SYMPTOMATIC SIDE EFFECTS OF COMBINED ORAL CONTRACEPTIVE PILLS

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ABSTRACT

A *prospective study was carried out during nine-month period (from 1st of December 2001 until the end of August 2002) in Basrah Maternity and Children Teaching Hospital. The aim is to assess the timing, frequency and severity of symptomatic effects of combined oral contraceptive (COC) users specifically to compare 21 days of active pill intervals with 7 days of hormone- free intervals in both current (COC user for ≥12 months) and new users (COC user for 3 months). Current users had pattern of symptoms that were observed significantly worse during hormone-free interval than during the three active-pill weeks for both 1st and 2nd cycles. 57% and 56% of them experienced mild pelvic pain during free period versus 19% and 16% during active-pills weeks in both cycles respectively (P=0.001), while moderate to severe pelvic pain, the corresponding percentages were 22% and 22% versus 9% and 8% (P=0.042). For Nausea, the percentages were 48% and 46% versus 31% and 30%. For bloating the corresponding percentages were 46% and 46% versus 18% and 16% (P>0.0001) and for breast tenderness the corresponding percentage in free period were 29% and 29% versus 16% and 15% in active pill interval in both cycles respectively (P=0.0004). The reverse was true when other symptoms were assessed like headache and mood changes. Regarding headache the corresponding percentages were 35% and 33% during free period versus 60% and 58% during active pill interval in both cycles respectively, and for mood changes, the percentages were 21% and 19% versus 50% and 47% respectively. Similar patterns for all previous symptoms were observed in new start COC users in both cycle 1 and 2 for pelvic pain, nausea, bloating and breast tenderness. These symptoms increased and became worse during hormone free interval while headache and mood changes became more severe during active hormone period than during hormone free interval. Breakthrough vaginal bleeding occurred more frequently in new start COC in comparison to current users. The percentages were 20% and 16% versus 5% and 3% in both cycles respectively. Menstrual flow decreased significantly in current users in comparison to new start COC (5% and 16%) respectively (Table-4). This study confirmed that most symptoms assessed were significantly worse during the 7 day hormone-free interval than during the 21 day of hormone-containing pills.*

INTRODUCTION

Oral contraceptives (OCs), the most common method of reversible birth control, are used by approximately 80% of women in the United States at some time during their reproductive years.[1] The COC contains both oestrogen, usually ethinyloestradiol, and a progestogen. The dose of oestrogen varies from 20-50µg. Most women are now using the so-called low dose pills containing 30-35µg.[2] Despite the continuous reduction in hormone content since OCs introduction almost 40 years ago, side effects continue to affect compliance.[3-5] The most commonly reported side effects are nausea and vomiting, breakthrough bleeding and spotting, headaches, bloating and breast tenderness.[5,6] The COCs confer a number of health benefits. Menstrual periods are usually lighter, shorter and more regular during pills use. They also tend to be less painful.[2] Although women are prescribed COC as a treatment for menorrhagia or dysmenorrhoea, the long term success rates of current low dose OCs in managing those common menstrual disorders is not known. There is also a lack of information comparing symptoms in new-start COCs users with long term users during the 21 days of hormone containing pills and the 7 days hormone-free interval. If the problems are a result of the 7 day hormone withdrawal, knowledge of the types and severity of complaints could lead to specific interventions.[7] In this study, we examined prospectively hormonal symptomatology in women currently using and new initiating COC to assess the frequency, timing and severity of complaints during each of the 21 days of active pills compared with 7 days of hormone-free pills.

PATIENTS AND METHODS

A prospective study was carried out on 360 women of 20931 who attended family planning clinic at Basrah Maternity and Children Hospital (from 1st of December 2001 until the end of August 2002). They requested COC pills for birth control. They were eligible for

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participation if they have recent COCs use for 3 months (162) (considered a new starts) or current users for ≥ 12 months (198). All women used low dose COC pills of 21 days active pills containing 0.03mg of ethinylestradiol (E_2), 0.15mg of levonorgestrel and 7 brown tablets, hormone free pills, each containing ferrous fumerate 75 mg. All selected women were apparently healthy and had no past medical or gynaecological problems. Demographic information was registered including age, gravidity, weight, occupation and education level. The socioeconomic status of women was determined based upon education level and occupation. All women were asked to keep daily calendars during their next two full cycles of COCs. Educated women recorded daily hormone-related symptoms like nausea, vomiting, bloating, breast tenderness, vaginal bleeding, headache and mood changes. Types and amounts of analgesics were, also, recorded. Illiterate women husbands were asked to record the daily hormone related symptoms. For pelvic pain, we considered pain as mild if there is no need for analgesic drugs, and moderate to severe whenever there was a need for analgesic drugs. Menstrual flow was assessed, comparing the 2nd cycle of new starts with the 1st reported cycle of current users. Menstrual flow was graded on a scale of 0-4 (0=no bleeding, I= spotting that did not require protection, 2= light flow that soaked a pad less frequently than every 8 hours, 3=moderate flow that soaked a pad every 3-8 hours, 4= heavy flow that soaked a pad more frequently than every 3 hours).[7] Women checked boxes on the calendar for the purpose of this study if they had any hormone related symptoms. Demographic and baseline characteristics were compared with the use of analysis of variance for continuous variables and X^2 test for categoric variables as a test of significance. It is regarded significant if the P-value < 0.05.

RESULTS

During the period of the study, 360 women were returned their detailed calendars for analysis. The demographic features of both groups (198 women were current users and 162 were new start users) were shown in (Table-1). There was no significant difference in the two groups, as the women education, age and parity were approximately similar. Also, it was found that more women had primary school education (38% versus 31%) and were housewives (79% versus 78%) in both groups respectively. The difference was statistically not significant. The symptomatic side effects among current users in cycle 1 and 2 were shown in (Table-2) during three weeks active hormone interval and the free week pills interval. Data of pelvic pain (mild and moderate to severe pain) were assessed and were well matched in both periods. It was found that the hormone-free interval had significantly higher prevalence of pelvic pain in both cycles. The weekly average of mild pelvic pain during the three active hormone weeks in cycle 1 and 2 were (19% and 16%) versus (57% and 56%) during the hormone-free week respectively (P=0.0001). The prevalence of severe pelvic pain during the three-active hormone weeks in cycle 1 and 2 were (9% and 8%) versus (22% and 22%) during the hormone-free interval respectively. The difference was statistically significant (P=0.042). Other symptoms, such as nausea, vomiting, bloating, breast tenderness, mood changes and breakthrough bleeding were also analyzed. The prevalence of nausea, vomiting, bloating and breast tenderness, as shown in (Table-2) , were higher among women during the hormone-free intervals in both cycles in comparison to active 3 hormone-weeks. For nausea, the corresponding percentages were (48% and 46%) versus (31% and 30%) for the free and active periods respectively (P=0.016). The corresponding percentages for vomiting in both periods were (15% and 14%) versus (11% and 10%) in both cycles respectively (P=0.244). Also the percentage of bloating were (48% and 46%) versus (18% and 16%) respectively, (P<0.0001), and for breast tenderness (29% and 29%) versus (16% and 15%) (P=0.0004). The number of women with headache and mood changes increased during the three week active hormone intervals. For headache in cycle 1 and 2 , the corresponding percentage were (60% and 58%) versus (35% and 33%) respectively (P=0.001) (Table-2).

The percentages for mood changes were (50% and 47%) versus (21% and 19%) respectively, (P=0.0002) (Table-2).

Same data were analyzed in new start COC pills in cycle 1&2 in hormone free interval and active 3 week hormone intervals. The hormone free

interval in each cycle had significantly higher symptomatic side effects prevalence in comparison to 3 week hormone intervals in regard to pelvic pain (mild and moderate to severe), nausea, vomiting, bloating and breast tenderness as shown in (Table-3).

The average prevalence of mild pelvic pain in cycle 1 during the active hormone week was 32% versus 72% during hormone free period and during cycle 2, the corresponding percentages were 27% versus 63% in free period respectively (P-value=0.0004).

For nausea, vomiting, bloating and breast tenderness the corresponding percentage in cycle 1 during active 3 week intervals were (53%, 16%, 20% and 22%) and in cycle 2 (53%, 15%, 18% and 20%) respectively in comparison to (65%, 20%, 60% and 49%) in cycle 1 and (62%, 19%, 58% and 47%) in cycle 2 during free hormone interval. The differences were statistically significant except for vomiting and as shown in (Table-3).

Headache and mood changes were also analyzed in both cycles and in both periods among new users. The corresponding percentages were higher in active 3 weeks hormone period in comparison to one week free period. For headache the percentages were (71% and 70%) versus (56% and 53%) in cycle 1 and 2 of active and free periods respectively (P=0.077), the difference was statistically not significant and for mood changes the corresponding percentages were (64% and 61%) versus (41% and 39%) respectively (P=0.013).

The percentage of breakthrough bleeding among current users in active period were (5% and 3%) in cycle 1 and 2 (Table-2). The percentages among new users were 20% and 16% in both cycles respectively (Table-3).

The pattern of menstrual blood flow in both new and current users groups were shown in (Table-4). The prevalence of mild to moderate withdrawal bleeding were comparable in both groups. The percentage of heavy menstrual flow among new start COC users and current users were 16% and 5% respectively, the difference was statistically significant (P=0.001).

Table 1 . ***Demographic distribution of women using COC pills (current and new start users).***

Characteristic	Current users Total No.: (198)	New users Total No.: (162)	P-value
Age (in years)	28±6	27±6	0.323 NS
Parity	5±2	5±3	0.963 NS
Height (cm)	165±5	164±5	0.595 NS
Weight (kg)	64±7	64±9	0.968 NS
Education			
Illiterate	52 (26%)	47 (29%)	0.372 NS
Primary	76 (38%)	50 (31%)	0.1767 NS
Intermediate	30 (15%)	33 (20%)	0.172 NS
Secondary	27 (14%)	17 (11%)	0.262 NS
Higher	13 (7%)	15 (9%)	0.247 NS
Occupation			
Housewives	165 (79%)	127 (78%)	0.519 NS
Employed	42 (21%)	35 (22%)	0.520 NS

Data presented as (mean±SD) or in (%)
NS: not significant

Table 2. ***The symptomatic side effects among 198 current COC users during three active hormone weeks and free pill interval.***

Symptoms	Active period		Free period		P- value
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	
Mild pelvic pain	38 (19%)	32 (16%)	113 (57%)	111 (56%)	0.0001 S
Moderate to severe pelvic pain	18 (9%)	16 (8%)	44 (22%)	44 (22%)	0.042 S
Nausea	61 (31%)	59 (30%)	95 (48%)	91 (46%)	0.016 S
Vomiting	22 (11%)	20 (10%)	30 (15%)	28 (14%)	0.244 NS
Bloating	36 (18%)	32 (16%)	95 (48%)	91 (46%)	<0.0001 S
Breast tenderness	32 (16%)	30 (15%)	58 (29%)	58 (29%)	0.0004 S
Headache	119 (60%)	114 (58%)	69 (35%)	65 (33%)	0.001 S
Mood changes	99 (50%)	93 (47%)	42 (21%)	38 (19%)	0.0002 S
Breakthrough bleeding	10 (5%)	6 (3%)			

S: significant
NS: not significant
Data are presented as the number of women reporting the side effect.

Table 3. ***The symptomatic side effects among 162 new start COC users during three active hormone weeks and free pill interval.***

Symptoms	Active period		Free period		P- Value
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	
Mild pelvic pain	52 (32%)	44 (27%)	117 (72%)	102 (63%)	0.0004 S
Moderate to severe pelvic pain	16 (10%)	16 (10%)	41 (25%)	39 (24%)	S
Nausea	86 (53%)	86 (53%)	105 (65%)	100 (62%)	0.032 S
Vomiting	26 (16%)	24 (15%)	33 (20%)	31 (19%)	0.233 NS
Bloating	32 (20%)	29 (18%)	97 (60%)	94 (58%)	<0.001 S
Breast tenderness	36 (22%)	32 (20%)	79 (49%)	76 (47%)	0.001 S
Headache	115 (71%)	113 (70%)	91 (56%)	86 (53%)	0.077 NS
Mood changes	104 (64%)	99 (61%)	66 (41%)	63 (39%)	0.013 S
Breakthrough bleeding	32 (20%)	26 (16%)			

S: significant
NS: not significant

Table 4. ***The pattern of menstrual flow in both groups (198 current users and 162 new start COC pills users).***

Bleeding score	Current users Total No.: 198	New users Total No.: 162	P-value
0	0	0	
1	6 (3%)	6 (4%)	0.977 NS
2	129 (65%)	94 (58%)	0.246 NS
3	53 (27%)	36 (22%)	0.306 NS
4	10 (5%)	26 (16%)	0.001 S

S: significant
NS: not significant
Score 0: no bleeding, 1: spotting, 2: light flow, 3: moderate flow, and 4: heavy flow.

DISCUSSION

Contraceptive steroids are metabolized by the liver and affect the metabolism of carbohydrates, lipids, plasma proteins, amino acids, vitamins and clotting factors. The COCs have an effect on almost every system in the body. Most side effects are minor and include fluid retention, headache, nausea, vomiting, mood changes and breast enlargement. Many improve within 3-6 months of starting the pills but side effect often lead to discontinuation. It is worth trying a different dose of oestrogen or different type of progestogen if time alone does not solve the problem.[2] In this study we document that symptomatic side effects of COC sometimes varied between the active pills and hormone free periods in both long-term users and new starts. Among current users the prevalence of pelvic pain and analgesic use was greatest during hormone-free intervals. Approximately 57% of women during two monitored cycles documented some degree of mild pelvic pain during the hormone-free interval compared with 19% during active pills weeks. The prevalence of moderate to severe pain was 22% during the hormone free week compared with 9% during active pill weeks during cycle 1 and approximately same findings during cycle 2 (P=0.042), this is in agreement to study done by Patricia et al.[7] Another finding in our study that the prevalence of nausea and vomiting among current users during both cycles were higher during free periods in comparison to active hormone periods (Table-2). These results were also noticed in new users (Table-3). This is in agreement to the study of Patricia J et al.[7] Most of current and new users experienced nausea and vomiting during the free pill interval. This may be due to using of hormone free pills, which contains 75mg ferrous fumerate. Taking COC pills after meal or at bed time, may also contribute. The prevalence of breast enlargement and tenderness among current users were 16% and 15% in cycle 1 and 2 during active pill interval in comparison to 29% and 29% during hormone free period respectively. The difference was statistically significant, and is in agreement to that reported by Milligan et al.[8] Bloating was more likely during hormone-free intervals, in both current and new starts COC users, and increased prevalence that began in the last few days of active pills before hormone-free intervals might correlate with serum oestradiol (E_2) levels. Studies have documented that serum FSH and 17-B-E2 levels were suppressed at the beginning of 7 day hormone-free periods, but gradually increasing over the next free days. No significant difference between FSH level on day 7 of hormone free interval were found compared with control in normal follicular phase of ovarian cycle, suggesting that gonadotrophin production is incompletely suppressed during hormone-free interval.[9] E2 levels began to rise during the end of hormone-free interval, peaking in the 1st half of OC cycle, then declining during the last-week of active pills before the hormone free interval.[10,11] Headaches were less common during hormone-free intervals compared with the active-pill weeks in both current and new users. Among

current users approximately 35% of women in the two monitored cycles reported headache during the hormone free intervals compared with prevalence of 60% during the active periods. The corresponding percentages in new users were approximately 56% versus 71% during free pill and active periods respectively (Table-3). This is in contrast to Patricia et al [7] and Silberstein et al.[12] Mood changes were noted significantly more during 3 weeks active pill interval, in current and new users in both cycles in comparison to hormone free period. This is in agreement to study done by Sulk et al.[13] The prevalence of breakthrough bleeding in both cycles were 5% and 3% among current users versus 20% and 16% among new users respectively. This is in agreement with the study of Patricia et al.[7] This type of bleeding occurred, particularly in early treatment cycles and was more common with the lower fixed-dose pills than it was with the older high dose pill. If mid-cycle spotting alone is present, then treatment should be continued as this usually settles after the 2nd or 3rd cycle. If it does not, higher-dose contraceptive pills may be needed. If frank and heavier breakthrough bleeding occur, the patient should be instructed to stop using pills, throw away the partially used packet of pills and start a new one 7 days later.[2] Evaluation of menstrual flow showed that heavy menstrual flow was noted less in current users than new starts (5% versus 16%) respectively (P= 0.026), this is in agreement with Patricia et al.[7] This significant reduction in blood flow is important when counseling those who have been prescribed OCs for menorrhagia, emphasizing the importance of explaining that significant reduction in flow might take several months.

Conclusions and recommendations: Our study confirmed significant symptomatology during the hormone-free interval including pelvic pain, nausea, vomiting bloating and breast tenderness in both new and current users groups. This can lead to poor compliance and discontinuation. Shortening the hormone free interval from 7 to 4 or 5 days could provide greater ovarian suppression and decrease the number of days of symptoms. Extending the number of active weeks to a maximum of 12 weeks of active pills followed by a 7 day hormone-free intervals (13 week cycles) will decrease frequency and severity of complaints. Continuous active pills for several months without a hormone-free interval has been advocated for decades as a treatment for pelvic pain associated with endometriosis.[14]

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