Prostaglandins and Cytokines in Pregnancy and Labor

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Summary: Prostaglandins and cytokine networks play an important role in a wide range of reproductive and pregnancy related processes. Both of these two classes of mediators influence a range of uterine functions during the menstrual cycle, implantation, pregnancy and labor. The synergistic interactions between individual cytokines are intricate and vibrant. They are modulated by pregnancy hormones. It is not surprising therefore, that perturbations in prostaglandins and cytokines signaling are associated with adverse pregnancy outcomes, such as miscarriage, pre-eclampsia, preterm labor and fetal brain injury. Further insights in to the complexity of prostaglandins and cytokine networks will be required to develop novel therapeutic strategies for the treatment of prostaglandins and cytokines imbalances in pregnancy. We have focused on changes in cytokines expression and actions as evidence of parturition as an inflammatory reaction. The evidence from the literature suggests that parturition can be regarded as a process in which specialized forms of inflammation are fundamental to a successful outcome.

Introduction

Prostaglandins are believed to be important factors in various physiologic processes that accompany pregnancy and labor [1, 2]. After the onset of labor and throughout active labor, concentrations of prostaglandins in amniotic fluid and maternal plasma are elevated compared with the levels of these substances before labor commences [1]. It is widely believed that prostaglandins produced by intrauterine tissues act directly in the myometrium to initiate labor [1, 3, 4]. In particular, the biosynthesis of prostaglandins by fetal membranes is thought to serve an important role in the molecular events of human parturition [5]. However, the basic mechanisms that control the rate of production of prostaglandins during pregnancy and parturition are not fully defined (4). It has been suggested that intrauterine prostaglandin synthesis during pregnancy may be tonically suppressed [6, 7]. An endogenous inhibitor of prostaglandin synthesis (EIPS) previously found in plasma and serum of several species may be present in human amniotic fluid [8]. An endogenous inhibitor of prostaglandin biosynthesis in amniotic fluid could constitute a local mechanism for regulating prostaglandin synthesis by fetal membranes during pregnancy and parturition. More recently our research group has identified the role of lipoproteins as endogenous inhibitors of platelet aggregation in hypercholesterolemia induced animal model [9].

Placental Cytokines

The placenta and its associated membranes produce a wide variety of cytokines throughout normal gestation which play an important role in reproductive biology [10]. Production of cytokines and cytokine distribution within the tissues of pregnancy varies with gestational age and likely effects specific functions within these tissues. Indeed, it is realized that within the placenta, as in other organs, cytokines often have pleiotropic functions and perform homeostatic or regulatory roles independent of their more widely-recognized immune-related function. Cytokines are produced by the resident cells of normal healthy placental tissues, as well as by infiltrating leukocytes. The realization that non-immune tissues have the ability to express and secrete cytokines was an important advance in the context of understanding inflammatory mechanisms of parturition. Cytokine receptors are expressed in placental tissues, indicating that they are both sources and targets of these important biological mediators [2].

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Inflammatory Cytokines

Inflammatory cytokines and extracellular matrix remodeling enzymes are involved in the initiation of labor [11]. Pregnancy has been considered to be a time relative immune response [2].

In the first trimester of pregnancy, mRNA for Tumor necrosis factor-alpha (TNF-α), Interleukin-1 alpha (IL-1α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Macrophage migration inhibitory factor (MIF) have been found in placenta/trophoblast and decidua. Placental trophoblasts are major producers of the inflammatory cytokines [12], however, inflammatory cytokines are also secreted by macrophages (Hofbauer cells) and stromal cells in the placenta. In first-trimester decidua, mRNA and protein for IL-1α IL-1β, IL-6, and TNF-α have been localized to cells of immune origin, but are also produced by other decidual cell types. Immunodetectable MIF has also been identified in first-trimester deciduas.

At term, mRNA for TNF-α, IL-1α, IL-1β, IL-6 have been identified in placenta/trophoblast and deciduas and these cytokines are produced and secreted by both tissue types (Table-1) [13]. In the fetal membranes it has been reported that the chorion contains mRNA for TNF-α, IL-1β, IL-6 but expresses protein for only IL-1β and IL-6, while amnion express all three proteins [13]. IL-1β is produced by both trophoblasts and placental macrophages [14]. Trophoblasts also release IL-1α and IL-1β which have been detected during the first trimester and at term, declining over the course of gestation [15]. IL-6 staining intensity and production rates in the placenta are increased at term compared to early pregnancy [16]. IL-6 is the only villous placental cytokine whose production has been shown to be up regulated with the onset of labor [15, 16].

Array studies of cytokine gene expression in extra-placental membranes have identified a significant number of cytokines and chemokines that are up regulated at term following spontaneous labor and vaginal delivery [17] (Table-2). There was reasonable agreement and consistency in this study between gene expression changes in amnion compared to choriodecidua. These expression data support measurements of IL-1β, IL-6 and IL-8 by ELISA in the same set of tissue samples, showing increased abundance of these proteins in the

Table-1: Cytokines produced by human gestational tissues during normal pregnancy [21].

Cytokines	Placenta	Decidua	Fetal membranes
Inflammatory Cytokines			
IL-1 α/β	Throughout gestation, localized to trophoblast and Hofbauer cells	Throughout gestation	Term, amnion and chorion
IL-6	Throughout gestation, localized to trophoblast and Hofbauer cells	Throughout gestation (choriodecidua included)	1st trimester & term amnion and chorion
IL-12	3rd trimester	3rd trimester & term	3rd trimester & term
IL-16	Not assessed	3rd trimester & term	3rd trimester & term
IL-18	1st trimester trophoblast	1st and 3rd trimester	3rd trimester (chorion)
TNF-α/β	Throughout gestation, localised to trophoblast and Hofbauer cells	1st trimester and term, including leukocytes	Term, amnion and chorion
MIF	1st trimester, trophoblast	1st trimester & term	Term, amnion and chorion
PBEF	Throughout gestation	Throughout gestation	Throughout gestation, amnion and chorion
Anti-inflammatory Cytokines			
IL-4	Throughout gestation, placenta including trophoblast,	Throughout gestation, also associated with leukocytes	1st trimester & term amnion and chorion
IL-10	Throughout gestation, trophoblast and Hofbauer cells,	1st trimester and term	Term, chorion (including decidua)
IL-13	Throughout gestation (1st trimester mainly)	1st trimester (weak)	Not assessed
IL-1RA	Throughout gestation, including Hofbauer cells	1st trimester and term	Term, amnion and chorion
Other cytokines			
IL-11	1st trimester, chorionic villi	1st trimester, term	3rd trimester & term
Oncostatin M	Not assessed	3rd trimester & term	3rd trimester & term
TRAIL	Throughout gestation, troplast and stromal cells	3rd trimester & term	3rd trimester & term
TWEAK	Throughout gestation	3rd trimester & term	3rd trimester & term
G-CSF	Throughout gestation, mostly term	3rd trimester	Term labor
GM-CSF	Term	3rd trimester & term	3rd trimester & term

Table-2: Cytokines expressed in human gestational membranes in increased amounts with normal labor, as determined by cDNA array [21].

Tissue	Cytokines	Others
Amnion	Il-1α	G-CSF
	IL-6	LIF
	IL-11	ST2
	PBEF	
Choriodecidua	IL-1α	G-CSF
	IL-6	GM-CSF
	IL-11	LIF
	IL-12	Oncostatin M
	IL-16	ST2
	PBEF	Activin βA

membranes with labor [18]. Exposure to labor at term results in increases in IL-1α production by the placenta, amnion, choriodecidua and unseparated fetal membranes. Expression of IL-1β mRNA is also increased with labor in the amnion, chorion and isolated decidua [12] pregnancy is characterized by marked increase in serum cytokine profile with advance gestation.

Synthesis and release of IL-6 also appears to be increased by labor in gestational tissues although *in vitro* production by amnion explants [18, 19] and isolated decidual cultures is not increased. Term labor is reportedly associated with strong immunoreactive staining for both IL-1β and IL-6 in endothelial cells of the placenta [20]. These authors earlier reported an increase in IL-6 production by the placenta following the onset of spontaneous term labor [15] which they attributed to placental endothelial cell production. However, other studies have reported that exposure to labor does not increase IL-6 release from placental cultures or IL-1β and IL-6 tissue content [18] Messenger RNA for TNF-α is increased in amnion, chorion, and deciduas with labor at term, although release from decidual cell cultures is not affected by labor. Release of TNF-α from placental cultures, in contrast, is increased following exposure to term labor apparently originating from placental macrophages.

Many studies have measured cytokines in amniotic fluids, but only a few of these have identified changes in cytokine concentrations with onset of normal term labor. Amniotic fluid IL-1β, IL-6 and TNF-α concentrations are all reported to increase during labor. Concentrations of these cytokines in amniotic fluid appear to correlate with the amount of granulocyte infiltration observed in the placenta. Of those cytokines found to be present in increased amounts with term labor, most have been shown to be unregulated at the mRNA level in fetal membranes (Table-2), suggesting that these tissues are the major source of the cytokines found in amniotic fluid. Fetal leukocytes and tissues (such as the lung) may also be contributing sources.

TNF-α, IL-1α, and IL-8 can be detected in cervicovaginal fluids before labor in the third trimester of pregnancy, particularly in women with bacterial vaginosis or who deliver preterm with associated intraamniotic infection . Concentrations of inflammatory cytokines in cervicovaginal secretions increase during spontaneous term labor, peaking at the time of complete cervical dilation [3, 21].

Intra utrine infection induces an intra-amniotic inflammatory response, involving the activation of several cytokines to trigger preterm contraction, cervical ripping and rupture of membranes [21].

Anti-Inflammatory Cytokines

Anti-inflammatory cytokines suppress the inflammatory reactions [22].

Inflammatory activation can both be stimulated and resolved by cytokines, and several potent anti-inflammatory cytokines have been characterized and studied in the context of pregnancy and parturition. Indeed, it has been suggested that successful pregnancy requires a withdrawal of the effects of anti-inflammatory cytokines, as well as an augmentation of the effects of pro-inflammatory mediators.

Messenger RNA and protein for IL-4 and IL-10 have been located in placenta/trophoblast and deciduas throughout pregnancy. Reports of IL-10 production in the fetal membranes have been inconsistent. Because the level of the cytokines and prostaglandins varies as the pregnancy progress. IL-10 is thought to be a key cytokine for the maintenance of pregnancy [13]. The chorion appears to secrete small quantities of IL-10 at term, while amnion production is low or undetectable. Immunohistochemical results indicate that placental abundance of IL-4 and IL-10 decreases with increasing gestational age while decidual production of these cytokines increases [23]. In contrast to secretion of IL-10 by trophoblasts in culture was stable over gestation.

IL-10, IL-4 and IL-1RA have been detected in amniotic fluid collected at term. Increases in amniotic fluid concentrations of both IL-10 and IL-1RA have been observed between the second trimester and term. The exact concentrations of these interleukins is still not mentioned in the literature. Interestingly, amniotic fluid concentrations of IL-1RA in the amniotic fluid may derive from the amnion and chorion, which are reported to produce this cytokine at term IL-1RA is also produced by first-trimester trophoblasts, first trimester deciduas and term decidual cultures. IL-13 mRNA has been identified in placental trophoblasts from all stages of gestation, but IL-13 immunoreactivity has only been identified in first trimester placenta.

With term labor, there are no consistent reports of increased expression or production of anti-inflammatory cytokines, in marked contrast to the data on pro-inflammatory cytokines (Table-2). While exposure to labor has been reported to decrease secretion of IL-10 from choriodecidua, others have reported no change in amniotic fluid IL-10 levels or in decidual IL-10 production with labor. Amniotic fluid IL-4 concentrations are only rarely elevated following normal term labor. IL-1 receptor antagonist (IL-1RA) is present in extremely high concentrations in amniotic fluid from mid to late gestation, but there is no evidence of an increase associated with parturition. Decidual IL-1RA expression is similarly unaffected by labor as are cord blood levels. Only maternal plasma levels of IL-RA have been reported to be elevated with labor. IL-1 beta and TNF- alpha are inflammatory cytokines. TGF-β and the related molecule MIC-1 are present in amniotic fluid at term [24], but there are no changes in MIC-1 concentrations in amniotic fluid with parturition [25].

Prostaglandins and Cytokine

a) Regulation in Labor

Production of mRNA or protein for many cytokines has been shown to change during normal labor and parturition. These alterations may play a significant role in the processes that culminate in successful delivery. Concentrations of inflammatory cytokines in amniotic fluid, for example, increase towards term in normal pregnancies, and play a regulatory role in parturition by stimulating the local production of chemokines, prostaglandins and collagenases.

Fetal membranes are primary source of prostaglandins and proinflammatory cytokines in human parturition [18, 19]. Prostaglandins PGE_2 and $PGF_{2\alpha}$ are specifically enhanced in the uterine contractility, promote ripping of cervix and are involved in the initiation of labor [3].

b) Regulation of Myometrial Contractility

The uterine smooth muscle remains quiescent throughout pregnancy, primarily as a result of progesterone-induced suppression of contractile associated proteins (CAPs). Initiation of myometrial contractions requires conversion of the myometrium from a quiescent to an activated tissue. Changes in local concentrations of several uterotonins (*e. g.* prostaglandins) and their receptors have been implicated in this transition. Cytokines have been investigated for their role in modulating PG biosynthesis and receptor activity in the pregnant uterus. Most recently, the amnion-derived cytokine PBEF has been reported to be a direct activator of human myometrium *in vitro* [26]. Expression of this cytokine in the fetal membranes [27, 28] was identified as being up regulated with term and preterm labor, and able to increase local PG biosynthesis. The recent findings of direct action in the myometrium support claims that this cytokine may be of pivotal importance in human parturition.

Recent discoveries relating to the expression and activity of uterine progesterone receptors (PR) have identified a role of cytokines and inflammation in the withdrawal of progesterone-mediated uterine quiescence at term [29]. This exciting development expands the sphere of influence of inflammatory processes in parturition. The intracellular nexus for inflammatory signaling is the transcription factor NF-$_k$B. Many parturition-related genes have NF-$_k$B response elements in their promoters and their expression is up regulated by NF-$_k$B activation. Pro-inflammatory cytokines and so-called pathogen-associated molecular patterns (PAMPs) such as bacterial lipopolysaccharide (LSP) are potent activators of the NF-$_k$B signaling pathway. Inhibitors of NF-$_k$B can suppress inflammatory cytokine production by gestational tissues *in vitro* [30, 31]. In amnion, labor is associated with NF-$_k$B activation, which drives the expression of COX-2, the enzyme responsible for the increased prostaglandin production during labor [32]. PR activity is repressed by NF-$_k$B activation in this tissue [32]. There is also

evidence that PR expression is down regulated in responses to prostaglandins [33]. Similarly, in myometrium, term labor is associated with increased NF-$_k$B activity [34] and increased expression of PRA. PRA acts as a dominant negative, resulting in an increase in the PRA/PRB ratio [35, 36] effectively reducing activity at the site of the PR promoter. Further effects on PR activity appear to be mediated by changes in co activator expression [37], although the significance of inflammatory signaling in this phenomenon is unknown. Finally, Dong *et al.* [38] have shown an increase expression of a novel co repressor of PR action called PSF. Cytokines are known to increase the levels of expression of this protein in mammalian cells, and it is speculated that this could provide an additional mechanism linking inflammation with functional progesterone withdrawal [38].

Prostaglandin E_2 and $F_{2\alpha}$ are potent stimulators of myometrial contractility and have long been appreciated to be critical factors in the initiation of labor. Production of prostaglandins by cells from the amnion, chorion, deciduas and myometrium [39] is enhanced by the inflammatory cytokines IL-1 and TNF-α, probably through increased expression of prostaglandin H synthase-2 [40]. IL-6 has also been shown to stimulate prostaglandin production by the amnion and deciduas at high doses, while MIP-1α stimulates amnion and chorion cell prostaglandin production. The activation of the utrine contractile system by prostaglandin and oxytocin during the intra-amniotic infection may cause preterm delivery [6].

Prostaglandin concentrations can also be modulated through regulation of metabolic inactivation. The enzyme that catabolizes prostaglandins to inactive metabolites, 15-hydroxyprostaglandin dehydrogenase (PGDH), is abundant in the chorion, placental trophoblast, and (to a lesser extent) the deciduas. Its activity is believed to prevent prostaglandins in the amniotic fluid from acting upon the myometrium. PGDH expression and activity in gestational membranes and cultured chorionic trophoblast is decreased by IL-1β and TNF-α [41]. PGDH protein and activity in chorionic trophoblasts of the lower uterine segment has been shown to decrease with term labor, possibly contributing to the activation of the myometrium.

Cytokines can also act to decrease prostaglandin production by gestational tissues.TGF-β_1 decreases basal and cytokine-stimulated prostaglandin production from amnion and decidual cells, while IL-1RA and TGF-β_1 both suppress IL-1-induced PG production in the myometrium. IL-4 decreases prostaglandin production from decidual cells while increasing production of IL-1RA, and decreases inflammatory cytokine-stimulated prostaglandin production by placenta/trophoblast cultures, as does IL-10 [42]. However, both IL-4 and IL-10 have also been reported to stimulate the release of prostaglandins and inflammatory cytokines by some gestational tissues while IL-1RA has been found to increase prostaglandin production by decidual cells. This has led to the hypothesis that term labor is associated with a withdrawal or reversal of anti-inflammatory agents as part of an evolutionary adaptation to accelerate inflammatory processes necessary for successful labor and delivery.

c) Membrane Remodeling and Rupture

Rupture of the fetal membranes is an essential part of normal parturition. Cytokines may be involved in the initiation and progression of processes involved in rupture of the membranes at term and preterm, particularly when associated with intrauterine infection and chorioamnionitis. Morphological examination of the amnion suggests that the membrane does not undergo a widespread process of degeneration at term; rather; localized weakening of the membranes, with reduced cytotrophoblast and decidual thickness, may occur at a specific rupture point overlying the cervix [43].

Digestion of extracellular matrix of the fetal membranes occurs at term and is carried out largely by locally-produced matrix metalloproteinases (MMPs), activity of which is negatively regulated by a family of inhibitory proteins (The inhibitor of matrix metalo proteins, TIMPS). Changes in activity of plasminogen activator, MMPs and TIMPs in amniotic fluid and gestational tissues are associated with the onset of labor and rupture of the fetal membranes. Cytokines drive the increased levels of MMP expression and activity in the membranes associated with rupture. Intrauterine infection has been associated with higher MMP-9 concentrations in amniotic fluid, whether or not membrane rupture occurred. This increase in MMP-9 may reflect an increase in leukocyte colonization of the amniotic fluid. TNF-α, IL-1β, IL-6 and M-CSF have all been shown to increase MMP gelatinase secretion by first trimester trophoblast [44]. TNF-α stimulates

production of MMPs (-1 and -3) and plasminogen activator by chorion and decreases the production of TIMP, while IL-1α increases synthesis of MMP-1 cultured chorionic cells. Treatment of amniochorion explants with lipopolysaccharide, a stimulator of cytokine release, also results in an increase in synthesis and release of MMP-2 and a decrease in the synthesis and release of its tissue inhibitor [45]. Relaxin, a hormone well-known for its ability to remodel extracellular matrix and accelerate membrane rupture, has recently been shown to super-induce cytokine (IL-1β and IL-6) expression in fetal membranes [46]. Concentrations of IL-8, a chemoattractant for leukocytes, have been significantly correlated with those of MMP-9 in the amnion and chorion during the later stages of cervical dilation [35, 36]. IL-8 production in chorion and amnion is stimulated by IL-1β and TNF-α. Interestingly, both IL-8 production and collagenase activity in the fetal membranes are increased by mechanical stretching, pointing to an indirect mechanism of action for these cytokines in the remodeling of the extracellular matrix.

In addition to digestion of the extracellular matrix, there is some evidence that apoptosis contributes to weakening of the fetal membranes prior to rupture, particularly in the chorion layer at the site of rupture [47]. Apoptotic cell death may be a reaction to the destruction of extracellular matrix in the membranes or a significant and separate part of membrane thinning and rupture. TNF-α, in concert with IFNγ, induces trophoblast apoptosis. TNF-α and other family members such as TNF-related apoptosis inducing ligands, (TRAIL) [48] may thus be involved in the normal rupture of fetal membranes at term, through induction of apoptosis.

d) Cervical Ripening

Cervical competence is a key function in a normal and abnormal labor. The processes of cervical ripening are similar to those involved in induction of membrane rupture, including changes in extracellular matrix composition, invasion of neutrophils, and tissue remodeling by proteolytic enzymes. Cytokines, particularly IL-8, have been implicated in this process (Table-3). IL-8 synthesis and secretion is greatly increased in the cervix with labor and concentrations of IL-8 in the cervix and lower uterine segment increase with cervical ripening [49, 50]. The increase in IL-8 during cervical ripening correlates

Table-3: Cytokines measured in amniotic and cervicovaginal fluids in increased amount with term labor [21].

Fluid	Cytokines	Others
Amniotic	Il-1β	G-CSF
	IL-2	
	IL-6	
	TNF-α	
Cervicovaginal	IL-1α/β	G-CSF
	IL-6	
	TNF-α	

with increases in leukocyte infiltration and concentrations of Macrophage inflammatory proteins (MIPs) in the tissue. Concentrations of IL-1β, TNF-α and IL-6 in the lower uterine segment also increase with cervical dilation and have been shown to affect production of TIMPs and MMPs by human cervical fibroblasts and smooth muscle cells. Increase in IL-6, G-CSF and Membrane cofactor protein-1 (MCP-1), cytokines which affect proliferation and activation of immune cells, also occur with cervical ripening [50, 51].

While the majority of cytokines effects on cervical ripening are likely to be induced by locally produced cytokines, it is possible that cytokines secreted by the placenta and membranes may have an indirect effect. IL-1β has been shown to induce IL-8 secretion by human cervical fibroblasts *in vitro*, alone and in concert with TGF-β_1 and growth factors. PGE_2 secretion which is influenced by many cytokines, also stimulates IL-8 release from cervical tissue [51, 52], affects proteolytic enzyme activity [52-54] and induces cervical ripening as reviewed by Kelly *et al.* [55]. Hence cytokines, acting through release of PGE_2, chemokines and MMP activation, are potent drivers of cervical ripening. A complex interaction between cytokines and prostaglandin is the key biochemical pathway accounting for the preterm ripping of the cervix [14].

Leukocyte Infiltration and Activation in Parturition

Accumulating evidence indicates that human parturition is an inflammatory process [5]. In human deciduas, a significant increase of leukocytes has been observed with the onset of pregnancy [56]. The concept that leukocyte recruitment and activation is a key process in the mechanisms of parturition is now well established, particularly in the context of cervical ripening [reviewed by Yellon *et al.* [57]]. In the cervix neutrophil recruitment and activation occurs in response to chemoattractants such as IL-8

and, in combination with local release of pro-inflammatory cytokines, prostaglandins, and MMPs, plays a crucial role in cervical ripening. Leukocyte subpopulations (T cells, macrophages and neutrophils) increase markedly in the cervix in late pregnancy, with additional increases after labor onset. The factors responsible for the pre-labor initiation of cervical leukocytes are not known, but prostaglandins, cytokines and steroids (DHEA) are all possibilities that have been explored. Cervical leukocytes are accompanied by increased expression of cytokines in the cervix and myometrium [53]. Macrophages are also a significant source of prostaglandins and NO (in addition to cytokines and MMPs) both of which are promoters of cervical ripening. Parturition is composed of five separate events: fetal cervical dilatation, myometrial contractility, placental separation and uterine contraction. Prostaglandins have a central role in these specially in myometrium contraction. Elevated uterine prostaglandins (PGE_2 and $PGF_{2\alpha}$) lead to increased contraction and labor [1].

A recent study quantified infiltrating inflammatory cells in myometrium with onset of normal term labor. Leukocytosis was greatest in the lower uterus, suggesting a degree of regionality exists in this process (an appreciation of which has been lacking in many studies). Elevated expression of adhesion molecules has also been documented in the myometrium and cervix, while at least in part is likely to be a consequence of leukocytosis. Leukocytes in filtrate the myometrium, Extensive leukocyte infiltration was recently documented after ruptured fetal membranes, with minimal changes detectable before parturition [54]. Leukocytosis in myometrium is associated with the progression and squeal of labor than its initiation. Labor at term and preterm results from activation and the stimulation of myometrium [4].

Within the membranes, although extensive leukocyte infiltration is commonly seen in pregnancies with intra-amniotic infection (*i.e.* chorioamnionitis), in normal pregnancies inflammatory cells in the gestational membranes are relatively rare prior to labor. Modest infiltration of the deciduas is relatively common after onset of labor, correlating with cervical dilatation [55]. The fetal membranes, on the other hand, show minimal infiltration either before or after labor. However, the importance of regionality should not be underestimated, particularly in light of the literature findings there is marked histological and structural changes in the region of membranes over lying the cervical of the so-called "zone of altered morphology" (ZAM). The interrelationship between leukocytosis, inflammatory activation, and the formation of the ZAM has not yet been clarified, although the finding of a recently presented paper did not support the concept of a region specific increase in leukocyte infiltration or cytokine expression in association with term labor [58].

Is parturition an inflammatory reaction or process? We can summarise with some studies of key investigators. Studies by Wang *et al.* [59] have demonstrated elegantly that inflammatory reactions occur within the gestational tissues and fetus with parturition. Other studies from Osman and colleagues [53] have described findings consistent with this viewpoint and have extended their data sets to include myometrium [52, 54, 60]. Previous data support the view that cervical ripening has elements in common with an inflammatory reaction [52, 61]. Although we have focused on the changes occurring in cytokines expression and actions as evidence of parturition as an inflammatory reaction [61], there are also data form changes in expression and actions of many other mediators (*e.g.* nitric oxide, MMPs, *etc.*) [62, 63] to support this view. Hence, the evidences from the scientific literature reviewed suggest that parturition can be regarded as a process in which specialized forms of inflammation are fundamental to a successful outcome [3].

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