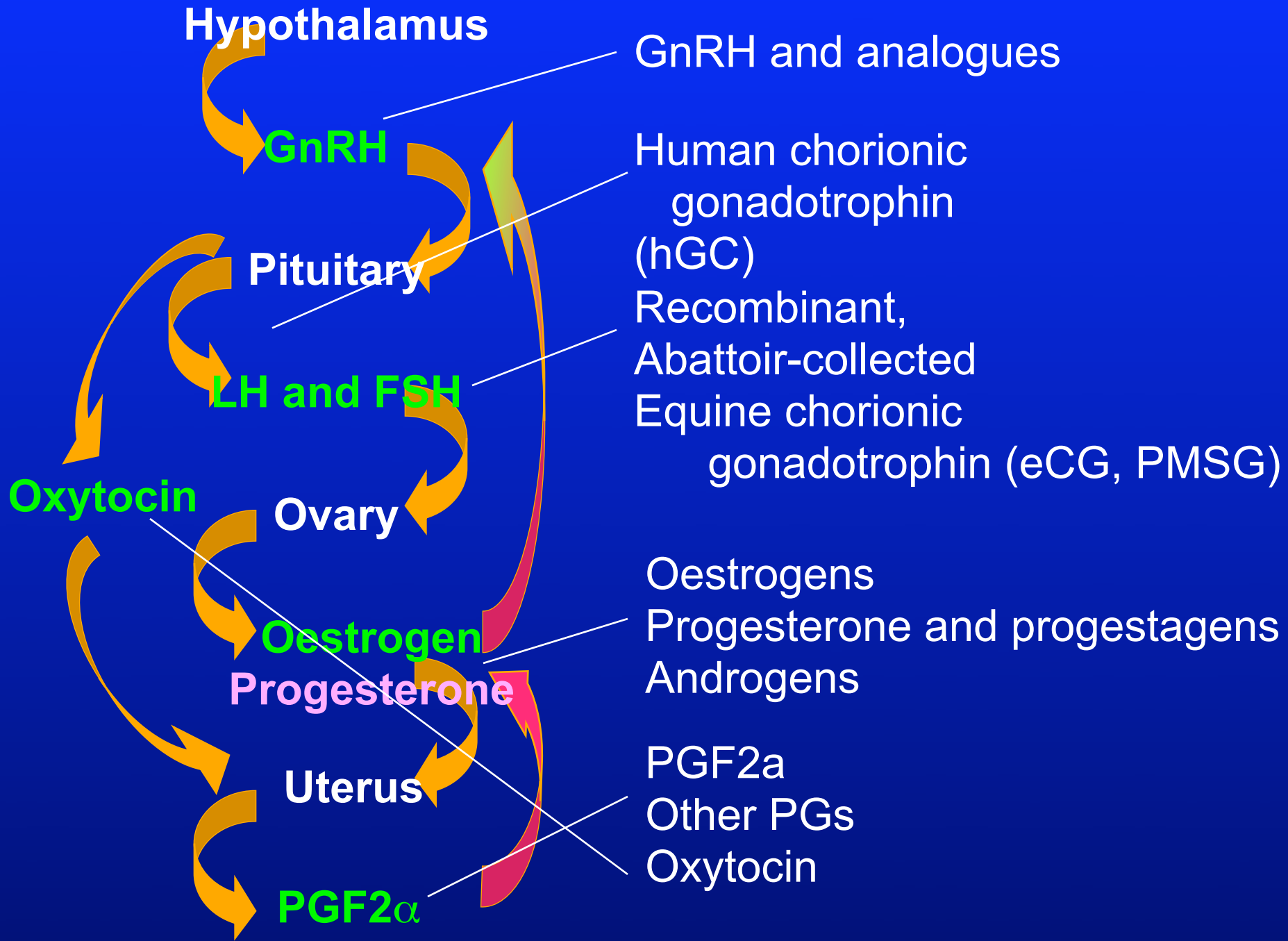


Pharmacological agents acting upon the reproductive system





Gonadotrophins

- Stimulate reproductive activity in anoestrous animals
- Stimulate animals to breed during their non-breeding season
- Superovulation for embryo transfer
- For diagnostic use (e.g. in testing for rig horses)

GnRH and analogues

Produce reflex secretion of LH

Limited effect on FSH

- Causes luteinisation of a large follicle
- Causes ovulation of pre-ovulatory follicles
- May help recruit follicles in suboestrous animals

Buserelin (analogue)

Receptal (native hormone)

GnRH and analogues

- 1) In oestrus synchronisation programmes (ovsynch)
- 2) In superovulation programmes to tighten the time of ovulation
- 3) In the mid-luteal phase, to try to increase pregnancy rates
- 4) To stimulate oestrus in anoestrous animals (not very efficient!)

Gonadotrophins: LH

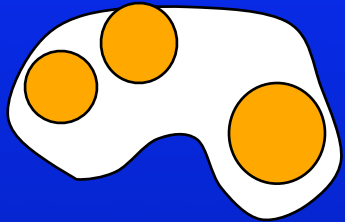
LH is not available

hCG is used in horses (and cows) to tighten timing of ovulation

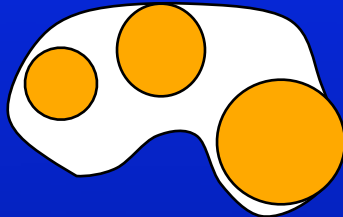
hCG is used for endocrine challenge tests

hCG can be used to stimulate libido in low-libido males (better than testosterone)

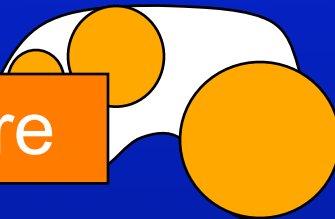
Controlling the time of ovulation



Coming into heat

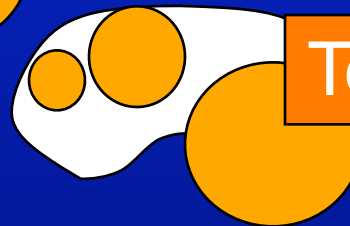


In heat: +ve teasing response



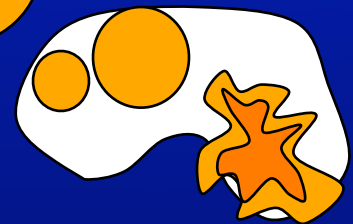
In heat: not ready to be covered

hCG to get from here



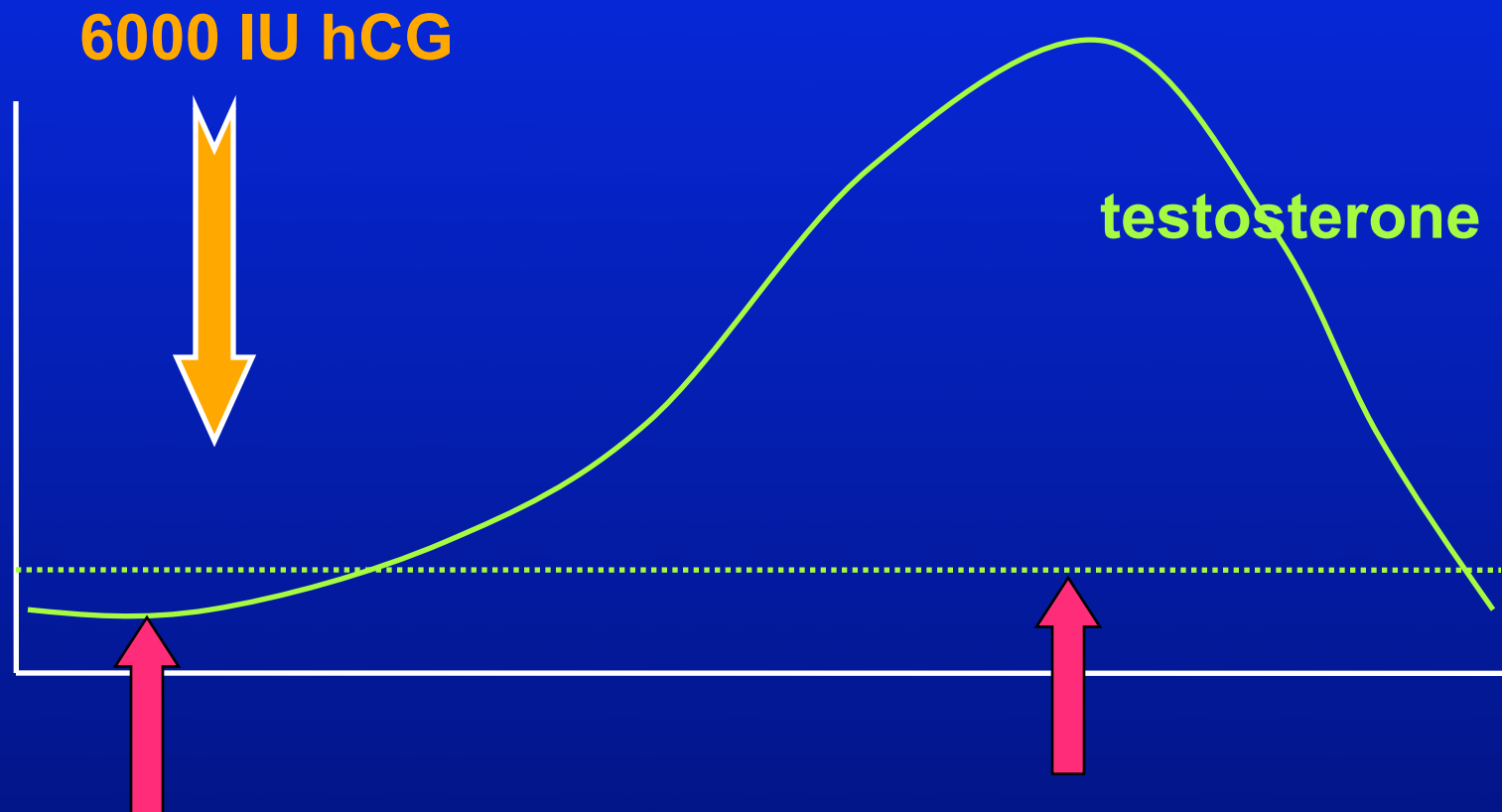
To here

In heat: ready to be covered



Still in heat: TOO LATE!!

hCG challenge test for rigs



Gonadotrophins: FSH

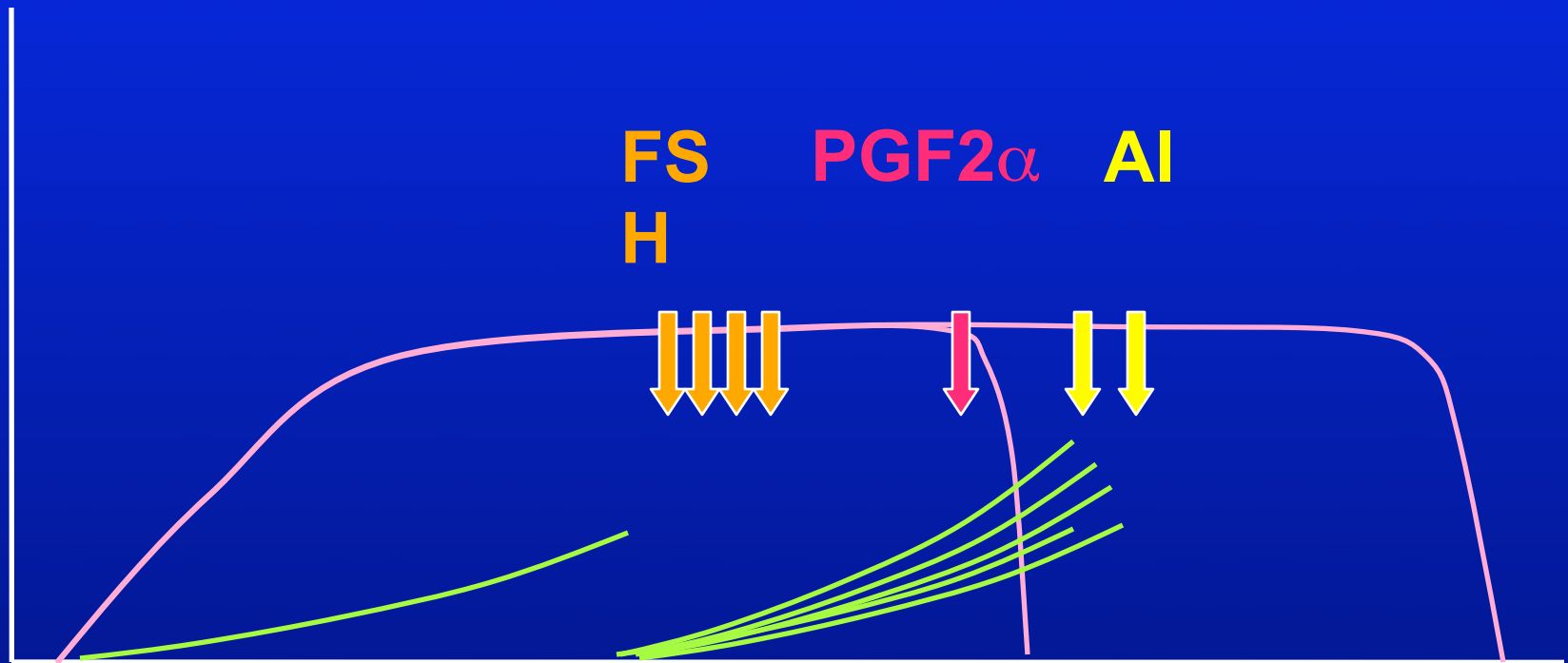
FSH is available as recombinant or abattoir-derived material

Used for superovulation

Has a short $T_{1/2}$ so has to be given often

Is the only hormone that can be used to superovulate mares

Typical superovulation regimen for cattle



Gonadotrophins: eCG

Equine Chorionic Gonadotrophin (also known as Pregnant Mares' Serum Gonadotrophin)

Long $T_{1/2}$ so can be given once

But has variable LH activity, as well as its FSH activity

... hence superovulation responses are unpredictable (so FSH is now more favoured)

Gonadotrophins: eCG

Also used to stimulate ovulation rate in out-of-season breeding in sheep

And to improve responses of anoestrous beef cattle to oestrus induction / synchronisation regimens

In both, it is acting by 'boosting' endogenous gonadotrophin activity

Steroids: Oestrogens

- Affect uterine muscle and blood flow
- Stimulate uterine immunity
- Causes oestrous behaviour (after progesterone priming)
- Weakly luteolytic
- Affects follicular waves
- Promotes mammary development

Oestrogen:- uses in oestrus synchronisation programmes

- To regulate follicular waves, by causing regression of all large antral follicles and emergence of a new follicular wave
- To cause +ve feedback secretion of LH
- To augment oestrus behaviour
 - Oestradiol (benzoate)
 - Ethinyloestradiol
 - Stilboestrol

Oestrogen:- other uses

- To stimulate uterine immunity and responsiveness to oxytocin
- To treat misalliance in dogs, by altering tubal transport of gametes/zygote
- To cause oestrus behaviour, in (e.g.) ewes that are used in sheep AI centres

Oestrogen:- disadvantages of use

- Down regulates hypothalamus OE-Rs in postpartum period
- Long-term treatment results in masculinisation
- Treating bitches runs the risk of causing pyometra
- Behavioural oestrus DOES NOT mean that there is physiological oestrus

Progesterone and progestagens

- Progesterone can be given by injection or absorbed through the vaginal mucosa
- Progestagens can be absorbed orally (monogastric animals) or (some) through the vaginal mucosa
- Or can be given as s/c implants (e.g. in the ear)

Progesterone and progestagens

- Progesterone (injection, CIDR)
 - Altrenogest (Regumate; oral in sow and mare)
 - Megestrol
 - Proligesterone
 - Hydroxyprogesterone
 - Medroxyprogesterone
 - Flugestone
 - Norgestomet (ear implant in cow)
-
- Oral; for cycle regulation in the bitch (queen)
- Oral; in the bitch intravaginal in the ewe and doe

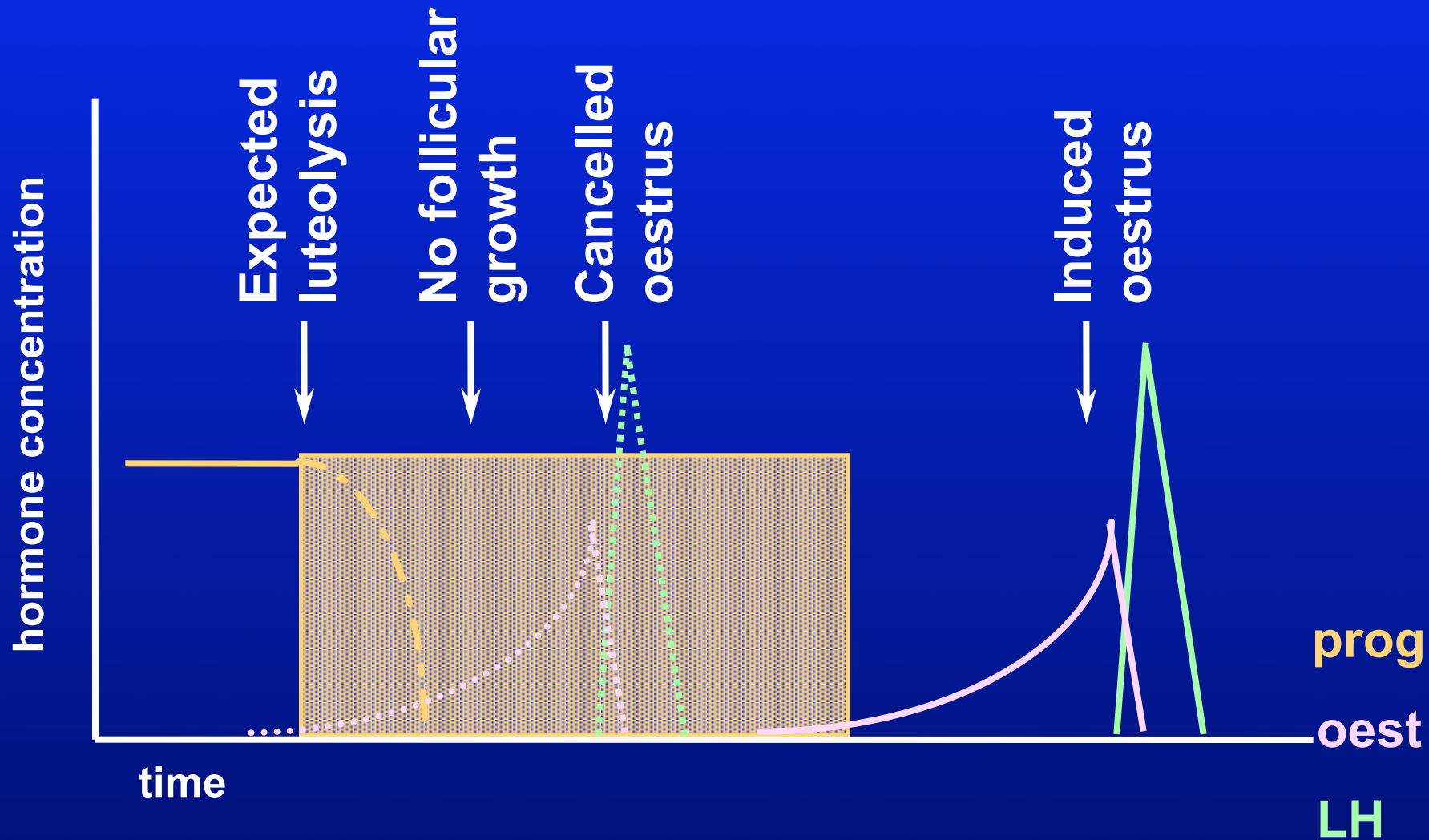
Effects of progestagens

- Cause -ve feedback on gonadotrophin secretion
- Stimulate (short term) synthesis and accumulate of gonadotrophins in the pituitary
- Eliminate oestrus behaviour in females
- Reduce aggressive/masculine behaviour in males

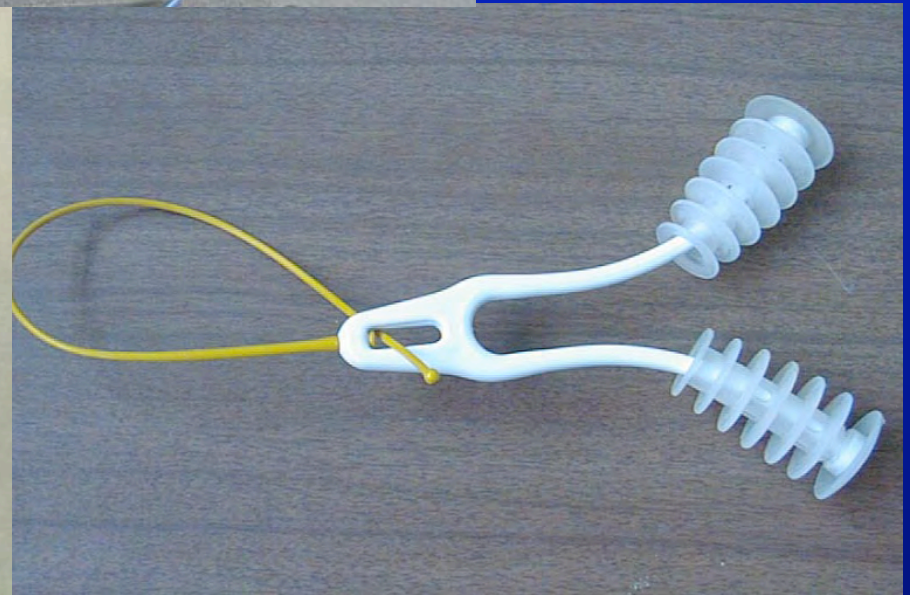
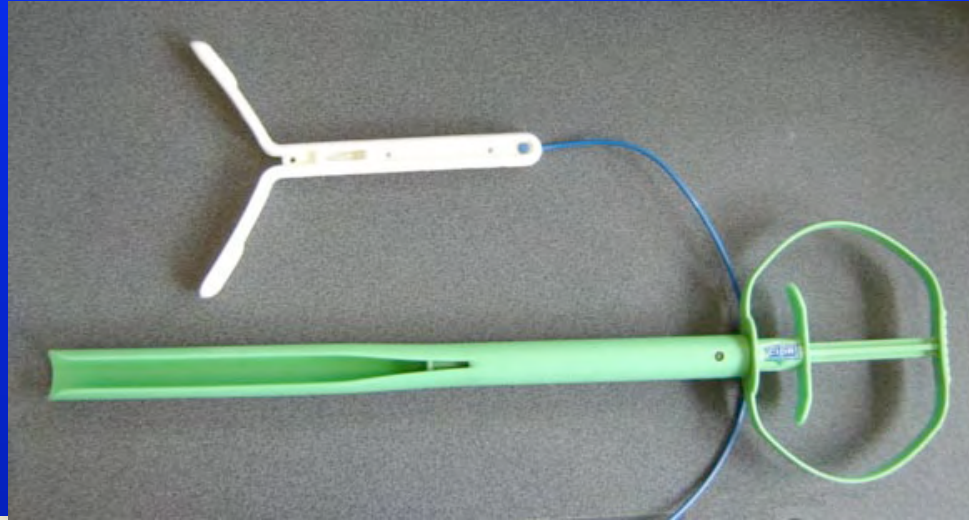
Uses of progestagens

- Main use is in oestrus synchronisation programmes or in the treatment of anoestrus
- Inducing out-of-season breeding in horses and sheep
- Regulation of the bitch's oestrous cycle
- Treatment of aggressive/wandering dogs
- Treatment of pseudopregnancy in dogs
- Augment pregnancy rate in cattle (mares)

Controlling oestrus with progesterone: principle



Intravaginal progesterone inserts



Inserting norgestomet implants



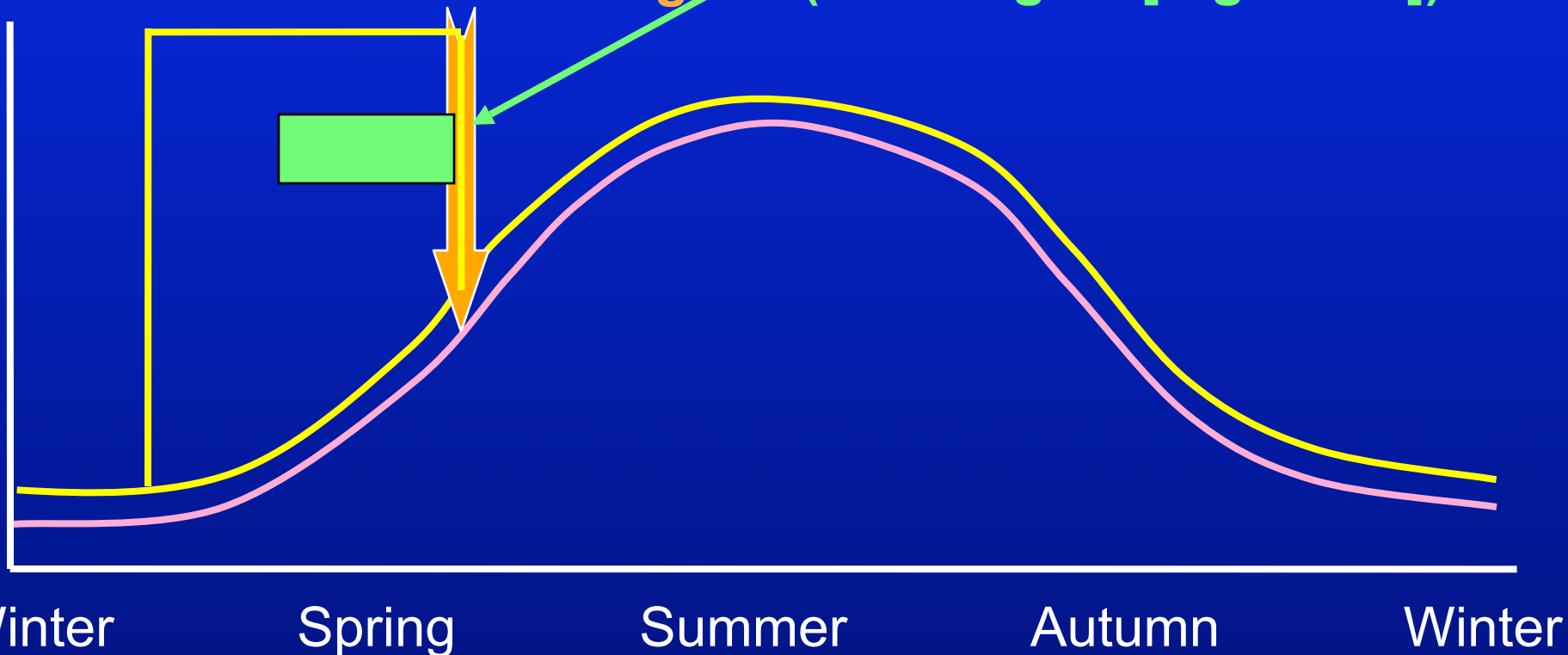
Early breeding in mares

Daylength

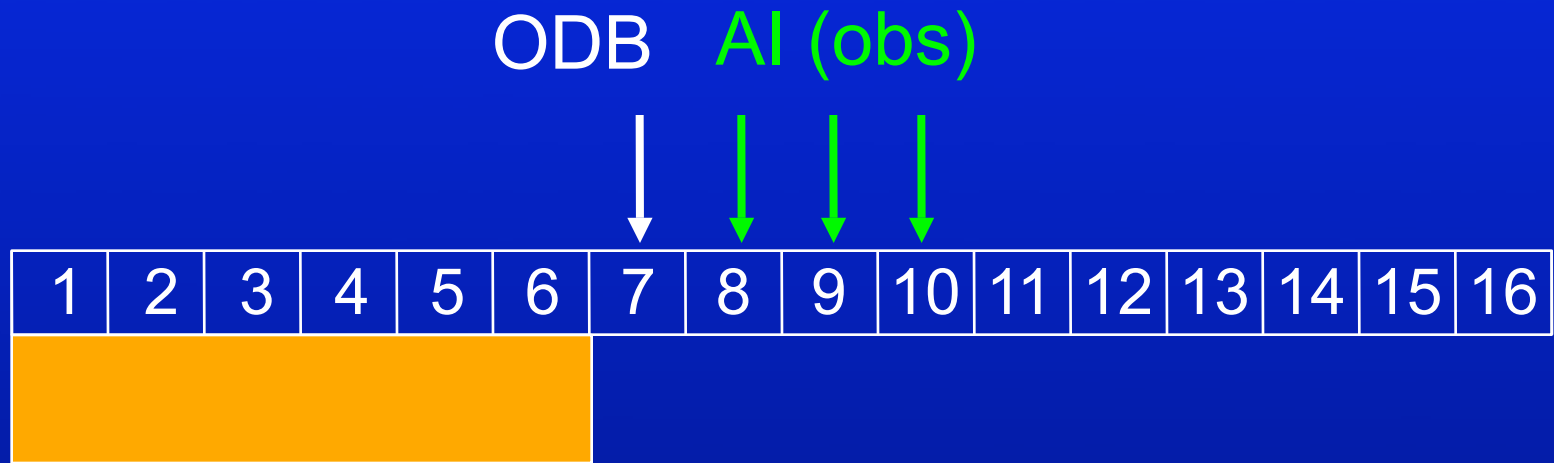
Gonadotrophin secretion

Oral progestagen
(Altrenogest [regumate])

Start of covering

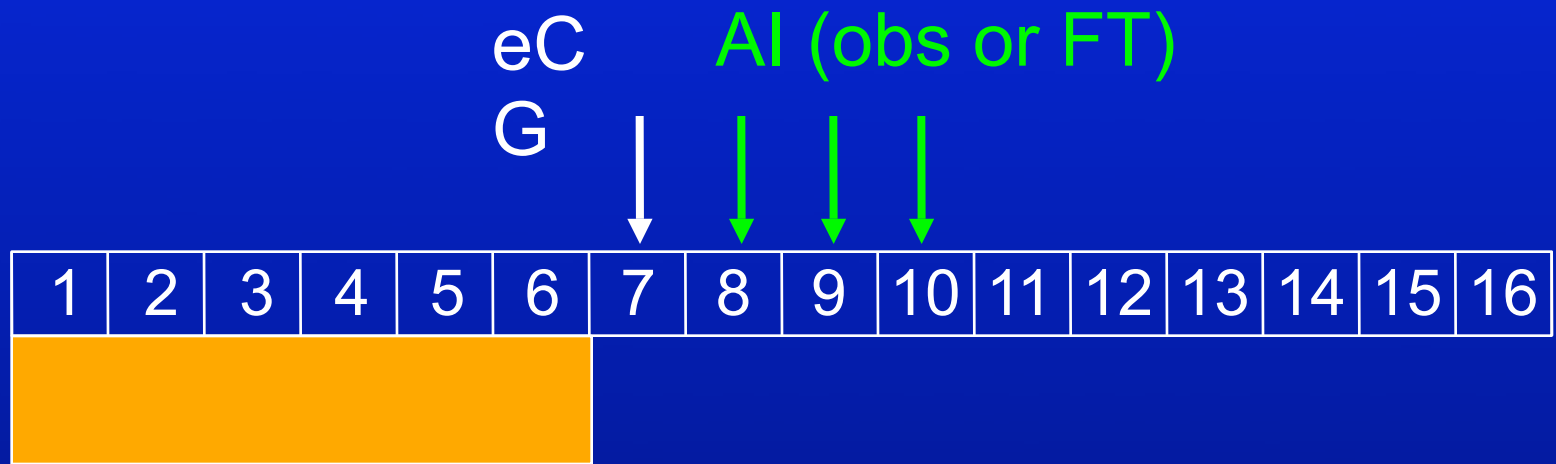


Progesterone and oestrogen for treating bovine anoestrus



ODB = oestradiol benzoate

Progesterone and gonadotrophins for treating anoestrous beef cattle



Progesterone and gonadotrophins for inducing out-of-season breeding in sheep



Problems of progestagens

- Adversely affect uterine immunity, so there are potential contraindications in animals with uterine/vaginal infections
- Long-term progesterone treatment reduces conception rates
- Predisposes to pyometra in the bitch
- Long-term treatment results in increased appetite and fluid retention (esp. in the bitch)

Androgens

- Use for anabolic effect (anabolic steroids)
- Control of the oestrous cycle in the bitch (safer than progestagens?)
- SHOULD NOT be used to stimulate libido in low-libido males
 - Testosterone
 - Boldenone
 - Stanozolol
 - Nandrolone
 - Methandrol
 - Ethylestrenol

Antiprogesterone

- Being developed as an abortifacient for the bitch (safer than misalliance injections)

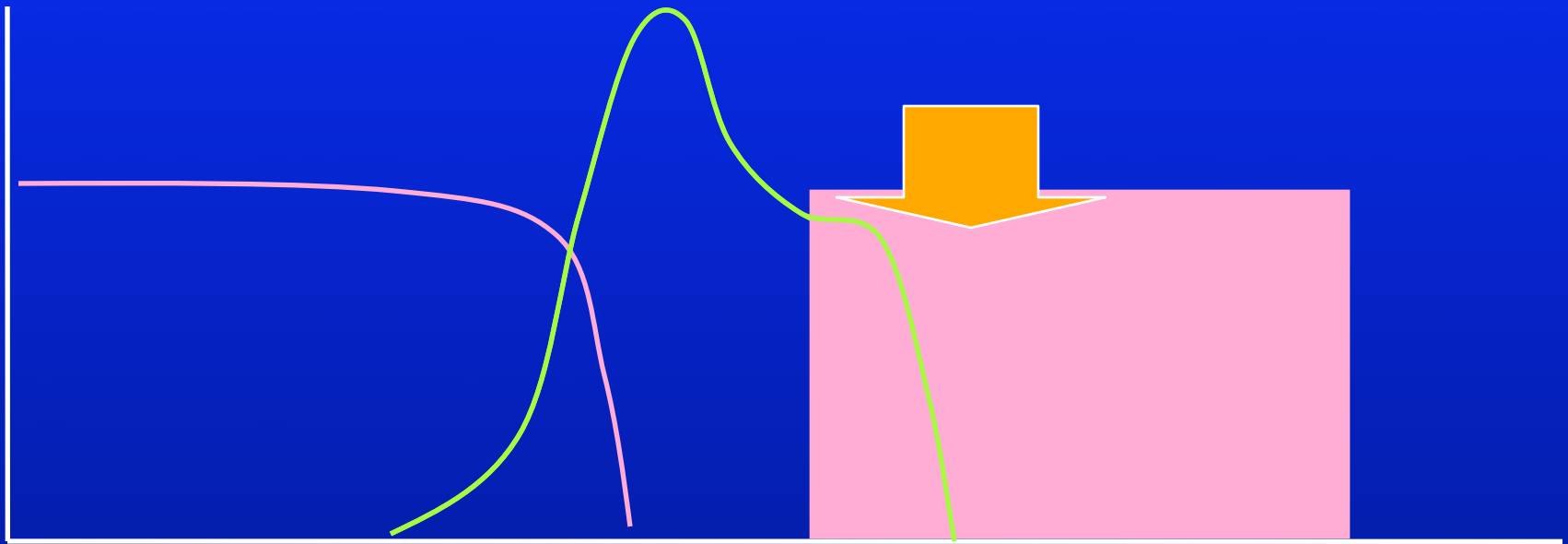
How to manage misalliance in the bitch?

- Oestrogen/progesterone predispose to pyometra
- PGF2a is poorly tolerated
- RU486 only moderately successful

Therefore

- Spey or allow the bitch to go to term

Pseudopregnancy in the bitch



Dopamine agonists, e.g. bromocriptine or cabergoline

Prostaglandins

- $\text{PGF}_2\alpha$ causes luteal regression
- and has a moderate ecboic action
- PGE_2 may have useful pharmacological actions within the reproductive tract
 - $\text{PGF}_2\alpha$ (native) dinoprost
 - analogues: cloprostenol (“estrumate”)
luprostenol and etiproston
 - PGE_2 : dinoprostone

Prostaglandins

Given by

- Intramuscular injection
- Injection under the mucosa of the vagina
- Intracervical pessary

Use of prostaglandins

Oestrus synchronisation

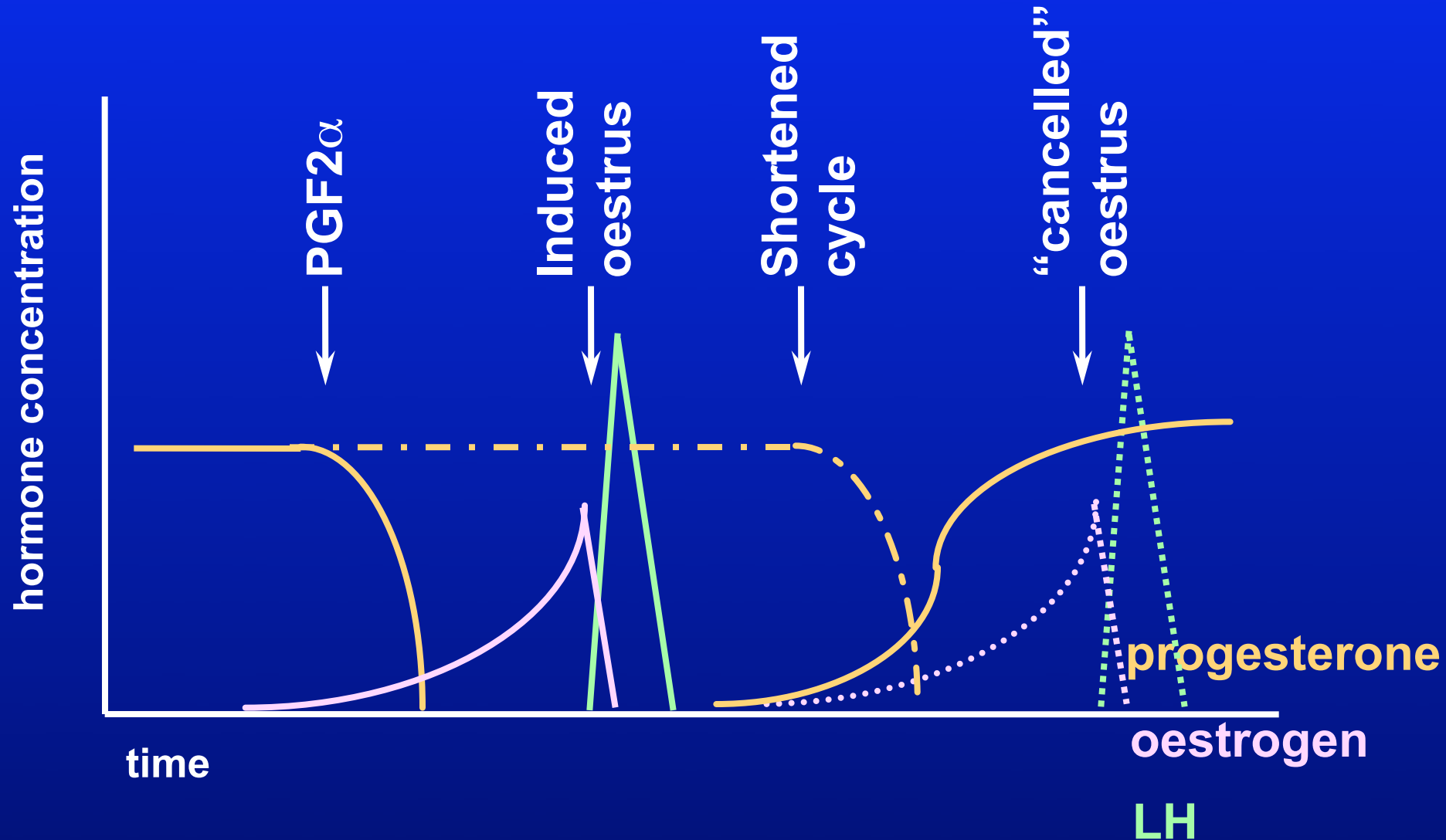
Induction of oestrus (e.g. in non-observed oestrus)

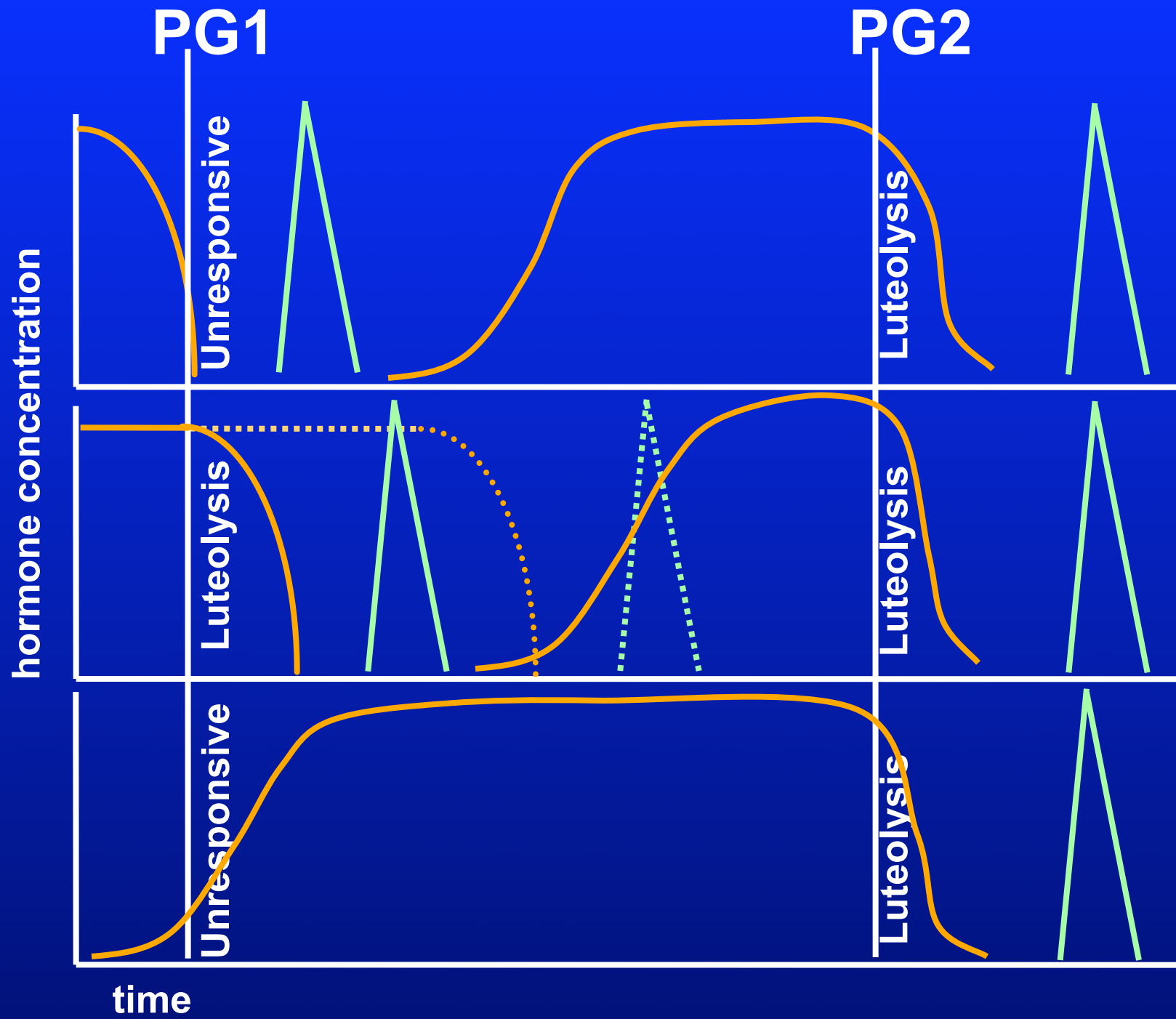
Induction of oestrus in cows with uterine infection and a persistent corpus luteum

Induction of parturition (full term) in cows

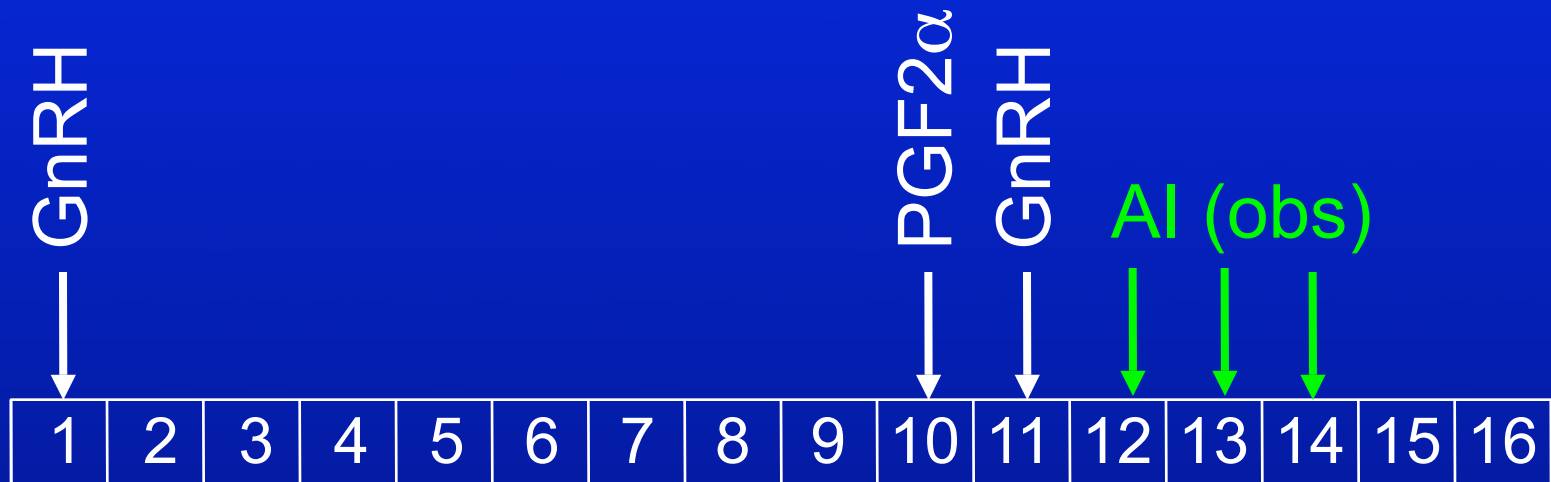
Maybe use PGE to force cervical dilation (e.g. in sheep with 'ringwomb')

Manipulating oestrus by controlling the length of the luteal phase with $\text{PGF2}\alpha$

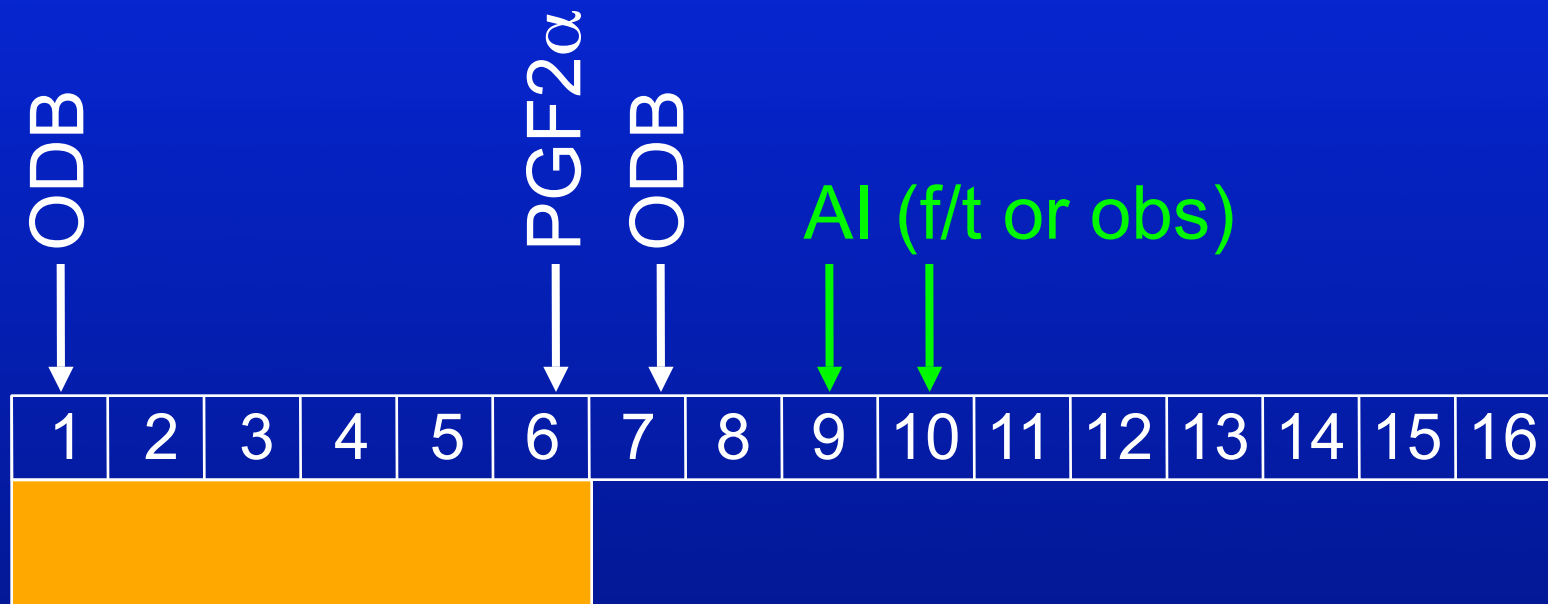




Gonadotrophin and PGF2 α to induce or synchronise oestrus (Ovsynch)



Progesterone, oestrogen and PGF2 α to induce or synchronise oestrus (Genermate)



Drugs that act upon uterine muscle

Oxytocin: contraction, also milk let-down

Prostaglandin F_{2α}: short-term ecbolic action

Ergot alkaloids (ergotamine, ergotoxine)

Clenbuterol (smooth muscle relaxant)

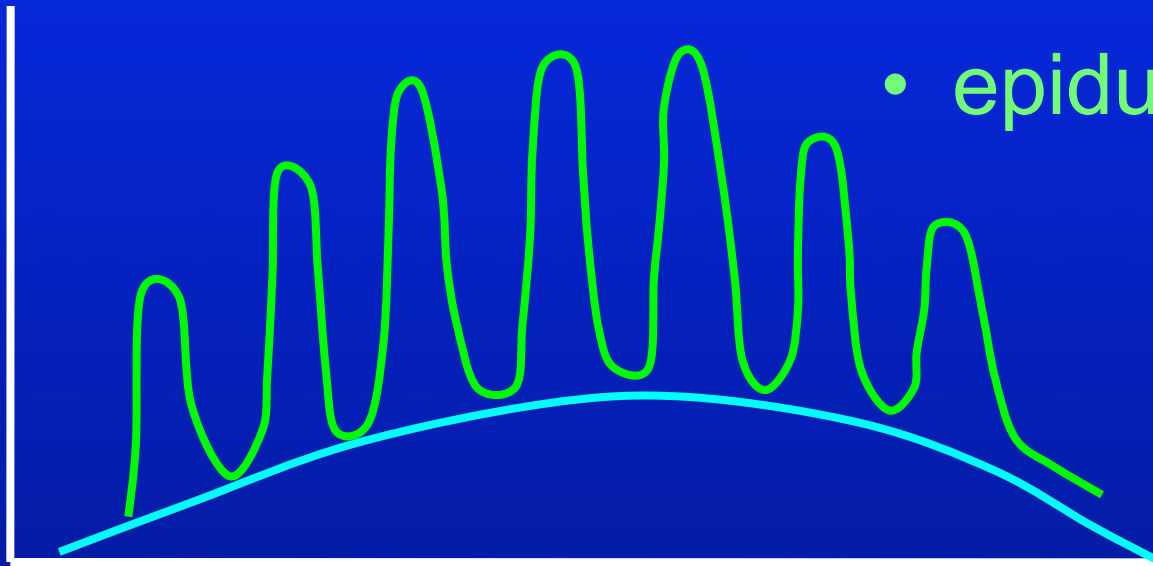
Isoxpurine (smooth muscle relaxant)

[“ecbolic” = making uterine muscle contract]

Control of expulsive forces in parturient cows

Abdominal contraction:

- epidural



Uterine contraction

- +ve: oxytocin
- -ve: clenbuterol, isoxpurine