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Menstrual pattern and lipid profiles during use of medroxyprogesterone acetate and estradiol cypionate and NET-EN (200 mg) as contraceptive injections

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Abstract

The objectives of this study were to compare effects of medroxyprogesterone acetate 25 mg + estradiol cypionate 5 mg (Cyclofem) and norethisterone enanthate (NET-EN) upon the menstrual pattern and determine changes in lipoprotein parameters after 12 months of use. One-hundred females were included and 87 (45 with Cyclofem and 42 with NET-EN) women completing 12 months were evaluated. Menstrual changes were the leading complaint among users. At the end of 12 months, 20/45 (44.4%) and 18/41 (43.9%) Cyclofem and NET-EN users, respectively, had normal menstrual pattern. Irregular and infrequent bleeding were the two most important changes that occurred. The discontinuation rate at 12 months due to menstrual disturbances did not show any significant differences between the two preparations, but showed lower incidence compared to other studies. Total cholesterol, high-density, low-density and very low-density lipoprotein cholesterol and triglyceride levels decreased at 12 months in both groups and these changes were statistically significant.

Keywords: Lipid profiles; Injectables contraceptives; NET-EN; Cyclofem

1. Introduction

Injectable contraceptives have been shown to provide a safe and effective contraceptive option. There are two types of injectable contraceptives: progestogen-only injectable preparations and monthly combined injectable preparations. Progestin injectables are highly effective but side effects, especially abnormal uterine bleeding, limit their use [1–4]. The addition of estrogen to once monthly injectables results in more regular vaginal bleeding and mitigates the adverse effects of progestin-only injectables [5,6].

Depot medroxyprogesterone acetate and norethisterone enanthate (NET-EN) are the two progestogen-only injectable preparations currently available. Two once-a-month injectable contraceptive preparations, namely, Cyclofem and Mesigyna, have been developed by the Special Programme of Research in Human Reproduction of the World Health Organization; both have been proven to be effective contraceptives [7–9]. Women have used injectable contraception in developing countries since the 1960s. Today, nearly 12 million women worldwide use injectable steroid formulation progestin-only injectables and combined monthly contraceptive [1]. In Mexico it was reported that in 1997, the distribution of injectable contraceptive use was 4.6% among users of contraceptive methods [10].

The goal of monthly injectables was to decrease bleeding irregularities, including breakthrough bleeding (mid-cycle spotting requiring sanitary protection) and spotting (not requiring protection) as well as amenorrhea (absence of withdrawal bleeding) and other side effects that represent a major obstacle to compliance [11,12] and have repercussions on method continuity. However, this problem persists and some studies allow us to suppose differences in discontinuation due to bleeding may reflect population differences in tolerance to such problems, which may result from cultural or religious factors and compliance

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with the method will improve with adequate counseling [13,14].

Sufficient experience exists with NET-EN (200 mg administered every 60 ± 5 days), which indicates that the injectable offers desirable contraceptive efficacy but that it is associated with disruption of menstrual cycle in the majority of users [5,15]. Monthly injection of Cyclofem is efficacious and produces a more acceptable bleeding pattern [3]. The effect of contraceptive steroids on metabolism may have an important effect on cardiovascular health. Studies have shown that low levels of high density-lipoprotein cholesterol (HDL-C) increase risk of subsequent coronary heart disease in women [16–18].

It has been reported that users of injectables NET-EN and Cyclofem show decrease in plasma HDL-C of 20% and 12–16%, respectively [19,20]. Data suggest that the once-a-month combination products have considerably less effect on lipid metabolism, particularly on HDL-C [21].

Because there has been no direct clinical comparison of a bimonthly injectable (NET-EN) and monthly contraceptive injections in Mexican women, we proposed this study to compare the effects of two injectables on menstrual pattern and determine changes in lipoprotein parameters after 12 months of use.

2. Materials and methods

The study was conducted at the Family Planning Clinic of the Hideyo Noguchi Research Center in Merida, Yucatán, México, from January 1998 through September 1999, with users who voluntarily chose their contraceptive methods. A total of 100 sexually active women between the ages of 18 and 49 years were included in the study. Elegible subjects included nonlactating women, who were menstruating regularly (cycle length, 25–35 days) during the 6 months prior to enrollment and who had not received injectable contraceptives nor oral contraceptives in the 3 months prior to admission to the study.

Exclusion criteria were: pregnancy, lactation, active liver disease, severe hypertension (blood pressure >140/90 mmHg), diabetes mellitus, Papanicolau smear of stage III or more, disorders of lipid metabolism, epileptic disorders, migraine headaches, cerebrovascular disorders, history of thromboembolism, vaginal bleeding of unknown etiology, known or suspected malignancy, menstrual abnormalities and smoking (>l0 cigarettes per day). The method was chosen solely as an interval method of fertility regulation.

Before the injectable was administered, low-density lipoproteins (LDL), HDL, very low-density lipoprotein (VLDL), total cholesterol and triglyceride levels were measured in blood drawn from fasting subjects.

Cyclofem was administered once every 28 ± 5 days by deep intramuscular injection (i.m.) into the gluteus. NET-EN (200 mg) was given i.m. every 60 days ± 5 days. The first injection was administered within 5 days of start of the menstrual cycle. Subjects were requested to return each month or every 2 months, respectively, for repeat injections and follow-up. At each follow-up visit, medical history was recorded, relevant examinations were performed, menstrual pattern and side effects were recorded, and every effort was made to reassure participants concerning side effects, but they were free to discontinue at any time.

Women were required to maintain a menstrual diary card on which they recorded their bleeding patterns each day. At the end of 12 months, serum lipid measurements were repeated.

Measurements are expressed as mean ± standard deviation (SD). Differences between pretreatment and posttreatment serum lipid values and changes in weight and body mass index (BMI) and systolic and diastolic blood pressure within the same group were assessed with paired t test. A p value < 0.05 was considered statistically significant.

Comparison between the two groups regarding characteristics at admission and at the 12-month visit was carried out using two independent sample t tests.

The study was designed as a nonrandomized clinical trial, open label, controlled study. Treatment assignment was unblinded and based on decisions made by the women studied.

3. Results

A total of 100 women were enrolled for the study (50 with Cyclofem and 50 with NET-EN); 45 (90%) and 42 (84%) users, respectively, completed 1 year. The remaining subjects discontinued the method. Five women in the Cyclofem group discontinued (two for prolonged bleeding, one for irregular bleeding, one due to amenorrhea and one reported as lost to follow-up). In the group of NET-EN users, eight were reported as discontinuation (three for amenorrhea, one for prolonged bleeding, two for irregular bleeding and two lost to follow-up).

Table 1 shows the characteristics of the enrolled women. Both groups were comparable in all aspects except for initial mean age. There were no significant differences in parity, weight, height, education, blood pressure, and length and flow duration of menstrual cycle. Nonetheless, mean age of NET-EN users (36 ± 7.3 years) was significantly higher ($p < 0.05$) than mean age of Cyclofem users (29 ± 5.5 years). There was no statistical difference in mean body weight between both groups at initiation study (55.5 ± 8.1 and 55.0± 9.1 for Cyclofem and NET-EN, respectively). Both groups showed progressive increase in weight, which at the end of the year was 60.0 ± 8.8 and 63.0 ± 8.9 for Cyclofem and NET-EN, respectively. When we compared initial with final weight in each group, we found the changes were statistically significant ($p < 0.05$).

Table 1
Baseline characteristics of study participants

	Cyclofem (n = 45) Mean ± SD		NET-EN (n = 42) Mean ± SD	
Age	29.0 ± 5.5*		36.0 ± 7.3*	
Parity	3.9 ± 1.4		4.1 ± 1.7	
Weight (kg)				
Initial	55.5 ± 8.1		55.0 ± 9.1	
Final	60.8 ± 8.8		63.0 ± 8.9	
Height (cm)	146.0 ± 4.2		147.0 ± 3.4	
BMI (kg/m^2)				
Initial	25.7 ± 3.9		26.0 ± 4.3	
Final	28.3 ± 4.5*		29.3 ± 4.4*	
Blood pressure (mmHg)				
Systolic	110.4 ± 8.0		114.0 ± 9.0	
Diastolic	80.0 ± 5.6		78.0 ± 3.2	
Education (y)	n	%	n	%
None	7	15.9	6	14.6
1–6	25	56.8	22	53.6
7–12	10	22.7	9	21.9
> 12	2	4.5	4	9.7

* $p < 0.05$.

3.1. Lipid fractions

Changes in serum lipoprotein are shown in Table 2. Total cholesterol, HDL-C, LDL-C, VLDL and triglyceride levels all decreased at 12 months in both groups and these changes were statistically significant.

3.2. Menstrual pattern

Menstrual changes were the leading complaint among users. At the end of 6 months, no change in menstrual pattern occurred in 28/45 (62.2%) and in 22/41 (53.6%) Cyclofem and NET-EN users, respectively, while at the end of l2 months, 20/45 (44.4%) and 18/41 (43.9%) Cyclofem and NET-EN users, respectively, had normal menstrual pattern.

At the end of 12 months, incidence of amenorrhea in the first group was 8.9% (four cases), in the second group, amenorrhea occurred in 12.3% (five cases); eight and six (17.8% and 14.6%, respectively) presented infrequent bleeding; only two women (4.4%) and one (2.4%) presented frequent bleeding; eight (17.8%) and nine (21.9%), irregular bleeding and three (6.7%) and two (4.8%) had prolonged bleeding. Therefore, irregular and infrequent bleeding were the two most important changes that occurred (Table 3). There were no pregnancies in either of the study groups.

Table 3
Bleeding pattern at the end of 12 months in the Cyclofem and NET-EN groups

	Cyclofem		NET-EN	
	No.	%	No.	%
Amenorrhea	4	8.9	5	12.3
Infrequent bleeding	8	17.8	6	14.6
Frequent bleeding	2	4.4	1	2.4
Irregular bleeding	8	17.8	9	21.9
Prolonged bleeding	3	6.7	2	4.8
Total	25	55.6	23	56.0

4. Discussion

The effects of injectables on lipid metabolism may be important because of association of adverse lipid patterns with atherogenesis and cardiovascular disease of women. In our study, a nonrandomized clinical trial, we confirmed findings in other countries in which changes in lipid metabolism were observed during treatment in women with injectables [1,7,20,22,23] and these changes were similar in both groups (Cyclofem and NET-EN users). The data suggested that the once-a-month combination injectable has considerably less effect on lipid metabolism, particularly on HDL-C [1,7]. Although there was no regimented diet or exercise, it is reasonable to assume that both treatment groups had similar biases.

Disruption of regular menstrual bleeding and amenorrhea is the most common side effect of injectables and the main reasons women stop using them. The majority of users reported weight gain. Thus, during counseling, all women who choose injectables should be told of these likely

Table 2
Serum lipoprotein levels of study participants

	Cyclofem		NET-EN	
	Preinjection	At 12 months	Preinjection	At 12 months
HDL-C	50.0 ± 9.0	42.5 ± 5.5*	52.1 ± 8.8	43.07 ± 5.5*
LDL-C	75.5 ± 35.5	68.4 ± 35.5*	82.0 ± 42.2	75.2 ± 41.3*
Cholesterol	156.5 ± 45.5	152.1 ± 34.3*	165.7 ± 49.2	160.6 ± 44.6*
Triglycerides	108.0 ± 45.1	98.2 ± 46.4*	118.0 ± 50.1	106.3 ± 48.2*
VLDL	24.0 ± 18.8	20.0 ± 13.3*	25.9 ± 14.0	21.2 ± 13.2*

Values are mean ± SD.
* $p < 0.05$.

changes. Program managers need to decide what other side effects to mention based in part on side effects most often reported by clients. These decisions should be made with the goal of helping clients to make a fully informed choice and to use the method effectively and confidently and to improve continuity of the method. In our study, the rate of irregular bleeding among Cyclofem and NET-EN users (55.5 and 57.1%, respectively) at 12 months was higher than reported in other studies [7,24,25]. Likewise, although several reports show that the majority of women experienced regular menstrual cycles at the end of 6 months, our users presented more disturbances at the end of 12 months. We do not know whether this is due to greater BMI.

The higher continuation rate at 12 months in our users in spite of menstrual disturbance was probably due to counseling provided at the clinic, although cultural attitudes may play a significant role in continuation of any contraceptive method. Recently, one article concluded that strengthened counseling on method acceptance was identified as a strategy to decrease frequency of breaks in injectable method use [26].

We conclude that both injectables (Cyclofem and NET-EN) cause disturbances in menstrual cycles. However, discontinuations due to bleeding problems were significantly lower in the present study, than in other reports [5,7,9,12,25]. Similarly, results of this longitudinal study on serum lipids in Mexican women confirm other findings in users in other countries [7,23,24,27].

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