Recording of biosignals from the human uterus, a basis for the development of new therapies in preterm labour and primary dysmenorrhoea

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The uterine contractility of labour preterm and at term pregnancy can be monitored by external recording by a pressure sensor and quantified as frequency of uterine contractions. After rupture of the fetal membranes intrauterine pressure can be studied and various parameters analysed, e.g. frequency and amplitude of contractions and the basal tone. The area under the curve (AUC) constitutes a summary of these parameters. The activity of the pregnant human uterus on a cellular level can be investigated *in vitro* by recording of isometric contractions of myometrial strips obtained at caesarean section. These methods have been a basis for the development of antagonists to the hormones oxytocin and vasopressin, which via an action over oxytocin and vasopressin V_{1a} receptors play a central role in the onset of preterm labour (see Åkerlund, Roczniki Akademii Medycznej w Białymstoku 2004; 49: 18-21).

Oxytocin and vasopressin are synthesised in the hypothalamus and released to the blood via the posterior pituitary lobe. During the stress of labour the uterus also produces oxytocin and vasopressin in substantial amounts. Recently, immunoreactive oxytocin and vasopressin have been demonstrated in the myometrium of pregnant women. The uterine oxytocin and vasopressin receptors vary to some extent during pregnancy and seem to be somewhat up-regulated at the onset of labour preterm and at term. After infusion of oxytocin and at advanced labour the receptor concentrations decrease.

Irrespective of the source of origin, antagonists of the oxytocin and vasopressin V_{1a} receptors may have a therapeutical effect in preterm labour and a project to develop receptor antagonists was commenced more than 20 years ago by our group in Lund together with the pharmaceutical company Ferring in Malmoe, Sweden. During the development phase different compounds were first investigated *in vitro* as to potency and duration of effect as well as regarding intrinsic agonistic action. They were later studied *in vivo* in non-pregnant, healthy volunteers by recording of intrauterine pressure and in patients with preterm labour in pregnancy weeks 33-35. The lead compound, atosiban, was also studied in women with very early preterm labour and then extensively in huge multi-centre trials. This substance was found to be at least as potent as previous therapies but to have a much higher specificity in action, leading to markedly reduced side effects. Atosiban is now marketed word-wide.

In non-pregnant condition uterine contractility *in vivo* can be measured by recording of intrauterine pressure by microtransducer catheters with one or several pressure sensors. Uterine blood flow in women is usually measured by thermodilution techniques or Doppler ultrasound. *In vitro*, the most common method of studying contractility for the non-pregnant uterus is by recording isometric contractions of myometrial strips obtained at hysterectomy.

The myometrial activity and uterine blood flow in women vary in a characteristic way during the menstrual cycle with well-coordinated contractions of high amplitude at the onset of menstruation and lower, localised contractile activity with higher basal tone at midcycle. In women with primary dysmenorrhoea the myometrial activity is increased and uterine blood flow reduced, which to a large extent causes the pain of the condition. Prostaglandins have a well-established role in the aetiology of the increased uterine contractility of primary dysmenorrhoea. An even more forceful uterine stimulant, which has to be shown of importance in the condition is vasopressin. The circulating level of this hormone in women with primary dysmenorrhoea is elevated 2-4 times, which can induce endometrial synthesis of contractile prostaglandins. Furthermore, in dysmenorrhoea the uterine sensitivity of vasopressin as well as the concentration of vasopressin V_{1a} receptors is increased. Oxytocin is a five times

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weaker uterine stimulant than vasopressin in non-pregnant condition. However, our group recently demonstrated oxytocin mRNA in the endometrium of non-pregnant women by in-situ hybridisation and real time PCR. The amount seems to vary during the menstrual cycle reaching the highest level around the time of ovulation. The importance of oxytocin as an aetiological agent of primary dysmenorrhoea is not clear.

A new therapeutic approach for primary dysmenorrhoea is to develop orally active antagonists of uterine vasopressin V_{1a} receptors. In the process of developing vasopressin V_{1a} and oxytocin antagonists for using non-pregnant condition, recording of contractile activity of human myometrial strips and uterine arteries of different diameters is a useful approach. Studies on such tissues from other species give little guidance. *In vivo*, initial testings in healthy, sterilised women with recordings of intrauterine pressure, experienced pain and plasma levels of biomarkers of uterine ischemia during administration of vasopressin and antagonists are a suitable option. Such recording can then be performed in dysmenorrheic subjects before commencing larger clinical trials. A therapeutic effect of vasopressin V_{1a} and oxytocin receptor blocking agents have been demonstrated by our group in dysmenorrhoea both for the peptide analogue atosiban and for the orally active compound SR 49059.