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15-keto-13,14-dihydroprostaglandin $F_{2\alpha}$ and prolactin in maternal and cord blood during prostaglandin E_2 or oxytocin therapy for labor induction

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1 Introduction

In previous studies we have demonstrated a difference in the mode of action of prostaglandin E_2 versus oxytocin during induced parturition: prostaglandin E_2 gave a slower onset of contractions [2] and induced a parturition time dependent decrease in maternal serum prolactin levels [3]. Prostaglandin $F_{2\alpha}$ elevates maternal serum prolactin concentrations [7] and is a potent stimulator of uterine contractions [5]. Some investigators suggest that prostaglandin $F_{2\alpha}$ is formed in the uterus during contractions [16, 17, 28]. If this prostaglandin reaches the circulation one would expect an increase in maternal serum prolactin. However, the scarce data available from spontaneous labor rather indicate a decrease in serum prolactin during parturition [9, 15, 31, 32].

For reasons discussed in detail by GRANSTRÖM et al. [14], primary prostaglandins cannot be measured accurately in blood plasma samples. The major PGE_2 metabolite, 15-keto-13,14-dihydroprostaglandin E_2, is rearranged and its analysis requires special conditions [13]. The corresponding $PGF_{2\alpha}$ metabolite, 15-keto-13,14-dihydroprostaglandin $F_{2\alpha}$, can be determined in plasma and reflects the formation of F-prostaglandins [12]. Accordingly, it was selected for assay in the present communication. To explore whether changes in 15-keto-13,14-dihydroprostaglandin $F_{2\alpha}$ levels in maternal blood during induced parturition are related to serum prolactin changes, the present study was undertaken.

Curriculum vitae

KATARINA BREMME, *M. D., was graduated in 1969 and qualified as a specialist in Obstetrics and Gynecology in 1974. Since 1975 she has been on the staff of the Department of Obstetrics and Gynecology, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden.*

2 Materials and methods

The study comprised 83 healthy women in whom labor was induced mainly for reasons of post-datism (table I). All patients had a vertex presentation and a normal pelvic outlet. Patients with toxemia of pregnancy treated with more than 100 mg hydralazine (Apresoline®,

Table I. Clinical data on patients in whom labor was induced with prostaglandin E_2 (PGE_2) or oxytocin.

	PGE_2		Oxytocin	
Number of patients	44		39	
Age (years)	28.3	(21–34)	28.9	(18–40)
Week of pregnancy	41	(38–44)	42	(38–43)
Parity (nulli/multi)	20/24		15/24	
Parturition time (min)	371	(156–1740)	314	(88–1275)
Birthweight (g)	3571	(2480–4630)	3632	(3000–4510)
Placental weight (g)	554	(350–800)	583	(410–830)
Sex of neonate (♀/♂)	25/19		18/21	
Apgar score at 1′	8.7	(4–10)	8.9	(7–10)
Apgar score at 5′	9.8	(8–10)	9.7	(9–10)

Data in the table are mean values and ranges.

CIBA) and/or 1 g chlortiazide (Chlortride®, MSD) daily were excluded from the study, as were patients with any other disease.

Labor was induced by low amniotomy and intravenous infusion of oxytocin (Syntocinon®, Sandoz) in 5.5% glucose, starting at 8.30 a. m. with 5 mIU/min and increasing over three hours to a maximum of 20 mIU/min; or by low amniotomy and oral administration of PGE_2 (Upjohn Co., Kalamazoo, Mich., USA): dosage 0.5 mg initially, followed by 1.0 mg every hour until delivery. Treatment was randomized. The registration of uterine contractility was done with external and internal tocography according to established procedures [27]. Start of labor was defined as the time when three contractions with an amplitude of more than 25 mm Hg

Table II. 15-keto-13,14-dihydro-$PGF_{2\alpha}$ and prolactin in maternal blood during prostaglandin E_2 (PGE_2) or oxytocin therapy for labor induction. Mean values; 95% confidence limits.

Labor stage	15-ketodihydro-$PGF_{2\alpha}$ (pmol/l)		Prolactin (µg/l)	
	PGE_2 (n = 21)	Oxytocin (n = 23)	PGE_2 (n = 32)	Oxytocin (n = 30)
Start of treatment	473 (330–675)	347 (227–526)	144 (119–176)	163 (130–205)
	***[1]	***[2]	***[3]	*[4]
Immediately[5] prior to the delivery	1890 (1602–2232)	871 (588–1285)	92 (71–119)	130 (100–169)

[1]) Paired t-test; $t = -10.49$ $p < 0.001$
[2]) Paired t-test; $t = -5.70$ $p < 0.001$
Contrast between 1) and 2): $t = 2.23$, $p = 0.03$.
Tested contrast: $\overline{\text{Diff}}$ (15-ketodihydro-$PGF_{2\alpha}$) PG − $\overline{\text{Diff}}$ (15-ketodihydro-$PGF_{2\alpha}$) OXY
[3]) Paired t-test; $t = 3.90$ $p < 0.001$
[4]) Paired t-test; $t = 2.52$ $p = 0.017$
Contrast between 3) and 4): $t = 1.54$, $p = 0.13$.
Tested contrast: $\overline{\text{Diff}}$ (prolactin) PG − $\overline{\text{Diff}}$ (prolactin) OXY
[5]) Time difference (mean and ranges) between blood sample and parturition: in PGE_2 treated patients 33 (4–60) minutes; in oxytocin treated patients 34 (2–60) minutes.

were registered during 10 minutes [6]. The two patient categories were given the same type of analgesic treatment. Demerol® (Meperidine, Pethidine) 100 mg i.m. (ACO, Sweden), was administerd to 23 PGE_2 and to 29 oxytocin treated women. Epidural analgesia (bupivacaine-Marcaine®, Bofors, Sweden) was given to 12 PGE_2 and to 8 oxytocin treated patients, respectively.

Blood samples were drawn from the antecubital vein at the start of treatment, one hour into treatment, immediately prior to delivery and after delivery. Mixed umbilical blood was collected at parturition by section of the cord. Serum and plasma were isolated by centrifugation and stored at −20 °C until analyzed. The number of individuals from whom a complete set of analyzes could be obtained was few. Therefore, the results given in tables II to IV refer to patients in whom the appropriate samples were obtained to allow intra-patient comparisons.

Table III. 15-keto-13,14-dihydro-$PGF_{2\alpha}$ and prolactin in maternal blood during prostaglandin E_2 (PGE_2) or oxytocin therapy for induction of labor. Mean values; 95% confidence limits.

Labor stage	15-ketodihydro-$PGF_{2\alpha}$ (pmol/l)		Prolactin (µg/l)	
	PGE_2 (n = 16)	Oxytocin (n = 19)	PGE_2 (n = 24)	Oxytocin (n = 20)
Immediately[1]) prior to delivery	1778 (1445–2190)	***[3]) 840 (510–1386)	103 (98–212)	121 (92–160)
First sample[2]) after delivery	1980 (1576–2405)	*[4]) 1070 (703–1627)	145 (98–212)	143 (96–212)

[1]) Time difference, mean and range, between blood sample and delivery: 33 (4–60) minutes (PGE_2), and 34 (2–60) minutes (oxytocin).
[2]) Time difference, mean and range, between blood sample and delivery: 38 (2–60) minutes (PGE_2), and 39 (2–60) minutes (oxytocin).
[3]) Independent t-test: $p = 0.001$.
[4]) Independent t-test: $p = 0.016$.

Table IV. 15-keto-13,14-dihydro-$PGF_{2\alpha}$ and prolactin concentrations in blood in connection with partus induced by prostaglandin E_2 (PGE_2) or oxytocin. Mean values; 95% confidence limits.

Labor stage	15-ketodihydro-$PGF_{2\alpha}$ (pmol/l)		Prolactin (µg/l)	
	PGE_2 (n = 15)	Oxytocin (n = 13)	PGE_2 (n = 23)	Oxytocin (n = 24)
Immediately prior to delivery	1870 (1467–2383)	1058 (714–1568)	96 (67–137)	120 (94–154)
			***[1])	***[2])
Mixed umbilical	1467 (1151–1868)	913 (714–1123)	248 (204–301)	227 (176–292)

[1]) Paired t-test; $t = -4.63$ ($p < 0.001$).
[2]) Paired tested; $t = -5.57$ ($p < 0.001$).

Radioimmunoassay (RIA) of serum samples was performed in duplicate with commercial kits from Serono Diagnostics (prolactin) and Diagnostic Products Corp. (cortisol). Intraassay and interessay coefficients of variation were all below 10%. Levels of 15-ketodihydro-$PGF_{2\alpha}$ in plasma were determined by RIA as described in detail previously [12]. Specificity of the employed antiserum and accuracy data have been reported previously [26].

The study also included eight non-pregnant healthy women with normal menstrual cycles. These women were given a single dose of 0.5 mg PGE_2 orally. Blood was sampled after 10, 20, 30, 60 and 90 minutes. Levels of 15-ketodihydro-$PGF_{2\alpha}$ were determined as described above.

Statistical methods: Calculations were proformed on the logarithms of the measured values. Two-tailed 95% conficence intervals of the mean in terms of logarithmic values were calculated. Probability values (p-values) were determined in two-tailed tests. Geometric means and interval limits were obtained from the antilogarithms. When variances of two groups differed significantly, a separate variance estimate of Student's t-statistic was used, otherwise a pooled variance estimate, to test whether the means of the groups differed or not. Contrasts of means between more than two groups were also calculated. Student's t-statistic was used to test whether the formed contrasts differed from expectancy.

3 Results

The changes in maternal serum hormone levels during induced parturition are displayed in table II. Oxytocin and PGE_2 caused similar elevations in maternal serum cortisol (data not shown): whereas, decreases in the levels of prolactin seemed more pronounced in the PGE_2 group (table II). The changes observed in 15-ketodihydro-$PGF_{2\alpha}$ throughout parturition were highly significant in both treatment groups. The PGE_2 group showed a significantly higher increase than the oxytocin group.

In terms of onset of contractions, the median time for women in the PGE_2 group was 62 minutes and for women in the oxytocin group 45 minutes ($p = 0.004$; median test). The total time to delivery did not differ between the groups (table I). If onset of contractions is related to elevation of 15-ketodihydro-$PGF_{2\alpha}$, this should be reflected one hour into treatment. Among women receiving oxytocin, the 15-ketodihydro-$PGF_{2\alpha}$ level changed from 315 pmol/l (226–439) to 361 pmol/l (264–494) during the first hour of treatment ($n = 31$). This increase is not significant. In the PGE_2 group ($n = 31$) the corresponding figures were 396 pmol/l (282–556) and 821 pmol/l (614–1096). The elevation in the PGE_2 group is highly significant ($p < 0.001$; paired t-test). Tested for the contrast between the PGE_2 and oxytocin groups, a significant difference was found ($p < 0.001$), i.e. the elevation in the PGE_2 group was significantly higher than in the oxytocin group.

Following delivery, there was still a difference between PGE_2 and oxytocin treated women in terms of 15-ketodihydro-$PGF_{2\alpha}$ levels in maternal plasma; whereas, no significant difference was seen either in prolactin (table III) or in cortisol concentrations (data not shown). The level of 15-ketodihydro-$PGF_{2\alpha}$ in the mixed umbilical plasma in each treatment group was almost the same as in the maternal plasma immediately prior to delivery. When the two experimental groups were compared for hormone levels in mixed umbilical blood (table IV), a clearly significant difference was observed in 15-ketodihydro-$PGF_{2\alpha}$ concentration but not in prolactin.

The non-pregnant women responded to oral PGE_2 with an increase in levels of 15-keto-13,14-dihydro-$PGF_{2\alpha}$ which was already significant at 10 ($p = 0.034$; Wilcoxon) and 20 minutes ($p = 0.012$; Wilcoxon) after PGE_2 administration. The mean basal level was 160 pmol/l (129–218) and after PGE_2 administration 228 pmol/l (118–297) and 440 pmol/l (213–907) at 10 and 20 minutes, respectively. One hour after treatment the average concentration was 476 pmol/l (324–605), i.e. no significant in-

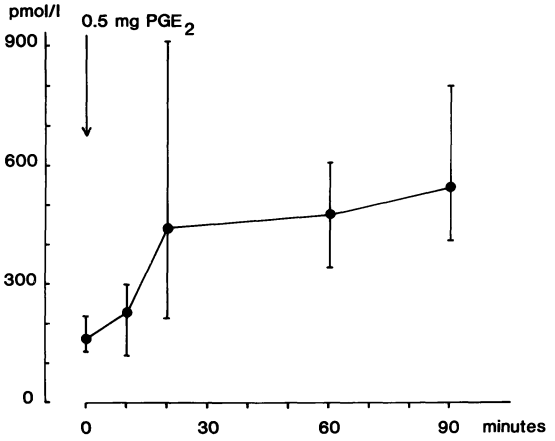

Figure 1. Plasma levels of 15-keto-13,14-dihydro-$PGF_{2\alpha}$ (geometric mean; 95% confidence limits for geometric mean) following a single oral dose of 0.5 mg PGE_2 in eight healthy non-pregnant female volunteers.

crease occurred between 20 and 60 minutes. None of the women experienced uterine contractions or complained of abnormal pain and after 90 minutes the average plasma level was still elevated, i.e. 543 pmol/l (409–789) (figure 1).

4 Discussion

The present report shows that oral PGE_2 treatment leads to increases in the plasma content of 15-ketodihydro-$PGF_{2\alpha}$ that are clearly above the levels induced by oxytocin and reportedly at hand during spontaneous labor [29, 36]. Yet, contractions appeared later in the PGE_2 treated group. The average time before contractions appeared in the PGE_2 treated pregnant women was 62 minutes. The women receiving oxytocin had a mean time to onset of contractions of 45 minutes but no increase in plasma concentrations of 15-ketodihydro-$PGF_{2\alpha}$ at 60 minutes. From two hours into treatment to the time immediately before parturition there was no significant difference in the increase in plasma 15-ketodihydro-$PGF_{2\alpha}$ between PGE_2 and oxytocin treated women. Thus, the present study fails to relate increases in plasma levels of 15-ketodihydro-$PGF_{2\alpha}$ to onset of uterine contractions [10, 21]. Nor was it possible to find a relation between the plasma concentration of the metabolite and delivery time [33]. The triggering of contractions may have been mediated by amniotomy and the locally formed prostaglandins may not have been reflected in the circulation [34, 35]. Once labor had been established, increases in plasma 15-ketodihydro-$PGF_{2\alpha}$ levels were similar in PGE_2 and oxytocin treated women. In spontaneous labor it has been reported that 15-ketodihydro-$PGF_{2\alpha}$ increased in parallel with cervical dilatation [16, 24], possibly reflecting formation of uterine $PGF_{2\alpha}$. However, it has been questioned whether local formation of $PGF_{2\alpha}$ in the uterus is soon reflected by 15-ketodihydrp-$PGF_{2\alpha}$ in plasma [25, 30]. Oral PGE_2 obviously led to an increase in plasma levels of 15-ketodihydro-$PGF_{2\alpha}$. A possible explanation is that PGE_2 itself may be converted to $PGF_{2\alpha}$ in the course of, or following, absorption [8, 18, 19, 20] and later be metabolized into 15-ketodihydro-$PGF_{2\alpha}$. This metabolite lacks biological activity and cannot be related as such to the clinical events or to prolactin levels. Thus, high levels of this metabolite caused by exogenous PGE_2 will shadow an endogenous production. Also in the case of non-pregnant women, a significantly elevated level of 15-ketodihydro-$PGF_{2\alpha}$ metabolite is seen 20 minutes after oral PGE_2. The levels remained high for as long as 90 minutes and, considering the short half-lives of PGE_2 and $PGF_{2\alpha}$ as well as of 15-ketodihydro-$PGF_{2\alpha}$ in the circulation, it seems likely that exogenous PGE_2 is not only converted to $PGF_{2\alpha}$ but may also have induced an ongoing endogenous prostaglandin – i.e. $PGF_{2\alpha}$ – biosynthesis, perhaps in the uterus. An alternative hypothesis for our findings is that an excess of PGE_2 and its circulating metabolites could well overload enzyme systems to such an extent that this results in a longer circulating half-life of the $PGF_{2\alpha}$ metabolites [11].

Since $PGF_{2\alpha}$ and PGE_2 exert antagonistic effects on prolactin levels in pregnant women [4, 7], the lowering of prolactin during oral PGE_2 therapy indicates that PGE_2 effects dominate over $PGF_{2\alpha}$ effects, even though E_2 to

some extent is converted to $PGF_{2\alpha}$ or induces $PGF_{2\alpha}$ biosynthesis. Since the stress of labor measured as serum cortisol (data not shown) was the same in both oxytocin and PGE_2 treated women, this factor is likely not directly involved in prolactin release, as previously suggested [38].

The possibility exists that the epidural analgesia might have influenced circulating prolactin and 15-ketodihydro-$PGF_{2\alpha}$ levels [22, 23, 37]. But the relative frequency of this therapy was very similar in the two treatment groups. It is thus less likely that epidural analgesia influenced our results.

About half an hour after delivery, maternal serum prolactin levels were the same in both treatment groups, indicating that the PGE_2 induced effects on maternal pituitary prolactin release had stopped or been counteracted. However, 15-ketodihydro-$PGF_{2\alpha}$ levels were at least as high some 30 minutes after as before delivery, which makes it less likely that 15-ketodihydro-$PGF_{2\alpha}$ in itself participates in maternal pituitary prolactin release. The levels of 15-ketodihydro-$PGF_{2\alpha}$ in the mixed umbilical cord blood seem to be close to the maternal plasma concentration in both treatment groups. Since there is no artero-venous difference in umbilical blood for 15-ketodihydro-$PGF_{2\alpha}$ [1], a maternal origin for the 15-ketodihydro-$PGF_{2\alpha}$ measured in mixed umbilical blood may be suggested. The data also indicate that the placenta does not metabolize 15-ketodihydro-$PGF_{2\alpha}$ to any major extent.

In conclusion, our data show that there was no correlation between 15-keto-13,14-dihydro-$PGF_{2\alpha}$ concentration and onset of contraction or labor time in either the PGE_2 or the oxytocin treated group. The higher values of plasma 15-keto-13,14-dihydro-$PGF_{2\alpha}$ in women receiving PGE_2 tablets as compared to those treated with oxytocin suggest that exogenous PGE_2 is to some extent reduced to $PGF_{2\alpha}$. Such a reduction seems also to take place in non-pregnant women, in whom administration of oral PGE_2 gave rise to marked increases in plasma 15-keto-13,14-dihydro-$PGF_{2\alpha}$. The marked decrease in serum prolactin in the PGE_2 treated pregnant women, which normalized following parturition, suggests a PG involvement in serum prolactin control.

Summary

15-keto-13,14-dihydroprostaglandin $F_{2\alpha}$ plasma levels were measured in pregnant women following labor induction with either oral PGE_2 treatment or intravenous oxytocin, both combined with amniotomy. The median time to start of contractions was 62 minutes in the PGE_2 treated group and 45 minutes in the oxytocin treated group ($p < 0.01$; median test). The increase in 15-ketodihydro-$PGF_{2\alpha}$ appeared earlier in the PGE_2 group but not in the oxytocin group ($p < 0.001$ and $p = 0.210$, respectively). At delivery, the 15-ketodihydro-$PGF_{2\alpha}$ values had further increased in both treatment groups. The increase was significantly higher in the PGE_2 treated patients compared with oxytocin treated patients ($p = 0.03$; contrast test). Despite higher 15-ketodihydro-$PGF_{2\alpha}$ concentrations throughout parturition, PGE_2 women did not deliver more rapidly than oxytocin infused women. There was no correlation between 15-ketodihydro-$PGF_{2\alpha}$ blood concentrations and either onset of contrations or labor time. The decrease in maternal serum prolactin concentration during parturition was pronounced ($p < 0.001$) in the PGE_2 group but occurred also in oxytocin treated patients ($p < 0.02$). A single oral dose (0.5 mg) of PGE_2 taken by non-pregnant women led to significant ($p < 0.05$) increases in 15-ketodihydro-$PGF_{2\alpha}$ levels in blood plasma after 10 minutes. This increase persisted for at least 90 minutes. It is suggested that oral PGE_2 may be transformed into $PGF_{2\alpha}$ and/or induce endogenous $PGF_{2\alpha}$ biosynthesis.

Keywords: Cord blood, labor induction, maternal blood, prolactin, 15-keto-13,14-dihydroprostaglandin $F_{2\alpha}$.

Zusammenfassung

15-Ketodihydro-$PGF_{2\alpha}$- und Prolaktinspiegel im mütterlichen Serum und Nabelvenenblut während der Geburtseinleitung mit Prostaglandin E_2 oder Oxytozin

Wir bestimmten die Plasmaspiegel von 15-Keto-13,14-dihydroprostaglandin $F_{2\alpha}$ bei schwangeren Frauen nach Geburtseinleitung mit oraler PGE_2-Gabe bzw. intravenöser Oxytozingabe und artefizieller Blaseneröffnung. In der PGE_2-Gruppe setzten die Wehen nach durchschnittlich 62 Minuten ein, in der Oxytozingruppe nach 45 Minuten ($p < 0.01$; Mediantest). In der PGE_2-Gruppe kam es früher zu einem Anstieg des 15-Ketodihydro-$PGF_{2\alpha}$. Eine Stunde nach Behandlungsbeginn war der $PGF_{2\alpha}$-Spiegel in der PGE_2-Gruppe signifikant erhöht, nicht aber in der Oxytozingruppe ($p < 0.001$ versus $p = 0.210$). Zum Zeitpunkt der Geburt waren die 15-Ketodihydro-$PGF_{2\alpha}$-Werte in beiden Gruppen weiter angestiegen, wobei der Anstieg in der PGE_2-Gruppe signifikant größer war als in der Oxytozingruppe ($p = 0.03$ bei Gegenüberstellung). Trotz höherer 15-Ketodihydro-$PGF_{2\alpha}$-Konzentrationen in der PGE_2-Gruppe war der Geburtsverlauf hier nicht kürzer als in der Oxytozingruppe. Die Höhe des 15-Ketodihydro-$PGF_{2\alpha}$-Spiegels im Blut und das Einsetzen bzw. die Geburtsdauer korrelierten nicht miteinander. Der Abfall des Serumprolaktins war unter der Geburt in der PGE_2-Gruppe besonders ausgeprägt ($p < 0.001$), zeigte sich aber auch in der Oxytozingruppe ($p < 0.02$). Eine einmalige Gabe von 0,5 mg PGE_2 an nichtgravide Frauen führte nach 10 Minuten zu einem signifikanten Anstieg des 15-Ketodihydro-$PGF_{2\alpha}$ ($p < 0.05$), das über mindestens 90 Minuten erhöht blieb. Wir meinen, daß oral verabreichtes PGE_2 zu $PGF_{2\alpha}$ metabolisiert wird und/oder die endogene $PGF_{2\alpha}$-Biosynthese induziert.

Schlüsselwörter: Geburtseinleitung, Nabelschnurblut, mütterliches Serum, Prolaktin, 15-Keto-13,14-dihydroprostaglandin $F_{2\alpha}$.

Résumé

Taux de 15-céto-13,14 dihydroprostaglandine $F_{2\alpha}$ et de prolactine dans le sang maternel et dans le sang du cordon lors des déclenchements du travail par prostaglandine E_2 ou par ocytocine

On a mesuré les taux plasmatiques de 15-13,14 dihydroprostaglandine $F_{2\alpha}$ chez des femmes enceintes après induction tu travail avec soit PGE_2 per os soit ocytocine intra-veineuse, les deux methodes étant associées à la rupture des membranes. Le délai moyen du début des contractions a été de 62 minutes dans le groupe traité par prostaglandines et de 45 minutes pour le goupe traité par ocytocine ($p < 0,01$). L'élévation des 15-cétodihydro-$PGF_{2\alpha}$ est apparue plus tôt chez les femmes traitées par PGE_2. Au bout d'une heure de traitement l'augmentation était significative dans le groupe PGE_2 mais pas dans le groupe ocytocine ($P < 0,001$ et $p = 0,210$, respectivement). Au moment de l'accouchement, les valeurs de $PGF_{2\alpha}$ se sont encore plus élevées et celà dans les deux groupés. L'élévation a été de façon significative plus importante dans le groupe PGE_2 que dans le groupe ocytocine ($p = 0,03$). Malgré des taux de 15-cétodihydro $PGF_{2\alpha}$ plus élevés tout au long de l'accouchement les femme sous PGE_2 n'accouchent pas plus rapidement que les femmes sous perfusion d'ocytocine. Il n'y a pas de corrélation entre les concentrations sériques de 15-cétodihydro $PGF_{2\alpha}$ ni avec le début des contractions ni aved la durée du travail. La diminution des taux maternels de Prolactine sérique au cours de l'accouchement est nette ($p < 0,001$) dans le groupe PGE_2 mais existe également chez les patientes sous ocytocine ($p < 0,02$). Une dose orale unique (0,5 mg) de PGE_2 prise par une femme non enceinte entraine une augmentation significative ($p < 0,05$) des 15-cétodihydro-$PGF_{2\alpha}$ plasmatiques au bout de 10 minutes. Cette augmentation persiste au moins 90 minutes. Les auteurs suggèrent que les PGE_2 orales peuvent être transformées en $PGF_{2\alpha}$ et/ou induire la synthèse de PGF_2 endogènes.

Mots-clés: Déclenchement du travail, prolactine, sang du cordon, sang maternel, 15-céto-13,14-dihydroprostaglandine, $F_{2\alpha}$.

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