presence of inflammation in biopsies taken at the time of emergency Caesarean section

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and suggested that there was an underlying infective cause (Azziz *et al.* 1988). Lopez-Bernal and colleagues first raised the key question of how much of the inflammatory change in the myometrium was a consequence of the labour process (Bernal *et al.* 1993). This question was partially addressed in a series of papers by Norman and coworkers in which the nature of the cellular infiltration, the changes in cytokine levels and the cells producing the cytokines were defined (Bollopragada *et al.* 2009). These papers established that TL is an inflammatory event showing that the myometrium is infiltrated by neutrophils, macrophages and T lymphocytes (Fig. 1) and that these cells are the predominant source of the inflammatory cytokines (Young 2002). Later studies have shown that the myometrial expression of chemokines and endothelial adhesion molecules are increased with the onset of labour, suggesting a potential underlying mechanism for the cellular infiltration of the myometrium (Young 2002). The drivers of the chemokine expression have also been studied and may include mechanical stretch and cytokines (see below). However, it remains unclear whether the inflammatory infiltration of the myometrium is a cause or consequence of labour. Human studies show that levels of IL-8 (Table 1) rise with established labour only (Osmers 1995, Elliott *et al.* 2001, Kemp *et al.* 2002*a*,*b*). In rodent pregnancies, it seems apparent that the inflammatory infiltration precedes the onset of labour (Mackler 1999, Shynlova *et al.* 2012*b*), but various groups have depleted pregnant animals of neutrophils (Timmons 2006) or studied animals with no mast cells (Menzies *et al.* 2011), without delaying labour onset. Others have used chemokine knockouts, which deliver at the same time as their wild-type controls (Menzies *et al.* 2012). A number of animal studies have attempted to address this question using LPS, a bacterial wall polysaccharide (Fang *et al.* 2000). Lye and coworkers found that pre-treatment with a non-specific chemokine antagonist delayed labour onset in association with a reduced inflammatory infiltration (Shynlova *et al.* 2014), suggesting that the inflammatory infiltration is important in inflammation-induced labour onset. Indeed, macrophage depletion prevents LPS-induced PTL in pregnant mice (Gonzalez *et al.* 2011), but neutrophil depletion had no effect (Rinaldi *et al.* 2014). These data suggest that macrophages but not neutrophils are important for this process.

Inflammation in reproductive tissues/compartments

The inflammatory changes may be a consequence of inflammation in other areas.

Maternal circulation

The changes in the innate immune system during pregnancy are characterised by increased numbers of circulating monocytes and granulocytes, resulting in a higher number of total leukocytes (Tang *et al.* 2015). Peripheral monocyte numbers are higher, mainly due to

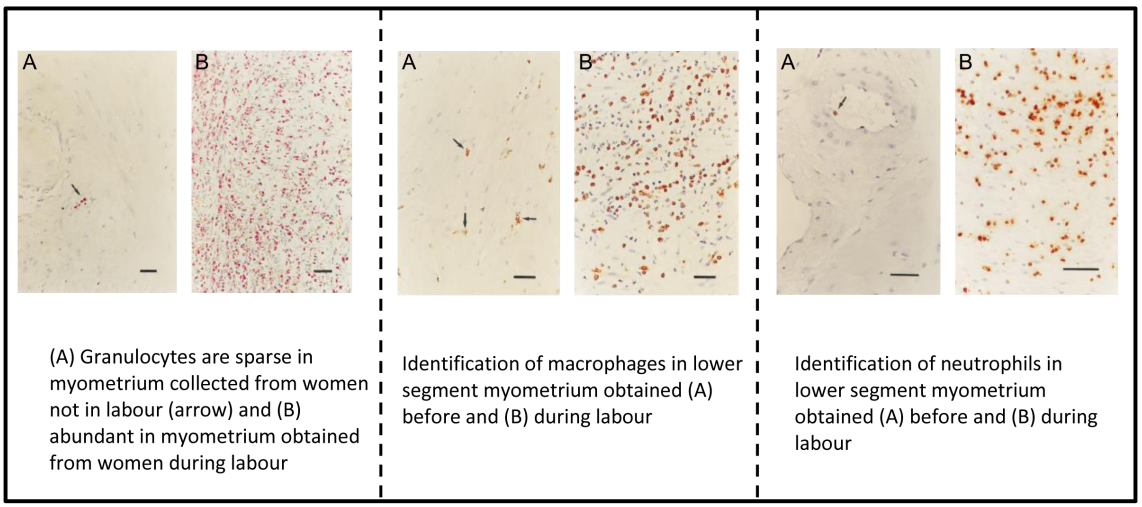

Figure 1
Leukocytes infiltrating the myometrium during parturition. Reproduced from Thomson AJ, Telfer JF, Young A, Campbell S, Stewart CJR, Cameron IT, Greer IA & Norman JE, Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process, *Human Reproduction*, 1999, volume 14, issue 1, pages 229–236, by permission of Oxford University Press.

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Table 1 Summary of nature and role of key soluble mediators in myometrium.

Cytokine/Chemokine	Role in myometrium	Evidences
IL-1β	• Pro-inflammatory IL-1 cytokine superfamily • Source – monocytes, macrophages mainly • Stimulates arachidonic acid release, activate phospholipid metabolism and increase the production of prostaglandins by the myometrium • IL-1β activates a signal transduction system involving NF-κB to increase the expression of *COX-2*, which is increased in the myometrium during labour and stimulates the production of PGE2 by myometrial cells	Peltier (2003), Krishnan *et al.* (2014)
IL-6	• Pro-inflammatory cytokine and anti-inflammatory myokine • Source – monocytes, macrophages, endothelial cells • IL-6 has no effect on prostaglandin production by myometrial cells and is unable to stimulate myometrial contractions • This cytokine may play a role in labour by increasing the expression of oxytocin receptors on myometrial cells to increase their responsiveness to oxytocin • IL-6 can also increase oxytocin secretion by myometrial cells	Peltier (2003)
IL-8	• Chemotactic and pro-inflammatory cytokine • Source – macrophages, endothelial cells • IL-8 is chemotactic to neutrophils • Increase in myometrium in term labour compared to preterm labour; may work by increasing PGE_2 • Progesterone and dexamethasone have been shown *in vitro* to inhibit IL-8	Baggiolini *et al.* (1995), Keelan *et al.* (2003), Terzidou *et al.* (2006)
TNF-α	• Pro-inflammatory cytokine • Source – macrophages, monocytes • Stimulates arachidonic acid release, activate phospholipid metabolism and increase the production of prostaglandins by the myometrium	Peltier (2003), Idriss & Naismith (2000)
CCL2	• Pro-inflammatory soluble chemoattractant cytokine • Source – monocytes, lymphocytes, endothelial cells, fibroblasts • Chemotactic to monocytes, NK cells, $CD4^+$ T cells • Uterine smooth muscle cells can secrete CCL2, which can lead to inflammation by promoting recruitment of monocytes to myometrium • Mechanical stretch of the myometrium increases expression of CCL2	Shynlova *et al.* (2008)

an increase in the intermediate monocyte subset (Melgert *et al.* 2012). These monocytes are pro-inflammatory, producing IL-1β, IL-6 and TNF-α (Tang *et al.* 2015) (Table 1) and are recruited into gestational tissues, especially the decidua, during labour (Tang *et al.* 2015). Peripheral circulating leukocytes have also been noted to display early chemotactic responsiveness during late gestation, which would aid their infiltration into uterine tissues (Gomez-Lopez *et al.* 2013). Recently, Srikhajon and coworkers reported that monocytes are recruited first to the myometrium by various cytokines and chemokines. Following this transmigration, activated monocytes in turn limit further chemotaxis by disrupting locally established CCL2 gradients (Table 1) (Srikhajon *et al.* 2014). This may serve as a negative feedback loop to control the local inflammation. On the other hand, this group also suggested that generic inhibition of chemokines limited inflammation and reduced PTB (Shynlova *et al.* 2014). These seeming contradictions may reflect species differences or be determined by the stimulant. Circulating neutrophil numbers are higher in women in PTL and TL (Yuan *et al.* 2009). These neutrophils are likely to be drawn into the myometrium by chemokines in particular IL-8 which is significantly higher in myometrium at term during labour than in women not in labour (Gomez-Lopez *et al.* 2010) and may contribute to the changes in whole blood gene expression noted in women with threatened PTL (Heng *et al.* 2014).

Amniotic fluid Inflammatory cytokines are known to increase in AF towards term in human pregnancy and may play a role in labour by stimulating local production

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of prostaglandins (PGs) and collagenases (Bowen *et al.* 2002). With the onset of TL, there are increased concentrations of IL-1β and TNF-α in AF (Romero *et al.* 1990, Laham *et al.* 1993). IL-6 has been noted to be raised in AF in women with spontaneous labour (Andrews *et al.* 1995) and particularly raised in PTL associated with intra-amniotic infection; and even considered a predictor for PTL before 34 weeks gestation (Chaemsaithong *et al.* 2015). IL-8 concentrations in AF increase progressively from early pregnancy to term and more markedly with the onset of spontaneous TL (Romero *et al.* 1991, Saito *et al.* 1993, Laham *et al.* 1994). The rise in AF IL-6 precedes that of IL-8, suggesting that IL-6 has a role in the initiation of the inflammatory cascade required for the onset of labour (Kemp *et al.* 2002*a*,*b*). Recent work by Romero and coworkers have shown varying cytokine networks noted in the AF associated with PTL with intact membranes and intra-amniotic inflammation (both microbial and sterile) (Romero *et al.* 2015). Interestingly, the chemokine CCL-20, which targets immature dendritic cells, effector/memory T cells and B lymphocytes increases in AF with advancing gestational age. It is further increased in the absence of infection in spontaneous TL and PTL, which suggests it has a role in the common parturition pathway (Hamill *et al.* 2008).

Amnion/Chorion Inflammation has been seen in amnion and chorion with IL-1β and IL-8 increasing in concentration in the third trimester (Keelan *et al.* 1999, Elliott *et al.* 2001). This is a key observation as it implies that the inflammatory process begins before the onset of labour. The expression of both cytokines was increased after labour with chorion producing more of each cytokine than the amnion (Elliott *et al.* 2001). In addition foetal membranes have exhibited selective chemotaxic activity in human labour, consequently increasing monocytes, T cells and NK cells (Gomez-Lopez *et al.* 2009). IL-6 and TNF-α are also increased (Young 2002), contributing to the chemotaxis of monocytes and other immune cells into the gestational tissues, including into the myometrium and cervical stroma (Elliott *et al.* 2001, Golightly *et al.* 2011).

Choriodecidua (CD) The decidua is a highly immunologically active region of a pregnant uterus. Hamilton and coworkers used a rat model to investigate the pre-labour changes and found a significant increase in the numbers of macrophage infiltration of the decidua in the days before labour, which preceded inflammatory changes in the myometrium (Hamilton *et al.* 2011). This suggests that decidual inflammatory events are important in the initiation of labour (Sindram-Trujillo *et al.* 2004, Castillo-Castrejon *et al.* 2013), supporting the hypothesis first proposed in the 1980s that decidual activation is an early event in the labour cascade (Casey & MacDonald 1988). IL-8 is raised in CD at labour, with almost a 30-fold change in TL compared with term no labour (Hamilton *et al.* 2013), resulting in neutrophil recruitment. These cells can release several inflammatory mediators and MMPs, which could degrade the extracellular matrix of the foetal membranes during both TL and PTL, contributing to ROM during TL and PTL (Gomez-Lopez *et al.* 2010). CD changes are of particular interest in PTL, where it has been shown that CD56+ NK cells and T cells are increased (Hamilton *et al.* 2013) along with an elevated expression of CCL8, which is a chemoattractant for NK and T cells (Proost *et al.* 1996). These inflammatory changes implicate both the innate and adaptive immune system in the pathological process of PTL and interestingly the imbalance among these two immune systems in PTL have been demonstrated via a mouse model (Arenas-Hernandez *et al.* 2016).

Placenta In contrast to the foetal membranes and decidua, the evidence of placental inflammation is poor (Keelan *et al.* 1999). The placenta is a site of peripheral monocytic activation, where monocytes encounter the villous trophoblast (Tang *et al.* 2015). Studies of placental cells and tissue *in vitro* have demonstrated their ability to respond to inflammatory stimuli such as pathogenic bacteria, LPS or IL-1 with increased production of cytokines (IL-1, IL-6, IL-10), chemokines (macrophage chemotactic protein-1 (MCP-1), IL-8) and prostanoids (Denison *et al.* 1998, Goodwin *et al.* 1998, Gniesinger *et al.* 2001). This highlights the capacity of the placenta to play a key role in the inflammatory process associated with PTL triggered by abruption or infection.

Overall, inflammation does play a critical role in the onset and progression of labour, but where this is initiated and then propagated to is still a point of much discussion and research. It seems likely that the decidua being the maternal foetal interface is immunologically crucial, and our data (unpublished) suggests that it is the most inflammatory in PTL. Further work looking at inflammation in all compartments with comparison to peripheral blood is necessary to improve our understanding. The exact triggers for the onset of this inflammatory process is yet another uncertainty; some

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have suggested that the foetus releases surfactant proteins as a signal of maturity (Reinl & England 2015), others that there is a change in maternal tolerance and still others that uterine stretch is responsible.

Physiology

Stretch effect Throughout pregnancy, the uterus is dramatically remodelled to accommodate the growing pregnancy. Despite the progressive increase in size, uterine quiescence is maintained, until the onset of labour, be it at term or preterm; then when the uterus transforms into an actively contractile organ, to efficiently expel the pregnancy. The growing conceptus increases intra-uterine pressure, but for the majority of pregnancy, the uterus is able to adapt and remodel to avoid any increase in wall tension. It is possible that once this adaptive mechanism is lost or overcome, the tension in the wall of the uterus rises, initiating the process, which culminates in the onset of labour. Progesterone has been suggested to play a key role in this adaptive process, particularly in animal models, where the loss of progesterone repression is associated with an increase in stretch-related pro-contraction proteins (Shynlova *et al.* 2012*a*) (connexin-43 and oxytocin receptor (OTR)). *In vitro* stretch models of human myometrial cells (Terzidou *et al.* 2005) and strips (Moraitis *et al.* 2015) showed increased OTR expression and responsiveness, respectively, while *in vivo*, acute uterine stretch increases PG synthesis (Manbe *et al.* 1982). Interestingly, no difference in prolabour gene expression was seen when comparing twin and singleton pregnancies (Lyall 2002). Equally, excessive uterine stretch, seen in polyhydramnios, multiple pregnancy or a singleton pregnancy in a unicornuate uterus are all associated with increased rates of PTL (Rodriguez 1992, Reichman *et al.* 2009, Conde-Agudelo & Romero 2014) (Fig. 2).

In vivo animal models of stretch in pregnancy has been pioneered by Lye and coworkers who uses a unilateral pregnant rat model and compares the effect of mechanical strain imposed by the growing foetus in the gravid horn to the changes observed in empty horn. Lye and coworkers showed that CCL-2 levels increased in the gravid uterine horn and reproduced this effect by *in vitro* stretch of myometrial cells (Shynlova *et al.* 2008). More recently, Adams-Waldorf, using a non-human primate model, demonstrated the effect of stretch on the inflammatory response of the uterus by recreating uterine distension through balloon inflation. There was significant elevation of pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, CCL-2 and TNF-α, which was compared with the inflammatory response observed in human twin PTL (Adams Waldorf *et al.* 2015).

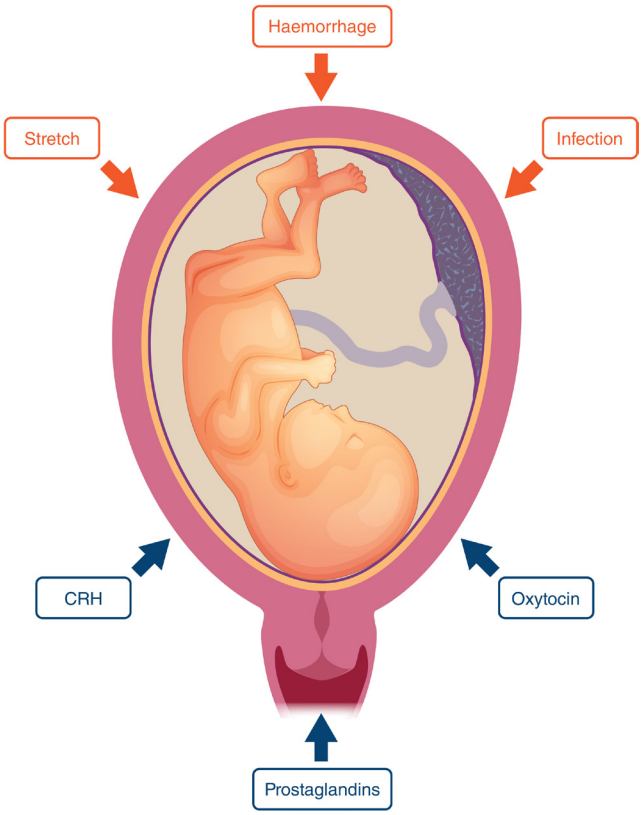

Figure 2
Pathology and hormones that promote myometrial contractility. Adapted, with permission, from Romero R, Dey SK & Fisher SJ, 2014, Preterm labor: one syndrome, many causes, *Science*, volume 345, pages 760–765. Reprinted with permission from AAAS.

Some studies have stretched human myometrial strips and shown an increase in IL-8 levels (El Maradny *et al.* 1996). More recent studies revealed that prolonged stretch of human myometrial strips under high tension resulted in increased myometrial contractility (Tattersall *et al.* 2012). The pathway by which the myometrial contractility is enhanced has not been defined; however, there is evidence the stretch stimulates the expression of a known smooth muscle stimulatory agonist, gastrin-releasing peptide (Tattersall *et al.* 2012). Another theory that has been postulated is that stretch of myometrium under high tension induces constitutive activation of the OTR (Moraitis *et al.* 2015). This was supported by the observation that retosiban, an OTR blocker, reduced the pro-contractile effects of stretch (Moraitis *et al.* 2015).

In vitro studies of human and rat myometrial cells show that mechanical stretch upregulates pro-inflammatory factors (Shynlova *et al.* 2012*b*). Our studies showed that

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stretch upregulated IL-8 and COX-2 in a MAPK-dependent manner (Loudon 2004, Sooranna 2004, Sooranna *et al.* 2005). Later studies confirmed that stretch of myometrial cells increased the expression and release of IL-8, while showing that other chemokines and inflammatory cytokines are also increased in a predominantly NFkB-dependent manner (Hua *et al.* 2012). More recently, Lye and coworkers showed that conditioned media from stretched myometrial cells induced endothelial activation and the expression of adhesion molecules, promoting the extravasation of inflammatory cells (Lee *et al.* 2014).

Lee and coworkers tested the hypothesis that the stretch enhances peripheral leukocyte extravasation into the term myometrium through the release of various soluble mediators, including cytokines and chemokines, by human uterine myocytes. Nine cytokines/chemokines were significantly increased by stretch: IL-6, IL-12p70, IL-8, CXCL1, MIF (macrophage migration inhibitory factor), G-CSF, bFGF (basic fibroblast growth factor), VEGF, and PDGF-bb (platelet-derived growth factor subunit B). The greatest effect of stretch was seen on CXCL1 and IL-8 (Lee *et al.* 2014). In human myometrial cells, the stretch-induced increase in CXCL1 and IL-8 was greatest at 6 h (Hua *et al.* 2012). CXCL1 and IL-8 have been widely reported to be associated with TL, when both are likely to interact with neutrophils expressing CXCR1 and CXCR2, promoting myometrial infiltration of neutrophils in the gestational tissues (Elliott *et al.* 2000, Bollopragada *et al.* 2009).

Chemokines are essential for inflammatory cell migration and also modulate immune cell activation (Griffith *et al.* 2014). The main chemokines implicated in the inflammatory process of labour are IL-8 and CCL-2, which act via CXCR2 and CCR-2, respectively. IL-8 is a potent chemokine for neutrophils; and its mRNA expression is increased in myometrium of women in PTL and TL (Keelan *et al.* 2003). Indeed, a recent myometrial transcriptome study reported that IL-6, CXCL1 and IL-8 exhibited the greatest increase in labouring samples (Mittal *et al.* 2010). A more detailed study revealed that IL-8 levels increased in parallel with cervical dilation (Hebisch *et al.* 2001). In PTL, IL-8 concentrations are markedly elevated in chorioamnionitis (CA) (Yoneda *et al.* 2015). Interestingly, myometrial expression of CXCR2 declined with the onset of TL (Hua *et al.* 2012), perhaps as a result of higher IL-8 levels or the effects of increased levels of OT and PGF_{2a}, which can also repress CXCR2 expression via phospholipase C (Hua *et al.* 2012). Alternatively, IL-1β and TNF-α also reduce CXCR2 expression and may also be responsible for the labour-associated decline (Hua *et al.* 2012).

CCL-2 is a member of the CC chemokine family and is also called MCP-1 (Esplin *et al.* 2005, Griffith *et al.* 2014). It is expressed by decidual cells (Critchley *et al.* 1996), endometrial and myometrial cells (Arici *et al.* 1995, Jones *et al.* 1997) therefore it is ideally positioned to recruit macrophages to cervix, myometrium and foetal membranes with the onset of labour. Indeed, CCL-2 is markedly upregulated in both term and preterm myometrium (Esplin *et al.* 2005). CCL-2 is increased in amniotic fluid (AF) from women in PTL, particularly in the presence of infection (confirmed by histological CA) (Esplin *et al.* 2003).

Stretch clearly has an impact on not only pro-inflammatory mediators such as CCL-2, IL-8 and IL-6, but also on activity of OTRs and smooth muscle agonists such as gastrin-releasing peptides. Much of the *in vivo* model findings have been confirmed in our *in vitro* work; however, further work looking into the interactions among electro-mechanical signalling, hormonal interference and inflammation is necessary to understand when adaptive mechanisms that maintain uterine quiescence falter.

Maternal tolerance Pregnancy has often been compared with a transplanted organ as both foetus and placenta express maternal and paternal antigens hence are like semi-allografts (Erlebacher 2012). Breakdown in immune tolerance has been linked to rejection, which in pregnancy can have variable consequences depending on the gestation: recurrent miscarriages (Kuon *et al.* 2015), PTL (Romero *et al.* 2014*a*) and pre-eclampsia (Dietl 2000). Tolerance is maintained via factors produced at the implantation site, one such promoter of tolerance is IL-10, an anti-inflammatory cytokine (Thaxton & Sharma 2010). IL-10 was demonstrated to be a modulator of uterine NK cell cytotoxicity; in an IL-10 depleted mice model, very low doses of LPS led to uterine NK (uNK) cell activation and foetal demise (Murphy *et al.* 2008). In a non-human primate model, IL-10 has been shown to inhibit IL-1β-induced uterine activity (Sadowsky *et al.* 2003) and it seems to also have an inhibitory effect on LPS induction of matrix metalloproteinase 2 and 9 in foetal membranes (Fortunato *et al.* 2001).

Interferons, known for their anti-viral potential, also have an immunomodulatory role (Racicot *et al.* 2014). Hertelendey and coworkers showed via human myometrial cell line cultures that cell cultures primed with IFN-γ produced significantly less PGs and reduced COX-2 expression (Hertelendy & Zakár 2004). It has been suggested that trophoblasts enable appropriate tolerance by 'educating' macrophages and adapting the cytokine

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profile of the local macrophages. Fest and coworkers showed that monocytes cultured with trophoblasts (Fest *et al.* 2007) increased production of RANTES (which recruits T-regulatory cells) and MIP-1β, which both have immunosuppressive functions (Wang *et al.* 1999, Ramhorst *et al.* 2004). Dendritic cells (DC) promote cell tolerance particularly at the maternal–foetal interface, by priming T-regulatory (T_{reg}) cells (Blois *et al.* 2007). T_{reg} cells, part of the adaptive immune system play a pivotal role in promoting foetal survival by avoiding the recognition of semi-allogenic tissues by the maternal immune system (Somerset *et al.* 2004, Tilburgs *et al.* 2009, La Rocca *et al.* 2014). This was seen in a mice model where depletion of $CD25^+$ T_{reg} cells led to gestation failure (Aluvihare *et al.* 2004) and a certain systemic composition of T_{reg} cells with distinct subsets have been associated with PTL (Steinborn *et al.* 2011).

Maternal tolerance is no doubt vital to support a pregnancy to term, and to avoid pregnancy complications such as foetal loss and pre-eclampsia. PTL without an obvious cause, commonly referred to as idiopathic PTL is presumed by many as an immunological phenomenon with various immune cells considered culprits including high uNK cells or low T_{reg} cells. Many of these conclusions have arisen from *in vivo* models, which although highly informative, cannot take into consideration the movement, interaction and adaptability of immune cells between gestational tissue layers, between the periphery and the uterus and the mother and foetus.

Feto-placental signalling Corticotropin-releasing hormone (CRH) is synthesised in the placenta and the levels of placental CRH increases as the pregnancy advances, peaking at delivery with a rapid decline postnatally (Sasaki *et al.* 1987). CRH can induce the breakdown of mast cells, releasing histamine (Lytinas *et al.* 2003) and has been widely associated with cytokines especially the pro-inflammatory cytokine IL-6 (Venihaki *et al.* 2001). Raised maternal levels of CRH have been associated with PTL (Fig. 3), suggesting a possible causative link (Vitoratos *et al.* 2007). Indeed, CRH can stimulate the myometrium to produce pro-inflammatory cytokines and chemokines, in particular IL-6, IL-1β, TNF-α, IL-8 and CCL2. However, this effect appears to be dependent on cAMP-PKA signalling pathway and possibly NF-κB (You *et al.* 2014). These cytokines can induce the chemotaxis of monocytes to the myometrium and promote inflammation, which is thought to be key for the onset of labour. For example, IL-1β and IL-6 stimulate uterine activation by increasing CX43, PGFR and OTR. In addition, CRH has been reported to have a stimulatory effect on PGs (PGE2, $PGF2_{\alpha}$) (You *et al.* 2014).

IL-6 is a pro-inflammatory cytokine that is also recognised as a myokine. IL-6 and CRH are secreted in a pulsatile manner during active labour, with the increases in IL-6 preceding those of CRH (Papatheodorou *et al.* 2013). This suggests the hypothesis that IL-6 promotes the release of placental CRH and in a direct or indirect manner is associated with uterine contractility (Papatheodorou *et al.* 2013). IL-6 has been identified in cervico-vaginal fluid as a predictive marker of PTL in the subsequent 7 days (Jung *et al.* 2015). Some studies have suggested this to be secondary to sub-clinical CA as a majority of PTL is associated with infection (Jung *et al.* 2015). IL-6 concentrations, along with other cytokines, do not correlate with cervical shortening (Chandiramani *et al.* 2012).

Aside from CRH, surfactant protein-A (SP-A) from the foetal lung can induce parturition. Surfactant is a glycerophospholipid-rich lipoprotein, produced by alveolar type II pneumocytes and is secreted into AF with foetal breathing movements (Mendelson 2009). In murine models, injection of SP-A into the amnion resulted in preterm delivery (Reinl & England 2015), interestingly this was done by shuttling AF macrophages to the myometrium and increasing uterine IL-1β levels (Condon *et al.* 2004). SP-A-deficient mice demonstrated a delay in parturition associated with suppressed myometrial inflammation and increased maternal progesterone (Reinl & England 2015). In human models, SP-A stimulated PG synthesis (Bernal *et al.* 1988) and Johnston and colleagues have proposed that platelet-activating factor, a phospholipid component of foetal lung surfactant that is secreted into AF near term, may play an important role in the activation of myometrial contractility (Toyoshima *et al.* 1995).

CRH and SP-A are known proteins that can increase the production of cytokines and PGs, consequently triggering myometrial activity. In addition, there are likely to be other molecules released from not only the foetus and the placenta, but also from the membranes that increase myometrial inflammation. Further work to identify such molecules and its role and interactions is required.

Progesterone and progesterone receptor The withdrawal of progesterone (P4) has long been

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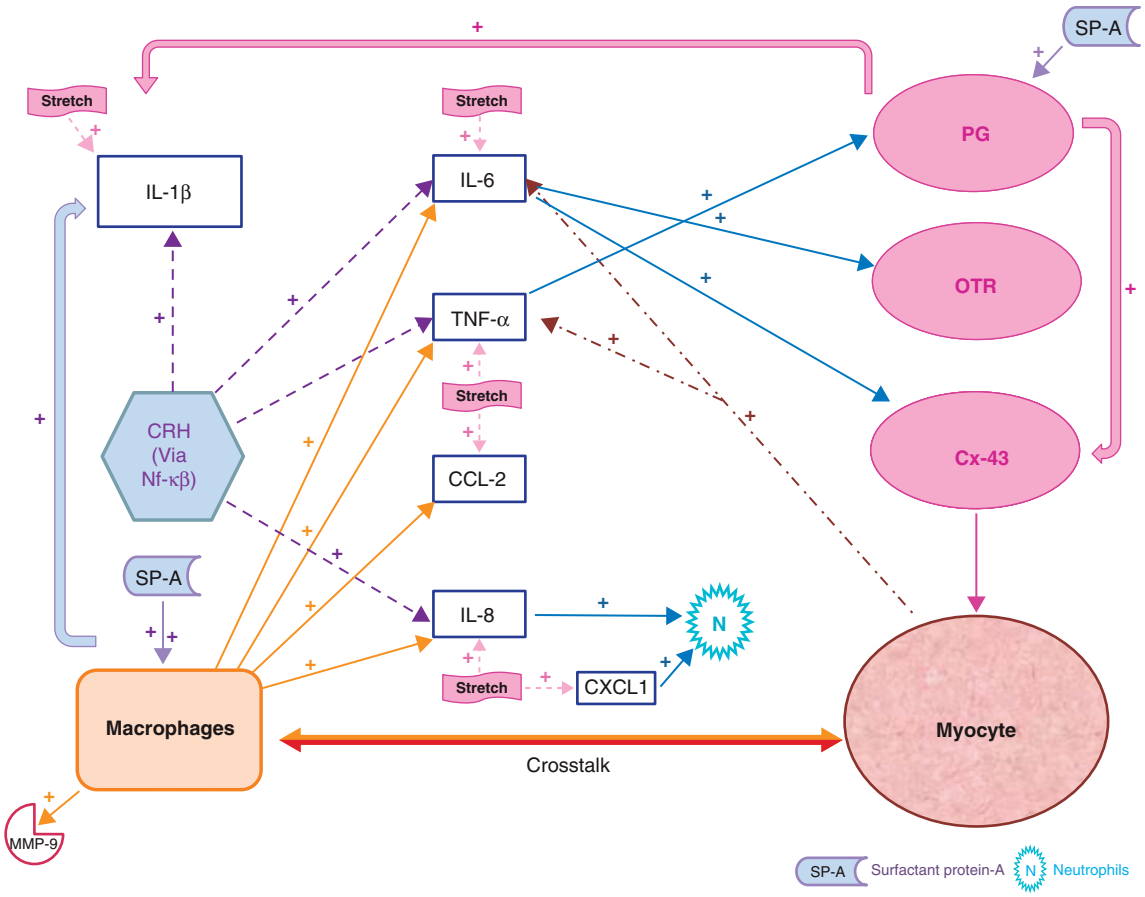

Figure 3
The effect of physiology (including stretch, surfactant protein-A and corticotropin-releasing hormone) on cytokines and myometrial contractility.

hypothesised to be the trigger of labour, with supportive evidence from animal models, in particular sheep and goat where a fall in P4 and a concurrent increase in oestradiol precedes the onset of labour (Ravanos *et al.* 2015). This does not apply to humans, as there is no decline in circulating maternal P4 levels before labour. Interestingly, guinea pigs are similar to humans in that they labour in the presence of high maternal progesterone levels. Such model has recently shown that decreasing P4 receptors leads to a physiological mechanism of functional P4 withdrawal, which is enhanced by endogenous/exogenous PG administration (Welsh *et al.* 2014).

P4 maintains uterine quiescence through suppression of contraction-associated proteins such as connexin 43 (Challis *et al.* 2000). It also exerts an anti-inflammatory action via inhibition of cytokine production and immune cell migration into the uterus and suppresses the transcription of genes that promote contractility. Interestingly, in human labour, a functional impairment in P4 receptor levels have been reported near term, which may reverse P4's suppressive actions, therefore, promoting myometrium's sensitivity to contract (Ravanos *et al.* 2015).

P4 has been suggested to maintain pregnancy primarily by inhibiting inflammation through repression of the archetypical inflammatory transcription factor NFκB (Wissink 1996). This is mediated both via a direct interaction between the P4 receptor, PR-B, and the principle NFκB subunit, p65, and by increasing IκB levels, which binds to p65 maintaining it in an inactive state (Hardy *et al.* 2006). The onset of human labour is suggested to occur after P4 influence is lost by a combination of increased expression of PR-A (Mesiano *et al.* 2002), which inhibits PR-B, a reduction in the level of the PR co-activator, SRC1 (Condon *et al.* 2006) and by increased activity of NFκB, which represses PR activity via a direct interaction (Condon *et al.* 2003). Much of these data are based on over-expression of PR and p65, and have often

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been carried out in cell lines of various types. Our data suggest that P4 represses IL-1β-driven COX-2 expression via the glucocorticoid receptor and not PR, despite the presence of sufficient PR to modulate the expression of the P4-responsive genes (Lei *et al.* 2012). Further, we show that P4 reduced IL-1β-driven COX-2 expression via the inhibition of AP-1 action rather than NFκB (Lei *et al.* 2015). Most work has focused on the effect of IL-1β-driven activation of NFκB on PR function, but other cytokines may also modulate PR function. Confirmation of these potential interactions awaits further study.

Pathology

Infection Infection is the leading known cause of PTL and unfortunately one in three preterm infants are born to mothers with an intra-amniotic infection that is largely subclinical (Romero *et al.* 2001). Ascending infection is seen as the main source; however, there is an association between periodontal disease and PTL (Manegold-Brauer *et al.* 2014), which suggests a possible systemic dissemination and transplacental passage (Fig. 4).

Ascending infection is usually caused by common vaginal pathogens such as Group B *Streptococcus*, *Mycoplasma* and *Ureaplasma*, whereas periodontal disease is commonly caused by gram-negative anaerobic bacteria such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleate* and *Campylobacter rectus*. These microorganisms and their products are typically identified by pattern recognition receptors such as toll-like receptors, which induce the production of chemokines (IL-8, IL-1, CCL-2) and cytokines (IL-1β, TNF-α) (Romero *et al.* 2014*a*). With regard to periodontitis pathogens it is likely that their effect is triggered by translocation of bacterial products, such as LPS, which can trigger common parturition pathway via inflammatory mediators such as IL-6 and TNF-α (Parthiban 2015).

PTL like TL require PGs. The rate-limiting enzyme in PG synthesis, PGHS-2, is required to increase PG just

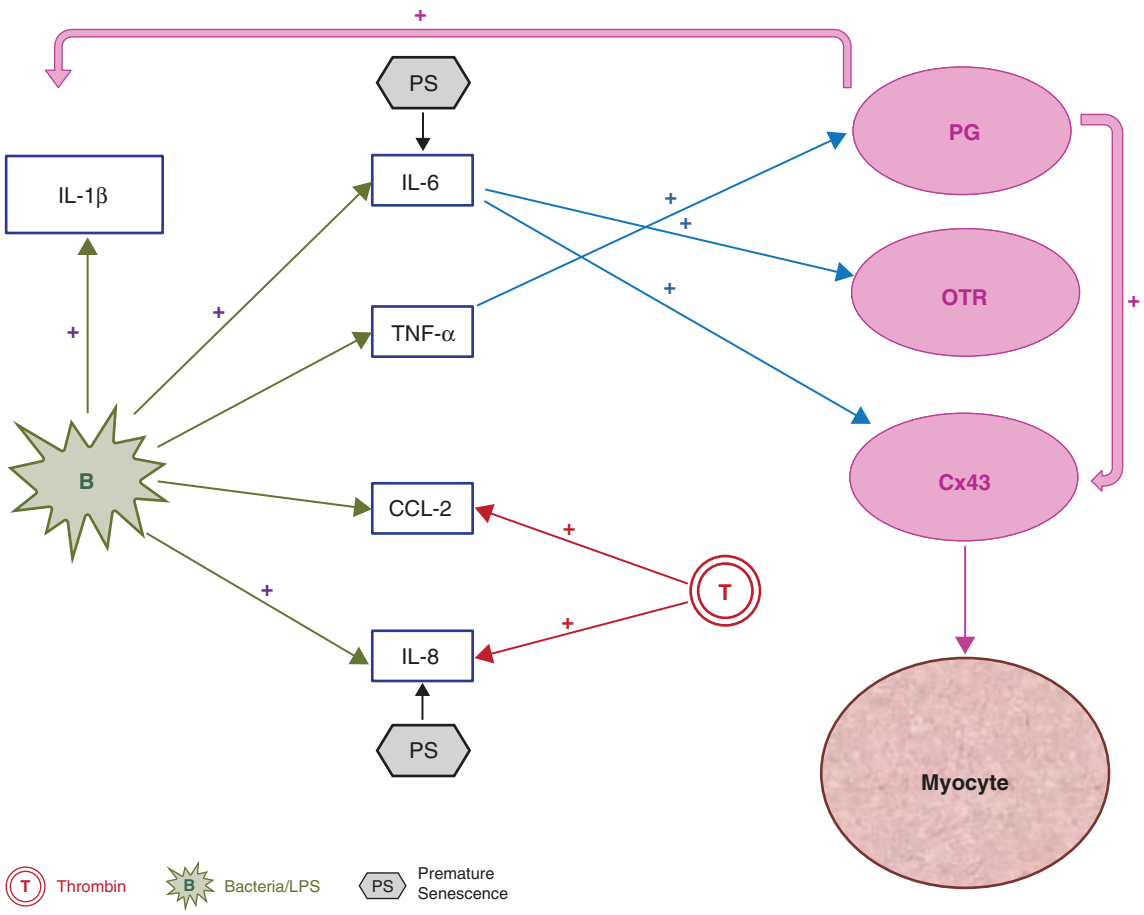

Figure 4
The effect of pathology (including haemorrhage, infection and premature senescence) on cytokines and myometrial contractility.

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before parturition (Hirst *et al.* 1995) and, interestingly, this is stimulated by cytokines including IL-1β and TNF-α. The key role played by these specific cytokines is shown in mice lacking receptors for both IL-1β and TNF-α, which have significantly lower levels of PGHS-2 mRNA in the myometrium following *E. coli* administration (Hirsch *et al.* 2006).

Aside from the above-mentioned infections, bacterial vaginosis (BV) and STIs are recognised as a risk factor for PTL, although treatment of asymptomatic women with BV does not reduce the rate of preterm births (Romero *et al.* 2001). One possible explanation for this association may be that BV induces the release of cytokines that trigger the onset of labour. Masson and coworkers identified that IL-1β (in cervico-vaginal fluid) as one of most useful immunologic biomarkers that could be used to diagnose treatable discharge-causing STIs and BV (Masson *et al.* 2016).

CA is a robust inflammatory response to intra-amniotic infection, and commonly associated with an infiltration of neutrophils in response to IL-8 and CXCL-6, amongst other chemokines (Kim *et al.* 2015*b*). Damage-associated molecular pattern molecules (see below) are also able to induce such neutrophil-attracting chemokine, which led to the possibility of a mutual parturition pathway. Recent work on immune cells involved in acute and chronic CA resulting in PTL has shown the importance of macrophages. It has highlighted differences in the anatomical distribution of macrophages within the foetal membranes, as well as the differing functions – both pro-inflammatory and immunomodulatory (Bae *et al.* 2016). The plasticity and flexibility of macrophages (Brown *et al.* 2014), enables macrophages to acquire altered phenotypes in response to different situations. This is further complicated by the uncertainty of where these macrophages originate (foetal vs maternal) and the continuing conundrum of understanding the role of inflammatory signals in both TL and PTL. Indeed, variations in the onset of PTL and TL suggest that they may involve distinct inflammatory pathways, but as yet there are no definitive data on this subject.

It is important to note that sterile inflammation (defined as an inflammatory process without the presence of microorganisms) has also been associated to PTL and is more common in PTL with intact membranes than microbial-associated inflammation (Romero *et al.* 2014*b*). The aetiology of sterile intra-amniotic inflammation is unknown; however, the inflammation is understood to result from activation of the innate immune system by endogenous danger signals, derived from necrosis or cellular stress, termed damage-associated molecular pattern molecules, or alarmins (Gomez-Lopez *et al.* 2016). One such alarmin is HMGB1, which has been shown to induce PTL in a mouse model (Gomez-Lopez *et al.* 2016). For further detail on proposed theories on sterile inflammation please refer to Faranak Behnia's review (Behnia *et al.* 2016).

Haemorrhage Decidual haemorrhage is associated with PTL (Romero *et al.* 2014*a*) and it complicates 0.5–2% of all pregnancies (Buhimschi *et al.* 2010). Decidual haemorrhage was generally accepted as an acute event; however, histological evaluation of the vasculopathy accompanying decidual haemorrhage provides compelling evidence that the damage is frequently chronic (Salafia *et al.* 1995, Elsasser *et al.* 2010). Placental abruption has been shown to be associated with inflammatory lesions of the placenta, in particular at preterm gestations (Nath *et al.* 2007) and interestingly a strong association has been noted between severe CA and abruption at term (Nath *et al.* 2007). This suggests that inflammatory pathways are common to both infection and decidual haemorrhage.

Local decidual injury leads to production of cytokines, some of which lead to drive the inflammatory labour pathway. Additionally, thrombin, which is generated from decidual-cell-expressed tissue factor (Buhimschi *et al.* 2010), can itself enhance the activity of cytokines such as IL-8 (Lockwood *et al.* 2005) and CCL-2 (Matta *et al.* 2007), which enhance neutrophil and macrophage infiltration, promoting inflammation. Thrombin, acting via decidual cell membrane-bound protease-activated receptors, can also induce MMPs, which enable extracellular matrix breakdown, leading to the rupture of membranes (Han *et al.* 2011). This process has been associated with preterm premature rupture of membranes (PPROM) in the absence of infection (Han *et al.* 2011) and probably explains the linkage of PPROM and placental abruption in the absence of infection (Harger *et al.* 1990).

Thrombin has also been shown to be a direct potent uterotonic agent in both *in vitro* and *in vivo* models (Elovitz *et al.* 2000). *In vitro* fresh whole blood stimulated myometrial contractions in a dose-dependent manner and this effect was supressed with thrombin inhibitors (Elovitz *et al.* 2000). *In vivo* thrombin increased the frequency, intensity and tone of myometrial contractions in a dose-related fashion (Elovitz *et al.* 2000). Thrombin's potential to be an

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enzymatic, immunological and contractile inducer defines how decidual haemorrhage can expedite labour at term and unfortunately cause PTL when occurring at an early gestation.

Premature senescence Senescence refers to the physiologic and biomolecular mechanisms that are normal and naturally associated with ageing of a living organism (Muñoz-Espín & Serrano 2014); however, premature senescence is associated with pathology such as diabetes (Barzilai *et al.* 2012) and chronic inflammatory conditions (Gubbels Bupp 2015). Senescence is also associated with a set of biomarkers that are referred to as senescence-associated secretory phenotype (SASP). SASP is recognised by production of natural compounds such as cytokines, chemokines, matrix degrading enzymes and many more (Behnia *et al.* 2015). Behnia and coworkers showed that TL is associated with senescence of chorioamniotic membrane cells and increased pro-inflammatory SASP factors (IL-6, IL-8, GM-CSF) could function as triggers of labour (Behnia *et al.* 2015). Evidence of decidual senescence has been demonstrated in the basal plate of the placenta in cases with PTL, but not in women who delivered at term (Cha *et al.* 2013). Some regard senescence as an initiator of sterile inflammation, while Menon and colleagues suggest that inflammation at term, and maybe even preterm is secondary to foetal cell senescence (Behnia *et al.* 2015).

Pathological triggers of labour include infection (systemic and localised, i.e. CA), haemorrhage, and physiological deficits such as premature senescence. They all trigger pro-inflammatory markers and in general results in labour. However, it is unclear why some infections potentiate PTL and others only cause ruptured membranes and allow the pregnancy to continue to term. These variations may be due to the inflammatory marker response being stimulant (type of bacteria/antigenicity) and exposure (localised vs systemic) specific and may suggest triggering distinct inflammatory pathways.

Myometrial contractility The myometrium has the ability to contract both in a non-pregnant uterus in varying phases of the menstrual cycle and also importantly, in a pregnant uterus (Pehlivanoglu *et al.* 2013). This is evidently necessary as the process of parturition can only be completed with the establishment of regular and effective contractions. The switch from uterine quiescence to the active stage of contractility is considered to be dependent on a group of proteins referred to as contraction associated proteins (CAP) (Hutchings *et al.* 2009) whilst the excitation-contraction coupling required for contractility is understood to occur via elevated intracellular calcium levels (Wray 2003). For more detail please see Roger Smith's review (Smith 2007).

The direct effects of inflammation on contractility The upregulation of pro-inflammatory cytokines within labouring myometrium stimulates and potentiates uterine contractions (Voltolini *et al.* 2015). IL-1β enhance myometrial contractility via different pathways, promoting basal and store-operated calcium entry (Tribe 2002), upregulating TrpC expression (calcium entry channels; Dalrymple *et al.* 2004) and increasing the expression of selected phosphodiesterases, enzymes involved in the control of intracellular levels of cyclic nucleotides (Oger *et al.* 2002). TNF-α reduces the expression of Galphas, the component of the G-protein receptor complex that links to adenylyl cyclase and which increases intracellular cAMP levels promoting myometrial relaxation (Chapman *et al.* 2005). Interestingly, LPS increased the contraction of an isolated mouse uterine horn preparation (Mackler 2003) and uterine myocytes *in vitro* through the Rho/ROCK signalling pathways (Hutchinson *et al.* 2013) and co-culture of uterine myocytes and monocytes enhances cytokine production and contraction (Rajagopal *et al.* 2015). Myometrial cells are able to produce cytokines such as IL-1β, IL-6, IL-8, TNF-α, which is enhanced by infiltrating immune cells (Young 2002) such as macrophages, promoting a positive feedback loop to sustain the myometrial contractility. It is important to recognise that the effect of both cytokines and pro-inflammatory agents such as LPS are dose-dependent based on *in vitro* data; this is unlikely to reflect the reality of an *in vivo* system as other confounders may modify the effect. Such confounders may be innate control agents, which limit the severity of inflammation such as the production of IL-10 in response to IL-1β (Sadowsky *et al.* 2003). The production/release of such immunomodulatory cytokines may be derived from other tissues, for example decidua; this is difficult to factor into *in vitro* models and does limit interpretation of such data. However, some models have attempted to address this crosstalk by co-culturing with agents such as progesterone and IL-10 (Rajagopal *et al.* 2015).

The indirect effects of inflammation Inflammation drives the expression of CAPs, include the OTRs, PG receptors (Fig. 3) and the gap junction protein connexin 43 (Hutchings *et al.* 2009).

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Myometrial oxytocin system OTR mediates the effects of oxytocin (OT) on the myometrium. It is a key regulator of myometrial function. Its expression increases with advancing gestation (Fuchs *et al.* 1991), peaking in early labour (Rivera *et al.* 1990), corresponding to the clinical observation of increased uterine sensitivity to OT (Kimura *et al.* 1996). OT increases myometrial contractility via increases in intracellular calcium, mediated through its G-protein-coupled receptor, OTR. How inflammatory cytokines affect OTR expression is debated. Some authors show that IL-1β downregulates myometrial OTR expression (Rauk & Frieve-Hoffmann 2000, Schmid *et al.* 2001, Helmer 2002), while others have shown that it increases OTR expression (Terzidou *et al.* 2006). The effect is certainly time dependent and may explain some of the conflicting data (Terzidou *et al.* 2006). Myometrial and decidual synthesis and release of OT was increased by IL-6 and IL-1β (Friebe-Hoffmann *et al.* 2001), suggesting that the acute effects of inflammation would be to increase the activity of the myometrial OT system, consistent with the observation that acute exposure to IL-1β increases OT-induced contractility, but chronic exposure reduces it (Molnár *et al.* 1993, Rauk 2000). Intriguingly, OT has been shown to activate the NF-κB pathway, increasing the expression of several key inflammatory labour-associated genes in both myocytes and amnion cells including IL-8, IL-6, CCL-5 and COX-2 (Kim *et al.* 2015*a*). The level to which OT initiates the NF-κB pathway is comparable with IL-1β in the amnion; however, in the myometrium IL-1β is still the stronger inducer of the pathway (Kim *et al.* 2015*a*).

PG/PG receptors and cytokines PGs are known to initiate labour and enable contractions via cervical ripening, membrane rupture and uterine contractility. Phospholipase A2 releases arachidonic acid, which is converted into PGH_2 by cycloxgenase 1 and 2 (Simmons 2004). PGH_2 can be converted into the four main PGs: PGE_2, $PGF_{2\alpha}$, PGD_2 and prostacyclin (PGI_2) (Sykes *et al.* 2014), of which PGE_2 and $PGF_{2\alpha}$ are known be potent inducers of uterine contractility in spontaneous labour (Crankshaw & Dyal 1994). Inflammatory cytokines have long been recognised to drive PG synthesis in human myometrial cells (Hertelendy *et al.* 1993, Molnár *et al.* 1993, Pollard & Mitchell 1996) via the activation of NFkB and MAPK, p38 (Belt *et al.* 1999, Bartlett *et al.* 1999). PGs are recognised to be pro-inflammatory and contribute to inflammatory conditions throughout the body such as in asthma (Claar *et al.* 2014) and cancer (Rose *et al.* 2015). PGs can act as cytokine amplifiers and in particular increases activity of IL-1β (Aoki & Narumiya 2012), which as mentioned plays a substantial role in initiating labour and contractility. PGs contribute to the physiological inflammatory reaction seen in labour; for example PGE_2 enhances migration of leukocytes towards the cervix, which in turn leads to an increased production of IL-8 (Hertelendy & Zakár 2004). $PGF_{2\alpha}$ indirectly can activate IL-1β in the decidua and consequently increase production of MMP-9 (Christiaens *et al.* 2008), which is known to participate in breakdown of the extracellular matrix leading to ruptured foetal membranes (Vadillo-Ortega & Estrada-Gutiérrez 2005). Additionally, PGE_2 interacts with LPS to induce IL-6, COX-2 and IL-1β via EP_4 on macrophages (Aoki & Narumiya 2012) indicating PGs' role in infection associated PTL.

Connexin 43 and cytokines Connexins are a family of homologous proteins (21 in humans), each of which is the product of a distinct gene (Söhl & Willecke 2003). Connexins differ greatly in size, providing a convenient method of distinguishing them: connexin 43 (Cx43) is 43 kD. Their best known function is to form the intercellular membrane channels of gap junctions, which allow direct sharing of small molecules between cells in a process known as gap junctional intercellular communication (Winterhager & Kidder 2015). Cx43 is recognised as one of the contraction associated proteins (Hutchings *et al.* 2009).

Cx43 gap junctions are scarce in the myometrium of the non-pregnant uterus but increase in size and abundance with parturition in both humans and animals (Chow & Lye 1994, Orsino 1996). Doring and coworkers has shown in a mouse model that ablation of Cx43 delays parturition. This was shown both *in vitro* and *in vivo* (Doring 2006). Cx43 is impacted by inflammation. In an *in vitro* model, monocytes in the presence of TNF-α and IFN-γ increased protein and mRNA levels of Cx43 (Eugenin *et al.* 2003). This would increase the contractility potential of the myometrium. It is also raised in response to LPS (Chang *et al.* 2012) and is raised in association with PTL (Balducci *et al.* 1993).

$PGF_{2\alpha}$ has also been shown to increase Cx43 and *PTGS2* expression in myocytes, the effect of which is enhanced by IL1β (Xu *et al.* 2013).

In summary, the three CAPs have been shown to be stimulated by cytokines, in particular IL-1β, but as noted with OTR, exposure duration may have variable effect on the CAPs (this has not been studied with

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regard to PG and Cx43). Interactions between CAPs and cytokine/chemokines draw a variety of immune cells; however, the particular role of these cells are unclear, as they may be acting in an immunomodulatory capacity as opposed to the presumed inflammatory role.

Future research

Labour at term is clearly associated with inflammation. Inappropriate initiators of this inflammation seem to trigger PTL as described above. It is evident from this review that there is a multitude of factors that enable and promote the myometrium to contract (Figs 2, 3 and 4). In fact, there is a growing body of evidence to suggest that the beginning of labour may be initiated in other gestational tissues before the myometrium is involved.

Cytokines play a significant role in establishing the inflammatory environment that is associated with labour; however, there is much more to understand. Certain cytokines are repeatedly implicated in the various steps of labour; however, the exact role of each cytokine is unclear. It is understood that they are chemotactic to leukocytes, but there is little understanding of the leukocytes' exact function. Further work to identify leukocyte phenotype and function needs to be considered

Future work needs to focus on the trigger of labour as this seems to be the only question that we are unable to truly answer. By unravelling this mystery, it could be possible to identify effective therapeutic targets for those at risk of PTL. Longitudinal studies will be necessary to understand the molecular and immunological changes in normal pregnancy as this may enable identification of biomarkers and improve risk assessment. Newer high-throughput techniques such as metabolomics and proteomics could complement our current methods, and enhance our understanding of labour, which is the ultimate key in tackling PTL.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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All authors were involved in drafting and editing the manuscript.

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