Pharm-09B6 Discuss the pharmacodynamics of drugs that affect uterine tone.

**Background**

Uterus is an organ of the female reproductive system responsible for:
(1) providing an environment suitable for fetal growth
(2) delivery of fetus and placenta

Pharmacological manipulation of uterine tone serves many purposes:
↑uterine tone → induction of labour and minimise post-partum haemorrhage
↓uterine tone → slow down labour/prevent pre-mature labour

**Oxytocics – agents that ↑uterine tone**

(1) **Oxytocin**

Endogenous nonapeptide hormone
Produced in the hypothalamus and stored in the posterior pituitary
Syntocinon = synthetic oxytocin → commonly used clinically

Clear colourless liquid, vials of 5 or 10 IU/mL for IV or IM administration
Used to induce/accelerate labour, treatment of PPH
Mechanism of action – syntocinon binds oxytocin receptors → GPCR (Gq) → PLC
  → ↑IP$_3$/DAG → ↑[Ca$^{2+}$] → myometrial contraction
Note: pregnancy → ↑oestrogen → ↑oxytocin receptors in myometrium

Dose related ↑amplitude and frequency of uterine contractions with complete relaxation in between

**Pharmacodynamics**

CVS = vasodilatation → ↓MAP → reflex ↑HR; ↓coronary perfusion
RENAL = mild ADH effect → fluid retention ± volume overload
MATERNAL = ↑uterine contraction (esp. in multigravid) → possible uterine rupture
FETAL = ↓uterine blood flow → possible fetal distress

(2) **Ergometrine**

Ergot alkaloid
Clear colourless solution 500 microg for IM administration
Used in the treatment of PPH

Mechanism of action = agonist at $\alpha_1$, 5HT and D receptors
↑force of uterine contraction and ↑basal tone

**Pharmacodynamics**

CVS – vasoconstriction → ↑MAP; ↓coronary perfusion; ↑PVR
CNS – D$_2$ receptor stimulation @ CTZ → nausea and vomiting; cerebral vasoconstriction → headache, blurred vision and seizures
MATERNAL – uterine spasm
(3) Prostaglandins

Endogenous prostaglandins are produced by the endometrium. PGE and PGF are commonly used for:
- induction of labour
- ripening of cervix
- control PPH
- termination of pregnancy

e.g. PGE₂ = dinoprostone → vaginal pessaries used to prepare cervix for labour

e.g. PGE₁ = misoprostol → induce labour; induce abortion

e.g. PGF = dinoprost → induce labour, induce abortion

Mechanism of action – PG receptors → promote co-ordinated uterine contractions, ↑basal tone, cervix relaxation and ripening

Pharmacodynamics
CVS – ↑HR, ↓MAP
RESP – bronchospasm, ↑RR
RENAL – ↑RBF
MATERNAL – uterine spasm

Tocolytics – agents that ↓uterine tone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Mechanism</th>
<th>Comments</th>
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<tbody>
<tr>
<td>NSAIDs (e.g. indomethacin)</td>
<td>dysfunctional uterine bleeding</td>
<td>↓prostaglandins</td>
<td>risks: GI ulcers, renal dysfunction, hypertension</td>
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<tr>
<td>β2-agonists (e.g. salbutamol, terbutaline)</td>
<td>Prevent premature labour, delay labour by ~ 48 hours</td>
<td>smooth muscle relaxation</td>
<td>risks: tachycardia, tremor</td>
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<tr>
<td>Atosiban</td>
<td>inhibit premature labour</td>
<td>oxytocin receptor antagonist</td>
<td>risks: vasodilation, N+V</td>
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<tr>
<td>MgSO₄</td>
<td>treat blood pressure and pre-eclampsia</td>
<td>Smooth muscle relaxation</td>
<td>risks: fetal hypotonicity, fetal respiratory distress</td>
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<tr>
<td>Nifedipine</td>
<td>L-type Ca²⁺ channel antagonist</td>
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<td>risks: hypotension, peripheral oedema</td>
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<td>Volatiles (except N₂O)</td>
<td>Smooth muscle relaxation</td>
<td>NO release → smooth muscle relaxation</td>
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Examiner’s comments – 48% of candidates passed this question.

Candidates interpreted this question in a variety of different ways. The marking scheme was structured so that it was possible to do well with any reasonable interpretation. As the question clearly relates to uterine pharmacology, however, some part of the answer had to pertain to the actions of the drug on the uterus. It was not possible to pass, for example, by writing an essay purely on the non-uterine effects of volatile agents. A suitable approach would have been to list the common drugs which affect uterine tone, noting which increase and which decrease tone, and then to discuss the important drugs in more detail. Points which could be elaborated on
include, a) **the mode of action**, b) **the effect on basal tone and contractions**, both **force and frequency**, c) **how that effect varies with stage of pregnancy** and **dose of the drug**, d) **other actions on the uterus and cervix**, e) **important side effects**—particularly those on the uterus, or those which might limit the drug’s use.

Common mistakes were to confuse smooth and skeletal muscle; beta agonists and beta blockers; alpha, beta-1 and beta-2 effects; and the effects of nitrous oxide, volatile agents and intravenous anaesthetic agents. Many candidates were unsure as regards the relationship between systemic vascular resistance, heart rate and blood pressure. Candidates often included unnecessary information on dosage, pharmacokinetics and usage. Vague answers attracted no marks.