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Original Article

The effect of combined oral contraceptive and hormonal implant on plasma glucose level and liver function in women: A cross-sectional study

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Abstract

Background: Long-term use of combined oral contraceptives and implant contraceptives was associated with some adverse metabolic effects, including effects on serum glucose, body weight, and liver enzymes. However, recent epidemiological reports suggest a possible increased risk of diabetes and liver disease among users. The aim of this study is to assess the effect of hormonal implants and combined oral contraceptives use on glucose metabolism and liver function among women who attend family planning services**.**

Methods: An institution-based comparative cross-sectional study was conducted to assess the effect of hormonal implant contraceptives and combined oral contraceptives on glucose metabolism and liver function status among women of reproductive age from September 15- June 30, 2022. A total of 162 women (86 hormonal implant users, 26 combined oral contraceptive users, and 50 non-users) were included in the study. A one-way analysis of variance was used to examine differences in outcomes. Pearson correlation was used to identify the association between outcome variables and the duration of implant use.

Results: The prevalence of diabetes among study participants in Leku General Hospital and Yirba Primary Hospital of Sidama Region was 10.5% (95% CI: 6.2- 15.4%). The prevalence of diabetes was 11.6% (95% CI: 5.8-18.6), 11.5% (95% CI: 0-26.9), and 8% (95% CI: 2.0-16.0) among implant users, combined oral contraceptives users and non-users, respectively. From Bonferroni's post-hoc analysis, implant users had a significantly higher mean hip-to-waist ratio than non-users (p=0.024). Implant users had significantly higher mean systolic blood pressure (p = 0.027) than combined oral contraceptive users. Longer implant use was associated with lower ALT levels (p = 0.044 and r = -0.22).

Conclusion: Longer implant use was associated with lower ALT levels and higher waist-to-hip ratio

mean values than non-users.

Keywords: Combined oral contraceptive, diabetes mellitus, implant, liver enzyme

Introduction

Hormonal contraceptives are widely used for the prevention of pregnancy in women. Globally, contraception utilization has increased slightly, from 54.0% in 1990 to 57.4% in 2015 (1). In Ethiopia, the overall prevalence of modern contraceptive utilization rate was 20.42%, and the implant was the second most used (24.32%) followed by pills (7.9%) (2). Hormonal contraceptives are available in many forms, including oral combined pills made of estrogen and progesterone, progesterone-only pills, progesterone-only injections or implants, and progesterone intrauterine systems (3).

Hormonal implants are thin, flexible, matchstick-sized rods made of soft plastic. The rods contain the hormone progestin, which is similar to the natural hormone progesterone in a woman's body, and is surgically placed beneath the skin of the client's upper arm by a trained provider (4). Implants majorly prevent pregnancy by increasing the viscosity of the cervical mucus to prevent sperm penetration and thinning the endometrium to create a hostile uterine environment (5). However, long-term use of Combined oral contraceptive (COC) and hormonal implants was associated with some adverse metabolic effects, including effects on serum glucose body weight, blood pressure (BP), liver enzymes, and lipid profile (6, 7). COC is mainly metabolized in the liver affects hepatic function and possibly has a direct adverse effect on the liver (8). Studies have shown an association between oral contraceptive use and hepatocellular adenoma (9, 10). The liver alters the actions of sex hormones through their metabolism and transport of proteins (11).

Frequency of implant usage, in women who became pregnant following discontinuation of a progestin implant, a comparable synergism contributed to an increase in gestational diabetes (12). Furthermore, some published metabolic studies have generally found no association between women's use of implantable progestin-only contraceptives and the development of glucose intolerance. However, recent epidemiological reports suggest a possible increased risk of diabetes among users of implants (13). However, the available information is still insufficient to rule out possible long-term effects of hormonal implants on glycemia and liver function. Besides, to the best of our knowledge, no research has been conducted on the effect of contraception implants and COC on glucose metabolism and liver function status in women of reproductive age in Ethiopia. Therefore, this study aims to determine and compare the effect of COC and contraceptive implant usage on glucose metabolism and liver function status among women in the reproductive age group attending Leku General Hospital (LGH) and Yirba Primary Hospital (YPH).

Methods and materials

Study Area and Period

This was a comparative cross-sectional study conducted in LGH and YPH from September 15-June 30, 2022. Leku is the capital of Shebedino district which is located in the Sidama Region and 300 km to the South direction of Addis Ababa, the capital city of Ethiopia. This hospital is one of the few general hospitals in the region that provides public health and clinical services for the community. Yirba Primary Hospital is located in Yirba City which is the capital of the Boricha district of Sidama region and 31 km South-east of Hawassa City.

Study subject

The study was conducted on sampled women attending the Family planning clinic for hormonal implants. Women who had been using implants for at least one month and who signed informed consent were included in the study. Women with inconsistent contraceptive use, poor health care compliance, and chronic disease (diabetes, hypertension, cardiovascular disease) were excluded. In addition, women taking medication known to affect liver function tests and glucose metabolism were also excluded.

Sample Size Determination and Sampling Procedures

The sample size was estimated using G*power software version 3.1.9 for the mean difference between two independent groups assuming a 5% level of significance (α) and 80% power (β) with an effect size of 0.56. The mean and standard deviation (100.9mg/dl and 33.4 respectively) of fasting plasma glucose among implant users were taken from a study done in Nigeria (14) which produced a minimum sample size of 86 women. For COC user women, the mean (X= 82) fasting plasma glucose is taken from a study conducted in non-obese healthy US women of reproductive age (15) which resulted in a total sample size of 26 women. A total of 50 women who do not use any of the contraceptives will be selected as controls (non-users).

The total number of women population (N) using implant contraceptives and COC at LGH was 327 and 163 respectively and YPH was 174 and 121 respectively. A systematic random sampling method was used to select each study participant. The total sample sizes of 162 women were proportionally allocated to LGH and YPH (Table 1)

Implant and COC users at LGH were selected at every 6^{th} and 9^{th} interval, respectively until the calculated sample size for each contraceptive method was obtained. Whereas, Implant and COC users at YPH were selected at every 7^{th} and 15^{th} interval until the calculated sample size for each contraceptive method was obtained.

Implant users' women were selected from the registration log book referring to women who received implant insertion service one month and are registered at the family planning. Clients were communicated through their contact address from the register book. Data collectors visited clients at their homes and appointed them to come to the hospital next the day after an overnight fasting. COC user women were selected upon their arrival at the family planning clinic according to their appointment.

Data collection methods

Socio-demographic, and Clinical data collection

Trained nurses collected the socio-demographic data like age, sex, residence, marital status, ethnicity, religion, educational level, employment status, monthly income, diet habit, physical activity, smoking habit, and drinking habits collected by interviewing the participants. Data on diet habits, physical activity, smoking, and drinking habits were used to assess risk factors.

Weight was measured in kg using a person scale, and height in cm by a statometer. Waist and hip circumferences were assessed in cm using a measuring tape (all devices, SECA, Germany). Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated as: BMI (kg/m2) = weight (kg)/[height (m)]2 and WHR = waist (cm)/hip (cm).

BP was taken both from the supine and standing position. BMI and WHR were used for the assessment of central obesity. Moreover, body mass index (BMI) was calculated as the weight in kilogram divided by height squared (m^2).

Laboratory analysis

About 4–5 ml venous blood sample was collected by trained laboratory technologists from each study subject after overnight fasting for serum biochemical determination of liver

enzymes (AST and ALT). Fasting plasma glucose was assayed by an automated spectrophotometer and enzymatic colorimetric method with the help of COBAS 6000 Random Access chemistry instrument (Roche Diagnostics. Switzerland). The serum was separated from whole blood and transported to Hawassa University Comprehensive Specialized Hospital Clinical chemistry laboratory department. The blood glucose level was measured using a Human Diagnostic test kit (Germany), using the glucose oxidase method, and the two liver enzymes, AST and ALT, were measured by a modified IFCC method(16). The total bilirubin was measured by the Jendrassik - Grof method (17).

Table 1: Proportional allocation of sample size for Implant and COC and non-users between LGH and YPH , 2022

S. No.	FP type	LGH		YPH		Total
		N	N	n	N	
1	Implant	59	327	27	174	86
2	COC	18	163	8	121	26
3	Non-user	34		16		50
4	Total sample size	111		51		162

Operational definition:

Diabetes mellitus (DM): - defined as the fasting glucose greater than 126 mg/dL(18).

BMI: women were categorized as underweight, normal, overweight or obese using BMI values of <18.5,18.5-24.9, 25-29.9 and 30kg/m2 respectively(19).

Data Management and Analysis

Data was collected by the KOBO collect data collection tool, and exported to the Statistical Package for Social Sciences (SPSS) version 20.0 for analysis. Descriptive statistics using frequency distribution were performed for socio-demographic, clinical, and laboratory values. Continuous variables were expressed as means ± standard deviation, and categorical data as percentages. One-way ANOVA was used to compare the mean of plasma glucose, ALT, and AST among implant users, COC users, and non-users. Pearson correlation was used to identify the association between outcome variables (fasting plasma glucose, AST, and ALT) and the duration of implant use. A variable with a p-value < 0.05 was considered statistically significant

Results

Socio-demographic characteristics

This survey has a total of 162 participants. The mean± standard deviation (SD) of respondents' ages was 29.62 ± 5.58 years, with a range of 20–52 years. The majority (56.2%) of women were between the ages of 25 and 34. One hundred two (63%) women live in cities, while 60 (37%) live in rural areas. There were 92 (56.8%) women who completed secondary school, 29 (17.9%) a higher education. The majority of respondents (38.9%) were housewives, and 90.1% were currently married (Table 1).

Behavioral and lifestyle characteristics

Respondents with a history of alcohol consumption were 8.6%) and 25.3% of the walking and 31.5% by jogging. Fourteen (8.6%) respondents reported a history of chewing khat (Table 3)

Table 2: Socio-demographic and economic characteristics of the study participants in LGH and YPH, Sidama region, Ethiopia, from September 15- June 30, 2022 (N = 162)

Variables	Categories	Frequency	Percent
Residence	Urban	102	63
	Rural	60	37
Educational level	Primary school	41	25.3
	Secondary school	92	56.8
	Higher education	29	17.9
	Farmer	2	1.2
Occupation	Housewife	63	38.9
	Merchant	49	30.2
	Government employee	35	21.6
	Daily laborer	13	8
Marital status	Currently in marriage	146	90.1
	Currently not in marriage	16	9.9
Religion	Orthodox	22	13.6
	Protestant	99	61.1
	Muslim	32	19.8
	Catholic	9	15.6
	Sidama	130	80.2
Ethnicity	Amhara	16	9.9
	Wolayita	12	7.4
	Others	4	2.5
Monthly income	<1000 USD	151	93.2
	1001-4000 USD	11	6.8

Table 3: Behavioral and lifestyle characteristics among the study participants in the five districts of Sidama region, Ethiopia, from September 15- June 30, 2022 (N = 162)

Variables	Categories	No.	%
Do you drink alcohol?	Yes	14	8.6
	No	148	91.4
Regular exercise	Yes	41	25.3
	No	121	74.7
Type of exercise	Walking	25	65.7
	Jogging	12	31.5
	Aerobics and others	1	2.8
Chewing chat	Yes	14	8.6
	No	148	91.4

Anthropometric characteristics

Respondents' mean and SD weight and MBI were 58.21 (3.38) kg and 23.63 (0.94) kg/m^2, respectively. Respondents' mean and SD WC was 81.85 (11.30) cm. The majority of respondents (94.4%) had a normal BMI, although 9(5.6%) were overweight. Twenty-six (14%) of respondents had an abnormal WC, and 136 (86%) had an abnormal hip circumference (Table *4*).

Table 4: Anthropometric characteristics among the study participants in the five districts of the Sidama region, Ethiopia, from September 15- June 30, 2022 (N = 162)

Variables	Category	No.	%
BMI	18.5-24.9 kg/m^2	153	94.4
	25.0-29.9 kg/m^2	9	5.6
WC	Normal	136	86
	Non-normal	26	14
HC	≤ 93	117	72.2
	≥ 94	45	27.8
WHR	<0.9	66	40.7
	0.9-0.99	87	53.7
	≥ 1	9	5.6

BMI, Body mass index; WHC, Waist-to-hip circumference ratio; HC, Hip circumferences

Comparisons of the mean for anthropometric indices, plasma glucose, and liver enzymes among FP users

The mean (+SD) glucose value of study participants was 137+90.1, 134.7+49.8, and 136+99.8 among implant users, COC, and non-users respectively. The overall prevalence of diabetes among the study participants in LGH and YPH was 10.5% (95% CI: 6.2- 15.4%). The prevalence of diabetes was 11.6% (95% CI: 5.8-18.6), 11.5% (95% CI: 0-26.9), and 8% (95%CI: 2.0-16.0) among implant users, COC users, and non-users respectively. The prevalence of diabetes among implant users was 11.6% (95%CI: 5.8-18.6) and COC users were 11.5% (95% CI: 0-26.9). The prevalence of diabetes among non-users was relatively low (8% (95%CI: 2.0-16.0) when compared to that of implant and COC users (Figure *1*).

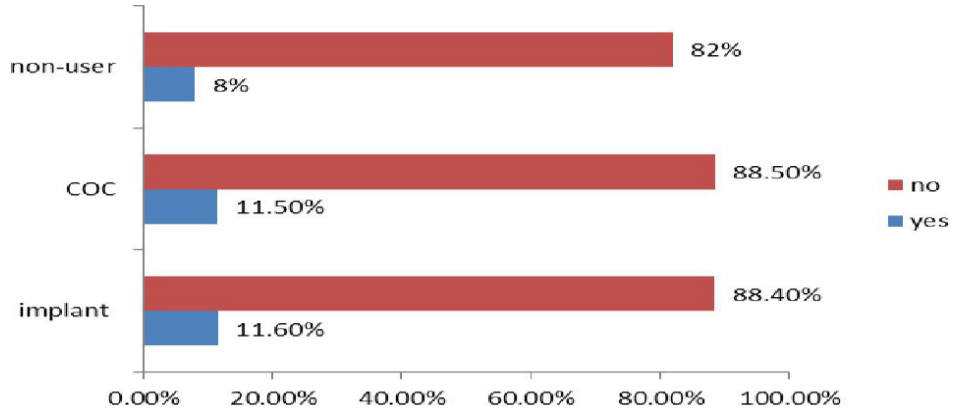

Figure 1: Prevalence of diabetes mellitus among Family planning users in LGH and YPH of Sidama region, Ethiopia, from September 15- June 30, 2022

The overall prevalence of liver enzyme abnormalities among study participants was 30.9% (95%CI: 23.6-37.7) and 37% (95%CI: 30.3-45.1) for ALT and AST respectively. The highest prevalence of liver enzyme abnormalities was among COC users; 42.3% (95%CI: 23.1-61.5) followed by implant users (Figure 2)

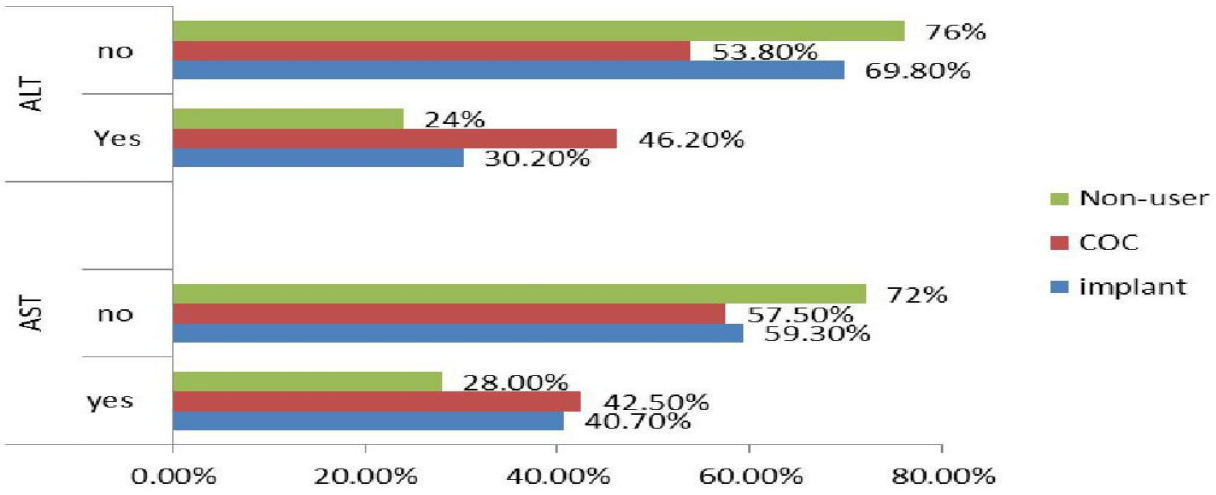

Figure 2: Prevalence of liver enzyme abnormalities among Family planning users in LGH and YPH of Sidama region, Ethiopia, from September 15- June 30, 2022

The result showed a significant mean age difference between implant users, COC users, and non-users (p=0.002). The mean age (years) of implant users, COC users, and non-users were 30.62±5.63, 26.32±3.71, and 29.54± 5.65 respectively. Results from one-way ANOVA showed that there was a statistically significant mean difference in waist circumference (p=0.002), hip circumference (p=0.00), hip-to-waist ratio (p=0.016), systolic blood pressure (SBP, p=0.032) between the three groups of participants (implant users, COC users, and non-users) (Table 5)

Table 5: Comparisons of the mean for (one-way ANOVA output) anthropometry, blood pressure, and liver enzymes among the users and non-users in LGH and YPH of Sidama region, Ethiopia, 2022

Variables	Mean ±SD			p-value
	Implant (n=86)	COC (n=26)	Non-users(n=50)	
FBG	137.9 ± 90.1	134 ± 49.8	136 ± 99.8	0.95
AST	30.4 ± 15.6	32.1±27.4	27.56 ±14.7	0.52
ALT	30.1±14.54	31.1± 16.5	26.3±12.42	0.24
BMI	23.7 ± 0.97	23.26 ± 0.9	23.68 ± 0.88	0.095
DBP	76.22 ± 10.5	72 ± 15. 8	76.3 ± 10.3	0.24
SBP	115 ±12.05	108.8 ± 13.9	114.4 ± 10.9	0.032*
WC	80.3 ± 6.4	93.4 ± 38.4	83.8 ± 7.7	0.002*
HC	86.67 ± 7.39	98.3 ± 28.6	93.3 ± 7.44	0.00*
WHR	0.93 ± 06	0.93 ± 08	0.89 ± 05	0.016*

AST; Aspartate aminotransferase; ALT: Alanine aminotransferase; BMI, Body mass Index; DBP, Diastolic blood pressure; HC, Hormonal contraceptive; FBG, Fasting blood glucose; SBP, Systolic blood pressure; WC, Waist circumference; WHR, Waist-to-hip ratio

Results from Bonferroni post-hoc analysis showed that implant users had a significantly higher mean hip-to-waist ratio than non-users (p=0.024). Implant users had significantly higher mean systolic blood pressure (p=0.027) than COC users. However, COC users have lower mean systolic blood pressure (p=0.13) than non-users although in all cases, the differences were not statistically significant (Table 6).

Table 6: Bonferroni post hoc output of lipid profile among each group of participants in LGH and YPH of Sidama region, Ethiopia, from September 15- June 30, 2022

Dependent variable	(I)Type	(J)type	Mean difference	p-value
SBP	implant	COC	6.91	0.027*
		Non-user	1.63	1.00
	COC	Implant	-6.91	0.027*
		Non-user	-5.59	0.13
WC	Implant	COC	-13.08	0.002*
		Non-user	-3.50	0.703
	COC	Implant	13.08	0.002*
		Non-user	-9.58	0.053*
WHR	Implant	COC	-0.004	1.00
		Non-user	0.03	0.024*
	COC	Implant	0.004	1.00
		Non-user	0.003	0.07
HC	Implant	COC	-11.64	0.00*
		Non-user	6.67	0.015*
	COC	Implant	11.64	0.00*
		Non-user	4.27	0.42

DBP, Diastolic blood pressure; HC, Hormonal contraceptive; SBP, Systolic blood pressure; WC, Waist circumference; WHR, Waist-to-hip ratio

Correlation between duration of use and outcomes

The mean duration of implant use and COC was 37.5 and 60.46 months, respectively. Results from bivariate Pearson correlation analysis showed the duration of use did not have a significant linear relationship with plasma glucose and AST levels (Table 7). However, there was a statistically significant negative linear relationship between the duration of implant use and plasma ALT level (p=0.044 and r= -0.22) (Figure 3).

Table 7: Bivariate Pearson correlation analysis between duration of use in months with plasma glucose, and liver enzymes level among family planning users at LGH and YPH of Sidama region, Ethiopia, from September 15- June 30, 2022

	Variables	Implant users	COC users
Glucose	R	-0.016	0.115
	p-value (2-tailed)	0.885	0.57
AST	R	-0.046	0.38
	p-value (2-tailed)	0.67	0.85
ALT	R	-0.22	-0.001
	p-value(2-tailed)	0.044*	0.99

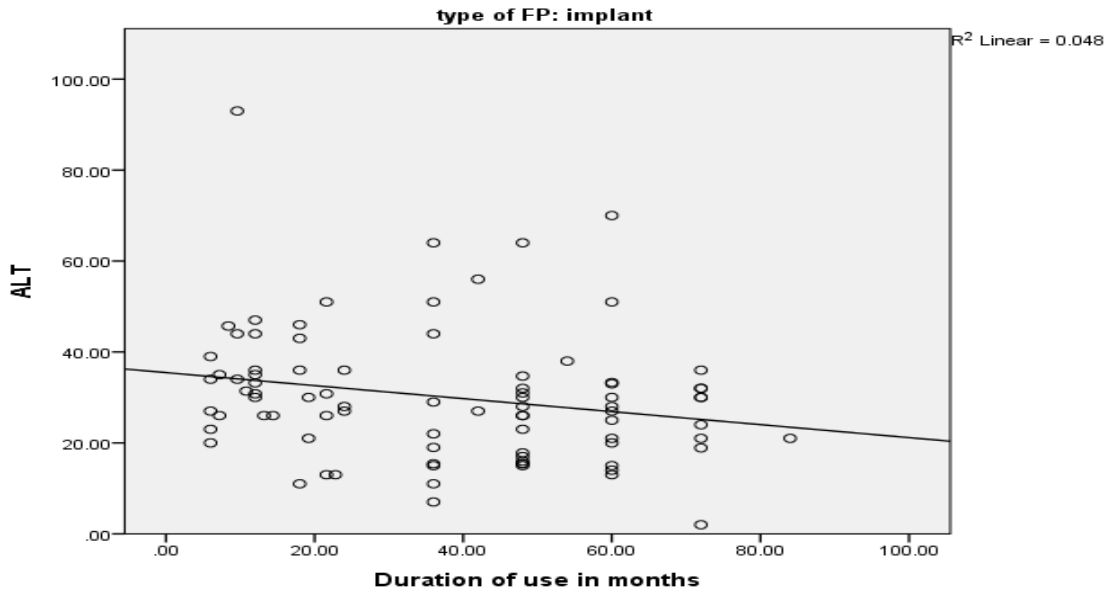

Figure 3: Correlation of implant use with the duration of uses among family planning users at LGH and YPH of Sidama region, Ethiopia, 2022

Discussion

The overall prevalence of diabetes among study participants in the study area was 10.5%. However, the prevalence of diabetes was 11.6%, 11.5%, and 8% among implant users, COC users and non-users, respectively. The finding of this study is higher than most studies conducted in Hosana, Hadiya, Southern Ethiopia (4.5%) (20), much higher than a study done in Bona district, Sidama Region, Southern Ethiopia (1.2%) (21). A Hospital-based study reported a diabetes prevalence of 6.5% in Addis Ababa (22), which is relatively closer to the finding of the current study. In comparison to prior data, our estimations revealed a higher prevalence of diabetes. However, no significant conclusions can be drawn about diabetes prevalence across countries because previous studies in variable environments were conducted on participants of both sexes. The reason for these variations could be that female sex is included in the study. Another possible explanation for these discrepancies could be the study settings. Earlier studies were conducted in the community, whereas ours is conducted in institutions. Furthermore, the differences in sample size across studies may explain these discrepancies.

The mean serum concentration of glucose among implant users was higher compared to COC users and non-users. The findings of this study showed non-significant changes in mean serum glucose levels among implant users and COC users compared to non-users. The finding is consistent with other studies (23, 24). However, other studies conducted in Iran showed that the mean serum glucose concentration was significantly higher among hormonal contraceptive users compared to non-users (25). The difference may be explained by the variations in dose of hormonal formulations. Furthermore, the differences in sample size across studies may explain these discrepancies

Data obtained in this study showed non-significant differences between liver enzyme activities of the contraceptive users and non-users. A review of the literature cleared that the effect of hormonal contraceptives on liver

enzyme activities was controversial. Consistent with our study, a study done in Egypt (26) and elsewhere (27) showed a non-significant change in liver function tests. In contrast, other studies (28, 29) reported a reduction in liver enzyme activities. The difference may be explained by the fact that the study participants received low doses of hormonal formulations. Furthermore, the differences in sample size across studies may explain these discrepancies.

The bivariate Pearson correlation analysis showed that there was a statistically significant negative linear relationship between the duration of implant use and plasma ALT enzyme concentration. A unit increase in the duration of use of the implant in a month causes a decrease in serum ALT enzyme concentration by 22%.

The results of this study showed that the mean BMI difference between contraceptive users and non-users was not statistically significant. This finding is in line with other studies (30). However, this finding is different from a study conducted in the Ghanaian community (31). The discrepancy in the findings can be attributed to the fact that the studies used different study designs and sample sizes.

The current study showed that the mean WHR was significantly higher among implant users than non-users. This finding is in contrast with that of a study in Jimma town (32), which showed there is no statistically significant mean difference between contraceptive users and non-users. Weight gain is also associated with hormonal contraceptive utilization. It was postulated that weight gain could be due to fluid retention, fat deposition, or an increase in muscle mass (33).

There was no statistically significant difference in both mean SBP ($p = 1.00$) between implant users and non-users in this study. The finding is consistent with that of another study (30). However, there is a statistically significant difference in mean SBP between implant users and COC users.

Conclusion

In conclusion, the findings of this study showed that the prevalence of diabetes mellitus among implant users is higher than among non-users. More importantly, the duration of use of the contraceptive implant has a statistically significant negative linear relationship with ALT serum concentration. The findings of the study further show that implant users had statistically significantly higher WHR mean values than non-users. The findings suggest the need for family planning service providers to undertake appropriate client profiling before recommending a particular method for women seeking the services to minimize adverse health risks, especially for those who may have pre-existing conditions.

Acknowledgment

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Ethical considerations

This study was reviewed and approved by the Institutional Review Board (IRB) of Hawassa University College of Health Science. Administrative clearance was obtained from the Leku General Hospital and Yirgalem General Hospital. Informed written consent was taken from each study participant before enrollment in the study. To ensure the confidentiality of the participant's information, anonymous typing was applied whereby the name of the participant and any identifier of participants will not be written on the questionnaire.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available. It can be made available through the corresponding author upon reasonable request.

Conflicts of interest

The authors declare that there is no conflict of interest.

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