Pathophysiological mechanisms of maternal pro-inflammatory mediators in preterm labour

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Abstract

Available therapeutic interventions for managing preterm labour have not been consistently successful due to controversies related to its aetiology. However, multiple mechanisms including inflammation play a significant role in the pathogenesis of preterm labour. The extracellular matrix of the amniochorion contains collagen fibres that maintain the tensile strength of the amniochorion, resisting mechanical stress and preventing rejection of the foetal allograft. Expression of pro-inflammatory mediators in the amniochorion triggers production of prostaglandins in the uterus and enzymatic degradation of the resilient extracellular matrix of the foetal membranes by matrix metalloproteinases leading to uterine contractions, cervical remodelling resulting in preterm labour.

Introduction

Preterm labour is defined as the spontaneous onset of regular and painful uterine contractions resulting in the dilatation of the cervix or cervical effacement prior to 37 weeks of gestation(1,2). Preterm labour may result in preterm birth which is generally classified based on the gestational age at birth as: extremely preterm (before 28 weeks), very preterm (between 28 and 32 weeks) and moderately preterm (after 32 weeks and before 37 weeks)(3,4). The moderate preterm birth can further be described as late preterm if the onset of it occurs between 34 and 37 weeks of gestation(3,4). Etiologically, preterm birth can either be spontaneous (natural onset of labour or preterm premature rupture of membranes) or provider-initiated (medically induced labour or caesarean delivery) depending on the clinical presentation(5–7).

The global incidence of preterm birth is 12% which is equivalent to approximately 15 million babies born preterm each year(8,9). The incidence ranges from 5% among the European countries to nearly 20% in some African countries(9–11). As the principal cause of increased morbidities and mortalities among children less than five years old, prematurity has become a major public health concern(9,12) and compromises the emotional and psychological states of many families with preterm infants born to them. This is attributable to the accelerated economic burdens exerted due to increased cost of health care and learning demands(5,10,11,13). Evidence has shown that infants who are born at the extremes of gestational age are at increased risk of severe longstanding health complications (11,13–15). The consequences of preterm birth are common during the neonatal period and may persist into adulthood. Studies have also shown that male infants born preterm have poorer prognosis and are at increased risk of health complications compared to their female counterparts(11,16,17).

The actual aetiology of preterm labour is not known, although multiple mechanisms have been propounded in the pathogenesis of preterm labour. For instance, intrauterine infections, inflammation, mechanical stress or over distension of the uterus, intrauterine growth restriction (IUGR) and uteroplacental hypoxia or haemorrhage are said to trigger the onset of preterm labour (5,11,15,18). Additionally, maternal race (black women, African-American or Afro-Caribbean) or ethnicity, younger maternal age, advanced maternal age

(>35 years), cigarette smoking, low maternal weight, obesity, multiple pregnancy, use of assisted reproductive techniques, maternal history of preterm birth and the marginalised may also contribute to the onset of preterm labour(11,19). Regardless of the predisposition, maternal pro-inflammatory mediators play a central role in the initiation of preterm labour.

Clinical management of preterm labour is extremely challenging with poor outcomes especially when uterine contractions are established with progressive cervical changes. The well-known unpredictability of the clinical course of preterm labour results from the unresolved pathophysiology of the condition. The major hypothesized pathophysiological mechanisms of preterm labour include inflammation resulting from multiple aetiological pathways. Improved understanding of the mechanistic role of pro-inflammatory mediators in preterm labour is critical in evidence-based clinical management especially inflammation associated with chorioamnionitis and urinary tract infections(8). The aim of this review was to appraise the pathophysiological mechanism of pro-inflammatory mediators in spontaneous preterm labour and their associations with multi-factorial etiological pathways. The paper also recognises the discusses the pathophysiology of uterine contractions and the phases of uterine smooth muscle activity in the non-pregnant state, during pregnancy and parturition. In this paper, essential physiological pathways and the biological basis of available therapeutic agents for preterm labour are explored.

Probable causes of preterm labour

The role of genetics in the pathogenesis of preterm labour has been duly recognised and well documented. Emerging evidence indicates that preterm birth appears to be transmitted primarily in a matrilineal manner across generations and is greatly influenced by mutual environmental factors. Thus, the risk of a woman having a preterm delivery is heightened if her maternal biological relations had preterm deliveries but appears not to follow paternal lines(20,21). In human genomic studies, changes in single gene sequence were found to be associated with disorders such as polyhydraminos, myotonic dystrophy, cervical incompetence(10,21,22) and twin gestation which increase the risk of preterm labour and may be transmitted from one generation to the next(23,24). These observed single nucleotide polymorphisms in the gene can respond to inflammatory stimuli such as infection resulting in the production of pro-inflammatory mediators and breakdown of extracellular matrix by matrix metalloproteinases leading to preterm labour (figure 1) (23). Also because of the genotypic variations among different individuals, exposure to environmental pollutants put them at increased risk of preterm labour(10,22).

Evidence has shown that maternal psychological stress, anxiety, financial difficulties and other life events increase endogenous catecholamines and cortisol release which stimulate premature production of placental corticotrophin-releasing hormone (CRH) thereby activating the biological cascade leading to the onset of preterm labour(24). Psychological stress also increases maternal vulnerability to infection and inflammation due to weakened immune system (figure 1) (24). Behavioural factors such as smoking and alcohol use are associated with increased risk of preterm labour. Given that smoking and alcohol have teratogenic effects and habitual engagement in these agents during pregnancy puts them at high risk of sudden infant death syndrome (SIDS) due to variability in autonomic nervous system function(25–27). The Nicotine and carbon monoxide contained in smoke cause foetal hypoxia due to carboxyhaemoglobin and vasoconstriction(27). They increase the risk of low birth weight, foetal defects and placental complications and compromise immune response to inflammation leading to preterm premature rupture of membranes and preterm labour (figure 1) (24,25,27). Consumption of alcohol during pregnancy has also proven to have detrimental effect on foetal growth and development leading to intrauterine growth restriction (IUGR) which poses a potential risk for preterm labour (figure 1) (24,28).

Furthermore, pervasive indulgence in illegal drugs such as marijuana and cocaine as well as the use of herbal medications in pregnancy have severe embryotoxic and teratogenic effects increasing the risk of small-for gestational age and foetal defects(29,30). Marijuana smoking also increases the risk of carboxyhaemoglobin leading to foetal hypoxia. On the other hand, cocaine causes elevated blood pressure due to vasoconstriction since these psychoactive agents appear to interfere with the reuptake of serotonin and catecholamines leading to compromised immune response to inflammation (figure 1) (24,29).

Nutritional deficiencies (e.g. deficiencies in iron, folate or zinc, low pre-pregnancy weight) have been implicated in preterm labour. For instance, deficiency in iron causes iron deficiency anaemia which increases the synthesis and hypersensitivity to endogenous catecholamines leading to maternal and foetal hypoxia which in-turn stimulates synthesis of foetal CRH and cortisol. The increased cortisol production may activate the biological cascade leading to preterm premature rupture of membranes, gestational hypertension, eclampsia IUGR and preterm labour (24,31,32). In another pathway, iron deficiency anaemia increases risk of infection and inflammation leading to preterm birth (figure 1) (31,32). Physiologically, vitamin C stimulates the synthesis of collagen fibres of connective tissue extracellular matrix of the amnionchorion and deficiency in vitamin C depletes collagens leading to preterm premature rupture of membranes and preterm labour(figure 1) (24,33,34). Similarly, folate, zinc and pre-pregnancy weight deficiencies increase the risk of restricted foetal growth and birth defects(figure 1) (24,35). To buttress the importance of specific nutrients, adequate maternal levels of fat-soluble nutrients provide antioxidative, anti-inflammatory, and immunomodulatory health benefits which are vital in preterm birth prevention. For instance, omega-3 fatty acids facilitate increased production of specialized anti-inflammatory mediators with resultant reduction in preterm birth risk (figure 1). Combined effects of these nutrients support appropriate placental organogenesis and function(36).

Uterine smooth muscle activity in the non-pregnant state

The uterus acts as a temporal receptacle which nurtures and nourishes the implanted blastocyst while thwarting early expulsion of the product of conception throughout pregnancy. It is a contractile smooth muscular organ made up of fibrous connective tissue (37) that exhibits spontaneous and rhythmic contraction and relaxation before, during and after pregnancy(38,39). The non-pregnant uterus is not totally a quiescent organ and exhibit intrinsic contractile properties. However, contractions in the non-pregnant uterus vary physiologically from the uterine contractile activities during pregnancy(40). Accordingly, both non-invasive intrauterine pressure (IUP) and invasive ultrasound (US) scan recordings have demonstrated that the non-pregnant uterus undergoes patterns of phasic wave-like contractions throughout the menstrual cycle(39,41–45) which are governed by ovarian steroid hormones (i.e. oestrogen and progesterone)(38). Within the subendometrial layer of the myometrium, cyclic patterns of oestrogen and progesterone receptors are expressed which modulate the activity of the non-pregnant uterus(38,44). These wave-like contractile patterns of the non-pregnant human uterus vary depending on the phase of the menstrual cycle(figure 2) (42,44). The rhythmic uterine contractions in the non-pregnant uterus favours sperm transport and oocyte migration in the fallopian tubes, fertilization and embryonic transport from the tubes into the uterine cavity to facilitate embryonic nidation and implantation to occur(39,41,42,44). Disruptions in this physiological uterine smooth muscle property are associated with disorders such as dysmenorrhoea, spontaneous and recurrent abortions, endometriosis, implantation failures and infertility(42,44).

During menstruation or early follicular phase, the uterus exhibits primarily antegrade (from fundus to cervix) labour-like and expulsive contractions (figure 2) involving all layers of the myometrium to evacuate the content of the uterus (menses). Uterine contractions during menstruation are often felt and can be associated with blunt pain (dysmenorrhoea) requiring medications if contractions are vigorous(44,45). This period of luteofollicular changeover is largely under the influence of progesterone depletion due to spontaneous degeneration of the corpus luteum and increased gene expression for prostaglandins by uterine tissues (figure 2) (39,45). In both mid and late follicular phase of the menstrual cycle, only the subendometrial layer exhibits a progressive increased in wave-like uterine contraction patterns which are retrograde (from cervix to fundus) (figure 2). This retrograde uterine contractions, often not perceived by the woman, coupled with proliferation of endometrial glands which aid the transport of sperm towards the distal end of the fallopian tubes where fertilization takes place and normally terminates at the pre-ovulatory period(41,42,44–46). These wave-like contractions and glandular proliferation during the follicular phase are controlled by increased oestrogen (E2) levels (figure 2) (41,42,44,46) indicative of oestrogen predominance in the proliferative phase of the uterine cycle.

The post-ovulation period is characterized by progressive uterine quiescence facilitated by significant rise in progesterone levels following the successful development of the corpus luteum from the ruptured ovarian follicle which terminates at the middle of the luteal phase (figure 2). This luteinisation associated uterine quiescence promotes successful establishment of pregnancy characterised by embryonic transfer from the fallopian tube into the endometruim depending on the biochemical readiness of the endometruim for implantation of the embryo and placentation(39,41,42,46). Following implantation, the uterus is transitioned from a non-pregnant state to a pregnant milieu (figure 2) which allows the developing blastocyst to differentiate into the foetal membranes comprising rich in connective tissues in both the amnion and the chorion(47). The connective tissue extracellular matrix of the amniochorion contains collagen fibres that maintain the tensile strength of the amniochorion; resisting mechanical stress and prevents rejection of the foetal allograft. Specific collagen fibres of the fibrous connective tissue within the amniotic compact layer provide the tensile strength while collagen fibres of both reticular and spongy layers of the chorion provide mechanical support(47). The major types of collagen fibres include: type I, II, III, IV, V and VI collagens which are embedded in the fibrous tissue(47).

Typically, the inner layer of the placenta is made up of the amniontic membrane which is composed of amnion and chorion. The amnion has five separate layers; the epithelium, basement membrane, compact layer, fibroblast layer and spongy layer(48,49). The epithelium which consists of a single layer of epithelial cells is proximal to the developing foetus. The basement membrane of the amnion is a thin layer composed of collagens III and IV and noncollagenous glycoproteins laminin, nidogen, and fibronectin. The compact layer is dense nearly without cells and forms the main fibrous structure of the amnion. The fibroblast layer of the amnion is the thickest and consists of fibroblasts embedded in a loose collagen network with abundance of noncollagenous glycoproteins. The outermost spongy layer forms the interface between the amnion and chorion and composed of a nonfibrillar meshwork of collagen III and an abundant content of proteoglycans and glycoproteins(48,49).

The chorion is made up of a reticular layer, basement membrane and trophoblast layer which is adhered to the maternal decidua. The reticular layer contacts the spongy layer of the amnion and forms a majority of chorion's thickness. The reticular network is composed of collagens I, III, IV, V, and VI. The basement membrane anchors the trophoblasts to the reticular layer with collagen IV, fibronectin, and laminin. The trophoblast layer is the deepest layer which attaches to the decidua(48). Type I and III collagen fibres are known to provide tissue support while type II, IV, V and VI provide scaffoldings in maintaining tensile strength(47). Distortion in the nomenclature of these collagen fibres diminishes the tensile strength of the amniochorionic extracellular matrix which increases myometrial activity and cervical remodelling leading to the onset of preterm labour(47).

Physiological uterine activity during pregnancy and parturition

During pregnancy and labour, the myometrium undergoes distinct molecular changes from noncontractile phynotype (quiescence) to contractile phynotype depending on the gestational age (37,50,51). This process of uterine activity during pregnancy and parturition can be divided into at least four separate phases(52–54). The four recognized phases of uterine activity include quiescence, activation, stimulation and involution (figure 2).

In the first phase (uterine quiescence) which occurs in pregnancy, there is increased inhibition of uterine activity by either separate or combined autocrine-paracrine signalling transduction stimulated by pro-pregnancy factors such as progesterone, prostacyclin (PGI2), relaxin, parathyroid hormone-related peptide (PTHrP), calcitonin gene-related peptide, adrenomedullin, vasoactive intestinal peptide (VIP), nitric oxide, and CRH, which maintains the uterus in a relatively quiescent state (52,53,55). This allows angiogenesis and tissue remodelling especially around the placentation site to improve adequate placental circulation, foetal nutrition and intrauterine growth (figure 2) (56). Alteration in the production of these agents during late gestation may lead to the onset of preterm or term labour, whereas administration of these compounds or their analogues may help maintain uterine quiescence. Uterine smooth muscle relaxants act by signalling through binding and activation of G-protein stimulatory (Gαs) subunit of the G-protein coupled receptor (GPCR)

located on the surface of the myocytes. Activated GTP bound Gαs activates adenylate cyclase or guanylate cyclase causing increased intracellular concentrations of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). These nucleotides interfere with intracellular calcium release and reduce the activity of myosin light chain kinase (MLCK) which are required for shortening of the myofilaments and smooth muscle contractions (figure 4) (52,53,55).

As pregnancy approaches term, the myometrium transitions from its quiescence state to activation. This second phase of uterine activity is characterised by progesterone diminution to oestrogen and CRH dominance associated with increased mechanical stretch or uterotrophic sensitisation (figure 2) (51,53,55). This leads to increased expression of contraction-associated proteins (CAPs) including connexion 43 (Cx43, a key component of gap junctions), agonist receptors (prostaglandins and oxytocin) as well as increased influx of calcium ions into the uterine myocytes(51–53,55). During the second phase of uterine activity, upregulation of GJA1/Cx43 gene mediate hypersensitivity of receptors to uterotonic agonists such as PGs and oxytocin which generate high intensity and coordinated phasic uterine contractions(55,57). Cx43 is a gap junction channel formed from hexamers of connexion proteins that plays a critical role in cell to cell coupling and generates synchronous myometrial contractions(57,58). It allows direct exchange of macro molecules, ions, and second messengers such as cAMP, cGMP, inositol phosphate and Ca2+ between cells which enable channels control and coordinate cellular activity (figure 4) (58).

Stimulation represents the third phase of uterine activity during parturition and is typified by increased uterine smooth muscle tone stimulated by uterotonins such as PGs, oxytocin, and CRH. This phase is characterised by increased synthesis of pro-inflammatory mediators (i.e. IL-1β, IL-8, TNF-α etc.), prostaglandins and white cell (e.g. monocytes and neutrophiles) infiltration of the uterus, foetal membranes and cervix; activating a biochemical process that triggers inflammatory reactions within the uterus. Production of pro-inflammatory mediators causes release of matrix metalloproteinases which breakdown the extracellular matrix and increased gene expression for prostaglandins in uterine tissues (figure 2). This leads to uterine contractions, cervical remodelling and ripening(51,59,60). Increased expression of prostaglandins receptors and gap junctions also occurs in the third phase of parturition. Prostaglandins stimulate functional fundal contractions, lower segmental contraction of the uterus and facilitate cervical ripening while gap junctions permit cell to cell communication by allowing intercellular exchange of macro molecules such as calcium, cAMPs and cGMPs (figure 4) (59,60).

The last phase of uterine activity is characterised by massive uterine involution to resemble the pregnancy stage and tissue remodelling after delivery of the foetus and placenta, and has been attributed primarily to the release of neuroendocrine oxytocin(51–53,55,60). During this phase, there is a rapid withdrawal of pro-pregnancy factors (e.g. progesterone) that maintains uterine quiescence and increased recruitment of pro-labour factors (e.g. gap junctions, calcium-sensitive potassium channels, and connexions) that stimulate the biochemical changes similar to those occurring in labour (figure 2) (59,61).

Pro-inflammatory mediators and spontaneous preterm labour

Inflammation plays a crucial role in the process of parturition(11,62). Most conditions that lead to spontaneous preterm labour are associated with preterm premature rupture of membranes (PPROM). In preterm labour, pathological mechanisms involving the cervix, foetus, foetal membranes, placenta, and myometrium activate prematurely one or more of the components of the pathway of parturition(62). During preterm labour, uterine activity is changed from a state of quiescence to a pro-inflammatory milieu in a three-step process characterized by uterine contractility, cervical remodelling and membrane activation/rupture which is modulated by pro-inflammatory mediators/cytokines(11,62,63). Intrauterine infection is one of the most frequent conditions leading to preterm labour and the pathogenic mechanisms are related to activation of receptors (toll-like receptors) on the innate immune system(62). The significant components of the innate immune system are pattern recognition receptors. Toll-like receptors (TLRs) are a class of pattern recognition receptors that detect pathogen-associated molecular patterns (PAMPS) derived from microorganisms and damage-associated molecular patterns (DAMPS) released from immune cells, stressed and dying cells. This stimulates intracellular signalling cascades leading to the expression of pro-inflammatory mediators/cytokines

by innate immune cells resulting in normal or preterm labour (figure 3) (64,65).

Pro-inflammatory mediators are structurally classified into 4 groups: the 4α helix family members - interleukin 2 (IL-2), interferon gamma (IFN-γ) and IL-10; IL-1 family; IL-17 family; and chemokines. Functionally, these pro-inflammatory mediators/cytokines are grouped into T helper type 1 (Th1) cell reactions (cell-mediated immunity) and T helper type 2 (Th2) reactions (humoral immunity)(62). Inflammatory cytokines are produced by T Lymphocytes (CD4+) which modulate immune response to inflammatory stimuli. Primarily, Th1 cells produce IL-1, IL-2, IL-6, IL-12, IL-15, IL-18, IFN-γ, and tumor necrosis factor alpha (TNF-α) and Th2-cells produce IL-4, IL-5, IL-10, IL-13, and granulocyte macrophage colony stimulating factor (GM-CSF)(62,66).

The presence of intrauterine infection causes infiltration of circulating monocytes and neutrophils into the myometrium and cervix leading to significant gene expression for interleukins (IL-1β, IL-6, IL-8) and Tumour Necrosis Factor alpha (TNF-α)(11,62). Myometrial contractions are stimulated by the increase of IL-1 and TNF-α which promote influx of calcium into myometrial smooth muscle cells(11,67). Pro-inflammatory mediators also cause increased gene expression for prostaglandin synthase coupled with cyclooxygenase-2 gene expression leading to up-regulation of prostaglandins and collagenases in uterine tissues and cervix (65). Prostaglandins, PGF2 and PGE2 are also involved in the stimulation of myometrial contractions and cervical ripening(68–70). Cervical shortening and softening is due to the progressive increased in the amount of hyaluronidase and other enzymes that break down the glycosaminoglycans (GAGS) while collagenases break down the cervical collagen. This leads to increased water absorption by the cervix. IL-4, IL-5, IL-10 and IL-13 produced by Th2-cells play a rather potential protective role in the feto-maternal relationship and prevent preterm labour (figure 3)(62).

In early stage of inflammation, activation and maturation of neutrophils and macrophages occur by stimulatory effect of pro-inflammatory cytokine such as IL-6 in addition to increased differentiation of natural killer cells resulting in invasion of the cervical and endometrial tissue with subsequent stimulatory effect on the uterine contractility(71). Similarly, IL-6 causes increased oxytocin receptors expression on myometrial cells with further enhancement of their responsiveness to oxytocin. In another pathway, IL-6 causes increased production of prostaglandins from activation of the hypothalamic-pituitary-adrenal axis and this result in initiation of uterine contraction and progressive cervical dilatation(72).

Pro-inflammatory mediators also stimulate matrix metalloproteinases (MMPs) such as collagenase, gelatinase and stromelysin, hyaluronidases and prostaglandins expression which promote extracellular matrix degradation, uterine contractions and cervical ripening leading to preterm labour (figure 3)(47,62,73,74). Major proteinases associated with this mechanism are collagenases: 1, 2, 3 and 4, also known as MMP-1, MMP-8, MMP-13 and MMP-18; gelatinases A and B (MMP-2 and MMP-9, respectively); and stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) are normally expressed during labour(47,75).

Physiological pathways and biological mechanisms of uterine contraction

Series of physiological events occur before, during and after pregnancy which modulate myometrial contractility throughout the menstrual cycle in the non-pregnant uterus, maintenance of pregnancy, promotion of child birth and enhance involution(40,73,76,77). These events may include both maternal and foetal characteristics which generate signalling molecules necessary for the stimulation of myometrial contractions during labour(73,76). Knowledge about the biological mechanisms and pathways that control myometrial contraction and relaxation and how these pathways can be regulated is paramount for clinical practice. Conventional trials in animal models showed that parturition is determined by activation of the foetal hypothalamic-pituitary adrenal (HPA) axis with increased foetal cortisol secretion. Following mechanical stress, activation of HPA pathway leads to reduction in maternal progesterone levels and increased levels of oestradiol. This endocrine imbalance promotes increased intrauterine production of prostaglandins, cervical softening and the onset of myometrial contractions (78,79).

The contractile state of the myometrium is determined by the interaction of the two major muscle proteins, actin and myosin. This interaction of actin-myosin is influenced by myometrial signalling pathways which are

broadly categorised into signalling cascades regulating intracellular calcium (Ca2+) concentration and those controlling the contractile apparatus itself(40,77). Abundant in the plasma membrane of the uterine myocytes are L-type calcium ion (Ca2+) channels which are ubiquitous, large conductance, voltage-gated calcium channels (VGCC) (76,80). Binding of an agonist (e.g. oxytocin) to specific receptor causes depolarisation of the myocyte's membrane potential and opening of the L-type calcium channels leading to rapid influx of extracellular calcium ions and dramatic rise in intracellular calcium ion concentration(73,76). The plasma membrane of the myocyte also contain other types of calcium channels (i.e. T-type calcium channels) which exhibit faster kinetics and greater conductance than the L-type (figure 4) (76).

Within the myometrium, agonist interaction with GPCR on the plasma membrane (PM) of myocytes leads to activation of the Gαq subunit of the trimeric G-protein. Activated Gαq subunit also binds and activates membrane-bound phospholypase Cβ which hydrolyzes phosphatidylinositol bisphosphate (PIP2) into inositol-triphosphate (IP3) and diacylglycerol (DAG)(73,76,77). IP3 interact with IP3-sensitive receptors (IP3-Rs) on sarcoplasmic reticulum (SR) which causes release of calcium from its storage sites in the SR into the cytosol. Increased cytosolic calcium concentration also stimulates the rynodine receptors to cause Ca2+-induced Ca2+ release (CICR)(40,73,76). Another mechanism, called store-operated Ca2+ entry (SOCE), also regulates Ca2+ flux occurs when the intracellular Ca2+ stores in the SR are exhausted, it stimulates the PM to permit influx of extracellular Ca2+ into the cytosol(76). Increased concentration of Ca2+ in the cytosol leads to binding of calcium to calcium-sensitive protein, Calmodulin. The Calcium-Calmodulin complex activates the enzyme Myosin Light Chain Kinase (MLCK) which in turn causes increased phosphorylation of Myosin Light Chain (MLC) leading to actin-myosin cross-bridge formation and activation of the contractile machinery (figure 4)(40,73,76).

Relaxation of uterine smooth muscles occur when removal of cytosolic Ca2+ occurs through closure of PM L-type Ca2+ channels, efflux of Ca2+ into the extracellular compartment through Ca2+-ATPase pumps on plasma membrane and into intracellular Ca2+ stores in SR via SR/ER Ca2+-ATPase (SERCA) pumps(40,73,76,77). Also, Myosin Light Chain Phosphatase (MLCP) causes dephosphorylation of the myosin light chain which is regulated by signalling through the small G-protein rhoA–rho-associated kinase and protein kinase C (PKC) pathways. Dephosphorylation of the myosin light chain inhibits actin-myosin cross-bridge formation leading to smooth muscle relaxation (figure 4) (76).

Conversely, in postterm pregnancy although the actual aetiology is not yet known, genetics and maternal and fetal factors are implicated in its pathogenesis(73,81,82). Unlike preterm labour, fetal hypothalamic pituitary adrenal (HPA) insufficiency and a disorder in placental sulphatase activity (an X-linked recessive gene disorder) result in reduced production of eostriol (E3) which plays a fundamental role in the pathogenesis of postterm pregnancy(81,82). Subsequently, placental CRH production declines with diminution in the positive feedback mechanism on the production of foetal adrenal dehydroepiandrosterone (DHEA). Decreased production of foetal eostriol and cortisol ensue which interferes with the biological pathways for spontaneous onset of labour(81).

Biological basis of therapeutic agents for preterm labour

In recent times, the prevention, prediction and treatment of preterm labour has remained a

major focus for contemporary research in obstetrics (83). Generally, the use of tocolytics has become a fundamental pharmacological therapy in the clinical management of preterm labour(84). The biological basis for the use of tocolytics is to delay delivery for at least 48hours to allow for corticosteroids and magnesium sulphate administration to enhance foetal lung maturation and prevention cerebral palsy respectively and transfer to a tertiary healthcare facility with neonatal intensive care facilities(83,84).

Proinflammatory cytokines such as IL-1β, IL-6, and IL-8 have been strongly associated with cervical dilation in preterm labour and medications the decrease the concentration of these mediators constitutes potential preventive interventions(72). The common therapeutic agents which are currently used to abort uterine contractions or maintain uterine quiescence include beta adrenergic receptor agonists (ritodrine, isoxsuprine, salbutamol, terbutaline), prostaglandin -Synthase inbibitors [including NSAIDS (e.g indomethacin)

and COX-2 inhibitors (e.g Celecoxib)], oxytocin receptor antagonists (atosiban), calcium channel blockers (nifedipine) and Magnesium sulphate. Tocolytics are usually administered as a monotherapy although a combination of more than one agent maybe required in some cases. However, a recent systematic review by Vogel et al did not support the use of a polytherapy of tocolytics over monotherapy and this is partly due to lack of trials of combination regimens of commonly used tocolytics(85).

Beta agonists (betamimetics) bind to beta 2 adrenergic receptors on surface membranous myometrial smooth muscle cells which activate adenyl cyclase leading to increased intracellular levels of cAMPs and activation of protein kinase A. Increased cAMPs levels decrease intracellular calcium which specifically suppresses spontaneous and oxytocin-induced uterine contractions. Three different subtypes of beta adrenergic receptors are located in the uterus and beta 2 adrenergic receptors constitutes approximately 80%(86). However, the use of beta 2 adrenergic receptors is associated significant maternal side effects such as palpitations, chest pain, breastlessness and pulmonary oedema in severe cases which limits their clinical use for extended duration(86).

Atosiban is a nona-peptide, desamino-oxytocin analogue and a competitive vasopressin/oxytocin receptor antagonist(87). Atosiban blocks oxytocin receptors and prevents oxytocin-induced hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to IP3 and calcium efflux into the cytoplasm(88). Thus, it inhibits signalling transduction on the uterine smooth muscle leading to uterine relaxation (83,89). Atosiban has minimal side effects with higher safety profile as compared to the other tocolytics(90).

Selective COX-2 inhibitors such as celecoxib and non-specific COX inhibitors such as indomethacin which are prostaglandin synthase-2 inhibitors inhibit the synthesis of prostaglandins (e.g. PGF2α & PGE2) but do not affect the production of pro-inflammatory mediators (e.g. IL-1β, IL-6, and TNFα) because the action of pro-inflammatory mediators is upstream of COX-2 expression(91,92). Prostaglandins induce uterine contraction via facilitation of myometrial gap junction formation and increasing the concentration of intracellular calcium concentration. Therefore, prostaglandin synthase inhibitors are considered effective tocolytics. However, their usage is limited because they cause premature constriction of the ductus arteriosus, inhibit platelets aggregation and impair renal function and decreased urine production resulting in oligohydramnios. Therefore, the duration of indomethacin use should be restricted and limited to gestational age of 32 weeks(93).

Magnesium sulphate is used broadly as a tocolytic and proven to be more effective in fetal neuroprotection and preventing cerebral palsy(94,95). Magnesium sulphate competitively blocks intracellular calcium influx and activation of myosin light chain kinase leading to decreased myometrial contractility. It also inhibits acetyl choline release by competing with calcium at the motor end plate of the neuromuscular junction. Perhaps, its usage is not primarily intended to delay delivery but to prevent cerebral palsy via neuroprotection(94–97). The common side effects include flushing, respiratory depression and cardiac arrest(88). Based on our review, all the tocolytic agents in recent use appear to act on areas that interfere with either calcium entry or prostaglandins production which are downstream of pro-inflammatory mediators' production.

Conclusion

Pro-inflammatory mediators play a central role in the pathophysiology of preterm labour and may constitute the main targets for therapeutic interventions in the prevention and clinical management of preterm labour. Imbalances in the pro- and anti-inflammatory pathways maybe responsible for preterm labour and postterm pregnancies respectively. Increased expression of pro-inflammatory mediators such as IL-1β, IL-6, IL-8 and TNF-α are associated with increased risk of preterm birth. Although the etiology of preterm labour remains elusive, alteration in multiple maternal and foetal physiological mechanisms are implicated including genetic predisposition, psychological and environmental influences.

Available medical therapies for preterm labour have not been consistently effective in aborting uterine contractions due to its ill-defined pathophysiology. However, therapeutic interventions primarily targeting the pro-inflammatory pathway seem promising as inflammation plays a central role in the pathogenesis. In-depth understanding of the mechanistic role of proinflammatory mediators remains vital to the development of more

efficacious therapies and interventions for prevention and treatment of preterm labour. Further research of high methodological quality is recommended to provide adequate understanding of the pathophysiological mechanisms of maternal pro-inflammatory mediators in preterm labour.

Disclosure of interest

The authors of this article declare that, no conflict of interest exists.

Contribution to Authorship:

FB gathered, analyzed and compiled data sources and literature regarding the pathophysiological mechanisms of maternal pro-inflammatory mediators in preterm labour and was the major contributor in writing the manuscript. KAB edited the manuscript for its intellectual content and coherence. All authors read and approved the final manuscript.

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Figure 2: Physiological uterine activity during the non-pregnant state, pregnancy and parturition: During early follicular phase or menses there is increased labour-like uterine contractions modulated by increased prostaglandins and progesterone withdrawal(38,44,45); follicular phase is characterised by progressive increased in wave-like uterine contractions which terminate at pre-ovulation influenced by rise oestrogen levels(41,42,44–46); there is low amplitude contractions during ovulation; luteal phase is characterised by uterine quiescence which favours fertilisation, implantation and placentation. Angiogenesis and tissue remodelling controlled by release of anti-inflammatory mediators (IL-3, IL-4, IL-5, and IL-10) by trophoblast cells occur during the luteal phase. Fertilisation results in increased uterine relaxation controlled by rise in the levels of progesterone. There is profound inhibition of uterine activity during the first phase of pregnancy influenced by pro-pregnancy factors such as progesterone, relaxin, prostacyclin, vasoactive intestinal peptide (VIP), nitric oxide (NO) etc.; second phase of pregnancy is characterised by uterine activation stimulated by progesterone withdrawal to oestrogen and corticotrophin-releasing hormone (CRH) leading to gene expression for contraction-associated proteins (CAPs); third phase is characterised by increased responsiveness to uterotonins and uterine contractions with progressive cervical dilation and effacement; fourth phase is characterised by uterine involution and tissue remodelling governed by withdrawal of pro-pregnancy factors (e. g progesterone, etc.) and recruitment of pro-labour factors (e. g oxytocin) and gap junctions such as connixion43 (cx43)(51,55,59)

Figure 4 : **Physiological pathways and biological mechanisms of uterine activity** : Binding of pro-pregnancy factors (progesterone, relaxin vasoactive intestinal peptide etc.) to GPCR especially G-protein stimulatory receptor (Gs-R) on plasma membrane (PM) activates adenylate cyclase resulting in rise in cytosolic concentration of cyclic adenosine monophosphate (cAMPs). Increased cAMPs inhibit Ca+ entry and Myosin light chain kinase (MLCK) which leads to uterine muscle relaxation. Pro-labour factor (oxytocin, prostaglandin etc.) binding activates trimeric G-protein coupled receptor (GPCR) results in opening of voltage-gated Ca+ channels (VGCC) in PM. Activated G-protein Gq subunit stimulates phospholypase Cβ (PLCβ) to hydrolyze PIP2 into DAG and IP3, IP3 activates IP3-sensitive receptor at the level of the sarcoplasmic reticulum (SR) to induce calcium ions (Ca2+) release from internal stores. These result in an increased in cytosolic Ca2+ levels which ultimately activates MLCK through the intermediary activation of Ca2+-Calmodulin (Ca2+-CM) complex. MLCK phosphorylates myosin light chain (MLC) resulting in cross-bridge formation and muscle contraction. Pro-labour factors inhibit cAMPs production by activating

the G-protein inhibitory receptor (Gi-R) on PM. Ca2+ signals are terminated by extrusion of Ca2+ from the cytosolic compartment or sequestration into internal stores via PM Ca2+ ATPases (PMCA) and SR Ca2+ ATPases (SERCA), respectively. Activation of Ca2+-sensitive K+ channels serves to repolarise the myocytes membrane and induces closure of VGCCs, limiting further Ca2+ entry. Dephosphorylation of MLC by MLC Phosphatase (MLCP) when specific GPCR activation stimulates RhoA-rho kinase results in resetting of the contractile system and relaxation at the level of the tissue. Nitric oxide binds to membranous Gq subunit of the GPCR resulting in increased cyclic guanosine monophosphate (cGMPs) levels which stimulates MLCP leading to smooth muscle relaxation (76).

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