Effect of hormonal contraceptives on serum lipids: A prospective study

Huma Dilshad[1,2*] , Rabia Ismail[1], Safila Naveed[1,2] Khan Usmanghani[2], M. Tanweer Alam[2] and Ghulam Sarwar[2]

[1]Faculty of Pharmacy, University of Karachi, Pakistan
[2]Faculty of Pharmacy, Jinnah University for Women Karachi, Pakistan

Abstract: To estimate the effects of using hormonal contraceptives on serum lipoprotein levels. Lipid profile was measured at baseline and afterward at 3, 6, 9 and 12 months. 1391 Pakistani females taking COCs, DMPA, or non hormonal (NH) contraceptives. The results were calculated by repeated measure ANOVA subsequent to tukey's post hoc test for the multiple comparisons. Statistical examination revealed that differences in lipid profile were significant ($p < 0.001$) among all treated group in comparison with control. DMPA also caused significant rise in Castelli index-I and Castelli index-II as compared to COCs group and control group. This study demonstrated raise in total cholesterol (TC) and triglycerides (TG) as well as very low density lipoprotein (VLDL-C) and low density lipoprotein cholesterol (LDL-C). Whereas, an obvious decrease was observed in high density-lipoprotein cholesterol (HDL-C) in the DMPA-treated group. We concluded that, this inductive study specifies atherogenic cardiovascular risk in women using DMPA on long term basis.

Keywords: Contraception, Depo-medroxy progesterone Acetate (DMPA), Combined Oral Contraceptives (COCs) lipid profile.

INTRODUCTION

Hormonal contraceptives (HCs) (oral and injectable) are the most accepted type of birth control, most widely used in Pakistan in order to avoid unintended pregnancy. These contraceptives prevent ovulation, inhibiting the ovaries to release eggs and also cause thick cervical mucus, forming it difficult for sperm to go into the uterus (Rivera, Yacobson *et al*., 1999).

Obesity, nausea, breakthrough bleeding, breast tenderness, hypertension (high blood pressure), increased level of cholesterol, any sign of a blood clot and bloating are commonly reported HCs side effects (Poulter, Chang *et al*., 1998). Moreover, HCs increase a female's liability to cerebrovascular disease and cervical cancer. A female using oral contraceptive pill is1.9 times more expected to die due to cerebrovascular disease and 2.5 times more at risk to cervical cancer (Lock, 2001). Worldwide approximately 100 million women are using oral contraceptives. Previous studies have revealed that synthetic hormones present in oral contraceptives significantly improved the risk of blood clots. These clots are usually formed in the legs and can reason severe damage and death if they move to the heart, lungs or brain (Zabut and Abu-Hani, 2013).

MATERIALS AND METHODS

It is a multicenter case control study including females of reproductive age. A total of 1391 women were selected according to inclusion and exclusion criteria described below with the age range of 19-49 years. Among these 477 females who were initiating DMPA (Depot-Medroxy progesterone Acetate) and 498 females were initiating COCs (combined oral contraceptives) for the indication of contraception whereas 416 were the matched controls of same age and socioeconomic status. The lipid profiles and complete blood count (CBC) were evaluated before initiation of contraceptives use and thereafter 3, 6, 9 and 12 months. As well as controls were analyzed for the same parameters periodically in the same way as that of treated group. The results were calculated by repeated measure Two Way ANOVA subsequent to tukey's post hoc test for the multiple comparisons.

Inclusion criteria

Following women were selected for the study

1. Healthy women of fertile age using hormonal contraceptives (HCs) for the first time.
2. Females using HCs for the indication of contraception.

Exclusion criteria

Following women was refused to be the part of the study:

1. Nursing females
2. Females with well diagnosed disease (e.g Diabetes, cardiovascular disease, hormonal disorders, hypertension, hyperlipidemia etc)

Blood sampling and processing

Seven ml blood was drawn from each female agreed to participate in study. Serum is separated by centrifugation at 3000 rpm for 15-20 min. The separated serum was stored at 2-5˚C for less than 24 hours preceding to blood parameters evaluation. Serum levels of total cholesterol, HDL-C, LDL-C and TAG were analyzed through

**Corresponding author:* e-mail: humapharmacist@gmail.com

HUMALYZER Germany using standard kits provided by Human Germany.

STATISTICAL ANALYSIS

The data was analyzed by using a software statistical package for the social science (SPSS version 13). All the values are expressed as mean ± S.D. Repeated measures two way ANOVA followed by Tukey's post hoc analysis was used to compare control and treated groups. P value less than 0.05 would be taken as significant.

RESULTS

The current study was a case control and included 1391 females (Controls n=416, DMPA n=477 and COC n=498). table 1 shows the mean concentration of lipid parameters of control group, DMPA and COCs users. All results are indicated in terms of mean ± S.D. The serum levels of total cholesterol, triglycerides, LDL and VLDL in DMPA group noticed comparatively higher than control group with the exemption of HDL that showed declined levels with the value of 39.67±3.6mg/dl vs 44.13±4.22 mg/dl.

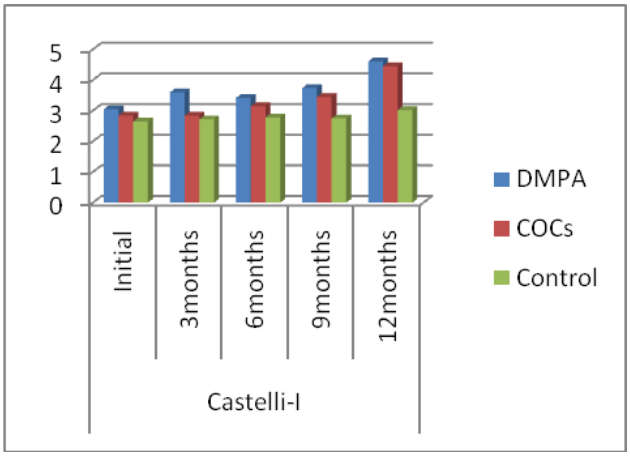

Fig. 1: Castelli Index 1 (cholesterol- HDL ratio) of COCs Vs DMPA Vs Control

As shown in table 1, the mean levels ± SD of serum cholesterol, triglycerides, LDL-C, VLDL-C and total cholesterol were significantly higher among the cases of COC (p=0.0001) compared to the controls. The differences among the study groups (COC and DMPA) with respect to lipid levels were also very significant (p= 0.0001). The mean values ± SD of HDL-C among the cases of COC (44.08±3.671mg/dl) was not significant (p=0.822) compared to the controls (44.13±4.22mg/dl) (table: 1)

DISCUSSION

The current study was designed to examine the after comes of extended administration of two HRT preparations, combined oral contraceptive (COC) with 0.15mg Levonorgestrol+0.03mg Ethinyl estradiol and progestrone only injectable contraceptive (DMPA) with depotmedroxy progesterone acetate 150mg/ml. Even though various researches have been done on the association between depot medroxyprogesterone acetate (DMPA) and lipid concentration, outcomes were not constant among different studies. For instance, some have confirmed that DMPA has not influence on lipid profile whereas other studies have revealed an undesirable correlation (Fahmy, Khairy *et al*., 1991, Kongsayreepong, Chutivongse *et al*., 1993, Mia, Siddiqui *et al*., 2005, Oyelola, 1993). Two others reported a beneficial effect (Lizarelli, Martins *et al*., 2009, Tankeyoon, Dusitsin *et al*., 1976). Results of these entire studies are restricted since they are cross-sectional in plan (Fajumi, 1983, Kongsayreepong, Chutivongse *et al*., 1993, Lizarelli, Martins *et al*., 2009, Virutamasen, Wongsrichanalai *et al*., 1986) or contain extremely little sample. Just three huge researches have been available which pursued women for comprehensive period and they do not in agreement in their results (Grossman, Asawasena *et al*., 1979, Kaunitz, Miller *et al*., 2006, Liew, Ng *et al*., 1985).

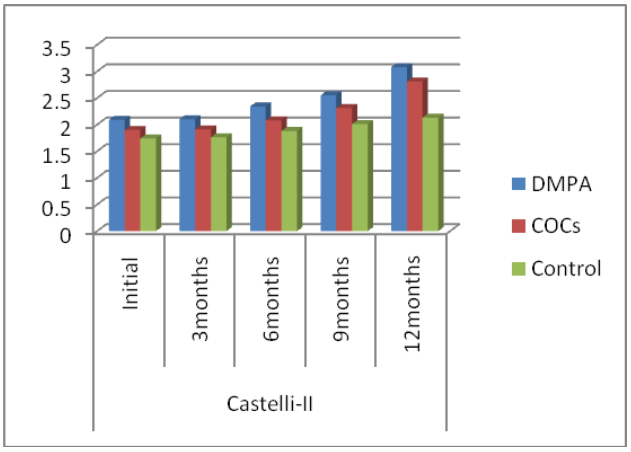

Fig. 2: Castelli index II (LDL-HDL ratio) of COCs vs DMPA Vs Control

Estrogen also affects the cardiovascular system diffusely through its concussion on cardiovascular risk factors for example the lipid profile. Oral contraceptives change the lipid levels via the genomic pathway, in which estrogen modifications affect hepatic apolipoprotein regulation or control (Epstein, Mendelsohn *et al*., 1999, Jones, Schmidt *et al*., 2002, Sitruk-Ware, Menard *et al*., 2007). The estrogen component of COCs enhances removal of LDL cholesterol and raises levels of high-density lipoprotein cholesterol. Orally administered estrogen increases triglyceride levels as well, conversely in the situation of concurrently improved HDL and lower LDL levels, the modest triglyceride elevation due to oral use of estrogen do not emerge the risk of atherogenesis (Shufelt and Merz, 2009).The progestin component of COCs counteracts these lipid changes induced by estrogen,

Table 1: Effect of hormonal contraceptives on lipid profiles

Parameters	Treatment Groups / no. of subjects in each group		
	Control group	DMPA group	COCs group
	N= 416	N=477	N=498
Cholesterol	133.03±14.8mg/dl	180.7±38.8mg/dl ***	195.14±38.167***,###
Triglycerides	99.03±30.6 mg/dl	126.33±48.8mg/dl***	120.78±49.400***,##
HDL	44.13±4.22 mg/dl	39.67±3.6mg/dl***	44.08±3.671###
LDL	94.27±19.6 mg/dl	120.04±36.2mg/dl ***	123.01±31.343***
VLDL	20.99±8.66 mg/dl	24.6±10.0mg/dl ***	23.50±10.006***,#
Total Cholesterol	569.19±80.4 mg/dl	713.05±110.2 mg/dl***	753.78±105.994***,###

Significant difference by repeated measure with two-way ANOVA. $^{***}P\leq0.001$, highly significant difference in comparison with control. $^{###}P\leq0.001$, highly significant, $^{##}P\leq0.025$, moderately significant, $^{#}P\leq0.05$, significant difference in comparison with DMPA.

which increases levels of LDL and decreases concentration of HDL and triglyceride(TGS. COCs formulated with more androgenic progestins raise HDL and TGS levels not more than formulations with less androgenic progestins (van Rooijen, von Schoultz *et al*., 2002). Overall modern COCs have little effect on lipid metabolism in normal weight women (Beasley, Estes *et al*., 2012).In contrast to COCs, administration of DMPA lowers HDL levels, raises LDL levels, and does not raise triglyceride levels (Berenson, Rahman *et al*., 2009).From the previous studies there were inconsistent information regarding the effects of hormonal contraceptives. Some reported an adverse relationship (Mia, Siddiqui *et al*., 2005) while others reported beneficial relationship (Lizarelli, Martins *et al*., 2009).

In order to evaluate the risk of cardiovascular diseases (CVD), the castelli index I and II were also calculated. For normal subjects the limit of castelli index I must be less than 4, that was found to be ranging from 3.02 to 4.61,where DMPA exhibited the highest ratio (4.61) and control group showed minimum value (3.02), whereas COCs revealed the value in between these two extremesi-e (4.55). The value of castelli index II (LDL/HDL-C) was recognized promising near to the upper limit of the normal range (<3). It ranges from 2.13 to 3.08 where DMPA revealed the maximum and COCs ascertained minimum value .The plan of this study was to immerse the gap in the literature by assesment the outcome of DMPA as well as OC consist of 30 micrograms ethinyl estradiol (EE) and 0.15mg Levonorgestrol on serum lipid levels over one year of contraceptive use in women living in Karachi (Pakistan). Lipid profile was measured at baseline and at every 3 months interval.

CONCLUSION

Although the results showed minimum risks due to close clinical monitoring but comparison among different groups have that the use of DMPA was more associated with the highest atherogenic index as compare to COCs and controlled group. DMPA pose the risk of predisposition to sub clinical cardiovascular disease (CVD) in young females, which may present a well defined CVD later in their lives.

REFERENCES

Beasley A, Estes C, Guerrero J and Westhoff C (2012). The effect of obesity and low-dose oral contraceptives on carbohydrate and lipid metabolism. ***Contraception,*** **85**(5): 446-452.

Berenson AB, Rahman M and Wilkinson G (2009). Effect of injectable and oral contraceptives on serum lipids. *Obstetrics and Gynecology,* **114**(4): 786.

Epstein FH, Mendelsohn ME and Karas RH (1999). The protective effects of estrogen on the cardiovascular system. *New England Journal of Medicine,* **340**(23): 1801-1811.

Fahmy K, Khairy M, Allam G, Gobran F and Alloush M (1991). Effect of depo-medroxyprogesterone acetate on coagulation factors and serum lipids in Egyptian women. *Contraception,* **44**(4): 431-444.

Fajumi JO (1983). Alterations in blood lipids and side effects induced by depo-provera in Nigerian women. *Contraception* **27**(2): 161-175.

Grossman R, Asawasena W, Chalpati S, Taewtong D and Tovanabutra S (1979). Effects of the injectable contraceptive depot medroxyprogesterone acetate in Thai women with liver fluke infestation: Final results. Bulletin of the World Health Organization**,** **57**(5): 829.

Jones DR, Schmidt RJ, Pickard RT, Foxworthy PS and Eacho PI (2002). Estrogen receptor-mediated repression of human hepatic lipase gene transcription. *Journal of Lipid Research,* **43**(3): 383-391.

Kaunitz AM, Miller PD, Rice VM, Ross D and McClung MR (2006). Bone mineral density in women aged 25-35 years receiving depot medroxyprogesterone acetate: Recovery following discontinuation. *Contraception,* **74**(2): 90-99.

Kongsayreepong R, Chutivongse S, George P, Joyce S, McCone J, Garza-Flores J, de Bourges VV, de La Cruz D, Perez-Palacios G and Rosseneu M (1993). A

multicentre comparative study of serum lipids and apolipoproteins in long-term users of DMPA and a control group of IUD users. *Contraception,* **47**(2): 177-191.

Liew DF, Ng CS, Yong Y and Ratnam S (1985). Long-term effects of depo-provera on carbohydrate and lipid metabolism. *Contraception,* **31**(1): 51-64.

Lizarelli PM, Martins WP, Vieira CS, Soares GM, Franceschini SA, Ferriani RA and Patta MC (2009). Both a combined oral contraceptive and depot medroxyprogesterone acetate impair endothelial function in young women. *Contraception,* **79**(1): 35-40.

Lock S (2001). Michael Bliss, William Osler: A life in medicine, Oxford University Press, 1999, pp. xiv, 581, illus., £27.50 (hardback0-19-512346-8). *Medical History,* **45**(01): 128-129.

Mia A, Siddiqui N, Islam M, Khan M, Shampa S and Rukunuzzaman M (2005). Effects of prolonged use of injectable hormonal contraceptive on serum lipid profile. *MMJ.,* **14**(1): 19-21.

Oyelola OO (1993). Fasting plasma lipids, lipoproteins and apolipoproteins in Nigerian women using combined oral and progestin-only inject able contraceptives. *Contraception,* **47**(5): 445-454.

Poulter N, Chang C, Farley T, Marmot M and Meirik O (1998). Cardiovascular disease and use of oral and inject able progestogen-only contraceptives and combined inject able contraceptives. Results of an international multicenter case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Contraception,* **57**(5): 315-324.

Rivera R, Yacobson I and Grimes D (1999). The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. *American Journal of Obstetrics and Gynecology,* **181**(5): 1263-1269.

Shufelt CL and Merz CNB (2009). Contraceptive hormone use and cardiovascular disease. *Journal of the American College of Cardiology,* **53**(3): 221-231.

Sitruk-Ware RL, Menard J, Rad M, Burggraaf J, de Kam ML, Tokay BA, Sivin I and Kluft C (2007). Comparison of the impact of vaginal and oral administration of combined hormonal contraceptives on hepatic proteins sensitive to estrogen. *Contraception,* **75**(6): 430-437.

Tankeyoon M, Dusitsin N, Poshyachinda V and Larsson-Cohn U (1976). A study of glucose tolerance, serum transaminase and lipids in women using depot-medroxyprogesterone acetate and a combination-type oral contraceptive. *Contraception,* **14**(2): 199-214.

van Rooijen M, von Schoultz B, Silveira A, Hamsten A and Bremme K (2002). Different effects of oral contraceptives containing levonorgestrel or desogestrel on plasma lipoproteins and coagulation factor VII. *American Journal of Obstetrics and Gynecology,* **186**(1): 44-48.

Virutamasen P, Wongsrichanalai C, Tangkeo P, Nitichai Y and Rienprayoon D (1986). Metabolic effects of depot-medroxyprogesterone acetate in long-term users: a cross-sectional study. *International Journal of Gynecology & Obstetrics,* **24**(4): 291-296.

Zabut BM and Abu-Hani IM (2013). Evaluation of some physiological and biochemical parameters of healthy Women administrated oral contraceptive pills in Gaza city, -20(2)