5 DALMAZIN: Dextrorotatory cloprostenol Results (over 4,800 clinical cases)

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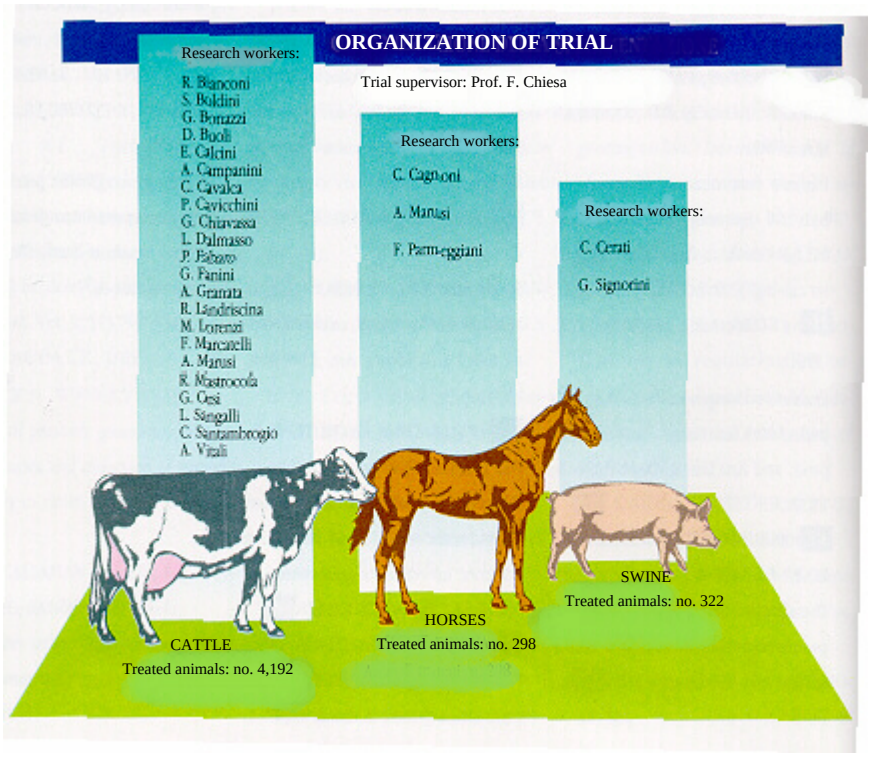
During the period, February-December 1991, with the aid of 27 veterinary gynaecologists, a very large-scale trial was carried out under the supervision of Prof. F. CHIESA.



This trial, given the number of treated animals, and the various geographic areas, zootechnical, environments and genetic contexts involved, makes up one of the largest and most precise prostaglandin trials ever carried out.

Apart from the specific numerical data and percentages, other very important information was also collected during the DALMAZIN field trial. During this trial, the vets attended three seminars during which gynaecological problems and, above all, the use of prostaglandins were discussed. Furthermore, throughout the trial period, the operatives were in direct contact with the FATRO trial staff and with the supervisor.

CATTLE

At the beginning of the trial, clinical record cards were distributed to the researchers for data collection purposes (see Card 1).

CLINICAL RECORD CARD (CATTLE)

Research worker: Dr. _____

Date: _____

Herd: _____

Treated cow no.: _____ Name: _____

INDICATIONS	POSOLOGY	RESULTS*			PREGNANCY				PROGESTERONE LEVEL (FACULTATIVE) ng/ml	
					1st insem.		2nd insem.			
	ml	O.	M.	N.	YES	NO	YES	NO	BEFORE	AFTER
PERSISTENT CORPUS LUTEUM										
LUTEAL CYST										
ENDOMETRITIS/PYOMETRA										
EXPULSION OF MUMMIFIED FOETUS										
UNDESIRED INTERRUPTION OF PREGNANCY										
INDUCTION OF CALVING										
PLACENTAL RETENTION										
DELAYED UTERINE INVOLUTION										
INDUCTION OF FERTILE HEAT IN SUBJECTS DISPLAYING WEAK OR SILENT HEAT										
SYNCHRONIZATION OF ESTRUS										

Notes: _____

* Legend: O. = Optimum M. = Moderate N. = Nil

The clinical record cards for cattle required specification of indications, used dosage, the results of treatment and pregnancy (if and when occurring after first or second insemination following treatment with DALMAZIN). Lastly, two columns are given for assessment of progesterone levels before and after treatment with DALMAZIN.

Great care had to be taken over assessment of the results. The researchers assessed the results of treatment with DALMAZIN on the basis of objective and subjective parameters arising out of comparison with other prostaglandins available on the market.

To provide a clearer picture, please note the results in terms of the indications for which onset of estrus is desired following treatment with DALMAZIN (persistent CL, luteal cyst, induction of fertile heat in subjects displaying weak or silent heat, and synchronization of estrus) (see Diagram 1).

ASSESSMENT OF RESULTS

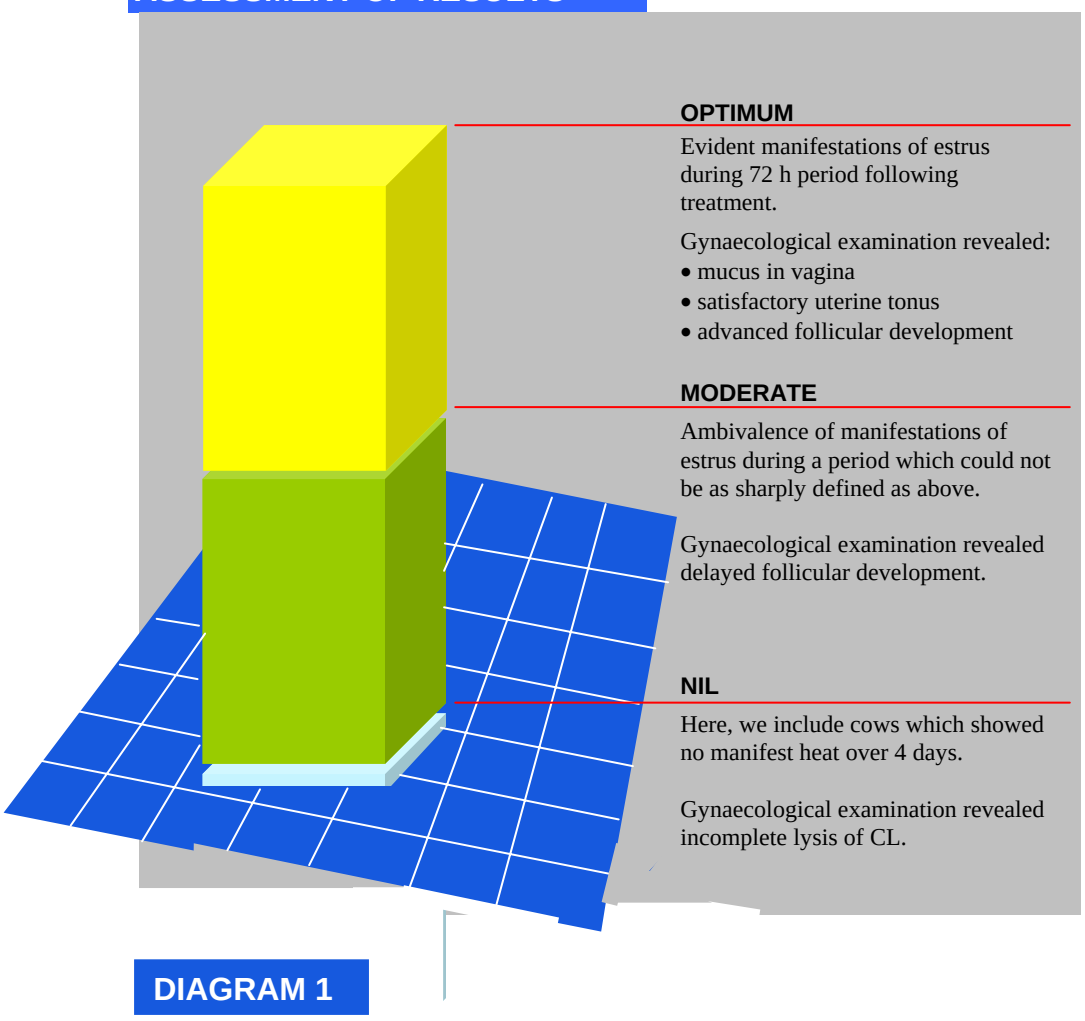


DIAGRAM 1

USE OF DALMAZIN ACCORDING TO INDICATIONS FOR CATTLE

PERSISTENT CORPUS LUTEUM

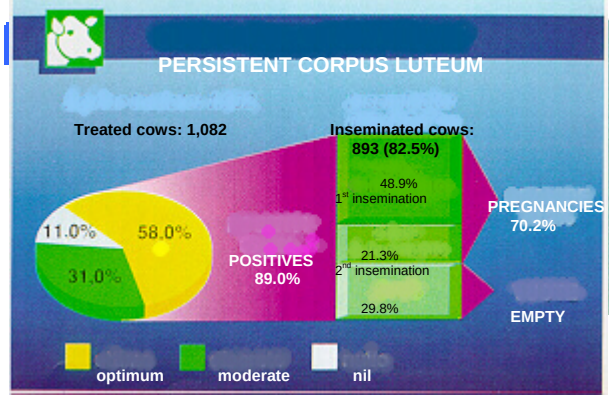
Persistent CL is a pathological state of the ovary which determines anestrus. This is due to maintenance of high progesterone blood levels are maintained (leading to inhibition of the release of follicle-stimulating gonadotropins).

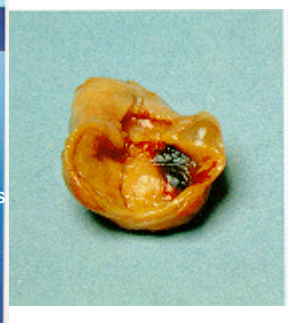
Symptomatologically, recovery of cycling is not observed in the cow after calving. Alternatively, there is no estrus after a number of regular cycles.

From the symptomatological angle, a 10-15 mm CL may be noted, in the absence of follicles or significant structures (Figure 1).

FIGURE 1 - *Persistent CL*

In many cases, the presence of a persistent CL is associated with uterine diseases which inhibit physiological endogenous prostaglandin synthesis (endometritis, pyometra, and foetal mummification or maceration).





In anestrous cows with ovarian CL, absence of estrus or subestrus might be wrongly diagnosed as persistent CL.
Persistent CL therapy consists of administration of PgF2α to induce luteolysis and obtain physiological recovery of the ovary.

RESULTS Figure 2

Diagnosis of persistent CL was mainly based on clinical and case history data (5% of cases on blood progesterone assay).

LUTEAL CYSTS

The luteal cyst (diam. more than 25 mm) is a follicular liquid-filled structure and features a luteal tissue membrane.
The duration of luteal cysts is generally quite considerable. Luteal cysts are accompanied by anestrus.
PgF2α is therapy of choice for luteal cysts since lysis of the luteal membrane tissue takes place thereby permitting recovery of cycling activity (Figures 3 and 4).

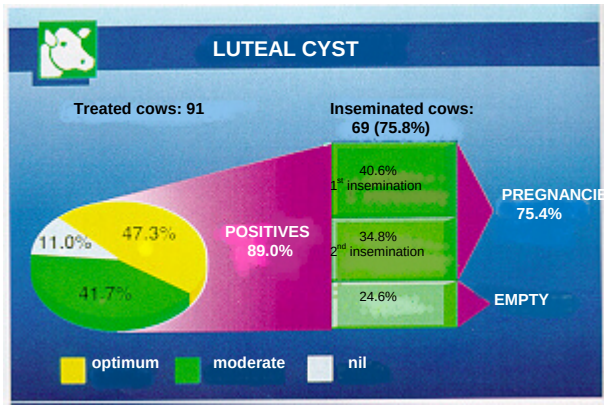
- Luteal cyst

- Section of luteal cyst.
Note wall consisting of luteal tissue

With regard to this indication, diagnosis must be carried out with care, since follicular cysts will not respond to PgF2α. In borderline cases, corroboration of the results of rectal palpation by verification of high progesterone levels on diagnostic testing, is recommended.

RESULTS Figure 5
Progesterone assay was carried out in 8% of the cases for purposes of corroboration.

FIGURE 5



ENDOMETRITIS/PYOMETRA

As a general rule, all infections of the uterus which are a cause or result of persistence of the CL may be treated successfully with PgF2α. The classic example is pyometra (Figure 6).

FIGURE 6 - *Section of frozen uterus displaying pyometra. Note persistent CL in ovary*

Moreover, endometritis also reacts positively to PgF2α in cycling cows.

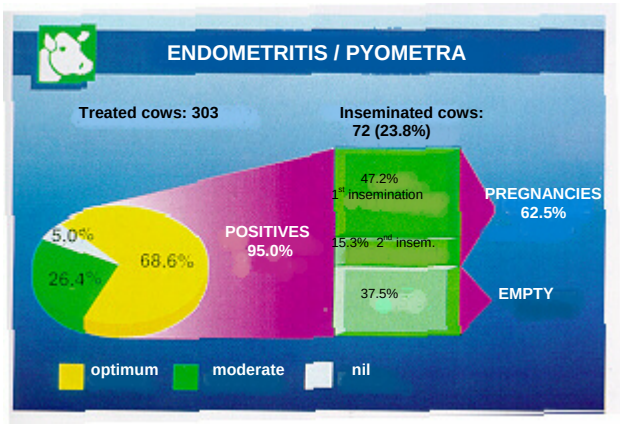
During estrus, uterine defences are strengthened. At this time, uterine evacuation of possibly diseased materials is facilitated.

According to Paisley (1986), PgF2α may have a direct effect, since it stimulates uterine leukocyte phagocytosis.

RESULTS Figure 7

In 27% of the cases, the dosage was divided into more than one administration (the most frequently adopted practice being 2 ml DALMAZIN followed by 1 ml over the following two days). No difference was noted between single and divided-dose administration.

FIGURE 7



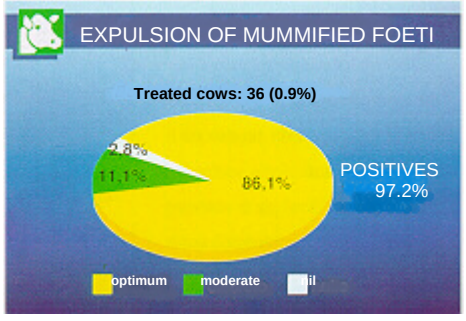
EXPULSION OF MUMMIFIED FOETI

Mummified bovine foeti are generally associated with persistence of a functioning CL. Thus, PgF2α, since it is l uteolytic, will lead to expulsion of the foetus and evacuation of uterus.

RESULTS Figure 8

Expulsion of the foetus takes place in 30-72 h following administration of DALMAZIN.

FIGURE 8



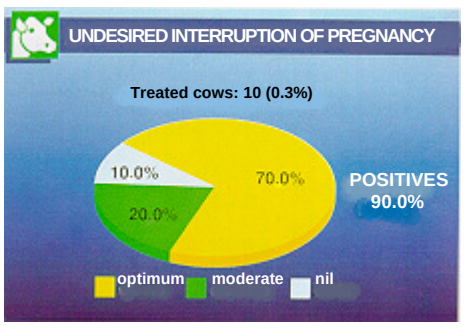
INTERRUPTION OF UNDESIRED PREGNANCY

PgF2α may be used as a means of interrupting undesired pregnancies before the 150th day of gestation. After the 150th day, maintenance of gestation no longer depends on the CL.

RESULTS Figure 9

The only negative result noted was a consequence of administration of DALMAZIN without certain knowledge of the stage of gestation (it was discovered later that the cow in question had reached more or less the sixth month of gestation).

FIGURE 9



INDUCTION OF CALVING

Administration of PgF2α after the 270th day of pregnancy induces calving.

RESULTS Figure 10

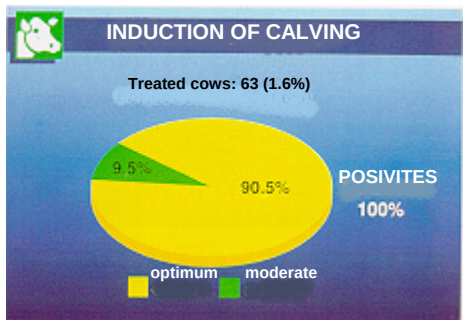
Calving usually took place 12-24 h after administration to Friesians.

In beef cows or cows with a double "vocation" (Piedmontese or Red Pied), calving took place, instead, at the 30th h following administration of DALMAZIN.

The researchers agree that DALMAZIN induced calving sooner and with a lower incidence of placental retention than other prostaglandins available on the market.

In 10% of the cases, DALMAZIN was adminstered together with glucocorticoids. Compared with single administration of DALMAZIN, there were no greater advantages to be gained through adoption of this method.

FIGURE 10



PLACENTAL RETENTION

PgF2α administration in the absence of CL for the treatment of placental retention - although not yet a widespread practice – was found to be efficacious (Herschler & Lawrence, 1984; Studer & Holtan, 1986) (Figure 11).

FIGURE 11 - *Section of uterus at 16th day after calving accompanied by placental retention. Note acute metritis and diseased material*

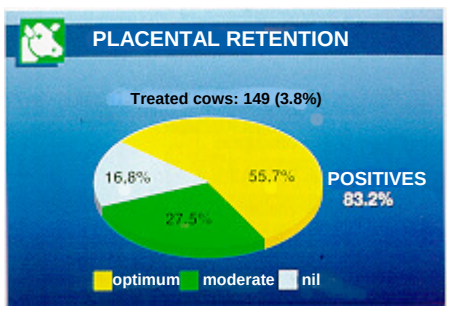
RESULTS Figure 12

In most cases, DALMAZIN was administered to cows 24-36 h after calving when placental expulsion had not taken place.

In some cases, due to dystocic parturition, DALMAZIN was administered as a preventive measure immediately after calving.

Dosage division was carried out in 25% of the cases, as follows: 1st day 1 dose of DALMAZIN (2 ml); for the following 2 days 1/2 dose (1 ml). The results were a great improvement single administration.

FIGURE 12



DELAYED UTERINE INVOLUTION

In cows, continued release of endogenous prostaglandins induces rapid uterine involution (Eley et al., 1981; Lindell et al., 1982).

Conversely, delayed uterine involution is often related to lack of endogenous prostaglandin secretion. Retarded uterine involution leads to delayed recovery of cycling activity after calving, and a lengthening of empty cow periods.

It has been scientifically proved that administration of prostaglandins during the early post partum stage is beneficial in terms of muscular tonus of the uterus and will speed up the process of uterine involution (Lindell et Kindhal; Young, 1989).

After comparison with control animals, McClary and others (1988) showed that administration of prostaglandins, at days 14-16 post partum, improves conditions with regard to all reproductive parameters in all cows, and does so over and above the condition of the uterus in question (Figure 13).

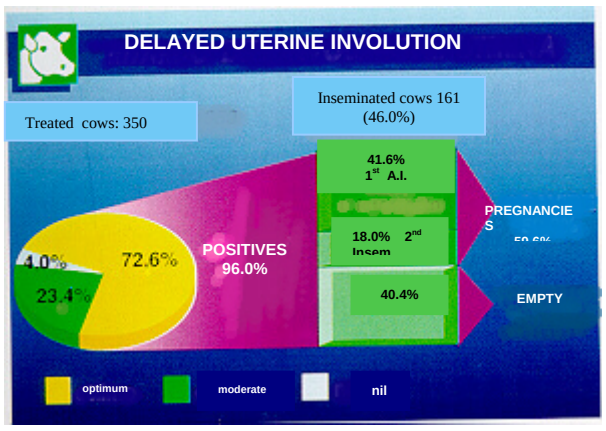
FIGURE 13 - *Section of uterus in normal conditions 22 days after calving. Note near-complete regression of caruncles*

RESULTS Figure 14

DALMAZIN was administered after the 15th day post partum.

For this indication, divided dosages were found to be signficantly more beneficial than single administrations.

FIGURE 14



INDUCTION OF FERTILE HEAT

Subestrus is a state of reduced cycling activity. However, in many cows (above all, high-yield animals during peak lactation), estrus which is not manifest may be mistaken for subestrus.

In cases such as these, the activity of the ovary may be normal even if it is accompanied by manifestations of estrus. However, these manifestations may be so weak or few and far between that they may not even be noticed.

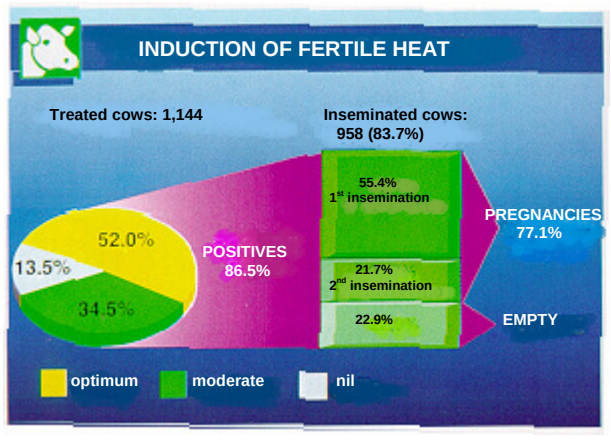
In any case, if CL is noted on rectal palpation, administration of PgF2α will induce heat in 48-60 h (Figure 15).

FIGURE 15 - *Induction of fertile heat. Bovine ovary at 9th-10th day of cycle. Note CL and follicle*

RESULTS Figure 16

The response to administration of DALMAZIN was found to be greater than with other prostaglandins, above all in heifers.

FIGURE 16



SYNCHRONIZATION OF ESTRUS

The benefits of synchronization of estrus are well known. Indeed, this practice has become a standard dairy herd management technique applied, above all, to heifers.

Basically, the most widespread synchronization techniques are:

1. **Single treatment**: PgF2α administered after the presence of the CL has been ascertained
2. **Double treatment**: the presence of the CL is not ascertained but PgF2α is administered to all cows (on the off chance of this being the case) (treatment is repeated 11 days after first administration).

FIGURE 17 - *Ovary at 16th-17th day of cycle. Note regressing CL and development of follicles*

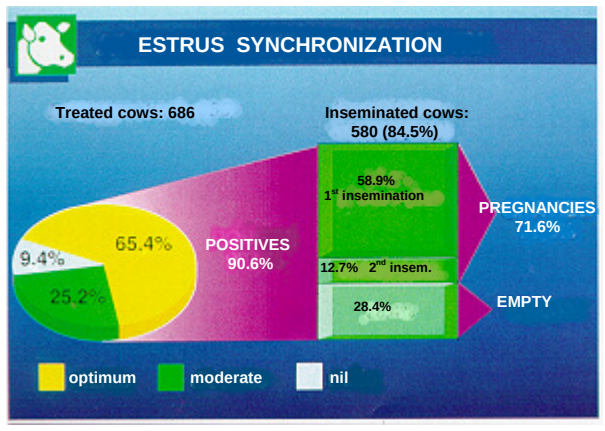
FIGURE 18 - *Assessment of conditions of ovary by means of rectal palpation (R. Landriscina)*

RESULTS Figure 19

Double treatment was carried out in approx. 43% of cases. Single treatment was carried out in approx. 57% of cases. In approx. 1% of cases a combined progesterone implant+DALMAZIN was used.

There were no significant differences between the methods in terms of results.

FIGURE 19



GENERAL SUMMARY (CATTLE)

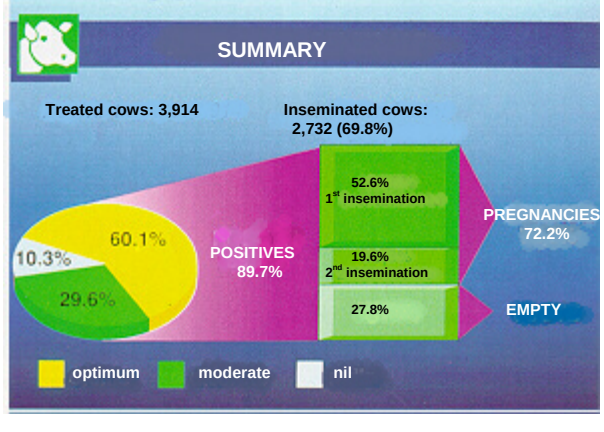
RESULTS

The results of the DALMAZIN trial in cows are extremely encouraging (see Figure 20). Positive results in cows is practically 90% and cases of pregnancy on first insemination are well above 50%.

These results are superior to those found in the literature for other prostaglandins.

The researchers evinced particular satisfaction at the clinical responses to in-field use of DALMAZIN.

FIGURE 20

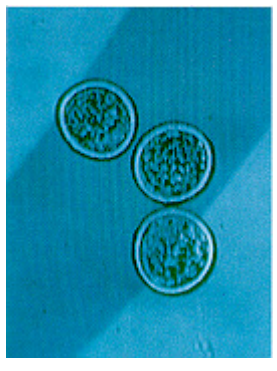


THE USE OF DALMAZIN FOR SYNCHRONIZATION OF EMBRYO TRANSFER DAMS

During the DALMAZIN trials involving cows, synchronization of the embryo transfer dams was also considered. For these dams, a special record card was drawn up (Card 2) in order to obtain more specific data.

In the embryo transfer record card we find two columns one of which is for purposes of control of the state of the CL prior to administration of DALMAZIN and the other for control at the 6th and 7th days after induced heat. This was decided because, according to the embryo transfer trial operatives, the dams often develop small corpora lutea which readily regress thereby causing death of transferred embryo and absence of pregnancy.

Embryos at blastocyst stage (on screen) (R. Landriscina)



CLINICAL RECORD CARD (CATTLE – EMBRYO TRANSFER)

Research worker: Dr. _____

Date: _____

Herd: _____

Treated cow no.: _____ Name: _____

INDICATION	TREATMENT WITH PgF90		STATE OF C.L.*						FITNESS OF RECIPIENT DAM		PREGNANCY AFTER TRANSFER	
	Single	Double	Before treatment			After treatment						
			O.	M.	P.	O.	M.	P.	YES	NO	YES	NO
SYNCHRONIZATION OF RECIPIENT DAM OESTRUS												

Notes: _____

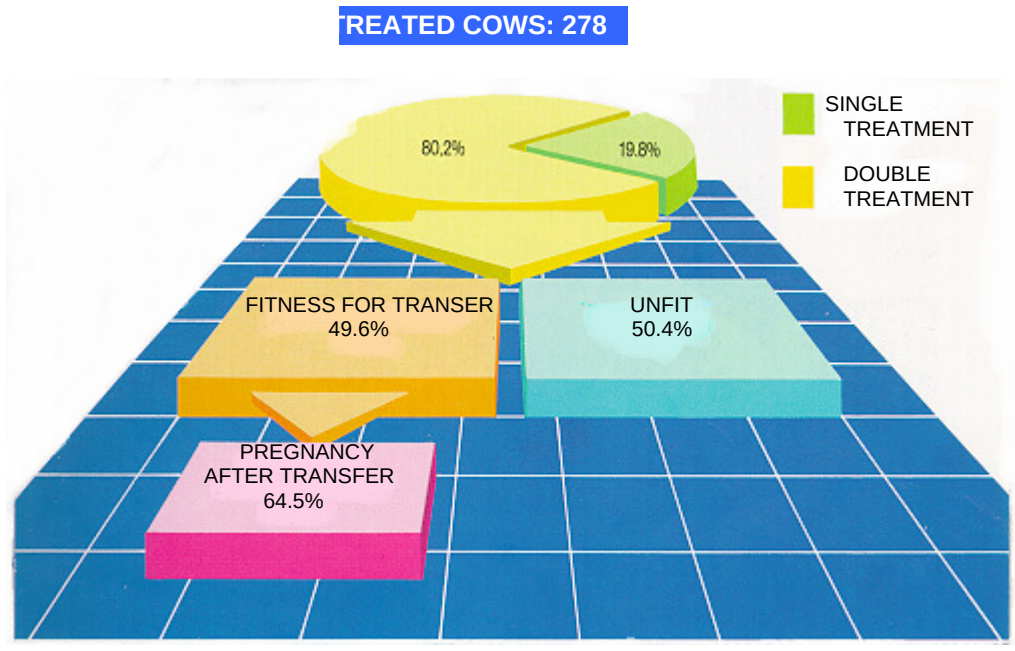
* Legend: O. = Optimum M. = Moderate P. = Poor

RESULTS (Figure 21)

There were no significant differences between single and double administration with regard to the parameters considered (state of CL and suitability for transplant and pregnancy).

It should be stressed that, in nearly all cases, the state of the CL after treatment was similar to that prior to synchronization. In the light of this observation, we may conclude that administration of DALMAZIN did not have an adverse effect on CL development after synchronization and that the CL depends to a greater extent on the conditions of the ovary of each animal.

FIGURE 21



Non-surgical flushing (R. Landriscina)

HORSES

USE OF DALMAZIN IN HORSES

The record card prepared for data on mares is very similar to that for cattle, the only difference being the indications (see Card 3).

CLINICAL RECORD CARD (HORSES)

Research worker: Dr. _____

Date: _____

Herd: _____

Treated mare no.: _____ Name: _____

INDICATIONS	POSOLOGY	RESULTS*			PREGNANCY				PROGESTERONE LEVEL (FACULTATIVE) ng/ml	
					1st insem.		2nd insem.			
	ml	O.	M.	N.	YES	NO	YES	NO	BEFORE	AFTER
PERSISTENT DIESTRUS										
LACTATIONAL DIESTRUS										
INDUCTION OF ESTRUS										
PLANNING OF INSEMIN.										
EARLY FOETAL DEATH										
PSEUDOPREGNANCY										
INDUCTION OF FOALING										

Notes: _____

* Legend: O. = Optimum M. = Moderate N. = Nil

Artificial insemination in the mare (F. Parmeggiani)

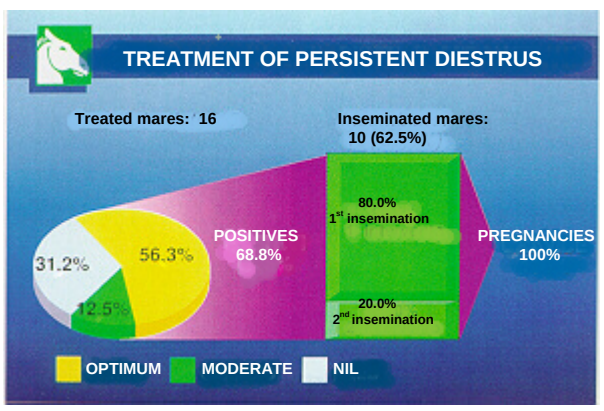
TREATMENT OF PERSISTENT DIESTRUS

Occasionally, some non-pregnant mares display no cycling activity.

A considerable proportion of these cases involve prolonged diestrus, as opposed to anestrus, above all toward the end of the mare's reproductive career. Ovary cycling reappears after PgF2α administration.

RESULTS Figure 22

FIGURE 22



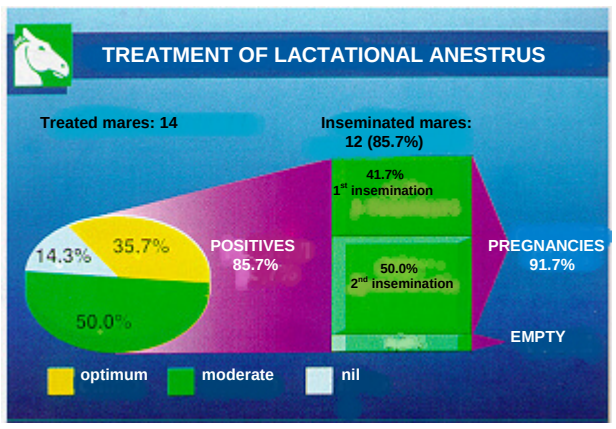
TREATMENT OF LACTATIONAL ANESTRUS

During the suckling period, the mare often displays irregular cycling activity. In these animals, post partum heat is noted some days after foaling (after which, over the following two or three months, no cycling activity is observed whatsoever).

Such anestrus is caused by persistent CL. Administration of PgF2α therefore leads to a recovery of the normal manifestations of estrus and ovulation.

RESULTS Figure 23

FIGURE 23



INDUCTION OF ESTRUS

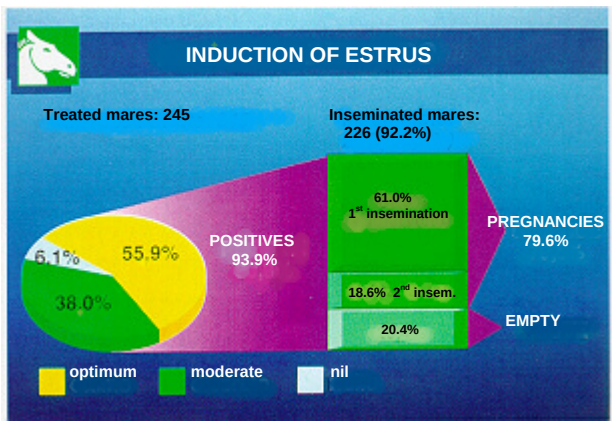
Treatment of mares displaying diestrus with PgF2α induces heat in 2-4 days. Such treatment permits synchronization of estrus in groups of mares and permits more efficient exploitation of stallions for reproduction purposes.

For this indication, it is recommended that the presence of the functioning CL be ascertained through blood progesterone assay.

RESULTS Figure 24

In 35% of the cases considered here, progesterone assay was carried out prior to DALMAZIN treatment.

FIGURE 24



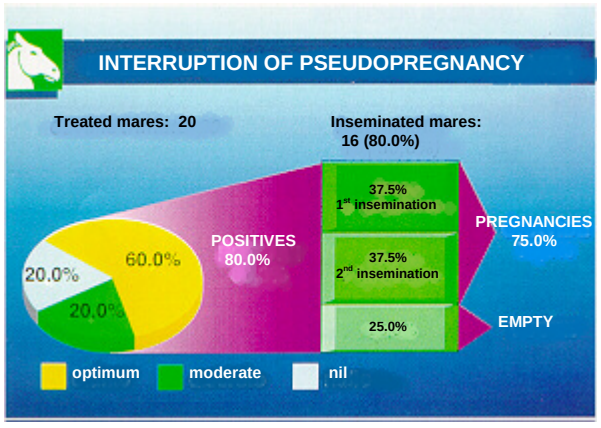
INTERRUPTION OF PSEUDOPREGNANCY

A number of mares which were inseminated during normal heat and which were then found to be empty (in the absence of foetal death or mummification) may display the typical symptoms of pregnancy (presence of CL - i.e. high blood progesterone levels - suppression of sexual cycles and swollen uterus).

These pseudopregnant mares were treated with PgF2α, which led to recovery of sexual cycles and ovulation.

RESULTS Figure 25

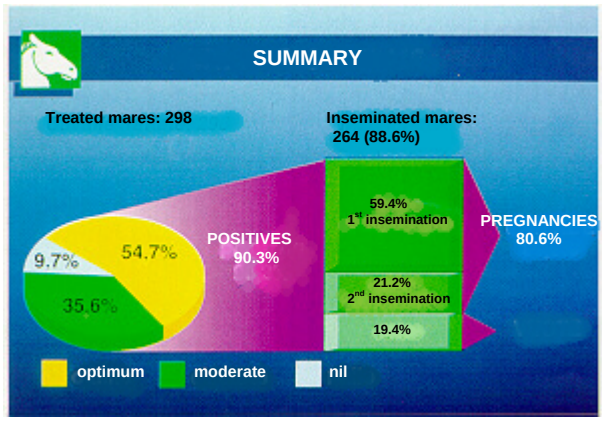
FIGURE 25



GENERAL SUMMARY (HORSES)

RESULTS Figure 26

FIGURE 26



DALMAZIN was found to be most efficacious in mares (more than 90% positive responses); it was also found to be most beneficial with regard to fertility (more than 80% pregnancy rate).

Furthermore, DALMAZIN was found to be perfectly tolerable in this species which is well known to be particularly susceptible to the side effects of prostaglandins.

The researchers stated that they were most satisfied with the efficacy of DALMAZIN and, most of all, they appreciated this drug from the safety and safety margin angles (no side effects noted in any of the treated mares).

SWINE

THE USE OF DALMAZIN IN SWINE

The CL of sows (as opposed to mares and cows) is not very susceptible to the activity of exogenous prostaglandins. Exogenous prostaglandins are therefore not used for management of cycling in empty adult or young sows.

On the other hand, prostaglandins are a very useful economic and farm management resource with regard to planned farrowing.

For DALMAZIN experimentation purposes, a farrowing induction record card was prepared with three treatment programmes (Card 4).

CLINICAL RECORD CARD (SWINE)

Research worker: Dr. _____

Date: _____

Herd: _____

Treated sow no.: _____ Name: _____

TREATMENT PROGRAMME	RESULTS			
	TREATMENT/ FARROWING TIME (h)	DURATION OF FARROWING (h)	No. OF PIGLETS	
			LIVE	STILLB.
1 ml PgF 90 *				
1 ml PgF 90 + 20 I.U. of Oxytocin; 20 h interval				
1 ml PgF 90 + 1 ml PgF 90; 6 h interval				

Notes: _____

SCHEME 4

** PgF90 = trial code name for DALMAZIN*

During the trial, for practical reasons, only two programmes were actually adopted:

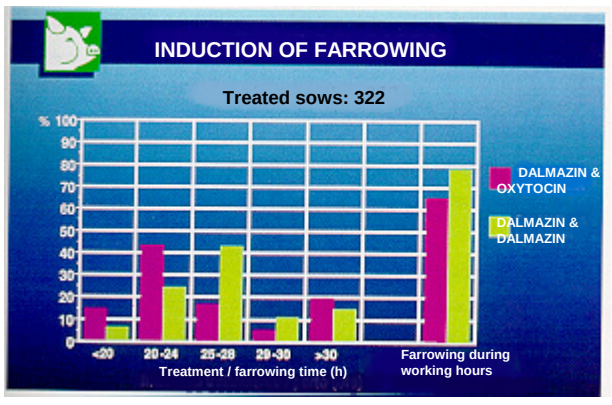
PROGRAMME Ist	PROGRAMME IInd
1 ml of DALMAZIN at midday followed by 20 IU of oxytocin 20 h later (i.e. at 8:00 the following day).	1 ml of DALMAZIN at midday followed by 1 ml DALMAZIN at 18:00 (same day).

These two programmes were adopted so that injection could take place during working hours (8-18) and so that most farrowing would take place during the working hours of the following day (8-18) - i.e. interval of 20-30 h following first injection of DALMAZIN.

RESULTS

The best treatment programme (in terms of farrowing occurring during working hours) was the double DALMAZIN injection programme with a 6 h interval. Nearly 80% of farrowings took place during working hours (8-18) on the day following administration of DALMAZIN (Table 1).

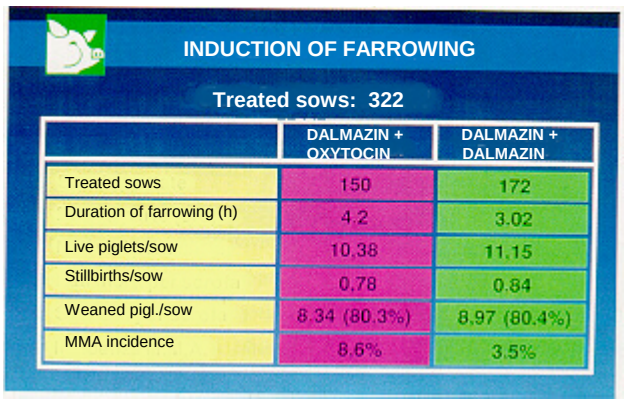
TABLE 1



As to the parameters considered during assessment of these results, the only significant difference concerned duration of farrowing and incidence of puerperal disease in sows (MMA). With regard to both considerations, the most favourable results are noted using the double DALMAZIN administration programme.

With swine too, the researchers declared that they were most satisfied with DALMAZIN's efficacy and above all at the complete absence of the side effects (bronchospasms and watery diarrhoea) which are frequently associated with administration of prostaglandins to sows. Due to the very broad safety margin of DALMAZIN, trials with sows could carry on even into July and August (treatment with other prostaglandins is usually interrupted at this time of the year due to the heat and the high relative humidity levels which bring out marked respiratory problems in treated sows) (Table 2).

TABLE 2



CONCLUSIONS

The trials involved more than 4,800 animals (3 species) and proved:

1 that the clinical efficacy of DALMAZIN shown by these trials is greater than for any other prostaglandin in any other previous trial.

2 The total absence of side effects in treated animals (of interest, above all, with regard to the more sensitive species: horses and swine).

3 DALMAZIN's efficacy at the indicated dosages, irrespective of the weight of the treated animal.

4 Positive responses of animals to treatment with DALMAZIN (over and above the variables considered in such a large-scale trial considering, furthermore, not only the numbers of animals but also of the seasons of the year, feeds, breeds and strains, geographic areas, age etc.).

5 That DALMAZIN is endowed with greater uterine myokinetic activity than other prostaglandins (this is evident above all with regard to the treatment of endometritis, pyometra, placental retention and delayed uterine involution).

6 Marked synchrony regarding treatment and onset of (manifest) estrus (observed above all, in heifers the reaction times of which, as is known, vary greatly after PgF2α treatment).

We may conlcude by noting that the clinical trials herein corroborate the results of the DALMAZIN *in vitro* laboratory trials using isolated organs or laboratory animals. In both cases, it was noted that dextrorotatory cloprostenol, due to its greater affinity to the specific receptors present in the uterus and ovary, is to a greater extent given over to the desired (luteolytic and uterotonic) activities than to the side effects. Indeed, the side effects (bronchospasms, colic syndromes, diarrhoea and profuse sweating) may even be eliminated, and are, in any case the result of non-specific prostaglandin activity toward the smooth muscles of other organs.