

Definitive surgical castration or chemical reversible castration ?

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Castration

Objectives in general





Castration

- Loss of fertility
- Loss of sexual behaviour
- Simple practical delivery
- Safe and no deleterious side effects
- Good efficacy
- Technically feasible
- Affordable and cost effective



Surgery objections

- Surgery will be painful
- Risk because general anaesthesia
- Unnatural and objectionable
- Not necessary effective: aggressiveness, ...

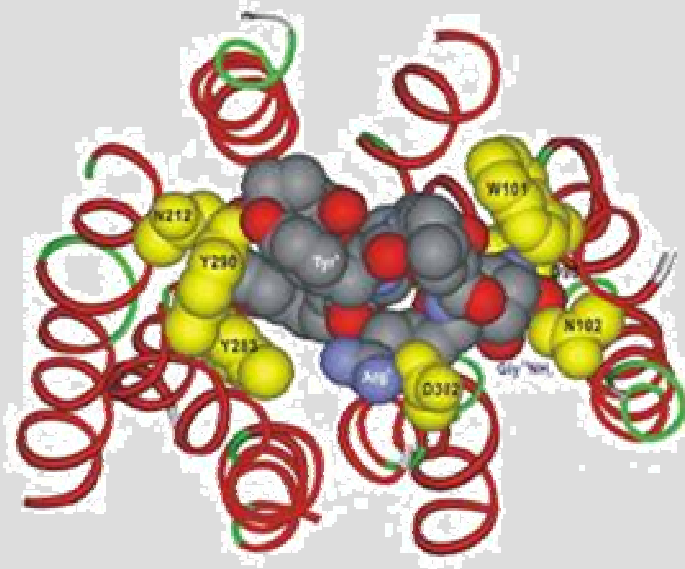


« Anti-androgenic » progestins

- Behavior : **low** efficacy
 - N.B.: D2 dopaminergics receptor blockage
 - No prediction of surgical castration
- Libido: **medium** efficacy
- Sterility : **medium** efficacy
- **Not recommended** diabetics, ...



GnRH, a major indication

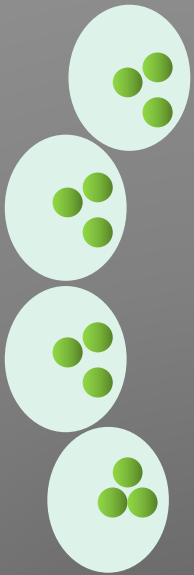


Primary regulation of reproduction



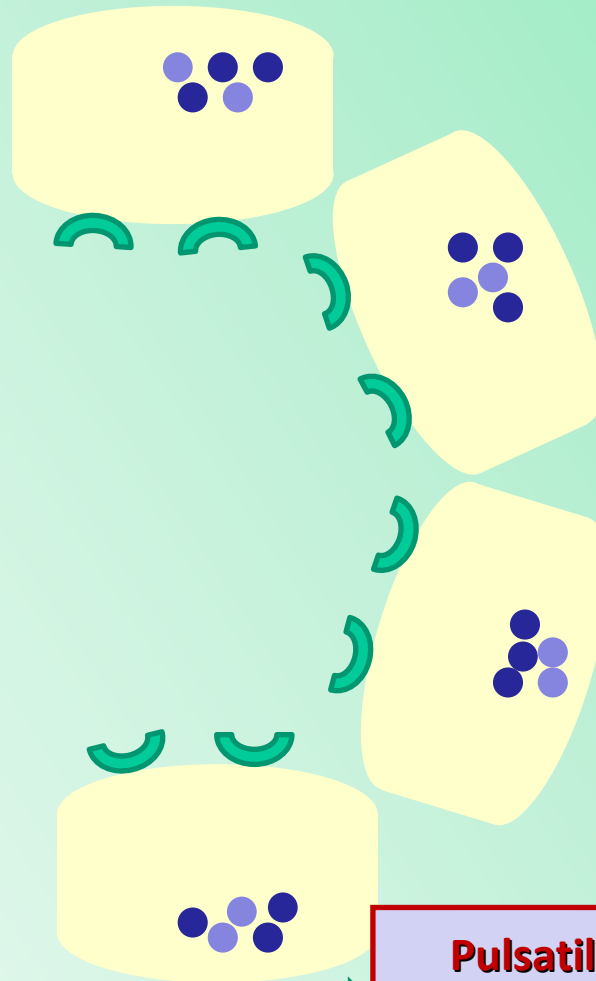
GnRH reminds

Hypothalamus



*Système porte
hypothalamo-hypophysaire*

Pituitary gland



Systemic circulation

Testis

Spermatogenesis

Sexual steroids
synthesis

**Pulsatile secretion of
GnRH**

**Pulsatile secretion of
FSH/LH**

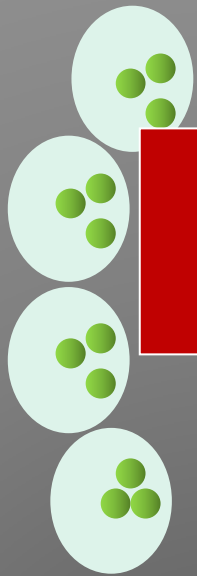


GnRH reminds

Hypothalamus

Pituitary gland

Testis



saire

**Stop fonctionnement =
Stop reproduction**

Sys
hypothal

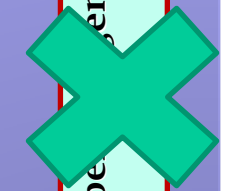
Circulation systémique

Spé
gènes

Sys
des

**Pulsatile secretion of
GnRH**

Pulsatile secretion of





How ?

- **Many strategies:**
 - Act on GnRH: anti-GnRH vaccines
 - Act on pituitary receptor via analogues
 - Antagonistes
 - Agonistes

Anti-GnRH vaccines

Immunocontraception





Anti-GnRH vaccines

Many publications

Singh V, 1985, Ind J Exp Biol, 23:667-72

Gonzales et al, 1989, J Reprod Fertil Suppl, 39: 189-98

Ladd et al, 1994, Biol Reprod, 51:1076-83

Ferro et al, 2004, Vet Immun Immunopath, 101: 73-86

Walker et al, 2007, Vaccine, 25: 7111-9



**Temporary
sterilization**

BUT

Very high variability

In vaccinal response

Length efficacy



Anti-GnRH vaccines

- **Problemes**
 - Low molecular weight
 - Pulsatile secretion
 - Short acting-life
- **Perspectives**
 - New antigens
 - New adjuvants



Anti-GnRH vaccines

- In practice:
 - In USA
 - Canine Gonadotrophin Releasing Factor Immunotherapeutic[®], Pfizer AH
 - Protocol: Primo-injection then two injections at 2 and 4 weeks
 - *GonaCon TM, single injection IM >2.5 years efficacy (trials)*

BUT:

Indication: *BPH*

« *Efficacy and potency of this product has not been fully demonstrated* »

GnRH antagonists

CRECS

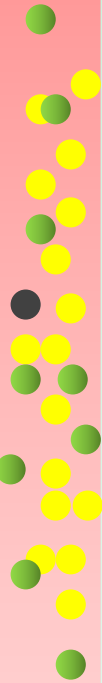




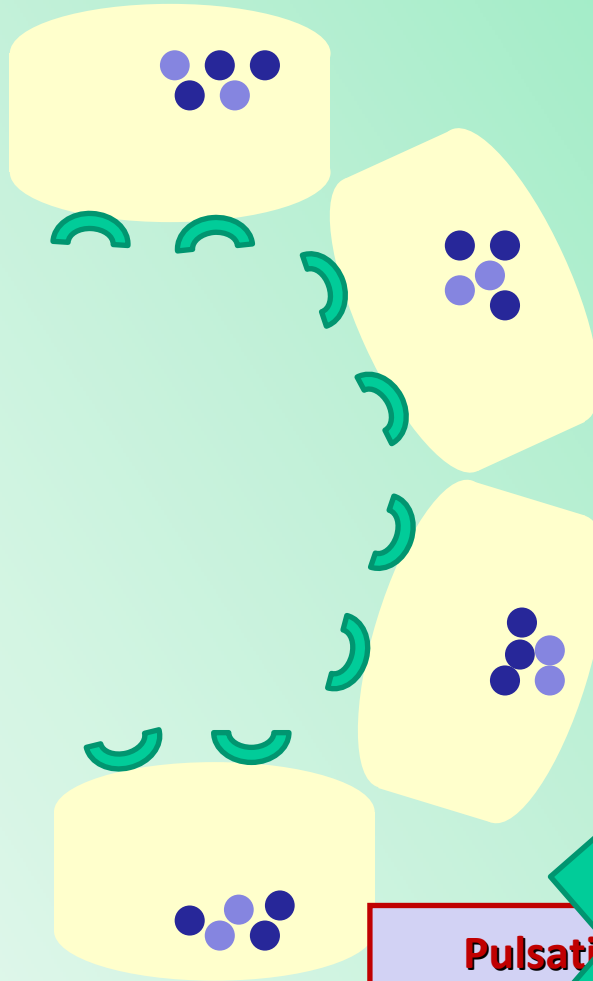
GnRH Antagonists

PRINCIPE

Systeme porte
hypothalamo-hypophysaire



Pituitary gland



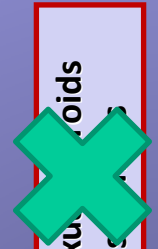
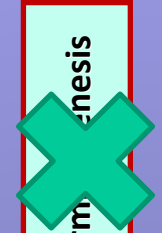
Circulation systemique

Pulsations

Testis

Spermatogenesis

Sexual steroids





GnRH Antagonists

- Single acycline injection (330 μ g/kg):
 - ↘ testis diameter
 - ↘ ejaculat volume
 - ↘ number of spermatozoïdes
 - ↗ % morphology abnormalities
 - ↘ concentrations in LH/FSH/T

duration \approx 14 days

Garcia Romero et al (2009)

Valiente et al (2007)

GnRH Agonists

CRECS

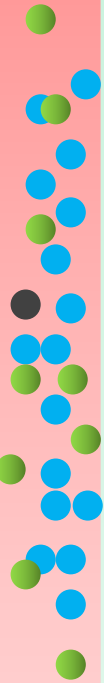




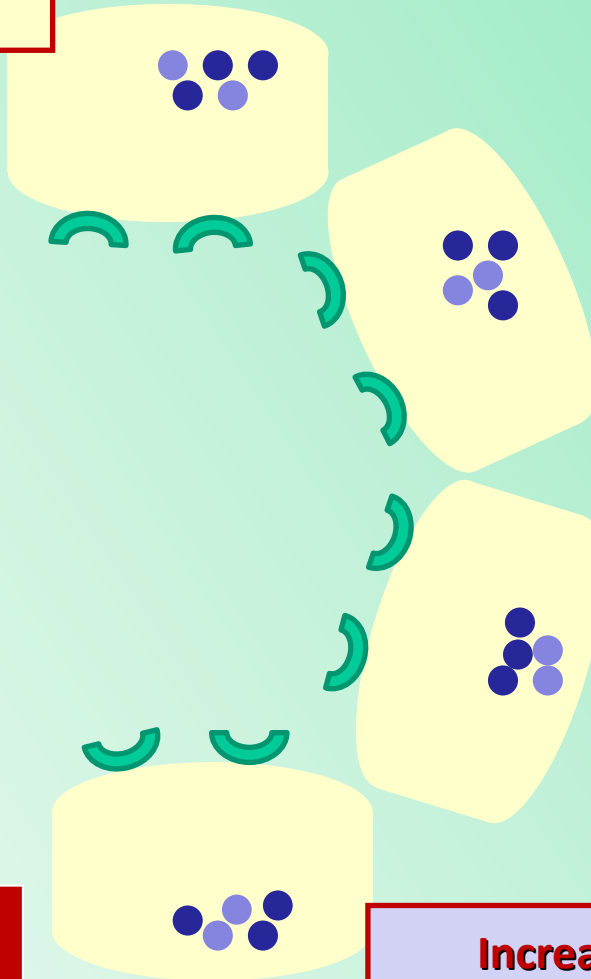
GnRH Agonistes

PRINCIPE
In two steps

Système porte
hypothalamo-hypophysaire

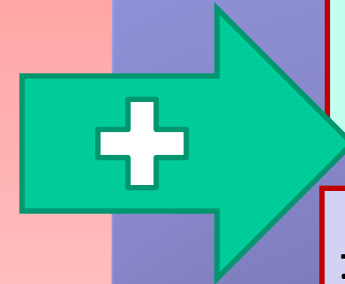


Pituatiry



Circulation systémique

Testis



Spermatogenéis

Sexual steroid
synthesis

« Flare up »
effect

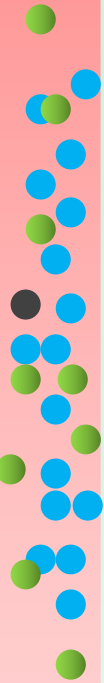
Increase of LH/FSH
secretion



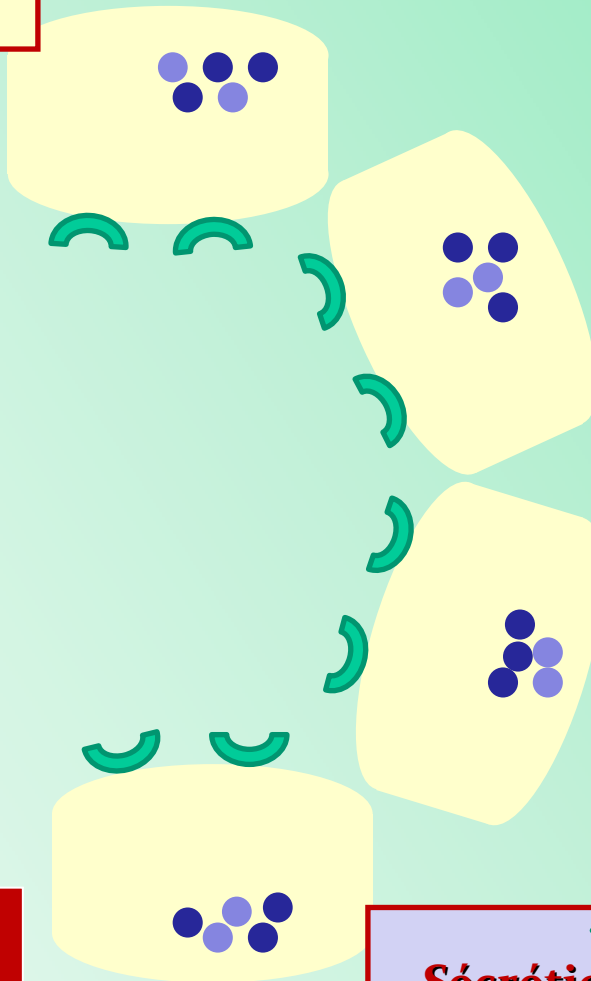
GnRH Agonistes

PRINCIPE
In two steps

Système porte
hypothalamo-hypophysaire



Pituitary



Circulation systémique

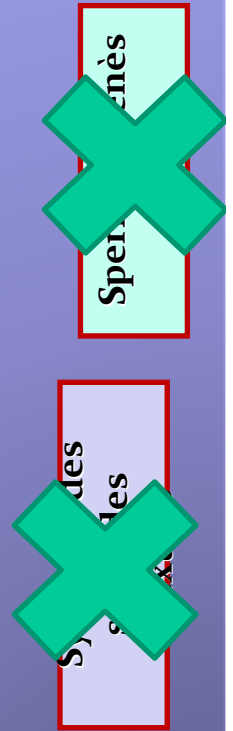
Testis

Spermatozoïdes

Système endocrinien

Desensibilization

Sécrétion de FSH/LH





GnRH agonists

■ Compounds:

- > 700 synthetics GnRH agonists
 - 1 or 2 aa exchange
 - Fertireline, busérelina, nafareline, lutréline, desloréline, leuprolide ...
- In normal conditions : very short acting effect



■ Prolonged liberation compounds:

- IM injection (oil adjuvant)
- Implants SC → 3 - 6 or 12 months



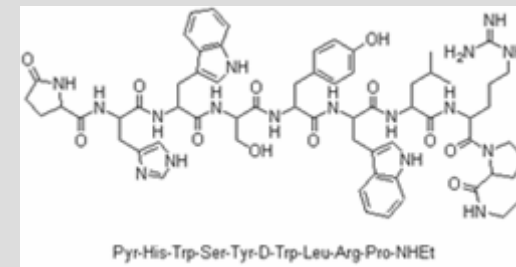
GnRH implants

■ Molecules:

- Nafarline (Gonazon[®] - Intervet Inc.)
- Desloreline: sensitivity 150 x more than natural GnRH
 - Implants 2,1 mg (Ovuplant[®]- Fort Dodge Inc.)
 - Implants 4,7 mg and 9,4 mg (Suprelorin[®] S6/S12 – Peptech Inc.)

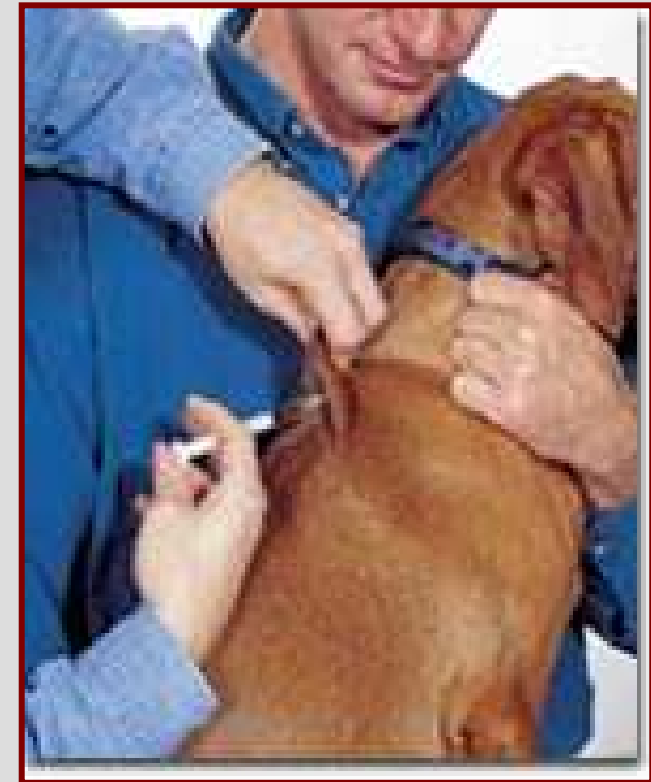
■ In Europe:

- Suprelorin[®] (Virbac Inc.)
- Contenant 4,7 mg of desloréline
- Biodegradable matrix





How to use ?



Implantation:
Sub-cutaneous tissue
Size: 2.3 x 12.5mm

GnRH
a real
« Chemical » castration





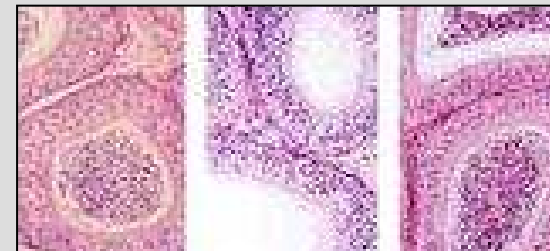
Exams

■ Libido

- Suppression in 30 to 35 days *Trigg et al. 2006*
- Be careful of the first dayx stimulation
 - Agression in a kennel !

■ Testis volume reduction:

- 35% of initial volume *Junaidi et al. 2003*
- $46.3 \pm 2.0 \text{ mm} \rightarrow 37.7 \pm 2.0 \text{ mm}$ *Romagnoli 2006*





Exams

- Semen volume reduction
 - None > 6 weeks *Trigg et al. 2006*
- Reduction of semen quality
 - Increase of sperm abnormalities : 7 à 70%
 - In 35 days





Clinical effects

- Semen volume reduction
 - None > 6 weeks *Trigg et al. 2006*
- Sperm quality decrease
 - Morphological abnormalities increase : 7 à 70%
 - in 35 days

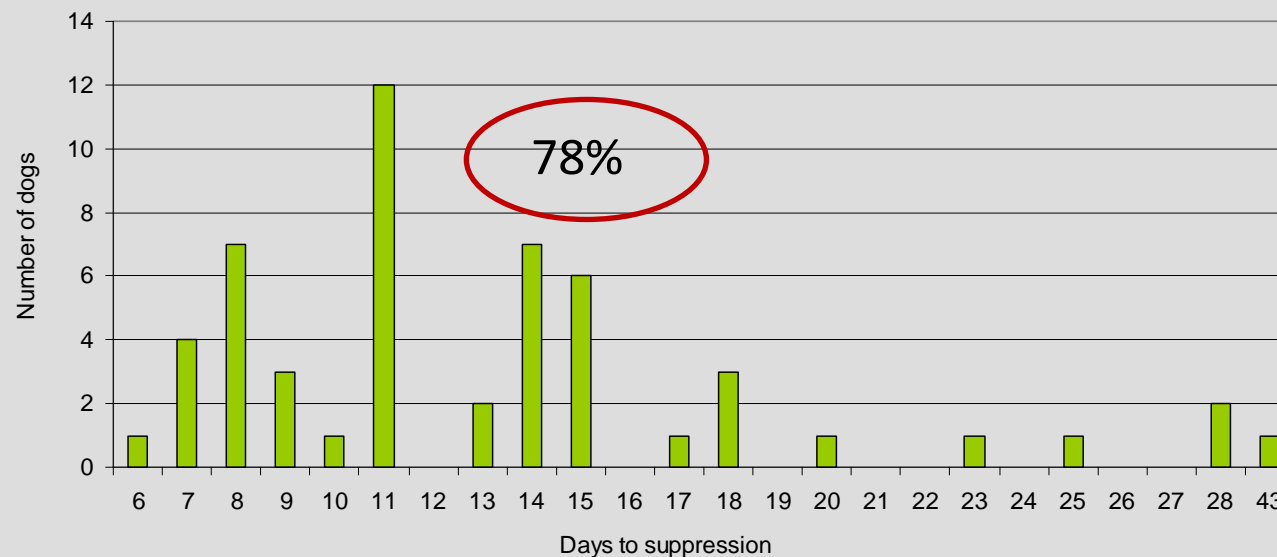
Sterility in max

6 weeks



Hormonal effects

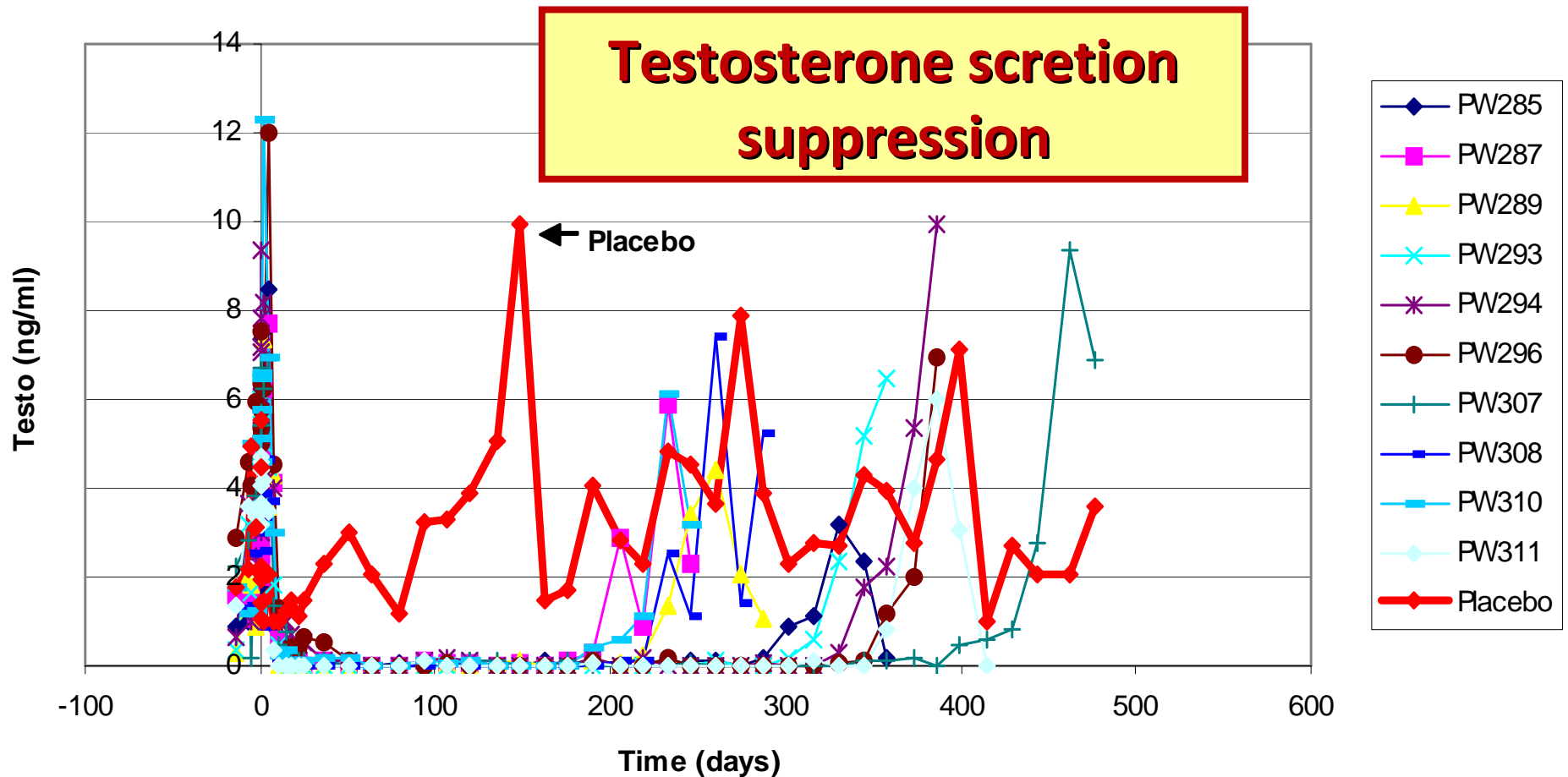
- *Hoffmann 2005*
 - Buseriline implant (Profact®)
 - T₄ low value : around 15 d
- *Trigg et al. 2001, 2006, 2008*
 - Implants 4,7 et 9,1 mg of desloréline
 - LH and testostérone: low value in 78% of dogs in 15 d





A single implantation

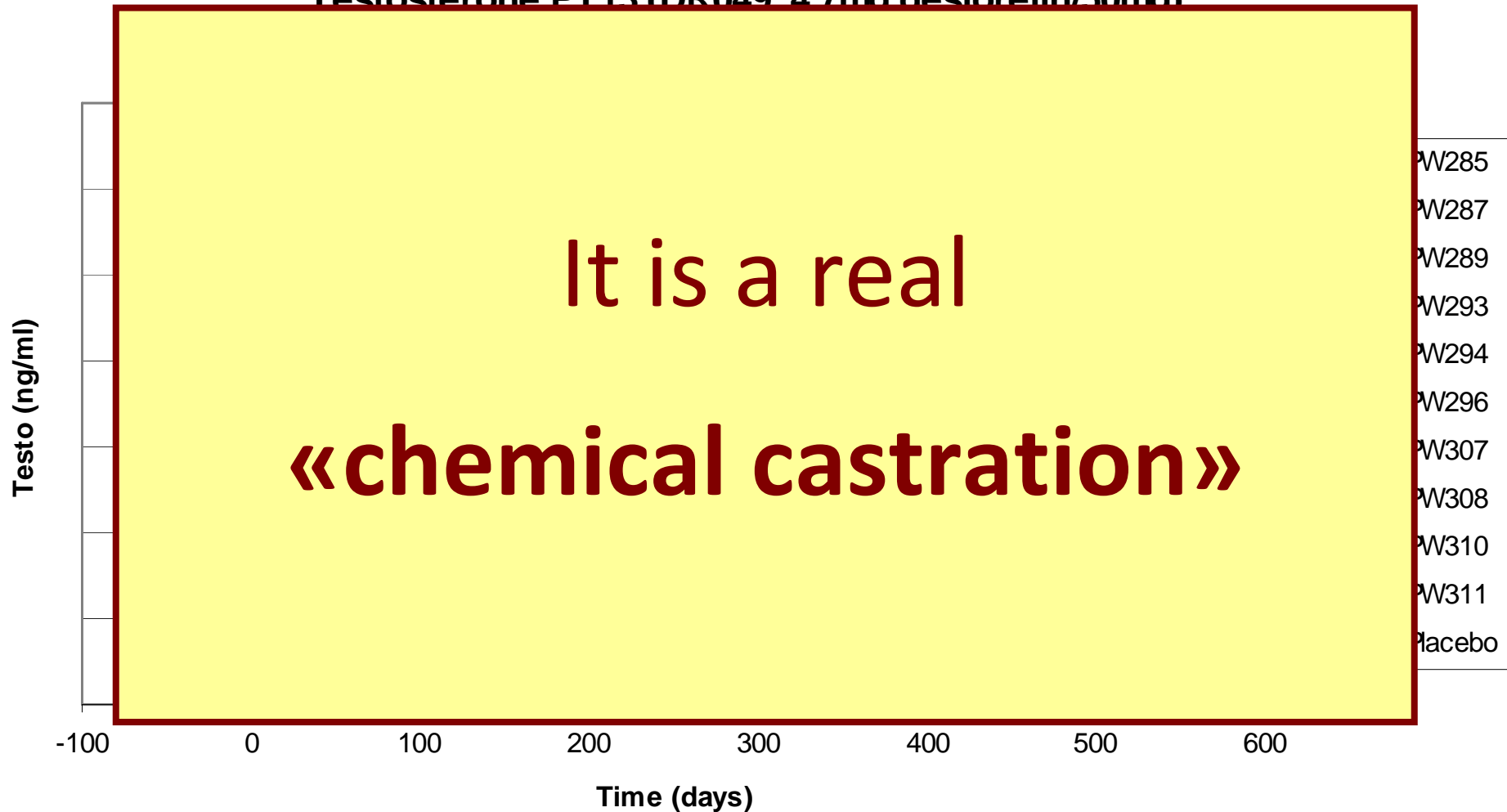
Testosterone PT13 (DR049: 4.7mg deslorelin/50mg)





A single implantation

Testosterone PT13 (DR049: 4.7mg deslorelin/50mg)

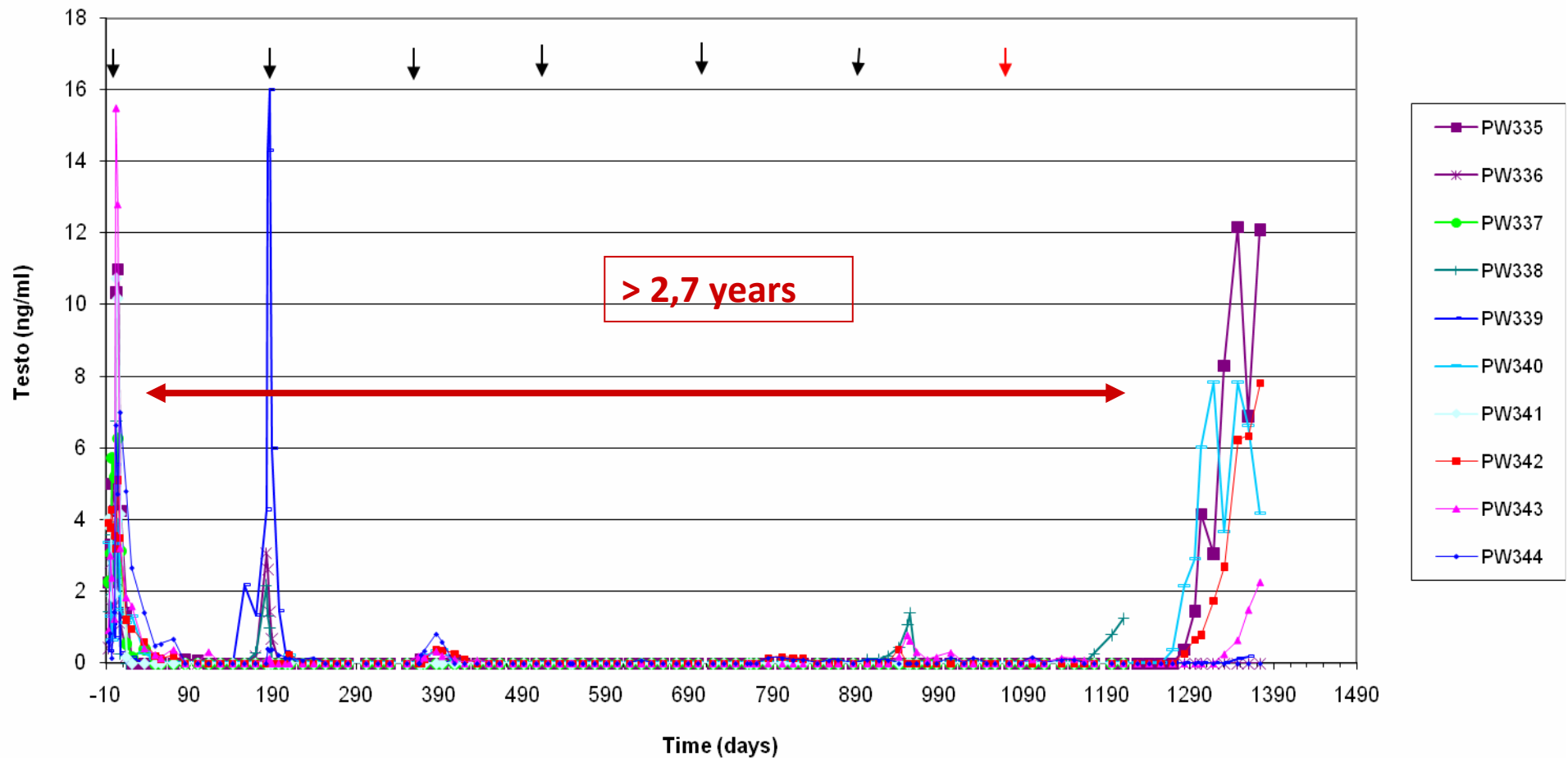




Repeated Implantations

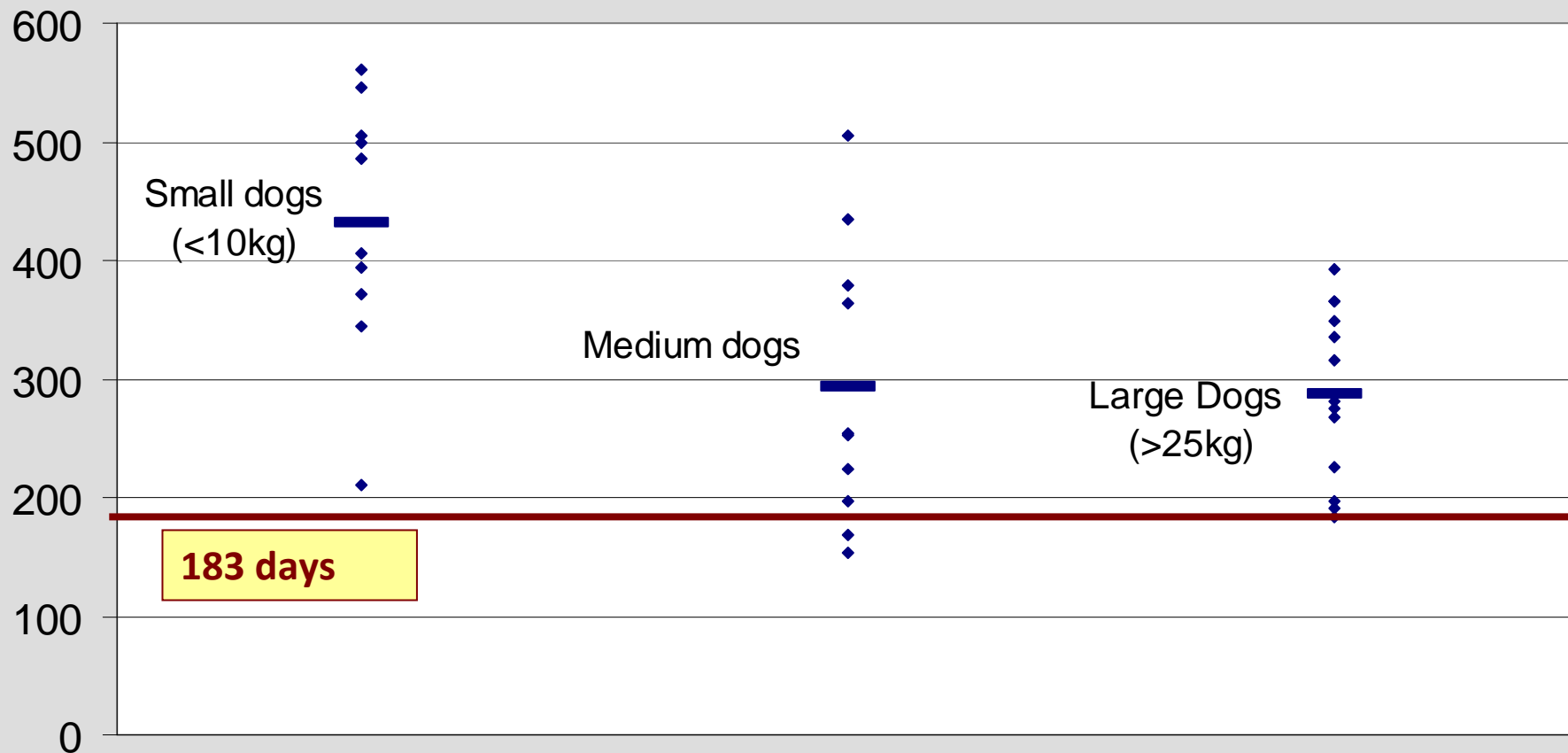
Trigg et al. 2006

Testosterone PT17: 4.7mg deslorelin/50mg (Implantation 1,2 ,3, 4, 5 & 6)



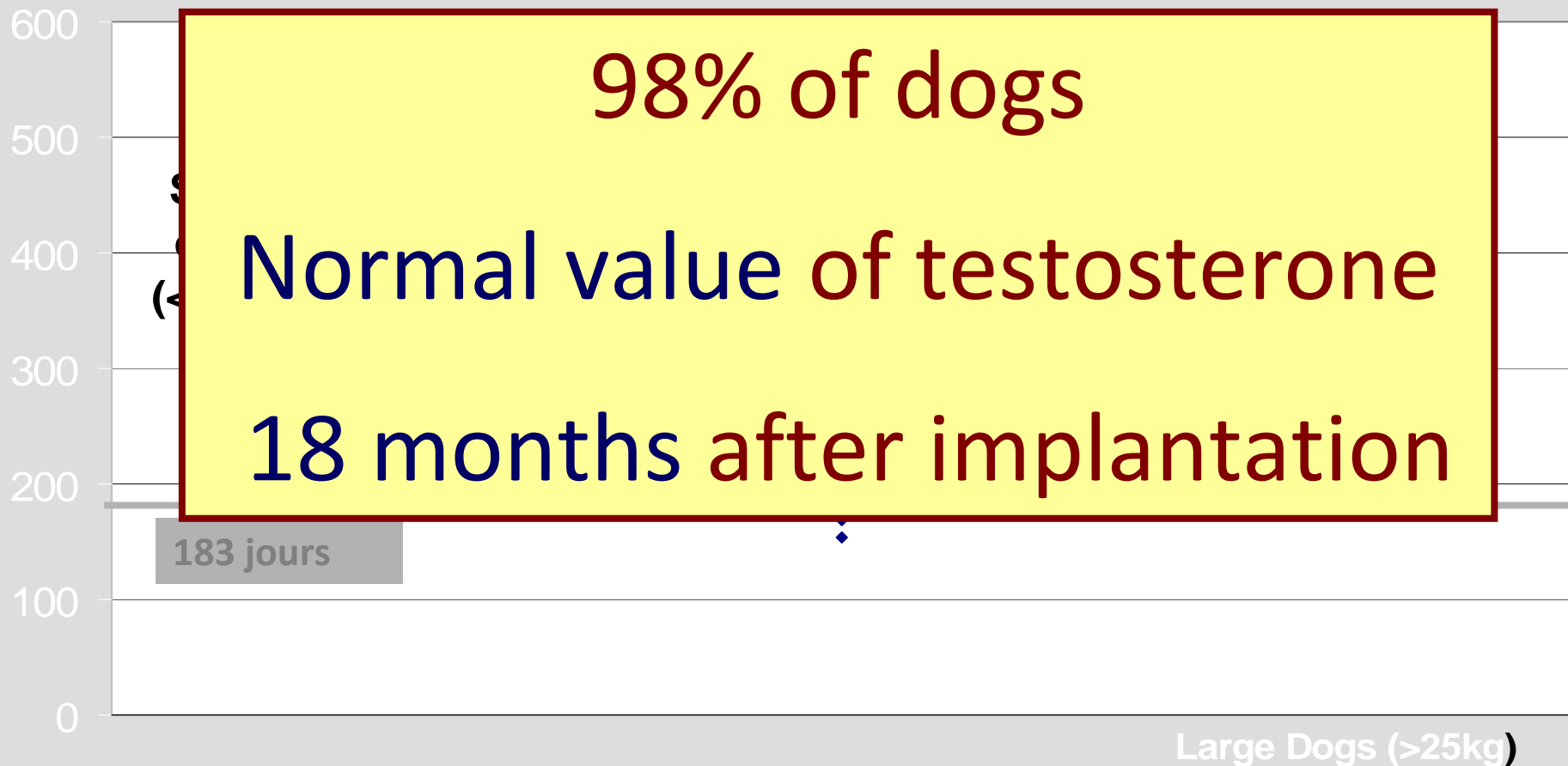


Length effect hormonal suppression





Length effect hormonal suppression





Prostate gland effect

- 50% reduction of volume at 6 weeks
- Reduction during 11 months
- Initial volume at 1 year

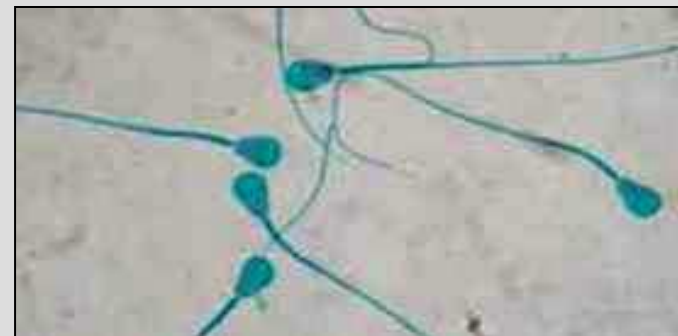


Gobello 2006
Romagnoli 2006



Fertility return

- Semen quality:
 - 5 weeks after T4 normal value *Trigg et al. 2001*
 - $1,08 \pm 0,1$ ml
 - Numeration : 619 millions / Motility : 83% / Abnormalities: 6%
- Return to fertility at 60 weeks (14 mois) *Trigg et al. 2006*



« In situ » chemical castration





Neutersol[®]

- Zinc gluconate solution neutralised by arginine.
- Injected directly into the testicle
 - atrophy of the testes and prostate gland resulting in permanent sterilisation.
 - USA: approved for use in dogs aged between 3 and 10 months although it is being tested for use in older animals.
- Sedation is highly recommended during injection procedure
 - if injected outside the testicle (during insertion or withdrawal) the substance can be highly irritating
 - and lead to ulceration of the tissues.
- 41–52% reduction in testosterone levels
 - Might not alter sexually dimorphic behaviour: roaming, marking, aggression and mounting



Neutersol[®] and others

■ Adverse reactions

- swelling of the testes, scrotal pain when palpated (6.3%)
- anorexia (4.1%), diarrhoea (2%) and lethargy (2.2%). S
- Severe scrotal ulceration in 4% of dogs: 2% of which required scrotal ablation and removal of the affected necrotic tissue

■ Other Products in development for intra testicular injection:

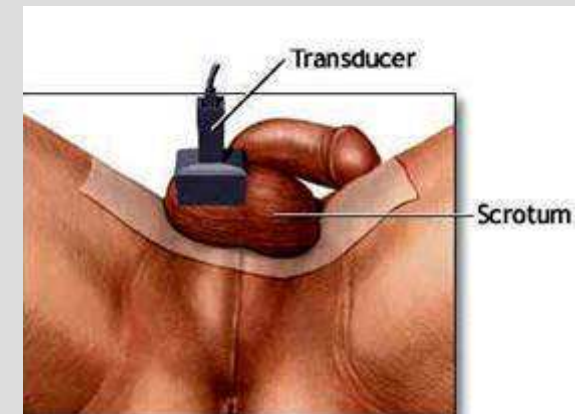
- calcium chloride⁶ and a novel zinc-based solution





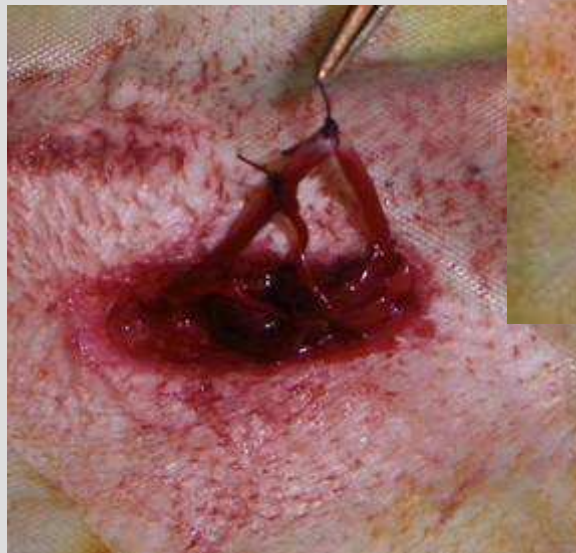
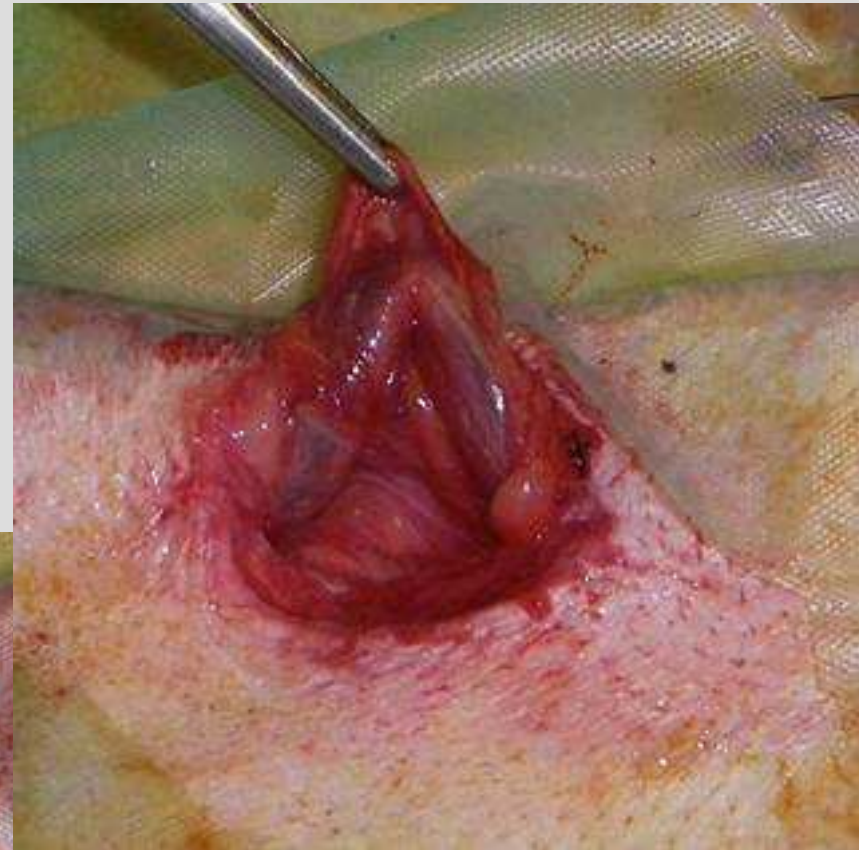
Ultrasound castration

- Suppress spermatogenesis
 - Combined effect of heat and mechanics.
- A high intensity focused ultrasound beam is used on testes, epididymis or vas deferens.
 - US waves induced thermal coagulative necrosis of sub-surface structures.
- However, skin burns occurred in approximately 20% of cases if single high level are used
 - Repeat low-levels seems to have less side-effects





Vasectomy procedure



Interests of castration





Cryptorchidism

- Absence of one or both testis in the scrotum after 4-8 weeks
- Right > Left testis
- Hereditary and an autosomal recessive trait
 - carried by both maternal and paternal lines
- When bilateral abdominal ectopia: sterile but produce testosterone
 - even at higher concentration
- In a line of a dog with a retained testis:
 - report of delayed testicular descent or retained testis



Cryptorchidism

- **Promotes testicular tumors**
 - 21% of dogs suffering from a testicular neoplasia have a retained testis
 - 45% of sertoli cell tumors and 30 % seminomas grow in an abdominal retained testis
 - Abdominal retained testis are predisposed to sertoli cells tumor
 - risk is 9-14 times higher than normal
 - Inguinal position are predisposed to seminoma
 - more moderate temperature in agreement with the survival of germ cells
- **Promotes in a lesser extent testicular torsion**
 - when abdominal ectopia
- **Exclusion of all affected males from the breeding programme**
 - Some authorities recommend the exclusion of their parents and their potential offspring !
 - Hemi-castration and contro-lateral vasectomy is enough

Sexual behaviour mounting, agressiveness, fugue





Sexual behaviour and castration

- Fugue significantly improved *Nielson, 1997*
 - 50-60%
- Urine marking and mounting
 - 60 %
 - Up to 90% in 25 to 40 % of dogs
- Effects on aggressiveness are much less encouraging
 - reduction toward humans: 25% of dogs
 - In females, may even be associated with increased aggressiveness.
 - Increased reactivity after sterilization at the approach of a stranger (females German Shepherd)



Sexual behaviour and castration

- Age cognitive impairment
 - Circulating testosterone in aging sexually intact male dogs may slow the progression of cognitive impairment *Hart, 2001*
- Positive results seems not influenced by
 - age at sterilization
 - seniority of disorders



Sexual behaviour and castration

- **Results of sterilization are**
 - random and unpredictable
 - often disappointing and limited
- **Early sterilization**
 - does not prevent onset of behavior disorder
 - No less frequent in anglo saxon countries



Thank you for your attention !



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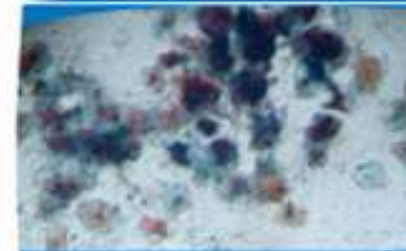
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Dr Philippe MIMOUNI - Dr Xavier LEVY
Centre de Reproduction des Carnivores du Sud-Ouest (CRECS)

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Infos

[Lutter contre les clostridies avec Clovern 10](#)

En cas de risque de mort subite, une protection très large est nécessaire.

[plus...](#)

Recherche

OK