**DRUGS ACTING ON GENITOURINARY SYSTEM:**

**Oxytoxic drugs, Ergot alkaloids and uterine relaxants.**

**Physiological roles of oxytocin:**

Stimuli for oxytocin secretion include sensory stimuli arising from dilation of the cervix and vagina and from suckling at the breast.

***Uterus:*** The human uterus has a very low level of motor activity during the first two trimesters of pregnancy but increase progressively until initiation of labor. Oxytocin stimulates the frequency and force of uterine contractions and is highly dependent on estrogen, which increases the expression of the oxytocin receptors. Progesterone antagonizes the stimulant effect of oxytocin in vitro, and a decline in progesterone receptor signaling in late pregnancy may contribute to the normal initiation of human parturition.

**Breast.** Oxytocin plays an important physiological role in milk ejection. Stimulation of the breast through suckling or mechanical manipulation induces oxytocin secretion, causing contraction of the myoepithelium that surrounds alveolar channels in the mammary gland. This action forces milk from the alveolar channels into large collecting sinuses, where it is available to the suckling infant.

**Clinical uses of oxytocin:**

***Labor induction:*** Especially in situations in which the risk of continued pregnancy to the mother or fetus is considered to be greater than the risks of delivery or of pharmacological induction, such as

* + premature rupture of the membranes,
  + isoimmunization,
  + fetal growth restriction, and
  + uteroplacental insufficiency (as in diabetes, preeclampsia, or eclampsia).

Before labor is induced, it is essential to verify that the fetal lungs are sufficiently mature (*i.e.,* the lecithin-sphingomyelin ratio in amniotic fluid is >2) and to exclude potential contraindications.

***Augmentation of Labor;***

***Third Stage of Labor and Puerperium;*** Postpartum hemorrhage is a significant problem, after delivery of the fetus or after therapeutic abortion, a firm, contracted uterus greatly reduces the incidence and extent of hemorrhage.

**DRUGS ACTING ON GENITOURINARY SYSTEM:**

**Oxytoxic drugs, Ergot alkaloids and uterine relaxants.**

**Ergot alkaloids:**

* Ergot alkaloids are produced by *Claviceps purpurea*, a fungus that infects grain, especially rye under damp growing or storage conditions.
* This fungus synthesizes histamine, acetylcholine, tyramine, and other biologically active products in addition to a score or more of unique ergot alkaloids. These alkaloids affect a adrenoceptors, dopamine receptors, 5-HT receptors, and perhaps other receptor types.
* Examples of ergot alkaloids are
  + Amine ergot alkaloids
    - Ergonoveine (ergometrine)
    - Methysergide
    - Lysergic acid &
    - 6-Methylergoline
  + Peptide alkaloids
    - Ergotamine
    - Bromocryptine &
    - α-Ergocrytptine

**Mechanism of action of ergot alkaloids:**

* The ergot alkaloids act on several types of receptors. Their effects include agonist, partial agonist, and antagonist actions at
* alpha-adrenoceptors and
  + serotonin receptors (especially 5-HT1A and 5-HT1D; less for 5-HT1C, 5-HT2, and 5-HT3); and
  + Agonist or partial agonist actions at central nervous system dopamine receptors (Table 1).
* Furthermore, some members of the ergot family have a high affinity for presynaptic receptors, whereas others are more selective for postjunctional receptors.
* There is a powerful stimulant effect on the uterus that seems to be most closely associated with agonist or partial agonist effects at 5-HT2 receptors.

**Effect on vascular smooth muscles:**

* Ergotamine is typical of the ergot alkaloids that have a strong vasoconstrictor spectrum of action.
* Much of the vasoconstriction elicited by ergot alkaloids can be ascribed to partial agonist effects at a adrenoceptors, some may be the result of effects at 5-HT receptors.
* Ergotamine, ergonovine, and methysergide all have partial agonist effects at 5-HT2 vascular receptors. The remarkably specific antimigraine action of the ergot derivatives was originally thought to be related to their actions on vascular serotonin receptors. Current hypotheses, however, emphasize their action on prejunctional neuronal 5-HT receptors.
* Ergotamine and related compounds potently constrict most human blood vessels in a predictable, and prolonged manner. This response is partially blocked by conventional a-blocking agents. However, ergotamine's effect is also associated with "epinephrine reversal" and with *blockade* of the response to other a agonists. This dual effect represents partial agonist action. Because ergotamine dissociates very slowly from the a receptor, it produces very long-lasting agonist and antagonist effects at this receptor. There is little or no effect at b adrenoceptors.

**Uterine smooth muscle:**

* The stimulant action of ergot alkaloids on the uterus, as on vascular smooth muscle, appears to combine a agonist, serotonin, and other effects. Furthermore, the sensitivity of the uterus to the stimulant effects of ergot increases dramatically during pregnancy, perhaps because of increasing dominance of alpha-1 receptors as pregnancy progresses. As a result, the uterus at term is more sensitive to ergot than earlier in pregnancy and far more sensitive than the non-pregnant organ.  
    
  In very small doses, ergot preparations can evoke rhythmic contraction and relaxation of the uterus.
* At higher concentrations, these drugs induce powerful and prolonged contracture. Ergonovine is more selective than other ergot alkaloids in affecting the uterus and is the agent of choice in obstetric applications of these drugs

**Clinical uses of ergot alkaloids:**

**1. Migrain (hemicrania)**:

* Ergot derivatives are highly specific for migraine pain; they are not analgesic for any other condition. Although the triptan drugs discussed above are preferred by most clinicians and patients, traditional therapy with **ergotamine** can also be quite effective when given during the prodrome (early symptoms that might indicate the start of a disease before specific symptoms occur) of an attack; it becomes progressively less effective if delayed.
* The vasoconstriction induced by ergotamine is long-lasting and cumulative when the drug is taken repeatedly, as in a severe migraine attack. Therefore, patients must be carefully informed that no more than 6 mg of the oral preparation may be taken for each attack and no more than 10 mg per week.
* **2.Hyperprolactinemia**  
  Increased serum levels of the anterior pituitary hormone prolactin are associated with secreting tumors of the gland and also with the use of centrally acting dopamine antagonists, especially the D2-blocking antipsychotic drugs. Because of negative feedback effects, hyperprolactinemia is associated with amenorrhea and infertility in women as well as galactorrhea in both sexes.  
  **Bromocriptine** is extremely effective in reducing the high levels of prolactin that result from pituitary tumors, with dose of 2.5 mg two or three times daily.

**3. Postpartum hemorrhage**  
For postpartum hemorrhage, oxytocin is the preferred agent for control of postpartum hemorrhage, but if this peptide agent is ineffective, ergonovine maleate, 0.2 mg usually given intramuscularly, can be tried.   
  
4. **Diagnosis of variant angina**  
Ergonovine given intravenously produces prompt vasoconstriction during coronary angiography to diagnose variant angina if reactive segments of the coronaries are present.  
  
5. **Senile cerebral insufficiency**  
Dihydroergotoxine, a mixture of dihydro-a-ergocryptine and three similar dihydrogenated peptide ergot alkaloids (ergoloid mesylates), has been promoted for many years for the relief of senility and more recently for the treatment of Alzheimer's dementia. There is no useful evidence that this drug has significant benefit.

**Toxicity & contraindications of ergot alkaloids:**

* ***GIT:***
* The most common toxic effects of the ergot derivatives are gastrointestinal disturbances, including diarrhea, nausea, and vomiting. Activation of the medullary vomiting center and of the gastrointestinal serotonin receptors is involved

***Vasospasm:***

* A more dangerous toxic effect of overdosage with agents like ergotamine and ergonovine is prolonged vasospasm, leads to gangrene and require amputation.

***Contra-indications:***

* + Obstructive vascular diseases and
  + Collagen diseases.