Effects of Ethinyl Estradiol plus Desogestrel on Premenstrual Symptoms in Iranian Women

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Abstract- Marvelon®, a combined oral contraceptive, contains 30 µg ethinyl estradiol (EE) and 150 µg desogestrel (DE), and has been shown to be a well-tolerated and effective combination that provides high contraceptive reliability and good cycle control. However, its efficacy has not been yet evaluated among Iranian women. Thus, the study aimed to determine the effect of oral contraceptive pill on treating premenstrual symptoms and on various parameters associated with well-being and health in a sample of Iranian. This clinical trial (before- after) study was performed at the family-planning clinic of the centers under the supervision of Tehran University of Medical Sciences on sixty-one women. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences and all participants received a 21/7-day regimen of oral contraceptive containing 150 µg desogestrel (DE) and 30 µg ethinyl estradiol (EE) for six cycles. Efficacy parameters included changes in premenstrual symptoms were also assessed. Clinical data was collected by calendar of premenstrual experiences (COPE) at baseline and treatment cycles 1,2, 3 and 6. Clinical variables were measured including low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride levels for two timing periods (baseline and last visit). Linear mixed model analyses were used to analyze differences in changes of the four factors of premenstrual syndrome (PMS), weight and blood pressure during these timing periods. The mean age of the women was 28.52 (SD=6.75) years. Participants on average had been pregnant 1.13 (SD=1.16) times. The linear mixed model analyses indicated that premenstrual syndrome symptoms reduced significantly over time (P<0.05). Marvelon® showed no significant effect on reducing LDL and HDL levels, and participant's weights were also stable during five-time assessments (P>0.05). A combined oral contraceptive containing ethinyl estradiol and desogestrel has a positive effect on women's health and reduces premenstrual symptoms.

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Keywords: Oral contraceptive; Premenstrual symptoms; LDL; HDL; COPE questionnaire

Introduction

Most oral contraceptives (OCs) are a combination of estrogen and progestin which have been used more than 50 years worldwide (1).

Second- and third-generation OCs differ in their progestin component. Third-generation OCs contains desogestrel or gestodene. Third generation oral contraceptives were developed in the 1980s with a goal of producing an oral contraceptive that had less androgenic adverse effects such as hirsutism and acne typically associated with the first and second generation oral contraceptives (2).

One of hormonal components of oral contraceptives is ethinyl estradiol (EE), influencing carbohydrate metabolism, while the other one is desogestrel (DE) (13-ethyl-11 -methylene- 18, 19-dinor-17-alpha-pregn-4-en-20-yn- 17-01), synthesized for first time in 1973 (3,4).

Results arose from animal examination showed that DE is strong progesterone, so it avoids the androgenic adverse effect such as acne, oily skin, hair growth and the negative effect on high-density lipoproteins (HDL),

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while increases their progestational potency (5-7). It is thought to be generally devoid of androgenic effects probably caused by an increase in serum SHBG as well as by a possible decrease in ovarian testosterone production (6,7).

Although oral hormonal contraceptives has been considered as a good cycle control, a low incidence of side effects, and an inexpensive method which are mostly available free of charge in Iran, the numbers of women of reproductive age using OCs are low. It is reported that only 23% of married women taking OCs in Iran (8). The desogestrel (150 μg) in combination with ethinyl estradiol (30 μg) is known as Marvelon® in European countries. Previous studies have revealed that the Marvelon® is known as a good and safe contraceptive method for women. A study from Thailand has also revealed that the Marvelon® is effective and acceptable contraceptive method among Thai women. Moreover, compared to Caucasian women, the incidences of irregular bleeding and side effects were apparently low in these Asian women (9). Premenstrual syndrome (PMS), a common problem, are experienced by up to 90% of women of childbearing age(10), whereas it involves a variety of physical, emotional and psychological symptoms experienced by some women during the late luteal phase of menstrual cycle (7 to 14 days prior to menstruation) (11).

Combined oral contraceptives (COCs), have been examined for their ability to relieve premenstrual symptoms (12). Although Marvelon® has been used in many countries; its efficacy has not been yet evaluated among Iranian women. Thus, this study aimed to determine the effective of the oral contraceptive pill on treating premenstrual symptoms and on various parameters associated with well-being and health in a sample of Iranian women.

Materials and Methods

Subjects

From January to November of 2009, we recruited sixty-one women referred to family planning-clinic of the centers under the supervision of Tehran University of Medical Sciences. The recruitment method used was based on a convenience sampling approach. Inclusion criteria were as follows:married,18-40 years old, normal body mass index ranged from 20 to 27 kg/m2, no use of any OCP during the last three months, a normal menstruation cycle for the last three cycles, having at least one of mental and behavioral symptoms during premenstrual period (fatigue, mood changes, lack of energy, irritability, aggression, depression, decreased concentration, decreased social relationships, having a greed and increased appetite to eating food),having at least one of physical symptoms (breast sensitivity, swelling and flatulence), and having a plan to use OCP for six consecutive months.

Women with the following conditions were excluded from the study: pregnancy; anorexia; bulimia; breastfeeding; smoke cigarette; using Marvelon® as a treatment for premenstrual syndrome (PMS);taking sleeping pills more than three days per month; as well as injection of estrogen, progesterone or androgen during the past three months. In addition, we excluded individuals with following contraindications for OCP including: thrombophlebitis, severe liver disease, cerebrovascular accident, heart disease, unexplained uterine bleeding, lupus, breast cancer, migraines, sickle cell anemia, epilepsy, gallbladder disease, kidney problems and family history thrombosis. The study was conducted in accordance with the Declaration of Helsinki.

The study received approval from the Ethics Committee of Tehran University of Medical Sciences. All participants gave their written consent after being informed about the purpose of the study.Subjects received Marvelon® (Aboreihan Co., Iran) including 30 μg EE and 150 μg DE in a blister pack containing 21 tablets with instructions to start the first tablet on the first day of their menstruation, taking one tablet per day, at intervals not exceeding 24 hours, daily pill intake of 21 days, and followed by 7 tablet-free days for a continuous period of six cycles. Assessments were performed at baseline and treatment cycles 1,2, 3 and 6.Lipid and lipoprotein assessment were collected in a laboratory at baseline (during the last 8 days of the pretreatment cycle) and at treatment cycles of 1,2, 3 and 6 (on days 15–21 of the respective cycles) .Subjects had fasted 14 hours before blood was drawn for lipid and lipoprotein determinations during the luteal phases of the menstrual cycle(on days 15–21 of the respective cycles).For each participant, weight and blood pressure were measured at study visits.

The questionnaire

Symptom information was collected by Calendar of Premenstrual Experiences (COPE), while the COPE was used as a self-report instrument in this study (13).The COPE has 22 items comprising 10 physical symptoms (including headache, breast tenderness, bloating and acne) and 12 psychological symptoms (including irritability, mood swings, angry outbursts and depression).

These items are rated on a 4-point Likert scale (0=

not at all, 1= a little, 2= somewhat, and 3= a great deal).

Moreover, a questionnaire was also used to collect demographic and clinical data. The questionnaire consisted of three parts. First part includes questions regarding age, age of menarche, number of pregnancies, childbirths, abortions and living children, time since last pregnancy, last childbirth method, method of contraception during the past 12 months, history of taking OCP and duration of using OCP. The second part includes some of clinical variables like weight, height, blood pressure, triglyceride level, high-density lipoprotein (HDL) level and low-density lipoprotein (LDL) level.

These questionnaires were completed by the women for five timing periods including; at baseline and the end of the first, second, third and sixth cycles. Before taking Marvelon® by the participant's necessary information were delivered, including symptoms, side effects, and forgetting consumption of OCP.

According to a study by Mortola JF *et al*., the items of COPE could be yielded 4 factors (13). Mood swings, angry, irritable, sensitive, crying, anxious, and alone and depressed could be located in factor 1. Fatigue, dizziness, confused, forgetful, hot flushes, palpitations, headache and nausea could be located in factor 2. Acne, Appetite and cravings could be located in factor 3. Finally, swelling, bloating and breast tenderness could be located in factor 4.The symptom scores of the 8 premenstrual days in the pre-treatment cycle and of the last 8 days in the treatment cycle were used as test variables.

Statistical analysis

Linear mixed model (LMM) regression was used to analyze changes of the four factors of COPE, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP)in each cycle compared to baseline assessment. Cycles were entered into the model by dummy coding. Clinical data including LDL, HDL and triglyceride levels were analyzed between two timing points (baseline and last visit) by paired t-test. Statistical analyses have been performed with statistical analysis software (SAS) version 9.1.

Results

The Sixty-one women participated in the study. The mean age of the women was 28.52 (SD=6.75).Our findings showed that, 20% of participants (n=12) did not experience any childbirth (nulliparus), while 80% (n=49) had 1.13 (SD=1.16) pregnancies and1. 41 children (SD= 2.21) on average, among whom31% (n=19) had a natural childbirth method). The most of the participants (n=38) used a non-hormonal contraceptive including condom, OCP) and intrauterine device (IUD). Lost to follow up percentage were 9.8%, 14.7% and 1.6% for first, second and sixth cycles, respectively. The characteristics of the participants are shown in table 1.

Tables 1. Demographic characteristics of the subjects

	Mean (SD)
Age (years)	28.52(6.75)
Number of pregnancies	1.13(1.16)
Number of childbirths	0.86 (0.99)
Number of abortions	0.33 (0.67)
Time since last pregnancy (months)	47.05(63.76)
Number of living child	1.41(2.21)
Method of contraception during the past 12 months	
Natural contraceptive method	15(24.6%)
Condom	19(31.2%)
OCP	12 (19.7)
IUD	8(13.1%)
Unknown	7 (11.5%)
History of taking OCP	
Yes	44(72.1%)
No	11 (18.0%)
Unknown	6.0(9.8%)

Values are given as percent (%) or Mean (SD)

Figure 1 shows all factor of COPE had a decreasing trend through time. Factor 1 was 1.24 at baseline on average and decreased to 0.67 at sixth cycle. Linear mixed model (LMM) analysis revealed that consumption of OCP had significantly lower rate of symptoms located in factor 1 in cycles (P<0.001). Moreover, factor 2 was 0.58 at first measurement and decreased to 0.33 at last follow-up. Analysis of LMM showed that symptoms located in factor 2 reduced significantly in cycles (P<0.01). Furthermore, the

analysis revealed that consumption of the OCP containing 30 µg ethinyl estradiol and 150 µg desogestrel had a significant effect on factor 3 after first cycle (P<0.05). On the other words, the OCP decreased symptoms including acne, appetite and cravings located in factor3, and the mean score of factor 3 changed from 0.74 at baseline assessment to 0.41 at sixth cycle. Factor 4 was 1.42 on average at baseline and decreased to 1.25 at last follow-up. Participants had a significant reduction in symptoms in factor 4 in all cycles (P<0.01) (Table 2).

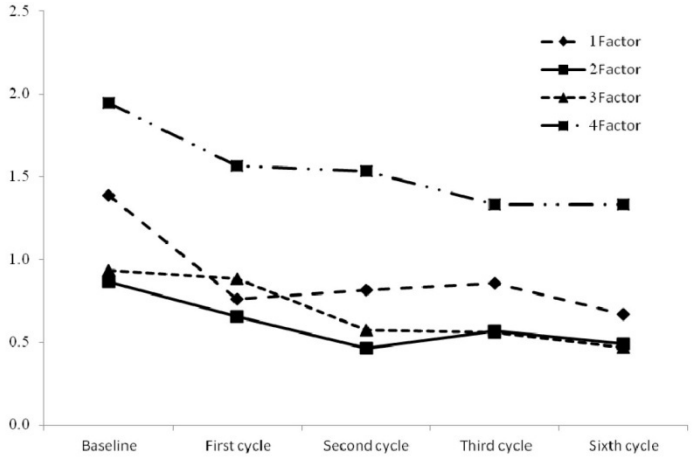

Figure 1. Trend of COPE factors on cycles

Table 2. Estimates from the Linear Mixed Model for COPE factors adjusting for age

	Response variable							
	Factor 1		**Factor 2**		**Factor 3**		**Factor 4**	
	β (SE)	***P*-value**	**β (SE)**	***P*-value**	**β (SE)**	***P*-value**	**β (SE)**	***P*-value**
First cycle	-0.63 (0.10)	<0.001	-0.25 (0.07)	<0.001	-0.08 (0.11)	0.449	-0.32 (0.10)	<0.001
Second cycle	-0.52 (0.13)	<0.001	-0.33 (0.09)	<0.001	-0.32 (0.13)	0.018	-0.33 (0.12)	0.007
Third cycle	-0.57 (0.12)	<0.001	-0.40 (0.09)	<0.001	-0.32 (0.12)	0.010	-0.58 (0.11)	<0.001
Sixth cycle	-0.66 (0.14)	<0.001	-0.28 (0.10)	0.007	-0.32 (0.15)	0.032	-0.51 (0.13)	<0.001
Age	-0.02 (0.01)	0.113	-0.02 (0.01)	0.016	-0.01 (0.01)	0.317	-0.01 (0.01)	0.437
Intercept	1.97 (0.36)	<0.001	1.55 (0.34)	<0.001	1.35 (0.41)	0.001	2.14 (0.26)	<0.001
$\hat{\sigma}_s^2$ **(subject)**	0.30 (0.07)	<0.001	0.23 (0.05)	<0.001	0.39 (0.09)	<0.001	0.11 (0.04)	0.003
Intra-class correlation	0.56		0.68		0.63		0.34	

Moreover, linear mixed model analyses were performed to assess the effectiveness of Marvelon® on blood pressure and weight on four cycles after treatment. The average weight of the participant was approximately unchanged through the study as it was 62.37 kg at baseline and reached 62.35 kg at sixth cycle. The analysis showed that Marvelon® did not have any significant effect on weight as the participant's weights were stable during assessment times (P>0.05) (Figure 2).

Figure 3 shows that systolic and diastolic blood pressures were partly stable through the time. As systolic and diastolic blood pressure were 99.5 and 64.0 mmHg at baseline and became 97.0 and 66.5 mmHg at final assessment, respectively Analysis showed Marvelon® had no significant effect on systolic and diastolic blood pressure(P>0.05) (Table 3).

Finally, results arose from paired t-test analysis showed that the OCP (Marvelon®) had no effect on clinical variables including LDL and HDL levels (Table 4). In addition, HDL and LDL levels were stable for two assessments (baseline and six month later). Furthermore, the participants had a higher level of triglyceride at the end of sixth cycles (six months later from baseline) in comparison with baseline.

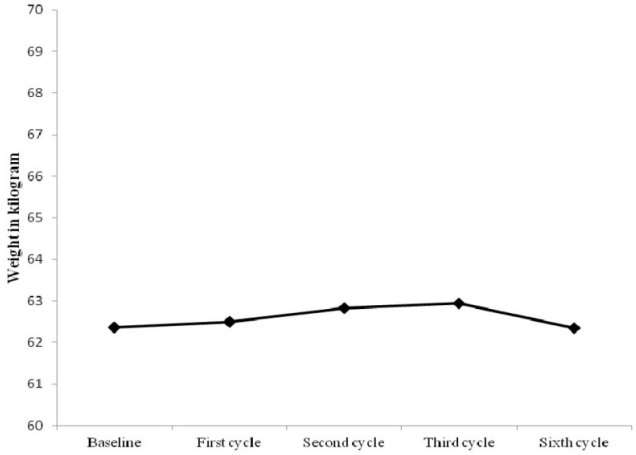

Figure 2. Weight trend on cycles

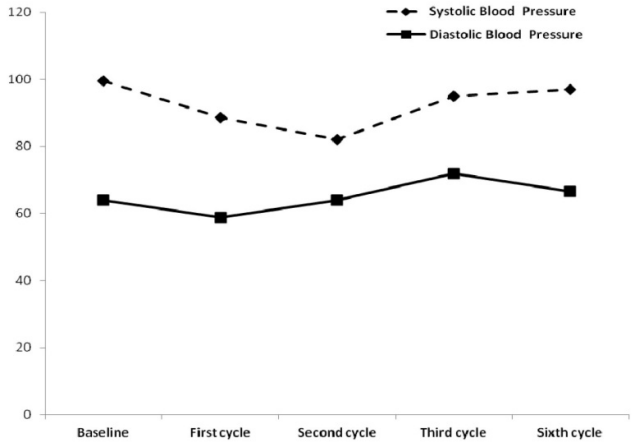

Figure 3. Systolic and Diastolic blood pressure trend on cycles

Table 3. Estimates from the linear mixed model for weight, SBP and DBP adjusting for age

	Response variable					
	Weight		SBP		DBP	
	β (SE)	*P*-value	β (SE)	*P*-value	β (SE)	*P*-value
First cycle	0.56 (0.35)	0.114	4.97 (3.95)	0.208	-1.77 (2.85)	0.535
Second cycle	0.50 (0.44)	0.255	-8.46 (4.75)	0.075	-2.47 (3.44)	0.474
Third cycle	0.22 (0.40)	0.587	4.66 (4.53)	0.304	5.84 (3.28)	0.075
Sixth cycle	0.71 (0.45)	0.114	8.51 (5.21)	0.103	4.99 (3.78)	0.185
Age	0.86 (0.19)	<0.001	0.46 (0.32)	0.159	0.66 (0.26)	0.011
Intercept	39 (5.58)	<0.001	77.57 (9.57)	<0.001	46.03 (7.68)	<0.001
$\hat{\sigma}_s^2$ **(subject)**	94.63 (17.69)	<0.001	123.18 (49.04)	0.012	95.02 (31.33)	0.002
Intra-class correlation	0.97		0.26		0.35	

Table 4. Comparison of clinical variables at two visits (base linea nd six months later)

	Baseline	Second visit (six months later)	*P*-value
	Mean (SD)	Mean (SD)	
LDL mg/dL	96.8(36.6)	96.0(42.3)	0.85
HDL mg/dL	62.6(34.8)	60.4(32.1)	0.28
Triglyceride level mg/dL	110.5(48.6)	133.9(39.4)	0.05

Discussion

The study was evaluated a unique OCs (Marvelon®) on premenstrual experiences in a sample of Iranian women. In general, the OCs had a positive effect on women's health as it reduces symptoms reported by the participants. To best our knowledge, this is the first study reporting short-term clinical experiences among Iranian women consuming Marvelon®. Walling *et al.*, assessed the efficacy and safety of Marvelon® in a multicenter study. They found that Marvelon®was generally well tolerated with excellent cycle control. Furthermore, there was no adverse effect on cervical cytology, blood pressure, and body weight or laboratory variables (14). In a randomized clinical trial in 2011, to compare complications of third and second-generation oral contraceptive pills (OCPs), 100 healthy Iranian women of reproductive age were included in a study, and results showed desogestrel (DSG) + ethinylestradiol (EE)is a contraceptive pill that significantly decreases the severity of acne and hirsutism, without any significant change in weight (15), which are consistence with our results. Our results also indicate that mental symptoms (Factor 1) reduced significantly after six months of using Marvelon®. Zaho *et al.,* evaluated the impact of Marvelon® on quality of life in Chinese rural women and found that the different aspects of life including health were improved significantly among these women using Marvelon® (16).A study by Backstorm (1992) about PMS mood changes on37 women revealed that there was a beneficial effect of OCP treatment on mood scores as compared with pretreatment control group), so it can be noted the monophasic DSG pill provokes less negative mood changes. These results showed desogestrel is less likely to cause adverse mood effects in the brain, which could be related to its lower androgenic effect (17).

This study is one group before and after cure and compares Marvelon® in reducing symptoms and has not been done with other types of birth control pills. We failed to include a control group to compare symptoms of using another type of birth control pills with our treatment group. Therefore, a comparative study with other types of OCP on PMS among Iranian women is recommended.

Our results also showed that the consumption of Marveon had a positive effect on Acne (Factor 3). Bilotta *et al,.* found that the incidence rates of both acne and seborrhea were also reduced with a monophasic OC containing DSG (18). They observed that after six cycles of treatment, preexisting acne had disappeared in more than 80% of the 1021 women with acne at baseline, so their findings support the use of low-dose OCs (such as Marveoln) for the treatment of acne.

In conclusion, the modern low-dose oral contraceptive (Marvelon®) has demonstrated beneficial effects on certain aspects of Iranian women's health, including mental health (Factor 1), physical symptoms (Factor 2), acne, appetite and cravings.

This study revealed that Marvelon® had no significant effect on LDL, HDL and cholesterol levels.

in a double-blind, randomized, two-center study in a total of 60 women over one year, plasma levels of lipids, lipoproteins and sex hormone binding globulin (SHBG), (except HDL-3, HDL-2, apolipoprotein A-1 and total phospholipids, were elevated, and the results confirmed a decrease in testosterone level (19).

More than 50 prospective studies have reported about the effects of the monophasic OC containing 30 mcg of ethinyl estradiol and 150 mcg of desogestrel. The results of a cross-sectional study between925 women receiving combination OCs and 418 untreated controls were reported that the desogestrel-containing OC induced a statistically significant increase in high-density lipoprotein cholesterol (HDL-C) in 40% of the observations and a decrease in low-density lipoprotein cholesterol (LDL-C) in 10% of the observations and (25% increase in plasma triglyceride levels compared). In this series, 54% of the studies reported an increase in HDL-C in women taking the desogestrel-containing OC (20).

When the estrogen component of hormonal contraceptives is administered orally, it tends to increase the production of lipoproteins. The effect of progestin's due to (androgenicity, dose and regimen are opposed some of the estrogenic responses (21).

The chemical structures of T-related progestin have been later modified to decrease the frequency of undesirable androgenic side effects such as acne, oily skin, and hair growth, and the negative effect on high-density lipoproteins (HDL), while to increase their progestational potency, thus allowing its use at lower dosages. New progestin has been developed from the progesterone structure to avoid the androgenic adverse effect (6,7,21). It is noted that the higher triglyceride concentrations are due to the estrogenic compound (22). So, effect on LDL cholesterol may suggest a slightly advantageous effect of Marvelon® in this aspect.

These results from clinical trials with EE/DOG indicate that it is a combined oral contraceptive with a

lack of androgenicity; therefore, it has a positive effect on body weight, skin and the symptoms of premenstrual syndrome. Overall, the comparative study with another OCP is recommended.

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