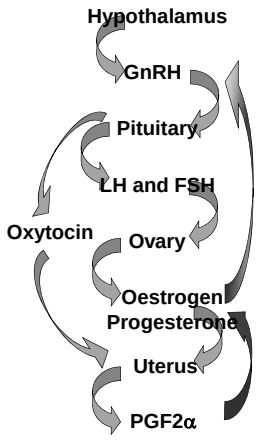
Pharmacological agents acting upon the reproductive system

Massey University

Female hormones



Hypothalamus	**GnRH**	GnRH and GnRH analogues
Pituitary	**LH**	Human chorionic gonadotrophin (hGC)
	FSH	Recombinant, Abattoir-collected FSH Equine chorionic gonadotrophin (eCG, PMSG)
Ovary	**Oestrogen**	Oestrogens
	Progesterone	Progesterone and progestagens Androgens
Uterus	**PGF2α**	PGF2a Other PGs
	Oxytocin	Oxytocin

GnRH and analogues – what do they do?

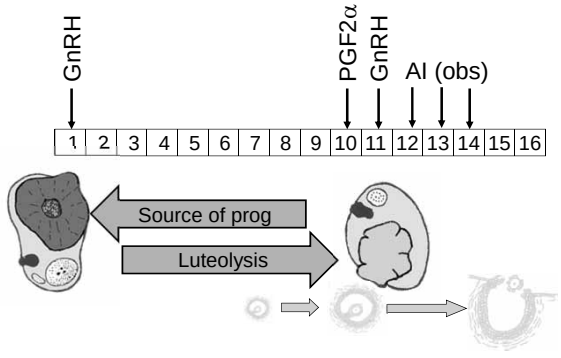
Buserelin (analogue)
Receptal (native hormone)

Produce reflex secretion of LH
Limited effect on FSH

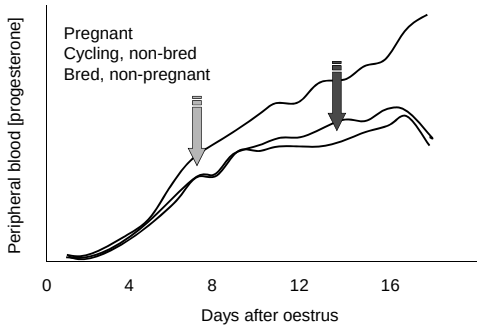
GnRH and analogues – what do they do?

- Causes luteinisation of a large follicle
- Causes ovulation of pre-ovulatory follicles
- Stimulates the CL to produce progesterone
- May help recruit follicles in suboestrous animals

Gonadotrophin and PGF2α to induce or synchronise oestrus (Ovsynch)

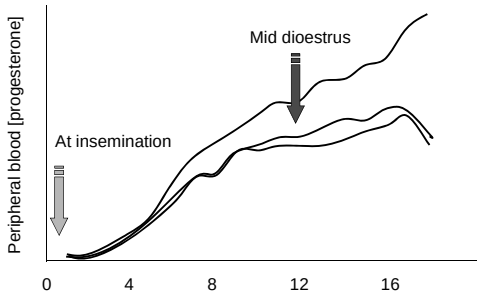


Progesterone, pregnancy and GnRH



From Bulman & Lamming, 1978

GnRH to increase pregnancy rate?



Pregnant
Cycling, non-bred
Bred, non-pregnant

GnRH at insemination or in dioestrus

- In normal cows GnRH at insemination may ↑ PR by 5-12%, depending on dose, service # etc (up to 22% in subfertile cows
- GnRH on Day 11 to 13 is the most consistently beneficial:

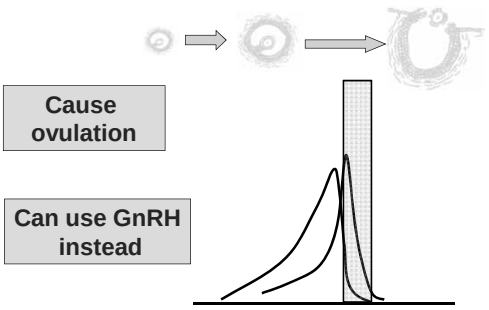
  Range of responses: 0.91-1.35 x untreated controls, 95%CI 1.03-1.11

(Lean *et al*., 2004)

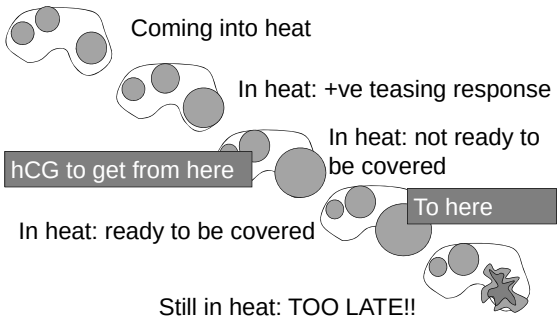
Gonadotrophins: LH- what does it do?

- LH is not available
- hCG is the closest drug that is licenced for use in animals
- It 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)*

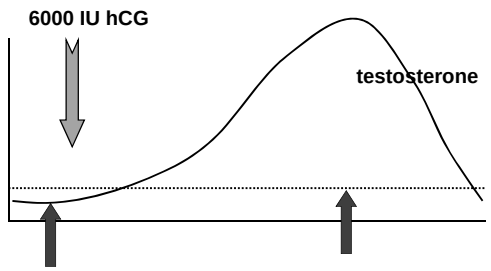
Gonadotrophins: LH



Controlling the time of ovulation



hCG challenge test for rigs



Gonadotrophins: FSH – what does it do?

FSH is available as recombinant or abattoir-derived material

Equine Chorionic Gonadotrophin (a.k.a. Pregnant Mares' Serum Gonadotrophin)…. Not the same as FSH

Increases ovulation rate

Gonadotrophins: FSH and eCG

FSH is only used for superovulation

Has a short $T_{½}$ so has to be given often

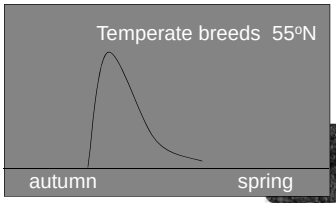
eCG has a ong $T_{½}$ so can be given once

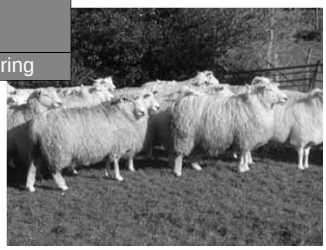
But has variable LH activity, as well as its FSH activity

Gonadotrophins: eCG

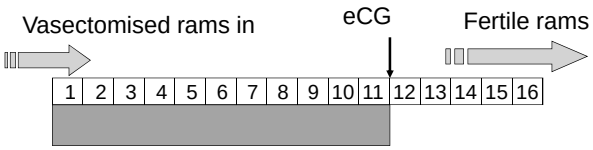
- Also used to stimulate ovulation rate in out-of-season breeding in sheep
- And to improve responses of anoestrous beef cattle to oestrus induction / synchronisation regimens
- In both, it is acting by 'boosting' endogenous gonadotrophin activity

Sheep breeding seasons….





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



Steroids: Oestrogens – what do they do?

- Oestradiol (benzoate, cyprionate)
- Ethinyloestradiol
- Stilboestrol

Steroids: Oestrogens – what do they do?

- Stimulate uterine muscle, blood flow and immunity
- Cause oestrous behaviour after progesterone priming
- Weakly luteolytic
- Affect follicular waves
- Act as a growth promotant

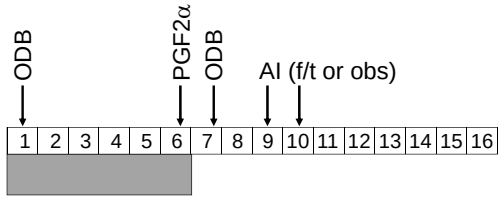
There are lots of things you *can* do with oestrogens… BUT

- EU regulations state that oestrogens cannot be used in the lifetime of animals that produce food that is sold in the EU
- Hence, oestrogens cannot be used in any farm species in NZ

Use in oestrus synchronisation

- Regulate follicular waves, by causing regression of all large antral follicles and emergence of a new follicular wave
- Cause +ve feedback secretion of LH
- Augment oestrus behaviour

Progesterone and oestrogen (± PGF2α) to induce or synchronise oestrus



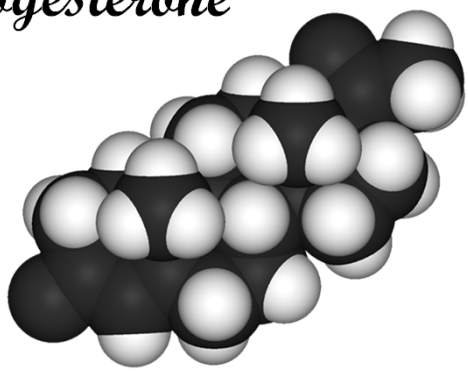
Oestrogen:- other uses

- 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



Progesterone and progestagens

- Progesterone (injection, intravaginal)
- Altrenogest (Regumate; oral in sow and mare)
- Megestrol
- Proligesterone
- Hydroxyprogesterone

  } Oral; for cycle regulation in the bitch (queen)

- Medroxyprogesterone
- Flugestone

  } Oral; in the bitch intravaginal in the ewe and doe

- Norgestomet (ear implant in cow)

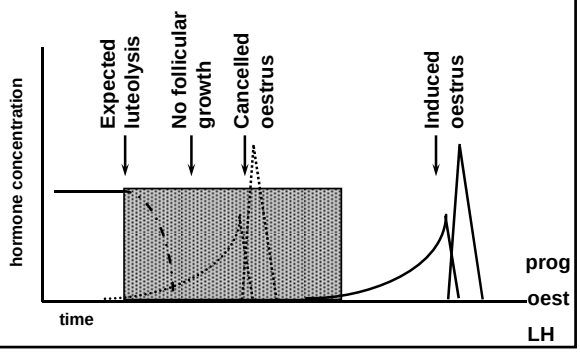
Progesterone – what does it do?

- 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

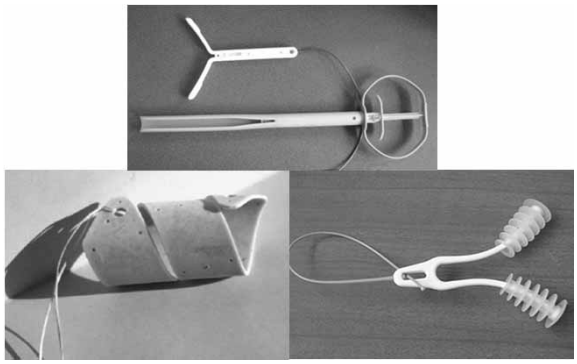
Progesterone – how do we use it?

- Oestrus synchronisation programmes or treatment of anoestrus
- 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)

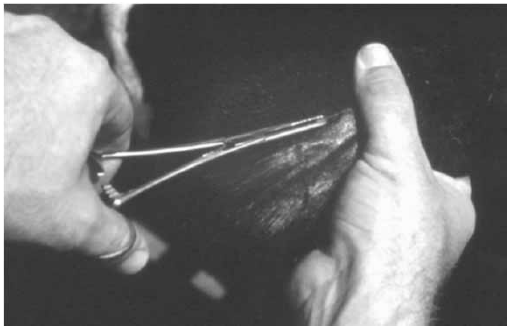
Controlling oestrus with progesterone: principle



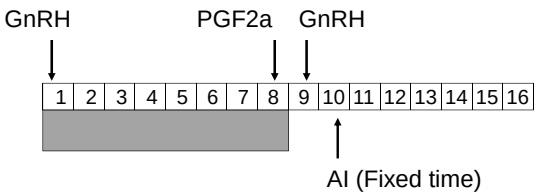
Intravaginal progesterone inserts



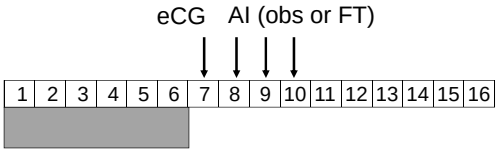
Inserting norgestomet implants



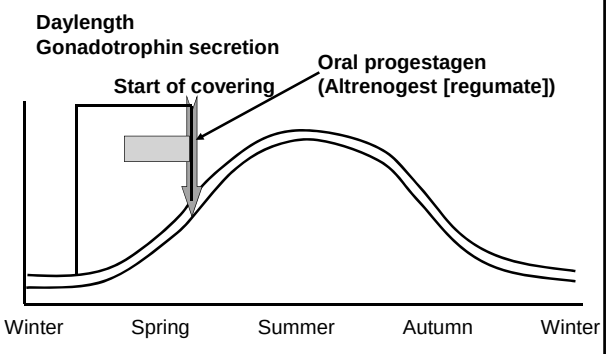
Treating bovine anoestrus



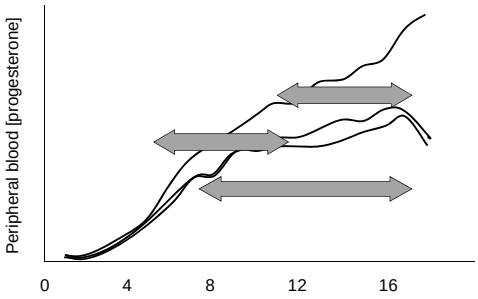
Progesterone and eCG for treating anoestrous beef (?dairy) cattle



Early breeding in mares



Progesterone to improve pregnancy rate in cattle



Pregnant
Cycling, non-bred
Bred, non-pregnant

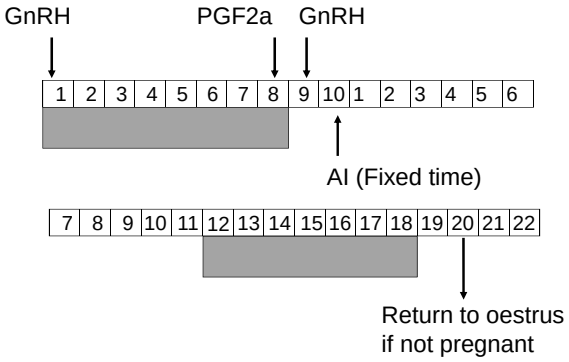
Resynchronisation

- Variable results, which differ greatly between both trials and herds within trials
- Overall, little benefit from supplementing progesterone during dioestrus (0.96 to 1.07 x untreated controls),

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)

Resynchronisation



Antiprogesterone

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

Antiprogesterone

How to manage misalliance in the bitch?

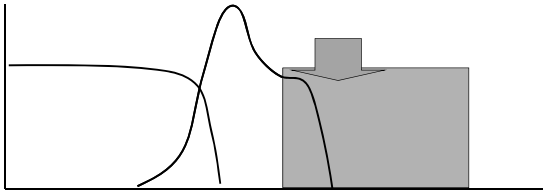
- Oestrogen/progesterone predispose to pyometra
- PGF2a is poorly tolerated
- Mifepristone and aglepristone (prog receptor antagonists) are only moderately successful

Therefore

- Spey or allow the bitch to go to term

Misalliance….?

Pseudopregnancy in the bitch



Dopamine agonists, e.g. bromocryptine or cabergoline

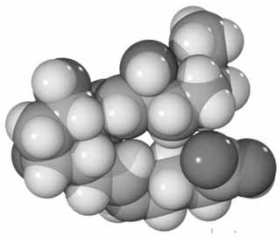
Androgens

- Testosterone
- Boldenone
- Stanozolol
- Nandrolone
- Methandrol
- Ethylestrenol

Androgens

- Use for anabolic effect (anabolic steroids) and as growth promotants
- Risk of causing aggression if too much like testosterone
- Control of the oestrous cycle in the bitch (safer than progestagens?)
- Suppression of endogenous testosterone in intact males… so, SHOULD NOT be used to stimulate libido in low-libido males

Prostaglandins



PGF2α (native)
dinoprost

Analogues:
cloprostenol
("estrumate")
luprostenol
and etiproston

PGE2:
dinoprostone

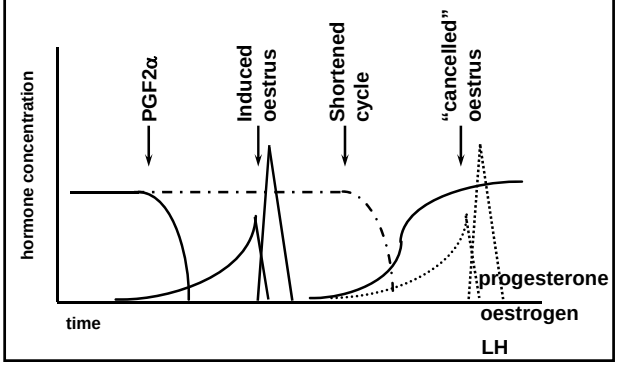
Prostaglandins – what do they do?

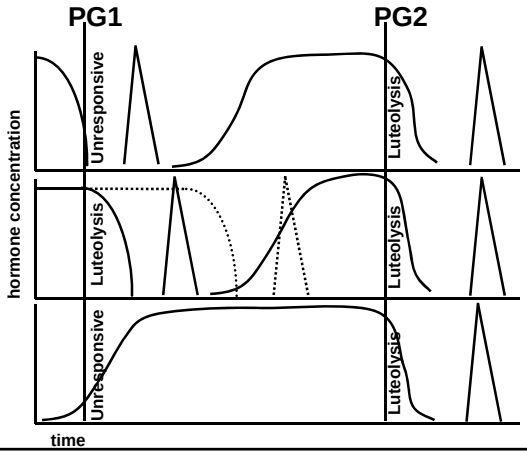
- PGF2α causes luteal regression
- and has a moderate ecbolic action
- PGE2 may have useful pharmacological actions within the reproductive tract
- (main use of PGE2 is protection of the gastric mucosa during chemotherapy)
- Both PGE and PGF are used in human obstetrics to cause cervical dilation

Use of prostaglandins

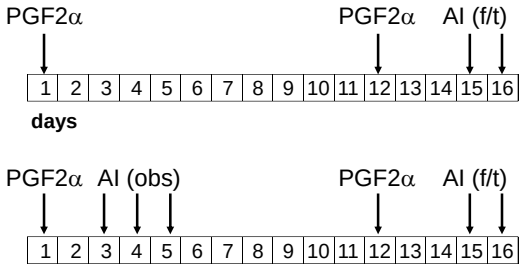
- Oestrus synchronisation
- Induction of oestrus (e.g. in non-observed oestrus)
- Induction of oestrus in cows with uterine infection and a persistent corpus luteum
- Induction of parturition (full term) in cows

Manipulating oestrus by controlling the length of the luteal phase with PGF2α

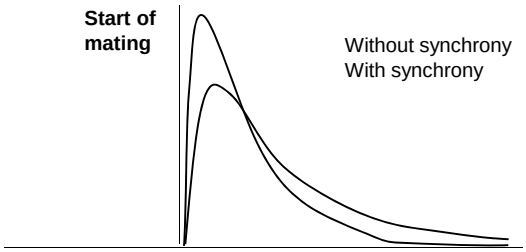




Basic PGF2α regimens

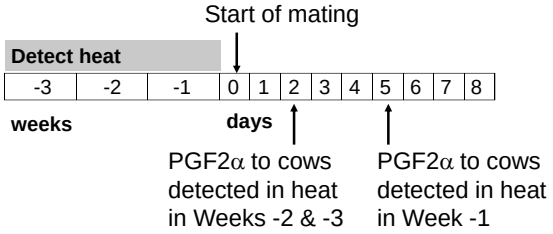


Use of whole herd synchrony to advance conception date



PG in seasonally calving herds

"Double Why Wait"

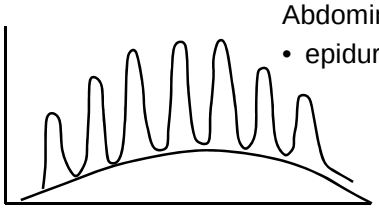


Drugs that act upon uterine muscle

- Oxytocin: contraction, also milk let-down
- Prostaglandin F2α: 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