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Depot-medroxyprogesterone acetate: Lipid profile changes and associated cardiovascular risks among acceptors in Sagamu, South West Nigeria

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Abstract. Depot-medroxyprogesterone acetate (DMPA) is a highly effective long acting reversible contraceptive. Alterations in lipid profile have been associated with use of DMPA, however there is considerable debate about how profound these effects are. Hence the aim of this study is to determine the effect of DMPA on lipid profile and the associated cardiovascular risks. This was a prospective longitudinal study conducted at the family planning clinic of Olabisi Onabanjo University Teaching Hospital Sagamu, Ogun State. Sixty eight new acceptors of DMPA who had their blood samples collected for lipid profile assays at initiation of DMPA, and then at 3 months and 6 months. Data were analyzed using SPSS version 24. After 3 months of DMPA use, there was statistically significant increase in serum Total Cholesterol (TC) concentration (P=0.022), serum Low Density Lipoprotein (LDL) concentration (P=0.033), non significant increase in serum Triglyceride (TG) concentration (P=0.150) and non-significant decrease in serum Higher Density Lipoprotein (HDL) concentration (P=0.076). However, after 6 months of DMPA use, there was statistically significant increase in serum TC concentration (P=0.002), serum LDL concentration (P=0.003), serum TG concentration (P=0.001) and significant decrease in serum HDL concentration (P=0.001). DMPA use is associated with increased serum TC, TG, LDL, and reduction in HDL after 6 months of use. These changes in lipid profile may increase the risk of cardiovascular diseases.

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Introduction

The world population has been characterized by unprecedented growth and this is associated with enormous consequences on environmental, social and economic development (1). In 2019, the world population was estimated to be about 7.7 billion with Africa being the second most populated continent accounting for 16.4% of the world population (1.2 billion) (1,2). Nigeria is the most populous country in Africa with an estimated population of about 200 million people (3); this huge population is partly responsible for the widespread poverty in the country (4). Hence there is a need to ensure a gradual decline in fertility rate thereby enhancing population stabilization (5). This can be achieved by encouraging contraceptive uptake by women of reproductive age group (6,7). Contraception is the procedure employed to interfere at one of the stages of the normal sequence of events in the process of reproduction leading to failure of conception (8).

Progesterone-only contraceptive contains artificial progestin preparation of either three monthly depot-medroxyprogesterone acetate or two monthly Norethisterone enanthate (9). About 90 million women are using long-acting injectable contraceptives, mostly in developing countries (10). In Nigeria, according to a demographic health survey (2018), injectable hormonal contraceptives were the most commonly used modern contraceptives accounting for 3% out of the 17% of total contraceptive prevalence in Nigeria (11). The mechanism of action is to inhibit the pituitary gonadotropin secretion thereby preventing follicular maturation and ovulation (12). Also, the cervical mucus is thickened thus blocking the ascent of sperm into the upper genital tract (12). DMPA also induces endometrial atrophy thereby preventing pregnancy (13). Apart from prevention of unwanted pregnancy, it has non-contraceptive advantages which include reduction of dysmenorrhea, endometrial protection in endometrial hyperplasia and carcinoma, in alleviating symptoms of premenstrual syndrome and treatment options in the management of endometriosis (13,14). Other advantages of DMPA include: reducing the risk of developing pelvic inflammatory disease, reduction in crises in patients with sickle cell diseases and protection against epithelial ovarian cancers (14,15).

DMPA is a long-acting, highly effective contraceptive with failure rate of 0.1-2 pregnancies per hundred women years and has a long-term clinically established good safety profile. However, one of the major concerns with the use of DMPA is the alteration in the lipid profile of users. DMPA has been reported to cause unfavourable changes in lipid metabolism by lowering the high density lipoprotein (HDL) with relative increase in very low density lipoprotein (VLDL) and low density lipoprotein (LDL) (16,17). Abnormal alteration in lipid profile is a major risk factor for cardiovascular disease which is a major cause of death worldwide (18). There is considerable debate about how profound the effects of DMPA on lipid metabolism are, moreover many of the studies were done in developed countries.

There are limited data available concerning the effects of DMPA on lipid profile and associated cardiovascular risk in Nigeria. Hence, the aim of this study is to assess the effect of the use of DMPA on the lipid profile and the associated cardiovascular risk at 3 months and 6 months.

The outcome of this study will form the basis for comparison with studies done on Caucasian population. The findings will also assist in the counseling and care of prospective users of this contraceptive method.

Materials and methods

The study was conducted in the family planning unit of the department of Olabisi Onabanjo University Teaching Hospital Sagamu. The hospital serves as a referral centre for Obstetrics and Gynecological services from neighbouring towns and villages of Ogun State and Lagos state. This was a prospective longitudinal study conducted from July 2018 to May 2019.

The minimum sample size required for the study was estimated using the formula for quantitative data (19). From a previous study (20), the mean value of serum low density lipoprotein cholesterol among DMPA users was 85.3±20.1 mg/dl. The minimum sample size calculated was 62. However, to increase the power of the study and allow for attrition, a sample size of 68 was used for the study.

New acceptors of three monthly DMPA who were aged between 20-and 40 years and with Body Mass Index (BMI) less than 30 kg/m^2 served as subjects of the study. The exclusion criteria included women who were on other hormonal contraceptives in the preceding two years, women with pre-existing medical conditions (hypertension and diabetes), women with risk factors for coronary heart diseases (those engaged in smoking, alcohol, caffeine, or tobacco use), women with a history of familial hypercholesterolemia, thyrotoxicosis, liver disease and thromboembolic phenomenon and women using lipid lowering drugs. The new acceptors of DMPA that met the inclusion criteria were recruited consecutively until the sample size of 68 was reached.

The study participants were adequately counseled about the study and written consent obtained. Intramuscular depot medroxylprogesterone acetate (DMPA) 150 mg manufactured by Pharmacia, N.V/S.A. Puurs-Belgium was administered to the study participants. They had repeat doses of DMPA at 3 months and 6 months after the initiation. All the participants recruited were followed up with mobile phone calls and messages to ensure compliance, hence there was no attrition.

The data capture sheet was used to collect information on study participants. The client's family planning card was reviewed, medical history was also obtained and physical and systemic examination was done to ascertain the eligibility of the client for the study. Thereafter information on socio-demographic characteristics of the subject (age, marital status, religion, educational status, occupation, parity, and ethnicity), the height, and weight were recorded on the data capture sheet. The study participants were assured of the confidentiality of the information obtained from them.

The eligible participants were asked to fast overnight. Five milliliters (5 mls) of venous blood was drawn using a sterile syringe from each participant between 8:00 am to 11:30 am following overnight fasting (for at least 8 h) into a plain bottle. The blood was allowed to clot and retract for 30 to 40 min. The clotted blood was then centrifuged for 10 min at 4,000 revolutions per minute (RPM). The serum was taken with a Pasteur pipette and stored in an Eppendorf tube, frozen at a temperature of -4˚C to -8˚C and batched. All batched samples were analyzed for HDL-Cholesterol, Triglycerides, and Total Cholesterol within 7 days. The analysis for HDL-Cholesterol and Total Cholesterol was done using commercial kits manufactured by RANDOX LABORATORIES (UNITED KINGDOM) i.e Randox HDL kit and Randox Total-Cholesterol. Triglycerides were assayed using the commercial assay kit manufactured by AGAPPE DIAGNOSTICS SWITZERLAND. Absorbance was measured at 546 nm. Randox Liquid Chemistry Premium Level 2 and 3 controls were included in each assay to ensure accuracy and precision. The inter-assay and intra-assay Coefficient of Variation calculated were below 2.5 and 1.5% respectively. The serum samples were assayed in duplicates. The LDL-Cholesterol values obtained using Friedewald's formulas were reliable provided that no chylomicrons were present in the sample, and the triglyceride concentration does not exceed 400 mg/dl.

The results of the fasting lipid profile (triglyceride, total cholesterol, low density lipoprotein cholesterol and higher density lipoprotein cholesterol) were recorded on the data capture sheet. The risk of cardiovascular disease was assessed by calculating the Castelli index. Castelli index I was calculated by dividing the serum concentration of TC by the serum concentration of HDL while Castelli index II was calculated by dividing the serum concentration of LDL by HDL (18).

All the information obtained on the data capture sheet were entered into a personal computer and analyzed using the statistical package for social science for window software version 24 (Armonk, NY: IBM Corp).

Categorical variables were summarized using numbers and percentages while mean and standard deviation and range were used for continuous variables. For bivariate analyses, paired t-test was used to evaluate the statistical difference between normally distributed continuous variables. The serum level of lipid profile at 3 months and 6 months were compared with pretreatment values using paired t-test. Statistical significance will be set at P-value less than 0.05. The primary outcome that was measured in the study was the changes in serum lipid profile among DMPA users. The secondary outcome was Castelli index among DMPA users.

Ethical approval for the study was obtained from the health research and ethics committee of Olabisi Onabanjo University Teaching Hospital Sagamu (reference number: OOUTH/HREC/174/2017).

Results

The sociodemographic characteristics of the subjects are depicted in Table I. The mean age was 32.7±5.1 years with age range of 21-39 years. The modal age group was 31-35 years accounting for 31 (45.6%) of the subjects. Sixty-seven (98.5%) of the women were married. Majority of the subjects 52 (76.5%) were of Yoruba ethnicity. The parity range was 1 to 5; half of the clients (50.0%) were within parity group 3-4 while twenty-eight clients (41.2%) were within parity group 1-2 and 6 (8.8%) subjects had parity greater than 4. The mean parity was 2.90±1.11.

The mean serum TC concentration was 181.0±20.8 mg/dl at baseline and 182.5±21.3 mg/dl at 3 months; the increase in TC concentration was statistically significant (t=2.351, P=0.022).

The pretreatment mean serum TG concentration was 88.8±15.6 mg/dl whereas the concentration at 3 months was 90.3±17.9 mg/dl. The mean change in serum TG concentration after 3 months of DMPA use was 1.5±8.4 mg/dl (1.7%); however, the increase was not statistically significant (t=1.456, P=0.150). The baseline mean serum LDL concentration was 119.5±21.7 mg/dl while the mean serum concentration at 3 month was 121.76±21.64. There was 2.18% increment (mean difference=2.2±8.3 mg/dl) in mean serum LDL concentration which was statistically significant (t=2.182, P=0.033). The pre-initiation serum HDL concentration among prospective DMPA clients was 42.8±7.4 mg/dl. After 3 months, the mean serum concentration declined to 42.3±7.2 mg/dl. The mean difference of -0.5±2.4 mg/dl was not statistically significant (t=-1.802, P=0.076) (Table II).

The baseline mean serum TC concentration was 181.0±20.8 mg/dl while the mean serum TC concentration at 6 months was 183.8±22.3 mg/dl. There was 1.6% (mean difference was 2.9±7.1 mg/dl) rise in mean serum concentration which was statistically significant (t=3.296, P=0.002). The serum TG concentration among DMPA users rose to 94.8±16.8 mg/dl at 6 months from the baseline mean serum concentration of 88.8±15.6 mg/dl. The mean difference of 5.9±3.2 mg/dl was statistically significant (t=15.257, P=0.001). The pre initiation and 6 months mean serum LDL concentration were 119.6±21.7 mg/dl and 123.1±22.8 mg/dl respectively. The percentage increase was 3.3% (mean difference=3.6±9.4 mg/dl), and this was statistically significant (t=3.115, P=0.003). The serum HDL concentration among DMPA users declined to 40.1±7.1 mg/dl at 6 months from the baseline mean serum concentration of 40.2±7.1 mg/dl at initiation. The mean change of -2.6±2.7 mg/dl (6.0%) was statistically significant (t=-7.890, P=0.003) (Table III).

The mean serum lipid concentration were compared at 3 months and 6 months using paired t-test. The mean differences in serum TC (1.4±5.4 mg/dl), TG (4.4±8.9 mg/dl), HDL (-2.2±1.5 mg/dl) and LDL (1.4±5.4 mg/dl) were statistically significant [(t=3.296, P=0.038), (t=4.966, P=0.001), (t=-11.594, P=0.001), (t=2.217, P=0.030)] respectively (Table IV).

The mean baseline Castelli index I (TC/HDL) was 4.4±1.2, whereas Castelli index II (LDL/HDL) was 2.9±1.0. After using DMPA for 6 months, the mean Castelli index I and Castelli index II were 4.5±1.4 and 3.0±1.3 respectively. Using paired t-test, at 6 months, the mean changes for the Castelli index I was 0.4±0.4, and the difference was statistically significant (t=7.927, P<0.001). For Castelli index II, the mean difference was 0.3±0.4 and was also statistically significant (t=6.86, P<0.001) (Table V).

Table I. Socio-demographic characteristics.

Socio-demographics	Frequency	Percentage
Age (years)		
21-25	8	11.8
26-30	17	25.0
31-35	31	45.6
36-40	12	17.6
Mean ± SD 32.7±5.1 years		
Marital status		
Single	1	1.5
Married	67	98.5
Parity		
1-2	28	41.2
3-4	34	50.0
≥5	6	8.8
Mean ± SD 2.9±1.1		
Ethnicity	52	76.5
Yoruba	10	14.7
Igbo	6	8.8
Hausa		
Occupation		
Unemployed	14	20.6
Artisan	12	17.6
Trader	24	35.3
Civil servant	10	14.7
Professional	8	11.8
Religion		
Christianity	43	63.2
Islam	24	35.3
Traditional	1	1.5
Educational status		
Informal	7	10.3
Primary	10	14.7
Secondary	32	47.1
Tertiary	19	27.9

Discussion

Depot Medroxyprogesterone Acetate is a synthetic microcrystalline progestin suspension that is highly effective as a contraceptive (21). One of the major concerns with the use of DMPA has been the alteration in the lipid profile of users. This study assessed the effects of DMPA on the lipid profile of family planning clients in Sagamu and findings suggest a significant increase in serum total cholesterol, low density lipoprotein, and triglyceride after 6 months of DMPA use; however, serum level of higher density lipoprotein was significantly decreased.

Table II. Serum lipid concentration at baseline and at 3 months.

Lipid profile	Serum level ($\bar{X}$ ± SD)		Mean difference ($\bar{X}$ ± SD)	% Mean difference	t-test value	P-value
	Pretreatment	3 months				
TC	181.0±20.8	182.5±21.3	1.5±5.1	0.8	2.351	0.022
TG	88.8±15.7	90.3±17.9	1.5±8.4	1.7	1.456	0.150
LDL-C	119.5±21.7	121.8±21.6	2.2±8.3	2.2	2.182	0.033
HDL-C	42.8±7.4	42.3±7.2	-0.5±2.4	-0.9	-1.802	0.076

TC, total cholesterol; TG, triglyceride; HDLc, high density lipoprotein; LDLc, low density lipoprotein.

Table III. Serum lipid concentration at baseline and at 6 months.

Lipid profile	Serum level ($\bar{X}$ ± SD)		Mean difference ($\bar{X}$ ± SD)	% Mean difference	t-test value	P-value
	Pretreatment	6 months				
TC	181.0±20.8	183.8±22.3	2.8±7.1	1.6	3.296	0.002
TG	88.8±15.6	94.8±16.8	5.9±3.2	6.7	15.257	0.001
LDL-C	119.6±21.7	123.1±22.8	3.6±9.4	3.3	3.115	0.003
HDL-C	42.8±7.5	40.2±7.1	-2.6±2.7	-6.0	-7.890	0.001

Table IV. Serum lipid concentration at 3 months and 6 months Changes in serum lipid concentration between values at 3months and at 6 months.

Lipid profile	Serum level ($\bar{X}$ ± SD)		Mean difference ($\bar{X}$ ± SD)	% Mean difference	t-test value	P-value
	3 Months	6 Months				
TC	182.5±21.3	183.8±22.3	1.4±5.4	0.8	2.116	0.038
TG	90.3±17.9	94.8±16.8	4.4±8.9	5.0	4.080	0.001
LDL-C	121.7±21.6	123.1±22.8	1.4±5.1	1.1	2.217	0.030
HDL-C	42.3±7.2	40.2±7.1	-2.1±1.5	-5.1	-11.594	0.001

Table V. Changes in castelli index after 6 months.

Variable	Pretreatment	6 months	Mean change	t-test value	P-value
Castelli Index I	4.4±1.2	4.5±1.5	0.4±0.4	7.927	0.001
Castelli Index II	2.9±1.0	3.0±1.3	0.3±0.4	6.868	0.001

The serum TC concentration increased significantly after 3 months of DMPA use, and this finding at 3 months was similar to studies conducted by Ahmed *et al* (22) and Torgrinsim *et al* (23) where both experienced an increase in serum TC concentration at 3 months over the pre-injection value. Similarly, the serum TC concentration also increased significantly after 6months of use. This result corroborates the findings reported by Fekadie *et al* (24), Asare *et al* (25), and Yadav *et al* (26). Long term use of DMPA is associated with a hypo-estrogenic state. Declining estrogen level causes increased cytokines release including tumour necrotic factors alpha and interleukin 6, and it has been reported that cholesterol elimination through bile synthesis and export is strongly inhibited by increased cytokines level; this ultimately leads to increased serum total cholesterol.

In this study, the mean change in serum triglyceride concentration at 3 months and 6 months were increased respectively. While the increase at 3 months was not statistically significant, the increase at 6 months was statistically significant. The

finding from this study was in consonance with finding from Al-youzbaki *et al* (16) where the researchers demonstrated a significant increase in serum TG concentration after 6 months of using DMPA. Other studies by Fekadie *et al* (24), and Yadav *et al* (26) reported no significant increase in serum TG concentration after using DMPA for at least 6 months, and 2 years respectively. The differences in findings between this present study and other previously published studies might be due to variations in the consumption of fatty diets. Triglycerides are the most common fats in the body and are mainly derived from ingested food substances. Furthermore, excess calories metabolized from other food substances (carbohydrate and protein) in the body are converted to triglycerides and subsequently stored in the adipose tissue (27).

DMPA users experienced an increase in mean serum Low density lipoprotein concentration after a period of 6 months and this increase was statistically significant. This was consistent with studies conducted by Yadav *et al* (17) and Fekadie *et al* (24). In the contrary, Torgrimson *et al* (23), and Ahmed *et al* (22) found a non-significant rise of LDL among DMPA users. These distinctions might be attributed to possible differences in intake of saturated fatty acids which are predominant in dairy foods and red meat; this tends to raise serum LDL concentration. The reason being that the saturated fatty acid increases serum LDL concentration by suppressing the activity, and also reducing the number of LDL receptors present on the cell membranes of the hepatocytes, a stage in the mechanism responsible for the removal of LDL from circulation (28).

The change in mean serum HDL concentration after 3 months was -0.52±2.35 which was not statistically significant. This was at variance with the outcome of Ahmed *et al* (22) which found a significant decrease in serum HDL concentration at 3 months. This could be ascribed to the fact that subjects with age up to 49 years were included in his study, and it has been reported that individuals above the age of 45 years have significantly lower HDL compared to those below the age of 45 years (28). After 6 months of using DMPA, the mean change in serum HDL was significantly lower the han baseline value. This result was consistent with Berenson *et al* (29), Lizarelli *et al* (20), Fekadie *et al* (24) and Ahmed *et al* (22). This reduction in serum HDL could be attributed to the fact that DMPA induces hepatic triglyceride lipase activity that degrades HDL. The anti-oestrogenic effect of DMPA could have also contributed to the decrease in HDL associated with its use (30).

Serum total cholesterol and low density lipoprotein are independent predictors of cardiovascular disease (16). CVD mortality accounts for more than one-third of all deaths in adults in developed countries (30). Dyslipidaemia is known to precipitate atherosclerotic change in the blood vessels. Castelli index I (TC/HDL) and Castelli index II (LDL/HDL) are used in assessing the risk associated with coronary heart disease, the normal range for healthy individuals being less than 4 and 3 respectively (31). Although studies have shown that TC and LDL were linearly associated with atherosclerosis, the ratio indices had been proved to have better prognostic value in determining individuals at risk of coronary artery disease than the value of each lipid profile parameter alone (32).

From this study, the mean Castelli index I increased from the baseline value of 4.40±1.24 to 4.48±1.42 at 6 months and Castelli index II from 2.93±1.04 to3.03±1.32 after 6 months of using DMPA, and the mean change was statistically significant. This result was in consonance with study done by Dilshad *et al* (33) where the mean change in Castelli index I and II were significant after 12 months of using the contraception. Also, Fekadie *et al* (24) stated that the mean changes in the Castelli index I and II after using DMPA for 2 years were significant compared to control. The baseline indices in this study indicate that the study population had a background risk of developing cardiovascular disease despite the strict inclusion and exclusion criteria used to eliminate those with known cardiovascular risk factors. Castelli *et al* stated that for every 1% increase in total cholesterol, a 2% rise in the incidence of coronary artery disease is found (34). Since the percentage increase in total cholesterol was 1.6%, we can extrapolate the risk of atherogenesis to be 3.2% in this study. It is however important to note that despite the significant changes in the mean serum lipid concentrations, the values were within the normal reference range. Hence, the effect might be reversed after cessation of the contraception.

The Limitation of the study were the effects of potential confounders like physical activity and intake of fatty rich diet which could alter serum lipid concentrations of participants, were not considered in the study.

In conclusion, this study found a significant increase in serum total cholesterol, low density lipoprotein, and triglyceride after 6 months of DMPA use; however, serum level of higher density lipoprotein was significantly decreased. These alterations were associated with a statistically significant increased risk of coronary heart disease as assessed by the Castelli index.

Based on the outcome of the study, the serum lipid profile should be assessed before the initiation of DMPA. Thereafter, strict monitoring of lipid profile at each follow-up visit is advocated before administering a repeat dose. Individualized counseling of prospective DMPA users on lifestyle modification to prevent risk factors associated with cardiovascular disease is necessary. DMPA use should also be avoided in women with high risk of cardiovascular diseases as indicated by high basal castelli index.

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Conflict of interest

There is no conflict of interest. The authors were solely responsible for financing this research work.

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