Journal of Public Health in Africa
Received 28 Sep 2020 | Revised 6 Oct 2021 | Accepted 28 Oct 2023 | Published Online 28 Dec 2023

DOI: https://doi.org/10.4081/jphia.2023.1664
JPHIA 14 (11), (2023)

ISSN (O) 2038-9922 IF: 0.8

ORIGINAL ARTICLE

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

Oluwaseyi Odelola[1,2*] | Adebayo Akadri[2]

[1]Department of Obstetrics and Gynaecology, Olabisi Onabanjo University Teaching Hospital Sagamu, Ogun State, Nigeria

[2]Department of Obstetrics and Gynaecology, Babcock University, Ilishan Remo, Nigeria

Abstract

Depot-medroxyprogesterone acetate (DMPA) is a highly efficient form of long-acting reversible contraception. The use of DMPA has been linked to changes in lipid profile, although there is much controversy on the extent of these effects. Therefore, the objective of this investigation is to ascertain the impact of DMPA on the lipid profile and the corresponding cardiovascular hazards.

Methods: This study was a forward-looking investigation carried out in the family planning clinic of Olabisi Onabanjo University Teaching Hospital Sagamu, Ogun State. A total of sixty-eight individuals who recently started using DMPA had their blood samples taken to assess their lipid profile at the beginning of DMPA use, as well as at 3 months and 6 months thereafter. The data were analyzed utilizing SPSS version 24.

Results: After 3 months of using DMPA, there was a significant increase in the concentration of Total Cholesterol (TC) in the blood (p=0.022), as well as a significant increase in the concentration of Low Density Lipoprotein (LDL) (p=0.033). There was a non-significant increase in the concentration of Triglycerides (TG) (p=0.150) and a non-significant decrease in the concentration of Higher Density Lipoprotein (HDL) (p=0.076). Nevertheless, following 6 months of DMPA usage, there was a statistically significant rise in serum TC concentration (p=0.002), serum LDL concentration (p=0.003), serum TG concentration (p=0.001), and a substantial decline in serum HDL concentration (p=0.001).

Conclusion: The use of DMPA is linked to elevated levels of blood TC, TG, and LDL, as well as a decrease in HDL after 6 months of treatment. These alterations in lipid profile may elevate the susceptibility to cardiovascular illnesses.

Keywords: Contraceptive, Cardiovascular disease, Depot-medro-xyprogesterone acetate, Family planning, Lipid profile.

INTRODUCTION

The world population has experienced remarkable expansion, resulting in significant implications for environmental, social, and economic progress[1]. The global population in 2019 was approximately 7.7 billion, with Africa being the second most populous continent, representing 16.4% of the world's population, which is equivalent to 1.2 billion people. One, two. Nigeria, with an approximate population of around 200 million individuals, holds the title of being the most populated nation in Africa. The substantial size of its population contributes significantly to the prevalence of poverty throughout the country. Therefore, it is necessary to maintain a progressive decrease in the fertility rate in order to promote population stabilization. This can be accomplished by promoting the adoption of contraceptives among women in the reproductive age group[6,7.] Contraception refers to the deliberate intervention at any point in the natural reproductive process to prevent pregnancy from occurring.

The progesterone-only contraceptive consists of a synthetic progestin formulation, which can be either a three-monthly depot-medroxyprogesterone acetate or a two-monthly Norethisterone enanthate[9]. Approximately 90 million women are utilizing long-acting injectable contraceptives, primarily in developing nations10. According to a demographic health survey conducted in Nigeria in 2018, injectable hormonal contraceptives were the most often utilized modern contraceptives, representing 3% of the total contraceptive prevalence of 17% in Nigeria[11]. The mechanism of action involves the inhibition of pituitary gonadotropin release, which effectively prevents the maturity of follicles and the process of ovulation[12]. In addition, the cervical mucus undergoes thickening, which effectively obstructs the movement of sperm into the higher reproductive system[12]. DMPA also causes the thinning of the uterine lining, therefore preventing conception.The number is 13. In addition to preventing unwanted pregnancy, it has non-contraceptive benefits such as reducing dysmenorrhea, protecting the endometrium in cases of endometrial hyperplasia and cancer, easing symptoms of premenstrual syndrome, and providing therapy choices for managing endometriosis[13,14]. Additional benefits of DMPA include: decreased susceptibility to pelvic inflammatory illness, decreased incidence of sickle cell disease crises, and protection against epithelial ovarian malignancies.[14,15]

DMPA is a reliable contraceptive method that is effective for a long duration, with a failure rate of 0.1-2 pregnancies per hundred woman years. It has been extensively studied and has a well-established safety record over the long term. Nevertheless, a significant issue associated with the utilization of DMPA is the modification of lipid profile among those who use it. Studies have indicated that DMPA can lead to undesirable alterations in lipid metabolism, namely by reducing the levels of high density lipoprotein (HDL) while increasing the levels of very low density lipoprotein (VLDL) and low density lipoprotein (LDL)[16,17]. Anomalous modification in lipid profile is a significant predisposing factor for cardiovascular disease, a leading cause of mortality globally[18]. There is a significant ongoing discussion on the extent of the impact of DMPA on lipid metabolism. Furthermore, it is worth noting that a majority of the studies on this topic have been conducted in industrialized nations.

Insufficient data exists about the impact of DMPA on lipid profile and the associated cardiovascular risk in Nigeria. Therefore, the objective of this study is to evaluate the impact of DMPA usage on the lipid profile and the corresponding cardiovascular risk after 3 and 6 months.

The results of this study will serve as a foundation for comparing with studies conducted on the Caucasian population. The results will also aid in the counseling and provision of care for potential users of this contraceptive approach.

Supplementary information The online version of this article (doi:10.4081/jphia.2023.1664) contains supplementary material, which is available to authorized users.

Corresponding Author: *Oluwaseyi Odelola*
Department of Obstetrics and Gynaecology, Olabisi Onabanjo University Teaching Hospital Sagamu, Nigeria.
Email: seyodelola@yahoo.com

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 (5mls) 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 8hours) into a plain bottle. The blood was allowed to clot and retract for 30 to 40 minutes. The clotted blood was then centrifuged for 10 minutes 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^{0}C to -8^{0}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 546nm. 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/dlL.

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 3months 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 1. 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 was181.0±20.8 mg/dL at baseline and182.5±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±15.6mg/dl whereas the concentration at 3 months was 90.3±17.9mg/dl. The mean change in serum TG concentration after 3 months of DMPA use was 1.5±8.4mg/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±7.4mg/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 2).

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 significan (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±22.8mg/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 3).

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±5.4mg/dl), TG (4.4±8.9mg/dl), HDL (-2.2±1.5mg/dl) and LDL (1.4±5.4mg/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 4).

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 5).

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.

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 3months 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 Yadavet 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 6months 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 Dilshadet 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.

Acknowledgements: We hereby acknowledge the member staff in the teaching hospital their contribution toward the completion of the manuscript. We also acknowledge the all the participants that consented to be part in the study. Oluwaseyi Odelola conceptualized the study, and also involved in data collection, analysis, and manuscript writing. Adebayo Akadri was involved in data collection, analysis, manuscript writing, and proofreading of the manuscript.

Conflict of Interest: There is no conflict of interest.

Funding: The authors were solely responsible for financing this research.

Table 1. 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 yrs		
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		
Yoruba	52	76.5
Igbo	10	14.7
Hausa	6	8.8
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

Table 2. Serum lipid concentration at baseline and at 3 months.

Lipid Profile	Serum Level($\bar{X} \pm SD$)		Mean Difference ($\bar{X} \pm SD$)	% 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 3. Serum lipid concentration at baseline and at 6 months.

Lipid Profile	Serum Level ($\bar{X} \pm SD$)		Mean Difference ($\bar{X} \pm SD$)	% 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 4. Serum lipid concentration at 3 months and 6 months.

Changes in serum lipid concentration between values at 3 months and at 6 months

Lipid Profile	Serum Level ($\bar{X} \pm SD$)		Mean Difference ($\bar{X} \pm SD$)	% 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 5. 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