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Effect of a Prostaglandin $F_{2\alpha}$ Analogue Prostinfenem (15-Methyl-$PGF_{2\alpha}$), to Induce Luteolysis and Oestrus in Heifers

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Aiumlamai, S.: Effect of prostaglandin $F_{2\alpha}$ analogue, prostinfenem (15-methyl-$PGF_{2\alpha}$), to induce luteolysis and oestrus in heifers. Acta vet. scand. 1991, 32, 327–335. – Different doses of 15-methyl-$PGF_{2\alpha}$ (0.125–10 mg) were used to induce luteolysis and oestrus in 7 heifers with 28 treatments on day 8–12 of the oestrous cycle. Twenty-three out of 28 treatments gave the desired response and the animals showed signs of oestrus within 5 days post-injection. The doses of 0.25–10 mg can be used to induce luteolysis and oestrus. The dose of 0.125 mg was not effective to induce luteolysis and only 1 out of 4 treatments responded. When higher doses were given (1–10 mg), progesterone levels decreased more rapidly and reached 1 nmol/l 16.2 h earlier than in animals which responded to doses < 1 mg. The minimum effective dose was considered to be 0.25 mg. Clinical signs of oestrus, regression of corpus luteum and variation in the interval to oestrus were similar as for $PGF_{2\alpha}$ or its other analogues. By measurement of the main circulating prostaglandin $F_{2\alpha}$ metabolite, it was found that an endogenous $PGF_{2\alpha}$ release occurred 1–3 days post-injection of 15-methyl-$PGF_{2\alpha}$. Furthermore in cases of post-oestrous bleedings an endogenous $PGF_{2\alpha}$ release was also seen concomitantly with the bleeding. This prostaglandin analogue seems to be useful for farm management and can be an alternative to other $PGF_{2\alpha}$ analogues.

reproductive hormones; ultrasound scanning; heat synchronization; bovine species.

Introduction

During the bovine oestrous cycle, there is a dramatic increase of endogenous prostaglandin $F_{2\alpha}$ of uterine origin which causes luteal regression and initiation of a new cycle (*Peterson et al.* 1975, *Kindahl et al.* 1976a, b). These findings have also found practical application in cattle breeding. The reports on the use of prostaglandin $F_{2\alpha}$ in cattle reproduction appeared in 1972 (*Rowson et al.* 1972, *Lauderdale* 1972). The luteolytic properties of prostaglandin $F_{2\alpha}$ such as the dinoprost tromethamine salt and its analogue such as cloprostenol have been described to effectively control corpus luteum function and oestrus in dioestrous cattle (*Cooper* 1974, *Lauderdale et al.* 1974, *Macmillan & Curnow* 1976, *Seguin* 1980, 1983, *Macmillan & Day* 1982, *Santos et al.* 1988).Today, it is an accepted method to use prostaglandin $F_{2\alpha}$ as a tool to induce luteolysis and oestrus.

The 15-methyl-$PGF_{2\alpha}$ (Prostinfenem®), an analogue of prostaglandin $F_{2\alpha}$, has been used for interruption of pregnancy or induction of labour during normal deliveries in woman. The route of administration has been intra-

venous, intramuscular, intraamniotic, extra-amniotic and intravaginal and the doses have varied from 2 to 5 mg (*Bergström* 1981, *Bygdeman* 1981, 1984). This analogue has also been used to induce oestrus in cattle and buffaloes (*Narayana & Honnappa* 1986).

It is of economic value to facilitate distribution, that this analogue of prostaglandin $F_{2\alpha}$ can be used both in humans and animals. The objectives of this work were to study the effect of 15-methyl-$PGF_{2\alpha}$ to induce luteolysis and oestrus in heifers and to find the effective dose in cattle for heat synchronization. The peripheral plasma levels of progesterone, prostaglandin $F_{2\alpha}$ metabolite and oestradiol-17β were analysed and related to the findings of ultrasound scanning of the reproductive tract to evaluate the efficacy of the drug.

Materials and methods

Animals

Six Swedish Red and White breed (SRB) and 1 Swedish Friesian breed (SLB) heifers, 1.5–3 years old, with normal oestrous cycles were used repeatedly at 3 to 5 occasions during the experimental period. All animals were housed in pens and fed individually with hay and concentrate according to Swedish standard. The heifers were daily checked for oestrous behaviour and rectal palpation was done every 2nd day in the cycle before the experiment started. The cyclicity of all animals was found to be normal.

15-Methyl-$PGF_{2\alpha}$ (Prostinfenem®)

15-Methyl-$PGF_{2\alpha}$ (as the tromethamine salt Prostinfenem®, The Upjohn Company, Kalamazoo, MI, USA), was injected intramuscularly in the heifers. In the treatment programme, 28 treatments were done in the 7 heifers and the animals were given 15-methyl-$PGF_{2\alpha}$ in different doses (Table 1). The animals were injected once at day 8–12 of the oestrous cycle. At least 1 untreated cycle was allowed until the same animal was treated again.

Clinical examination

The animals were observed for oestrous behaviour twice daily during the period of study. The corpus luteum diameter and time of ovulation were monitored by rectal palpation and ultrasonography (real-time, B-mode, 5 MHz, SSD-210 DX, Aloka Co Ltd., Japan) every second day. The examination started 1 week before injection of 15-methyl-$PGF_{2\alpha}$ until the animals showed signs of oestrus or 7 to 9 days after injection in animals which did not respond.

Blood sampling

Ten ml of blood was collected from the jugular vein twice a day, from 3 days before injections of 15-methyl-$PGF_{2\alpha}$ until the animals showed clear signs of oestrus or 7 to 9 days post-injection. Blood samples were withdrawn into heparinized Vacutainer tubes (Becton and Dickinson, Rutherford, NJ, USA) and centrifuged within 15 min at 2000 r.p.m. Plasma was removed and stored at –20°C until hormone analysis.

Hormone analysis

The plasma samples were analysed using radioimmunoassay for the content of progesterone (*Bosu et al.* 1976, *Kindahl et al.* 1976b) and 15-ketodihydro-$PGF_{2\alpha}$ (*Kindahl et al.* 1976b, *Granström & Kindahl* 1982). From 4 different treatment periods samples were analysed for oestradiol-17β using enzyme immunoassay (*Jones & Madej* 1988). The practical limit of sensitivities are 0.5 nmol/l, 25–30 pmol/l and 1.1 pmol/l, respectively.

Table 1. Different doses of 15-methyl-$PGF_{2\alpha}$ used i.m. in 7 heifers (18 treatments) by number of treatments, day of the cycle and interval from injection to oestrus in the group of "responding" (< 5 days) versus the group of "non-responding" (> 5 days).

Dose i.m. mg	No. of treatments	Animal no.	Day of cycle	Interval (days) from injection to	
				oestrus < 5	oestrus > 5
10.0	1	A	12	A(2.5)	–
5.0	2	B C	12	B(3.5) C(4.0)	–
2.5	2	B C	12	B(4.0) C(4.5)	–
1.0	2	A C	10,12	A(3.5) C(5)	–
0.5	9	A^2 B C D^2 F^2 G	8–10	A^2 B C D F^2 G (3–5;4.0±0.3)*	D(13)
0.25	8	A D^2 F^2 G^3	10–12	D^2 F^2 G^3 (3–5;3.7±0.2)*	A(7)
0.125	4	D E F G	11–12	G(5)	D(10) E(7) F(10)
Total	28		8–12	23	5

2 = injected twice
3 = injected thrice
* = figures indicate range and mean ± S.E.

Statistical analysis

The changes in levels of progesterone and 15-ketodihydro-$PGF_{2\alpha}$ throughout the experimental period were evaluated by analysis of variance. The Scheffe multiple range test was used to compare means of progesterone levels. The Scheffe multiple range and Confident Interval tests were used to compare means of 15-ketodihydro-$PGF_{2\alpha}$.

Results

Table 1 presents the results obtained for the 28 treatments of the 7 heifers.

The animals which showed signs of oestrus within 5 days after prostaglandin treatment with various doses were grouped as "responding treatments". Twenty-three out of 28 treatments responded. Oestrous behaviour of the responding animals were similar as clinical signs of natural oestrus: vulva swollen, clear vaginal discharge, uterine contraction and standing heat (observed or checked by bull). The animal which was injected with 10 mg got diarrhoea and hyperemia which disappeared within 12 h after the injection. No side-effects were found with the other doses. In 5 out of the responding 23 treatments and in 1 of the non-responding treatment (no. E) post-oestrous bleedings were found. The size of corpus luteum decreased in the responding animals from 2.41 ± 0.06 (X ± SE) cm to 1.56 ± 0.05 cm within 48 h. At 7 occasions a central cavity with diameter of 0.7–1.0 cm was found in the corpus luteum before prostaglandin injections. This occurred 3 times in animal C (doses of 15-methyl-$PGF_{2\alpha}$ 1.0, 2.5 and 5.0 mg), twice in animal F (both at dose 0.25 mg), once in animals A (dose 0.5 mg) and G (dose 0.25 mg). After 2 treatments in animals C and F with doses of 2.5 and 0.25 mg respectively, follicles developed into follicular cysts. Follicles during midcycle were between 1.0–1.5 cm and several smaller follicles were also present in the ovaries. In the responding animals, one follicle ovulated 1.42 ± 0.11 days after the animal showed signs of oestrus except in animal D (dose 0.25 mg); she ovulated 4.5 days post-oestrus. In the responding treatments the ovulatory follicle was in 21 cases bigger than 1.0 cm at the time of treatment

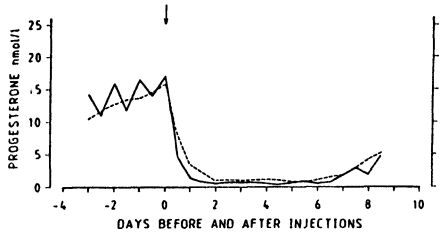

Figure 1.1. Average progesterone levels in the high doses group of 15-methyl-$PGF_{2\alpha}$ (1–10 mg (——) and in the low doses group (0.125–0.5 mg) (– – – –) of animals responding with induction of oestrus < 5 days after injections (indicated by arrow).

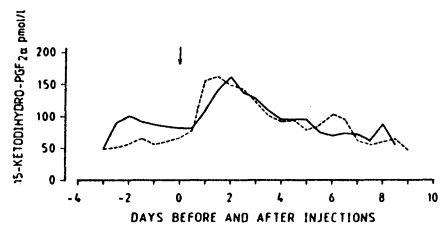

Figure 1.2. Average 15-ketodihydro-$PGF_{2\alpha}$ levels in the high doses group of 15-methyl-$PGF_{2\alpha}$ (1–10 mg) (——) and in the low doses group (0.125–0.5 mg) (– – – –) of animals responding with induction of oestrus < 5 days after injections (indicated by arrow).

and in 2 cases ovulation occurred from a small follicle of the other ovary.

In the responding treatments, after intramuscular injections of 15-methyl-$PGF_{2\alpha}$, blood plasma progesterone levels fell significantly from 15.9 ± 0.6 nmol/l (X ± SE) to 6.2 ± 0.4 nmol/l within 12 h and to 2.4 ± 0.2 nmol/l within 24 h (Fig. 1.1). Progesterone levels were lower than 1.0 nmol/l from day 2 to day 6 post-injection and then increased slowly in the new cycle. With doses of 15-methyl-$PGF_{2\alpha}$ of 1 to 10 mg (high doses), progesterone levels decreased significantly 12 h after injections; doses of 0.125 to 0.5 mg (low doses) of 15-methyl-$PGF_{2\alpha}$, progesterone levels decreased significantly 24 h after injections. At 24 h and 36 h post-injection, the levels in the low dose group were significantly higher in the high dose group. We arbitrarily defined the time required from injection to reach the 1 nmol/l level of progesterone as an important measure; in the high dose group this time was 30.6 h and in the low dose group 46.8 h. Thus the difference was 16.2 h. Furthermore, in the high dose group the levels of progesterone during the heat period was lower (0.43 ± 0.05 nmol/l) as compared to the low dose group (0.85 ± 0.08 nmol/l). This difference was significant ($P < 0.05$).

Endogenous release of prostaglandin $F_{2\alpha}$ was found after injection of 15-methyl-$PGF_{2\alpha}$ (Fig. 1.2). The levels of the 15-ketodihydro-$PGF_{2\alpha}$ increased significantly, according to confident interval test, 1 day post-injection from 67.1 ± 9.2 to 143.9 ± 13.9 pmol/l, remained high and declined at 3 days post-injection in both high and low dose groups. In the low dose group, the prostaglandin metabolite reached the high level earlier than when high doses were given. In the low dose group, the prostaglandin levels had a tendency to be slightly elevated again on day 5.5 to day 7 post-injection and in 3 out of 5 responding animals these elevations were seen concomitant with a post-oestrous bleeding.

One treatment with dose 0.5 mg, 1 treatment with dose 0.25 mg and 3 treatments with dose 0.125 mg did not respond; the animals showed oestrus later than 5 days post-injection (Table 1).

The "non-responding" animal (no. D), with the dose of 0.5 mg was injected on day 8 of the cycle. However, low levels of progesterone (3.4 nmol/l) were found at the time of injection. The levels slowly increased reaching about 10 nmol/l 6 days post-injection. No drop in progesterone levels was seen after injection (Fig. 2) and prostaglan-

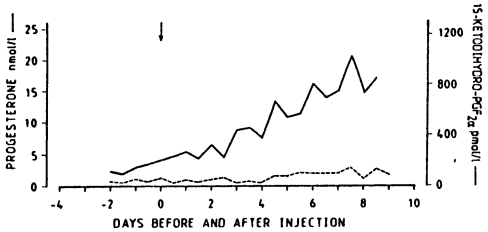

Figure 2. Progesterone —— and 15-ketodihydro-$PGF_{2\alpha}$ levels - - - - in the non-responding animal (no. D) with a dose 0.5 mg of 15-methyl-$PGF_{2\alpha}$. An arrow indicates time of 15-methyl-$PGF_{2\alpha}$ injection.

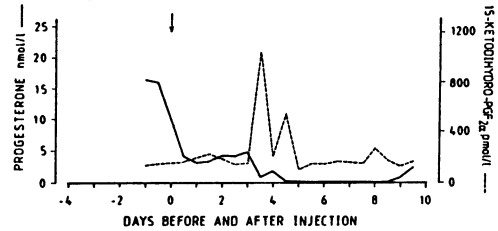

Figure 4. Progesterone —— and 15-ketodihydro-$PGF_{2\alpha}$ levels - - - - in the non-responding animal (no. E) with a dose 0.125 mg of 15-methyl-$PGF_{2\alpha}$ which came in heat 7 days after injection (indicated by arrow).

din levels increased to 145 and 139 pmol/l on days 8 and 9 post-injection, respectively. The corpus luteum grew continuously after injection and the animal showed signs of oestrus 13 days post-injection.

The "non-responding" animal (no. A), given 0.25 mg, which was injected on day 12 of the cycle had a decrease of progesterone levels 12 h after injection from 24.7 nmol/l to 10.5 nmol/l and to 6.6 nmol/l at 24 h post-injection. The progesterone levels slightly increased again to between 10–14 nmol/l but did not reach pretreatment levels and later decreased concomitantly with a peak of the prostaglandin metabolite. The animal showed oestrus 7 days post-injection (Fig. 3). One treatment with 0.125 mg (no. E) resulted in decreased progesterone levels from 14.3 nmol/l to 4.1 nmol/l 12 h post-injection but the levels remained above 1.0 nmol/l (2.5–4.1 nmol/l) also 3 days after injection (Fig. 4). Endogenous prostaglandin metabolite peaks occurred 3 to 5 days post-injection and the animal showed signs of oestrus 7 days after injection.

Two treatments with 0.125 mg which were given on day 11 and 12 of the cycle did not respond (nos. D and F). Progesterone levels declined temporarily within 12 h after injection, but the animals did not express oestrus and the decline was followed by a rebound in plasma progesterone levels. Peaks of the prostaglandin metabolite levels were found 6 and 7 days post-injection (777 pmol/l and 1173 pmol/l, respectively) concomitantly with decreasing levels of progesterone (Fig. 5

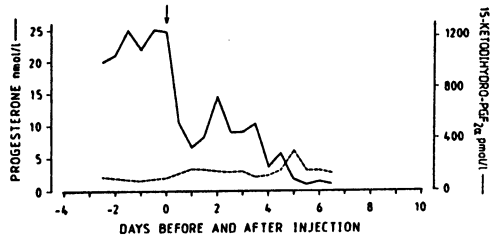

Figure 3. Progesterone —— and 15-ketodihydro-$PGF_{2\alpha}$ levels - - - - in the non-responding animal (no. A) with a dose 0.25 mg of 15-methyl-$PGF_{2\alpha}$. An arrow indicates time of 15-methyl-$PGF_{2\alpha}$ injection.

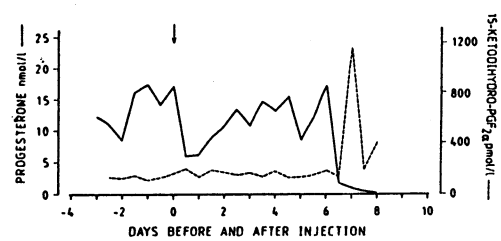

Figure 5. Progesterone —— and 15-ketodihydro-$PGF_{2\alpha}$ levels - - - - in the non-responding animal (no. D) with a dose 0.125 mg of 15-methyl-$PGF_{2\alpha}$. An arrow indicates time of 15-methyl-$PGF_{2\alpha}$ injection.

shows the endocrine profiles in animal no. D). Both of them showed signs of oestrus 10 days after injection.

Three out of 24 treatments which responded and 1 which did not respond were analysed for the plasma content of oestradiol-17β to confirm the ovulatory peaks. The levels of oestradiol-17β increased to high levels which were related to the time of the induced oestrus in the responding animals. However the variation in the low levels was considerable before the animals showed signs of oestrus. The non-responding animals showed a peak in oestradiol-17β levels concomitant with oestrus 13 days after the prostaglandin injection.

Discussion

Animals showed clinical signs of oestrus after injection of this prostaglandin analogue as during the natural oestrous cycle and the size of corpus luteum decreased after injection. The report from *Louis et al.* (1973) found that the corpus luteum diameter declined continuously during the 72 h after injection from 2.3 ± 0.1 to 0.6 ± 0.3 cm. *Edqvist et al.* (1975) reported that in 24 h after $PGF_{2\alpha}$ injection the corpus luteum diameter decreased about 40 % and also *Hardin & Randel* (1982) found that cloprostenol depressed the corpus luteum weight compared to controls. In general, when heat syncronization is used, oestrus should be observed within 2–5 days. There are many reports claiming that the interval between injection to oestrus varies due to the stage of the cycle at injection. One agreement is that injection early in the cycle causes a shorter interval to oestrus than does injection late the cycle (*Refsal & Seguin* 1980, *King et al.* 1982, *Macmillan & Henderson* 1983/1984). However observed oestrus response rates are higher in late cycle than in early cycle (*Tanabe & Hann* 1984, *Watts & Fuquay* 1985). During mid-cycle (days 10–13) cattle have the widest range of response (*Momont & Seguin* 1988). In our study, injections were done on days 10–12 and 2 animals were injected on day 8 and 9, and the interval to oestrus varied from 2.5 to 5 days. Variability in the return to oestrus after $PGF_{2\alpha}$ injection during mid-cycle can be different among cattle and depend on doses of $PGF_{2\alpha}$, ability to ovulate and/or status of large follicles present at the time of injection. In our study the biggest follicle, which was found at time of each injection, was still large at oestrus and presumably the ovulatory follicle. However, in 2 out of 21 occasions the largest follicle at injection regressed and was replaced at oestrus by a follicle that grew from a pool of small follicles. Examination of the ovaries was only done every 2nd day, which might not be enough to follow the growth of follicles and some regression might not have been detected.

In previous studies, it was seen that blood progesterone levels decreased markedly within 12 h and by 24 h they are at base-line concentrations (*Edqvist et al.* 1975, *Kindahl et al.* 1980, *Cornwall et al.* 1985, *Momont & Seguin* 1988, *Jiménez et al.* 1988). Similar decreases were found in this study when 15-methyl-$PGF_{2\alpha}$ was injected. In the high doses, a significant decrease was seen after 12 h and in the lower doses after 24 h. Furthermore during the oestrous period progesterone levels were significantly lower in the high doses group than in the lower doses group. *Gustafsson et al.* (1986) found that in repeat breeder heifers the progesterone levels were higher ($P < 0.05$) than in the virgin heifers during oestrus. These findings are important in relation to fertility after insemination since the higher progesterone levels can disturb transport of the ovum in the oviducts.

At 5 occasions (0.25, 0.5 and 3 times 0.125

mg) no response was achieved. In 4 out of these cases progesterone levels decreased but rebounded before final decline below 1.0 nmol/l and signs of oestrus were seen at a later stage. Similar finding of progesterone profile was seen in a previous study (*Edqvist et al.* 1975) using varying doses of $PGF_{2\alpha}$. In general it is expected that too low doses of a luteolytic compound should show a rebound effect of progesterone levels. The animal which did not respond to 0.5 mg might be special since she showed a slow development of the corpus luteum as compared to normal cows. A similar cow has been demonstrated by *Kindahl et al.* (1977) where 1 animal repeatedly showed a slow development of the corpus luteum and progesterone levels were not at maximum until at about day 9–10 of the oestrous cycle. Animals with slow development of the corpus luteum function can easily fail to be synchronized in the herd. The results of the present study showed that high doses (1–10 mg) had a good response but also 0.25 mg and 0.5 mg can be used. The dose of 0.125 mg was not a proper dose to induce luteolysis.

The levels of 15-ketodihydro-$PGF_{2\alpha}$ increased during 1 to 3 days post-injection as has been presented by *Kindahl et al.* (1980) after use of cloprostenol. This might be due to that the uterus is stimulated by exogenous prostaglandins and thus an endogenous release of $PGF_{2\alpha}$ from the uterus occurs. Post-oestral bleeding was related with an increase of the prostaglandin metabolite levels which was found in 3 out of 6 occasions. This has earlier been reported by *Kindahl et al.* (1976a, 1980). In animals which did not respond, peaks of endogenous $PGF_{2\alpha}$ were found during luteolysis before they showed oestrus. This is the normal luteolytic release of $PGF_{2\alpha}$ seen at the end of the oestrous cycle, but the schedule of blood sampling was not frequent enough to detect all of the peaks.

Small doses of other $PGF_{2\alpha}$ products (less than the recommended therapeutic dose) can be effective in some cows as reported in field trials (*Seguin et al.* 1980, *Harrison et al.* 1983). *Narayana & Honnappa* (1986) reported that the use of carboprost tromethamine (15-methyl-$PGF_{2\alpha}$) in cattle at doses of 20–200 μg i.m. caused animals to respond in 68.9 % and that oestrus occurred 2 to 3 days post-injection. However it is surprising that the effective doses were very low in that study as compared to the present. The reasons for these differences are not known.

In conclusion, 15-methyl-$PGF_{2\alpha}$ can be used to induce luteolysis in heifers. High doses (1–10 mg) are more effective to induce luteolysis than lower ones. The minimum effective dose seems to be 0.25 mg, however fertility trials are needed to obtain a better knowledge of the efficacy. Clinical signs, hormonal profiles and variation in interval to oestrus are similar as with $PGF_{2\alpha}$ and other $PGF_{2\alpha}$ analogues. No side-effects were found except a relative mild effect in the highest dose (10 mg).

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Sammanfattning

Effekt av en prostaglandin $F_{2\alpha}$ analog, Prostinfenem (15-Methyl-PGF $_{2\alpha}$), för att inducera luteolys och brunst hos kvigor.

Tjugoåtta injektioner av 15-metyl-$PGF_{2\alpha}$ i doserna 0,125–10 mg gavs för att inducera luteolys och brunst på 7 kvigor på dag 8–12 av brunstcykeln. I 23 av 28 fall gav behandlingen önskat resultat och djuren visade brunst inom 5 dagar efter injektionen. Doser mellan 0,25 mg och 10 mg kan användas för att inducera luteolys och brunst. Dosen 0,125 mg inducerade luteolys endast i 1 fall av 4. När högre doser gavs (1–10 mg) minskade progesteronnivåerna snabbare och nivån < 1 nmol/l nåddes 16,2 timmar tidigare än hos djur som svarade på doser under 1 mg. Minsta effektiva dos var 0,25 mg. Kliniska brunstsymptom, gulkroppens regression och variationen i tiden till brunst efter injektion liknade svaret efter injektion av $PGF_{2\alpha}$ och andra prostaglandinanaloger. Genom att mäta prostaglandin $F_{2\alpha}$'s huvudmetabolit, påträffades en endogen frisättning av $PGF_{2\alpha}$ 1–3 dagar efter injektionen. I de fall där blodflytning förekom efter brunsten kunde också en endogen frisättning uppmätas. Sammanfattningsvis kan sägas att denna nya prostaglandinanalog är ett fullgott alternativ till tidigare använda prostaglandinanaloger.

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