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Prostaglandins and cellular reaction in uterine flushings. I. Effect of IUD insertion

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Abstract

Uterine prostaglandin (PG) levels and cellular reaction in response to IUDs were elevated in sixty women. Short-term users ($n=30$) were studied in a control cycle and 3 months after IUD insertion, and long-term users ($n=30$) were studied at least 2 years after device insertion. A uterine wash was performed in the proliferative and luteal phase of each investigated menstrual cycle; the cellular components were counted and levels of PGE2, PGF2alpha and their 13,14-dihydro-15-keto metabolites measured. A significant rise in PG levels was observed in the uterine wash shortly after IUD insertion, particularly in the luteal phase. However, there was a significant reduction in PG levels among long-term users, though the cellular reaction showed a continued increment. The absence of correlation between the biochemical and biological responses indicated that neither of them was totally dependent on the other. The decreased PG levels among long-term users does not support the concept of a key role for these substances in the mechanism of action of IUDs. The temporary post-insertion rise in PG levels coincides with the phase of increased bleeding and pain.

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Introduction

Intrauterine contraceptive devices (IUDs) have been used for more than a quarter of a century. As yet, the true mechanism of the antifertility action remains poorly defined. The numerous cellular and biochemical alterations induced in the endometrium by the IUDs are believed to be responsible for the contraceptive effect [1]. The increased number of neutrophils and macrophages in the uterine flushings following IUD insertion has been confirmed by many investigators [2,3].

It has been shown that macrophages on the surface of IUDs can serve as a potent source for increased prostaglandins (PGs). Zurier and Sayadoff found that human polymorphonuclear leukocytes released PGs in the surrounding medium [4]. Goldstein and associates demonstrated that intact polymorphonuclear leukocytes also generate thromboxanes in response to surface stimulation [5]. Chaudhury suggested PGs as a possible link between the presence of an intrauterine foreign body and the target response that blocks conception [6]. Moreover, in a recent study, the number of spermatozoa recovered from the fallopian tubes has been shown to be markedly reduced in IUD users [7]. Also, studies of the recovery of ova and their microscopic examination indicate that IUDs may exert their antifertility effect on the ova at a stage prior to reaching the uterine cavity [7].

The present work was aimed at evaluating the relationship between the PG levels and inflammatory cell reaction in the uterine cavity in response to IUD use.

Materials and methods

Sixty healthy fertile women aged between 20 and 37 years (mean, 29.7 years) with regular menstrual cycles and normal blood loss were recruited in the study.

Group I (short-term IUD users): This group included thirty women who opted to use IUDs for contraception.

Group II (long-term IUD users): This group also consisted of thirty subjects who had worn IUDs (Lippes Loop size C) for at least two years.

None of the women was lactating or using hormonal therapy or anti-inflammatory drugs. Their pelvic examination findings were within normal limits.

Uterine washing (25 ml normal saline) was performed using a Gravlee jet washer [8] (Sterile disposable Gravlee Jet washer with reservoir and 30 cc syringe, Bord Parker, Rutherford, New Jersey 07070, USA) around the sixth to the eighth day of the menstrual cycle and two weeks afterwards. This was done twice in short-term IUD users (before and three months after insertion of a Lippes Loop size C and once in long-term IUD users.

The recovered fluid, containing a prostaglandin synthetase inhibitor (indomethacin, 50 mg/liter saline) to prevent production of PGs by the cells *in vitro* [9], was filtered through millipore filters with 0.45 micron pores (Millipore Corporation,

Bedford, Massachussetts, USA) and the entangled cells were stained, identified and counted. PGE2, PGF2alpha and their 13,14-dihydro-15-keto metabolites, were measured in the cell-free uterine wash using their respective radioimmunoassays [10]. The antigen, antiserum, buffer dextran coated charcoal and PG standard were purchased from Steranti Research Ltd (14 St Albans Road, London, England), while the high-specific activity tritiated tracers were available from New England Nuclear. The extraction of PGs was modified from a previously reported method in uterine wash and in biological fluids [10,11].

Cross reactivity of antisera was tested relative to various PGs (E2, F2alpha, E1, F1alpha, A1, B1, A2, and B2). As differences in the molecular structure of various PGs from the tested antiserum increased, the degree of cross reactivity decreased. The cross-reaction curves indicated that the utilized antisera were fairly specific, as in none of the tests the cross reactivity exceeded 12.5%. Dilution of the uterine fluid indicated that with increasing dilution, there was a linear decrease in concentration, thereby assuring the accuracy of the assay. This was sustained for all PG fractions. The accuracy of the technique was also tested by the extent to which the value obtained in an assay corresponded to true value. This was examined by determining the recovery of an added substance (identical to the one which is intended to be measured). Intra- and inter-assay precision for each PG metabolite was determined using the coefficient of variation, which varied between 3-5% and 6-10% for intra- and inter-assay precision, respectively, for the various PG metabolites.

Results

The prostaglandin level in the uterine wash fluid

A. Prostaglandin E2: In the follicular phase, the PGE2 level (mean $\pm$ SE) was 227.5 $\pm$ 60.2 pg/ml before and 452.4 $\pm$ 102.9 pg/ml after IUD insertion. The difference was not statistically significant ($p > 0.05$). In long-term IUD users the PGE2 level was 70.4 $\pm$ 10.4 pg/ml. This level in long-term users was statistically lower than that among short-term users ($p < 0.05$). In the luteal phase, the PGE2 level (mean $\pm$ SE) before IUD insertion was 144.3 $\pm$ 30.9 pg/ml while after short-term IUD insertion it increased to 366.6 $\pm$ 107.5 pg/ml. This increase was statistically significant ($p < 0.05$). In long-term IUD users the PGE2 level was significantly ($p < 0.05$) lower, 81.3 $\pm$ 14.1 pg/ml (Figure 1).

B. 13,14-Dihydro-15-keto PGE2: In the follicular phase, the PGE2 metabolite level (mean $\pm$ SE) before and after IUD insertion was 11.7 $\pm$ 1.7 pg/ml and 17.1 $\pm$ 3.9 pg/ml, respectively; the difference was not statistically significant ($p > 0.05$). In long-term IUD users, the PGE2 metabolite level was 12 $\pm$ 1.5 pg/ml. The difference between long- and short-term IUD users was statistically insignificant ($p > 0.05$) (Figure 2).

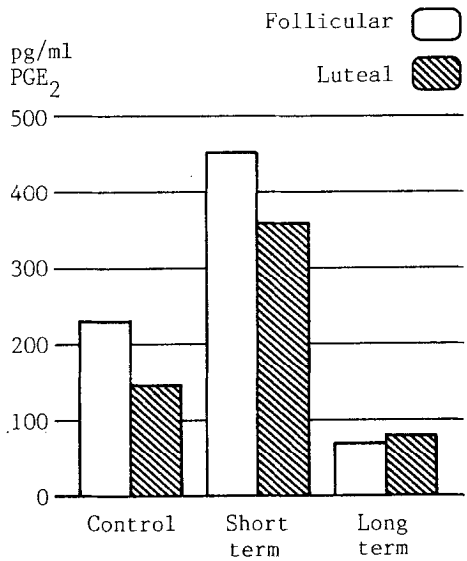

Figure 1 PGE_2 levels (pg/ml) in the uterine flushings (follicular and luteal phases) of control cycles, short-term IUD users 3 months after insertion (group I) and among long-term users (group II)

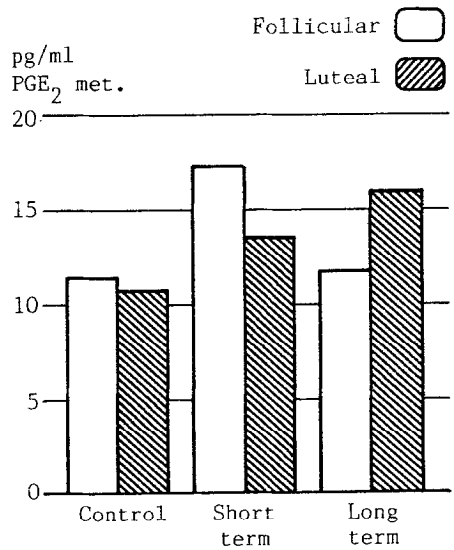

Figure 2 Levels (pg/ml) of 13,14-dihydro-15-keto PGE_2 (PGE_2 met.) in the uterine flushings of control cycles, short-term IUD users (group I) and among long-term users (group II)

In the luteal phase, the PGE2 metabolite level (mean ± SE) before IUD insertion was 11.1 ± 2.08 pg/ml and after IUD insertion it was 14 ± 2.2 pg/ml. The difference was statistically insignificant ($p > 0.05$). In long-term IUD users the level was 16.4 ± 1.7 pg/ml, which was not significantly different from short-term IUD users ($p > 0.05$) (Figure 2).

C. PGF2alpha: In the follicular phase, the mean ± SE PGF2alpha level before insertion in the control cycle was 28.8 ± 2.6 pg/ml, and after IUD insertion in short-term users, the level was 34.2 ± 4.8 pg/ml. The difference was not statistically significant ($p > 0.05$). In long-term IUD users the level was 18.3 ± 2.3 pg/ml and this value was significantly lower than that of short-term users ($p < 0.05$) (Figure 3).

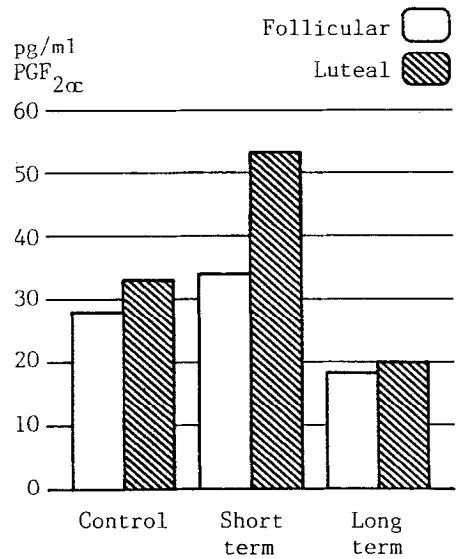

Figure 3 PGF2alpha levels (pg/ml) in uterine flushings of control cycles, 3 months after IUD insertion (group I) and among long-term users (group II, > 2 years)

In the luteal phase, the mean ± SE PGF2alpha level before insertion was 33.1 ± 4.7 pg/ml and after IUD insertion, it increased to 53.6 ± 4.9 pg/ml which was statistically significant from the pre-insertion values ($p < 0.05$). In long-term IUD users, the mean ± SE luteal PGF2alpha level was 20 ± 2.1 pg/ml, a difference from short-term users which was highly significant ($p < 0.01$) (Figure 3).

D. 13,14-Dihydro-15-keto PGF2alpha: In the follicular phase, the PGF2alpha metabolite level (mean ± SE) before insertion was 16.9 ± 1.8 pg/ml and after IUD insertion the level rose to 24.8 ± 3.3 pg/ml. The difference was statistically significant ($p < 0.005$). In long-term users, the level was 13.3 ± 1.4 pg/ml. The difference in levels between short- and long-term IUD users was statistically significant ($p < 0.05$) (Figure 4).

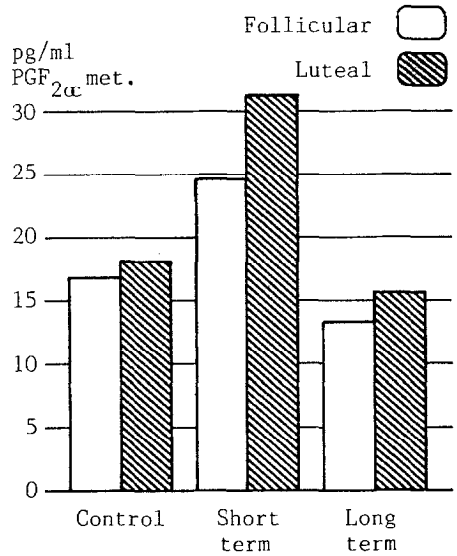

Figure 4 Levels (pg/ml) of 13,14-dihydro-15-keto PGF2alpha (PGF2 met.) in the uterine flushings of control cycles, short-term IUD users (group I) and among long-term users

In the luteal phase, the PGF2alpha metabolite level (mean ± SE) before IUD insertion was 18.2 ± 0.8 pg/ml and after IUD insertion the level increased to 31.3 ± 3.3 pg/ml ($p < 0.05$) which was statistically significant. In long-term users the level was 15.8 ± 1.9 pg/ml ($p < 0.05$) which was significantly lower than in short-term users (Figure 4).

The cellular environment in the uterine wash fluid

A. Control cycles of short-term users: The mean ± SE of the total cell count was 50 ± 3.5/10 HPF in the follicular phase. The polymorphonuclear leukocytes constituted 52.4%, the macrophages 37.3% and the lymphocytes 10.2% of the total cell count (Table 1 and Figure 5).

In the luteal phase, the total cell count (mean ± SE) was 55.7 ± 2.9 / 10 HPF. The polymorphonuclear leukocytes constituted 53.3%, the macrophages 39.7% and the leukocytes 6.8% of the total cell count (Figure 5).

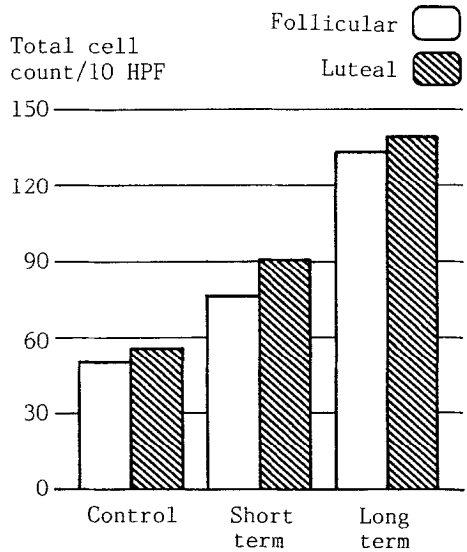

Figure 5 Total number of cells/10 HPF in the follicular and luteal phases of control cycles, 3 months after IUD insertion (group I) and among long-term users (group II, > 2 years). Note the continued increment in the number of cells as the duration increases

B. Short-term IUD users after device insertion: There was a statistically significant increase in the number of the total cells/10 HPF in both the follicular and the luteal phase. In the follicular phase, the mean ± SD of the total cell count was 77.0 + 3.4/10 HPF after IUD insertion ($p<0.05$) and in the luteal phase it was 91.3 ± 9.3/10 HPF ($p<0.05$). There was a statistically significant increase in the polymorphonuclear leukocytes and in the macrophages after IUD insertion in both the follicular and luteal phases ($p<0.05$) (Table 1 and Figure 5).

C. Long-term IUD users: There was a significantly greater number of the total population among long-term IUD users, both in the follicular and luteal phases, compared with short-term users ($p<0.05$). In the follicular phase, the total cell count (mean ± SD) was 134.2 ± 10.8/10 HPF. The polymorphonuclear leukocytes were 70.3 ± 5.3/10 HPF, the macrophages were 53.2 ± 6.3/10HPF ($p<0.05$), while the lymphocytes were not significantly higher ($p>0.05$). In the luteal phase, the total cell count was 139.4 ± 12.1/10 HPF ($p<0.05$). There was a statistically greater number of polymorphonuclear leukocytes among long-term IUD users, which was 87.9 ± 7.6/10 HPF ($p<0.05$), while macrophage and lymphocyte counts were not different from those of short-term users in the luteal phase (Table 2 and Figure 5).

Table 1 Effect of IUD insertion on the cellular environment (count/10 HPF) in the uterine wash fluid in the follicular and luteal phases (short-term users)

		Polymorphs		*Macrophages*		*Lymphocytes*		*Total count*	
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
Follicular phase	Mean ± SE	26.2 ± 1.7	42.3* ± 1.6	18.6 ± 2.3	28.9* ± 1.5	5.1 ± 0.8	5.8 ± 0.7	50.0 ± 3.5	77.0* ± 3.4
	%	52.4	54.9	37.3	37.5	10.2	7.5	100.0	100.0
Luteal phase	Mean ± SE	29.7 ± 2.2	42.9 ± 6.6	22.1 ± 0.9	40.4* ± 3.4	3.8 ± 0.4	8.0* ± 0.7	55.7 ± 2.9	91.3* ± 9.4
	%	53.4	46.9	39.7	44.2	6.8	8.8	100.0	100.0

* = Significant at $p < 0.05$ compared with pre-insertion values
SE = Standard error

Table 2 Comparison of the cellular environment (count/10 HPF) in the uterine wash fluid in the follicular and luteal phases between long and short-term IUD users

		Polymorphs		*Macrophages*		*Lymphocytes*		*Total count*	
		Short term	*Long term*	*Short term*	*Long term*	*Short term*	*Long term*	*Short term*	*Long term*
Follicular phase	Mean ± SE	42.3 ± 1.6	70.3* ± 5.3	23.9 ± 1.5	53.2* ± 6.3	5.8 ± 0.7	10.6 ± 2.3	77.0 ± 3.4	134.2* ± 10.8
	%	54.9	52.3	37.5	39.6	7.5	7.9	100.0	100.0
Luteal phase	Mean ± SE	42.9 ± 6.6	87.9* ± 7.6	40.4 ± 3.4	44.2 ± 4.5	8.0 ± 0.7	7.2 ± 1.1	91.3 ± 9.4	139.4* ± 12.2
	%	46.9	63.9	44.2	31.0	8.7	5.2	100.0	100.0

* = Significant at $p < 0.05$ compared with short-term users

Correlation between the prostaglandin levels and the cellular counts in the uterine wash fluid

Evaluation of the correlation coefficient (r) between the measured PGs and the count of the macrophages in the uterine wash fluid in the follicular and luteal phases of the control cycle, short-term and long-term IUD users indicated absence of a significant correlation. A similar evaluation between the different PGs and the total cellular count was done, where a significant negative correlation was observed only with respect to PGE in the follicular phases of the control cycle ($r=0.72$).

In all other phases of control and IUD cycles, no significant correlation was seen.

Discussion

In the present work, the uterine wash was selected for measuring PG levels instead of tissue measurements to minimize false values resulting from the trauma to tissue during sample collection. Moreover, the additional precaution of having non-steroidal anti-inflammatory drugs (NSAIDs) was taken, using a PG synthetase inhibitor in the wash fluid to avoid PG formation *in vitro* during sample collection. The present data indicate that the presence of an IUD stimulates an increased production of PGs, which is particularly evident in the luteal phase.

However, Green and Hagenfeldt, using a large non-medicated device, the Dalkon Shield, did not find any significant change in PGF2alpha or PGF2alpha metabolite in the endometrium after 3 months of IUD use [12]. Hillier and Kasonde, using inert and copper bearing devices, did not observe any significant changes in endometrial PGF2alpha level after device insertion, but reported a significant increase in the E type of PGs [13]. Scommegna and associates also reported no change in endometrial PGF levels after IUD insertion (Lippes Loop or progesterone releasing IUD) [14]. The different types of IUDs used, the different phases of the cycle and the methodological limitations of tissue measurements versus uterine wash samples could explain the discrepancy between the results of the present work and studies mentioned above.

In the present work, the increase in PG levels after IUD insertion was observed only in the first few months, and coincided with the phase of increased side effects, such as pain and irregular bleeding, commonly reported following insertion. Another PG, the prostacyclin, which is a potent vasodilator and inhibitor of platelet aggregation and was not measured in this study, may contribute to the hemostatic defect if released in excess [15]. Other prostanoids, namely the thromboxanes, possess opposing properties to prostacyclin and may also be involved in these problems if their production is suppressed [15]. The role of lipo-oxygenase products in this context remains a theoretical assumption and an exciting new area of interest. Thus, the increased production of PGs may contribute to the occurrence of pain and bleeding, since they possess both spasmogenic and some pro-hemorrhagic properties [16,17]. This is further documented in several published reports showing that IUD-related heavy bleeding and pain could be prevented by treatment with PG synthetase inhibitors such as non-steroidal anti-inflammatory drugs [18].

The significant short-term rise in PG levels after IUD insertion appears to be an acute response to the mechanical irritation induced by the insertion of the foreign body. This acute reaction seems to disappear in time among long-term users, probably because of uterine adaptation or partial endometrial compression by the device. It is also well known that PG release is more pronounced in acute rather than in chronic reactions [19]. The low levels of PGs among long-term users with continued contraceptive efficacy contradicts any key role for these substances in the mechanism of action of IUDs.

Many of the cellular and vascular changes associated with the presence of IUDs can, in theory, be induced by arachidonic acid metabolites synthetized along the cyclo-oxygenase pathway [17]. Other metabolites produced along the lipo-oxygenase pathway, such as leukotrienes and lipoxins, can be produced by human polymorphonuclear leukocytes [20]. These compounds possess diverse biological properties such as cytotoxic effects, chemotaxis, and increased vascular permeability. The uterine levels of these compounds and their relevance to the clinical performance of IUDs have yet to be established.

Although PGs are chemotactic and can attract various types of cells, and polymorphs and macrophages are capable of synthesizing PGF and E types, the present study was unable to confirm the existence of any linear correlation between these biochemical and biological parameters [21,22].

The continued increase in the cellular response and decrease in PG levels in the uterine flushings with the duration of IUD insertion indicates the lack of total dependency of either component on the other. Moreover, the data support the existing belief that the cellular reaction probably plays an important role in the contraceptive mechanism of IUDs.

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Resumé

Les niveaux de prostaglandine utérine (PG) et les réactions cellulaires aux DIU ont été évalués chez soixante femmes. Celles qui utilisaient ces dispositifs depuis peu de temps (n = 30) ont été étudiées dans un cycle contrôle et 3 mois après l'insertion, alors que les utilisatrices à plus long terme (n = 30) ont été examinées au moins 2 ans après l'insertion du dispositif. On a procédé à un lavage utérin pendant la phase prolifératve et lutéinique de chaque cycle menstrual examiné; les constituants cellulaires ont été comptés et les niveaux de PGE_2 et PGF_{2alpha}, ainsi que leurs métabolites 13,14-dihydro-15-cétones ont été mesurés. On a constaté une élévation significative des niveaux de PG dans le lavage utérin effectué peu de temps après l'insertion du DIU, notamment pendant la phase lutéinique. On a toutefois observé une réduction significative des niveaux de PG chez les utilisatrices de longue date, bien que la réaction cellulaire ait marqué une augmentation continue. L'absence de corrélation entre les réactions biochemique et biologique laisse penser qu'aucune des deux ne dépendait totalement de l'autre. La baisse des niveaux de PG chez les utilisatrices à long terme ne vient pas à l'appui du concept qui attribue un rôle-clé à ces substances dans le mécanisme d'action des DIU. L'élévation passagère des niveaux de PG après l'insertion coincïde avec la phase d'augmentation de l'écoulement sanguin et des douleurs.

Resumen

En sesenta mujeres se evaluaron los niveles de prostaglandina uterina (PG) y la reacción celular en respuesta a los DIU. Se estudiaron pacientes que los usaron por poco tiempo (n = 30) en un ciclo de control y 3 meses después de la inserción de un DIU. Las pacientes que los usaron por largo tiempo (n = 30) fueron estudiadas a no menos do dos años despues de la inserción del dispositivo. Se hizo un lavado uterino en la fase proliferativa y luteal de cada ciclo menstrual investigado; se contaron los

componentes celulares y se midieron los niveles de PGE_2, PGF_{2alpha} y sus 13,14-dehidro-15-keto-metabolitos. Se observó un aumento significativo en los niveles de PG en el lavado uterino poco despues de la inserción del DIU, particularmente en la fase luteal. Sin embargo, hubo una reducción significativa en las usuarias a largo tiempo aunque la reacción celular mostró un incremento continuo. La ausencia de correlación entre las respuestas bioquímicas y biológicas indicó que ninguna era totalmente dependiente de la otra. Los disminuidos niveles de PG en las usuarias a largo tiempo, no corroboran el concepto de un rol clave para estas substancias en el mecanismo de acción de los DIU. El aumento temporario en los niveles de PG posterior a la inserción, coincide con la fase de mayor sangrado y dolor.