

## PROSTAGLANDIN F2 ALPHA AND PROSTACYCLIN IMBALANCE IN COWS WITH PLACENTAL RETENTION : NEW FINDINGS

A.E.M. HORTA<sup>1</sup>, Michelle CHASSAGNE<sup>2</sup> and M. BROCHART<sup>2</sup>

1 : Departamento de Reproducao Animal, EZN-INIAER, 2000 Santarem, Portugal  
2 : Laboratoire d'Éco-Pathologie, CRZV-INRA Theix, 63122 Ceyrat, France

### Résumé

DÉSÉQUILIBRE RELATIF DE PgF2 ALPHA ET Pgl2 CHEZ LES VACHES A RÉTENTION PLACENTAIRE. NOUVELLES DONNÉES. — Le but de ce travail était de détecter d'éventuelles différences des concentrations plasmatiques au niveau périphérique de la 13,14 dihydro 15 céto PgF alpha (PGFM) et de la 6 céto PgF1 alpha (PGIM) entre vaches à rétention (RP) et vaches à vêlage sans rétention (NRP) du placenta (vêlage normal). Des prélèvements de sang ont été effectués 5, 30, 60 minutes *postpartum* sur 8 vaches à rétention et 17 vaches à vêlage normal. Les teneurs plasmatiques en PGFM étaient plus faibles chez les vaches à non-délivrance que chez les vaches à vêlage normal 60 minutes *postpartum* (8156 pg/ml vs 12016 pg/ml,  $P \leq 0,05$ ). Une augmentation significative du taux de PGFM a eu lieu entre 30 et 60 minutes *postpartum* chez les vaches du groupe NRP (6225 pg/ml vs 12016 pg/ml,  $P \leq 0,01$ ) tandis que dans le groupe RP, le niveau de PGFM est resté constant au cours de la période étudiée. Aucune différence significative n'est apparue en ce qui concerne le métabolite de Pgl2 malgré des valeurs légèrement supérieures pour le groupe RP. Le rapport PGFM/PGIM était significativement plus haut 60 minutes après le vêlage dans le groupe NRP que dans le groupe RP (15,5 vs 8,8 ;  $P \leq 0,01$ ). Ce rapport a augmenté entre 30 et 60 minutes (7,2 vs 15,5 ;  $P \leq 0,01$ ) chez les vaches à vêlage normal, résultat non observé chez les vaches à non-délivrance. Il n'est pas apparu de corrélation significative entre les niveaux de PGFM et PGIM au cours des soixante premières minutes du *postpartum* pour les vaches du groupe NRP. Cependant, une telle corrélation était significativement positive pour les vaches du groupe RP ( $r = 0,75$ ,  $P \leq 0,01$ ). Les résultats suggèrent que la synthèse de PgF2 alpha entre 30 et 60 minutes *postpartum* est significativement moindre chez les vaches à non-délivrance comme le reflète le niveau de PGFM. Ils suggèrent en outre que la synthèse de prostacycline semble stable chez les vaches à vêlage normal au cours des 60 premières minutes *postpartum*, mais non chez les vaches à rétention dont la concentration en PGIM augmente en même temps que celle de PGFM. Il est proposé qu'un déséquilibre de synthèse de PgF2 alpha et Pgl2 au cours des 60 premières minutes suivant le part, conduisant à un défaut de PgF2 alpha et une augmentation relative de Pgl2, est associé à la rétention anoxiologique chez la vache.

The role of prostaglandins upon the physiological mechanism of placental separation in the cow has been stated in an earlier study (Horta, 1981), where it was shown that cyclooxygenase inhibition early after calving leads to a retention of the afterbirth for a period longer than 24 hours.

Later, further experiments confirmed and added

new knowledge to the previous finding. In one of these experiments, it was studied the pharmacological effects of prostaglandins E2 and F2 alpha in relation to the time needed for placental separation and expulsion, and to the strength of uterine contractions (Horta, 1984). The results obtained suggested that PGE2 inhibits the normal placental

separation process and PGF2 alpha seems to stimulate this mechanism. These effects were found in the same study to be independent of the oxytocic action of the drugs and it was postulated that an imbalance in PGE2/PGF2 alpha synthesis early in postpartum, could be associated with placental retention.

The previous findings are in agreement with those of Leidl *et al.* (1980) who found that fetal cotyledons and uterine caruncles from cows with placental retention synthesize significantly less PGF2 alpha *in vitro* than those from non retaining placenta cows.

Kindhal *et al.* (1982) found that PGF2 alpha synthesis lasts for a longer period after calving in cows with placental retention.

Bosu *et al.* (1984) found that peripheral blood samples taken once daily before calving from cows retaining later on their placenta contained a significantly higher concentration in 13,14 dihydro 15 keto PGF alpha (the main metabolite of PGF2 alpha) at the day of calving than those from cows without placental retention.

The aim of this work was to investigate differences in the synthesis of PGF2 alpha and prostacyclin, in cows retaining (RP) and not retaining (NRP) their placenta, reflected by the levels of their main metabolites, 13,14 dihydro 15 keto PGF alpha (PGFM) and 6 keto PGF1 alpha (PGIM) respectively, closely after the second stage of labour.

## Materials and Methods

### 1 - Animals

Twenty five Holstein Friesian cows were observed during the peripartum so as to register the moment of calving as well as the time needed for placenta to be expelled. All cows had calved at least once and belonged to the same herd. Placental retention was defined as a lack of placental expulsion within 12 hours after calving. None of these animals received any treatment with drugs known to affect the biosynthesis of prostaglandins, at least during the last month of gestation.

During the dry period, the cows were fed *ad libitum* with chopped fresh sorghum (75 % of the total), corn silage (20 %) and lucerne hay (5%).

### 2 - Blood collection and plasma conservation

All animals were bled by venipuncture strictly five, thirty and sixty minutes after the expulsion of the fetus. Blood samples were taken from the jugular vein into a syringe tube containing EDTA K (anticoagulant) and lysine acetyl-salicylate (cyclooxygenase inhibitor, 18 µg/ml of blood). After collection, blood samples were immediately refrigerated at + 4 °C and centrifuged 15 minutes at 2500 rpm. Then, plasma was decanted and frozen at -20 °C until analysis were performed.

### 3 - Analytical steps

The main metabolites of PGF2 alpha and PG12,

respectively the 13,14 dihydro 15 keto PGF alpha (PGFM) and 6 keto PGF1 alpha (PGIM), were measured by radioimmunoassay (RIA) according to the following procedures :

#### 3-1 Extraction

- 1000 µl of each plasma sample, acidified to pH 3 with 100 µl of citric acid (1M), were twice treated with 3 ml of ethyl acetate in an assay tube. After a 5 minutes stirring, the tubes were centrifuged during 10 minutes at 3500 rpm. The upper organic phases were transferred into conic tubes and the solvent evaporated under a nitrogen flow at room temperature.

- Each dry lipid extract, containing prostaglandins, was reconstituted in 1 ml of phosphate buffer at pH 7.4; the solution was stirred for 1 minute and maintained overnight at 4 °C for complete dissolution.

#### 3-2 Radioimmunoassay

- 100 µl of solution were used for each RIA determination after (or without any) dilution of the reconstituted prostaglandin extract with buffer according to the prostaglandin measured (1/10 for dhk PgF, no dilution for 6k PgF). The radioimmunological reactions were developed in presence of the specific antisera (Institut Pasteur) and the tritiated metabolites (about 5000 dpm), during overnight incubation at + 4 °C. After that time, 1 ml of a dextran-coated charcoal suspension (T70) was added and the tubes were centrifuged at 3500 rpm 10 minutes at + 4 °C. An aliquot of 0.5 ml of the supernatant (bound fraction) was counted in the presence of 5 ml of scintillation fluid (Aquasol 2) in a Packard counter.

#### 3-3 Concentrations determination

The concentrations of the metabolites were calculated in relation to a standard curve ranging from 0 to 400 pg/100 µl (400, 200, 100, 50, 25, 12.5, 6.25 pg treated in the same conditions) after logit transformation of the binding percentages (Granström and Kindahl, 1978).

The sensitivity of the assay, defined as the smallest quantity of each metabolite to be detected, was 20 pg/ml for PGFM and 70 pg/ml for PGIM. The mean repeatability for a same sample was 13.7 % and 10 %, and the reproductibility of the assay was 6.5 % and 7 %, for each prostaglandin respectively.

#### 3-4 Statistical analysis

Statistical differences in variations, for RP and NRP cows, of the plasma concentrations of PGFM and PGIM found for each of the sample collections were tested using analysis of variance (ANOVA) and PGFM/PGIM ratio were compared in the same way. Differences for mean concentrations of each group (RP and NRP) were compared for each sampling session by the «t» Student's test after or no logarithmic transformation.

Regression analysis were performed between the levels of PGFM and PGIM during the first 60 minutes postpartum. The linear regression equations found for each group were compared by ANOVA.

## Results

Eight out of the total 25 cows studied retained

Table 1. — Mean lactation numbers, gestation lengths, calf weights and number of twins in the two groups.

	placental retention (no. of cows)	
	yes (8)	no (17)
lactation number	2.8 ± 1.1 (1.9-3.8) <sup>a</sup>	2.9 ± 1.1 (2.3-3.5) <sup>a</sup>
gestation length (days)	279 ± 5 (275-283)	280 ± 4 (278-283)
calf weight (kg)	40 ± 5 (36-44)	40 ± 2 (39-42)
twin birth	1	0

a : mean ± sd (confidence limits for P < 0.05)

Table 2. — PGFM, PGIM and PGFM/PGIM ratio in blood during the first 60 minutes post-partum in cows retaining and not retaining their placenta.

metabolites and ratio animal group	time after parturition (min)			statistical signification
	5	30	60	
<i>13,14-dihydro-15-keto prostaglandin F2 alpha (PGFM)</i>				
placental retention without	6422 ± 3527a <sup>z</sup>	6225 ± 2288a	12016 ± 6811a	F(2,32) = 10.524 P < 0.01 F(2,14) = 1.657 P > 0.05
with	5537 ± 6867a	5302 ± 3287a	8156 ± 6965b	
<i>6-keto-prostaglandin F1 alpha (PGIM)</i>				
placental retention without	764 ± 163a	851 ± 94a	766 ± 153a	F(2,32) = 2.716 P > 0.05 F(2,14) = 3.627 P > 0.05
with	804 ± 233a	1000 ± 246a	931 ± 418a	
<i>PGFM/PGIM</i>				
placental retention without	8.37 ± 4.23a	7.26 ± 2.25a	15.54 ± 8.56a	F(2,32) = 11.100 P < 0.01 F(2,14) = 1.874 P > 0.05
with	5.90 ± 4.89b	5.05 ± 2.12b	8.78 ± 6.69b	

z : for a metabolite or for ratio, within a same column, values with different letters differ (P < 0.05)

their placenta for a period longer than 12 hours after calving (all, except one, longer than 48 h) and were included in the RP group. The others 17 cows delivered their placenta 5.5 ± 2.2 hours postpartum. They had identical mean lactation numbers and gestation lengths, and gave birth to calves of similar mean weights; the number of twins was 1 pair in the RP group and none in the NRP one (table 1).

The mean level of PGFM in peripheral blood plasma from the RP cows was significantly lower than that from the NRP cows 60 minutes postpartum (8156 ± 6965 vs 12016 ± 6811 pg/ml; P ≤ 0.05, table 2).

One of the cows belonging to the RP group

presented very high values of PGFM in relation to the mean found for the group (22257, 11285 and 17255 pg/ml, respectively at 5, 30 and 60 minutes). The individual discrepancy in the PGFM level of the RP group, which does not appear in the NRP one, is reflected by the F value (6.788; P ≤ 0.01) of the analysis of variance.

The interesting feature is the significant increase of PGFM 60 minutes postpartum in the NRP cows (table 2). This pattern was not observed in the RP cows where the levels of PGFM remained fairly constant along the period studied.

Although the mean values of PGIM found in RP cows tended to be higher than those from NRP cows, the differences were not statistically signifi-

cant ( $P \geq 0.05$ , table 2) and remained constant during the same period. The individual variance is significant too in this group ( $F = 11.338$ ;  $P \leq 0.01$ ).

The mean value of the PGFM/PGIM ratio in samples taken 60 minutes postpartum was significantly lower in RP cows than that from NRP cows ( $8.8 \pm 6.7$  vs  $15.5 \pm 8.9$ ;  $P \leq 0.01$ , table 2). In RP cows the PGFM/PGIM ratio remained constant, while in NRP cows it rose significantly between 30 and 60 minutes postpartum ( $F = 11.100$   $P \leq 0.01$ ; table 2).

In order to investigate whether the differences found in PGFM/PGIM ratio were due to fluctuations of PGFM, PGIM or both, figures 1 and 2 present the regression equations between the levels of these prostanoids during the first 60 minutes, respectively in RP and NRP cows. In RP cows, a positive correlation was found between the levels of PGIM and PGFM during this time ( $r = 0.75$ ;  $P \leq 0.01$ , fig. 1). On the other hand, no correlation could be found between PGIM and PGFM levels in the NRP group ( $r = 0.23$ ;  $P \geq 0.05$ , fig. 2). The linear regression equations found for each group were statistically different, as well as their interception and regression coefficient values ( $F = 20.87$ ;  $P \leq 0.01$ ).

## Discussion

The identical calving conditions of the cows of both groups indicate that retention of the membranes was not due to four of the main known causes of this pathology in our work (table 1).

The results presented (table 2) strongly suggest

that at least, during the first 60 minutes postpartum, the capacity to synthesize PGF2 alpha is lower in RP than in NRP cows. Differences in peripheral plasma PGFM levels between RP and NRP are evident but only significant 60 minutes postpartum, traducing a rise of the PGFM levels between 30 and 60 minutes postpartum in NRP cows, and relative stability of the metabolite in the RP cows.

Bosu *et al.* (1984) found lower levels for PGFM than us; that may have been due to differences in timing of blood samples since these authors analysed daily samples.

Although cyclooxygenase inhibition early in the postpartum period can induce placental retention (Horta, 1981), the lower production of PGF2 alpha in RP cows at this time is suggested to be due to causes others than a lack of the cyclooxygenase activity. This assumption arises from the fact that instead of being depressed, PG12 synthesis seems to be stimulated in RP cows, as reflected by the tendency of PGIM to be higher in this group and by the positive correlation between the synthesis of PGFM and PGIM in RP cows. On the other hand, the higher PGFM/PGIM ratio in NRP cows, when compared to RP cows, strongly suggests that the metabolism of the PGG2 and PGH2 endoperoxydes is altered in RP cows, leading to a lack of PGF2 alpha and an increase in PG12 synthesis.

Some unknown factor seems to maintain PG12 synthesis constant during the first 60 minutes after birth of the calf in NRP cows since when PGFM, increases, there is no related increase in PGIM, as opposed to what occurs in RP cows, where the correlation between the synthesis of both prostanoids is significantly positive (fig. 1 and 2).

Furthermore, the positive correlation between PGFM and PGIM production in RP cows, suggests

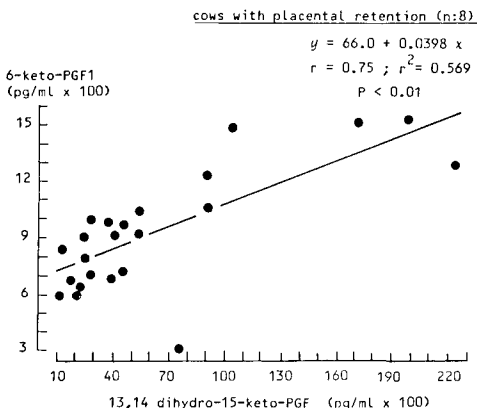


Fig.1. — Relationship between production of 13, 14 - dihydro - 15 keto PGF alpha and 6 - keto - PGF1 alpha during the first 60 min postpartum in cows with placental retention.

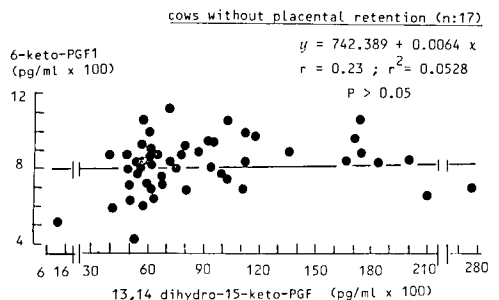


Fig.2. — Relationship between production of 13, 14 dihydro - 15 keto - PGF alpha and 6 - keto - PGF1 alpha during the first 60 min postpartum in cows without placental retention.

that PGI<sub>2</sub> and PGF<sub>2</sub> alpha seem to have antagonist effects regarding to the ultimate stage of parturition : PGI<sub>2</sub> would have an anti-placental separation activity, a similar effect to that which was previously demonstrated for PGE<sub>2</sub> (Horta, 1984), while PGF<sub>2</sub> alpha would stimulate placental separation and expulsion.

The results here obtained give support to the proposed action for PGF<sub>2</sub> alpha of stimulating placental separation in the cow (Horta, 1984). This effect was also observed by Herschler and Lawrence (1984) in a clinical trial using fenprostalene, a long-acting PGF<sub>2</sub> alpha analogue.

Although the key step of physiological mechanisms leading to the normal separation of fetal membranes are not yet perfectly understood, it is thought that changes in connective tissue together with vascular changes in microcirculation of placentomes, play an important role in the physiology of the third stage of labour (Grunert, 1984). Otherwise, it seems that the maintenance of the number of the giant epithelial cells of placentomes from parturition by 1 h postpartum is related with placental retention (Grunert, 1980 ; Margolis *et al.*, 1983 ; Williams *et al.*, 1984).

PGI<sub>2</sub> and PGE<sub>2</sub> are both implicated in breakdown of collagen (Ellwood, 1980) and vasodilatation in several microcirculations (Bell *et al.*, 1980). Congestion of the vascular bed of the placentomes was reported to be associated with placental retention in cows (Dzuvic *et al.*, 1976 ; Grunert, 1980). Sclerosis of the maternal placenta, which is achieved through a progressive collagenization of the caruncles, is thought to be an important prerequisite for uncomplicated delivery of fetal membranes (Grunert, 1980, 1984).

One of the roles we propose for the imbalance in prostaglandin synthesis towards PGI<sub>2</sub> in RP cows and for the pharmacological action of PGE<sub>2</sub> in placental retention induction, is their ability to induce collagen breakdown and consequently to inhibit the collagenization process of the caruncles near term.

However, it will be necessary to undertake further studies to explain the linkage between the imbalance found in this work concerning prostaglandin synthesis and the changes found by others

at the placentome level regarding placental retention.

Immunological disturbance, which was recently found in RP cows by Gunnink (1984 a, b, c, d), and traduced by a lack of chemotaxis of leukocytes, may be related with our results. Recently, it was found that leukotrienes, lipoxygenase-pathway metabolites of arachidonic acid, are the main regulators of chemotaxis and chemokinesis of the leukocytes (Samuelsson, 1981). On the other hand, 5-hydroxyeicosatetraenoic acid (HETE) and other products of the lipoxygenase pathway, can selectively inhibit prostacyclin synthetase activity as it was recently found in bovine luteal cells (Alila *et al.*, 1983 ; Milvae and Hansel, 1984). So, it is possible that the factors regulating PGI<sub>2</sub> synthesis in NRP cows may be the lipoxygenase products, and that these factors do not act in RP cows as a consequence of reduction of the number of leukocytes, and/or a depressed synthesis of leukotrienes in these cows.

Other mediating mechanisms leading to imbalanced prostaglandin synthesis are known to exist, such as the 9 - ketoreductase, an enzyme proposed by Williams and Gross (1981) to be responsible for the conversion of PGF<sub>2</sub> alpha into PGE<sub>2</sub> in placentomes of bovine after calving.

The results presented here strongly suggest that cows with placental retention synthesize significantly less PGF<sub>2</sub> alpha in the very early postpartum, which seems to be primarily due to a change in the metabolism of the prostaglandin endoperoxides towards PGI<sub>2</sub> and probably PGE<sub>2</sub> (earlier postulated by Horta, 1984), rather than PGF<sub>2</sub> alpha synthesis. They also suggest that in cows delivering their placenta in due time, prostacyclin synthetase activity seems to be maintained at a basal level, compared to what happens in cows with retention of placenta.

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### **Summary**

The aim of this work was to investigate possible differences in peripheral blood concentrations of 13,14 dihydro 15 keto PGF alpha (PGFM) and 6 keto PGF1 alpha (PGIM), between dairy cows retaining (RP) and not retaining (NRP) their placenta. Blood samples were collected 5, 30, and 60 minutes postpartum from 8 RP and 17 NRP cows. PGFM concentrations were significantly lower in RP cows than in NRP cows 60 minutes after birth (8156 pg/ml vs 12016 pg/ml ;  $P \leq 0.05$ ). There was a significant rise of PGFM levels between 30 and 60 minutes in NRP cows (6225 pg/ml vs 12016 pg/ml ;  $P \leq 0.01$ ), while in RP cows PGFM levels remained fairly constant along the period studied. No significant differences were found between RP and NRP cows regarding PGIM levels during this period although absolute

values were slightly higher in RP cows. The PGFM/PGIM ratio was significantly higher 60 minutes postpartum in NRP cows than in RP cows (15.5 vs 8.8 ;  $P \leq 0.01$ ). This ratio increased significantly in NRP cows between 30 and 60 minutes (7.2 vs 15.5 ;  $P \leq 0.01$ ), a pattern not observed in RP cows. There was no correlation between PGIM and PGFM levels during the first 60 minutes postpartum in the NRP cows. However, the same correlation was significantly positive in the RP cows ( $r = 0.75$  ;  $P \leq 0.01$ ). The above results suggest that the synthesis of PGF2 alpha between 30 and 60 minutes postpartum is significantly decreased in cows with placental retention as reflected by the levels of PGFM. They further suggest that prostacyclin synthesis in cows not retaining their placenta does not increase during the first 60 minutes postpartum, as it does in cows with placental retention as reflected by the positive correlation between the levels of PGIM and PGFM found in these animals during the same period. It is proposed that an imbalance in the synthesis of PGF2 alpha and PGI2 during the first 60 minutes conducting to a lack of PGF2 alpha and a relative increase in PGI2 is associated with placental retention in bovine.

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