Mechanisms contributing to Failure-to-Progress in human labour

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Dysfunctional contraction resulting in failure to progress (FTP) in labour is a common indication for caesarean delivery (CD). For the mother, CD increases the incidence of serious, life-threatening conditions in future pregnancies (placenta praevia and accreta). For the offspring, a study of 1.9 million children born in Denmark and followed for 16 years found that those delivered by CD were at increased risk of diseases associated with immune deficiency (asthma, juvenile arthritis, inflammatory bowel disease, type 1 diabetes, celiac disease, leukaemia) (Sevelsted *et al*, 2015). Obesity and increased maternal age at first labour increase the risk of CD.

Strong labour contractions require calcium influx through voltage-gated calcium channels. Thus, uterine smooth muscle membrane potential is critical for strong labour progress. Poor contraction, resulting in failure to progress, is associated with prolonged labour. On the other hand, strong contractions must be separated by full uterine relaxation since this is essential for the restoration of placental blood flow, mandatory in the long hours of human labour. Failure of adequate relaxation results in non-reassuring fetal welfare, also necessitating CD. We have investigated the role and nature of potassium (K) channels in determining the resting membrane potential (RMP) and the relaxation between contractions before and during established labour in women.

In women progressing normally in labour RMP in myometrial strips was similar to that in non-labouring strips at term. High body-mass index (BMI), suggesting obesity, did not influence RMP. However, the action potential duration in labouring myometrium was significantly more brief and the associated contraction of smaller amplitude in a strong inverse relationship with maternal BMI. Action potential duration and contraction amplitude could be restored by agents that blocked the hERG channel, $K_V11.1$. Western blotting revealed that expression of the inhibitory regulatory subunit of hERG, KCNE2 protein, failed to increase in labour in high BMI women. During inhibition of hERG, complete repolarization and excellent relaxation occurred between action potentials and associated contractions, which would preserve placental perfusion.

The situation in older women giving birth for the first time was very different. Myometrial strips had very negative RMPs, -70 to -80mV, and RMP increased linearly with maternal age. This made it difficult to evoke depolarization to threshold for the initiation of contraction, thus contractions did not occur spontaneously, as usually occurs in term and labouring myometrium. Oxytocin caused the usual depolarization but this also failed to reach threshold for action potential initiation and contraction, and explains the well-known failure of this hormone to augment contraction. Western blotting suggests a role for $K_V7.4$ and/or $K_{IR}7.1$ in the very negative RMP in myometrium of older first-time labouring women. Blocking $K_{IR}7.1$ channels had a very detrimental effect on myometrial relaxation between action potentials.

Potassium channels have a major input in determining the level of membrane potential in human myometrium, facilitating relative quiescence before labour and contraction during labour. Dysfunction in the expression of these channels in labour is associated with FTP necessitating CD. Our results provide novel insights into the complexity underpinning the control of uterine contractility before and during labour in women. Failure to progress in labour can result from an excessive influence of the hERG potassium channel, in obesity, or result from an excessive influence of K_V7 and/or $K_{IR}7.1$ channels in older first-time labouring women. However, blocking these channels, to expedite the labour process, would likely give rise to a dangerous increase in contraction frequency with insufficient time for adequate restoration of placental blood flow between contractions and hence would threaten fetal wellbeing. On the other hand, agents that activate these K channels might be considered as candidates for suppressing preterm labour, but much additional investigation is required.

Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. (2015) Cesarean section and chronic immune disorders. *Pediatrics* **135**, 92-98.