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Drugs acting on the pregnant uterus

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Summary
Parturition is a multifactorial, physiological process involving numerous interrelated maternal and fetal pathways, which may be both positive feed-forward and negative feedback. The mechanisms that initiate human parturition are not yet fully understood, despite decades of clinical, physiological and biochemical research by many investigators. However, it has been proposed that there are a number of stages that promote the myometrium to a contractile state, including the upregulation of receptors, prostaglandin production, and increased formation of intracellular contraction-associated proteins. The exact trigger for uterine contractions and which pathway is pre-eminent is yet to become clear. Cervical ripening is independent of the initiation of uterine contractions, although the pathways are not yet fully known, it does involve the release of proinflammatory cytokines, leukocyte infiltration into the cervix, the release and activation of extracellular matrix metalloproteinases, other proteins and glycoproteins. Drugs that act upon the pregnant uterus can be thought of as modifiers of these endogenous physiological pathways controlling normal myometrial contractility and cervical ripening. They may be characterized by their sites of action into agents acting upon prostaglandin pathways, progesterone receptors, β-adrenergic receptors, calcium channels, the oxytocin receptor and via nitric oxide. Drugs may also be functionally classified into agents used for the induction and augmentation of labour, for the termination of pregnancy, to treat postpartum haemorrhage, and to treat threatened preterm labour. This review aims to discuss the therapeutic drugs that act on the pregnant uterus.

Induction and augmentation of labour

Prostaglandins (PGs)

Endogenous PGs play a central role in human labour, acting to stimulate myometrial contractility and ripen the cervix in human parturition. PGs are derived from arachidonic acid (AA) found in membrane phospholipids of the cell. Human amnion is a major source of PGs and exhibits a substantial increase in the synthesis of PGE_2 with the onset of labour. This is associated with selective induction of the cyclo-oxygenase type-2 (COX-2) gene, with increased COX-2 activity and mRNA levels reported after spontaneous delivery, but no changes in COX-1. Pro-inflammatory cytokines induce COX-2 expression in amnion, chorio-decidual, and myometrial cells.

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Dinoprostone (PGE_2)

The local application of PGE_2 (dinoprostone) has been used for over three decades to induce softening of the cervix. The changes in the composition of the cervical connective tissue after PGE_2-induced cervical ripening are similar to those occurring in spontaneous cervical ripening. PGE_2 acts through the seven-transmembrane domain, G protein-coupled receptors, called EP receptors. These receptors are present in the human myometrium and cervix. PGE_2 is available as oral, cervical, vaginal and extramniotic preparations. Intravenous PGE_2 has been shown to have no advantage over oxytocin in augmentation of labour with an increased side effect profile. The use of intramniotic infusion and transcervical infusion of PGE_2 for second trimester termination of pregnancy are now largely obsolete. Intravaginal and intracervical PGE_2 are equally efficacious but the cervical route should be avoided, as it is more invasive. Oral administration is associated with increase incidence of side effects. A recent meta-analysis of the vaginal preparations revealed that PGE_2 tablet, gel and pessary were equally effective.

Gemeprost (PGE_1 analogue)

Gemeprost is a PGE_1 analogue that is relatively selective for the uterus and cervix. Its actions are similar to $PGF_{2\alpha}$ but are more 'potent' because of a modification to the 15-carbon position, which protects it from degradation. There is a time delay of several minutes between giving gemeprost and peak myometrial activity. One milligram of gemeprost administered vaginally is the optimum therapeutic dose. Three to 4 h are required for maximal effect to be observed. Contractile effects will occur in other smooth muscles notably the gastrointestinal tract and this causes the relatively infrequent side effects of nausea, vomiting and diarrhoea. Contraindications include severe asthma and known hypersensitivity to any PGs. Gemeprost is used for cervical softening before surgical termination of first trimester pregnancy, induction of second trimester abortion or following mifepristone for medical termination up to 63 days gestation or less. Because of its potency it is not recommended for induction of labour.

Dinoprost ($PGF_{2\alpha}$)

$PGF_{2\alpha}$ acts through the FP receptor, a G-coupled, seven transmembrane domained receptor. Administration of $PGF_{2\alpha}$ to pregnant women produces a dose-dependant increase in the force and frequency of uterine contractions. Uterine sensitivity to PGs increase with advancing gestation. Indications for use include termination of pregnancy in the second trimester, local application for tubal pregnancy and for post-partum haemorrhage. $PGF_{2\alpha}$ may be an effective agent for post-partum haemorrhage refractive to oxytocin treatment.

Misoprostol (PGE_1 analogue)

Misoprostol is a PGE_1 analogue developed for the treatment of peptic ulceration. It has been used for first and second trimester pregnancy termination administered either orally, in combination with mifepristone or intravaginally. It has also been used for induction of labour at term and for induction after fetal demise. Misoprostol has been used routinely as an alternative in the active management of the third stage of labour and as a treatment in post-partum haemorrhage. Published work to date suggests that misoprostol is as efficacious as vaginal or cervical PGs for the induction of labour. Oral misoprostol may be less effective, but may be associated with a lower Caesarean section rate. Misoprostol has several potential advantages for obstetric and gynaecological practice. It costs approximately 100 times less than other PGs, has a long shelf life, is easy to administer and does not require refrigeration.

Meta-analyses comparing misoprostol with other PGs are confounded by differences in doses and timing of misoprostol, routes of administration. A recent review suggests that misoprostol should not replace injectable uterotonics in the routine management of the third stage of labour. It is not clear whether the increased rates of tachysystole or maternal hyperstimulation associated with misoprostol use are associated with negative maternal or fetal outcomes.

Ergometrine

Ergometrine is an ergot alkaloid derivative. Historically it was used for induction of labour but this was associated with high fetal and maternal morbidity. It is now used as an agent in the third stage of labour and after evacuation of the uterus. It has good oral bioavailability, unlike ergotamine that has extensive first pass hepatic metabolism. Oral ergometrine has an onset of effect within 10 min whereas intravenous administration has onset in less than 1 min. Although it has a half-life of less than 2 h, it has a clinical effect that can last 3–6 h.

Ergometrine is a partial α-adrenergic agonist (weaker than ergotamine) and a partial agonist at 5-HT receptors. It is both a weak agonist and weak antagonist of dopaminergic receptors in various areas of the central nervous system (CNS).

Ergometrine causes dose-related increases in uterine smooth muscle contraction with an increase in resting tone and an even sustained contracture. This causes a non-physiological contraction making ergometrine inadvisable for use in management of labour but ideal in the use of post-partum haemorrhage and uterine atony. The gravid uterus is more sensitive to the effects of ergometrine than the nongravid uterus. In the UK, ergometrine is also available in combination with oxytocin (syntometrine).

Maternal adverse effects include nausea and vomiting. Cardiac arrhythmias (both tachyarrhythmias and bradyarrhythmias) have been reported as have acute hypertensive crises, seizures, cerebrovascular accidents and retinal detachment. Consequently ergometrine should be avoided if possible in pregnancy-induced hypertension or if there is an underlying hypertensive disorder.

Oxytocin

Oxytocin is a naturally occurring nonapeptide consisting of a ring structure of six amino acids and a side chain of three