Is hypoxia good for labour?

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My research is focussed on understanding the relationships between function and metabolism in smooth muscle; the signalling pathways, interactions and relation to pathophysiology and clinical conditions. A focus of this work is the myometrium.

During labour contractions are of such intensity that blood vessels travelling through the uterus are compressed. The myometrium (and the fetus) experiences this intermittent hypoxia and we have shown *in vivo* that transient decreases of myometrial pH and ATP are associated with each contraction (Harrison *et al.*, 1994). Prolonged myometrial hypoxia and the fall in pH associated with it, can inhibit or even abolish uterine contractions. We have recently found that lactate can reduce myometrial force, pH and intracellular calcium transients (Hanley, Weeks & Wray, 2015). These local changes (myometrial capillary blood) are significantly associated with dysfunctional labour, *i.e.* those characterized by weak contractions, which is a major cause of unplanned Caesarean section (Quenby *et al.*, 2004). These changes in amniotic fluid lactate are prognostic for difficult labours (Wiberg-Itzel *et al.*, 2014). The results from a small randomized trial where the fall of pH is antagonised by bicarbonate are very exciting (Wiberg-Itzel, Wray & Åkerud, 2017). Dysfunctionally labouring women in a Swedish hospital were either given standard treatment, *i.e.* oxytocin, or oral bicarbonate in the form of an effervescent antacid drink, followed an hour later by oxytocin. This simple and cheap intervention significantly increased the number of vaginal deliveries.

A conundrum arises associated with these metabolic changes that are part of normal maternal physiology and labour. How in labour, despite repeated, transient episodes of local ischaemia, hypoxia and acidity, do contractions become progressively stronger, increasing in amplitude, frequency and duration over many hours? The mechanism of this vital increased contractility in the face of deleterious metabolic changes is not understood. We have however recently found that repetitive brief periods of hypoxia produce large and sustained increases in contractility, such as occurs in labour, in samples from pregnant but not non-pregnant uterus (Alotaibi, Arrowsmith & Wray, 2015). These findings suggest that ischemic tolerance is an adaptive response of the term uterus and is initiated when contractions reduce uterine blood flow and produce repeated hypoxic stresses. The released metabolites such as adenosine stimulates contractility *via* increasing Ca entry and stimulating intracellular pathways especially prostaglandin, suggesting the mechanism may be related to hypoxic preconditioning, which known for limiting infarct size in the heart. These findings also suggest that in women, whose labours are dysfunctional, this inherent mechanism is not working and thus therapeutic strategies to stimulate it would be of benefit.

Harrison N, Larcombe-McDouall JB, Earley L, Wray S. (1994). An *in vivo* study of the effects of ischaemia on uterine contraction, intracellular pH and metabolites in the rat. *J Physiol* **476**, 349-354.

Hanley JA, Weeks A, Wray S. (2015). Physiological increases in lactate inhibit intracellular calcium transients, acidify myocytes and decrease force in term pregnant rat myometrium. *J Physiol* **593**, 4603-14.

Quenby S, Pierce SJ, Brigham S, Wray S. Dysfunctional labor and myometrial lactic acidosis. *Obstet Gynec* **103**, 718-723.

Wiberg-Itzel E, Pembe AB, Wray S, Wihlbäck AC, Darj E, Hoesli I, Åkerud H. (2014) Level of lactate in amniotic fluid and its relation to the use of oxytocin and adverse neonatal outcome. *Acta Obstet Gynecol Scand* **93**, 80-55.

Wiberg-Itzel E, Wray S, Åkerud H. (2017) A randomized controlled trial of a new treatment for labor dystocia. *J Matern Fetal Neonatal Med* 2017 Jun 22: 1-8. doi: 10.1080/14767058.2017.1339268

Alotaibi M, Arrowsmith S, Wray S. (2015) Hypoxia-induced force increase (HIFI) is a novel mechanism underlying the strengthening of labor contractions, produced by hypoxic stresses. *Proc Natl Acad Sci USA* **112**: 9763-9768.