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Review article

Intrauterine inflammatory activation, functional progesterone withdrawal, and the timing of term and preterm birth

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ABSTRACT

The central role of inflammatory processes in labour and delivery is now well-recognised. However, the biomolecular, immunological and endocrine mechanisms involved in the labour process, and the clinical manifestations of inflammation in pregnancy, are complex, variable and modulated by factors such as aetiology, ethnicity and gestational age. In this review, evidence is presented of the pivotal relationship between progesterone and inflammation in pregnancy in terms of determining the timing of labour and delivery. The maternal inflammatory burden increases with advancing gestational age in response to endocrine, maturational, physical, metabolic and biochemical drivers, leading to functional progesterone withdrawal necessary for labour and delivery. Variability in the nature, timing and magnitude of these drivers influence the timing of delivery and the likelihood of preterm birth. Pathological inflammatory insults in pregnancy, such as infection, oxidative stress, senescence and maternal allograft rejection, can precipitate preterm birth, often involving common signalling pathways. Intrauterine infection is an important cause of early preterm birth, associated with delivery of the infants at greatest risk of death and disability; however, most preterm deliveries with intrauterine inflammatory activation are not infection-associated. This observation has important diagnostic and therapeutic implications and challenges. The key differences and similarities between infection-associated and sterile inflammation in this context are highlighted, and the clinical implications and significance of these processes and how they might be exploited are discussed.

1. Introduction

Inflammatory processes play key physiological roles in ovulation, implantation, decidualization, placentation and parturition, as well as having effects on maternal and placental health and fetal growth & development (Weiss et al., 2009; Dekel et al., 2014; Kalagiri et al., 2016, Nadeau-Vallee et al., 2016; Sheldon et al., 2016). The details of many of the underlying biomolecular pathways through which inflammation is linked to these processes, and the nature of the factors that trigger and control innate immune activation and the inflammatory cascade in maternal, placental and fetal tissues, have, to a significant extent, been elucidated – although of course there is more to learn. The underlying systems involved, and the clinical manifestations and consequences of inflammation, are highly complex, variable across individuals and species, and often obscured by differences in study design, choice of model and data interpretation.

In this article I provide an overview of what is known about the role of inflammation in term and preterm parturition from the perspective of physiology, pathophysiology and clinical and therapeutic significance. I offer an integrated perspective that views the timing of parturition as a balance between the maternal "inflammatory burden" and progesterone-mediated quiescence. Particular focus is applied to the roles and significance of sterile *vs.* infection-related inflammation, as this is an area of some controversy and clinical complexity.

1.1. Inflammation in the context of parturition: a misnomer?

The classical hallmarks of inflammation are pain, heat, redness, swelling and loss of function. While the reproductive literature is replete with studies of "inflammation", the processes which characterise parturition-associated inflammation do not readily fall within the classic definition. Here, I will use the term "inflammatory activation" to describe the general elaboration and activation of inflammatory cells, pro-inflammatory mediators and signalling cascades, which are central to the parturition process.

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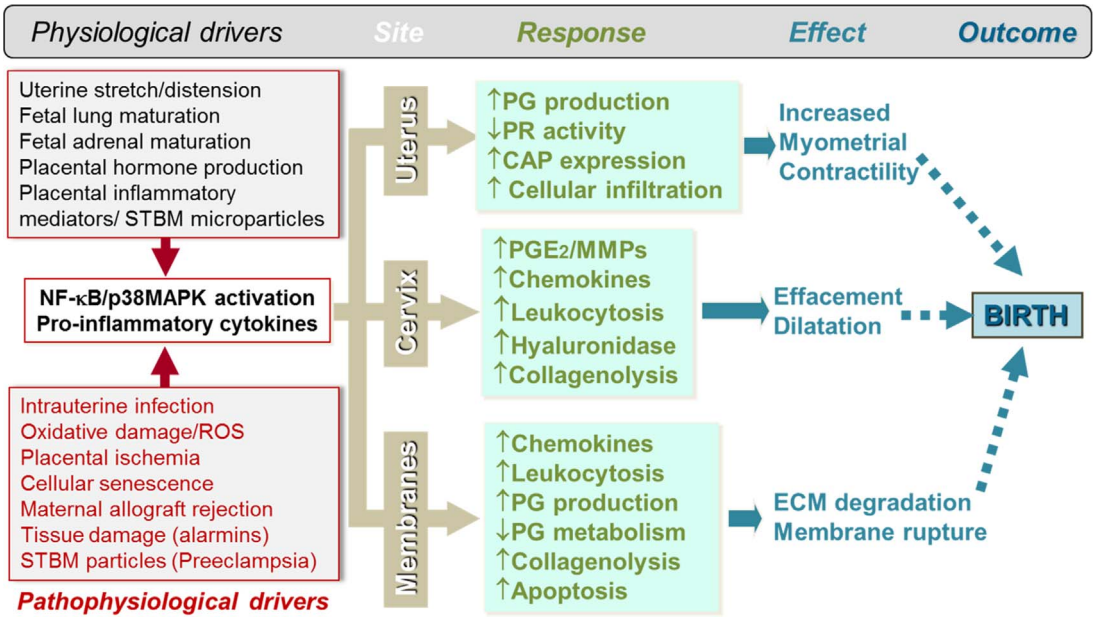

Fig. 1. Biomolecular mechanisms linking inflammation with parturition. Inflammatory activation plays key roles in all three major tissue sites necessary for coordinated labour and delivery. The drivers of inflammation include both physiological/maturational factors and pathophysiological drivers. Pre-labour changes (phase I) in the uterus commence around 37 weeks' of gestation, while in the fetal membranes and cervix changes commence as early as 25 weeks. Abbreviations: CAP, contractile-associated proteins; MMP, matrix metalloprotease; PG, prostaglandins; PGE2, prostaglandin E_2; PR, progesterone receptor; ROS, reactive oxygen species; STBM, syncytiotrophoblast membrane.

1.2. The roles of inflammatory activation in the mechanism of parturition

Various aspects of this topic have been thoroughly covered in many excellent articles and reviews, so a broad overview will be covered here to provide perspective for later sections (Challis et al., 2001; Norman et al., 2007; Romero et al., 2007a; Romero et al., 2007b; Kemp 2014, Romero et al., 2014a; Kalagiri et al., 2016).

Activation of inflammatory gene expression in the myometrium, fetal membranes and cervix plays a central role in triggering onset of contractions, membrane rupture and cervical effacement and dilatation (Challis et al., 2001; Norman et al., 2007; Romero et al., 2007b; Kemp 2014; Romero et al., 2014a). The process, summarised in Fig. 1, can begin several weeks prior to any physiological/anatomical changes becoming evident and months prior to term delivery. In response to physiological and maturational queues, inflammatory cells are recruited into the tissues and become activated, releasing proteases, chemoattractants, cytokines and uterotonins (e.g. oxytocin and prostaglandins [PGs]). The inflammatory mediators stimulate additional local expression of chemokines, cytokines/proteases and PG synthases, initiating changes in structure, apoptosis and cellular content (Fig. 1) (Norman et al., 2007; Romero et al., 2007b; Romero et al., 2014a; Kim et al., 2015a; Kim et al., 2015b; Kalagiri et al., 2016). Increases in accumulation of selected cytokines, prostanoids, metalloproteases and other proinflammatory mediators (e.g. IL-1β, TNF-α, IL-6, IL-8, PGE_2, $PGF_{2\alpha}$, MMP8) are detectable in the amniotic fluid (AF) with advancing gestational age and, more particularly, after onset of labour (Keelan et al., 2003; Romero et al., 2006; Christiaens et al., 2008; Vrachnis et al., 2012a). As discussed in detail below, progesterone exerts significant anti-inflammatory effects in pregnancy, maintaining uterine quiescence and cervical competence.

Not all cytokines are proinflammatory, however, and several so-called anti-inflammatory cytokines – namely IL-4, IL-10 and TGF-β – have been studied in the context of the inflammation-labour process (Gotsch et al., 2008). The most interesting and important of these is IL-10. IL-10 exerts classic inhibitory actions in the choriodecidua and placenta, suppressing pro-inflammatory cytokine and PTGS-2 expression (Pomini et al., 1999; Sato et al., 2003). There is some evidence, however, that it may exert atypical pro-inflammatory effects on amniotic epithelial cells (Mitchell et al., 2004). In addition, levels of IL-10 production by the choriodecidual membranes decreases with onset of labour (Simpson et al., 1998), leading to the suggestion that IL-10 may play both active and permissive roles in parturition, depending on the tissue concerned. IL-10 production by fetal membranes is stimulated by bacterial products (Sato et al., 2003; Zaga-Clavellina et al., 2007), and IL-10 levels in amniotic fluid are elevated with intraamniotic inflammation (Gotsch et al., 2008), the presence of bacteria in the amniotic cavity (Kacerovsky et al., 2013; Revello et al., 2016) and are predictive of risk of preterm birth (Tsiartas et al., 2012). These findings add some support to the hypothesis that IL-10 is part of a pro-labour inflammatory response. However, it should be noted that expression of the IL-10 gene in different cells and tissues is driven by intracellular signalling pathways (e.g. MyD88, STAT3, p38MAPK, CREB) that are ubiquitously activated by inflammatory stimuli (Gabrysova et al., 2014), so its presence in normal and preterm labour may simply be a reflection of local inflammatory activation, not a contributor or even a regulator.

In the myometrium, expression of contractile-associated proteins (CAPs) such as connexin 43 (Cx43), the oxytocin receptor (OTR) and prostaglandin H synthase-2 (PTGS2) increases prior to term labour, released from progesterone-mediated transcriptional repression (see below)(Smith, 2007; Mendelson 2009; Shynlova et al., 2009). This, combined with increasing levels of cytokines and ligands for pro-contractile receptors derived from the myometrium and extraplacental membranes (decidua, chorion and amnion), promote the conversion of the uterus from a quiescent organ to a contractile muscle, facilitating the propagation of regular, synchronous contractions (Fig. 1) (Smith, 2007; Mendelson, 2009; Shynlova et al., 2009). Although myometrial infiltration by inflammatory cells during labour is extensive (Thomson et al., 1999), infiltration pre-labour is only occasionally seen in normal pregnancies, unless inflammation in the decidua (deciduitis) is also present (Keski-Nisula et al., 2003).

Studies in mice suggest that TLR4, the principal receptor for Gram negative bacterial endotoxin (lipopolysaccharide, LPS) and a sensor of several other inflammatory mediators (see later), is pivotal in driving inflammation-associated changes in CAP expression in the myometrium in normal labour – even in the absence of bacteria (Wahid et al., 2015;