Prostaglandins: $PGF_{2\alpha}$, PGE_2, 6-keto-$PGF_{1\alpha}$ and TXB_2 serum levels in dysmenorrheic adolescents before, during and after treatment with oral contraceptives

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Summary

Ten adolescents with primary dysmenorrhea (PD) were treated with the oral contraceptive (OC) Lyndiol 2.5 mg (R) for one cycle. The levels of $PGF_{2\alpha}$, PGE_2 and the metabolites of PGI_2 and TXA_2: 6-keto-$PGF_{1\alpha}$ and TXB_2 were tested by a radioimmunoassay method during the 1st and 23rd day of the pre-treatment cycle (PrTC), the 23rd day of treatment (TC) and the 1st day of the post-treatment cycle (PoTC). The ratios $PGF_{2\alpha}/PGE_2$ and TXB_2/6-keto-$PGF_{1\alpha}$ were also tested and compared during the above-mentioned days.

Analytical comparison was made, for each Prostaglandin (PG) separately, between the 1st day of the PrTC and PoTC as well as the 23rd day of the PrTC and TC, respectively. All PG levels during TC and PoTC were found significantly lower, compared to those of the PrTC respectively. With regard to the ratios mentioned above, no statistically significant differences were found on the same days and cycles as previously stated.

The reduction of the PG levels in PD patients after treatment with oral contraceptives, together with an improvement of the clinical findings of the disease, support the theory that oral contraceptives can be used for the treatment of PD cases, especially for those adolescents who also desire a contraceptive method.

Dysmenorrhea; Prostaglandin; Oral contraceptive

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Introduction

Dysmenorrhea is a common menstrual disorder during adolescence. During this period of life, dysmenorrhea presents as painful periods which usually start 2–3 years after menarche with the onset of ovulation. In most cases no organic disease is present, so that dysmenorrhea is characterized as primary (PD). The incidence of dysmenorrhea during adolescence varies according to several studies. Kantero and Widholm [1] reported that among a large series of Finnish girls 10% and 20% had dysmenorrhea 1 and 5 years after menarche, respectively. On the other hand Klein and Litt [2], in a large survey of young women, found that 60% of menarchal adolescents reported dysmenorrhea. In our Institution the incidence of dysmenorrhea during adolescence varies between 8.1–10% [3].

Although there is still no satisfactory explanation for the etiology of PD, the high levels of PG found in the serum of dysmenorrheic adolescents is now the most suitable theory for the explanation of this syndrome. For this reason we examined the PG levels in the serum of dysmenorrheic adolescents before, during and after treatment with oral contraceptives.

Materials and methods

Ten dysmenorrheic adolescents aged 15–19 years were included in the present study. All patients reported dysmenorrheic episodes for the last 18 consecutive months.

Evaluation of dysmenorrhea and classification to various degrees was made according to the questionnaire given to these girls. The following symptoms were included in the questionnaire: abdominal pain and bloating, vomiting, nausea, diarrhea, headache, vertigo, irritability, fatigue, depression and lack of concentration. The patients were asked to indicate the significance of each symptom, from 1 to 3, as well as the duration per symptom in days, also from 1 to 3.

Thus for each patient a PD score was obtained, based on the number of symptoms and the significance and duration of each symptom (PD score = the sum of: duration in days (1 to 3) × severity of each symptom (1 to 3) (Table I). According to this score, three groups of PD cases were found and were classified as minor, moderate or severe. All cases included in the present study were of severe degree. Those suffering from other diseases or those taking any other medication were excluded from the present study.

TABLE I

Symptoms included in the questionnaire for the determination of PD score

Abdominal pain	Vertigo
Bloating	Irritability
Vomiting	Fatigue
Nausea	Depression
Diarrhea	Lack of concentration
Headache	

All patients included in the present study were treated with oral contraceptives: Lyndiol 2.5 mg (R) (Organon) – Lynestrenol 2.5 mg/Ethinylstradiol 0.05 mg. One pill was given every morning for 22 days.

The following kits were used for the determination of PGs by radioimmunoassay: Dupont's kits of the Institute of Isotope of the Hungarian Academy of Science for the assay of $PGF_{2\alpha}$ and PGE_2 and that of New England Nuclear for the metabolites 6-keto-$PGF_{1\alpha}$ and TXB_2.

Per patient four samples were obtained as follows: The 1st and 23rd day of the pre-treatment cycle (PrTC), the 23rd day of the treatment cycle (TC) and the 1st day of the post-treatment cycle (PoTC).

The following prostaglandins (PGs) were tested in the serum of the above mentioned samples before analytical comparison followed: $PGF_{2\alpha}$, PGE_2 and the metabolites of PGI_2 and TXA_2: 6-keto-$PGF_{1\alpha}$ and TXB_2.

Statistical analysis was performed using the Student's *t*-test.

Results

The following table (Table II) presents the levels of the studied PGs in the four samples tested.

Analytical comparison was made for each PG separately, between the 1st day of the PrTC and the 1st day of the PoTC, as well as between the 23rd day of the PrTC and 23rd day of the TC. All PG levels during TC and PoTC were to be found significantly lower, compared to those of PrTC, respectively ($p < 0.001$) (Figs. 1 and 2).

TABLE II

PG serum levels ($\bar{x} \pm SD$) (pg/ml) in four samples of PD patients before, during and after treatment with oral contraceptives

Type of PG	Day and cycle tested			
	1st day PrTC (a)	23rd day PrTC (b)	23rd day TC (c)	1st day PoTC (d)
$PGF_{2\alpha}$	18.8± 1.42	17.48± 1.56	14.71± 1.44	15.74± 2.02
PGE_2	14.44± 2.13	14.49± 1.25	11.56± 1.57	10.37± 1.64
6-Keto-$PGF_{1\alpha}$	120.98±27.43	133.04±18.14	93.86±13.26	99.79±18.77
TXB_2	128.6±13.53	116.09±12.96	81.02±23.43	95.76±17.90

TABLE III

Comparison of mean values ($\bar{x} \pm SD$) of $PGF_{2\alpha}/PGE_2$ (R1) found in the four samples tested

Ratios	Significance
R1a/R1d 1.338±0.300/1.541±0.261	Not significant $p > 0.1$
R1b/R1c (1.207±0.085/1.287±0.179)	Not significant $p > 0.1$

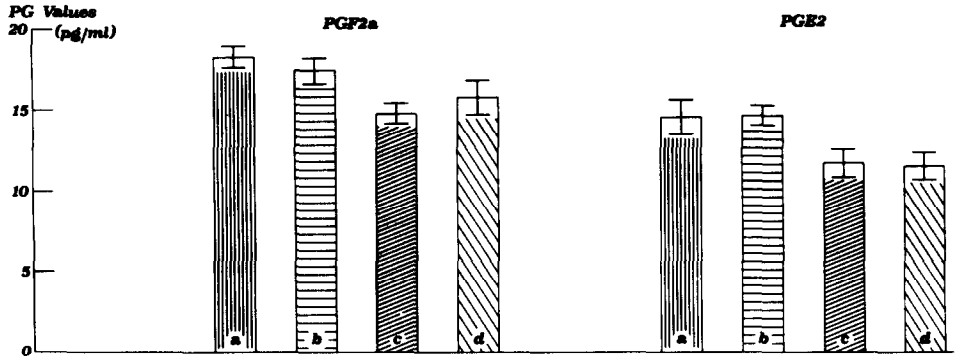

Fig. 1. Mean values and standard deviations of $PGF_{2\alpha}$, PGE_2 during: (a) The 1st day of the PrTC; (b) the 23rd day of the PrTC; (c) the 23rd day of the TC; and (d) the 1st day of the PoTC.

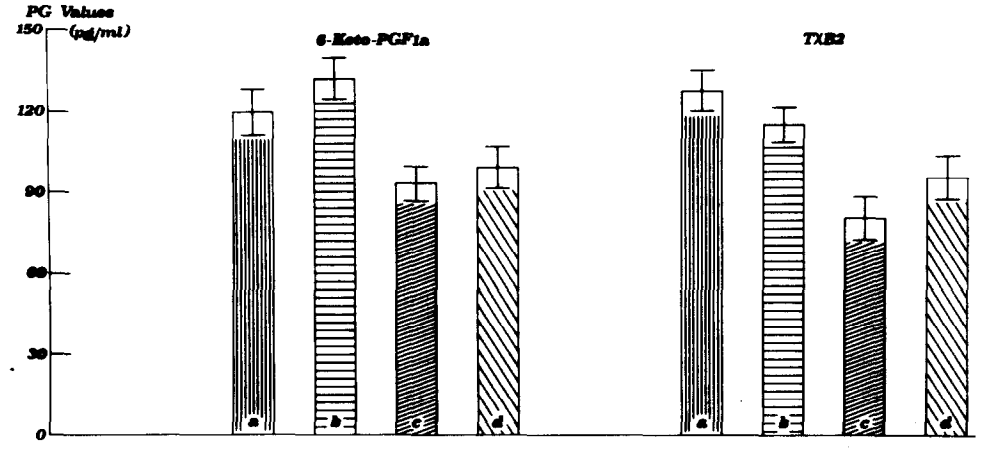

Fig. 2. Mean values and standard deviations of 6-keto-$PGF_{1\alpha}$ and TXB_2 during: (a) the 1st day of the PrTC; (b) the 23rd day of the PrTC; (c) the 23rd day of the TC; and (d) the 1st day of the PoTC.

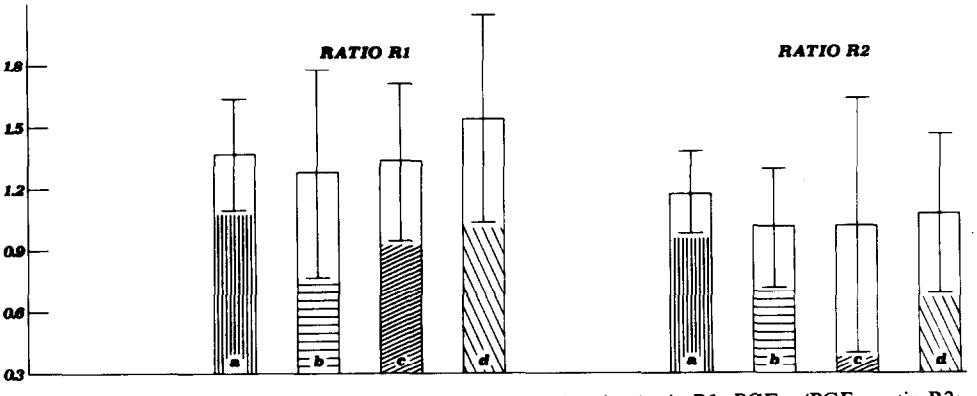

Fig. 3. Mean values and standard deviation of the R1 and R2 ratios (ratio R1: $PGF_{2\alpha}/PGE_2$; ratio R2: TXB_2/6-keto-$PGF_{1\alpha}$): (a) the 1st day of the PrTC; (b) the 23rd day of the PrTC; (c) the 23rd day of the TC; and (d) the 1st day of the PoTC.

TABLE IV

Comparison of mean values ($\bar{x} \pm SD$) of TXB_2/6-keto-$PGF_{1\alpha}$ (R2) found in the four samples tested

Ratios	Significance
R2a/R2d $1.104 \pm 0.244/0.984 \pm 0.254$	Not significant $p > 0.1$
R2b/R2c $0.861 \pm 0.149/0.857 \pm 0.198$	Not significant $p > 0.1$

TABLE V

PGs serum levels (pg/ml) in normal women during the 1st and 22nd or 23rd day of the menstrual cycle

Type of PG	1st day	22nd–23rd day
$PGF_{2\alpha}$	55.5 ± 73.6	44.0 ± 65.3
6-Keto-$PGF_{1\alpha}$	67.8 ± 79.3	58.3 ± 80.1
TXB_2	61.6 ± 75.2	53.4 ± 69.0

The ratios $R1 = PGF_{2\alpha}/PGE_2$ and $R2 = TXB_2$/6-keto-$PGF_{1\alpha}$ were also compared on the same days and cycles as previously stated. No statistically significant differences were found after comparison of the above-mentioned ratio ($p > 0.1$) (Tables III and IV; and Fig. 3).

PG levels ($PGF_2\alpha$, 6-keto-$PGF_{1\alpha}$ and TXB_2) during the 1st and 22nd or 23rd day of PrTC were found significantly higher compared to those found in normal individuals during the same days of the cycle. PG normal values for the $PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$ and TXB_2 were considered to be those presented in Table V and those reported in our previous study [4].

Discussion

It has been suggested that PD may be due to one of the following factors. (1) Increased PG production by the endometrium; (2) other than PG endocrine factors (estrogens, progesterone, vasopressin, endorphins); (3) hypoplastic uterus; (4) cervical stenosis (obstruction of outflow of the menstrual blood); (5) abnormalities of uterine contractility (increased endometrial pressure); (6) neurogenic factors; and (7) emotional and psycological factors [6,7].

Pickles in 1957 and 1960 [8,9] first described the presence of $PGF_{2\alpha}$ and PGE_2 in the menstrual blood of normal and dysmenorrheic patients. Chan [10] and Poizat [11] also found increased levels of $PGF_{2\alpha}$ and PGE_2 in the endometrium of dysmenorrheic women. The high PG levels overstimulate the endometrium and cause ischemia and pain [10,12,13]. Endometrial $PGF_2\alpha$ levels have also been found in higher values during the secretory phase of the cycle as well as in ovulatory than anovulatory cycles [5,14].

Yen [15] on the other hand reported that $PGF_{2\alpha}$ levels in the serum of dysmenorrheic patients were found to be 4-times higher than those of normal women. This

observation is in accordance with the findings of the present study. Winqvist et al. [16] and Wilhelmsson et al. [17] studied the activity of the metabolites of arachidonic acid: tromboxane and prostacyclin. In the present study, the metabolites of PGI_2 and TXA_2: 6-keto-$PGF_{1\alpha}$ and TXB_2 were tested and were found in higher levels than those in normal individuals [4].

Most treatments proposed for the management of PD cases are related to the pathophysiology of the disease, such as inhibition of ovulation, reduction of PG production and regulation of the myometrial tone. The method of choice is related to the severity of symptoms, the age of the patient, the need for contraception and the pattern of the menstrual cycle.

Oral contraceptives have been used during adolescence for the regulation of the menstrual cycle in cases of menstrual disturbances, such as oligomenorrhea and dysfunctional uterine bleeding [18]. Oral contraceptives are also among the treatments currently in use for the management of PD. Treatment with oral contraceptives has also the advantage of inhibition of ovulation and endometrial development so that menstrual blood, production of PGs and uterine contractility is reduced [10,19–21]. Our study shows the statistically significant reduction of the PGs serum values in PD cases after treatment with oral contraceptives and supports the above-mentioned theory for the role of oral contraceptives in the management of PD cases.

Bydgeman et al. [22] reported increase of uterine tonicity after intravenous or endometrial administration of $PGF_{2\alpha}$. On the contrary, it was noted that the administration of PGE_2 given by the same route reduces the myometrial tone. It is suggested that the appropriate ratio of $PGF_{2\alpha}/PGE_2$ is necessary for the regulation of the myometrial tone [8,9,23]. According to the results of the present study, no statistically significant differences were found in the ratios of $PGF_{2\alpha}/PGE_2$ and TXB_2/6-keto-$PGF_{1\alpha}$, before and after treatment with the oral contraceptives.

However, the improvement of clinical findings of dysmenorrhea in the patients studied after treatment with oral contraceptives support the suggestion that they can be used for the management of PD cases during adolescence, especially for those girls who also desire a contraceptive method.

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