HYPOXIA AND REPRODUCTIVE HEALTH

Hypoxia and labour

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Abstract

Intermittent myometrial hypoxia is a normal feature of labour, as the powerful contractions compress blood vessels. In this review, we focus on the relation between hypoxia, myometrial metabolism, and contractility. We dissect how hypoxia can feedback and limit an ongoing contraction and help prevent foetal distress. The mechanisms involve acidification from lactate, decreased excitability, and a fall of intracellular calcium concentration. As this cycle of contraction and relaxation repeats in labour, the hypoxia also engenders mechanisms that increase force; hypoxia-induced force increase, HIF1. We also discuss the role of the myometrial blood vessels in dysfunctional labour, which is associated with lactic acidosis. In synthesising these studies, we have attempted to unify findings by considering the importance of experimental protocols and finding direct mechanistic evidence from human myometrium or *in vivo* studies. We have made suggestions for future studies to fill the holes in our understanding and speed up the translation of our knowledge to improve births for mothers and babies everywhere.

*Reproduction (2021) 161 F67–F80***Introduction****Background**

For millennia birth attendants would be aware of what were normal or abnormal patterns of maternal activity during labour. These might include tightening of the stretched abdomen due to contractions, changes in respiratory patterns, experience pain, and dilation of the birth canal. Without forceps until the 17th century, pain relief in the 19th or access to safe Caesarean sections in the 20th century, it is not surprising that childbirth was feared and a significant cause of female and neonatal deaths. As these advances were made improving outcomes, attention shifted to the black box that was the uterus and its activity. Further technical advances enabled the monitoring of uterine contractions and foetal heart rate, and much greater survival of neonates born prematurely. Hypoxia, before or during labour, however, remains a significant challenge to clinical teams, from its origin, detection, prevention, and treatment. This review is addressing the first of these, its origin, and specifically the role of the myometrium in hypoxia. For over 60 years researchers have been studying the relation between uterine activity, perfusion, the course of labour and neonatal outcomes (references throughout). Here we introduce the key concepts, review, and synthesize data and suggest underlying, testable mechanisms for taking this crucial work further.

Focus

Labour presents several challenges to mother and fetus. The long-lasting physical and mental challenge has often been compared to a marathon and the effort required giving rise to its name, 'labour'. Physiologically and biochemically we understand that changes have occurred within the woman's reproductive tract ahead of labour starting. Most notably, these nearly always include softening and shortening of the cervix, Braxton Hicks contractions, the foetal head engaging with the cervix, and a biochemical preparedness for hypoxic conditions. At a molecular and hormonal level, the myometrium is being primed to produce strong, frequent, and coordinated contractions.

The focus of this review is hypoxia in labour. By this, we mean the effects of the normal and abnormal reductions of uterine blood flow that accompany contractions, and not any chronic pathology of the myometrium or its blood supply, nor the effects of living at high altitude. Myometrial hypoxia is a normal accompaniment to labour and indeed may play a role in strengthening uterine contractions. Hypoxia, if prolonged, however, will contribute to dysfunctional (slow to progress) labours. We are concerned with four major questions: (1) what is the evidence for hypoxia in the myometrium, (2) what is the functional effect of hypoxia on uterine contractility and labour, (3) what

mechanisms underlying these effects in the myometrium, and (4) what is the contribution of the myometrial vasculature. When possible, we have prioritised data obtained in women or human tissue, but much relevant information comes, of necessity, from studies in animal models, (species indicated if not rat or mouse).

Structure

To understand how uterine contractions, cause hypoxia, it is first necessary to consider the relative anatomy of the myometrium and its blood supply, and then myometrial physiology, specifically how uterine contractions in labour arise. Metabolism and function are closely linked in muscles and the myometrium is no exception. We, therefore, discuss the particular features of myometrial biochemistry and metabolism, including their shift to prepare for the hypoxic conditions which will occur in labour. This section of the review also brings in pH and its changes with contraction and hypoxia. We then discuss the critical evidence from *in vivo* and *in vitro* studies, made in animal models but also women, leading to the conclusion that uterine contractions occlude blood vessels. This causes hypoxia within the myometrium, reduces placental perfusion and can affect foetal oxygenation. The feedback of this hypoxia and acidification on the force of contractions are explained. The circumstances and mechanisms by which hypoxia may reduce or increase uterine contractions is explained. These findings have been translated to explain the physiological cause of dysfunctional labour, (slow to progress), labours, as lactate produced in hypoxic conditions, accumulates. Furthermore, we describe how lactate concentrations in amniotic fluid can be used to help predict the outcome of labour, and the trialling of oral bicarbonate to improve labour outcome in women labouring dysfunctionally. An area of much less certainty is the role of the uterine blood vessels in all these processes; how do they respond to repeated compressions and the need to fully relax between contractions. Is there a role for reactive hyperaemia for example? We finish by asking, is there a maternal phenotype that adds to the risk of the myometrium or its blood vessels, functioning poorly in labour. In the 21st century, there are still mothers dying in labour or having to have unplanned surgical interventions to safely deliver their child, because we still do not understand hypoxia in labour – a call to arms is made for future work.

Vasculature of the uterus

Anatomy

The blood supply to the pregnant and non-pregnant human uterus is well described and the latter shown in Fig. 1. Briefly, the supply comes mainly from the uterine artery, but also the ovarian arteries. The vessels form an anastomosing network, interconnecting across the circumference of the uterus (Farrer-Brown *et al.*

1970). This potentially bi-directional supply ensures considerable redundancy and helps maintain uterine perfusion. Arcuate arteries branch off the uterine artery and run circumferentially in the outer third of the myometrium. Radial arteries branch out and traverse the myometrium inwardly towards the endometrium. At the myometrial/endometrial boundary, the radial arteries branch to form the basal and spiral arteries. The tortuous course of the vessels through the myometrium allows for the enlargement of the uterine cavity and the inevitable stretching of the vessels as pregnancy progresses. Endometrial capillaries drain into venules that converge to form larger collecting veins that radially traverse the inner myometrium, growing in size until they join the circumferentially running arcuate veins in the outer myometrium and finally drain into the uterine vein (Farrer-Brown *et al.* 1970). The remodelling that occurs in pregnancy is beyond the scope of this review and has been covered elsewhere (Pijnenborg *et al.* 2006, Osol & Mandala 2009). Of note, however, uterine, arcuate, and radial arteries undergo outward remodelling and demonstrate reduced reactivity to vasoconstrictive agents, allowing a greater blood flow to the uterus, and the uterine veins increase in diameter and distensibility (Page *et al.* 2002).

Physiology

Vascular tone appears to be increased in myometrial arteries from pregnant women and animals compared to non-pregnant (Eckman *et al.* 2012, Xiao *et al.* 2013). An increase of intracellular Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) is integral to determining tone in smooth muscle, as detailed in the next section, and see Fig. 2. An important negative-feedback loop exists in vascular smooth muscle. Calcium ion entry stimulates release of Ca^{2+} via ryanodine receptors on the sarcoplasmic

Figure 1 Transverse section through the non-pregnant human uterus showing the embedded arteries. Drawn by Dr Clodagh Prendergast.

reticulum (SR) in the form of Ca^{2+} sparks, which activate large conductance Ca^{2+} -activated K^+ channels (BK_{Ca}). Opening of these channels produces a spontaneous transient outward K^+ current (STOC) that hyperpolarises the cell, thereby decreasing the opening of L-type, the voltage-operated Ca^{2+} channels (VOCC), and causing vasorelaxation (Jaggar *et al.* 1998). As part of the haemodynamic adaptation to pregnancy, there is an upregulation of BK_{Ca} channels and increased Ca^{2+} spark frequency in uterine arteries (Rosenfeld *et al.* 2005, Hu *et al.* 2011, 2019), presumably attenuating tone and aiding the larger blood flow experienced in pregnancy. Chronic hypoxia can downregulate BK_{Ca} channels in uterine arteries and lead to increased ovine vascular tone (Hu *et al.* 2012, Xiao *et al.* 2013).

The responsiveness of human term pregnant myometrial arteries has been well studied; vessels constrict in response to endothelin (ET-1), U46619, vasopressin, noradrenaline, angiotensin II. Of note, high concentrations of oxytocin can constrict myometrial vessels (Maigaard *et al.* 1986).

The endothelium also plays a vital role in the regulation of vascular tone by secreting several vasodilating (NO, PGI_2 , EDHF and H_2S) and vasoconstricting (ET-1, EDCF) substances (Galley & Webster 2004). The expression and activity of eNOS (endothelial nitric oxide synthetase), is increased in uterine artery in pregnancy (Nelson *et al.* 2000), but endothelial vasodilatory pathways are also altered in disease states, including pre-eclampsia (Vanhoutte *et al.* 2017).

Physiology of myometrial contraction

The mechanism of force production in the myometrium is like that in other smooth muscles and has been reviewed elsewhere, and see Fig. 2 (Wray & Prendergast 2019). The interaction of myosin heads with actin filaments is the culmination of a pathway that starts with excitation of the myocyte membrane and opening of voltage-dependent L-type Ca^{2+} channels (Shmigol *et al.* 1998). Excitation may be initiated by specialised

Figure 2 Signalling pathways controlling contraction and relaxation of myometrial and vascular smooth muscle and effects of hypoxia. In smooth muscle (SM), action potentials depolarise the membrane causing opening of voltage-operated calcium channels (VOCC) and Ca^{2+} influx. Agonists, such as oxytocin and adenosine, also cause a rise in $[\text{Ca}^{2+}]_i$. Ca^{2+} combines with calmodulin, activates myosin light-chain kinase (MLCK), resulting in cross-bridge cycling and contraction. Relaxation occurs when $[\text{Ca}^{2+}]_i$ falls or when myosin light-chain phosphatase (MLCP) activity exceeds MLCK activity. In vascular SM, Ca^{2+} sparks activate BK_{Ca} channels, leading to hyperpolarisation, inhibition of VOCC and thus relaxation. Endothelial NO causes cGMP-mediated relaxation of vascular SM. Red arrows indicate contraction pathways via a rise in $[\text{Ca}^{2+}]_i$. Black arrows indicate relaxing pathways. Labour contractions occlude vessels, producing hypoxia, resulting in oxidative stress, decreased pH and $[\text{ATP}]_i$. Hypoxia modulates $[\text{Ca}^{2+}]_i$ and thus contraction by inhibiting VOCC, activating K_{ATP} channels, altering SR activity, inhibiting Ca^{2+} sparks and BK_{Ca} activity. Hypoxia inhibits NO production. In myometrium, brief repetitive bouts of hypoxia, acting, for example, on adenosine receptors (A1), can increase force. HIFI. Hypoxia also has Ca^{2+} -independent effects, leading to increased MLCP activity. Blue arrows indicate where hypoxia affects these pathways. A1, adenosine receptor 1; Ca-CaM, Ca^{2+} -calmodulin complex; HIFI, hypoxia-induced force increase; IP_3R , IP_3 receptor; PLC, phospholipase C; PKG, protein kinase G; SR, sarcoplasmic reticulum; sGC, soluble guanylyl cyclase; ROS, reactive oxygen species; RyR, ryanodine receptor. With thanks to Dr Sarah Arrowsmith for giving us the cell template.

myocytes acting as pacemakers, causing depolarisation, and thus, opening of L-type channels (Lutton *et al.* 2018). The action potential in human myometrium propagates over a distance of a few cm and additional mechanisms, such as mechanotransduction (Young 2016) may be needed for contractions to be synchronised throughout the myometrium. The resulting rise in $[Ca^{2+}]$ leads to formation of Ca-calmodulin complex. This complex combines with, and switches, myosin light chain kinase (mlck) to its active form, promoting phosphorylation of the regulatory light chains of myosin. This activates the myosin head ATPase, actin attachment and crossbridge cycling. Contraction occurs and is followed by relaxation as $[Ca^{2+}]$ falls due to Ca^{2+} channel inactivation, mlck dissociating from 4Ca-calmodulin, and mlc phosphatase (mlcp) removing the phosphate group from the light chains. In this way phasic contractions, governed by changes in excitability and thus $[Ca^{2+}]$, occur. In labour the increased strength, duration and frequency of contractions is due to the action potential changing from spike-like to plateau type, leading to increased Ca^{2+} entry, and increased firing of action potentials. Unlike myometrial arterial smooth muscle, the relaxing role of Ca^{2+} , mediated via the Ca^{2+} -sparks-STOCs pathway is not present in the smooth muscle of the myometrium itself (Shmigol *et al.* 1999, Burdyga *et al.* 2007, Noble *et al.* 2014). Calcium release from the SR occurs via IP_3 binding and can augment agonist contractions (Arrowsmith & Wray 2014). Both vascular and myometrial contractility requires ATP, and thus metabolism and blood flow are discussed next.

Myometrial metabolism

Overview

Glucose appears to be the only energy substrate used by the human pregnant myometrium (Steingrimsdóttir *et al.* 1993). A significant amount of this glucose is consumed through the anaerobic pathway, resulting in lactate production, even when oxygen is not limited and the tissue is contracting at basal rates (Wray 1990, Steingrimsdóttir *et al.* 1997). A five-fold increase in lactate efflux occurs with metabolic inhibition (Wray 1990). It remains unclear why the anaerobic glycolytic pathway is part of the normal metabolism of myometrium, but compartmentation of ATP production between excitability (glycolytic) and oxidative (contractile) demands has been suggested (Campbell & Paul 1992). Interestingly, recent work in uterus and other tissue has shown that extracellular lactate has signalling roles (Brooks 2020). In the myometrium, lactate binding to its receptor-stimulated anti-inflammatory pathways (Madaan *et al.* 2017).

As first reported in pregnant rats (Dawson & Wray 1985) and then human (Steingrimsdóttir *et al.* 1997), [ATP] is ~3 mM and phosphocreatine (PCr) concentration is 3–5 mM. As with other smooth muscles, these values,

especially [PCr] are low compared to striated muscles, where it is present at around 30–40 mM.

Contractions in smooth muscle are energetically economical and relatively slow, and thus the [PCr] can maintain [ATP] and support myometrial contractions under the normal conditions. Animal studies have demonstrated however, that even modest decreases in blood flow affects metabolite concentrations; ATP and phosphocreatine (PCr) decrease, while inorganic phosphate (Pi) and lactate increase (Larcombe-McDouall *et al.* 1998).

Myometrial preparation for hypoxia at term

The human myometrium at term is prepared for hypoxia. It lays down metabolic reserves including glycogen and fatty acid droplets (Wynn 1967, Milwidsky & Gutman 1983). In hypoxia, glycogenolysis will produce ATP using glycogen and producing lactate. A switch occurs with the expression of isoforms of lactate dehydrogenase (LDH) which are least inhibited by product (i.e. lactate) at term (Makkonen *et al.* 1982). There are also modest increases in [ATP] and [PCr] at term in rat myometrium (Dawson & Wray 1985). Thus, the term-pregnant myometrium is better able to withstand hypoxic episodes, than non-pregnant. Given the low reserves of PCr in myometrium, we speculate that creatine supplementation may improve labour outcome. In mice, this approach has led to improved neuronal outcomes after induced hypoxia, but it is unclear whether improved contractions and delivery contribute to this cerebral effects (Ireland *et al.* 2011).

Myometrial pH

A switch to anaerobic respiration under hypoxic conditions, increases lactate production in vascular and myometrial smooth muscles (Lovgren & Hellstrand 1985, Wray 1990) and leads to intracellular acidification. A direct concentration-dependent effect of lactate on myometrial intracellular pH (pH_i) has been measured (Hanley *et al.* 2015), and under normoxic conditions, inhibition of lactate efflux will cause acidification (Wray 1990). Changes in pH_i in myometrial smooth muscles are limited by buffering and pH regulatory mechanisms (e.g. Na^+/H^+ exchanger) (Little *et al.* 1995). In myometrium buffering capacity ($\Delta H^+/\Delta pH_i$), has been calculated to be ~40, and the main contributors to it are bicarbonate, proteins and phosphates (Bullock *et al.* 1998). However, changes in pH_i will occur, especially if flow is restricted, such that external pH also falls. Intracellular acidification has been demonstrated in myometrium *in vivo* and *in vitro* during ischemia and hypoxia, respectively (Larcombe-McDouall *et al.* 1998). Furthermore, *in vivo* and *in vitro*, in pregnant rat myometrium, acidification occurs during each contraction, and is proportional to the strength of contraction (Taggart & Wray 1993,

Larcombe-McDouall *et al.* 1999), with pH_i recovering during the relaxation between contractions.

The mechanisms leading to the fall in myometrial pH with contraction are a mixture of changes of metabolic pathways, utilisation of metabolic reserves and accumulation of waste products (Taggart & Wray 1998). Initially, PCr breakdown maintains ATP in a reaction which is net proton absorbing, but is followed by net generation of protons, due to elevated lactate production, as metabolism shifts from aerobic to anaerobic. Anaerobic metabolism is stimulated because the contraction reduces its own blood supply.

Hypoxia in the myometrium

Uterine contractions reduce blood flow

The force generated by the contractile bundles in the myometrium during labour compresses the vessels lying within. This squeeze decreases inflow of blood, producing local transient ischemia and hypoxia and a switch from aerobic to anaerobic respiration, in the myometrial (and vascular) myocytes (Larcombe-McDouall *et al.* 1999).

Thus, during labour myometrial contractions decrease uterine blood flow, which recovers when the muscle relaxes (Greiss 1965, Brotanek *et al.* 1969, Brar *et al.* 1988). In women, this was first demonstrated using invasive methodologies (Borell *et al.* 1964, Brotanek *et al.* 1969) and confirmed using modern imaging-based techniques, for example, 3D power Doppler angiography (Jones *et al.* 2009). These data confirm reduced perfusion during uterine contractions in women in spontaneous labour. Such decreased blood flow will be expected to produce hypoxia. The extent of the hypoxia in women has not been quantified, but surrogates for hypoxia, such as a fall in pH and increased lactate from switching to anaerobic respiration, have, and *in vivo* studies in pregnant rats, found these and other metabolic parameters, all correlate well with the degree of occlusion of uterine vessels (Larcombe-McDouall *et al.* 1999). Thus, we can speculate that oxygenation during the peaks of contractions and before restoration of perfusion, will reduce by 50%

Fetal hypoxia in labour due to myometrial activity

The decrease in blood flow with each contraction is transmitted to, and detected by, the fetus, as there is a decrease in the placental blood flow which causes a less efficient gas and nutrient exchange, that can be detected by the fetus. This stimulates an increase of heart rate as force peaks. If, however, the myometrial contractions are too frequent, long-lasting or strong, then the changes to foetal blood delivery become more challenging and can lead to foetal distress and the need for an operative delivery. The effects of uterine contractions in women

on foetal cerebral oxygenation were shown using near-infrared spectroscopy, and as with uterine flow, an inverse relationship was found (Peebles *et al.* 1994). Over-administration of oxytocin, which can occur in cases of slow to progress labours, will also cause foetal distress due to excessive stimulation of the myometrium. Tonic-like contractions, whether caused by oxytocin or on occasion, spontaneously, greatly impair uterine perfusion.

Hypoxia and contractions

Contractions in human labour are of variable length, but generally last 2–4 min; those of rodents are an order of magnitude shorter and their frequency is greater than in women. Evidence from animal and human myometrial studies is clear; hypoxia can decrease myometrial contractility. In pregnant rat and human myometrium, blocking oxidative phosphorylation, for example, with cyanide, reduced spontaneous and agonist-augmented contractions (Wray 1990). Hypoxia *per se* was first shown to decrease contractions in biopsies of pregnant human myometrium (Monir-Bishty *et al.* 2003). This finding was extended by Bugg *et al.*, who also showed hypoxia decreased force in non-pregnant myometrium and in the presence of oxytocin (Bugg *et al.* 2006). Thus, agonists slow, but do not prevent, the fall in force in the myometrium during hypoxia.

Mechanism

With hypoxia, as shown in Fig. 2, Ca^{2+} entry is decreased secondary to reduced excitability of the myometrium. This points to decreased oxygenation directly increasing K^+ channel conductance, causing hyperpolarisation, and/or inhibiting channels producing depolarisation, that is, VOCC or Ca^{2+} -activated chloride channels (Jones *et al.* 2004). The effects of hypoxia on ion channels may be secondary to changes of [ATP], pH and formation of reactive oxygen species (ROS).

A fall in [ATP] will activate ATP-gated K^+ channels (K_{ATP}), and [ADP] and pH modulate their conductance. This makes K_{ATP} channels good candidates for sensing metabolic changes and converting them into changes in excitability. They are abundant in myometrium (Teramoto 2006), but expression decreases at term (Sawada *et al.* 2005, Xu *et al.* 2011). In pregnant human myometrium, K_{ATP} channel openers inhibit spontaneous and oxytocin-stimulated contractility (Longo *et al.* 2003), but are less potent in myometrium from women in labour than those not in labour (Xu *et al.* 2011). Glibenclamide, an antagonist of K_{ATP} channels, has little effect on spontaneous or oxytocin-stimulated uterine contractions, nor does it modify *in vivo* activity (Piper *et al.* 1990). This suggests that K_{ATP} are closed at rest, do not contribute to resting membrane potential but open during metabolic stress. We tested this in rat myometrium,

by using cyanide to reduce [ATP] and measured K⁺ efflux. The decrease of contractility was accompanied by increased K⁺ (⁸⁶Rb) efflux (Heaton *et al.* 1993). Of this increase, about 50% occurred through K_{ATP} channels, and the hyperpolarisation this will produce, contributes to the fall in force.

In summary, the evidence shows that during prolonged hypoxia the abolition of contractions is likely due to hyperpolarisation produced by opening of a variety of K⁺ channels, and decreased Ca²⁺ entry.

Hypoxia-induced force increase, HIFI, in labouring myometrium

The previous *in vitro* studies of hypoxia or metabolic inhibition were conducted under conditions of a single, continued experimental intervention for tens of minutes. In labour, however, hypoxia will be briefer, lasting around a minute, but repeated many times. Recent work using a repetitive pattern of brief hypoxic episodes produced an exciting finding; force increased (Alotaibi *et al.* 2015).

Repetitive, brief (2–5 min) episodes of hypoxia to rat myometrium increased contraction force; the contractility fell during hypoxia but on return to normoxia gradually increased following successive hypoxic periods. We named this phenomenon hypoxia-induced force increase (HIFI) (Alotaibi *et al.* 2015). HIFI will be important in labour as: (1) it only occurs at term or in labour, (2) occurs in rat and human myometrium, (3) HIFI occurs in the presence of oxytocin, and further augments contractility, and can increase force when oxytocin receptors are blocked, (4) HIFI is long-lasting and, once primed, the increase of force is maintained for up to 12 h.

We have suggested that HIFI is a novel mechanism, produced by hypoxia, underlying the strengthening of labour contractions. Evidence for HIFI *in vivo* in women is hard to obtain, as it is intrinsic to the labouring myometrium. There is evidence for HIFI *in vivo* in pregnant rats: a HIFI-like increase of contractile force followed episodes of uterine artery occlusion and reperfusion (Harrison *et al.* 1995).

When considering the effects of hypoxia on the labouring myometrium, it is now clear that we need to distinguish between the acute strengthening effects of HIFI, and the weakening effects of prolonged hypoxia. The mechanisms underlying the repetitive, transient effects on contraction are likely to be different from those producing the chronic effects of hypoxia and are discussed next.

Mechanism of HIFI

Given that HIFI increases force, it was anticipated that it would increase Ca²⁺ entry, but simultaneous measurements of force and Ca²⁺ did not show this

(Alotaibi *et al.* 2015). Investigations of intracellular pathways however showed that both adenosine and prostaglandins were important. Enhancement of these (and probably other) stimulatory pathways by HIFI, and the promotion of mlck activity, and/or decreased mlcp would be expected to promote force (Fig. 2). It was also found that external acidification, but not alkalinisation, could reproduce HIFI, but not as powerfully as hypoxia. There are acid-sensitive ion channels expressed in myometrium. The TASK channels encoded by KCNK3 and KCNK9, in human myometrium, decrease their conductance with extracellular acidification (Duprat *et al.* 1997) and hypoxia. Two recent papers have shown in mouse myometrium that TASK2 channel inhibitors stimulate contraction, as does acidic pH (Hong *et al.* 2013, Kyeong *et al.* 2016). Acid-sensitive channels related to ENaC may also contribute, but little is known about these in myometrium (Boscardin *et al.* 2016). Thus, these acid-sensitive channels could be part of a mechanism such as HIFI, to keep labour progressing when hypoxic conditions arise.

Hypoxia and labour

Hypoxia and normal labour

The phasic contractions of labour produce hypoxia. As discussed, the term pregnant myometrium has increased its metabolic reserves and capacity to withstand hypoxia, and the HIFI mechanism adds to the contractile drive. The periods of muscle relaxation between contractions allow for reoxygenation of the tissues and removal of waste products from the myocytes. During labour, lasting for hours, the contractions build, until the cervix is fully dilated, and the baby, then umbilical cord and placenta delivered.

However, not all term-labours proceed well but instead arrest with the cervix incompletely dilated. Until relatively recently there were no data to explain why around 10% of births had contractions so poor, as to be incapable of dilating the cervix. These slow to progress, dysfunctional labours, are the leading cause of unplanned Caesarean sections, a source of trauma to women, contributors to neonatal complications, and a financial burden to healthcare systems.

Hypoxia and dysfunctional labour

We are focussing on physiological causes of dysfunctional labour, rather than obstructed labours (Neilson *et al.* 2003). The first clinical and physiological insight into dysfunctional labour came when myometrial capillary blood was analysed from women having Caesarean sections for a variety of reasons (Qunby *et al.* 2004). Based on the *in vitro* studies showing hypoxia and low pH can decrease uterine contractility, we tested the maternal blood for pH and lactate. The

results were clear; those labouring dysfunctionally had a more acidic blood than any other group (Quenby *et al.* 2004). Furthermore, the myometrial capillary blood, had significantly increased lactate, but there was no systemic acidosis or hypoxia. This suggested that in some women, hypoxia was detrimental to contractions. Under these circumstances, oxytocin is unlikely to overcome the poor, hypoxic myometrial environment – thus, these women required surgical delivery of their babies (Wiberg-Itzel *et al.* 2014). This is consistent with the *in vitro* findings of hypoxia on contractility in human myometrium; oxytocin cannot prevent the fall of force (Bugg *et al.* 2006).

Lactate as a predictor of dysfunctional labour

Another breakthrough in establishing a link between hypoxia and poor contractions in labour came from a study measuring lactate in amniotic fluid at the start of active labour and when labour arrested (Wiberg-Itzel *et al.* 2010). The investigators reasoned that high levels of lactate in dysfunctionally labouring myometrium would be reflected in the amniotic fluid. Collecting leaking amniotic fluid at the start of labour, established a range of values. Importantly, a lactate concentration above a threshold level was predictive of women who would labour dysfunctionally (Wiberg-Itzel *et al.* 2009, 2014). The authors conclude that amniotic fluid lactate levels >10.1 mmol/L has sensitivity of 39% and specificity of 90.3%, for detecting women who need a caesarean section (Wiberg-Itzel *et al.* 2016). Such a predictive test has utility in preparing the mother and clinical team, and guiding care. A recent extension of this work is the measurement of lactate in foetal scalp blood (Iorizzo *et al.* 2019).

pH and dysfunctional labour

Better however than prediction would be prevention. A recent clinical trial suggests that combatting the acidosis produced by excessive lactate levels in women labouring dysfunctionally, would be successful (Wiberg-Itzel *et al.* 2018). The *in vitro* and *in vivo* work discussed earlier shows that hypoxia during contractile activity is associated with a fall in pH, which can decrease force (Crichton *et al.* 1993, Austin & Wray 1994, Harrison *et al.* 1994, Taggart *et al.* 1997), and change the contraction pattern to one resembling a dysfunctional labour (Pierce *et al.* 2003). If, however, in these *in vitro* studies, the acidic pH change produced by lactate was nulled, by simultaneously applying a weak base (NH₄Cl), then force no longer fell (Hanley *et al.* 2015). The conclusion from this work was that elevated lactate in myometrium decreases force by acting as a weak acid. If the fall in pH can be prevented, then lactate will not reduce force. Putting these findings together, we hypothesized that labour outcome in women labouring dysfunctionally

would be improved if we reduced the acidification present in the myometrium. In this blinded randomised trial, women in their first labour, with a clinical diagnosis of dystocia, were either given the standard treatment, oxytocin, or a drink containing bicarbonate, followed an hour later by oxytocin. There was a statistically significant increase in the number of women who had a vaginal rather than operative delivery, in the women administered bicarbonate to decrease the lactic acidosis in their myometrium (Wiberg-Itzel *et al.* 2018).

Having made significant progress in understanding how hypoxia is an important determinant of dysfunctional labours, the next part of the puzzle becomes, why do only some women encounter excessive hypoxia and acidification?

Why do only some women have dysfunctional labours?

Researchers have worked to determine which maternal factors might lead to a dysfunctional labour (Zhang *et al.* 2007, Wray & Arrowsmith 2012). The data can be summarised as: some factors, such as obesity, age, diabetes, can increase the risk, none are predictive – young, fit, lean women also suffer unexplained dysfunctional labours. There is evidence for familial inheritance dysfunctional labour, but it cannot explain most cases (Algovik *et al.* 2010).

Transcriptional studies

In considering the link with hypoxia, it is known that many genes involved in metabolism and contraction are regulated by hypoxia. A key driver of this is hypoxia-inducible factor (HIF1A), a powerful transcription factor, which forms during hypoxia. Described as the master regulator of responses to hypoxia, it leads to the switching on of hundreds of genes, including those associated with angiogenesis, metabolism, pH regulation, apoptosis and endothelial homeostasis (Loboda *et al.* 2010). HIF1 expression is increased in ovine uterine arteries with chronic hypoxia (Xiao *et al.* 2013). To date, three studies have compared the myometrial transcript of women who had a dysfunctional labour and those who laboured successfully (Brennan *et al.* 2011, Mittal *et al.* 2011, Chaemsaitong *et al.* 2013). They report differential gene expression and two showed that HIF1 expression is increased in term pregnant labouring women with arrest of descent or dilation compared with normally labouring women. Genes linked to inflammation and contractility were also reported altered in all three studies. Of note, Mittal *et al.* found that one of the most marked changes was increased IL6 (interleukin 6) mRNA and protein. As muscle-derived IL6 increases in response to reduced intramuscular glycogen content (Shephard 2002), this suggests that myometrial glycogen stores are being depleted. It would be of interest to

know whether glycogen stores are lower at the start of labour in women who go on to labour poorly. Thus, from the studies so far, genes connected with hypoxia and inflammatory changes seem to be associated with dysfunctional labour, but more work is required in identifying causal relationships. For example, are some women expressing fewer transporters for lactate, or pH regulatory mechanisms, such that their myometrium builds up an environment that is hostile to contractions? Are there genetic differences leading to reduced glycogen deposition or utilisation, leading to exhaustion?

Role of the vasculature in dysfunctional labour

Background

This review started by exploring the relation between the myometrium and its blood supply, and documenting the repetitive compression of these vessels. The vital restoration of flow and with it metabolites, occurs between contractions. Here we address whether a failure in perfusion could create the conditions that lead to dysfunctional labour, and start by asking what hypoxia does to myometrial blood vessels, then discuss two specific features of the circulation; reactive hyperaemia and preconditioning, in relation to myometrial hypoxia and labour. We finish with how the maternal phenotype may contribute to dysfunction.

Hypoxia vascular smooth muscle

The effect of hypoxia on vascular smooth muscle function (Fig. 2) has been extensively studied and reviewed in peripheral vessels (e.g. Austin & Wray 1995, 2000, Smith *et al.* 1998) although studies focused on myometrial/uterine vessels tend to have only examined the effect of chronic hypoxia. Hypoxia produces varying responses depending on the vascular bed and on the length of the period of decreased O₂ supply. Acute hypoxia generally relaxes systemic vessels, a protective response to increase blood flow to endangered peripheral tissues, while the pulmonary vasculature vasoconstricts to divert blood from poorly ventilated to well-ventilated lung. Human fetoplacental vessels similarly constrict under low O₂ conditions (Howard *et al.* 1987). Many studies have demonstrated that hypoxia-induced vasodilatation occurs because of decreases in [Ca²⁺]_i in the peripheral vessels (Pearce *et al.* 1992, Smani *et al.* 2002). As discussed for myometrium, hypoxia decreases [Ca²⁺]_i in vascular myocytes via effects on calcium channels, VOCC, (Herrera & Walker 1998), SR (Guibert *et al.* 2002), or indirectly, by stimulating K⁺ channels causing hyperpolarisation. The K⁺ channels involved include, K_{ATP} (Shimoda & Polak 2011), voltage-dependent K⁺ (Hedegaard *et al.* 2014) and BK_{Ca} (Gebremedhin *et al.* 1994). Decreased Ca²⁺ spark frequency in myometrial arteries, would increase tone, compromising blood flow

to the placenta and limiting myometrial recovery between contractions. Hypoxia can also cause relaxation of vascular smooth muscle via Ca²⁺-independent methods (Aalkjaer & Lombard 1995). There appear to be no direct studies investigating how acute hypoxia affects human myometrial vessels.

In uterine arterial smooth muscle from pregnant animals, it has been shown that chronic hypoxia suppresses agonist-mediated contractile responses and intracellular Ca²⁺ mobilisation (Zhang & Xiao 1998), decreases K_{ATP} channel (Xiao *et al.* 2010) and BK_{Ca} channel activity (Kazmierczak *et al.* 2013) and increases ROS production (Kazmierczak *et al.* 2013).

Reactive hyperemia

After a tissue has been deprived of oxygen (arterial occlusion or peripheral compression), reactive hyperaemia is the process by which blood flow to that tissue is increased, to restore oxygen levels (Bliss 1998). The extent and duration of the increased flow increases with the duration of occlusion but varies between vascular beds. Reactive hyperaemia occurs in uterine vessels. It has been observed in sheep uterine arteries, albeit stronger in non-pregnant than pregnant sheep (Fleet & Heap 1982). In rat, it is seen following ~15% of uterine artery occlusions (Larcombe-McDouall *et al.* 1998). In pregnant women, no evidence of reactive hyperaemia was found (Jones *et al.* 2009). In brachial arteries, reactive hyperaemia is reduced in pregnancy (Dorup *et al.* 1999), perhaps because blood vessels are already more dilated than usual. The fundamental stimulus driving reactive hyperaemia is tissue hypoxia and K_{ATP} channels, adenosine, NO and prostaglandins have all been implicated. Repeated vessel occlusions decrease reactive hyperaemia when the inter-stimulus interval is short (Eikens & Wilcken 1973, Turturici & Roatta 2013, Messere *et al.* 2017). This may be relevant to labour when the contraction frequency is high.

Ischaemia-reperfusion and hypoxic preconditioning

Reperfusion of tissues following a period of ischemia is vital for tissue viability and function, but reintroduction of oxygen can paradoxically cause further damage. This is due to loss of ionic balance, oedema and the generation of ROS and inflammatory cytokines, (Gourdin *et al.* 2009). The endothelium is very sensitive to such injuries, producing a reduction in NO-mediated vasodilation and vasospasm (Gourdin *et al.* 2009). Intermittent hypoxia impairs uterine artery function in pregnant mice and increases markers of oxidative stress and inflammation (Badran *et al.* 2019). Indeed, ROS significantly inhibit myometrial contraction (Kirby *et al.* 2005) and therefore hypoxia-induced ROS production may lead to poorer myometrial contractions and thus contribute to dysfunctional labour.

The phenomenon of hypoxic preconditioning has been observed in some smooth muscles (Almohanna & Wray 2018), where exposure to small periods of hypoxia can provide resistance to a subsequent larger ischaemic insult. Protection of the endothelium is a major part of this mechanism in human (Corcoran *et al.* 2018). Hypoxic preconditioning has not been directly demonstrated in myometrial arteries, though based on other vascular beds, we might surmise that it should protect them. The repeated contractions of labour generate repeated ischaemia-reperfusion events and while we have seen that this can enhance the contraction of term pregnant myometrium (HIFI; Alotaibi *et al.* 2015), it is also clear that labour contractions generate oxidative stress, pro-inflammatory cytokines and apoptosis in placentas of women undergoing vaginal deliveries compared to non-labouring caesarean sections (Cindrova-Davies *et al.* 2007).

Maternal phenotype

It has become clear that maternal phenotype (e.g. BMI, diabetes, age) can have a detrimental effect on human myometrium (Al-Qahtani *et al.* 2012, Arrowsmith *et al.* 2012, Carlson *et al.* 2015, Wray 2015). The myometrial arteries from obese mothers exhibit deficits in endothelial cell calcium signalling and the eNOS system (Prendergast & Wray 2019), and alterations to both contractile and relaxation responses (Hayward *et al.* 2014). Myometrial arteries from diabetic mothers exhibit a deficit in endothelial-dependent relaxation (Fleischhacker *et al.* 1999, Chirayath *et al.* 2010) and hyperreactivity of vascular smooth muscle (Fleischhacker *et al.* 1999). Both conditions are associated with a

higher risk of dysfunctional labour and caesarean section (Prendergast 2020). Smoking can also adversely affect myometrial artery function (Andersen *et al.* 2011). The process of labour puts a strain on the myometrial vasculature and the ability of these vessels to adapt to conditions of intermittent hypoxia/changing pH will be instrumental in successful parturition. An ever-growing proportion of the population exhibit obesity/diabetes and the underlying vascular dysfunction in this population may make it harder to withstand the rigours of labour and risks further elevating the proportion of dysfunctional labours that require intervention or caesarean section. Dyslipidaemias associated with obesity and diabetes affect myometrial membrane microdomains (Draeger *et al.* 2005), which in turn affects ion channels and signalling (Noble *et al.* 2006, Shmygol *et al.* 2007).

Future research

It is clear that there are gaps in our knowledge concerning hypoxia in labour and new questions arising following recent research findings. The difficulties of obtaining data in pregnant women are obvious, and animal models naturally have their limitations. It would be a large step forward if we have proteomic and metabolomic data on the acute and long-term effects of hypoxia on the myometrium. These findings could then be linked to signalling pathways, including those illustrated in Fig. 2, but also associated with inflammation, and, importantly, unexpected candidates arising from such studies, investigated. These approaches could be linked to transcriptomic studies from women in normal and dysfunctional labours (Chaemsaihong *et al.* 2013). We also recommend in turn that there is a resurgence of

Relation between contractions, blood flow and labour

Figure 3 Relationship between contraction, hypoxia and labour. (1) Contractions occlude blood vessels, producing hypoxia, increased lactate, and a fall in pH. (2) These changes decrease the strength and duration of the contraction, protecting the fetus from hypoxia. Perfusion is restored as the contraction relaxes, and the myometrial metabolites and pH are restored. (3) If the blood vessels do not fully recover, normal metabolites and pH will not restore, and subsequent contractions will be poor and the labour dysfunctional. (4) In normal labours many cycles of moderate hypoxia occur and engender HIFI (hypoxia-induced force increase), which help maintain and increase contractility until the end of labour.

studies with more refined assays detailed the biochemical and metabolic activity of human myometrium and relating this to labour outcomes. For example, how and when do glycogen or fatty acid deposit build in human myometrium, and what are the consequences for labour if these are inadequate. Similarly, we lack an understanding of lactate transporters in human myometrium (Åkerud *et al.* 2009) or how switches in lactate dehydrogenase isoenzymes occur and the functional consequences of aberrant shifts (Makkonen *et al.* 1982). As indicated previously, we are missing much specific information on myometrial blood vessels. These could hold the key to future therapeutic targets. A more in-depth knowledge of all these interactions stemming from hypoxia in labour is required, that can then be personalised with effective interventions and therapies, that will enable women to have better labours and their babies, a better birth. That oral bicarbonate study (Wiberg-Itzel *et al.* 2018), powerfully demonstrates that when such knowledge of the physiology of labour is obtained, it can be translated.

Conclusions

The outcome of the intermittent hypoxia of labour will be a balance between the force enhancing effects on the myometrium and the detrimental oxidative, metabolic and inflammatory stress response experienced by the smooth muscle of the vasculature and myometrium. This balance is intimately related to the success of human parturition. There will be a subset of pregnancies including those with abnormal placental development, that cannot withstand the rigours of labour (Turner *et al.* 2020).

As shown in Fig. 3, the myometrial metabolite changes, especially pH that arise from hypoxia (1), will feedback during the contraction to prevent tonic activity, and protect the fetus from hypoxic distress (2). If the myometrial vessels do not recover from the repetitive compressions, then products of anaerobic metabolism will build, metabolites are not restored as reserves such as glycogen are exhausted. These changes are associated with dysfunctional labours (3). If blood vessels restore perfusion, metabolites, pH and excitability return to normal levels and the next labour contraction occurs. The effect of the hypoxia will also trigger changes in myometrial signalling pathways, such as that produced by purinergic agonists, that gradually and safely augment contractions, HIFI (4).

Declaration of interest

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

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Author contribution statement

S W conceived the structure. S W, M A and C P drafted the text. S W and C P edited the text.

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