

# SENSITIVITY OF THE CORPUS LUTEUM TOWARDS PROSTAGLANDIN F<sub>2a</sub> ( PGF<sub>2a</sub> ) DURING THE GESTATION PERIOD

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## ABSTRACT

Four groups of 10 ewes each were subjected to different synchronisation regimes. They were then randomly divided into two groups of twenty ewes each. Artificial insemination was applied to the one group and natural tupping to the other. Four groups of two ewes each were randomly selected from these two groups to test for the influence of PGF<sub>2a</sub> on pregnancy. Two trials were eventually performed under two different dosage applications. Receptivity towards PGF<sub>2a</sub> seems to be confined to early pregnancy and a minimum dose of PGF<sub>2a</sub> when progesterone is secreted by primarily the corpus luteum before the placenta becomes involved.

## INTRODUCTION

PGF<sub>2a</sub> plays a major role during parturition in most domestic species and is in this regard considered to be mainly of uterine origin (Fredriksson, 1985). During early pregnancy, the conceptus have a depressing effect on the response of the corpus luteum to PGF<sub>2a</sub>. 200 µg of PGF<sub>2a</sub> injected intrafollicularly 12 days post oestrus resulted in luteal regression occurring in only 17% of pregnant ewes compared with 83% in non-pregnant ewes (Reid *et al.*, 1980). Treatment of ewes on day 74 of gestation with 0.14 mg PGF<sub>2a</sub>/kg body weight resulted in regression of the corpus luteum of pregnancy as indicated by decreased serum progesterone by 24 hours after treatment. All ewes that received PGF<sub>2a</sub> during mid-gestation subsequently lambled however (Campbell, Hallford & Wise, 1994). The corpus luteum of the ewe is composed of a heterogeneous population of cells. Only about 45% of the cells of corpora lutea during the mid luteal phase of the oestrous cycle are capable of producing steroids. In populations of small and large luteal cells, the small steroidogenic cells are highly responsive to gonadotrophins while the large cells are relatively unresponsive to gonadotrophins but contain most of the binding sites for PGE<sub>2</sub> (stimulatory effect on luteal cell function) and PGF<sub>2a</sub> (inhibitory effect on luteal cell function). PGE<sub>1</sub> and PGE<sub>2</sub> appear to be blood-borne antiluteolysins that are delivered locally to prevent the actions of PGF<sub>2a</sub> during early pregnancy (Silvia & Niswender, 1984). The PGE:PGF<sub>2a</sub> ratio in the uterine vein is 12:1 at mid gestation. Administration of PGF<sub>2a</sub> increases the placental secretion of oestradiol-17B which is followed by increases in PGE secretion. Oestradiol-17B and PGE may protect placental secretion of progesterone from PGF<sub>2a</sub>, since PGF<sub>2a</sub> causes the corpus luteum to regress. PGF<sub>2a</sub> given at mid gestation causes the corpus luteum to regress but does not affect placental progesterone secretion and fails to terminate pregnancy in the presence or absence of the ovary. (Weems, Vincent & Weems, 1992).

During early pregnancy, a specific class of interferon (omega interferon) is released from the developing embryo in sheep which inhibits pulsatile release of uterine PGF<sub>2a</sub> (Jenkin, 1992). Studies in ovariectomised, steroid treated ewes indicate that conceptus secretory proteins inhibit the pulsatile secretion of PGF<sub>2a</sub> directly via an effect on PG- synthesis and indirectly by maintaining a plasma progesterone concentration that inhibits the development of endometrial oxytocin receptors, which normally increase at the time of luteolysis. As pregnancy progresses, there is an increase in basal secretion of PGF<sub>2a</sub> and PGE from the uterus into the fetal and maternal circulation. The release of maternal PGF<sub>2a</sub> but not PGE, in response to oxytocin is also increased in late pregnancy. Endometrial oxytocin receptor concentrations follow a similar pattern, except at parturition, when there appears to be down-regulation of oxytocin receptors. However, release of PGF<sub>2a</sub> in response to oxytocin remains high at this time, and is further increased if progesterone receptors are blocked. Although oxytocin concentrations in maternal and fetal plasma are not increased until parturition, uterine oxytocin receptor concentrations, uterine activity and maternal PGF<sub>2a</sub> release in response to oxytocin are high in late pregnancy (Jenkin, 1992).

Under normal cyclic conditions, luteolysis in the ewe is induced by the uterine secretion of PGF<sub>2a</sub> which begins on day 12 post-oestrus. In order for pregnancy to be maintained therefore, the corpus luteum must continue to secrete progesterone through the first 50 days of gestation. The embryo must be present in the uterus on days 12 to 13 if the corpus luteum is to persist beyond day 14. This is a critical period for the corpus luteum during which luteolysis is either initiated or prevented. Because the presence of an embryo in the uterus does not appear to reduce secretion of PGF<sub>2a</sub> during the critical period, luteal maintenance must be due either to an insensitivity of the corpus luteum to PGF<sub>2a</sub> or to an inactivation of PGF<sub>2a</sub> before it reaches the corpus luteum (Silvia & Niswender, 1984).

## MATERIAL AND METHODS

Successive to applied synchronisation of the oestrous cycle, one pair of pregnant ewes were selected at random to represent a specific month of pregnancy (X1 - X4: 4 pairs). Each pair of ewes was consecutively, according to the month of gestation they represent, injected with 1 ml PGF<sub>2a</sub> (5 mg Dinoprost tromethamine) on days 30, 60, 90, and 120 of gestation respectively. Blood samples were collected every 12 hours from treatment for three days and then once daily until abortion occurred, or alternatively for 10 days following treatment. Since no abortions occurred during the first trial, it was supplemented by a second trial to test for PGF<sub>2a</sub> sensitivity:

12 Damara ewes were divided into three groups of 4 ewes each viz. Group A representing day 30, Group B representing day 60 and Group C representing day 90 of the gestation period. All ewes were synchronised with the aid of progestagen pessaries which were left in tact for a period of 12 days. On sponge removal each ewe was treated intramuscularly with 300 units of PMSG while each group was exposed to a fertile ram for a period of 7 days. After this period has expired, the rams were removed for a period of 7 days after which they were again introduced for another period of 7 days. During the second introduction the rams were fitted with raddling blocks and interchanged between groups. Since no ewes were marked during the second introduction, it was accepted that all ewes conceived during the first introduction of the rams. Each group of 4 ewes was again subdivided into two groups of 2 ewes as follows:

Group A (30 days): A1 and A2  
 Group B (60 days): B1 and B2  
 Group C (90 days): C1 and C2

with Groups A1, B1 and C1 treated with 1 ml PGF<sub>2a</sub> and Groups A2, B2 and C2 treated with 2 ml PGF<sub>2a</sub> on days 30, 60 and 90 of the gestation period respectively.

## RESULTS AND DISCUSSION

The higher levels of progesterone that Group X4 displayed (Figure 1.4), are in accordance with the late stage of pregnancy Group X4 represented. Figures 1.1 to 1.4 show that progesterone concentration levels dropped on average for Group X1 from 2.999 ng/ml to 1.487 ng/ml, for Group X2 from 3.445 ng/ml to 1.444 ng/ml, for Group X3 from 3.486 ng/ml to 2.073 ng/ml and for Group X4 from 7.135 ng/ml to 4.842 ng/ml after treatment with PGF<sub>2a</sub> with a mean average decline of 1.805 ng/ml. Apart from Group X2 of which the levels maintained a declining tendency towards day 10 after treatment, all other groups showed a recovery within 24 hours. During the supplementary trial (Trial 2, Table 1.1), abortions only occurred in Group A2 representing day 30 of pregnancy and treated with 10 mg dinoprost.

Silvia *et al.* (1984) reported that the minimum luteolytic dose of PGF<sub>2a</sub> defined as the lowest dose of PGF<sub>2a</sub> that resulted in a significant reduction in the concentration of serum progesterone, is 4mg/58 kg bodyweight. At this dose, corpora lutea from five of eight non-pregnant ewes regressed while none of the corpora lutea from nine pregnant ewes regressed.

## CONCLUSION

In pregnant ewes with one and two corpora lutea, the minimum luteolytic doses of PGF<sub>2a</sub> are 6 and 10 mg/58 kg body weight respectively (Western range ewes, Colorado). Luteal regression was induced with 6mg/58 kg body weight in three of four pregnant ewes with one corpus luteum, but in none of five ewes with two corpora lutea (Silvia *et al.* 1984). Since no abortions resulted during the present study from treatment with 5mg PGF<sub>2a</sub> of pregnant ewes with an average body weight of 45 kg at any stage of pregnancy and no abortions apart from the first month of pregnancy occurred as a result of treatment with 10 mg PGF<sub>2a</sub>, the resistiveness of the Damara sheep towards PGF<sub>2a</sub> seems to fall more or less in the same category as quoted by above mentioned

authors both with regard dosage per kg bodyweight and stage of pregnancy.

## REFERENCES

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TABLE 1.1 THE EFFECT OF PGF<sub>2a</sub> ON PREGNANCY (TRIAL 2)

Group	Ewe No (ml PGF <sub>2a</sub> )	Treatment	Observation
Day 30			
A1	72	1 ml	lambd
A1	23	1 ml	lambd
A2	245	2 ml	aborted
A2	228	2 ml	aborted
Day 60			
B1	244	1 ml	lambd
B1	223	1 ml	lambd
B2	31	2 ml	lambd
B2	139	2 ml	lambd
Day 90			
C1	394	1 ml	barren
C1	173	1 ml	barren

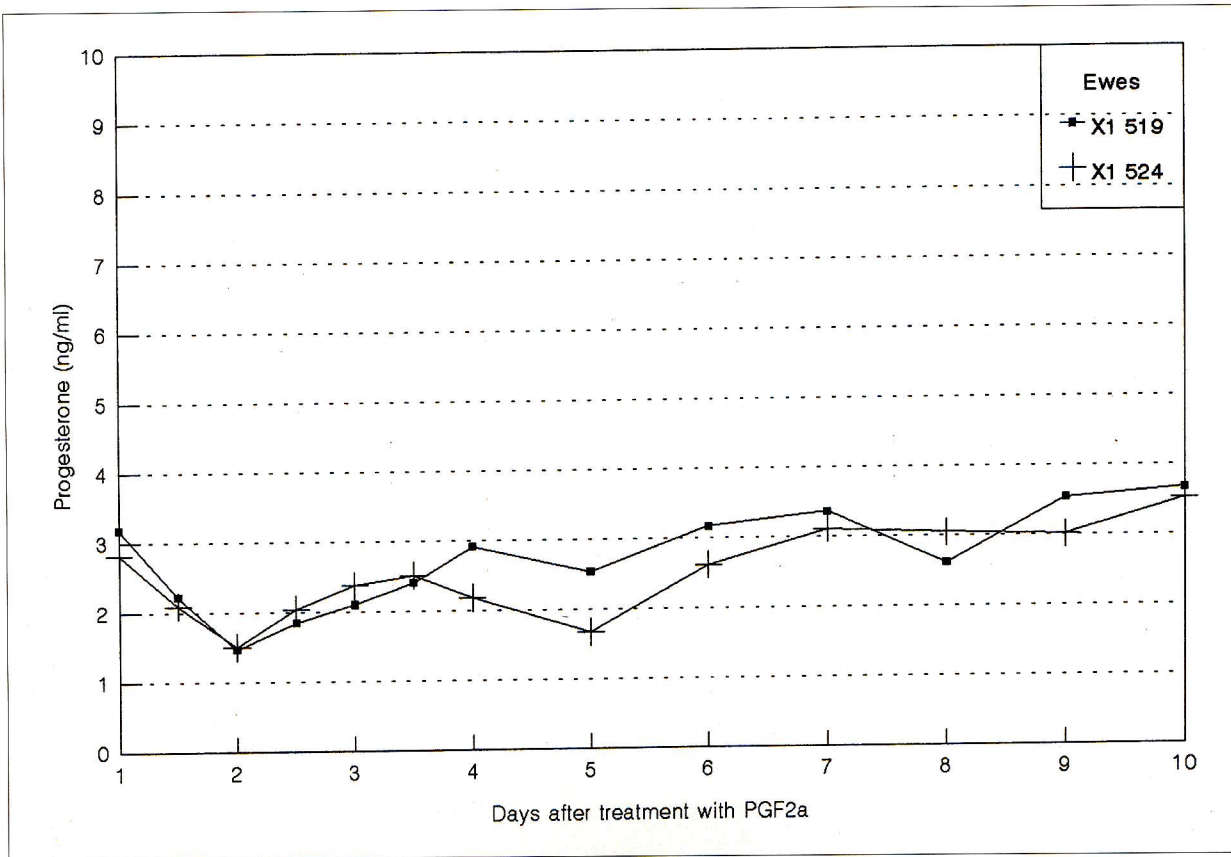


FIGURE 1.1: PGF<sub>2a</sub> SENSITIVITY DURING THE GESTATION PERIOD IN DAMARA EWES. (DAY 30)

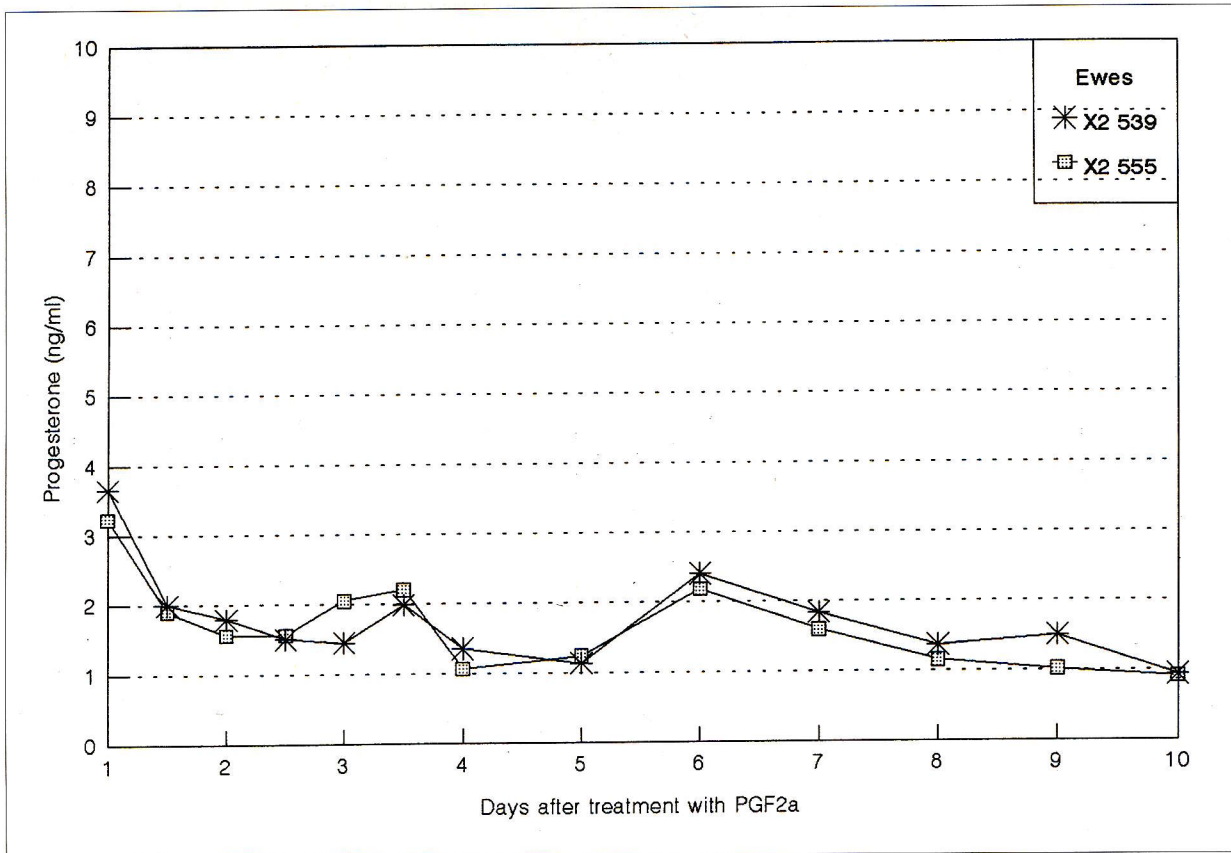


FIGURE 1.2: PGF<sub>2a</sub> SENSITIVITY DURING THE GESTATION PERIOD IN DAMARA EWES. (DAY 60)

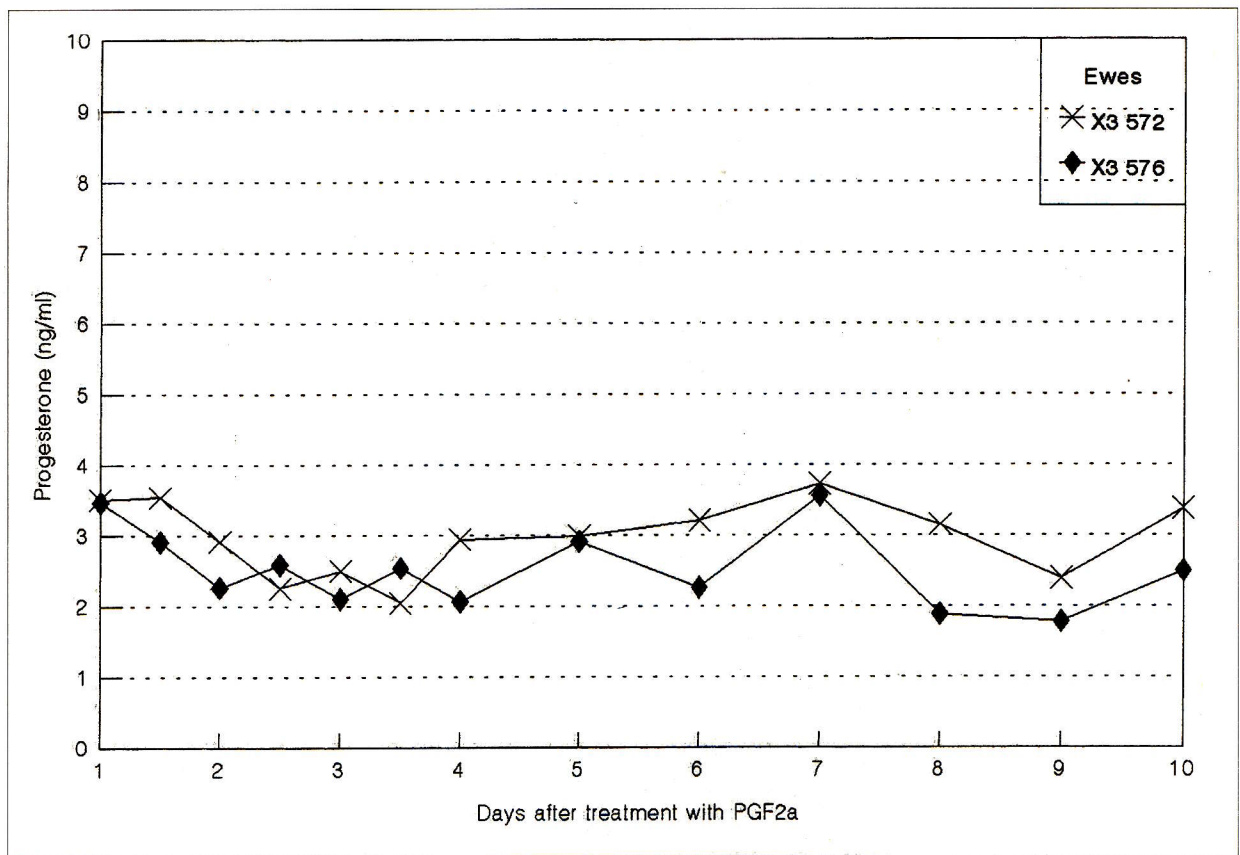


FIGURE 1.3: PGF<sub>2a</sub> SENSITIVITY DURING THE GESTATION PERIOD IN DAMARA EWES. (DAY 90)

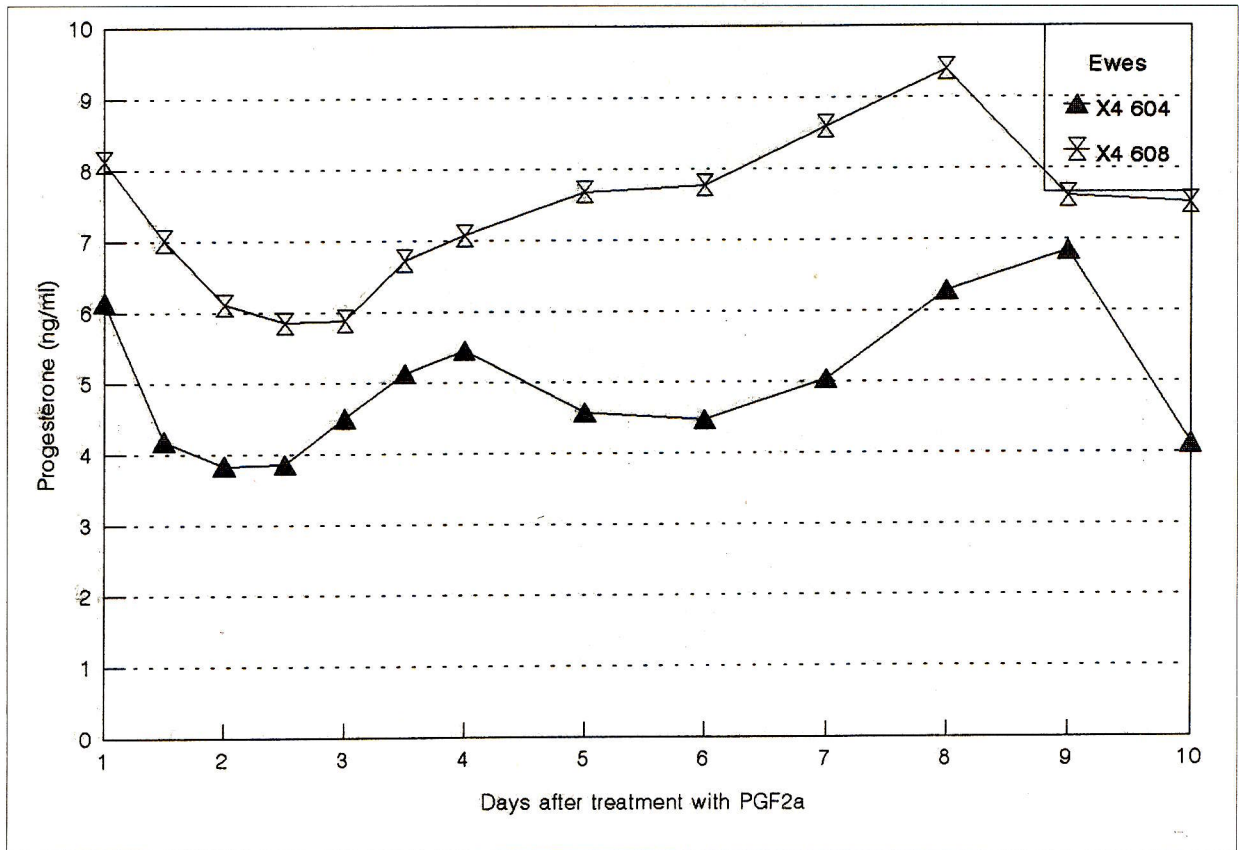


FIGURE 1.4: PGF<sub>2a</sub> SENSITIVITY DURING THE GESTATION PERIOD IN DAMARA EWES. (DAY 120)