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Association Between Oral Contraceptive use and Some Biochemical Changes in Saudi Women

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ABSTRACT

Millions-of females worldwide use oral contraceptive pills (OCs) to improve their health outcomes and for family planning. Oral contraceptive (OCs) use has been associated with an unfavorable impact on lipid metabolism by increasing the level of atherogenic lipids, which are strongly associated with cardiovascular disorders. The aim of this study was to evaluate the effect of oral contraceptive pills on lipid profile and liver function in Saudi females. A total of 55 Saudi women aged (20-40)years old were divided into two groups: users oforal contraceptive pills (OCs, N=30) for at leastone year and non-users (NOCs, N=25). The current study was based on the questionnaire having the data includes age, height, weight, body mass index (BMI), blood pressure, physical activity, duration of OCs, and types of OCs. Blood specimen from both groups were drawn after 8 hours of fasting to estimate serum glucose, lipid profile (TC, TG, LDL, HDL) and liver function (TBIL, TP, ALB, and globulin) tests and some enzymes, which include ALP, AST, ALT, GGT, and CK. The results showed a significant increase in serum glucose, TC, TG, LDL, TBIL, TP, ALB, globulin, ALP, AST, ALT, GGT, and CK with no significant changes HDLin the oral contraceptive users as compared to the control group. In conclusion,using OCs affects lipid profile and liver function compared to the control group.

KEY WORDS: MILLIONS-OF FEMALES, CONTRACEPTIVE PILLS (OCS) LIVER FUNCTION.

INTRODUCTION

Millions-of females worldwide use oral contraceptives pills (OCs) to improve their health outcomes and family planning (Hall and Klein, 2017, Montoya and Bos, 2017). The changing beliefs toward fertility and birth spacing and the rapid change in the socio-demographic pattern in the Saudi Arabian Community have resulted in a notable increase in the use of OCs (Yasmeen et al., 2020). Al-Harazi et al., (2019) conducteda cross-sectional survey through web in all the regions of the kingdom of Saudi Arabia and found that OCs was the first choice (40.3%). Moreover, Alhusain et al., (2018) reportedthat OCs were the most commonly used contraceptive type used (31.8%) inthe Jeddah region of Saudi Arabia. Suleiman(2013) concluded that OCs are obtainable withouta prescription, and pharmacist counseling might sometimes be users' only source of information in Saudi Arabia.

OCs are used to prevent gestation by inhibiting ovulation and implantation(Bawah et al., 2018).Two main types of OCs;Combined Oral Contraceptive pills (COCs) which contain both estrogen and progesterone and, progestogen-only pills (POCs) (Busund et al., 2018). OCs use has been related to an unfavourable influence on lipids

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metabolism byincreasing the level of atherogenic lipids which are strongly associated with cardiovascular disorders (Ferreira et al., 2017a, Elekima and Inokon, 2019). OCs influence on lipid levels dependent on the estrogen dosage respective to the progestin dosage, and androgenic of the progestin (Sirmans and Pate, 2014). Estrogen tends to have beneficial influence by increasing high-density lipoprotein (HDL) and diminishing low-density lipoprotein(LDL).However, triglycerides (TGs) concentration as well increases(Shufelt and Merz, 2009). Progestin appear to have a reverse influence, where, they cause diminishing in HDL levels and rises in LDL(van Rooijen et al., 2002).

Mohammed (2018) observed a correlation between the use of COC and the increase in total cholesterol(TC), LDL-C and the decrease HDL-C in women who used COC. Other studies revealed a significant rise in serum levels of TC, TGs, LDL-C, and decreased HDL-C in the oral contraceptive users compared to the control groups(Mohamed, 2016, Ferreira et al., 2017b). The change in serum lipid profile are key factors in cardiovascular disease (Kazemi et al., 2018).For better estimation and forecasting riskiness of cardiovascular diseases (CVD), many clinical studies have a go at to introduce other markers of atherogenic dyslipidemia, such as coronary risk index (CRI) and atherogenic index (AI) (Ebrahimzadeh et al., 2016). Minahan et al., (2015) reported that CK to be significant higher in OCs users (low estrogen levels) compared to nonusers.

Liver is play a major role in the metabolism of progesterone and oestrogens (Liu and Lebrun, 2006).Estrogens and OCs are both of them associated with several liver-related complications, including intrahepatic cholestasis, hepatic adenomas, sinusoidal dilatation, hepatocellular carcinoma, peliosis hepatis, hepatic venous thrombosis, and a raised risk of gallstones(Diseases, 2012). Kowalska et al., (2018) concluded that OCs could induce alterations in liver enzymes activities and proteins concentration in serum women users OCs.

A study conducted by Boshra (2017) on rats exposed toethinyl estradiol(EE)(100 ugs/kg b.w.) had a significant raising of biochemical markers: AST, ALT, ALP, GGT, and TBIL.Egoro, Tokoni, and Anakwe in (2018) have reported the long-run users of OCs containing a lower dosage of progestin and estrogen composition for a period of ≥ 2 years induced a significant rise in AST, ALT, ALP, and TBIL. Ekhato et al., (2014) observed that administration of lower doses of synthetic OCs to normal rabbits group induced a significant rise in total bilirubin, direct bilirubin, total protein, ALT, and AST compared to non-administrated control rabbits which may impact the liver function and cellular integrity. Therefore, this study aimed to assess the incidence of biochemical changes in lipid profile levels and liver function in Saudi females using OCs.

MATERIALS AND METHODS

Subject and study design: This study was carried out on a total number of 55 Saudi women between ages 20 and 40 years. Participants' were divided into two groupings: 30 women used OCs for a minimum time of one year, and 25 health woman controls. The criteria for inclusion in this study were no evidence of pregnancy and diseases. Lifestyle, physical activity, and medical history information, such as age, use of OCs, duration of OCs use, and OCs type, were obtained through an interview with the subjects. Reproductive history includes the number of pregnancies, age at menarche, parity; characteristic of initial menstrual flow (irregular or regular) was also collected. After the interview, weight, height, blood pressure, glucose was measured, and the (BMI) was estimated.

Blood sample collection: A blood specimen was collected by venipuncture after 10-12h of fasting and put in tubes with a clot activator and serum gel separator. Specimens allowed to clot for two hours at room temperature then centrifuged by for three minutes at 4000 g. The supernatant was collected immediately and stored -24 C.

Biochemical analysis: Serum was used for estimated blood glucose and lipid profile: total cholesterol (TC), triglycerides (TGs), high-density lipoprotein(HDL), and low-density lipoprotein (LDL) levels by colorimetric technique using mercantile Kit.The activity of serum Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), GGT Gamma-glutamyl transferase (GGT), Creatine kinase (CK) and total bilirubin (TBIL), total protein (TP), albumin (ALB), and globulin were also estimated by colorimetric technique using mercantile Kit from SIMENS. Was calculated Atherogenic Index (AI) = (LDLC)/(HDLC), Coronary risk index (CRI)= (TC)/(HDLC) by using the formula suggested by (Kazemi et al., 2018a; Kinosian, Glick, & Garland, 1994), and Cardiovascular risk index (CVRI) = (TG)/(HDLC) was also estimated by (Ramli et al., 2018).

Statistical analysis: The data was analyzed using SPSS. The final results were expressed as mean ± standard deviation (SD). An independent t-test was used to analyze the differences between bath oral contraceptives users and of non-user control. The relationship between variables was ascertained by means of Spearman's correlation coefficient. Values of $P > 0.05$ were considered non significantly different, while those of $P < 0.01$ and $P < 0.05$ were considered highly significant and significant, respectively.

RESULTS AND DISCUSSION

The present study intended to determine the effects of OCs use on biochemical changes included 30 women who had used OCs for at least 12 months and 25 women who had never used OCs. There was no significant difference in the age, height, weight, body mass index (BMI), systolic and diastolic blood pressure, physical activity, and types of OCs between the two groups.

The current results showed that lipid profile levels (TC, TG, LDL) and serum glucose were significantly increased (p = 0.000, 0.027, 0.000, 0.007 respectively) accompanied with non-significant change (p =0.422) in HDL among women using OCs when compared to control group (Table 2).As shown in table (3), there was a highly significant (P=0.000) elevation in the (AI) and (CRI) in women OCs users compared to the control group. However, there was no significant difference (P=0.136) in (CVRI) between the cases and control.

Table 1. Characteristics of the Oral Contraceptive users and non-users

Demographics variables	Mean±SD	Mean±SD	P-vale	Sig
Age (Years)	33.64±6.06	33.866±4.70	0.877	No Sig
Height (m)	1.63±0.049	1.627±0.097	0.873	No Sig
Weight (Kg)	68.88±10.78	63.80±12.63	0.119	No Sig
BMI (Kg/m)	25.79±3.088	24.16±4.80	0.150	No Sig
SBP	122.0±4.25	122.3±11.3	0.87	No Sig
DBP	78.0±4.50	78.2±2.96	0.84	No Sig
Physical activity	N (%)	N (%)		
Yes	4(16.0%)	4(13.3%)		
No	21(84.0%)	26(86.7%)		
Type of OCs	-			
Combined (Gynera)	-	4(13.3%)		
Combined (Yasmine)		17(56.7%)		
Progesterone (Microlot)	-	9(30.0%)		

NOC non-oral contraceptives, OCs oral contraceptives, BMI body mass index, SBP Systolic blood pressure, DBP diastolic blood pressure.
Values are as Mean±SD, p<0.05 significant as compared to the non-users

Table 2. The effect of OCs on lipid profile and glucose level

Variables	Group	N	Mean±SD	P-value	Sig
Glucose	NOC	25	4.3240±0.5125	0.007	Sig
	OCs	30	4.860±0.8810		
Total Cholesterol (mmol/L)	NOC	25	3.2296±0.94734	0.000	H. Sig
	OCs	30	5.2073±0.63847		
Triglycerides (mmol/L)	NOC	25	0.7972±0.36199	0.027	Sig
	OCs	30	1.0953±0.59341		
LDL (mmol/L)	NOC	25	1.8356±0.71385	0.000	H. Sig
	OCs	30	3.2683±0.68374		
HDL (mmol/L)	NOC	25	1.3712±0.28744	0.422	No. Sig
	OCs	30	1.4380±0.31817		

NOC non-oral contraceptives, OCs oral contraceptives, LDL low-density lipoprotein, HDL high-density lipoprotein. Values are as Mean±SD, p<0.05 significant as compared to the non-users

As demonstrated in the table (5), observed a significant increase in serum TBIL, TP, ALB, and globulin levels (P=0.000, 0.000, 0.001, 0.012) between controls and OCs users, respectively. The effect of the duration (12 months and above) of using OCs on all the pervious parameters, showed a statistically significant difference in TC, LDL, Glu, AI, CRI, ALT, AST, ALP, GGT, TB, TP, ALB, and globulin. Also, TG was significantly higher started after five years. However, no significant differences in the CVRI and HDL were noticed (Table 6).

The primary health hazards of OCs are cardiovascular diseases, particularly coronary artery disease, stroke, and venous thromboembolism (Poulter et al., 1996).

OCs adversely effects of lipid profile in women of child bearing age (Faryal,Rashid and Hajra, 2012). Prolonged use of OCs by women during their reproductive age can induce metabolic changes that may contribute to an raised risk of coronary heart (Jamil and Siddiq, 2012). In the current study, there is a significant increase in serum glucosein the OCs users as compared to control group. A similar result was reported by Kofole et al.,(2019). The mechanism through which hormonal contraception causes blood glucose levels to rise has yet to be elucidated (Kofole et al., 2019). One possible mechanism as demonstrated in rats investigated the influence of estradiol on the insulin receptor of ovariectomized rats treated with different hormonal doses that high-doses of estradiol decrease the sensitivity of insulin via the carbohydrate mechanism (González et al., 2002).

Table 3. Comparison of atherogenic indices among OCs users and non-users

Variables	Group	N	Mean±SD	P-value	Sig
AI	NOC	25	1.38±059	0.000	H. Sig
	OCs	30	2.40±0.78		
CRI	NOC	25	2.41±0.81	0.000	H. Sig
	OCs	30	3.80±0.97		
CVRI	NOC	25	0.63±0.37	0.136	N. Sig
	OCs	30	0.84±0.59		

NOC non-oral contraceptives, OCs oral contraceptives. Values are as Mean±SD, p<0.05 significant as compared to the non-users

Table 4. The effects of OCs users on enzymes activity

Variables	Group	N	Mean±SD	P-value	Sig
ALT (U/L)	NOC	25	16.04±2.24	0.000	H. Sig
	OCs	30	26.00±7.268		
AST (U/L)	NOC	25	16.72±4.64	0.000	H. Sig
	OCs	30	25.66±7.40		
ALP (U/L)	NOC	25	59.12±8.67	0.001	H. Sig
	OCs	30	75.60±22.33		
GGT(U/L)	NOC	25	6.48±3.73	0.000	H. Sig
	OCs	30	20.86±12.73		
CK (U/L)	NOC	25	52.84±19.34	0.000	H. Sig
	OCs	30	102.13±51.13		

NOC non-oral contraceptives, OCs oral contraceptives, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, CK: Creatine kinase. Values are as Mean±SD, p<0.05 significant as compared to the non-users

The present study reported a significant increase in total-cholesterol, triglyceride and LDL and no significant change in HDL in the OCs users as compared to control group. A similar result was reported by Asara et al.,(2014). Giribela et al.,(2015) observed that taking OCs containing estradiol and drospirenone during six months resulted in significant increases in TC and TG levels, but no significant changes in HDL and LDL levels when compared to non-OC users. Other studies revealed a significant increase in serum levels of TC, TG, LDL, and decreased HDL in the OCs users compared to the control group (Mohamed, 2016, Ferreira et al., 2017b, Mohammed, 2018). Kowalska et al., (2018) observed higher TG and lower LDL levels between users and nonusers of OCs with no changes in TC and HDL levels. The increase in total Cholesterol levels among women using oral contraceptive might be due to impaired lipoprotein metabolism and increased in β-lipoprotein cholesterol (Naz et al., 2012).

Triglyceride level was significantly higher among women using OCs. The use of estrogens is associated with increased hepatic synthesis of triglycerides and suppression of hepatic lipase expression, resulting in increased serum levels of triglycerides (Hassan et al., 2014). LDL- cholesterol levels was significantly higher in women using OCs might be because increase lipoprotein synthesis rather than impaired lipolytic catabolism, in association with accumulation of cholesterols as result increased LDL (Yesmin et al., 2013). Estrogen reduces LDL cholesterol levels, and progestin may oppose this effect (Bradley et al., 1978). Combination OCs also may increase serum LDL levels and androgenic steroids appear to cause elevation of LDL levels (Tikkanen and Nikkila, 1986).

Table 5. Serum of total bilirubin, total protein, albumin, and globulin in OCs users and non-users.

Variables	Group	N	Mean±SD	P-value	Sig
TBIL (umol/L)	NOC	25	4.124±2.096	0.000	H. Sig
	OCs	30	7.766±3.692		
TP(g/L)	NOC	25	69.08±12.16	0.000	H. Sig
	OCs	30	82.20±4.57		
ALB(g/L)	NOC	25	34.62±5.146	0.001	H. Sig
	OCs	30	40.60±6.88		
Globulin(g/L)	NOC	25	34.46±12.92	0.012	Sig
	OCs	30	41.59±7.07		

NOC non-oral contraceptives, OCs oral contraceptives, TBIL total bilirubin, TP total protein, ALB albumin values are as Mean±SD, p<0.05 significant as compared to the non-users

Regarding the atherogenic index (AI) and coronary risk index (CRI), there was a significant increase in the OCs users compared to the control group. These results were agreement with Asare et al., (2014). The elevated atherogenic indicators point toward their increased

susceptibility for (CVD) complications (Chakraborty et al., 2019). According to Chait and Eckel (2016), the atherogenesis occurs due to a possible endothelial injury. When there is endothelial injury, macrophages move to the site to clear off oxidized LDL. Macrophages ingest extra lipids and become foam cells, releasing cytokines with the consequent increase in cell proliferation and a further decrease in the diameter of the lumen of blood vessels; this hardens to form a plaque within the lumen (Chait and Eckel, 2016).

Table 6. Effect of duration of OCs use on biochemical parameters

	Control N = 25	Duration of OCs		
		1-2 years n = 7	3-4 years n = 10	5-7 years n = 13
TC	3.230 ± 0.947	4.753± 0.409	4.989 ± 0.529	5.620 ±0.589
		P= 0.000	P= 0.000	P= 0.000
TG	0.797 ± 0.362	1.020 ± 0.501	0.968 ± 0.600	1.234 ±0.646
		P= 0.305	P= 0.661	P= 0.029
LDL	1.836 ± 0.714	3.020 ± 0.614	2.949 ±0.698	3.648 ±0.546
		P= 0.000	P=0.001	P= 0.000
HDL	1.371 ± 0.287	1.210 ± 0.339	1.504 ±0.289	1.510 ±0.291
		P= 0.273	P= 0.235	P= 0.186
Glucose	4.324 ± 0.5126	4.200 ±0.698	4.960 ±0.917	5.139 ±0.810
		P= 0.855	P= 0.012	P= 0.002
AI	1.382 ±0.599	2.678 ± 0.880	2.027 ±0.570	2.552 ±0.829
		P=0.001	P=0.007	P= 0.000
CRI	2.416 ± 0.814	4.234 ± 1.308	3.410 ± 0.597	3.871 ± 0.960
		P=0.001	P=0.001	P= 0.000
CVRI	0.637 ± 0.374	0.955 ± 0.720	0.725 ± 0.607	0.876 ±0.547
		P= 0.261	P= 0.957	P= 0.210
ALT	16.040 ± 2.245	25.286 ±4.889	23.800 ±4.442	28.077 ±9.587
		P= 0.000	P= 0.000	P= 0.000
AST	16.720 ± 4.641	30.00 ±10.646	23.300 ±5.165	25.154 ±6.309
		P= 0.001	P=0.001	P= 0.000
ALP	59.120 ± 8.676	82.429 ±33.221	69.800±12.951	76.385 ±21.724
		P= 0.110	P=0.022	P= 0.009
GGT	6.480 ± 3.732	22.286 ±10.515	21.700 ±16.958	19.462 ±10.814
		P= 0.000	P=0.000	P= 0.000
CK	52.840 ±19.34	145.857 ± 52.740	93.600 ± 46.203	85.154 ± 42.879
		P= 0.000	P=0.002	P=0.009
TBIL	4.124 ± 2.096	7.843 ±3.804	7.730 ±4.798	7.754 ±2.908
		P= 0.013	P=0.022	P= 0.001
TP	69.080±12.165	81.571 ±3.867	82.00±5.185	82.692 ±4.733
		P= 0.000	P= 0.000	P= 0.000
ALB	34.620 ± 5.147	43.071 ±12.840	39.560 ±2.887	40.085 ±4.607
		P= 0.070	P=0.004	P= 0.005
Globulin	34.46 ± 12.926	38.500 ± 12.487	42.440 ± 5.385	42.608 ± 3.740
		P= 0.043	P=0.007	P= 0.001

The values are the mean ± S.D. of parameters measured, Significantly different from control value at P<0.05*, 0.01**, 0.001***

In this study, there was a significant increase in ALT, AST, ALP, and GGT activities in the OCs users compared to the control group. This result was in coincidence to Kowalska et al., (2018) , Toryila et al., (2018) in women and Ekhato et al., (2014) in rabbits. In the study by Al-Fartosi (2017), treated rats with combined oral contraceptive (COC) showed a significant increase in liver enzymes (AST, ALT) levels as compared to the control group. Raised serum level of ALP, AST, and ALT among women using OCs might be because functional

alterations involving the hepatic excretory mechanism (Taneepanichskul,Jaisamrarn and Phupong, 2007). Higher activities of ALT, AST, and GGT in the plasma of OCs users prove the adverse effect of OCs on the liver (Kowalska et al., 2018a).

The results indicated a significant increases in CK in the OCs users as compared to control group, this finding is in agreement with Hicks et al., (2017).Serum CK is an influential early diagnosis of not only myocardial infarction but also any kind of myocardial injury due to it is found in myocardial tissue abundantly, and its virtual absence from most other tissues and its consequent sensitivity(Priscilla & Prince, 2009).Minahan et al., (2015), reported that CK to be significantly higher in OCs users (low estrogen levels) compared to non-users. Estrogen has been reported to decrease cell membrane fluidity; this way, cell membrane stability increases, preventing CK's leakage from the intracellular membrane (Carter,Dobridge and Hackney, 2001). The findings of this study showed a significant increase in serum TBIL, TP and ALB in the OCs users as compared to control group. Our results were in agreement with previous studies (Ekhato et al., 2014, Iyomon et al., 2015, Kowalska et al., 2018b).

Administration of lower doses of synthetic OCs affect on liver functionality by increasing red blood cell destruction which lead to rise of TBIL level. This is suggested considering the function of the liver in filtration, storage, and metabolism of blood and the formation and excretory of bile (Guyton and Hall, 2006). The hyper-proteinaemic impact of OCs indicated by Hall (2015) who suggested that OCs effect on protein metabolism and the colloid osmotic pressure of plasma, muscle devastation, and transport functions via the protein transporting mechanism through ALB. This effect perhaps because the estrogen contained in OCs is known to stimulate the hepatic synthesis of various nutrient-specific transport proteins. Estrogens have long been known to cause intrahepatic cholestasis in susceptible women during pregnancy, during postmenopausal hormone replacement therapy, or after administration of OCs. Estrogen receptor alpha-mediated repression of hepatic transporters and alterations of bile acid biosynthesis may contribute to the development of the estrogen-induced hepatotoxicity (Yamamoto et al., 2006). All hormonal contraceptives contain progestogens. The liver processes progestogens and estrogens differently due to liver cells have estrogen receptors but no progestogen receptors (Sitruk-Ware, 2008).

This study evaluates the effects of duration of OCs use on lipids profile, which is represented by a significant increase in TC, TG, and LDL levels. Also, glucose, AI, and CRI have shown the same results. These results agree with a study by (Sufa,Abebe, and Cheneke, 2019). Similarly, Sultana and Khatun, (2016) have reported serum TC, TG, and LDL were significantly higher among contraceptive users of > 5 years duration than those among five or < 5 years duration. Furthermore, change substantially ($p \leq 0.05$) in ALT, AST, ALP, GGT, CK, TB, TP, ALB, and Globulin in women used OCs for more than one year compared to non-users (control group). However, observed a significant change was in ALP after two years of using OCs. Egoro et al., (2018) demonstrated that elevated levels of plasma ALT, AST, ALP, and TB in long-term users of OCs containing lower doses of estrogen and progestin composition for ≥ two years as compared to(control group). Similarly, significant elevations in GGT and globulin in OCs users after one and two years compared to the non-users (Naz et al., 2016).However, the long-term users of the OCs on HDL and CVRI have shown no significant difference ($p \geq 0.05$) compared to the mean value of non-users of OCs (control group). These results were concord with findings of Bawah et al., (2018).

CONCLUSION

In this study, there was an effect of using OCs on lipid level and liver function compared to the control group. Moreover, there is a statistically significant relationship between the duration of OCs use and the lipid profile. Therefore, the lipid profile must be evaluated while using oral contraceptives and women should be aware of the type of contraception that is appropriate for them.

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