

1 **Cytokines and Myometrial Signalling in Human Labour**

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28 **Introduction**

29 Human labour is an inflammatory event, physiologically driven by an interaction between
30 hormonal and mechanical factors and pathologically associated with infection, bleeding and
31 excessive uterine stretch (Golightly, Jabbour, and Norman, 2011). However, the processes
32 involved are not fully understood, especially the triggers/activators of labour. Local pro-
33 inflammatory cytokine and chemokines have been implicated in the pathophysiology of
34 human labour since the 1980s; with more recent data strongly linking increased intrauterine
35 cytokine and chemokine production with both term and preterm labour (Keelan et al.,
36 2003).

37 Various inflammatory mediators have been studied in reproductive tissues obtained at the
38 time of term labour (TL) and preterm labour (PTL) showing the involvement of a range of
39 cytokines and chemokines in the choridodecidua (Hamilton, Tower, and Jones, 2013),
40 amnion (Gomez-Lopez et al., 2010), and placenta (Haugueldemouzon and Guerremillo,
41 2006). This review will be focused on recent work and current understanding of the nature
42 and role of cytokines, chemokines and hormones and their involvement in signalling within
43 the myometrium particularly during labour.

44

45 **Myometrial inflammation**

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

58 The first reports of myometrial inflammation in association with labour appeared in the
59 later 1980's. Azziz *et al* reported the presence of inflammation in biopsies taken at the time
60 of emergency Caesarean section and suggested that there was an underlying infective cause
61 (Azziz, Cumming, and Naeye, 1988). Lopez-Bernal and colleagues first raised the key
62 question of how much of the inflammatory change in the myometrium was a consequence
63 of the labour process (Bernal et al., 1993). This question was partially addressed in a series
64 of papers by Norman et al, in which the nature of the cellular infiltration, the changes in
65 cytokine levels and the cells producing the cytokines were defined (Bollopragada et al.,
66 2009). These papers established that term labour is an inflammatory event showing that the

67 myometrium is infiltrated by neutrophils, macrophages and T lymphocytes (Figure 1) and
68 that these cells are the predominant source of the inflammatory cytokines (Young, 2002).
69 Later studies have shown that the myometrial expression of chemokines and endothelial
70 adhesion molecules are increased with the onset of labour, suggesting a potential
71 underlying mechanism for the cellular infiltration of the myometrium (Young, 2002). The
72 drivers of the chemokine expression have also been studied and may include mechanical
73 stretch and cytokines (see below). However, it remains unclear whether the inflammatory
74 infiltration of the myometrium is a cause or consequence of labour. Human studies show
75 that levels of IL-8 (Table 1) rise with established labour only (Osmers, 1995, Elliott et al.,
76 2001, Kemp et al., 2002) In rodent pregnancies, it seems apparent that the inflammatory
77 infiltration precedes the onset of labour (Mackler, 1999, Shynlova et al., 2012), but various
78 groups have depleted pregnant animals of neutrophils (Timmons, 2006) or studied animals
79 with no mast cells (Menzies et al., 2011), without delaying labour onset. Others have used
80 chemokine knockouts, which deliver at the same time as their wild-type controls (Menzies
81 et al., 2012). A number of animal studies have attempted to address this question using LPS,
82 a bacterial wall polysaccharide (Fang, Wong, and Mitchell, 2000). Lye et al found that pre-
83 treatment with a non-specific chemokine antagonist delayed labour onset in association
84 with a reduced inflammatory infiltration (Shynlova et al., 2014), suggesting that the
85 inflammatory infiltration is important in inflammation-induced labour onset. Indeed,
86 macrophage depletion prevents LPS induced PTL in pregnant mice (Gonzalez et al., 2011),
87 but neutrophil depletion had no effect (Rinaldi et al., 2014). These data suggest that
88 macrophages but not neutrophils are important for this process.

89

90 **Inflammation in reproductive tissues/compartments**

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

92 **Maternal circulation:**

93 The changes in the innate immune system during pregnancy are characterised by increased
94 numbers of circulating monocytes and granulocytes, resulting in a higher number of total
95 leukocytes (Tang et al., 2015). Peripheral monocyte numbers are higher; mainly due to an
96 increase in the intermediate monocyte subset (Melgert et al., 2012). These monocytes are
97 pro-inflammatory, producing IL-1 β , IL-6 and TNF- α (Tang et al., 2015) (Table 1) and are
98 recruited into gestational tissues, especially the decidua, during labour (Tang et al., 2015).
99 Peripheral circulating leukocytes have also been noted to display early chemotactic
100 responsiveness during late gestation which would aid their infiltration into uterine tissues
101 (Gomez-Lopez et al., 2013). Recently Srikhajon et al reported that monocytes are recruited
102 first to the myometrium by various cytokines and chemokines. Following this
103 transmigration, activated monocytes in turn limit further chemotaxis by disrupting locally
104 established CCL2 gradients (Table 1) (Srikhajon et al., 2014). This may serve as a negative
105 feedback loop to control the local inflammation. On the other hand, this group also
106 suggested that generic inhibition of chemokines limited inflammation and reduced PTB
107 (Shynlova et al., 2014). These seeming contradictions may reflect species differences or be

108 determined by the stimulant. Circulating neutrophil numbers are higher in women in
109 preterm and term labour (Yuan et al., 2009). These neutrophils are likely to be drawn into
110 the myometrium by chemokines in particular IL-8 which is significantly higher in
111 myometrium at term during labour than in women not in labour (Gomez-Lopez et al., 2010)
112 and may contribute to the changes in whole blood gene expression noted in women with
113 threatened preterm labour (Heng et al, 2014).

114 **Amniotic fluid (AF):**

115 Inflammatory cytokines are known to increase in AF towards term in human pregnancy and
116 may play a role in labour by stimulating local production of prostaglandins and collagenases
117 (Bowen et al., 2002). With the onset of TL, there are increased concentrations of IL-1 β and
118 TNF- α in AF (Romero et al., 1990, Laham et al., 1994). IL-6 has been noted to be raised in AF
119 in women with spontaneous labour (Andrews et al., 1995) and particularly raised in PTL
120 associated with intra-amniotic infection; and even considered a predictor for PTL before 34
121 weeks gestation (Chaemsaitong et al., 2015). IL-8 concentrations in AF increase
122 progressively from early pregnancy to term and more markedly with the onset of
123 spontaneous term labour (Romero et al., 1991, Saito et al., 1993, Laham et al., 1994). The
124 rise in AF IL-6 precedes that of IL-8, suggesting that IL-6 has a role in the initiation of the
125 inflammatory cascade required for the onset of labour (Kemp et al., 2002). Recent work by
126 Romero et al have shown varying cytokine networks noted in the AF associated with PTL
127 with intact membranes and intraamniotic inflammation (both microbial and sterile)
128 (Romero et al., 2015). Interestingly, the chemokine CCL-20, which targets immature
129 dendritic cells, effector/memory T-cells and B-lymphocytes increases in AF with advancing
130 gestational age. It is further increased in the absence of infection in spontaneous TL and PTL,
131 which suggests it has a role in the common parturition pathway (Hamill et al., 2008).

132

133 **Amnion/Chorion**

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

144

145 **Decidua (CD)**

146 The decidua is a highly immunologically active region of a pregnant uterus. Hamilton *et al*
147 used a rat model to investigate the pre-labour changes and found a significant increase in

148 the numbers of macrophage infiltration of the decidua in the days prior to labour, which
149 preceded inflammatory changes in the myometrium (Hamilton et al., 2011). This suggests
150 that decidual inflammatory events are important in the initiation of labour (Sindram-Trujillo
151 et al., 2004, Castillo-Castrejon et al., 2013,)), supporting the hypothesis first proposed in the
152 1980s that decidual activation is an early event in the labour cascade (Casey and
153 MacDonald, 1988). IL-8 is raised in CD at labour, with almost a 30 fold change in TL
154 compared to term no labour (Hamilton, Tower, and Jones, 2013), resulting in neutrophil
155 recruitment. These cells can release several inflammatory mediators and MMPs, which
156 could degrade the extracellular matrix of the fetal membranes during both TL and PTL,
157 contributing to ROM during term and preterm labour (Gomez-Lopez et al., 2010).
158 Choriodecidual changes are of particular interest in PTL, where it has been shown that
159 CD56+ NK cells and T cells are increased (Hamilton, Tower, and Jones, 2013) along with an
160 elevated expression of CCL8 which is a chemoattractant for NK and T cells (Proost, Wuyts,
161 and Damme, 1996). These inflammatory changes implicate both the innate and adaptive
162 immune system in the pathological process of PTL and interestingly the imbalance between
163 these two immune systems in PTL have been demonstrated via a mouse model (Arenas-
164 Hernandez et al., 2015).

165

166 **Placenta**

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

176 Overall, inflammation does play a critical role in the onset and progression of labour, but
177 where this is initiated and then propagated to is still a point of much discussion and
178 research. It seems likely that the decidua being the maternal fetal interface is
179 immunologically crucial, and our data (unpublished) suggests that it is the most
180 inflammatory in PTL. Further work looking at inflammation in all compartments with
181 comparison to peripheral blood is necessary to improve our understanding. The exact
182 triggers for the onset of this inflammatory process is yet another uncertainty; some have
183 suggested that the fetus releases surfactant proteins as a signal of maturity (Reinl and
184 England, 2015), others that there is a change in maternal tolerance and still others that
185 uterine stretch is responsible.

186

187 **Physiology (Figure 2):**

188 Stretch Effect

189 Throughout pregnancy, the uterus is dramatically remodelled to accommodate the growing
190 pregnancy. Despite the progressive increase in size, uterine quiescence is maintained, until
191 the onset of labour, be it at term or preterm, when the uterus transforms into an actively
192 contractile organ, to efficiently expel the pregnancy. The growing conceptus increases intra-
193 uterine pressure, but for the majority of pregnancy, the uterus is able to adapt and remodel
194 to avoid any increase in wall tension. It is possible that once this adaptive mechanism is lost
195 or overcome, the tension in the wall of the uterus rises, initiating the process, which
196 culminates in the onset of labour. Progesterone has been suggested to play a key role in this
197 adaptive process, particularly in animal models, where the loss of progesterone repression
198 is associated with an increase in stretch-related pro-contraction proteins (Shynlova, Lee, et
199 al., 2012) (connexin-43 and oxytocin receptor). *In vitro* stretch models of human myometrial
200 cells (Terzidou et al., 2005) and strips (Moraitis et al., 2015) showed increased OTR
201 expression and responsiveness respectively, while *in vivo*, acute uterine stretch increases
202 prostaglandin synthesis (Manbe, Manabe, and Takahashi, 1982). Interestingly, no difference
203 in prolabor expression was seen when comparing twin and singleton pregnancies (Lyll,
204 2002). Equally, excessive uterine stretch, seen in polyhydramnios, multiple pregnancy or a
205 singleton pregnancy in a unicornuate uterus are all associated with increased rates of
206 preterm labour (Rodriguez, 1992, Reichman, Laufer, and Robinson, 2009, Conde-Agudelo
207 and Romero, 2014,).

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

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

228 *In vitro* studies of human and rat myometrial cells show that mechanical stretch up-
229 regulates pro-inflammatory factors (Shynlova et al., 2012). Our studies showed that stretch

230 up-regulated IL-8 and COX-2 in a MAPK-dependent manner (Loudon, 2004, Sooranna, 2004,
231 Sooranna et al., 2005). Later studies confirmed that stretch of myometrial cells increased
232 the expression and release of IL-8, while showing that other chemokines and inflammatory
233 cytokines are also increased in a predominantly NF κ B-dependent manner (Hua et al., 2012).
234 More recently, Lye et al showed that conditioned media from stretched myometrial cells
235 induced endothelial activation and the expression of adhesion molecules, promoting the
236 extravasation of inflammatory cells (Lee, Shynlova, and Lye, 2014).

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

248 Chemokines are essential for inflammatory cell migration and also modulate immune cell
249 activation (Griffith, Sokol, and Luster, 2014). The main chemokines implicated in the
250 inflammatory process of labour are IL-8 and CCL-2, which act via CXCR2 and CCR-2
251 respectively. IL-8 is a potent chemokine for neutrophils; and its mRNA expression is
252 increased in myometrium of women in preterm and term labour (Keelan et al., 2003).
253 Indeed, a recent myometrial transcriptome study reported that IL-6, CXCL1 and IL-8
254 exhibited the greatest increase in labouring samples (Mittal et al., 2010). A more detailed
255 study revealed that IL-8 levels increased in parallel with cervical dilation (Hebisch et al.,
256 2001). In preterm labour, IL-8 concentrations are markedly elevated in chorioamnionitis
257 (Yoneda et al., 2015). Interestingly, myometrial expression of CXCR2 declined with the onset
258 of TL (Hua et al., 2012) perhaps as a result of higher IL-8 levels or the effects of increased
259 levels of OT and PGF_{2 α} , which can also repress CXCR2 expression via phospholipase C (Hua et
260 al., 2012). Alternatively, IL-1 β and TNF- α also reduce CXCR2 expression and may also be
261 responsible for the labour-associated decline (Hua et al., 2012).

262 CCL-2 is a member of the CC chemokine family and is also called MCP-1 (Esplin et al., 2005,
263 Griffith, Sokol, and Luster, 2014). It is expressed by decidual cells (Critchley et al., 1996),
264 endometrial and myometrial cells (Arici, MacDonald, and Casey, 1995, Jones, Kelly, and
265 Critchley, 1997,) therefore it is ideally positioned to recruit macrophages to cervix,
266 myometrium and fetal membranes with the onset of labour. Indeed, CCL-2 is markedly
267 upregulated in both term and preterm myometrium (Esplin et al., 2005). CCL-2 is increased
268 in amniotic fluid from women in preterm labour particularly in the presence of infection
269 (confirmed by histological chorioamnionitis) (Esplin et al., 2003).

270 Stretch clearly has an impact on not only pro-inflammatory mediators such as CCL-2, IL-8
271 and IL-6 to name a few but also on activity of oxytocin receptors and smooth muscle

272 agonists such as gastrin-releasing peptides. Much of the *in vivo* model findings have been
273 confirmed in our *in vitro* work, however further work looking into the interactions between
274 electro-mechanical signalling, hormonal interference and inflammation is necessary to
275 understand when adaptive mechanisms that maintain uterine quiescence falter.

276 **Maternal tolerance**

277 Pregnancy has often been compared to a transplanted organ as both fetus and placenta
278 express maternal and paternal antigens hence are like semi-allografts (Erlebacher, 2012).
279 Breakdown in immune tolerance has been linked to rejection, which in pregnancy can have
280 variable consequences depending on the gestation: recurrent miscarriages (Kuon et al.,
281 2015), preterm labour (Romero, Dey, and Fisher, 2014), pre-eclampsia (Dietl, 2000) to name
282 a few. Tolerance is maintained via factors produced at the implantation site, one such
283 promoter of tolerance is IL-10, an anti-inflammatory cytokine (Thaxton and Sharma, 2010).
284 IL-10 was demonstrated to be a modulator of uterine NK cell cytotoxicity; in an IL-10
285 depleted mice model, very low doses of LPS led to uterine NK (uNK) cell activation and fetal
286 demise (Murphy et al., 2008). In a non-human primate model, IL-10 has been shown to
287 inhibit IL-1 β induced uterine activity (Sadowsky et al., 2003) and it seems to also have an
288 inhibitory effect on LPS induction of matrix metalloproteinase 2 and 9 in fetal membranes
289 (Fortunato et al., 2001).

290 Interferons, known for their anti-viral potential, also have an immunomodulatory role
291 (Racicot et al., 2014). Hertelendy *et al* showed via human myometrial cell line cultures that
292 cell cultures primed with IFN- γ produced significantly less prostaglandins and reduced COX-
293 2 expression (Hertelendy and Zakár, 2004). Trophoblasts have been suggested in enabling
294 appropriate tolerance by “educating” macrophages and adapting the cytokine profile of the
295 local macrophages. Fest *et al* showed that monocytes cultured with trophoblasts (Fest et al.,
296 2007), increased production of RANTES (which recruits T regulatory cells) and MIP-1 β which
297 both have immunosuppressive functions (Wang et al., 1999, Ramhorst et al., 2004).
298 Dendritic cells (DC) promote cell tolerance particularly at the maternal-fetal interface, by
299 priming T regulatory (T_{reg}) cells (Blois et al., 2007). T_{reg} cells, part of the adaptive immune
300 system play a pivotal role in promoting fetal survival by avoiding the recognition of semi-
301 allogenic tissues by the maternal immune system (Somerset et al., 2004, Tilburgs et al.,
302 2009, La Rocca et al., 2014). This was seen in a mice model where depletion of CD25⁺ T_{reg}
303 cells led to gestation failure (Aluvihare, Kallikourdis, and Betz, 2004) and a certain systemic
304 composition of T_{reg} cells with distinct subsets have been associated with PTL (Steinborn et
305 al., 2011).

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

314 **Feto-placental signalling**

315 Corticotropin-releasing hormone (CRH) is synthesised in the placenta and the levels of
316 placental CRH increases as the pregnancy advances, peaking at delivery with a rapid decline
317 postnatally (Sasak et al., 1987). CRH can induce the breakdown of mast cells, releasing
318 histamine (Lytinas et al., 2003) and has been widely associated with cytokines especially the
319 pro-inflammatory cytokine IL-6 (Venihaki et al., 2001). Raised maternal levels of CRH have
320 been associated with PTL (Figure 3), suggesting a possible causative link (Vitoratos et al.,
321 2007). Indeed, CRH can stimulate the myometrium to produce pro-inflammatory cytokines
322 and chemokines, in particular IL-6, IL-1 β , TNF- α , IL-8 and CCL2. However, this effect appears
323 to be dependent on cAMP-PKA signalling pathway and possibly NF- κ B (You et al., 2014).
324 These cytokines can induce the chemotaxis of monocytes to the myometrium and promote
325 inflammation, which is thought to be key for the onset of labour. For example, IL-1 β and IL-6
326 stimulate uterine activation by increasing CX43, PGFR and OTR. In addition, CRH has been
327 reported to have a stimulatory effect on prostaglandins (PGE2, PGF2 α) (You et al., 2014).

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

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

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

354

355 **Progesterone and Progesterone Receptor**

356 The withdrawal of progesterone (P4) has long been hypothesised to be the trigger of labour,
357 with supportive evidence from animal models, in particular sheep and goat where a fall in
358 P4 and a concurrent increase in oestradiol precedes the onset of labour (Ravanos et al.,
359 2015). This does not apply to humans, as there is no decline in circulating maternal P4 levels
360 before labour. Interestingly guinea pigs are similar to humans in that they labour in
361 presence of high maternal progesterone levels. Such model has recently shown that
362 decreasing P4 receptors leads to a physiological mechanism of functional P4 withdrawal
363 which is enhanced by endogenous/exogenous prostaglandin administration (Welsh et al.,
364 2014).

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

372 P4 has been suggested to maintain pregnancy primarily by inhibiting inflammation through
373 repression of the archetypical inflammatory transcription factor NFκB (Wissink, 1996). This
374 is mediated both via a direct interaction between the P4 receptor, PR-B, and the principle
375 NFκB subunit, p65 and by increasing IκB levels, which binds to p65 maintaining it in an
376 inactive state (Hardy et al., 2006). The onset of human labour is suggested to occur after P4
377 influence is lost by a combination of increased expression of PR-A (Mesiano et al., 2002),
378 which inhibits PR-B, a reduction in the level of the PR co-activator, SRC1 (Condon et al.,
379 2006) and by increased activity of NFκB, which represses PR activity via a direct interaction
380 (Condon et al., 2003). Much of these data are based on over-expression of PR and p65, and
381 have often been carried out in cell lines of various types. Our data suggest that P4 represses
382 IL-1β driven COX-2 expression via the glucocorticoid receptor (GR) and not PR, despite the
383 presence of sufficient PR to modulate the expression of the P4-responsive genes (Lei et al.,
384 2012). Further, we show that P4 reduced IL-1β-driven COX-2 expression via the inhibition of
385 AP-1 action rather than NFκB (Lei et al., 2015). Most work has focused on the effect of IL-1β-
386 driven activation of NFκB on PR function, but other cytokines may also modulate PR
387 function. Confirmation of these potential interactions awaits further study.

388

389 **Pathology (Figure 4)**

390 **Infection**

391 Infection is the leading known cause of preterm labour and unfortunately one in three
392 preterm infants are born to mothers with an intra-amniotic infection that is largely
393 subclinical (Romero et al., 2001). Ascending infection is seen as the main source; however

394 there has been an association with periodontal disease and PTL (Manegold-Brauer et al.,
395 2014), which suggests a possible systemic dissemination and transplacental passage.

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

406 PTL like TL require prostaglandins (PG). The rate limiting enzyme in prostaglandin synthesis,
407 PGSH-2, is required to increase PG just prior to parturition (Hirst et al., 1995) and,
408 interestingly, this is stimulated by cytokines including IL-1 β and TNF- α . The key role played
409 by these specific cytokines is shown in mice lacking receptors for both IL-1 β and TNF- α ,
410 which have significantly lower levels of PGHS-2 mRNA in the myometrium following E.coli
411 administration (Hirsch, Filipovich, and Mahendroo, 2006).

412 Aside from the above mentioned infections, bacterial vaginosis (BV) and STIs are recognised
413 as a risk factor for PTL although treatment of asymptomatic women with BV does not
414 reduce the rate of preterm births (Romero et al., 2001). One possible explanation for this
415 association may be that BV induces the release of cytokines that trigger the onset of labour.
416 Masson *et al* identified that IL-1 β (in cervico-vaginal fluid) as one of most useful
417 immunologic biomarkers that could be used to diagnose treatable discharge-causing STIs
418 and BV (Masson et al., 2015).

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

434 It is important to note that sterile inflammation (defined as an inflammatory process
435 without the presence of microorganisms) has also been associated to PTL and is more
436 common in preterm labour with intact membranes than microbial-associated inflammation
437 (Romero et al., 2014). The aetiology of sterile intra-amniotic inflammation is unknown;
438 however the inflammation is understood to result from activation of the innate immune
439 system by endogenous danger signals, derived from necrosis or cellular stress, termed
440 damage-associated molecular pattern molecules (DAMPs), or alarmins (Gomez-Lopez et al.,
441 2016). One such alarmin is HMGB1, which has been shown to induce PTL in a mouse model
442 (Gomez-Lopez et al., 2016). For further detail on proposed theories on sterile inflammation
443 please refer to Faranak Behnia's review (Behnia, Sheller, and Menon, 2016).

444

445 **Haemorrhage**

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

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

466 Thrombin has also been shown to be a direct potent uterotonic agent in both *in vitro* and *in*
467 *vivo* models (Elovitz et al., 2000). *In vitro* fresh whole blood stimulated myometrial
468 contractions in a dose-dependent manner and this effect was suppressed with thrombin
469 inhibitors (Elovitz et al., 2000). *In vivo* thrombin increased the frequency, intensity, and tone
470 of myometrial contractions in a dose-related fashion (Elovitz et al., 2000). Thrombin's
471 potential to be an enzymatic, immunological and contractile inducer defines how decidual
472 haemorrhage can expedite labour at term and unfortunately cause PTL when occurring at
473 an early gestation.

474

475 **Premature Senescence**

476 Senescence refers to the physiologic and biomolecular mechanisms that are normal and
477 naturally associated with aging of a living organism (Muñoz-Espín and Serrano, 2014);
478 however premature senescence is associated with pathology such as diabetes (Barzilai et al.,
479 2012) and chronic inflammatory conditions (Gubbels Bupp, 2015). Senescence is also
480 associated with a set of biomarkers that are referred to as senescence-associated secretory
481 phenotype (SASP). SASP is recognised by production of natural compounds such as
482 cytokines, chemokines, matrix degrading enzymes and many more (Behnia et al., 2015).
483 Behnia *et al.* showed that term labour is associated with senescence of chorioamniotic
484 membrane cells and increased pro-inflammatory SASP factors (IL-6, IL-8, GM-CSF) could
485 function as triggers of labour (Behnia et al., 2015). Evidence of decidual senescence has
486 been demonstrated in the basal plate of the placenta in cases with preterm labour, but not
487 in women who delivered at term (Cha et al., 2013). Some regard senescence as an initiator
488 of sterile inflammation, while Menon and colleagues suggest that inflammation at term, and
489 maybe even preterm is secondary to fetal cell senescence (Behnia et al., 2015).

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

497

498 **Myometrial Contractility**

499 The myometrium has the ability to contract both in a non-pregnant uterus in varying phases
500 of the menstrual cycle and also importantly, in a pregnant uterus (Pehlivanoglu, Bayrak, and
501 Dogan, 2013). This is evidently necessary as the process of parturition can only be
502 completed with the establishment of regular and effective contractions. The switch from
503 uterine quiescence to the active stage of contractility is considered to be dependent on a
504 group of proteins referred to as contraction associated proteins (CAP) (Hutchings et al.,
505 2009) whilst the excitation-contraction coupling required for contractility is understood to
506 occur via elevated intracellular calcium levels (Wray, 2003). For more detail please see
507 Roger Smith's review (Butler et al., 2013).

508 **The Direct Effects of Inflammation on Contractility**

509 The up-regulation of proinflammatory cytokines within labouring myometrium stimulates
510 and potentiates uterine contractions (Voltolini et al., 2015). IL-1 β enhance myometrial
511 contractility via different pathways, promoting basal and store-operated calcium entry
512 (Tribe, 2002), upregulating TrpC expression (calcium entry channels; Dalrymple et al., 2004)
513 and increasing the expression of selected phosphodiesterases, enzymes involved in the
514 control of intracellular levels of cyclic nucleotides (Oger et al., 2002). TNF alpha reduces the

515 expression of Galphas, the component of the G-protein receptor complex that links to
516 adenylyl cyclase and which increases intracellular cAMP levels promoting myometrial
517 relaxation (Chapman et al., 2005). Interestingly, LPS increased the contraction of an isolated
518 mouse uterine horn preparation (Mackler, 2003) and uterine myocytes *in vitro* through the
519 Rho/ROCK signaling pathways (Hutchinson et al., 2013) and co-culture of uterine myocytes
520 and monocytes enhances cytokine production and contraction (Rajagopal et al., 2015).
521 Myometrial cells are able to produce cytokines such as IL-1 β , IL-6, IL-8, TNF- α , which is
522 enhanced by infiltrating immune cells (Young, 2002) such as macrophages, promoting a
523 positive feedback loop to sustain the myometrial contractility. It is important to recognise
524 that the effect of both cytokines and pro-inflammatory agents such as LPS are dose-
525 dependent based on *in vitro* data; this is unlikely to reflect the reality of an *in vivo* system as
526 other confounders may modify the effect. Such confounders may be innate control agents,
527 which limit the severity of inflammation such as the production of IL-10 in response to IL-1 β
528 (Sadowsky et al., 2003). The production/release of such immunomodulatory cytokines may
529 be derived from other tissues e.g. decidua; this is difficult to factor into *in vitro* models and
530 does limit interpretation of such data. However some models have attempted to address
531 this crosstalk by co-culturing with agents such as progesterone and IL-10 (Rajagopal et al.,
532 2015).

533

534 **The Indirect Effects of Inflammation**

535 Inflammation drives the expression of CAPs include the oxytocin receptor, prostaglandin
536 receptors (Figure 3) and the gap junction protein connexin 43 (Hutchings et al., 2009).

537

538 **Myometrial oxytocin system**

539 The oxytocin receptor (OTR) mediates the effects of oxytocin (OT) on the myometrium. It is
540 a key regulator of myometrial function. Its expression increases with advancing gestation
541 (Fuchs et al., 1991), peaking in early labour (Rivera et al., 1990), corresponding to the clinical
542 observation of increased uterine sensitivity to OT (Kimura et al., 1996). OT increases
543 myometrial contractility via increases in intracellular calcium, mediated through its G-
544 protein coupled receptor, OTR. How inflammatory cytokines affect OTR expression is
545 debated. Some authors show that IL-1 β down-regulates myometrial OTR expression (Rauk
546 and Friebe-Hoffmann 2000, Schmid, Wong, and Mitchell, 2001, Helmer, 2002), while others
547 have shown that it increases OTR expression (Terzidou et al., 2006). The effect is certainly
548 time dependent and may explain some of the conflicting data (Terzidou et al., 2006).
549 Myometrial and decidual synthesis and release of OT was increased by IL-6 and IL-1 β
550 (Friebe-Hoffmann et al., 2007), suggesting that the acute effects of inflammation would be
551 to increase the activity of the myometrial OT system, consistent with the observation that
552 acute exposure to IL-1 β increases OT-induced contractility, but chronic exposure reduces it
553 (Molnár, Romero, and Hertelendy, 1993, Rauk, 2000). Intriguingly, OT has been shown to
554 activate the NF- κ B pathway, increasing the expression of several key inflammatory labour-
555 associated genes in both myocytes and amnion cells including IL-8, IL-6, CCL-5 and COX-2

556 (Kim et al., 2015). The level to which OT initiates the NF- κ B pathway is comparable to IL-1 β
557 in the amnion, however in the myometrium IL-1 β is still the stronger inducer of the pathway
558 (Kim et al., 2015)

559

560 **Prostaglandin/Prostaglandin receptors and Cytokines**

561 Prostaglandins (PG) are known to initiate labour and enable contractions via cervical
562 ripening, membrane rupture and uterine contractility. Phospholipase A2 releases
563 arachidonic acid, which is converted into PGH₂ by cyclooxygenase 1 and 2 (Simmons, 2004).
564 PGH₂ can be converted into the four main PGs: PGE₂, PGF_{2 α} , PGD₂ and prostacyclin (PGI₂)
565 (Sykes et al., 2014), of which PGE₂ and PGF_{2 α} are known to be potent inducers of uterine
566 contractility in spontaneous labour (Crankshaw and Dyal, 1994). Inflammatory cytokines
567 have long been recognised to drive PG synthesis in human myometrial cells (Hertelendy M et
568 al., 1993, Molnár, Romero, and Hertelendy, 1993, Pollard and Mitchell, 1996) via the
569 activation of NF κ B and MAPK, p38 (Belt et al., 1999, Bartlett, Sawdy, and Mann, 1999). PGs
570 are recognised to be pro-inflammatory and contribute to inflammatory conditions
571 throughout the body such as in asthma (Claar, Hartert, and Peebles, 2014) and cancer (Rose,
572 Gracheck, and Vona-Davis, 2015). PGs can act as cytokine amplifiers and in particular
573 increase activity of IL-1 β (Aoki and Narumiya, 2012), which as mentioned plays a
574 substantial role in initiating labour and contractility. PGs contribute to the physiological
575 inflammatory reaction seen in labour; for example PGE₂ enhances migration of leukocytes
576 towards the cervix, which in turn leads to an increased production of IL-8 (Hertelendy and
577 Zakár, 2004). PGF_{2 α} indirectly can activate IL-1 β in the decidua and consequently increase
578 production of MMP-9 (Christiaens et al., 2008) which is known to participate in breakdown
579 of the extracellular matrix leading to ruptured fetal membranes (Vadillo-Ortega and Estrada-
580 Gutiérrez, 2005). Additionally, PGE₂ interacts with LPS to induce IL-6, COX-2 and IL-1 β via EP₄
581 on macrophages (Aoki and Narumiya, 2012) indicating PGs' role in infection associated
582 preterm labour.

583 **Connexin 43 and Cytokines**

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

591 Cx43 gap junctions are scarce in the myometrium of the non-pregnant uterus but increase in
592 size and abundance with parturition in both humans and animals (Chow and Lye, 1994,
593 Orsino, 1996). Doring *et al* has shown in a mouse model that ablation of Cx43 delays
594 parturition. This was shown both *in vitro* and *in vivo* (Doring, 2006). Cx43 is impacted by
595 inflammation. In an *in vitro* model, monocytes in presence of TNF- α and IFN- γ increased
596 protein and mRNA levels of Cx43 (Eugenin et al., 2003). This would increase the contractility

597 potential of the myometrium. It is also raised in response to LPS (Chang et al., 2012) and is
598 raised in association with preterm labour (Balducci et al., 1993).

599 $PGF_{2\alpha}$ has also been shown to increase Cx43 and *PTGS2* expression in myocytes, the effect
600 of which is enhanced by $IL1\beta$ (Xu et al., 2013).

601 In summary, the three CAPs have been shown to be stimulated by cytokines, in particular $IL-$
602 1β , but as noted with OT, exposure duration may have variable effect on the CAPs (this has
603 not been studied with regards to PG and Cx43). Interactions between CAPS and
604 cytokine/chemokines draw a variety of immune cells, however the particular role of these
605 cells are unclear, as they may be acting in an immunomodulatory capacity as opposed to the
606 presumed inflammatory role.

607 **Future research**

608 Labour at term is clearly associated with inflammation. Inappropriate initiators of this
609 inflammation seem to trigger PTL as described above. It is evident from this review that
610 there is a multitude of factors that enable and promote the myometrium to contract (Figure
611 2 and 4). In fact there is a growing body of evidence to suggest that the beginning of labour
612 may be initiated in other gestational tissues before the myometrium is involved.

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

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

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

Figure 1 – Leukocytes infiltrating the myometrium during parturition. From Thomson A *et al.*, 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.

Figure 2 - The effect of physiology (including stretch, surfactant protein-A and Corticotropin-releasing hormone) on cytokines and myometrial contractility

Figure 3 - Pathology and hormones that promote myometrial contractility (adapted from Romero R *et al.*, Preterm Labour, one syndrome, many causes. *Science*, Aug 2014)

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

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

Cytokine/Chemokine	Role in myometrium	Evidence
IL-1β	<ul style="list-style-type: none"> • 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 <i>COX-2</i> 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Chemotactic and pro-inflammatory cytokine • Source – macrophages, endothelial cells • IL-8 is chemotactic to neutrophils • Increased in myometrium in term labour compared to preterm labour; may work by increasing PGE₂ • Progesterone and dexamethasone have been shown in vitro to inhibit IL-8 	Baggiolini , Loetscher , and Moser, 1995, Keelan et al., 2003, Terzidou et al., 2006.
TNF-α	<ul style="list-style-type: none"> • 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 and Naismith, 2000.
CCL2	<ul style="list-style-type: none"> • 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 	Shynlova et al., 2008.

	recruitment of monocytes to myometrium <ul style="list-style-type: none">• Mechanical stretch of the myometrium increases expression of CCL2	
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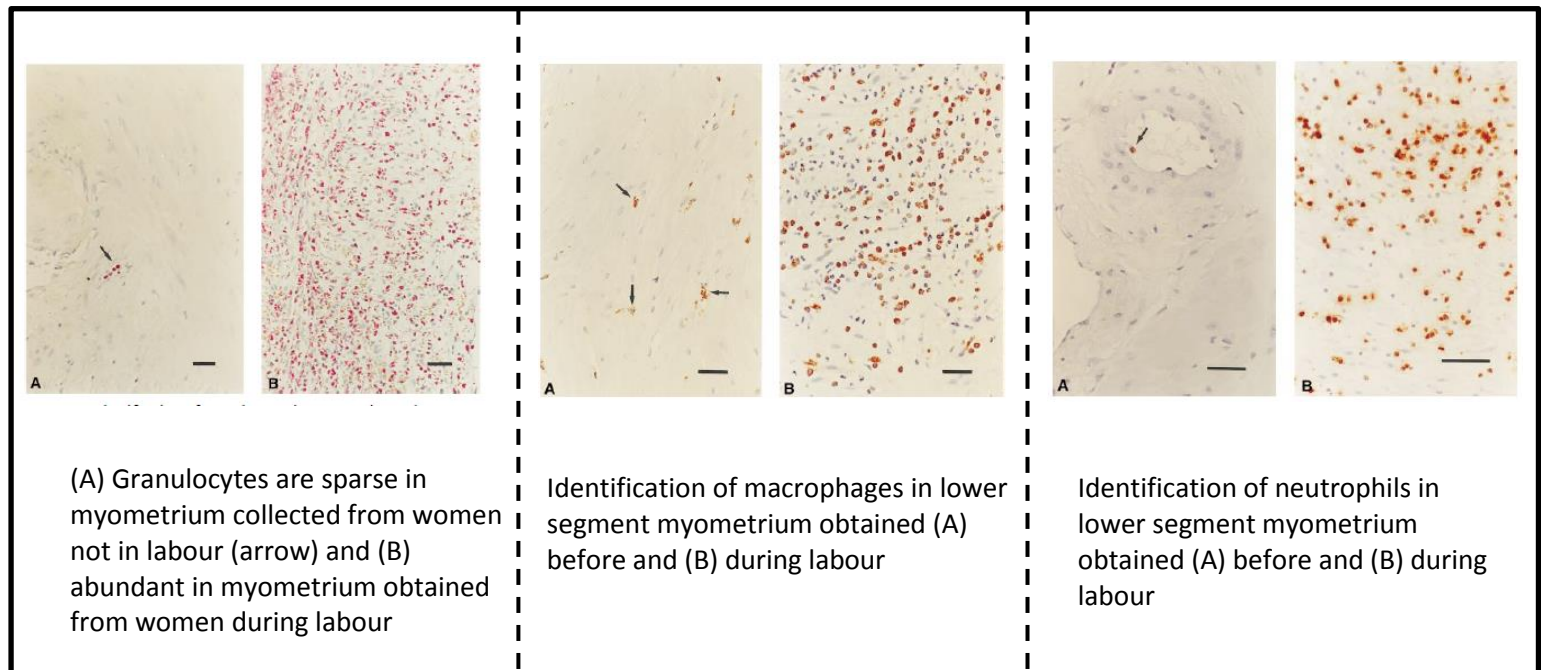


Figure 1 – Leukocytes infiltrating the myometrium during parturition. (Thomson A et al, Human Reproduction, 1999)

