

Original research article

# Effect of etonogestrel implant on serum lipids, liver function tests and hemoglobin levels

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## Abstract

**Background:** This study aimed to assess the possible effects of etonogestrel implant (Implanon®, Organon, Oss, The Netherlands) on total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and Hb levels in a sample of Turkish population.

**Study Design:** Healthy women of childbearing potential who had applied to our Family Planning Clinic for a contraceptive method and had chosen to have an Implanon insertion after thorough counseling about all family planning methods and screening for eligibility for Implanon use were enrolled in the study. Serum concentrations of TC, TG, HDL-C, LDL-C, AST, ALT and Hb levels were tested before and at 3 and 6 months after insertion. Baseline mean parameters were compared with mean parameters at 3 and 6 months for statistical significance using paired-samples *t* test.

**Results:** Eighty-two women eligible for the study were included. Mean age of the patients was 27.5±4.8 years. When compared to the baseline values, there was a statistically significant decrease in the TC ( $p<.001$ ), HDL-C ( $p<.001$ ) and TG ( $p=.006$ ) at the end of the third month, while there was a significant increase in Hb values ( $p=.01$ ). The decrease in TC ( $p=.001$ ) and HDL-C ( $p<.001$ ) and increase in Hb value ( $p=.03$ ) persisted by the end of sixth month while the decrease in TG was transient. A statistically significant increase in mean ALT level was observed at 6 months ( $p=.03$ ).

**Conclusion:** The effect of Implanon on liver functions and lipid metabolism does not lead to unhealthy alterations. Increase in Hb can be attributed to the high frequency of amenorrhea in patients.

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*Keywords:* Etonogestrel implant; Hemoglobin; Serum lipids; Liver function tests

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## 1. Introduction

Hormonal contraceptives, in particular combined oral contraceptives, are well known to affect the metabolic system and induce changes in serum lipids and lipoproteins. However, the metabolic effect of progestin-only contraceptives has been subject to investigation recently as subdermal contraceptive implant systems that provide a sustained release of low levels of progestins have been under development for over two decades. The Norplant system, which releases low levels of levonorgestrel, has long been the most widely available of progestin implants. Newer,

second-generation systems such as Implanon have recently become available [1]. The advantages of this estrogen-free contraceptive method over combined hormonal contraception can be summarized as high efficacy, good patient compliance and rapid return of fertility after discontinuation and safe use in adolescents, breast-feeding women and in women with hypertension, diabetes or anemia. Adverse effects shown in various studies are changes in bleeding patterns, weight gain, acne, breast pain, breast tenderness and headache [2].

Implanon® is a single-rod, 4 cm in length and 2 mm in diameter, containing approximately 68 mg of etonogestrel, synthetic biologically active metabolite of desogestrel in a polyethylene-vinyl acetate copolymer membrane [3]. The contraceptive effect of etonogestrel that binds strongly to the progesterone receptors is mainly based on two mechanisms: (1) prevention of the mid-luteal peak luteinizing hormone

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(LH) by inhibition of LH release; (2) decreasing the permeability of the cervical mucus for sperm penetration by increasing the viscosity of cervical mucus [4]. It also alters the endometrial lining, thus affects implantation.

After subdermal Implanon insertion, etonogestrel rapidly passes into circulation and serum levels reach levels sufficient for ovulation inhibition within 8 h after insertion [5]. The peak serum level of 813 pg/mL is reached in 4 days and then reaches steady-state values that will continue to suppress ovulation and remain within these limits for 3 years [5]. The estrogen levels remain within early or mid-follicular levels and follicle-stimulating hormone levels are almost normal while progesterone levels remain within the subovulatory range [6]. Etonogestrel has an elimination half-life of 25 h and is eliminated from the blood stream within a week after implant removal. Ovulation is observed within 3–4 weeks, enabling a prompt return of fertility in most of the cases [5].

Etonogestrel is highly protein bound and is transferred in blood stream bound to sex hormone-binding protein (32%) and predominantly albumin (68%). It is metabolized in the liver through P450 3A4 (CYP 3A4) isoenzymes into 3-keto-desogestrel and most of etonogestrel and its metabolites are excreted renally [5]. The metabolic effect of Implanon has been an area of interest. Published studies about the effects of Implanon® on lipid, liver function, metabolism and hemoglobin (Hb) levels are limited in comparison to combined oral contraceptives [7,8]. Implanon was registered in Turkey in 2002, and the aim of this study is to evaluate the effect of Implanon on total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and Hb in a sample of Turkish women at 3 and 6 months after insertion.

## 2. Materials and methods

Healthy volunteers of childbearing potential who had applied to our Family Planning Clinic for a contraceptive method and had chosen to have an Implanon insertion after thorough counseling about all family planning methods and screening for eligibility for Implanon use were enrolled in the study after having signed informed consent. Approval was obtained from the local ethics committee of our hospital.

Inclusion criteria included age (19–41 years), being mentally and physically healthy, body mass index (BMI) between 18 and 32 kg/m<sup>2</sup>, and normal pretreatment routine hematological and biochemical analyses. Exclusion criteria were smoking, irregular menstrual bleeding, depression, hypertension, diabetes mellitus, anemia, known or suspected pregnancy, current or past history of thrombosis or thromboembolic disorders.

Following a thorough history and gynecologic examination, etonogestrel implants (Implanon®, Organon, Oss, The

Netherlands) were inserted subcutaneously in the medial aspect of the nondominant upper arm to all subjects. The age, BMI, parity and the educational level of each woman were recorded. Serum concentrations of TC, TG, HDL-C, LDL-C, AST, ALT and Hb levels were tested before and at 3 and 6 months after insertion. The patients were given a calendar and were asked to record their bleeding and spotting days by marking the calendar. The bleeding patterns were evaluated using the bleeding calendars at the end of 6 months.

HDL-C concentrations were measured with enzymatic clearance assay (Randox Laboratories, UK) [9]. TG and TC were measured using automated analyzer equipment (Beckman Coulter LX 20) and reagents from Beckman Coulter (Ireland) [10]. LDL-C was calculated by the Friedewald formula since our TG concentrations were all <400 mg/dL. AST and ALT were measured by an automatic biochemical analyzer (Vitros Fusion 5.1, Ortho Clinical. Diagnostics, Johnson & Johnson Co., Rochester, NY) [11]. Hb levels were measured by the cyanmethemoglobin detection method (with computerized fully automated hematology analyzer; SE-9000, Symex, Kobe, Japan) [12]. All baseline parameters tested were within the laboratory reference ranges. The study was longitudinal, with each subject acting as her own control.

Statistical analysis was performed by using SPSS 10.0 for Windows (SPSS, Chicago, IL, USA). Descriptive statistics are shown as arithmetic mean±SD. After the tests of normality, we used paired-samples *t* test to investigate the differences between two groups. Comparisons of frequency variables were done using the McNemar test. A *p* value of <.05 was considered as statistically significant [13].

## 3. Results

Eighty-two women eligible for the study were included. The continuation rate was 82.9%. When the bleeding patterns were evaluated, 24 patients were amenorrheic (29.6%), while 27 (33.3%) had infrequent bleeding/spotting and 8 (9.8%) had frequent bleeding/spotting episodes. Prolonged bleeding/spotting episodes were observed in 7 patients (8.6%), while 15 patients (18.5%) had normal cycles. Fourteen women (17.1%) discontinued use of the implant because of dissatisfaction with bleeding patterns at the end of the sixth month. The reason for discontinuation was prolonged bleeding/spotting episodes (*n*=7, 8.6%), frequent bleeding/spotting episodes (*n*=4, 4.9%) and amenorrhea (*n*=3, 3.7%).

Mean age of the subjects was 27.5±4.8 years. The mean duration of time from their last pregnancy was 24.3±37.3 months. The gravidity and the parity of the patients ranged from 1 to 8 and from 0 to 3, respectively. Mean BMI of the women was 23.6±3.8 at the time of insertion. Forty-one patients (50%) completed primary school, 12 patients (14.6%) were secondary school graduates and one patient (1.2%) was illiterate. Four patients (4.9%) had graduated

from university, while the remaining 24 (29.3%) completed high school. There was no contraceptive failure during the study period.

The results of laboratory tests at the beginning, at three months and at six months are presented in Table 1. When compared to the baseline values, there was a statistically significant decrease in the TC ( $p<.001$ ), HDL-C ( $p<.001$ ), TG ( $p=.006$ ) at the end of the third month, while there was a significant increase in Hb values ( $p=.01$ ) (Table 1). Nevertheless, the decrease in TC and HDL-C and increase in hemoglobin value persisted by the end of the sixth month while the decrease in TG was transient.

Mean changes in TC ( $p=.001$ ), HDL-C ( $p<.001$ ), ALT ( $p=.03$ ) and Hb ( $p=.03$ ) levels were statistically significant at the end of the sixth month. Baseline mean TC and HDL-C levels were 160.23 and 49.5 mg/dL and decreased to 153.2 and 42.7 mg/dL 6 months later, respectively (Fig. 1). Although mean TG and LDL-C concentrations tended to decrease during the study period, these slight decreases from baseline levels were statistically nonsignificant.

Total cholesterol/HDL ratio  $>5$  as a risk factor for coronary artery disease was observed in three women (3.7%) at the beginning of the study. High TC/HDL ratio ( $>5$ ) was observed in 6 women (7.3%) at the third month and in 2 women (2.4%) at the sixth month of follow-up ( $p=.30$ ).

A statistically significant increase in mean ALT level was observed at 6 months. Mean baseline value of ALT was 17.9 and 20.9 U/L at 6 months. A slight increase was also seen in mean AST levels, but this increase was not significant ( $p=.1$ ). Statistically significant elevation in mean Hb levels (from 13.2 to 13.6 g/dL) was observed at the sixth month (Fig. 2). No statistically significant differences were observed between the initial and sixth-month follow-up levels of LDL-C, TG and AST.

**4. Discussion**

Implanon is a reliable, long-acting reversible method of contraception with a Pearl index of 0.05 [14]. No pregnancy was observed in the Implanon users during our study.

Alterations in bleeding patterns are common among Implanon users. In our patient group, most of the patients

Table 1  
Laboratory tests results at preinsertion, at third month and at sixth month of the study

Variable	Baseline	Third month	Sixth month
TC (mg/dL)	160±37	151.6±28*	153±28*
HDL (mg/dL)	49.5±12	42.8±11.2*	42.7±10*
LDL (mg/dL)	96.8±30	97.2±25	97.4±23
TG (mg/dL)	68.8±56	57.3±38*	62.4±34
AST (U/L)	20.5±4.3	20.3±3.8	21.8±5.9
ALT (U/L)	17.8±6.6	17.3±6.4	20.8±11*
Hemoglobin (g/dL)	13.2±1.3	13.6±1*	13.5±0.9*

\* Statistically significant difference from baseline value ( $p<.05$ ).

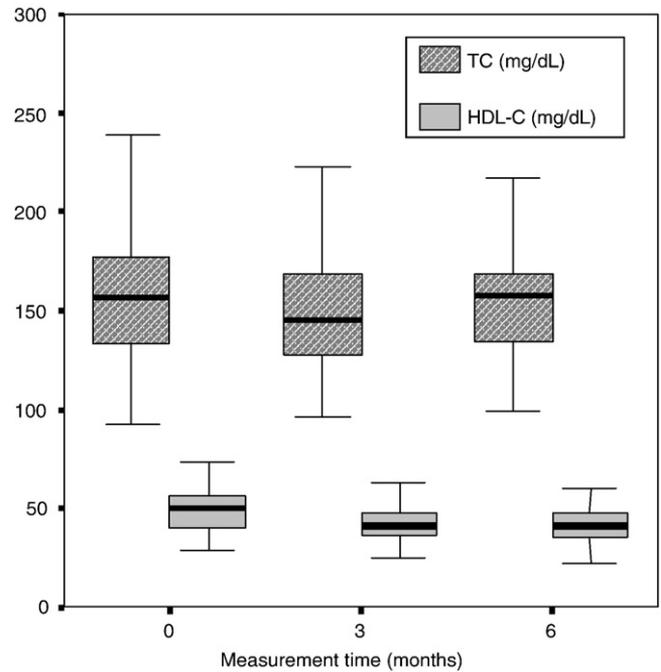


Fig. 1. Change in TC and HDL-C with time. Boxes represent median and interquartile range of TC and HDL-C in milligrams per deciliter.

were amenorrheic (29.6%), had infrequent bleeding/spotting (33.3%) or had normal cycles (18.5%). Analysis of the data about uterine bleeding from 11 clinical trials using reference periods by Mansour et al. [15] showed that the most common bleeding patterns observed in women using Implanon were amenorrhea (22.2%), infrequent (33.6%), frequent (6.7%) and/or prolonged bleeding (17.7%), and although the bleeding episodes were found to be unpredictable, bleeding–

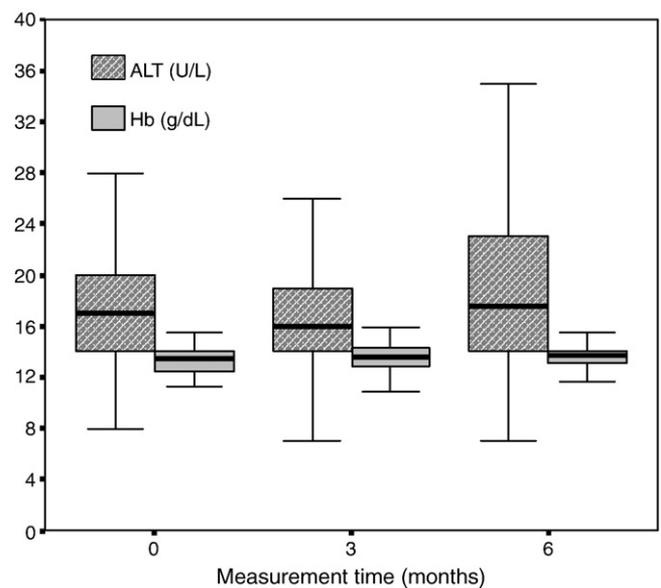


Fig. 2. Change in ALT and Hb with time. Boxes represent median and interquartile range of ALT level in U/L and Hb level in grams per deciliter.

Table 2  
Summary of studies on effect of Implanon on lipid profile

Investigator	No. of patients	Follow-up period	Results
Biswas et al. [20]	40	6, 12, 24 months	Decrease in TC, HDL-C and LDL-C levels during the 2 years of use, changes apparent at sixth month of use Decrease in TG is not statistically significant No significant change in HDL/TC ratio Significant decrease in HDL-C/LDL-C ratio after 1 year of use
Inal et al. [21]	70	3 years	No difference in LDL-C and HDL-C Increase in TC and TG
Yildizbas et al. [16]	41	6 months	Decrease in TC
Merki-Feld et al. [22]	18	3 months	Significant decrease in TC, HDL and LDL No change in T-C/HDL ratio
Suherman et al. [7]	90 (vs. Norplant and IUD users)	3, 6, 12, 18, 24, 36 months	TC, LDL and apolipoprotein AI concentrations tended to decrease during the study, but statistically significant changes from baseline were only occasionally observed, mean ratios of HDL/TC and the HDL/LDL cholesterol showed statistically nonsignificant increases.
Present study	82	3 months and 6 months	Decrease in TC and HDL at third month Decrease in TC and HDL is persistent at the sixth month

spotting days were found to be fewer than or comparable to those encountered during natural cycles in 75% of the reference periods. Rate of amenorrhea was found to be fairly high in our study group compared to the rates given in the literature; however, two studies from Turkey have reported an amenorrhea rate of 34.1% and 33%, much higher than given in the literature [16,17]. The statistically significant increase in Hb levels (Hb-pre: 13.2±1.3 g/dL, Hb-6th: 13.5±0.9 g/dL) in the present study can be explained by the high frequency of amenorrhea and infrequent bleeding/spotting episodes (overall 62.9%) observed in our patient group.

Progestin-only methods are known to cause irregular and unpredictable bleeding in some cases, and this leads to decreased acceptability. The continuation rate in our study group was 82.9% at the end of 6 months. Changes in bleeding patterns were the main reason for discontinuation in our patient group, similar to those reported in most series [18]. Counseling prior to Implanon insertion emphasizing the expected changes in menstrual pattern is strongly advised in order to reduce premature method discontinuation. The premature discontinuation rate in our patient group is compatible with the rates given in the literature [19]. In a study from Turkey, Yildizbas et al. [16] reported a premature method discontinuation rate of 19.5% at the end of sixth month of Implanon use. Gezginc et al. [17] reported a discontinuation rate of 25%.

The results of the studies on the effect of Implanon on lipid metabolism are given in Table 2 [7,16,20–22]. Though decrease in TC is an advantage, decrease in HDL-C is an unwanted effect. This point has clinical importance because increase in TC and decrease in HDL-C are well-known risks for coronary heart disease. The decrease of HDL-C in our study group is highly unlikely to be related with increased cardiovascular disease risk as HDL-C levels were within the ranges of normal reference values and did not fall to a value below normal in any of the subjects. The change in TG was transient.

Egberg et al. [8] evaluated liver functions of Norplant and Implanon users over a 6-month period and observed decreases in ALT and AST levels in both groups, while Biswas et al. [23] found ALT and AST unchanged. Inal et al. [21] observed no changes in AST and ALT levels at the end of 3 years of Implanon use in 70 patients. While a statistically significant increase in mean ALT level was observed at 6 months, the increased levels were within normal limits in our study group and there was a slight increase in mean AST levels that was not statistically significant. Nasr and Nafeh [24] reported a significant decrease in ALT and AST levels although the changes were within normal limits. There is no evidence of impaired liver function with Implanon use in the literature; however, a mild hepatic dysfunction might be thought to be associated with Implanon use [23].

Implanon is a safe, reliable, long-acting reversible method of contraception. The effect of Implanon on liver functions and lipid metabolism do not lead to unhealthy alterations. The rate of amenorrhea was found to be higher than expected. The published articles in the literature about the pattern of menstrual changes among Turkish women were slightly different from the data from other series. This matter requires further multicentric studies with higher numbers of recruitment.

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