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# Effect of depot medroxyprogesterone acetate on cardiometabolic risk factors among women of reproductive age in Rwanda: A prospective cohort study

Evelyne Kantarama[1], Dieudonne Uwizeye[2], Annette Uwineza[1], Claude Mambo Muvunnyi[1]

Departments of [1]Clinical Biology and [2]Development Studies, University of Rwanda, Kigali, Rwanda.

## ABSTRACT

**Objectives:** Depot medroxyprogesterone acetate (DMPA) injectable contraceptive is a widely used hormonal method that offers reversible and effective birth control for women worldwide. However, various studies have raised concerns regarding its potential association with increased cardiovascular disease risk, attributed to its influence on cardiometabolic risk factors. While previous studies have primarily focused on lipid profile, weight gain, blood pressure, and blood glucose, important aspects such as central obesity, glycated hemoglobin (HbA1C), and systemic inflammation have remained under-investigated. Thus, this study aimed to explore the influence of DMPA injectable contraceptives on lipid panel, HbA1C, visceral fat deposition, blood pressure, and inflammatory markers among women of childbearing age in Rwanda.

**Materials and Methods:** The study was a prospective cohort and recruited an equal number of DMPA users (45) as the study group and users of non-hormonal (NH) contraceptives (45) as the control group. We recruited participants from two selected family planning centers in Kigali and collected data at baseline, 6 months, and 12 months. We measured the waist circumference, blood pressure, lipids profile (high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], total cholesterol [TC], and triglycerides [TG]), HbA1C, and high-sensitivity C-reactive protein (hs-CRP). We run the Mann–Whitney to compare the median (MD) change between DMPA and NH users. Data were presented as MD (interquartile range), with a significance level of 5%.

**Results:** After a follow-up of 12 months, DMPA users experienced a significant increase in waist circumference, TG, LDL, TC, hs-CRP, and HbA1C ($P < 0.05$), whereas they experienced a significant decrease in HDL than controls ($P < 0.05$). However, our data did not indicate a significant difference in blood pressure changes between DMPA and NH users ($P > 0.05$).

**Conclusion:** The effect of DMPA injectable on cardiometabolic parameters was minimal in the first 6 months of use; however, it manifested statistically significant at 12 months of follow-up. It is recommended to initiate a follow-up with users at least 12 months of use and repeat every 6 months to check the status of cardiometabolic markers and intervene where necessary.

**Keywords:** Childbearing age women, Injectable contraceptives, Cardiometabolic risk factors, Follow-up

## INTRODUCTION

Depot medroxyprogesterone acetate (DMPA) is a largely used hormonal contraceptive method preferred by many women worldwide, especially in Sub-Saharan Africa and more so in East Africa, including Rwanda.[1,2] However, the previous studies highlighted the concerns about its potential impact on cardiometabolic risk factors that contribute significantly to the development of cardiovascular disease (CVD),[3-5] the main cause of long-duration illness and death globally.[6]

DMPA greatly affects cardiometabolic risk factors that mostly lead to cardiometabolic disease. It was reported to be associated with body weight increase and body fat deposition, especially abdominal fat,[7] a major risk factor for CVDs.[8] Abdominal fat deposition is highly associated with cardiovascular events such as heart failure, coronary heart diseases, and atrial fibrillation.[9] DMPA was also reported to be associated with high calcium levels,[10] a factor that reduces bone density and is associated with a high risk of vascular diseases and death.[11] Furthermore, it is associated with dyslipidemia,[12,13] also documented to be a major risk factor and predictor of atherosclerotic CVDs such as coronary artery disease, stroke, and peripheral vascular diseases.[14] Furthermore, various studies have consistently reported an association between DMPA and an elevated risk of venous thromboembolism.[15,16]

***Corresponding author:** Evelyne Kantarama, Department of Clinical Biology, University of Rwanda, Kigali, Rwanda. ekantarama@cartafrica.org

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Conventionally, CVD was a men's issue, and available documentation about the disease's characteristics and treatment mainly focused on men.[17] Although the incidence of CVD is still high in men, there is a concern that it is also increasing in young women and appears to be the primary cause of reduced quality of life and death in this group globally, particularly in developing countries.[18] Recent evidence indicates an equal risk of CVD for men and women, given that they have the same risk factors.[19,20] However, women who take hormonal contraceptives, mainly DMPA injection, have additional risks associated with its close association with these potential cardiometabolic risk factors.

The evidence that DMPA injectable greatly affects major cardiometabolic risk factors that put users at high risk of CVD suggests the necessity of follow-up for users. However, further research is needed to fully characterize this effect as previous studies focused on lipid profile, weight gain, blood pressure, and blood glucose, leaving central obesity, glycated hemoglobin (HbA1C), and systemic inflammation under-investigated. At the same time, these are potential cardiometabolic risk factors.[9,21,22]

Therefore, the purpose of this study was to evaluate the effect of DMPA compared to non-hormonal (NH) methods on cardiometabolic risk parameters among childbearing age women in Rwanda over 1 year. Specifically, we assessed changes in waist circumference, lipid profile, blood pressure, HbA1C, and systemic inflammation in DMPA users compared to NH users. By examining the impact of DMPA on cardiometabolic health in a Rwandan context, this study would contribute to the existing knowledge base and provide appreciated insights for healthcare providers and policymakers in making informed decisions regarding routine follow-up with users to ensure their better health and well-being.

## MATERIALS AND METHODS

The data were collected in selected family planning centers in Kigali. The chosen centers were among the limited number of public facilities that provide cost-free family planning services within Kigali city. Each center serves 30–40 women on average seeking family planning services.

### Sample size and sampling procedure

This formula is used to compare means between two groups.[23] Using this procedure, we estimated a sample of 25 individuals in each group (hormonal and NH contraceptive users). Considering four confounding factors (alcohol, physical inactivity, diet, and education level), the sample became 32 participants for each group. The sample size was 45 participants for each group, assuming a non-response rate of 20%.

The sample included two groups of participants, as earlier indicated. These were women wishing to initiate injectable hormonal contraceptives as a study group and NH users as a control group. We identified participants from family planning programs of two health centers in Kigali. Conveniently, all available participants that met inclusion criteria and consented to participate were consecutively recruited until the study reached the required sample.

### Inclusion criteria

Participants in the study group had to be healthy non-pregnant women whose choice of contraceptive method was injectable (DMPA) and without any other hormonal contraceptive method within 6 months before baseline. To be a control participant, a woman had to be physically healthy without pregnancy, whose choice of contraception was the NH method, and without a history of hormonal contraceptive use within 6 months before the baseline.

### Exclusion criteria

Based on personal and family history, participants with chronic conditions such as human immunodeficiency virus, chronic liver diseases, cancer, diabetes, hypertension, chronic renal failure, and heart diseases were excluded from the study as these conditions were reported to be associated with heart diseases. Baseline data allowed us to exclude individuals with dyslipidemia, abdominal obesity, systemic inflammation, hyperglycemia, and high blood pressure.

### Data collection

Data were collected 3 times: At baseline, at 6 months, and after 12 months. Baseline data were corrected from September to November 2020, the second from April to May 2021, and the third from November to October 2021. A structured questionnaire was used to record participants' waist circumference, blood pressure, and biodemographic characteristics of study participants, such as age, education attainment, alcohol use, parity, breastfeeding, and diet (the consumption frequency of meat, milk, fruits, and vegetables).

The age variable was counted in years and categorized as 24 years or less, 25–29 years, and 30 years or more, while education attainment was categorized as primary or less and secondary or tertiary. We recorded data about breastfeeding and the use of alcohol in binary format, indicating a simple "Yes" or "No" response. To record data on parity, we asked participants to disclose the total number of their offspring. "For analysis purposes, data were categorized as having two children or below" and "3 and above" to accommodate most participants who reported having 1 to 4 children.

We measured blood pressure following the International Society of Hypertension guidelines.[24] On the participant's arrival, measurements were recorded following 10 min of rest. These measurements were repeated twice, with a 5-min interval between each measurement. The individual's blood pressure was then determined by calculating the average of the two recorded readings. In addition, waist circumference was measured using a tape measure, specifically at the narrowest width between the lowest rib and the iliac crest. This measurement was taken on the bare skin, with the participant's arms resting naturally at their sides and at the end of a normal exhalation.

In addition, participants provided fasting blood samples to assess their lipid profile components including triglycerides (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and TC. Furthermore, the blood samples were tested for high-sensitivity C-reactive protein (hs-CRP) and HbA1C levels. The blood samples were analyzed using the clinical chemistry analyzer named Abbott ARCHITECTci4100. This clinical chemistry analyzer is an automated machine that detects lipids using enzymatic and colorimetric methods and expresses the results in mmol/L. It detects hs-CRP by immunoassay method and expresses it in mg/L, while it detects the HbA1C by enzymatic method and expresses it in %. For both the study group and controls, we took their phone contacts for regular calls to remind them about the study. The reference values for the measured cardiometabolic risk parameters indicated in Table 1 were drawn from previous studies.[25-27]

### Statistical analysis

We analyze data using the Statistical Package for the Social Sciences (SPSS version 21). Data distribution analysis for all studied variables in all conditions indicated that none respected normal distribution following the Shapiro–Wilk Test. Accordingly, non-parametric statistical tests were used to compare the data at each time point. To analyze the within-group changes, we ran the Wilcoxon signed-rank test, and the between-group changes were analyzed using the Mann–Whitney for continuous variables and the Chi-square for categorical variables. Data were presented as percentages or median (MD) (interquartile range), and the significance level was 5%.

### Ethical approval

The study gained approval from the Institutional Review Board of the College of Medicine and Health Sciences at the University of Rwanda (reference: 042/CMHS IRB/2020). Authorization was also obtained from the Rwanda Biomedical Center (approval reference: 417/RBC/2020) and the Ministry of Health, Government of Rwanda (ref: NHR/2020/PROT/030).

## RESULTS

The study started with 45 participants in each group. At 6 months, one DMPA user got pregnant due to poor adherence; another claimed bleeding problems and quit the method. At 12 months, the other three DMPA users left the study for an unknown reason. Only 40 DMPA users completed 12 months of follow-up. Out of 45 controls, only 39 completed 12 months of follow-up; at 6 months, all controls were reported, while at 12 months, three controls desired to get pregnant, and three changed the method and adhered to hormonal methods.

Table 2 displays the results of the biodemographic characteristics of the study participants. The results indicate no difference in age; $P = 0.246$, breastfeeding; $P = 0.057$, parity; $P = 0.059$, alcohol use; $P = 0.054$, meat; $P = 0.063$ and fruit consumption; $P = 0.624$ categories between DMPA and NH methods users. The results, however, indicated that 74% of all participants did not reach secondary school, with a high percentage (85%) of DMPA users than in the control group (62.5%); $P = 0.015$. Furthermore, 62% of all participants reported eating vegetables more or equal to 4 times a week, with a high percentage in NH users (75.6%) than in DMPA users (48.9); $P = 0.009$. Subsequently, 74% of all participants reported they took milk at least once per week, with a higher percentage in NH users (84%) than in the DMPA group (64%); $P = 0.030$.

Table 3 indicates the Wilcoxon signed-rank test results comparing changes in cardiometabolic risk parameters within DMPA users. From baseline to 6 months, the results indicated the statistically significant MD change in some

**Table 1:** Reference values for cardiometabolic risk parameters.

| Variable | Risk associated |
|---|---|
| WC (in cm) | |
| ≤88 | Low risk |
| >88 | High risk |
| HDL (in mmol/L) | |
| ≥1.04 | Low risk |
| <1.04 | High risk |
| hs-CRP (in mg/dL) | |
| <1 | Low risk |
| 1–3 | Moderate risk |
| >3 | High risk |
| TG (in mmol/L) | |
| <1.7 | Low risk |
| ≥1.7 | High risk |
| HbA1C (in %) | |
| <5.7 | Low risk |
| ≥5.7 | Increased risk |

WC: Waist circumference, HDL: High-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive protein, TG: Triglycerides, HbA1C: Glycated hemoglobin

parameters such as waist circumference, HDL, LDL, TG, and HbA1C; $P < 0.05$. Except for HDL, which shows a clinically significant decrease in the MD, other parameters indicated a non-clinically significant increase in the MD; $P > 0.05$. Comparing the 6th and 12 months results, all parameters except HbA1C indicated statistically significant MD changes, $P < 0.05$, with HDL continuing to decrease while other parameters increased. There were statistically and clinically significant alterations in HDL, hs-CRP, and waist circumference (WC), while other parameters (TC, LDL, and TG) were statistically significant but not clinically significant. The same, from baseline to 12 months, HDL indicated both statistically and clinically significant decrease; $P < 0.05$, whereas WC and hs-CRP indicated an increase. Other parameters such as TC, TG, LDL, HbA1C, systolic blood pressure (SBP), and diastolic blood pressure (DBP) indicated statistically, though not clinically, significant changes.

Table 4 shows the Wilcoxon signed-rank test results comparing changes in cardiometabolic risk parameters within NH users. Baseline and 6 months results did not indicate the difference in TC, SBP, and DBP; $P > 0.05$; WC, LDL, and HbA1C increased significantly while HDL, TG, and hs-CRP decreased significantly. From 6 to 12 months, there was a significant MD increase in HDL, LDL, and DBP, while other parameters remained unchanged. The baseline results were compared to 12 months, where WC, HDL, hs-CRP, DBP, and HbA1C increased significantly; however, the increase was not clinically significant. Contrary, TG indicated a significant decrease.

The observation of the results in Table 5 shows that at baseline, participants were not different in many cardiometabolic markers such as waist circumference ($P = 0.792$), TC ($P = 0.735$), LDL, ($P = 0.135$), TG ($P = 0.208$), HbA1C ($P = 0.100$), SBP ($P = 0.184$), DBP ($P = 0.129$), and hs-CRP (0.100). However, HDL was significantly greater in DMPA starters 1.26 (0.42) than in the control group 1.08 (0.26); $P = 0.008$. Furthermore, after 6 months of follow-up, no difference in WC, hs-CRP, TC, LDL, and SBP changes, $P > 0.05$, were detected between the two groups. However, the changes in HbA1C and TG were significantly more significant in the DMPA than in the NH users, with $P < 0.05$ different from changes in HDL, which were significantly lower in the DMPA users than in NH users, $P < 0.05$. The comparison between the 6th and 12 months' results indicates that DMPA users experienced a significant increase in levels of almost all studied cardiometabolic parameters than the NH users. The raised parameters included WC, hs-CRP, TC, LDL, HbA1C, and TG; $P < 0.05$. Differently, HDL indicated a significant decrease in the DMPA users than in the NH users; $P < 0.05$.

## DISCUSSION

The study used a prospective approach to explore the effect of DMPA on cardiometabolic risk parameters in women of reproductive age in Rwanda to document the need or not for the routine follow-up to them. The findings indicated a significant effect of DMPA on waist circumference, LDL, TC, TG, HDL, hs-CRP, and HbA1C. In general, the first 6 months' changes were not statistically significant for many of the studied parameters; however, at 12 months, the results

**Table 2:** Biodemographic characteristics of study participants.

| Parameters | Categories | DMPA group *n*=45 *n* (%) | NH users *n*=45 *n* (%) | *P*-value |
|---|---|---|---|---|
| Age (in years) | ≤24 | 17 (37.8) | 10 (22.2) | 0.246 |
| | 25–29 | 12 (26.7) | 13 (28.9) | |
| | ≥30 | 16 (35.6) | 22 (48.9) | |
| Education attainment | Less than secondary | 40 (85.11) | 27 (62.49) | 0.015* |
| | Secondary or tertiary | 7 (14.89) | 16 (37.21) | |
| Breastfeeding | Yes | 37 (82.2) | 29 (64.4) | 0.057 |
| | No | 8 (17.8) | 16 (35.6) | |
| Parity | <3 children | 40 (88.9) | 33 (73.3) | 0.059 |
| | ≥3 children | 5 (11.1) | 12 (26.7) | |
| Alcohol use | Yes | 16 (34.04) | 7 (30.43) | 0.054 |
| | No | 31 (65.96) | 36 (53.73) | |
| Eating meat | Not at all | 17 (37.8) | 9 (20) | 0.063 |
| | At least once a week | 29 (62.2) | 36 (80) | |
| Eating vegetables | <4 times a week | 23 (51.1) | 11 (24.4) | 0.009* |
| | ≥4 times a week | 22 (48.9) | 34 (75.6) | |
| Eating fruits | Not at all | 12 (26.7) | 10 (22.2) | 0.624 |
| | At least once a week | 33 (73.3) | 35 (77.8) | |
| Taking milk | Not at all | 16 (35.6) | 7 (15.6) | 0.030* |
| | At least once a week | 29 (64.4) | 38 (84.4) | |

*Means that the difference is statistically significant at 5%. DMPA: Depot medroxyprogesterone acetate, NH: Non-hormonal

**Table 3:** The results of the Wilcoxon signed-rank test comparing changes in cardiometabolic risk parameters within DMPA users.

| Variable | Baseline MD (IQR) | Six months MD (IQR) | Sig | Six months MD (IQR) | Twelve months MD (IQR) | Sig | Baseline MD (IQR | Twelve months MD (IQR) | Sig |
|---|---|---|---|---|---|---|---|---|---|
| WC | 82 (7) | 89 (14) | <0.001 | 89 (14) | 93 (10) | <0.001 | 82 (7) | 93 (10) | <0.001 |
| TC | 4.01 (2.43) | 3.79 (1.30) | 0.699 | 3.79 (1.30) | 4.53 (1.47) | <0.001 | 4.01 (2.43) | 4.53 (1.47) | <0.001 |
| HDL | 1.26 (0.42) | 0.66 (0.50) | <0.001 | 0.66 (0.50) | 0.89 (0.41) | 0.003 | 1.26 (0.42) | 0.89 (0.41) | 0.001 |
| LDL | 2.49 (0.94) | 2.89 (1.30) | 0.007 | 2.89 (1.30) | 3.55 (1.18) | <0.001 | 2.49 (0.94) | 3.55 (1.18) | <0.001 |
| TG | 0.98 (0.49) | 1.12 (0.41) | 0.009 | 1.12 (0.41) | 1.36 (0.77) | 0.008 | 0.98 (0.49) | 1.36 (0.77) | 0.003 |
| hs-CRP | 0.56 (1.53) | 0.95 (2.42) | 0.201 | 0.95 (2.42) | 3.78 (3.71) | <0.001 | 0.56 (1.53) | 3.78 (3.71) | <0.001 |
| HbA1C | 4.70 (0.50) | 5.61 (0.78) | <0.001 | 5.61 (0.78) | 5.50 (0.73) | 0.127 | 4.70 (0.50) | 5.50 (0.73) | <0.001 |
| SBP | 118 (15) | 119 (19) | 0.553 | 119 (19) | 126 (20) | <0.001 | 118 (15) | 126 (20) | 0.001 |
| DBP | 77 (11) | 76 (15) | 0.428 | 76 (15) | 86 (11) | <0.001 | 77 (11) | 86 (11) | <0.001 |

DMPA: Depot medroxyprogesterone acetate, MD: Median, IQR: Interquartile range, WC: Waist circumference (in cm), DBP: Diastolic blood pressure (in mmHg), HDL: High-density lipoprotein cholesterol (in mmol/L), LDL: Low-density lipoprotein cholesterol (in mmol/L), SBP: Systolic blood pressure (in mmHg), TC: Total cholesterol (in mmol/L), TG: Triglyceride (in mmol/L), HbA1C: Glycated hemoglobin (in %), hs-CRP-high-sensitivity C-reactive protein (in mg/L), Sig: Significance

**Table 4:** The results of the Wilcoxon signed-rank test comparing changes in cardiometabolic risk parameters within non-hormonal users.

| Variable | Baseline MD (IQR) | Six months MD (IQR) | Sig | Six months MD (IQR) | Twelve months MD (IQR) | Sig | Baseline MD (IQR) | Twelve months MD (IQR) | Sig |
|---|---|---|---|---|---|---|---|---|---|
| WC | 83 (9) | 86 (11) | <0.001 | 86 (11) | 88 (11) | 0.337 | 83 (9) | 88 (11) | <0.001 |
| TC | 3.79 (2.65) | 3.96 (1.28) | 0.509 | 3.96 (1.28) | 4.09 (1.30) | 0.439 | 3.79 (2.65) | 4.09 (1.30) | 0.097 |
| HDL | 1.08 (0.26) | 0.99 (0.22) | 0.002 | 0.99 (0.22) | 1.19 (0.58) | 0.001 | 1.08 (0.26) | 1.19 (0.58) | 0.016 |
| LDL | 2.63 (0.82) | 2.89 (0.94) | 0.006 | 2.89 (0.94) | 2.96 (1.00) | 0.015 | 2.63 (0.82) | 2.96 (1.00) | 0.660 |
| TG | 0.99 (0.78) | 0.82 (0.62) | <0.001 | 0.82 (0.62) | 0.79 (0.79) | 0.754 | 0.99 (0.78) | 0.79 (0.79) | 0.002 |
| hs-CRP | 1.18 (1.67) | 1.00 (3.09) | 0.006 | 1.00 (3.09) | 1.77 (2.39) | 0.426 | 1.18 (1.67) | 1.77 (2.39) | 0.003 |
| HbA1C | 4.70 (0.45) | 4.89 (0.98) | <0.001 | 4.89 (0.98 | 4.92 (0.92) | 0.872 | 4.70 (0.45) | 4.92 (0.92) | 0.004 |
| SBP | 118 (15) | 119 (19) | 0.459 | 119 (19) | 126 (20) | 0.780 | 118 (15) | 126 (20) | 0.310 |
| DBP | 79 (12) | 83 (10) | 0.428 | 83 (10) | 87 (6) | <0.001 | 77 (11) | 87 (6) | 0.007 |

NH: Non-hormonal; MD: Median, IQR: Interquartile range, WC: Waist circumference (in cm), DBP: Diastolic blood pressure (in mmHg), HDL: High-density lipoprotein cholesterol (in mmol/L), LDL: Low-density lipoprotein cholesterol (in mmol/L), SBP: Systolic blood pressure (in mmHg), TC: Total cholesterol (in mmol/L), TG: Triglyceride (in mmol/L), HbA1C: Glycated hemoglobin (in %), hs-CRP: High-sensitivity C-reactive protein (in mg/L), Sig: Significance

indicated a statistically significant increase in WC, hs-CRP, HbA1C, TC, LDL, TG, and lipid ratios in the DMPA group compared to NH users. Moreover, DMPA users experienced a significant decrease in HDL compared to NH users. Our findings did not indicate any influence of DMPA on blood pressure.

Various studies investigating the effect of DMPA on lipid profiles indicated an inconsistency in their findings. Our findings indicated a progressive rise in TG, TC, and LDL and a decline in HDL. It is consistent with the 6 months follow-up study done in Indian postpartum women, which also indicated a significant progressive increase in TG, LDL, TC, and a decrease in HDL in DMPA users.[28] It differs from the 2-year follow-up study conducted on Nepalese women, which reported a significant rise in TC and LDL with no significant changes in TG and HDL.[5] Again, the study on Nigerian women reported a significant increase in LDL and HDL without changes in TG and TC.[29] On the contrary, the study on Egyptian women concluded that injectables do not affect lipid metabolism in any way.[30] This inconsistency may be attributable to sociocultural and lifestyle factors influencing the lipid profile differently in different communities.

Our study did not show the difference in MD blood pressure between the DMPA group and NH group, and it agrees with the study done in Ethiopia, which also reported no difference in both SBP and DBP between injectable users and controls.[31] Other studies reported statistically significant differences; for example, a 1-year follow-up study in Ghana demonstrated a significant increase in DBP in injectable users when compared results at baseline (72.70 ± 3.47 mmHg) and results after 1 year (88.22 ± 4.32); however, it was not clinically significant. The same study also reported a significant increase in SBP, where it was 115.39 ± 5.03 mmHg at baseline and 130.52 ± 5.56 mmHg after a year; also, the difference was not clinically significant.[32] Another example is the study conducted in Pakistan women which reported a difference where both SBP and DBP were significantly high in injectable users (SBP: 118.33 ±

**Table 5:** Mann–Whitney analysis to compare changes in cardiometabolic parameters between DMPA and NH users during 12 months of follow-up.

| Variable | Baseline | | | After 6 months | | | After 12 months | | |
|---|---|---|---|---|---|---|---|---|---|
| | DMPA users MD (IQR) | NH users MD (IQR) | Sig | DMPA users MD (IQR) | NH users MD (IQR) | Sig | DMPA users MD (IQR) | NH users MD (IQR) | Sig |
| WC | 82 (7) | 83 (9) | 0.792 | 89 (14) | 86 (11) | 0.216 | 93 (10) | 88 (11) | <0.001 |
| hs-CRP | 0.56 (1.56) | 1.18 (1.67) | 0.100 | 0.95 (2.42) | 1.0 (3.09) | 0.386 | 3.78 (3.71) | 1.77 (2.39) | 0.002 |
| HbA1C | 4.70 (0.70) | 4.70 (0.45) | 0.100 | 5.61 (0.78) | 4.89 (0.89) | <0.001 | 5.50 (0.73) | 4.92 (0.92) | <0.001 |
| TC | 4.01 (2.43) | 3.94 (2.65) | 0.735 | 3.79 (1.30) | 3.96 (1.28) | 0.204 | 4.53 (1.47) | 4.09 (1.30) | 0.006 |
| HDL | 1.76 (0.42) | 1.08 (0.26) | 0.008 | 0.66 (0.50) | 0.99 (0.22) | <0.001 | 0.89 (0.41) | 1.19 (0.58) | <0.001 |
| LDL | 2.49 (0.94) | 2.63 (0.82) | 0.135 | 2.89 (1.30) | 2.89 (0.94) | 0.913 | 3.55 (1.18) | 2.76 (1.00) | <0.001 |
| TG | 0.98 (0.49) | 0.99 (0.78) | 0.208 | 1.12 (0.41) | 0.82 (0.62) | <0.001 | 1.36 (0.77) | 0.79 (0.79) | <0.001 |
| SBP | 118 (15) | 122 (16) | 0.184 | 119 (19) | 122 (20) | 0.279 | 126 (19) | 124 (14) | 0.181 |
| DBP | 77 (11) | 79 (12) | 0.129 | 76 (15) | 83 (10) | 0.036 | 86 (11) | 87 (6) | 0.590 |

DMPA: Depot medroxyprogesterone acetate, NH: Non-hormonal, MD: Median, IQR: Interquartile range, WC: Waist circumference (in cm), DBP: Diastolic blood pressure (in mmHg), HDL: High-density lipoprotein cholesterol (in mmol/L), LDL: Low-density lipoprotein cholesterol (in mmol/L), SBP: Systolic blood pressure (in mmHg), TC: Total cholesterol (in mmol/L), TG: Triglyceride (in mmol/L), HbA1C: Glycated hemoglobin (in %), hs-CRP: High-sensitivity C-reactive protein (in mg/L), Sig: Significance

9.85 mmHg; DBP: 80.83 ± 10.91 mmHg) compared to controls (SBP: 112.0 ± 7.61 mmHg; DBP: 77.0 ± 5.50 mmHg); again, this difference is not clinically significant.[33]

Among the objectives of this study were to evaluate the influence of DMPA on abdominal fat deposition as an independent risk factor associated with increased risk of CVD.[34] The results of this study indicated both statistical and clinically significant differences between DMPA users and controls at 12 months of use, where DMPA users indicated a higher MD waist circumference than controls. Even though there are limited data on these findings, related findings indicate a direct relationship between DMPA and weight gain. These include the study done on the adolescent population in a prospective study of 18 months follow-up where the increase in mean weight at 18 months was 9.4 in obese users and 3.5 in non-obese users.[31] The same was reported in Indian postpartum women, where the 6 months follow-up study indicated a significant progressive increase in weight.[28] A cross-sectional study in Ethiopia reported a significant rise in individual body weight from 1 to 14 kg and a mean increase of 5 kg/m$^2$ in body mass index regardless of the duration of use.[31] An increase in body weight is not enough to estimate the risk of CVDs; instead, the waist circumference measure provides a reasonable estimate of the risk of CDV.[35]

There is evidence that combined hormonal contraceptives, specifically oral contraceptives[36] and vaginal combined hormonal contraceptives,[37] induce chronic CRP production in the liver independently of age and in a different manner than that of the usual inflammatory processes.[38] This evidence has raised whether DMPA, a progesterone-only contraceptive, can induce CRP production. In our study, the observed change was minimal and not different between DMPA users and controls until 6 months. However, at 12 months, a clinically significant increase was observed in DMPA users but not in controls. Regardless of the mode of administration, hormonal contraceptives induce chronic inflammation that needs further evaluation to elucidate the cardiovascular consequences.

Various studies that assessed the influence of hormonal contraceptives on blood sugar have either considered all methods together or put their focus on oral contraceptives and ended with controversial findings. A cross-sectional study conducted on childbearing-aged women (20–49) in Indonesia indicated higher average blood glucose of 26 mg/dL above that of non-users.[39] The same study conducted in Nigeria showed a significant increase (5.2 ± 2.2 mg/dL) in users compared to non-users.[40] Contrary to that conducted in young American women, where the use of oral contraceptives reduced the blood glucose level, promising a protective effect on diabetes in users.[41] Our study intended to determine the effect of DMPA on HbA1C as a measure of average blood glucose within 3–4 months. Our findings indicated a higher mean in DMPA users than in controls. Even though we used different measures, our findings are comparable to the 3-month follow-up study, which indicated a significantly elevated blood glucose in DMPA users than in NH users.[4]

However, the study encountered some limitations, among them the self-report on the use of hormonal contraceptives and the duration of the previous use, which could introduce some bias in the results**.** Another limitation is the failure to control participants' lifestyles during the follow-up period, which could influence some of the factors investigated in the study. Further study that considers all those factors includes all types of hormonal contraceptives used in Rwanda, and extends the follow-up period would be appreciated.

## CONCLUSION

The study concludes that DMPA affects cardiometabolic parameters in users. The effect was minimal within the first 6 months of use but manifested significantly at 12 months of follow-up. The most affected parameters included waist circumference, lipid ratios, TG, HDL, hs-CRP, and HbA1C, and these are currently identified as potential cardiometabolic indicators of the high risk of CVD. We recommend a follow-up to users which are to be initiated at least 12 months of use and repeated every 6 months to check the status of cardiometabolic markers and intervene where necessary. Checking lipid profiles, blood sugar, and waist circumference would provide helpful information to health providers for a decision on an individual user.

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### Ethical approval

The study gained approval from the Institutional Review Board of the College of Medicine and Health Sciences at the University of Rwanda (reference: 042/CMHS IRB/2020). Authorization was also obtained from the Rwanda Biomedical Center (approval reference: 417/RBC/2020) and the Ministry of Health, Government of Rwanda (ref: NHR/2020/PROT/030).

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

1. United nations department of economic and social affairs. World family planning 2022: Meeting the changing needs for family planning: Contraceptive use by age and method. UN DESA/POP/2022/TR/NO. 4; 2022. Available from: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf [Last accessed on 2023 Jun 25].
2. Desire NJ, Bonaventure B, Claire IM, Diane MM, Michel KP. The utilisation of modern contraceptives in refugee camps. Rwanda Public Heal Bull 2020;2:15-8.
3. Kavanaugh ML, Anderson RM, Levy M, Magar V, Sialondwe D, De Oliveira LH, *et al*. Contraception and beyond: The health benefits of services provided at family planning centers. New York: Guttmacher Institute, Inc.; 2013. Available from: https://www.guttmacher.org/pubs/health-benefits.pdf [Last accessed on 2023 Jul 25].
4. Prihati DR, Rohmawati W. Effect of injectable combination estrogen-progesterone and progesterone-only contraceptives on glucose and malondialdehyde serum. Int J Nurs Midwifery Sci 2020;4:118-23.
5. Yadav BK, Gupta RK, Gyawali P, Shrestha R, Poudel B, Sigdel M, *et al*. Effects of long-term use of depo-medroxyprogesterone acetate on lipid metabolism in Nepalese women. Korean J Lab Med 2011;31:95-7.
6. World Health Organization. Noncommunicable diseases country profiles. Geneva. Licence: CC BY-NC-SA 3.0 IGO.; 2018. Available from: https://apps.who.int/iris/handle/10665/274512 [Last accessed on 2023 Jul 31].
7. Clark MK, Dillon JS, Sowers M, Nichols S. Weight, fat mass, and central distribution of fat increase when women use depot-medroxyprogesterone acetate for contraception. Int J Obes (Lond) 2005;29:1252-8.
8. Owolabi EO, Ter Goon D, Adeniyi OV. Central obesity and normal-weight central obesity among adults attending healthcare facilities in buffalo city metropolitan municipality, south africa: A cross-sectional study. J Health Popul Nutr 2017;36:54.
9. Bastien M, Poirier P, Lemieux I, Després JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis 2014;56:369-81.
10. Hameed A, Majeed T, Rauf S, Ashraf M, Nasrullah M. Effect of oral and injectable contraceptives on serum calcium, magnesium, and phosphorus in women. J Ayub Med Coll Abbottabad 2001;13:24-5.
11. Reid IR, Gamble GD, Bolland MJ. Circulating calcium concentrations, vascular disease and mortality: A systematic review. J Intern Med 2016;279:524-40.
12. Santa S, Asiedu B, Ngala RA, Adjei JK, Anyorikeya M, Amoah BY, *et al*. Chronic use of hormonal contraceptives

and its impact on cardiovascular risk. Br J Med Med Res 2016; 17:1-11.
13. Ahmed IT, Hussein AH. Lipid profile changes in women in reproductive age group using injectable medroxyprogesterone acetate contraception. Med J Babylon 2015;12:802-16.
14. Fodor G. Primary prevention of CVD: Treating dyslipidaemia. Am Fam Physician 2011;83:1207-8.
15. O'Brien SH, Koch T, Vesely SK. Hormonal contraception and risk of thromboembolism in women with diabetes. Diabetes Care 2017;40:233-8.
16. Vlieg AV, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot - medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol 2010;30:2297-300.
17. Humphries KH, Izadnegadar M, Sedlak T, Saw J, Johnston N, Schenck-Gustafsson K, *et al*. Sex differences in cardiovascular disease - impact on care and outcomes. Front Neuroendocrinol 2018;46:46-70.
18. Woodward M. Cardiovascular disease and the female disadvantage. Int J Environ Res Public Health 2019;16:1165.
19. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ 2017;8:33.
20. Peters SA, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. Circulation 2019;139:1025-35.
21. Bonaventura A, Mach F, Roth A, Lenglet S, Burger F, Brandt KJ, *et al*. Intraplaque expression of C-reactive protein predicts cardiovascular events in patients with severe atherosclerotic carotid artery stenosis. Mediators Inflamm 2016;2016:9153673.
22. Ewid M, Sherif H, Billah SM, Saquib N, AlEnazy W, Ragab O, *et al*. Glycated hemoglobin predicts coronary artery disease in non-diabetic adults. BMC Cardiovasc Disord 2019;19:309.
23. Kim H. Statistical notes for clinical researchers: Sample size calculation 1. Comparison of two independent sample means. Restor Dent Endod 2016;41:74-8.
24. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, *et al*. Hypertension Canada's 2016 canadian hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2016;32:569-88.
25. Calling S, Johansson SE, Wolff M, Sundquist J, Sundquist K. The ratio of total cholesterol to high density lipoprotein cholesterol and myocardial infarction in Women's health in the Lund area (WHILA): A 17-year follow-up cohort study. BMC Cardiovasc Disord 2019;19:239.
26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 Suppl 1:S62-9.
27. Vasudevan DM, Sreekumari SK. In: Vij JP, editor. Textbook of biochemistry for medical students. 6th ed. New Delhi: Jaypee brothers medical publishers (P) Ltd.; 2011.
28. Singhal S, Sarda N, Wadhawan D, Gupta S. Short term use of injectable DMPA for contraception in immediate postpartum women. Indian Obstet Gynaecol 2017;7:26-33.
29. Okeke CU, Braide SA, Okolonkwo BN, Okafor RA, Eneh PC, Adegoke A, *et al*. Comparative effects of injectable and oral hormonal contraceptives on lipid profile. Eur J Cardiovasc Med 2011;2:20-2.
30. Faddah LM, Al-Rehany MA, Abdel-Hamid NM, Bakeet AA. Oxidative stress, lipid profile and liver functions in average egyptian long term depo medroxy progesterone acetate (DMPA) users. Molecules 2005;10:1145-52.
31. Zerihun MF, Malik T, Ferede YM, Bekele T, Yeshaw Y. Changes in body weight and blood pressure among women using DepoProvera injection in Northwest Ethiopia. BMC Res Notes 2019;12:512.
32. Asare GA, Santa S, Ngala RA, Afriyie D, Asiedu B, Amoah AG. Effect of hormonal contraceptives on lipid profile and the risk indices for cardiovascular disease in a Ghanaian community. Int J Womens Health 2014;6:597-603.
33. Haroon S, Naveed AK. Effect of hormonal contraceptives on serum electrolytes and blood pressure. J Post Med Inst 2014;28:409-13.
34. Naqvi R, Nuhmani S. Current concepts in obesity management. Int J Sci Res 2015;6:2319-7064.
35. McKinney L, Skolnik N, Chrusch A. Diagnosis and management of obesity. American academy of family physician. 2013. Available from: https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=bdd1f85a6b96831b4aef1ecd633cffca39b53bce [Last accessed on 2023 Jun 25].
36. Kim SW, Jeon JH, Lee WK, Lee S, Kim JG, Lee IK, *et al*. Long-term effects of oral contraceptives on the prevalence of diabetes in post-menopausal women: 2007-2012 KNHANES. Endocrine 2016;53:816-22.
37. Divani AA, Luo X, Datta YH, Flaherty JD, Panoskaltsis-Mortari A. Effect of oral and vaginal hormonal contraceptives on inflammatory blood biomarkers. Mediators Inflamm 2015;2015:3759501.
38. Van Rooijen M, Hansson LO, Frostegård J, Silveira A, Hamsten A, Bremme K. Treatment with combined oral contraceptives induces a rise in serum C-reactive protein in the absence of a general inflammatory response. J Thromb Haemost 2006;4:77-82.
39. Sabania BF, Murti B, Hanim D. Association between hormonal contraception and blood glucose level among women of childbearing age in Sangkrah community health center, Surakarta. Indones J Med 2016;1:1-11.
40. Alisigwe OJ. An assessment of hormonal contraceptives on plasma glucose and lipid profile of women attending family planning clinic at Keffi, Nasarawa. Int J Res Sci Innov 2019;6:103-18.
41. Kim C, Siscovick DS, Sidney S, Lewis CE, Kiefe CI. Oral contraceptive use and association with glucose, insulin, and diabetes. Diabetes Care 2002;25:1027-32.

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