Dyslipidaemias in women using hormonal contraceptives: a cross sectional study in Mulago Hospital Family Planning Clinic, Kampala, Uganda

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ABSTRACT

Objective To determine the prevalence and factors associated with dyslipidaemias in women using hormonal contraceptives.

Design Cross-sectional study

Setting Mulago Hospital, Kampala, Uganda

Participants Three hundred and eighty-four consenting women, aged 18–49 years, who had used hormonal contraceptives for at least 3 months prior to the study.

Study outcome Dyslipidaemias (defined as derangements in lipid profile levels which included total cholesterol ≥200 mg/dL, high-density lipoprotein <40 mg/dL, triglyceride >150 mg/dL or low-density lipoprotein ≥160 mg/dL) for which the prevalence and associated factors were obtained.

Results The prevalence of dyslipidaemias was 63.3% (95% CI: 58.4 to 68.1). Body mass index (BMI) (PR=1.33, 95% CI: 1.15 to 1.54, p<0.001) and use of antiretroviral therapy (ART) (PR=1.21, 95% CI: 1.03 to 1.42, p=0.020) were the factors significantly associated with dyslipidaemias.

Conclusion Dyslipidaemias were present in more than half the participants, and this puts them at risk for cardiovascular diseases. The high-risk groups were women with a BMI greater than 25 Kg/m2 and those who were on ART. Therefore, lipid profiles should be assessed in women using hormonal contraceptives in order to manage them better.

INTRODUCTION

Globally, the use of contraception has risen slightly, from 54.7% in 1990 to 64% in 2015.1 In Uganda particularly, the contraceptive prevalence rate (CPR) is currently 27.2% with hormonal contraceptives (HCs) accounting for 77.9% of the total contraceptive use.1 Among the HCs used in Uganda, injectables are the most common (72.8%), followed by oral contraceptives (14.3%) and implants (12.9%).2 Several researchers have reported the complications and side effects associated with the use of HCs.3–5 The side effects include nausea and vomiting, headaches, dizziness, breast tenderness and enlargement, irregular bleeding or bleeding between periods, and weight gain. The adverse effects include metabolic impairment, cardiovascular complications, and an increased risk of cancer and liver problems.3 It has been suggested that some of these complications are a consequence of dyslipidaemias, a potential metabolic impairment effect of long-term use of some HCs.5 Furthermore, a study by Schueller and colleagues suggested that dyslipidaemias could also arise from the hormones increasing apolipoprotein B-100 synthesis which subsequently increases triglyceride and Low Density Lipoprotein (LDL) levels.4

Several factors predispose HC users to dyslipidaemias. The factors include age, race, lifestyle and diseases such as hypertension...
and diabetes mellitus. Medications especially ART and steroids also contribute.5–9 Many of these factors are common in Uganda. For example, 16% of the women in Uganda were found to be obese.10 Obesity is associated with alterations in lipid profile levels. In the presence of HC use, obesity makes the risk of dyslipidaemias worse.6 7 In addition, 79% of all women with HIV infection of reproductive age in Uganda are on antiretroviral therapy (ART).11 Some antiretroviral drugs alter lipid profile levels, hence causing dyslipidaemias.12 13

Poorly managed dyslipidaemias can result into cardiovascular diseases such as venous thromboembolism, myocardial infarction and stroke.14 However, lipid profile levels are not routinely measured in women using HCs in Uganda. Therefore, the objective of this study was to determine the prevalence and factors associated with dyslipidaemias in women using HCs at Mulago Hospital Family Planning Clinic, Kampala in Uganda.

METHODS

Study design, setting and population

This was a cross-sectional study employing both descriptive and analytical techniques carried out from Mulago Hospital Family Planning Clinic in Uganda’s Capital City, Kampala from March to April 2017. This clinic receives approximately 320 patients monthly, 215 of whom are on HCs. Using the consecutive sampling procedure, 384 consenting women aged 18–49 years were enrolled into this study. They had to have used HCs for at least 3 months prior to the study. Women who were unable to comprehend either English or Luganda (the local language used in Central Uganda) or those physically or mentally unable to adhere to study procedures such as giving of consent and the interview process, were excluded from the study.

Sample size calculation

The Leslie Kish formula15 was used to estimate the sample size for the prevalence objective. We assumed a prevalence of dyslipidaemias of 33.9% among women on oral contraceptives according to a study by Machado et al in Brazil16 and 95% CIs. This gave a sample size of 345. We also accounted for 10% missing data in the calculation of the sample size. Hence, the final sample size was 380.

For the factors associated with dyslipidaemias, the formula for comparing means in two proportions17 was used. We assumed an error of 0.05, power of 80% and 95% confidence level; and that 33.9% of women using oral contraceptives would develop dyslipidaemias compared with only 16.9% of those using non-oral contraceptives. We also assumed that the oral CPR in Uganda is 14.3%.2 This gave a sample size of 384.

Data collection

A questionnaire was administered to collect basic information on age, parity, highest level of education, occupation, type of HC used, duration of use of HCs, use of antiretroviral drugs and history of hypertension. Body mass index (BMI) was determined by measuring weight using the Seca weighing scale and height using a Seca stadiometer. BMI was then computed as weight (in kg)/height (in m²). Blood samples were aseptically collected from participants after a 6-hour fast and placed in a red top vacutainer without an anticoagulant for the determination of lipid profile levels. The samples were allowed to clot for at least 3 min and centrifuged at 2400 revolutions/min for 5 min. The serum obtained was pipetted into Cobas 6000 caps and taken for analysis using the Cobas 6000 chemistry analyser (Roche Diagnostics, USA). Fasting blood sugar levels were determined using a Freestyle glucometer (Abott Laboratories, Canada) for all the participants 6 hours after their last meal. A sterile single use lancet was used to prick the participant’s disinfected finger and a small drop of the blood placed onto the glucometer strip already mounted into the glucometer. The blood sugar level was read off and recorded in mg/dL.

Outcome variable

The outcome variable for this study was dyslipidaemias defined as derangements in lipid profile levels which included a total cholesterol of 200mg/dL or greater, a high-density lipoprotein cholesterol of less than 40mg/dL, triglyceride of greater than 150mg/dL or low-density lipoprotein cholesterol of 160mg/dL or greater according to the Guidelines for the Diagnosis and Management of Dyslipidaemias for Adults.18 A participant was said to have dyslipidaemias if he/she had any of the lipid profile parameters in ranges stated above. The presence of dyslipidaemias was coded as ‘1’ and its absence as ‘0’.

Statistical analysis

Data were analysed using STATA V.13.0 (StataCorp. 2013. Stata Statistical Software: Release 13) in which all continuous variables were summarised as medians and ranges while the categorical variables were summarised as percentages and proportions. The prevalence of dyslipidaemias was calculated as the percentage of women with dyslipidaemias over the total number of women in the study. The modified Poisson regression model was used to analyse the factors associated with dyslipidaemias in women using HCs. In the multivariate analysis, variables which were significantly associated with dyslipidaemias (p<0.05) were used to form two-way product terms that were used in the assessment of interaction using the chunk test. Where necessary, confounding was assessed for. Confounders were retained only if they changed the estimates by greater than or equal to 10%. CIs were presented at 95% level of significance along with the p values. Statistical significance was considered at a p value of less than or equal to 0.05.

Patient and public involvement

Due to patients’ experiences and concerns raised about excessive weight gain while on HCs, we felt the need to
determine whether long-term use of HCs (more than 3 months) has an effect on lipid profile levels. Hence, patient experiences informed our research questions and study outcomes.

Patients were involved in the design of the study through their contribution to the refining of the data-collection tool. This was mainly during pretesting or piloting of the questionnaires. Results were disseminated to study participants through the use of text messages and fliers. The fliers, printed both in English and Luganda, were issued out at the family planning clinic.

RESULTS
Participants’ characteristics
The median age of the 384 participants was 28 years (IQR: 18–49). An estimated 59.1% (227/384) of the participants had attained only up to secondary education, 74.2% (285/384) had at least two or more children and 39.6% (152/384) were self-employed. Only 11 (2.9%) had high fasting blood sugar levels (≥120 mg/dL), 14 (3.7%) had a history of hypertension, 140 (36.5%) had a BMI >25 and 78 (20.3%) were on ART. Most of the participants (48.2%) were using progestin-only injectables, and 219 (57%) had used HCs for over a year (table 1).

Prevalence of dyslipidaemias
The prevalence of dyslipidaemias among the 384 participants was 63.3% (95% CI: 58.4 to 68.1). Dyslipidaemias were higher in women aged above 28 years (68.0%) compared with those who were younger. The prevalence of dyslipidaemias was also higher in participants who had attained up to tertiary education (75%) than those who had acquired lower education. Furthermore, participants who had high fasting blood sugar levels (≥120 mg/dL) had more dyslipidaemias (81.8%) than those who had normal blood sugar levels (table 2).

Factors associated with dyslipidaemias
Variables significantly associated with dyslipidaemias included BMI greater than 25 kg/m² (PR=1.33, 95% CI: 1.15 to 1.54, p<0.001) and ART use (PR=1.21, 95% CI: 1.03 to 1.42, p=0.020). These variables were further assessed for interaction between each other and for confounding with other independent variables. However, there was no interaction and the association between dyslipidaemias and these variables was not confounded by any other independent variables. Therefore, BMI and ART use were the only independent factors associated with dyslipidaemias (table 3).

DISCUSSION
Dyslipidaemias were present in more than half the participants. This high prevalence of dyslipidaemias could be an overestimate in the general population because of the differences in these populations. This study had a higher prevalence of ART users (20.3%) than what is reported in the general population (less than 5%). Since ART use is associated with dyslipidaemias, the high prevalence obtained could have been as a result of the high percentage on ART.

The presence of dyslipidaemias in HC users has been reported by several other studies which found significant changes in the lipid profile levels of HC users. These

| Variable                      | Number (n=384) | Percentage (%) |
|-------------------------------|---------------|---------------|
| Age (categorised at the median) |               |               |
| 18–28                         | 215           | 56            |
| 29–49                         | 169           | 44            |
| Median (IQR): 28 (18–49)      |               |               |
| Education                     |               |               |
| No formal education            | 14            | 3.6           |
| Primary                       | 107           | 27.9          |
| Secondary                     | 227           | 59.1          |
| Tertiary                      | 36            | 9.4           |
| Parity                        |               |               |
| 0–1                           | 99            | 25.8          |
| Two or more                   | 285           | 74.2          |
| Fasting blood sugar           |               |               |
| Normal (<120 mg/dL)           | 373           | 97.1          |
| High (≥120 mg/dL)             | 11            | 2.9           |
| History of hypertension       |               |               |
| No                            | 370           | 96.3          |
| Yes                           | 14            | 3.7           |
| Body mass index (BMI)         |               |               |
| ≤25                           | 244           | 63.5          |
| >25                           | 140           | 36.5          |
| Antiretroviral therapy use    |               |               |
| No                            | 306           | 79.7          |
| Yes                           | 78            | 20.3          |
| Hormonal contraceptive used   |               |               |
| Progestin-only pill           | 5             | 1.3           |
| Combined oral pill            | 38            | 9.9           |
| Progestin-only injectable     | 185           | 48.2          |
| Combined Injectable Contraceptive (CIC) | 8 | 2.1 |
| Implant (one rod)             | 124           | 32.3          |
| Implant (two rods)            | 24            | 6.2           |
| Duration of use of hormonal contraceptive |       |               |
| <6 months                     | 124           | 32.3          |
| 6–11 months                   | 41            | 10.7          |
| ≥12 months                    | 219           | 57            |
changes in the lipid profile levels can be attributed to the lipogenic effect of oestrogen in which liver lipogenesis is increased and results in elevated levels of triglycerides and LDL levels.20 Furthermore, the progestin component of HCs increases hepatic lipase enzyme activity which increases the removal of HDL, hence decreasing the serum HDL levels.21

The factors significantly associated with dyslipidaemias in women using HCs were BMI and ART use. Participants who had a BMI greater than 25 kg/m² were 33% more likely to have dyslipidaemias compared with those who had a BMI of 25 kg/m² or less. This is in line with the findings from a systematic review by Halperin and colleagues in 2011. Halperin et al's study reported that differences in average BMI of women in the individual cohorts explained a portion of the heterogeneity found in High Density Lipoprotein-Cholesterol (HDL-C) levels.7 These changes can be attributed to BMI independently affecting lipid profile levels as reported by studies which observed a significant association between high BMI and the occurrence of dyslipidaemias.22 23 A study by Shamai and colleagues reported a significant association between

| Table 2 Prevalence of dyslipidaemias according to social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March–April 2017 |
|-------------------------------|--------------------|---------------------|----------------------|----------------------|
| Variable                      | Dyslipidaemias     | No dyslipidaemias, n (%) | Prevalence ratio (95% CI) | P values |
| Overall prevalence of dyslipidaemias | 243 (63.3) | 141 (36.7) | 58.4 to 68.1 |
| Age (categorised at the median) |                    |                       |                      |           |
| 18–28                          | 128 (59.5) | 87 (40.5) | 1 |
| 29–49                          | 115 (68.0) | 54 (32.0) | 1.14 (0.98 to 1.32) | 0.083 |
| Median=28 (18–49)               |                    |                       |                      |           |
| Education                      |                    |                       |                      |           |
| No formal education            | 6 (42.9) | 8 (57.1) | 0.68 (0.37 to 1.25) | 0.21 |
| Primary                        | 66 (61.7) | 41 (38.3) | 0.97 (0.81 to 1.16) | 0.759 |
| Secondary                      | 144 (63.4) | 83 (36.6) | 1 |
| Tertiary                       | 27 (75.0) | 9 (25.0) | 1.18 (0.96 to 1.46) | 0.124 |
| Parity                         |                    |                       |                      |           |
| 0–1                            | 59 (59.6) | 40 (40.4) | 1 |
| ≥2                             | 184 (64.6) | 101 (35.4) | 1.08 (0.90 to 1.30) | 0.394 |
| Fasting blood sugar            |                    |                       |                      |           |
| Normal                         | 234 (62.7) | 139 (37.3) | 1 |
| High                           | 9 (81.8) | 2 (18.2) | 1.30 (0.98 to 1.74) | 0.072 |
| History of hypertension        |                    |                       |                      |           |
| No                             | 235 (63.5) | 135 (36.5) | 1 |
| Yes                            | 8 (57.1) | 6 (42.9) | 0.90 (0.57 to 1.43) | 0.653 |
| Body mass index                |                    |                       |                      |           |
| ≤25                            | 138 (56.6) | 106 (43.4) | 1 |
| >25                            | 105 (75.0) | 35 (25.0) | 1.33 (1.15 to 1.53) | <0.001 |
| Antiretroviral therapy use     |                    |                       |                      |           |
| No                             | 186 (60.8) | 120 (39.2) | 1 |
| Yes                            | 57 (73.1) | 21 (26.9) | 1.20 (1.02 to 1.41) | 0.026 |
| Hormonal contraceptive used    |                    |                       |                      |           |
| Oral contraceptives            | 22 (51.2) | 21 (48.8) | 1.77 (0.57 to 1.05) | 0.1 |
| Injectables                    | 128 (66.3) | 65 (33.7) | 1 |
| Implants                       | 93 (63.8) | 55 (35.2) | 0.95 (0.81 to 1.11) | 0.508 |
| Duration of use of hormonal contraceptive | | | | |
| 77 (62.1) | 47 (37.9) | 1 |
| 6–11 months                    | 22 (53.7) | 19 (45.2) | 0.86 (0.63 to 1.19) | 0.366 |
| ≥12 months                     | 144 (65.8) | 75 (33.6) | 1.06 (0.90 to 1.25) | 0.504 |
BMI and both triglyceride and HDL levels which was attributed to insulin resistance.23

ART use was the other factor associated with dyslipidaemias in women using HCs. Women who were using ART were 21% more likely to have dyslipidaemias than those who were not. This is one of the first studies to report on dyslipidaemias in ART users on HCs; therefore, there are no studies with which to compare our results. These changes in lipid profile levels can be attributed to some ART regimens exerting distinct alterations in lipid metabolism, hence bringing about dyslipidaemias.13 A study by Bekolo and colleagues in 2014 demonstrated a high prevalence of dyslipidaemias in patients with HIV infection on first-line ART in Cameroon.12

Some of the strengths of this study are: this is one of the first studies assessing dyslipidaemias in women using HCs to be carried out in Uganda. This contributes to further understanding and possibly, better management of dyslipidaemias in women using HCs. In addition, standardised approaches were used when carrying out this study, and this permits the study to be replicated in different areas or over time with an assurance that the results produced will have comparable findings.

We acknowledge the following limitations. The findings of this study may not be generalisable to all HC users because the sample is not representative enough. The sampling procedure used was non-probability, and this does not allow equal opportunity to all women to participate. As this was a cross-sectional study, a causal relationship cannot be established between HC use and dyslipidaemias. Since questionnaires were used for data collection, some of the self-reported information may have been inaccurate, hence affecting some of the results. Finally, information on the physical activity and diet of the study participants was not collected. This information is important since these variables play a significant role in the study participants was not collected. This information

In conclusion, more than half the women using HCs have dyslipidaemias, and this in the long run increases their risk for cardiovascular disease.

We therefore recommend the Uganda Ministry of Health to formulate policy to better manage women using HCs. The policy should include checking lipid profile levels prior to initiation of HC use and also continued assessment at regular intervals while using contraceptives. The policy should in particular target the high-risk group that includes women whose BMI is greater than 25 kg/m² and/or are on ART. Further studies are urgently needed to explore whether the relationship between dyslipidaemias and HC use is causal.

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### Contributors

RB conceptualised the study, designed it, planned the analysis, did the result interpretation and wrote the manuscript. She is the guarantor and responsible investigator of the study. PB-K planned and supervised the study, interpreted results and revised the manuscript. JNK planned the study, contributed in acquisition of funds, interpreted results and revised the manuscript. GN, IN, GSN and FO; planned the study and contributed in analysis. CK conceptualised, planned and supervised the study, interpreted results and reviewed the manuscript. All authors have read the final manuscript.

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### Competing interests

None declared.

### Patient consent

Not required.

### Ethics approval

Ethical approval was obtained from the School of Medicine Research Ethics Committee and the Uganda National Council for Science and Technology. Administrative clearance was obtained from the Research and Ethics Committee of Mulago National Referral Hospital.

### Provenance and peer review

Not commissioned; externally peer reviewed.

### Data sharing statement

All available data can be obtained by contacting the corresponding author.

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