Original Article

The effects of etonorgestrel implant (Implanon^{R}) on the lipid profile of Nigerian women

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ABSTRACT

Background: Provision of contraceptive methods with minimal side effects will enhance uptake of contraception particularly in Nigeria where contraceptive prevalence rate remains low. The safety profile of Implanon^{R}, a long-acting hormonal subdermal contraceptive containing etonogestrel, has not been adequately evaluated among Nigerian women.

Objective: To assess the effects of etonogestrel subdermal implant (Implanon^{R}) on lipid profile among Nigerian women.

Materials and Methods: The study was a longitudinal follow-up of 54 consenting women selected over a 6-month period at the Family Planning Clinic of the University College Hospital, Ibadan. After Implanon^{R} insertion, each woman was followed-up monthly for a period of 12 months. Fasting venous blood samples were collected for quantification of serum lipids prior to insertion of the implant, then at 1st, 3rd, 6th, 9th, and 12th months of follow-up.

Results: The mean age of the women was 34.4 ± 5.6 with a range of 22–47 years. The modal number of children was 2 ranging from 1 to 6. Total cholesterol (TC) levels showed a general tendency toward a rise. The rise was, however, only significant in the 3rd and 12th months of use. Serum triglycerides showed a tendency toward reduced levels, which were only significant at the 6th and 9th months of use. High-density lipoprotein (HDL) levels were consistently and significantly elevated above baseline levels. Beyond the 3rd month, low-density lipoprotein (LDL) levels were lower but not significantly compared with baseline levels. HDL/TC and HDL/LDL ratios were consistently and significantly elevated in comparison with baseline values.

Conclusion: Etonogestrel implant seems to cause significant effects on the lipid profile of Nigerian women. The increases were mainly in the HDL fraction, which suggests that the atherogenic and cardiovascular disease risks are reduced. We recommend larger studies to confirm our findings.

Key words: Implanon; laevonorgestrel; subdermal implant.

Introduction

Recent developments in hormonal contraceptives have been directed toward lowering the dosage of steroid hormones to minimize their risk potentials: ischemic heart disease, stroke, myocardial infarction, thromboembolism, and changes in the blood clotting mechanism.[1]

Contraceptive implants are a milestone in contraceptive delivery systems for improving the quality of family planning programs. Up to 10 potential contraceptive implants have been tested in 5,000 women in the last three decades.

Their introduction was necessitated to ameliorate some side effects associated with previous contraceptives. Subdermal

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contraceptive implants provide constant delivery of a very low dose of progestin that offers effective contraception. The six-capsule levonorgestrel system (Norplant) was the first subdermal contraceptive implant introduced and it is estimated that approximately nine million women worldwide have used or are using this method.[2] Unlike other hormonal delivery systems, they do not cause unnecessary peaks in progestin levels and do not use estrogens, and thus, their health risks are minimal.

Thromboembolism has been shown to be the most fatal complication,[3] and over 75% of deaths result from ischemic and hypertensive heart diseases.[4] One of the major causes of morbidity and mortality worldwide is cardiovascular disease. In 2008, cardiovascular disease accounted for 31% of all global deaths, of which 80% occurred in developing countries.[5] Metabolic risk factors include obesity, hypertension, type 2 diabetes mellitus, high serum cholesterol, and dyslipidemia.[6]

Estrogen and progesterone levels present in contraceptives have different and sometimes opposite effect on lipid metabolism. Estrogen increases serum level of high-density lipoprotein cholesterol (HDL-C) whereas progesterone reduces HDL-C level and increases serum low-density lipoprotein cholesterol (LDL-C) leading to increase chances of thromboembolism.[7] Some of the metabolic risk factors for cardiovascular disease can arise consequent to the use of hormonal contraceptives.

Progestin hormonal contraceptives have been implicated in the possible alteration of lipid levels and transport mechanisms that are responsible for the risk of arterial thrombosis.[8] Similarly, 19-nor-steroid derivatives such as levonorgestrel have been reported to have a strong androgenic effect and may cause a significant alteration in the lipid profile thus, worsening the atherogenic indices.[9] These shortcomings led to the discontinuation of Norplant[10] and heralded the universal use of Implanon^{R}. The vast majority of evidence on implants arises from studies of levonorgestrel and other progestins and permit similar drug release from only one to two implants rather than six, leading to faster and easier placement and removal.[11]

Low dose progestin-only contraceptives may have deleterious effects on lipid profile. A study comparing the effects of non-hormonal contraceptive, combined oral contraceptive, and depo-medroxyprogesterone acetate (DMPA) on lipids reported that the depo-medroxyprogesterone acetate users gained significantly more weight compared with other groups and the patterns of change in LDL-C and triglycerides were not significantly different among groups. The significant change in HDL-C was observed only in combined oral contraceptive and nonhormonal contraceptive groups.[12] However, in a study by Okeke *et al*.[13] There was a significant change in triglyceride and LDL-C levels when comparing the effects of injectable and oral hormonal contraceptives on lipid profile. There was increase in the triglyceride levels but decrease in LDL-C levels in the injectable contraceptive group. There was no statistically significant change in total cholesterol and HDL-C levels in women on oral contraceptives but HDL-C was significantly increased in injectable contraceptive group.[13] A study evaluated effects of Norplant compared with depo-medroxyprogesterone acetate and low-dose oral contraceptives on lipid profile. There was decrease in the total cholesterol and LDL-C levels in all groups except depo-medroxyprogesterone acetate group where there was an increase. Triglycerides only increased in the oral contraceptive group. HDL-C increased with the oral contraceptives and decreased with Norplant and depo-medroxyprogesterone.[14]

Implanon is a reversible, long-acting, subdermal hormonal contraceptive with etonorgestrel (3-keto-desogestrel) as active ingredient. It is a progestogen-only method using a single-rod system with a disposable applicator. The method is suitable for a wide range of women: to postpone a first pregnancy, "space" pregnancies, and provide reversible, long-term contraception when the desired family size is reached. Each Implanon^{R} implant contains 68 mg of etonogestrel, the active metabolite of desogestrel, which is used in COC pills. The clinical pharmacology for desogestrel and etonogestrel has been well established. Implanon avoids the first-pass effect of orally taken hormonal contraceptives through the liver and has a potentially different clinical pharmacology.[11]

Since the introduction of Implanon, its effects on the lipid profile of users have not been comprehensively evaluated. The use of hormonal contraceptives has been associated with increased cardiovascular risk,[5] so also progestins have been associated with an increased risk of arterial thrombosis.[8] Race and ethnic groups may alter effect of progestins on lipid profile.[15] Studies on effects of Implanon on lipid metabolism serum immunoglobulins, albumin, and total proteins have not been reported in Nigeria. In view of these, we decide to determine the safety, considering the cardiovascular risks of Implanon^{R} use, among Nigerian women as regards its effects on their serum lipid profile.

Materials and Methods

This was a longitudinal study of apparently healthy clients of the Family Planning Clinic, University College Hospital, Ibadan. The sample size was calculated using previously

established methods.[16] The sample size was based on techniques described by Pocock.[17] Assuming a statistical power of 0.9 with 95% confidence, the minimum number of clients required to demonstrate a 15% change in serum level of cholesterol with a presumed drop-out rate of 20% is 44. The recruitment of subjects was over 6 months. Sixty consecutive clients were recruited. They were followed-up monthly for a period of 12 months.

Eligibility criteria included being women of reproductive age (18–45 years) who were not on any other medication. They had no contraindications to the use of hormonal contraceptives and were willing to use hormonal contraception as a method of fertility control for at least 1 year. Their menstrual cycles during the previous 3 months had been regular and they were living in the locality to allow adequate follow-up. They used Implanon^{R} alone for contraception.

The exclusion criteria were previous history or on-going thrombo-embolic disease, use of hormonal contraception in the preceding 6 months, presence of varicose veins or hypertension (BP ≥ 140/90 mm Hg), presence of liver disease or endocrine condition, especially diabetes mellitus. Others were the presence of mental disorders or known allergy to silastic materials or heavy smoking. Ethical approval was obtained from joint UI/UCH ethical committee.

After recruitment of participants, written informed consent was obtained followed by documentation of baseline characteristics including weight, height, and blood pressure. Baseline blood sample (10 ml of fasting venous blood) was taken and serum lipids: total cholesterol (TC), triglycerides (TG), LDL-C, and HDL-C were measured. The data were recorded on a proforma.

Each subject was seen between 8:00 and 9:00 a.m., and the insertion was performed by a trained personnel with the woman lying on her back using an aseptic technique. The insertion site was the sulcus bicipitalis medialis of the nondominant arm. After skin preparation and draping, 1% lignocaine local anesthetic infiltration was applied. The skin of the site was stretched and the preloaded inserter was used to penetrate the skin with the implant deposited in the subdermal area just like the reverse of an injection.

The follow-up involved monthly visits up to 12 months with a menstrual diary kept by each participant. At each visit, the participant's clinical status was reviewed with the findings carefully recorded in the follow-up cards. The menstrual diary was designed to keep a record of the menstrual flow and bleeding episodes. Fasting venous blood sample was collected at the 1st, 3rd, 6th, 9th, and 12th months following insertion and the participant's weight was also measured.

Fasting venous blood (10 ml) was collected from the antecubital vein of either arm, after application of a tourniquet, into an anticoagulant-free tube. After clot retraction, the bottle was spun at 3,000 rpm for 5 min followed by separation of sera and storage at −20°C until analysis was carried out at the end of the study. Serum total cholesterol and triglycerides were measured with a Hitachi 704 auto analyser (Boeringer Mannheim, Mannheim, Germany) using fully enzymatic procedures as in the commercial kits supplied by the company.[18] HDLs were measured after selective precipitation of LDL using phosphotungstic and magnesium chloride reagents. LDL was also estimated according to the method of Friedwald *et al*.[19]

We employed Microsoft Excel (Microsoft, Redmond, WA) version 8 for data entry whereas data analysis was performed with SPSS version 17. Mean levels at the 1st, 3rd, 6th, 9th, and 12th months for the various parameters were compared with the preinsertion value using the independent "*t*" test to determine the level of significance of any observed differences. The value of $P < 0.05$ was regarded as significant.

Results

The study was conducted between June 2008 and June 2010. Of the 60 women recruited, 54 women completed the study. The mean age of the women was 34.4 ± 5.6 years whereas the range was 22–47 years. The modal number of children was 2 with a range of 1–6. The serum levels of the various lipid fractions are as reflected in Tables 1 and 2.

Discussion

Implanon^{R} is acceptable to Nigerian women. In Jos, Implanon^{R} was accepted by almost 15% of contraceptive users with high continuation rates.[20] In Benin, no remarkable changes in weight or BP were reported among users.[21] In a recent study,[22] it was found that implanon users had higher diastolic blood pressure than the oral contraceptive or injectable contraceptive users. Women using oral contraceptives for more than 8 years presented higher age-adjusted blood pressure levels than women using oral contraceptives for shorter periods. An increase in diastolic blood pressure is a common feature of hormonal contraceptive use.

Menstrual changes are the major issues with the Implanon^{R} users. Its biochemical or hormonal effects among Nigerian women has not been fully evaluated. Studies in Europe[23,24] and

Table 1: Total cholesterol, triglycerides, high- and low-density lipoproteins (mg/dL)

Total cholesterol	Baseline	1st month	3rd month	6th month	9th month	12th month
Mean value	116.28±31.5	122.87±29.3	128.93±31.2	112.52±34.9	117.94±32.3	131.07±35.8
Mean difference		−6.6	−12.7	−3.8	1.7	14.8
P-value		0.263	0.038	0.56	0.79	0.025
Triglycerides						
Mean value	50.67±15.1	55.20±16.9	52.96±16.5	37.67±19.9	38.44±19.5	28.46±8.7
Mean difference		4.5	2.3	−13.0	−12.2	−5.1
P-value		0.15	0.45	0.000	0.000	0.07
High-density lipoprotein						
Mean value	15.06±5.9	20.13±5.6	26.22±6.8	22.85±8.5	25.26±9.0	28.46±8.725
Mean difference		5.1	11.2	7.8	10.2	13.4
P-value		0.000	0.000	0.000	0.000	0.000
Low-density lipoprotein						
Mean value	91.13±28.7	91.52±23.9	91.15±26.6	83.94±28.1	82.28±30.4	94.15±31.7
Mean difference		0.4	0.02	−7.2	−8.9	3.0
P-value		0.94	0.99	0.19	0.12	0.61

Table 2: High-density lipoprotein/total cholesterol ratio

	Baseline	1st month	3rd month	6th month	9th month	12th month
Mean value	0.13±0.05	0.17±0.03	0.21±0.04	0.22±0.14	0.22±0.08	0.22±0.06
Mean difference		0.04	0.08	0.09	0.09	0.09
P-value		0.000	0.000	0.000	0.000	0.000
Low-density lipoprotein/cholesterol						
Mean value	0.18±0.08	0.23±0.06	0.30±0.10	0.30±0.14	0.38±0.34	0.33±0.14
Mean difference		0.05	0.12	0.12	0.20	0.15
P-value		0.001	0.000	0.000	0.000	0.000

Asia[25,26] reveal no negative effects on cardiovascular risk factors. Implanon tended to be associated with a reduction in plasma lipids in most reports have provided assurance about safety of Implanon. In the Toronto Nutrigenomics and Health Study, which involved 783 subjects, lipid metabolism biomarkers were statistically significantly higher among hormonal contraceptive users.[27] Our data show variable changes in lipid profile. HDLs showed significant trend toward a rise from baseline values. Both HDL/total cholesterol ratio and HDL/LDL ratios showed consistent and significant rise from baseline levels.

It appears that hormonal contraceptive use indirectly affects cardiovascular risk through mechanisms involving weight gain and obesity. Obesity has been shown to reduce the efficacy of contraceptives because of their pharmacokinetic alterations. However, obesity is a well-established cardiovascular risk factor, associated with cardiometabolic risk factors including hypertension, type 2 diabetes, and high serum cholesterol.[6] The relationship between abnormal lipid levels and risk for coronary heart disease and myocardial infarction in all regions of the world has been established.[28] Dyslipidemia typified by high triglycerides and high LDLs as well as LDL/HDL ratios predispose subjects to atherosclerosis and myocardial infarction. In this study, the LDL remained unchanged; triglycerides were reduced whereas the HDL levels were increased. This pattern contradicts the reported trend in the literature. If this trend is confirmed by larger studies, it may be beneficial in women with a history of lipid disorders. This may then improve the uptake and continuation rates of Implanon[R].

Conclusion

Implanon[R] is acceptable to Nigerian women. It has some demonstrable effects on lipid profile. The increases were mainly in the HDL fraction, which suggests that the atherogenic and cardiovascular disease risks are reduced. Larger studies are required to establish its effects on lipid profiles among Nigerian women. If the safety and biochemical benefits are proven, then it may potentially improve uptake and acceptance of this method.

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Conflicts of interest

There are no conflicts of interest.

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