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

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

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ABSTRACT

Objective: The aim of this study was to determine the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

Design: Cross sectional study

Setting: Mulago Hospital, Kampala

Participants: 384 women aged 18 to 49 years who had used hormonal contraceptives for atleast three months and consented to participate in the study were included in the study.

Study outcome: Dyslipidemias defined as derangements in lipid profile levels for which the prevalence and associated factors were obtained.

Results: The prevalence of dyslipidemias was 63.3% (95% CI: 58.4 – 68.1), with the commonest form of dyslipidemias being elevated LDL levels (≥160 mg/dl) in 187 (48.7%) of the participants. Body Mass Index (BMI) (PR=1.33, 95% CI: 1.15-1.54, p<0.001) and use of anti-retroviral therapy (ART) (PR=1.21, 95% CI: 1.03-1.42, p=0.020) were the factors found to be significantly associated with dyslipidemias.

Conclusion: Dyslipidemias were present in more than half of the participants and this increases their risk for cardiovascular diseases. The high risk groups were women with a BMI greater than 25 and women who were on ART. Lipid profiles should therefore be assessed in women using hormonal contraceptives for their better management.

Keywords: Hormonal Contraceptives, Contraception, Dyslipidemias, Lipid profile

Strengths and limitations of the study

i)   This being one of the first studies in Uganda to assess dyslipidemias in women using hormonal contraceptives, the cross sectional study design used was the most appropriate to provide baseline information.

ii) Standard approaches were used to carry out the study to ensure repeatability and reproducibility.

iii) Selection procedure used is non-probability so results may not be generalisable to all hormonal contraceptive users.

iv) This being a cross-sectional study, a causal relationship between hormonal contraceptive use and dyslipidemias cannot be ascertained.

v) The results may have been subject to information bias because questionnaires were used to obtain information on some variables which are based on recall.

INTRODUCTION

Globally, the use of contraception has risen slightly, from 54.7% in 1990 to 64% in 2015 [1] and in Uganda particularly, the Contraceptive Prevalence Rate (CPR) is currently at 27.2% with hormonal contraceptives (HCs) accounting for 77.9% of the total contraceptive use.[1] HCs are the most commonly used contraception methods in Uganda, the injectables being the most common at a rate of 72.8%, followed by the oral contraceptive at 14.3%, and finally the implants at 12.9%.[2]

Several researchers have reported the complications and side-effects associated with the use of these hormonal contraceptives which include nausea and vomiting, headaches, dizziness, breast tenderness and enlargement, irregular bleeding or bleeding between periods, and weight gain as the side effects and adverse effects like metabolism impairment, heart and circulation complications, venous thromboembolism, an increased risk of cancer, and liver problems.[3] It has been suggested that some of the aforementioned complications are a consequence of dyslipidemias, a potential metabolic impairment effect of long term use of some of these hormonal contraceptives.[4] Furthermore, a study by Schueller and his colleagues suggested that these dyslipidemias could also rise as a result of these hormones

increasing apolipoprotein B-100 synthesis which subsequently increases triglyceride and LDL levels.[5]

Several factors have been reported to predispose hormonal contraceptive users to dyslipidemias like age, race, body weight, lifestyle, use of other medications like ART, steroids and pre-existing diseases like hypertension, diabetes mellitus and obesity. Many of these factors are common in Uganda. For example, 16% of the females in Uganda were found to be obese.[6] Obesity is associated with alterations in lipid profile levels, and this, in the presence of hormonal contraceptive use increases the risk of dyslipidemias.[7, 8] In addition, 38,484 women in Uganda were reported to be on anti-retroviral therapy (ART) between June 2010 and March 2017.[9] Some of these antiretroviral drugs alter lipid profile levels hence bringing about dyslipidemias.[10, 11]

Poorly managed dyslipidemias can result into cardiovascular diseases like venous thromboembolism, myocardial infarction and stroke.[12] However, lipid profile levels are not measured in women using hormonal contraceptives in Uganda because little is known about the dyslipidemic effect of hormonal contraceptives. This study therefore aimed at determining the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

METHODS

Study design, setting and population

This was a quantitative cross sectional study employing both descriptive and analytical techniques carried out from Mulago Hospital Family Planning Clinic, Kampala in March and April, 2017. Using the consecutive sampling procedure, a total of 384 women aged 18 to 49 years who had used hormonal contraceptives for atleast three months and consented to participate in the study were included in the study, and all women who were unable to comprehend either English or Luganda and could not adhere to study procedures were

excluded from the study. For ethical considerations, necessary permission to carry out this study was obtained from all relevant bodies, informed consent obtained from all the participants before enrolment into the study and confidentiality highly maintained.

Data collection

A questionnaire was administered to collect basic information on age, parity, highest level of education, occupation, type of hormonal contraceptive used, duration of use of hormonal contraceptives, use of anti-retroviral drugs and history of hypertension. Body Mass Index (BMI) was determined by measuring weight using the Seca weighing scale and height using a stadiometer. BMI was then computed as Weight (in Kg)/Height (in metres squared). Blood samples were collected from participants after a 6 hour fast for the determination of fasting blood sugar and lipid profile levels. Lipid profile levels were assessed using the Cobas 6000 Chemistry analyser.

Outcome variable

The outcome variable for this study was dyslipidemias defined as derangements in the lipid profile levels which included a total cholesterol level of 200 mg/dL or greater, a high-density lipoprotein cholesterol level of less than 40 mg/dL, a triglyceride level of greater than 150 mg/dL, or a low-density lipoprotein cholesterol level of 160 mg/dL or greater according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines.[13] A participant was said to have dyslipidemias if they had any of the lipid profile parameters in ranges stated above. The presence of dyslipidemias was coded as "1" and its absence as "0".

Statistical analysis

Data were analysed using STATA version 13.0 in which all continuous variables were summarised as medians and ranges while the categorical variables were summarised as percentages and proportions. The prevalence of dyslipidemias was calculated as the

percentage of women with dyslipidemias over the total number of women in the study. The modified Poisson regression model was used to analyse the factors associated with dyslipidemias in women using hormonal contraceptives. In the multivariate analysis, confounders were retained only if they changed the estimates by greater than or equal to 10%. Confidence intervals 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.

RESULTS

Participants' characteristics

The median age of the 384 participants was 28 years (IQR: 18 – 49) and 59.1% (227/384) of the participants had attained only up to secondary education, 74.2% (285/384) had atleast two or more children and 39.6% (152/384) were self-employed. Only 11 (2.9%) had high fasting blood sugar levels ($\geq$ 120 mg/dl), 14 (3.7%) had a history of hypertension, 140 (36.5%) had a BMI >25 and 78 (20.3%) were on anti-retroviral therapy (ART). Most of the participants were using Progestin-Only Injectables - 185 (48.2%) and 219 (57.0%) had used hormonal contraceptives for over a year (Table 1).

Table 1: Social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Number (N=384)	Percentage (%)
Age (Categorised at the median)		
18 – 28	215	56.0
29 – 49	169	44.0
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

ART Use
No   306   79.7
Yes   78   20.3

Hormonal Contraceptive Used
Progestin Only Pill (POP)   5   1.3
Combined Oral Pill (COP)   38   9.9
Progestin Only Injectable (POI)   185   48.2
Combined Injectable Contraceptive (CIC)   8   2.1
Implant (1 rod)   124   32.3
Implant (2 rods)   24   6.2

Duration of use of HC
<6 months   124   32.3
6 to 11 months   41   10.7
12 or more months   219   57.0

Prevalence of dyslipidemias

The prevalence of dyslipidemias amongst the 384 participants was 63.3% (95% CI: 58.4 –

68.1). Dyslipidemias were higher in women aged above 28 years – 68.0% (115/169)

compared to those who were younger. The prevalence of dyslipidemias was also higher in

participants who had attained up to tertiary education – 75% (27/36) than those who had

acquired lower education. Furthermore, considering the clinical factors, participants who had

high fasting blood sugar levels (≥120 mg/dl) had more dyslipidemias– 75% (9/12) than those

who had normal blood sugar levels (Table 2).

Table 2: Prevalence of dyslipidemias according to social demographic and clinical

characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning

Clinic in Kampala, March to April, 2017

Variable	Dyslipidemias Present	No Dyslipidemias	Prevalence Ratio (95% CI)	P-Value

	No. (%)	No. (%)		
Overall prevalence of dyslipidemias	243 (63.3)	141 (36.7)	58.4 – 68.1	
Age (Categorised at the median)				
18 – 28	128 (59.5)	87 (40.5)		
29 – 49	115 (68.0)	54 (32.0)	1.00	
Median = 28 (18 – 49)			1.14 (0.98 – 1.32)	**0.083**
Education				
No formal education	6 (42.9)	8 (57.1)	0.68 (0.37 – 1.25)	**0.210**
Primary	66 (61.7)	41 (38.3)	0.97 (0.81 – 1.16)	**0.759**
Secondary	144 (63.4)	83 (36.6)	1.00	
Tertiary	27 (75.0)	9 (25.0)	1.18 (0.96 – 1.46)	**0.124**
Parity				
0 - 1	59 (59.6)	40 (40.4)	1.00	
≥2	184 (64.6)	101 (35.4)	1.08 (0.90 – 1.30)	0.394
Fasting Blood Sugar				
Normal	234 (62.7)	139 (37.3)	1.00	
High	9 (81.8)	2 (18.2)	1.30 (0.98 – 1.74)	**0.072**
History of Hypertension				
No	235 (63.5)	135 (36.5)	1.00	
Yes	8 (57.1)	6 (42.9)	0.90 (0.57 – 1.43)	0.653
Body Mass Index				
≤25	138 (56.6)	106 (43.4)	1.00	
>25	105 (75.0)	35 (25.0)	1.33 (1.15 – 1.53)	<**0.001**
ART Use				
No	186 (60.8)	120 (39.2)	1.00	
Yes	57 (73.1)	21 (26.9)	1.20 (1.02 – 1.41)	**0.026**
Hormonal Contraceptive Used				
Oral Contraceptives	22 (51.2)	21 (48.8)	1.77 (0.57 – 1.05)	**0.100**
Injectables	128 (66.3)	65 (33.7)	1.00	
Implants	93 (63.8)	55 (35.2)	0.95 (0.81 – 1.11)	**0.508**
Duration of use of HC				
<6 months	77 (62.1)	47 (37.9)	1.00	
6 to 11 months	22 (53.7)	19 (45.2)	0.86 (0.63 – 1.19)	0.366
12 or more months	144 (65.8)	75 (33.6)	1.06 (0.90 – 1.25)	0.504

Factors associated with dyslipidemias

The variables that were found to be significantly associated with dyslipidemias were BMI (PR=1.33, 95% CI: 1.15 – 1.54, p<0.001) and ART use (PR= 1.21, 95% CI: 1.03 – 1.42, p=0.020). These variables were further assessed for interaction between each other and for

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confounding with other independent variables; however there was no interaction and the association between dyslipidemias and these variables was not confounded by any other independent variables. Therefore, BMI and ART use were the only independent factors associated with dyslipidemias (Table 3).

Table 3: Multivariate analysis of the factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Prevalence Ratio	95% Confidence Interval	P-value
Body Mass Index			
≤25	1.00		
>25	1.33	1.15 – 1.54	<0.001
ART Use			
No	1.00		
Yes	1.21	1.03 – 1.42	0.020

DISCUSSION

Dyslipidemias were found to be present in more than half of the participants. This high prevalence of dyslipidemias could be an overestimate in the general population because of the differences in these populations; the population in this study had a higher prevalence of ART users (20.3%) than what is reported in the general population (less than 5%),[9] and since ART use is associated with dyslipidemias, the high prevalence could have been as a result of the high percentage on ART. The presence of dyslipidemias in hormonal contraceptive users has been reported by several other studies which found significant changes in the lipid profile levels of hormonal contraceptive users.[8, 12, 14, 15] These changes in the lipid profile levels can be attributed to the lipogenic effect of estrogen in which liver lipogenesis is increased that results in elevated levels of Triglycerides and LDL

levels [16]. Furthermore, the progestin component of hormonal contraceptives increases hepatic lipase enzyme activity which increases the removal of HDL hence decreasing the serum HDL levels.[17] These results are however contradicted by a study in a China by Wei and his colleagues in 2011 which found no significant association between oral contraceptive use and the risk of dyslipidemias.[18] Wei's study used the same classification of dyslipidemias with the current study (as the presence of one or more abnormal serum lipid profile level), so the difference could have arisen from the fact that Wei's study used a case control design while the current study used a cross sectional design.

The factors found to be significantly associated with dyslipidemias in women using hormonal contraceptives were BMI and ART use. Participants who had a BMI greater than 25 were 33% more likely to have dyslipidemias compared to those who had a BMI of 25 or less. This is in line with the findings from a systematic review conducted by Halperin and his colleagues in 2011 which reported that differences in average BMI of women in the individual cohorts explained a portion of the heterogeneity found in HDL-C levels.[7] These changes can be attributed to the fact that BMI can independently affect lipid profile levels as reported by several studies which observed a significant association between high BMI and the occurrence of dyslipidemias.[19, 20] The study by Shamai and his colleagues found a significant association between BMI and both Triglyceride and HDL levels, which was explained by insulin resistance.[20]

ART use was the other factor associated with dyslipidemias in women using hormonal contraceptives. Women who were using anti-retroviral therapy (ART) were 21% more likely to have dyslipidemias than those who were not. These findings should however be treated with caution because of the small numbers who were on anti-retroviral therapy in this study. Unfortunately, this is one of the first studies to report on dyslipidemias in ART users on hormonal contraceptives; therefore there are no comparative study findings to use. These

changes in lipid profile levels can be attributed to the fact that different ART regimens have been reported to independently alter lipid profile levels hence aggravating the presence of dyslipidemias. A study by Bekolo and his colleagues in 2014 demonstrated a high prevalence of dyslipidemias in HIV patients on first line anti-retroviral therapy in Cameroon.[10] This was attributed to the fact that some ART regimens exert distinct alterations in lipid metabolism hence bringing about dyslipidemias.[11]

Some of the strengths of this study are: This is one of the first studies assessing dyslipidemias in women using hormonal contraceptives to be carried out in Uganda and this contributes to further understanding and possibly better management of dyslipidemias in women using hormonal contraceptives. 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 hormonal contraceptive users because the sample is not representative enough and also because the sampling procedure was non-probability which does not allow equal opportunity to all women to participate. This study was only a cross sectional study so a causal relationship cannot be ascertained between hormonal contraceptive use and dyslipidemias. Since questionnaires were used for data collection, some of the self-reported information may have been inaccurate or incomplete hence affecting some of the results. Finally, information on the physical activity and diet of the study participants was not collected which is deemed important for this study since these variables play a significant role in changing lipid profile levels.

In conclusion, more than half of the women using hormonal contraceptives have dyslipidemias and are thus at an increased risk of acquiring cardiovascular diseases. Hormonal contraceptive users who had a BMI greater than 25 and / or were on anti-retroviral

therapy were more likely to have dyslipidemias 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 hormonal contraceptives. The policy should include checking lipid profile levels prior to initiation of hormonal contraceptive use and also continued assessment of lipid profiles at regular intervals while using these contraceptives. The policy should in particular target the high risk group that includes women whose BMIs are greater than 25 and / or are on ART. We also recommend that future research is done to replicate the study in different populations and also explore whether the relationship between dyslipidemias and hormonal contraceptive use is causal.

Author contribution:

Ritah Bakesiima 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. **Pauline B Kibwika** planned and supervised the study, interpreted results, and reviewed the manuscript. **James Tumwine** planned the study, contributed in acquisition of funds, interpreted results and revised the manuscript. **Joan N Kalyango** planned and supervised the study and analysis, interpreted results, and revised the manuscript. **Gloria Nabaasa** planned the study, contributed in analysis and reviewed the manuscript. **Irene Najjingo** planned the study, contributed in analysis and reviewed the manuscript. **Grace S Nabaggala** planned the study, contributed in analysis and reviewed the manuscript. **Francis Olweny** planned the study, contributed in analysis and reviewed the manuscript. **Charles Karamagi** conceptualised, planned and supervised the study, interpreted results and reviewed the manuscript.

Competing interests: The authors declare no competing interests.

Ethical approval: Ethical approval was obtained from the School of Medicine Research Ethics Committee and administrative clearance obtained from Research and Ethics Board of Mulago National Referral Hospital.

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

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	4-6
5	Type of study designs used	5-7
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, Table 1
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	8, Table 2, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	Tables 2-7, Figs 2-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 3-7
26	Table giving descriptive information for each study included	Table 2
27	Results of sensitivity testing (eg, subgroup analysis)	Fig 3, Table 3
28	Indication of statistical uncertainty of findings	12-16

Item No	Recommendation	Reported on Page No
	Reporting of discussion should include	
29	Quantitative assessment of bias (eg, publication bias)	12, Fig 2
30	Justification for exclusion (eg, exclusion of non-English language citations)	6
31	Assessment of quality of included studies	6-7
	Reporting of conclusions should include	
32	Consideration of alternative explanations for observed results	17-19
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	20
34	Guidelines for future research	-
35	Disclosure of funding source	20

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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

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

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ABSTRACT

Objective: The aim of this study was to determine the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

Design: Cross sectional study

Setting: Mulago Hospital, Kampala

Participants: Three hundred eighty four women aged 18 to 49 years who had used hormonal contraceptives for atleast three months and consented to participate in the study were included in the study.

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

Results: The prevalence of dyslipidemias was 63.3% (95% CI: 58.4 – 68.1). Body Mass Index (BMI) (PR=1.33, 95% CI: 1.15-1.54, p<0.001) and use of anti-retroviral therapy (ART) (PR=1.21, 95% CI: 1.03-1.42, p=0.020) were the factors found to be significantly associated with dyslipidemias.

Conclusion: Dyslipidemias were present in more than half of the participants and this increases their risk for cardiovascular diseases. The high risk groups were women with a BMI greater than 25 and women who were on ART. Lipid profiles should therefore be assessed in women using hormonal contraceptives in order to manage them better.

Keywords: Hormonal Contraceptives, Contraception, Dyslipidemias, Lipid profile

Strengths and limitations of the study

i)   This being one of the first studies in Uganda to assess dyslipidemias in women using hormonal contraceptives, the cross sectional study design used was the most appropriate to provide baseline information.

ii)   Standard approaches were used to carry out the study to ensure repeatability and reproducibility.

iii)   The selection procedure used was non-probability so results may not be generalisable to all hormonal contraceptive users.

iv)   Since this was a cross-sectional study, a causal relationship between hormonal contraceptive use and dyslipidemias could not be ascertained.

v)   The results may have been subject to information bias because questionnaires were used to obtain information on some variables which are based on recall.

INTRODUCTION

Globally, the use of contraception has risen slightly, from 54.7% in 1990 to 64% in 2015 [1] and in Uganda particularly, the Contraceptive Prevalence Rate (CPR) is currently at 27.2% with hormonal contraceptives (HCs) accounting for 77.9% of the total contraceptive use.[1] HCs are the most commonly used contraception methods in Uganda, the injectables being the most common at a rate of 72.8%, followed by the oral contraceptive at 14.3%, and finally the implants at 12.9%.[2]

Several researchers have reported the complications and side-effects associated with the use of these hormonal contraceptives which include nausea and vomiting, headaches, dizziness, breast tenderness and enlargement, irregular bleeding or bleeding between periods, and weight gain as the side effects and adverse effects like metabolism impairment, heart and circulation complications, venous thromboembolism, an increased risk of cancer, and liver

3

problems.[3] It has been suggested that some of the aforementioned complications are a consequence of dyslipidemias, a potential metabolic impairment effect of long term use of some of these hormonal contraceptives.[4] Furthermore, a study by Schueller and his colleagues suggested that these dyslipidemias could also rise as a result of these hormones increasing apolipoprotein B-100 synthesis which subsequently increases triglyceride and LDL levels.[5]

Several factors have been reported to predispose hormonal contraceptive users to dyslipidemias like age, race, body weight, lifestyle, use of other medications like ART, steroids and pre-existing diseases like hypertension, diabetes mellitus and obesity.[6-10] Many of these factors are common in Uganda. For example, 16% of the females in Uganda were found to be obese.[11] Obesity is associated with alterations in lipid profile levels, and this, in the presence of hormonal contraceptive use increases the risk of dyslipidemias.[7, 8] In addition, an estimated 39,000 women in Uganda were reported to be on anti-retroviral therapy (ART) between June 2010 and March 2017.[12] Some of these antiretroviral drugs alter lipid profile levels hence bringing about dyslipidemias.[13, 14]

Poorly managed dyslipidemias can result into cardiovascular diseases like venous thromboembolism, myocardial infarction and stroke.[15] However, lipid profile levels are not measured in women using hormonal contraceptives in Uganda because little is known about the dyslipidemic effect of hormonal contraceptives. This study therefore aimed at determining the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

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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, Kampala in March and April, 2017. The family planning clinic of Mulago Hospital receives approximately 320 patients monthly, 215 of whom are hormonal contraceptive users. Using the consecutive sampling procedure, a total of 384 women aged 18 to 49 years who had used hormonal contraceptives for atleast three months and consented to participate in the study were includetted in the study, and all women who were unable to comprehend either English or Luganda and could not adhere to study procedures were excluded from the study. For ethical considerations, necessary permission to carry out this study was obtained from the School of Medicine Research and Ethics Committee, the Uganda National Counsel of Science and Technology and Mulago Hospital. Written informed consent was obtained from all the participants before enrolment into the study and confidentiality was highly maintained.

Data collection

A questionnaire was administered to collect basic information on age, parity, highest level of education, occupation, type of hormonal contraceptive used, duration of use of hormonal contraceptives, use of anti-retroviral drugs and history of hypertension. Body Mass Index (BMI) was determined by measuring weight using the Seca weighing scale and height using a stadiometer. BMI was then computed as Weight (in Kg)/Height (in metres squared). 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 collected samples were allowed to clot for atleast 3 minutes and centrifuged at 2400rev/min for 5minutes. The serum obtained from centrifugation was pipetted into Cobas 6000 caps and taken for analysis using the Cobas 6000 chemistry analyzer. Fasting blood sugar levels were

5

determined using a Freestyle glucometer for all the participants six hours after their last meal. A sterile single use lancet was used to puncture the participant's disinfected fingure 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 dyslipidemias defined as derangements in the lipid profile levels which included a total cholesterol level of 200 mg/dL or greater, a high-density lipoprotein cholesterol level of less than 40 mg/dL, a triglyceride level of greater than 150 mg/dL, or a low-density lipoprotein cholesterol level of 160 mg/dL or greater according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines.[16] A participant was said to have dyslipidemias if they had any of the lipid profile parameters in ranges stated above. The presence of dyslipidemias was coded as "1" and its absence as "0".

Statistical analysis

Data were analysed using STATA version 13.0 in which all continuous variables were summarised as medians and ranges while the categorical variables were summarised as percentages and proportions. The prevalence of dyslipidemias was calculated as the percentage of women with dyslipidemias over the total number of women in the study. The modified Poisson regression model was used to analyse the factors associated with dyslipidemias in women using hormonal contraceptives. In the multivariate analysis, variables which were found to be significantly associated with dyslipidemias ($p<0.05$) were used to form two-way product terms which 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%. Confidence intervals were

6

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 complaints raised by most of the patients that they gained weight while using hormonal contraceptives, we felt the need to determine whether long term use of hormonal contraceptives has an effect on lipid profile levels as well. This way, patient experiences informed our research questions and study outcomes.

Patients were involved in the design of the study by informing the design of the data collection tool. This was majorly during the pre-testing or piloting of the questionnaires, however patients were not involved in the recruitment to or the conduct of the study.

Results will be disseminated to study participants through the use of text messages and fliers that will be issued out at the family planning clinic printed both in English and Luganda.

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 atleast two or more children and 39.6% (152/384) were self-employed. Only 11 (2.9%) had high fasting blood sugar levels ($\geq$ 120 mg/dl), 14 (3.7%) had a history of hypertension, 140 (36.5%) had a BMI >25 and 78 (20.3%) were on anti-retroviral therapy (ART). Most of the participants were using Progestin-Only Injectables - 185 (48.2%) and 219 (57.0%) had used hormonal contraceptives for over a year (Table 1).

Table 1: Social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Number (N=384)	Percentage (%)
Age (Categorised at the median)		
18 – 28	215	56.0
29 – 49	169	44.0
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
ART Use		
No	306	79.7
Yes	78	20.3
Hormonal Contraceptive Used		
Progestin Only Pill (POP)	5	1.3
Combined Oral Pill (COP)	38	9.9
Progestin Only Injectable (POI)	185	48.2
Combined Injectable Contraceptive (CIC)	8	2.1
Implant (1 rod)	124	32.3
Implant (2 rods)	24	6.2
Duration of use of HC		
<6 months	124	32.3
6 to 11 months	41	10.7
12 or more months	219	57.0

Prevalence of dyslipidemias

The prevalence of dyslipidemias amongst the 384 participants was 63.3% (95% CI: 58.4 – 68.1). Dyslipidemias were higher in women aged above 28 years at 68.0% (115/169) compared to those who were younger. The prevalence of dyslipidemias was also higher in

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participants who had attained up to tertiary education at 75% (27/36) than those who had acquired lower education. Furthermore, considering the clinical factors, participants who had high fasting blood sugar levels (≥120 mg/dl) had more dyslipidemias at 81.8% (9/11) than those who had normal blood sugar levels (Table 2).

Table 2: Prevalence of dyslipidemias according to social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Dyslipidemias Present No. (%)	No Dyslipidemias No. (%)	Prevalence Ratio (95% CI)	P-Value
Overall prevalence of dyslipidemias	243 (63.3)	141 (36.7)	58.4 – 68.1	
Age (Categorised at the median)				
18 – 28	128 (59.5)	87 (40.5)	1.00	
29 – 49	115 (68.0)	54 (32.0)	1.14(0.98-1.32)	**0.083**
Median = 28 (18 – 49)				
Education				
No formal education	6 (42.9)	8 (57.1)	0.68 (0.37 – 1.25)	**0.210**
Primary	66 (61.7)	41 (38.3)	0.97 (0.81 – 1.16)	**0.759**
Secondary	144 (63.4)	83 (36.6)	1.00	
Tertiary	27 (75.0)	9 (25.0)	1.18 (0.96 – 1.46)	**0.124**
Parity				
0 - 1	59 (59.6)	40 (40.4)	1.00	
≥2	184 (64.6)	101 (35.4)	1.08 (0.90 – 1.30)	0.394
Fasting Blood Sugar				
Normal	234 (62.7)	139 (37.3)	1.00	
High	9 (81.8)	2 (18.2)	1.30 (0.98 – 1.74)	**0.072**
History of Hypertension				
No	235 (63.5)	135 (36.5)	1.00	
Yes	8 (57.1)	6 (42.9)	0.90 (0.57 – 1.43)	0.653
Body Mass Index				
≤25	138 (56.6)	106 (43.4)	1.00	
>25	105 (75.0)	35 (25.0)	1.33 (1.15 – 1.53)	**<0.001**
ART Use				
No	186 (60.8)	120 (39.2)	1.00	
Yes	57 (73.1)	21 (26.9)	1.20 (1.02 – 1.41)	**0.026**
Hormonal Contraceptive Used				

9

Oral Contraceptives	22 (51.2)	21 (48.8)	1.77 (0.57 – 1.05)	**0.100**
Injectables	128 (66.3)	65 (33.7)	1.00	
Implants	93 (63.8)	55 (35.2)	0.95 (0.81 – 1.11)	**0.508**
Duration of use of HC				
<6 months	77 (62.1)	47 (37.9)	1.00	
6 to 11 months	22 (53.7)	19 (45.2)	0.86 (0.63 – 1.19)	0.366
12 or more months	144 (65.8)	75 (33.6)	1.06 (0.90 – 1.25)	0.504

Factors associated with dyslipidemias

The variables that were found to be significantly associated with dyslipidemias were BMI (PR=1.33, 95% CI: 1.15 – 1.54, p<0.001) and ART use (PR= 1.21, 95% CI: 1.03 – 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 dyslipidemias and these variables was not confounded by any other independent variables. Therefore, BMI and ART use were the only independent factors associated with dyslipidemias (Table 3).

Table 3: Multivariate analysis of the factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Prevalence Ratio	95% Confidence Interval	P-value
Body Mass Index			
≤25	1.00		
>25	1.33	1.15 – 1.54	<0.001
ART Use			
No	1.00		
Yes	1.21	1.03 – 1.42	0.020

10

DISCUSSION

Dyslipidemias were found to be present in more than half of the participants. This high prevalence of dyslipidemias could be an overestimate in the general population because of the differences in these populations; the population in this study had a higher prevalence of ART users (20.3%) than what is reported in the general population (less than 5%),[12] and since ART use is associated with dyslipidemias, the high prevalence could have been as a result of the high percentage on ART. The presence of dyslipidemias in hormonal contraceptive users has been reported by several other studies which found significant changes in the lipid profile levels of hormonal contraceptive users.[7, 15, 17, 18] These changes in the lipid profile levels can be attributed to the lipogenic effect of estrogen in which liver lipogenesis is increased that results in elevated levels of Triglycerides and LDL levels [19]. Furthermore, the progestin component of hormonal contraceptives increases hepatic lipase enzyme activity which increases the removal of HDL hence decreasing the serum HDL levels.[20] These results are however contradicted by a study in China by Wei and his colleagues in 2011 which found no significant association between oral contraceptive use and the risk of dyslipidemias.[10] Wei's study used the same classification of dyslipidemias with the current study (as the presence of one or more abnormal serum lipid profile level), so the difference could have arisen from the fact that Wei's study used a case control design while the current study used a cross sectional design.

The factors found to be significantly associated with dyslipidemias in women using hormonal contraceptives were BMI and ART use. Participants who had a BMI greater than 25 were 33% more likely to have dyslipidemias compared to those who had a BMI of 25 or less. This is in line with the findings from a systematic review conducted by Halperin and his colleagues in 2011 which reported that differences in average BMI of women in the

individual cohorts explained a portion of the heterogeneity found in HDL-C levels.[8] These changes can be attributed to the fact that BMI can independently affect lipid profile levels as reported by several studies which observed a significant association between high BMI and the occurrence of dyslipidemias.[21, 22] The study by Shamai and his colleagues found a significant association between BMI and both Triglyceride and HDL levels, which was explained by insulin resistance.[22]

ART use was the other factor associated with dyslipidemias in women using hormonal contraceptives. Women who were using anti-retroviral therapy (ART) were 21% more likely to have dyslipidemias than those who were not. These findings should however be treated with caution because of the small numbers who were on anti-retroviral therapy in this study. This is one of the first studies to report on dyslipidemias in ART users on hormonal contraceptives; therefore there are no comparative study findings to use. These changes in lipid profile levels can be attributed to the fact that different ART regimens have been reported to independently alter lipid profile levels hence aggravating the presence of dyslipidemias. A study by Bekolo and his colleagues in 2014 demonstrated a high prevalence of dyslipidemias in HIV patients on first line anti-retroviral therapy in Cameroon.[13] This was attributed to the fact that some ART regimens exert distinct alterations in lipid metabolism hence bringing about dyslipidemias.[14]

Some of the strengths of this study are: This is one of the first studies assessing dyslipidemias in women using hormonal contraceptives to be carried out in Uganda and this contributes to further understanding and possibly better management of dyslipidemias in women using hormonal contraceptives. 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 hormonal contraceptive users because the sample is not representative enough and also because the sampling procedure was non-probability which does not allow equal opportunity to all women to participate. This study was only a cross sectional study so a causal relationship cannot be ascertained between hormonal contraceptive use and dyslipidemias. Since questionnaires were used for data collection, some of the self-reported information may have been inaccurate or incomplete hence affecting some of the results. Finally, information on the physical activity and diet of the study participants was not collected which is deemed important for this study since these variables play a significant role in changing lipid profile levels.

In conclusion, more than half of the women using hormonal contraceptives have dyslipidemias and are thus at an increased risk of acquiring cardiovascular diseases. Hormonal contraceptive users who had a BMI greater than 25 and / or were on anti-retroviral therapy were more likely to have dyslipidemias 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 hormonal contraceptives. The policy should include checking lipid profile levels prior to initiation of hormonal contraceptive use and also continued assessment of lipid profiles at regular intervals while using these contraceptives. The policy should in particular target the high risk group that includes women whose BMIs are greater than 25 and / or are on ART. We also recommend that future research is done to replicate the study in different populations and also explore whether the relationship between dyslipidemias and hormonal contraceptive use is causal.

13

Author contribution:

Ritah Bakesiima 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. **Pauline B Kibwika** planned and supervised the study, interpreted results, and reviewed the manuscript. **James Tumwine** planned the study, contributed in acquisition of funds, interpreted results and revised the manuscript. **Joan N Kalyango** planned and supervised the study and analysis, interpreted results, and revised the manuscript. **Gloria Nabaasa** planned the study, contributed in analysis and reviewed the manuscript. **Irene Najjingo** planned the study, contributed in analysis and reviewed the manuscript. **Grace S Nabaggala** planned the study, contributed in analysis and reviewed the manuscript. **Francis Olweny** planned the study, contributed in analysis and reviewed the manuscript. **Charles Karamagi** conceptualised, planned and supervised the study, interpreted results and reviewed the manuscript.

Role of sponsor: Financing of research and management of funds.

Competing interests: The authors declare no competing interests.

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Transparency declaration: *The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.*

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

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16

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3 - 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 - 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 - 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 – 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 – 8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	9 – 10 and

			Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8 – 9, Table 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2 and 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 – 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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ABSTRACT

Objective: The aim of this study was to determine the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

Design: Cross sectional study

Setting: Mulago Hospital, Kampala

Participants: Three hundred and eighty four women aged 18 to 49 years who had used hormonal contraceptives for atleast three months prior to the study and consented to participate in the study were included in the study.

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

Results: The prevalence of dyslipidemias was 63.3% (95% CI: 58.4 – 68.1). Body Mass Index (BMI) (PR=1.33, 95% CI: 1.15-1.54, p<0.001) and use of anti-retroviral therapy (ART) (PR=1.21, 95% CI: 1.03-1.42, p=0.020) were the factors found to be significantly associated with dyslipidemias.

Conclusion: Dyslipidemias were present in more than half of the participants and this increases their risk for cardiovascular diseases. The high risk groups were women with a BMI greater than 25 and women who were on ART. Lipid profiles should therefore be assessed in women using hormonal contraceptives in order to manage them better.

Keywords: Hormonal Contraceptives, Contraception, Dyslipidemias, Lipid profile

Strengths and limitations of the study

i)   This being one of the first studies in Uganda to assess dyslipidemias in women using hormonal contraceptives, the cross sectional study design used was the most appropriate to provide baseline information.

ii)   Standard approaches were used to carry out the study to ensure repeatability and reproducibility.

iii)   The selection procedure used was non-probability so results may not be generalisable to all hormonal contraceptive users.

iv)   Since this was a cross-sectional study, a causal relationship between hormonal contraceptive use and dyslipidemias could not be ascertained.

v)   The results may have been subject to information bias because questionnaires were used to obtain information on some variables which are based on recall.

INTRODUCTION

Globally, the use of contraception has risen slightly, from 54.7% in 1990 to 64% in 2015 [1] and in Uganda particularly, the Contraceptive Prevalence Rate (CPR) is currently at 27.2% with hormonal contraceptives (HCs) accounting for 77.9% of the total contraceptive use.[1] HCs are the most commonly used contraception methods in Uganda, the injectables being the most common at a rate of 72.8%, followed by the oral contraceptive at 14.3%, and finally the implants at 12.9%.[2]

Several researchers have reported the complications and side-effects associated with the use of these hormonal contraceptives which include nausea and vomiting, headaches, dizziness, breast tenderness and enlargement, irregular bleeding or bleeding between periods, and weight gain as the side effects and adverse effects like metabolism impairment, heart and circulation complications, venous thromboembolism, an increased risk of cancer, and liver

3

problems.[3] It has been suggested that some of the aforementioned complications are a consequence of dyslipidemias, a potential metabolic impairment effect of long term use of some of these hormonal contraceptives.[4] Furthermore, a study by Schueller and his colleagues suggested that these dyslipidemias could also rise as a result of these hormones increasing apolipoprotein B-100 synthesis which subsequently increases triglyceride and LDL levels.[5]

Several factors have been reported to predispose hormonal contraceptive users to dyslipidemias like age, race, body weight, lifestyle, use of other medications like ART, steroids and pre-existing diseases like hypertension, diabetes mellitus and obesity.[6-10] Many of these factors are common in Uganda. For example, 16% of the females in Uganda were found to be obese.[11] Obesity is associated with alterations in lipid profile levels, and this, in the presence of hormonal contraceptive use increases the risk of dyslipidemias.[7, 8] In addition, an estimated 39,000 women in Uganda were reported to be on anti-retroviral therapy (ART) between June 2010 and March 2017.[12] Some of these antiretroviral drugs alter lipid profile levels hence bringing about dyslipidemias.[13, 14]

Poorly managed dyslipidemias can result into cardiovascular diseases like venous thromboembolism, myocardial infarction and stroke.[15] However, lipid profile levels are not routinely measured in women using hormonal contraceptives in Uganda because little is known about the dyslipidemic effect of hormonal contraceptives. This study therefore aimed at determining the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala.

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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, Kampala in March and April, 2017. The family planning clinic of Mulago Hospital receives approximately 320 patients monthly, 215 of whom are hormonal contraceptive users. Using the consecutive sampling procedure, a total of 384 women aged 18 to 49 years who had used hormonal contraceptives for atleast three months prior to the study and consented to participate in the study were included in the study, while all women who were unable to comprehend either English or Luganda and were physically or mentally unable to adhere to study procedures like interviews were excluded from the study. For ethical considerations, necessary permission to carry out this study was obtained from the School of Medicine Research and Ethics Committee, the Uganda National Counsel of Science and Technology and Mulago Hospital. Written informed consent was obtained from all the participants before enrolment into the study and confidentiality was highly maintained.

Sample size calculation: The Kish Leslie formula was used to estimate the sample size for the prevalence objective, while the formula for comparing means in two proportions by Cummings was used to determine the sample size for the factors associated with dyslipidemias in women using hormonal contraceptives. In both formulas, we considered an error of 0.05, 95% confidence level and power of 80%. We also accounted for 10% missing data in the calculation of the sample size.

Data collection

A questionnaire was administered to collect basic information on age, parity, highest level of education, occupation, type of hormonal contraceptive used, duration of use of hormonal contraceptives, use of anti-retroviral drugs and history of hypertension. Body Mass Index

5

(BMI) was determined by measuring weight using the Seca weighing scale and height using a stadiometer. BMI was then computed as Weight (in Kg)/Height (in metres squared). 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 collected samples were allowed to clot for atleast 3 minutes and centrifuged at 2400rev/min for 5minutes. The serum obtained from centrifugation was pipetted into Cobas 6000 caps and taken for analysis using the Cobas 6000 chemistry analyzer. Fasting blood sugar levels were determined using a Freestyle glucometer for all the participants six hours after their last meal. A sterile single use lancet was used to puncture the participant's disinfected fingure 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 dyslipidemias defined as derangements in the lipid profile levels which included a total cholesterol level of 200 mg/dL or greater, a high-density lipoprotein cholesterol level of less than 40 mg/dL, a triglyceride level of greater than 150 mg/dL, or a low-density lipoprotein cholesterol level of 160 mg/dL or greater according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines.[16] A participant was said to have dyslipidemias if they had any of the lipid profile parameters in ranges stated above. The presence of dyslipidemias was coded as "1" and its absence as "0".

Statistical analysis

Data were analysed using STATA version 13.0 in which all continuous variables were summarised as medians and ranges while the categorical variables were summarised as percentages and proportions. The prevalence of dyslipidemias was calculated as the percentage of women with dyslipidemias over the total number of women in the study. The

modified Poisson regression model was used to analyse the factors associated with dyslipidemias in women using hormonal contraceptives. In the multivariate analysis, variables which were found to be significantly associated with dyslipidemias ($p<0.05$) were used to form two-way product terms which 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%. Confidence intervals 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 complaints raised by most of the patients that they gained weight while using hormonal contraceptives, we felt the need to determine whether long term use of hormonal contraceptives has an effect on lipid profile levels as well. This way, patient experiences informed our research questions and study outcomes.

Patients were involved in the design of the study by informing the design of the data collection tool. This was majorly during the pre-testing or piloting of the questionnaires. Results will be disseminated to study participants through the use of text messages and fliers that will be issued out at the family planning clinic printed both in English and Luganda.

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 atleast 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 anti-retroviral therapy (ART). Most of

7

the participants were using Progestin-Only Injectables - 185 (48.2%) and 219 (57.0%) had

used hormonal contraceptives for over a year (Table 1).

Table 1: Social demographic and clinical characteristics of women using hormonal

contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Number (N=384)	Percentage (%)
Age (Categorised at the median)		
18 – 28	215	56.0
29 – 49	169	44.0
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
ART Use		
No	306	79.7
Yes	78	20.3
Hormonal Contraceptive Used		
Progestin Only Pill (POP)	5	1.3
Combined Oral Pill (COP)	38	9.9
Progestin Only Injectable (POI)	185	48.2
Combined Injectable Contraceptive (CIC)	8	2.1
Implant (1 rod)	124	32.3
Implant (2 rods)	24	6.2
Duration of use of HC		
<6 months	124	32.3
6 to 11 months	41	10.7
12 or more months	219	57.0

8

Prevalence of dyslipidemias

The prevalence of dyslipidemias amongst the 384 participants was 63.3% (95% CI: 58.4 – 68.1). Dyslipidemias were higher in women aged above 28 years at 68.0% (115/169) compared to those who were younger. The prevalence of dyslipidemias was also higher in participants who had attained up to tertiary education at 75% (27/36) than those who had acquired lower education. Furthermore, considering the clinical factors, participants who had high fasting blood sugar levels (≥120 mg/dl) had more dyslipidemias at 81.8% (9/11) than those who had normal blood sugar levels (Table 2).

Table 2: Prevalence of dyslipidemias according to social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Dyslipidemias Present No. (%)	No Dyslipidemias No. (%)	Prevalence Ratio (95% CI)	P-Value
Overall prevalence of dyslipidemias	243 (63.3)	141 (36.7)	58.4 – 68.1	
Age (Categorised at the median)				
18 – 28	128 (59.5)	87 (40.5)	1.00	
29 – 49	115 (68.0)	54 (32.0)	1.14(0.98-1.32)	**0.083**
Median = 28 (18 – 49)				
Education				
No formal education	6 (42.9)	8 (57.1)	0.68 (0.37 – 1.25)	**0.210**
Primary	66 (61.7)	41 (38.3)	0.97 (0.81 – 1.16)	**0.759**
Secondary	144 (63.4)	83 (36.6)	1.00	
Tertiary	27 (75.0)	9 (25.0)	1.18 (0.96 – 1.46)	**0.124**
Parity				
0 - 1	59 (59.6)	40 (40.4)	1.00	
≥2	184 (64.6)	101 (35.4)	1.08 (0.90 – 1.30)	0.394
Fasting Blood Sugar				
Normal	234 (62.7)	139 (37.3)	1.00	
High	9 (81.8)	2 (18.2)	1.30 (0.98 – 1.74)	**0.072**
History of Hypertension				
No	235 (63.5)	135 (36.5)	1.00	

Yes	8 (57.1)	6 (42.9)	0.90 (0.57 – 1.43)	0.653
Body Mass Index				
≤25	138 (56.6)	106 (43.4)	1.00	
>25	105 (75.0)	35 (25.0)	1.33 (1.15 – 1.53)	<**0.001**
ART Use				
No	186 (60.8)	120 (39.2)	1.00	
Yes	57 (73.1)	21 (26.9)	1.20 (1.02 – 1.41)	**0.026**
Hormonal Contraceptive Used				
Oral Contraceptives	22 (51.2)	21 (48.8)	1.77 (0.57 – 1.05)	**0.100**
Injectables	128 (66.3)	65 (33.7)	1.00	
Implants	93 (63.8)	55 (35.2)	0.95 (0.81 – 1.11)	**0.508**
Duration of use of HC				
<6 months	77 (62.1)	47 (37.9)	1.00	
6 to 11 months	22 (53.7)	19 (45.2)	0.86 (0.63 – 1.19)	0.366
12 or more months	144 (65.8)	75 (33.6)	1.06 (0.90 – 1.25)	0.504

Factors associated with dyslipidemias

The variables that were found to be significantly associated with dyslipidemias were BMI (PR=1.33, 95% CI: 1.15 – 1.54, p<0.001) and ART use (PR= 1.21, 95% CI: 1.03 – 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 dyslipidemias and these variables was not confounded by any other independent variables. Therefore, BMI and ART use were the only independent factors associated with dyslipidemias (Table 3).

Table 3: Multivariate analysis of the factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Prevalence Ratio	95% Confidence Interval	P-value
Body Mass Index			
≤25	1.00		
>25	1.33	1.15 – 1.54	<0.001
ART Use			

No	1.00		
Yes	1.21	1.03 – 1.42	0.020

DISCUSSION

Dyslipidemias were found to be present in more than half of the participants. This high prevalence of dyslipidemias could be an overestimate in the general population because of the differences in these populations; the population in this study had a higher prevalence of ART users (20.3%) than what is reported in the general population (less than 5%),[12] and since ART use is associated with dyslipidemias, the high prevalence could have been as a result of the high percentage on ART. The presence of dyslipidemias in hormonal contraceptive users has been reported by several other studies which found significant changes in the lipid profile levels of hormonal contraceptive users.[7, 15, 17, 18] These changes in the lipid profile levels can be attributed to the lipogenic effect of estrogen in which liver lipogenesis is increased that results in elevated levels of Triglycerides and LDL levels [19]. Furthermore, the progestin component of hormonal contraceptives increases hepatic lipase enzyme activity which increases the removal of HDL hence decreasing the serum HDL levels.[20] These results are however contradicted by a study in China by Wei and his colleagues in 2011 which found no significant association between oral contraceptive use and the risk of dyslipidemias.[10] Wei's study used the same classification of dyslipidemias with the current study (as the presence of one or more abnormal serum lipid profile level), so the difference could have arisen from the fact that Wei's study used a case control design while the current study used a cross sectional design.

11

The factors found to be significantly associated with dyslipidemias in women using hormonal contraceptives were BMI and ART use. Participants who had a BMI greater than 25 were 33% more likely to have dyslipidemias compared to those who had a BMI of 25 or less. This is in line with the findings from a systematic review conducted by Halperin and his colleagues in 2011 which reported that differences in average BMI of women in the individual cohorts explained a portion of the heterogeneity found in HDL-C levels.[8] These changes can be attributed to the fact that BMI can independently affect lipid profile levels as reported by several studies which observed a significant association between high BMI and the occurrence of dyslipidemias.[21, 22] The study by Shamai and his colleagues found a significant association between BMI and both Triglyceride and HDL levels, which was explained by insulin resistance.[22]

ART use was the other factor associated with dyslipidemias in women using hormonal contraceptives. Women who were using anti-retroviral therapy (ART) were 21% more likely to have dyslipidemias than those who were not. These findings should however be treated with caution because of the small numbers who were on anti-retroviral therapy in this study. This is one of the first studies to report on dyslipidemias in ART users on hormonal contraceptives; therefore there are no comparative study findings to use. These changes in lipid profile levels can be attributed to the fact that different ART regimens have been reported to independently alter lipid profile levels hence aggravating the presence of dyslipidemias. A study by Bekolo and his colleagues in 2014 demonstrated a high prevalence of dyslipidemias in HIV patients on first line anti-retroviral therapy in Cameroon.[13] This was attributed to the fact that some ART regimens exert distinct alterations in lipid metabolism hence bringing about dyslipidemias.[14]

Some of the strengths of this study are: This is one of the first studies assessing dyslipidemias in women using hormonal contraceptives to be carried out in Uganda and this contributes to

further understanding and possibly better management of dyslipidemias in women using hormonal contraceptives. 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 hormonal contraceptive users because the sample is not representative enough and also because the sampling procedure was non-probability which does not allow equal opportunity to all women to participate. This study was only a cross sectional study so a causal relationship cannot be ascertained between hormonal contraceptive use and dyslipidemias. Since questionnaires were used for data collection, some of the self-reported information may have been inaccurate or incomplete hence affecting some of the results. Finally, information on the physical activity and diet of the study participants was not collected which is deemed important for this study since these variables play a significant role in changing lipid profile levels.

In conclusion, more than half of the women using hormonal contraceptives have dyslipidemias and are thus at an increased risk of acquiring cardiovascular diseases. Hormonal contraceptive users who had a BMI greater than 25 and / or were on anti-retroviral therapy were more likely to have dyslipidemias 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 hormonal contraceptives. The policy should include checking lipid profile levels prior to initiation of hormonal contraceptive use and also continued assessment of lipid profiles at regular intervals while using these contraceptives. The policy should in particular target the high risk group that includes women whose BMIs are greater than 25 and / or are on ART. We also recommend that future research is done to

13

replicate the study in different populations and also explore whether the relationship between dyslipidemias and hormonal contraceptive use is causal.

Author contribution:

Ritah Bakesiima 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. **Pauline B Kibwika** planned and supervised the study, interpreted results, and reviewed the manuscript. **James Tumwine** planned the study, contributed in acquisition of funds, interpreted results and revised the manuscript. **Joan N Kalyango** planned and supervised the study and analysis, interpreted results, and revised the manuscript. **Gloria Nabaasa** planned the study, contributed in analysis and reviewed the manuscript. **Irene Najjingo** planned the study, contributed in analysis and reviewed the manuscript. **Grace S Nabaggala** planned the study, contributed in analysis and reviewed the manuscript. **Francis Olweny** planned the study, contributed in analysis and reviewed the manuscript. **Charles Karamagi** conceptualised, planned and supervised the study, interpreted results and reviewed the manuscript.

Competing interests: The authors declare no competing interests.

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Ethical approval: Ethical approval was obtained from the School of Medicine Research Ethics Committee and administrative clearance obtained from Research and Ethics Board of Mulago National Referral Hospital.

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Transparency declaration: *The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.*

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

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15

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3 - 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 - 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 - 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 – 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 – 8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	9 – 10 and

			Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8 – 9, Table 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2 and 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 – 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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Dyslipidemias 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 dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic, Kampala, Uganda.

Design: Cross sectional study

Setting: Mulago Hospital, Kampala, Uganda

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

Study outcome: Dyslipidemias (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 dyslipidemias was 63.3% (95% CI: 58.4 – 68.1). Body Mass Index (BMI) (PR=1.33, 95% CI: 1.15-1.54, p<0.001) and use of anti-retroviral therapy (ART) (PR=1.21, 95% CI: 1.03-1.42, p=0.020) were the factors significantly associated with dyslipidemias.

Conclusion: Dyslipidemias 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 $25Kg/m^2$ and those who were on ART. Therefore, lipid profiles should be assessed in women using hormonal contraceptives in order to manage them better.

Keywords: Hormonal Contraceptives, Contraception, Dyslipidemias, Lipid profile

Strengths and limitations of the study

i)   This is one of the first studies in Uganda to assess dyslipidemias in women using hormonal contraceptives, hence providing baseline information.

ii)   Standard approaches were used to carry out the study to ensure repeatability and reproducibility.

iii)   Consecutive non-probability sampling was used so the results may not be generalisable to all hormonal contraceptive users.

iv)   Since this was a cross-sectional study, a causal relationship between hormonal contraceptive use and dyslipidemias could not be ascertained.

v)   The results may have been subject to information bias since questionnaires were used to obtain information on some variables based on recall.

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 commonest (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 hormonal contraceptives.[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 metabolism 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 dyslipidemias, a potential metabolic impairment effect of long term use of some hormonal contraceptives.[5] Furthermore, a study

3

by Schueller and colleagues suggested that dyslipidemias could also arise from the hormones increasing apolipoprotein B-100 synthesis, which subsequently increases triglyceride and LDL levels.[4]

Several factors predispose hormonal contraceptive users to dyslipidemias. 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 hormonal contraceptive use, obesity makes the risk of dyslipidemias worse.[6, 7] In addition, 79% of all HIV infected women of reproductive age in Uganda are on anti-retroviral therapy (ART).[11] Some anti-retroviral drugs alter lipid profile levels hence causing dyslipidemias.[12, 13]

Poorly managed dyslipidemias 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 hormonal contraceptives in Uganda. Therefore the objective of this study was to determine the prevalence and factors associated with dyslipidemias in women using hormonal contraceptives 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 hormonal contraceptives. Using the consecutive sampling procedure, 384 consenting women aged 18 to 49 years were enrolled into this study. They had to have used hormonal

4

contraceptives for at least three 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.

Ethical issues: Permission to carry out the study was obtained from the Makerere University School of Medicine Research and Ethics Committee, Mulago Hospital Ethics Committee, and the Uganda National Council of Science and Technology. Written informed consent was obtained from all participants before enrolment into the study and confidentiality was maintained.

Sample size calculation: The Kish Leslie formula [15] was used to estimate the sample size for the prevalence objective. We assumed a prevalence of dyslipidemias of 33.9% among women on oral contraceptives according to a study by Machado in Brazil [16] and 95% confidence intervals. 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 dyslipidemias, the formula for comparing means in two proportions [17] 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 dyslipidemias compared to only 16.9% of those using non oral contraceptives. We also assumed that the oral contraceptive prevalence rate 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 hormonal contraceptive used, duration of use of hormonal contraceptives, use of anti-retroviral drugs and history of hypertension. Body Mass Index (BMI) was determined by measuring weight using the Seca® weighing scale and height

5

using a Seca® stadiometer. BMI was then computed as Weight (in Kg)/Height (in metres squared). Blood samples were aseptically collected from participants after a six 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 three minutes and centrifuged at 2400rev/min for five minutes. The serum obtained was pipetted into Cobas® 6000 caps and taken for analysis using the Cobas® 6000 chemistry analyzer (Roche Diagnostics, USA). Fasting blood sugar levels were determined using a Freestyle® glucometer (Abott Laboratories, Canada) for all the participants six 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 dyslipidemias defined as derangements in lipid profile levels which included a total cholesterol of 200 mg/dL or greater, a high-density lipoprotein cholesterol of less than 40 mg/dL, triglyceride of greater than 150 mg/dL, or low-density lipoprotein cholesterol of 160 mg/dL or greater according to the Guidelines for the Diagnosis and Management of Dyslipidemias for Adults.[18] A participant was said to have dyslipidemias if they had any of the lipid profile parameters in ranges stated above. The presence of dyslipidemias was coded as "1" and its absence as "0".

Statistical analysis

Data were analysed using STATA version 13.0 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP) in which all continuous variables were summarised as medians and ranges while the categorical variables were summarised as percentages and proportions. The prevalence of dyslipidemias was calculated as the percentage of women with dyslipidemias over the total number of women in the study. The

6

modified Poisson regression model was used to analyse the factors associated with dyslipidemias in women using hormonal contraceptives. In the multivariate analysis, variables which were significantly associated with dyslipidemias ($p<0.05$) 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%. Confidence intervals 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 complaints raised about excessive weight gain while on hormonal contraceptives, we felt the need to determine whether long term use of hormonal contraceptives (more than three 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 pre-testing 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 ($\geq$ 120 mg/dl), 14 (3.7%) had a history of hypertension, 140 (36.5%) had a BMI >25 and 78 (20.3%) were on anti-retroviral therapy (ART). Most of

7

the participants were using Progestin-Only Injectables - 185 (48.2%) and 219 (57.0%) had

used hormonal contraceptives for over a year (Table 1).

Table 1: Social demographic and clinical characteristics of women using hormonal

contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Number (N=384)	Percentage (%)
Age (Categorised at the median)		
18 – 28	215	56.0
29 – 49	169	44.0
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
ART Use		
No	306	79.7
Yes	78	20.3
Hormonal Contraceptive Used		
Progestin Only Pill (POP)	5	1.3
Combined Oral Pill (COP)	38	9.9
Progestin Only Injectable (POI)	185	48.2
Combined Injectable Contraceptive (CIC)	8	2.1
Implant (1 rod)	124	32.3
Implant (2 rods)	24	6.2
Duration of use of HC		
<6 months	124	32.3
6 to 11 months	41	10.7
12 or more months	219	57.0

Prevalence of dyslipidemias

The prevalence of dyslipidemias amongst the 384 participants was 63.3% (95% CI: 58.4 – 68.1). Dyslipidemias were higher in women aged above 28 years (68.0%) compared to those who were younger. The prevalence of dyslipidemias 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 dyslipidemias (81.8%) than those who had normal blood sugar levels (Table 2).

Table 2: Prevalence of dyslipidemias according to social demographic and clinical characteristics of women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Dyslipidemias Present No. (%)	No Dyslipidemias No. (%)	Prevalence Ratio (95% CI)	P-Value
Overall prevalence of dyslipidemias	243 (63.3)	141 (36.7)	58.4 – 68.1	
Age (Categorised at the median)				
18 – 28	128 (59.5)	87 (40.5)	1.00	
29 – 49	115 (68.0)	54 (32.0)	1.14(0.98-1.32)	**0.083**
Median = 28 (18 – 49)				
Education				
No formal education	6 (42.9)	8 (57.1)	0.68 (0.37 – 1.25)	**0.210**
Primary	66 (61.7)	41 (38.3)	0.97 (0.81 – 1.16)	**0.759**
Secondary	144 (63.4)	83 (36.6)	1.00	
Tertiary	27 (75.0)	9 (25.0)	1.18 (0.96 – 1.46)	**0.124**
Parity				
0 - 1	59 (59.6)	40 (40.4)	1.00	
≥2	184 (64.6)	101 (35.4)	1.08 (0.90 – 1.30)	0.394
Fasting Blood Sugar				
Normal	234 (62.7)	139 (37.3)	1.00	
High	9 (81.8)	2 (18.2)	1.30 (0.98 – 1.74)	**0.072**
History of Hypertension				
No	235 (63.5)	135 (36.5)	1.00	
Yes	8 (57.1)	6 (42.9)	0.90 (0.57 – 1.43)	0.653
Body Mass Index				
≤25	138 (56.6)	106 (43.4)	1.00	

9

>25	105 (75.0)	35 (25.0)	1.33 (1.15 – 1.53)	**<0.001**
ART Use				
No	186 (60.8)	120 (39.2)	1.00	
Yes	57 (73.1)	21 (26.9)	1.20 (1.02 – 1.41)	**0.026**
Hormonal Contraceptive Used				
Oral Contraceptives	22 (51.2)	21 (48.8)	1.77 (0.57 – 1.05)	**0.100**
Injectables	128 (66.3)	65 (33.7)	1.00	
Implants	93 (63.8)	55 (35.2)	0.95 (0.81 – 1.11)	**0.508**
Duration of use of HC				
<6 months	77 (62.1)	47 (37.9)	1.00	
6 to 11 months	22 (53.7)	19 (45.2)	0.86 (0.63 – 1.19)	0.366
12 or more months	144 (65.8)	75 (33.6)	1.06 (0.90 – 1.25)	0.504

Factors associated with dyslipidemias

Variables significantly associated with dyslipidemias included BMI greater than 25kg/m^2 (PR=1.33, 95% CI: 1.15 – 1.54, p<0.001) and ART use (PR= 1.21, 95% CI: 1.03 – 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 dyslipidemias and these variables was not confounded by any other independent variables. Therefore, BMI and ART use were the only independent factors associated with dyslipidemias (Table 3).

Table 3: Multivariate analysis of the factors associated with dyslipidemias in women using hormonal contraceptives at Mulago Hospital Family Planning Clinic in Kampala, March to April, 2017

Variable	Prevalence Ratio	95% Confidence Interval	P-value
Body Mass Index			
≤25	1.00		
>25	1.33	1.15 – 1.54	<0.001
ART Use			
No	1.00		
Yes	1.21	1.03 – 1.42	0.020

DISCUSSION

Dyslipidemias were present in more than half the participants. This high prevalence of dyslipidemias could be an over estimate in the general population because of the differences in these populations. This study had a higher prevalence of anti-retroviral therapy (ART) users (20.3%) than what is reported in the general population (less than 5%).[11] Since ART use is associated with dyslipidemias, the high prevalence obtained could have been as a result of the high percentage on ART.

The presence of dyslipidemias in hormonal contraceptive users has been reported by several other studies which found significant changes in the lipid profile levels of hormonal contraceptive users.[5, 6, 14, 19] These changes in the lipid profile levels can be attributed to the lipogenic effect of estrogen in which liver lipogenesis is increased and results in elevated levels of Triglycerides and LDL levels [20]. Furthermore, the progestin component of hormonal contraceptives increases hepatic lipase enzyme activity which increases the removal of HDL hence decreasing the serum HDL levels.[21]

The factors significantly associated with dyslipidemias in women using hormonal contraceptives were BMI and ART use. Participants who had a BMI greater than $25kg/m^2$ were 33% more likely to have dyslipidemias compared to those who had a BMI of $25kg/m^2$ or less. This is in line with the findings from a systematic review by Halperin and colleagues in 2011. Halperin's study reported that differences in average BMI of women in the individual cohorts explained a portion of the heterogeneity found in 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 dyslipidemias.[22, 23] A study by Shamai and colleagues reported a significant association

between BMI and both Triglyceride and HDL levels, which was attributed insulin resistance.[23]

ART use was the other factor associated with dyslipidemias in women using hormonal contraceptives. Women who were using anti-retroviral therapy (ART) were 21% more likely to have dyslipidemias than those who were not. This is one of the first studies to report on dyslipidemias in ART users on hormonal contraceptives; 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 dyslipidemias.[13] A study by Bekolo and colleagues in 2014 demonstrated a high prevalence of dyslipidemias in HIV patients on first line anti-retroviral therapy in Cameroon.[12]

Some of the strengths of this study are: This is one of the first studies assessing dyslipidemias in women using hormonal contraceptives to be carried out in Uganda. This contributes to further understanding and possibly, better management of dyslipidemias in women using hormonal contraceptives. 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 hormonal contraceptive 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 hormonal contraceptive use and dyslipidemias. 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 changing lipid profile levels.

In conclusion, more than half the women using hormonal contraceptives had dyslipidemias and are thus at an increased risk of acquiring cardiovascular diseases. Hormonal contraceptive users who had a BMI greater than $25kg/m^2$ and / or were on anti-retroviral therapy were more likely to have dyslipidemias 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 hormonal contraceptives. The policy should include checking lipid profile levels prior to initiation of hormonal contraceptive 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 $25kg/m^2$ and / or are on ART. Further studies are urgently needed to explore whether the relationship between dyslipidemias and hormonal contraceptive use is causal.

Author contribution:

Ritah Bakesiima 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. **Pauline B Kibwika** planned and supervised the study, interpreted results, and reviewed the manuscript. **James Tumwine** planned the study, contributed in acquisition of funds, interpreted results and revised the manuscript. **Joan N Kalyango** planned and supervised the study and analysis and interpreted results. **Gloria Nabaasa** planned the study

and contributed in analysis. **Irene Najjingo** planned the study and contributed in analysis. **Grace S Nabaggala** planned the study and contributed in analysis. **Francis Olweny** planned the study and contributed in analysis. **Charles Karamagi** conceptualised, planned and supervised the study, interpreted results and reviewed the manuscript. All authors have read the final manuscript.

Competing interests: The authors declare no competing interests.

Ethical 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.

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

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15

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3 - 4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 - 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4 - 5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 - 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5 - 6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 - 7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6 – 7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7 – 8 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	9 – 10 and

			Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8 – 9, Table 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	2 and 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 – 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.