Medical Journal of Babylon
Vol. 12- No. 3: 802-816, 2015
http://www.medicaljb.com
ISSN 2312-6760©2015 University of Babylon

Original Research Article

Lipid Profile Changes in Women in Reproductive Age Group Using Injectable Medroxypogesterone Acetate Contraception

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Accepted 5 April,2015

Abstract

To evaluate lipid profile changes in women of reproductiveage group using Depot Medroxyprogesterone Acetate contraceptive lasting for three months. A prospective study in Al- Imamein Al- Kadhemein medical city from July 2013 to January 2014. The study included a total of 40 healthy multi para women in reproductive age group, visiting family planning clinic in Al- Imamein Al- Kadhemein medical city seeking for contraception.
Verbal consent obtained from participants. Baseline serum lipids wasassessed prior to the use of Depot Medroxyprogesterone Acetate and thenthree months after the use of injection in 10-12 hours fasting women.
A detailed questionnaire was designed, to be fulfilled by each clientincluding; all relevant issues: age, general health history, obstetric and gynecological history, menstrual cycle and relevant medical diseases andprevious use of contraception.In this study there was significant increase in serum LDL (p value <0.001) and significant decrease in serum HDL (p value<0.001) after three months of depot-medroxyprogesterone acetate injections in comparison to pre-injection group. There was insignificant increase in serum cholesterol (p value >0.05) and no changes in serum triglyceride, also there was no significant changes in BMI three months after injections (p value> 0.05).Depot medroxy progesterone acetate used in women with reproductive age group as injectable contraception, can cause significant changes in lipid metabolism.

التغيرات في معدلات الدهون لدى النساء في سن الانجاب اللواتي يستعملن مانع الحمل عن طريق الحقن العضلي المدروكسيبروجستيرون

الخلاصة

من اجل معرفة التغييرات التي تحصل في معدلات الدهون في الدم لدى الإناث في سن الإنجاب اللواتي يستخدمن موانع الحمل عن طريق الحقن العضلي (Depot Medroxyprogesterone Acetate) لمدة ثلاثة أشهر.اجريت دراسة مستقبلية في مدينة الاماميين الكاظميين (ع) الطبية. من٢٠١٣/٧/١٥ إلى ٢٠١٤/١/١٥ (ستة أشهر).الدراسة شملت عددا إجماليا قدره 40 امرأة متزوجة في سن الإنجاب وبحالة صحية جيدة راجعن عيادة تنظيم الأسرة في مستشفى مدينة الاماميين الكاظميين (ع) الطبية , وافقن على استخدام موانع الحمل عن طريق الحقن العضلي (Depot medroxyprogesterone acetate), تم سحب (٤ مليلتر) من الدم الوريدي صباحا بعد ١٠-١٢ ساعة من الصيام طوال الليل قبل الحقن العضلي, ثم بعد الحقن العضلي ٣ اشهر,تم اعادة سحب الدم بعد ١٠-١٢ ساعة صيام طوال الليل.أرسلت النماذج لمختبر مستشفى مدينة الاماميين الكاظميين (ع) الطبية لقياس نسب الدهون في الدم.لوحظ ان ليس هناك فرق في الوزن قبل و بعد الحقن العضلي لمانع الحمل.اما بالنسبة للدهون فقد وجدنا زيادة في نسبة الدهون القليلة الكثافة وذلك بعد ثلاثة اشهر من حقن (Depot medroxyprogesterone acetate) بالمقارنة مع ما قبل الحقن بقيمة بي < ٠.٠٠٠١ ,ووجدنا نقصان في نسبة الدهون العالية الكثافة بعد ثلاثة اشهر من الحقن بالمقارنة مع ما قبل الحقن بقيمة بي <٠.٠٠٠١.فقد وجد زيادة طفيفة في الكولستيرول بعد ٣اشهر من الحقن بالمقارنة مع ما قبل الحقن بقيمة بي>٠.05.بالنسبة للدهون الثلاثية لم يطرا اي تغيير بعد الحقن بالمقارنة مع ما قبل الحقن بقيمة بي>٠.٠٥. اظهرت دراستنا ان

Introduction

Contraception is a combination of two words: "Contra" which means against and " Ception" means meeting of the sperm cell and an egg cell. [1]. It's choice varies with age, ethnicity, marital status, fertility intensions and education [2]. The Egyptian EbersPaprus from 1550 BC and the Kahun Papyrus from 1850 BC, have the earliest documented birth control, the use of vaginal pessary including honey, acacia leaves and lint to be placed in the vagina to block sperm [3][4].

The effectiveness of contraceptive method is measured by its failure rate when been used and depending on it action and how easy its' use.

Oestrogens and progesterone can be used for contraception in the following ways; combined hormonal contraception: containing both oestrogen and progesterone as; COC., mono/bi /triphasic, trans-dermal patch and as vaginal ring.Progesterone, on the other hand, either as a tablet; the progesterone only pill (mini pills), or as a Depot: Nexiplanon, Depo-Provera or as in levonorgestrel containing intrauterine system [5]

Progesterone secreted by corpus luteum. It is a carbon 21and is secreted during the second half of menstrual cycle .It is also formed by placenta, in later part of the pregnancy, the testis and adrenal cortex.It is soluble in most organic solvents and in vegetable oils but is insoluble in water. Progesterone is an intermediate in biogenesis of adrenocortical hormones and of androgens.Progesterone is rapidly absorbed following any route of administration. It quickly undergos hepatic degredation following intramuscular administration. Progesterone in oil, rapidly absorbed and undergoes hepatic metabolism. Intramuscular progesterone is extensively bounded to serum proteins, and its metabolites are excreted 60% by the kidney and 10% through the bile and feces.[6]Depot medroxyprogesterone acetate (DMPA) inhibit follicular development and prevent ovulation as a primary mechanism of action .[7][8] A secondary mechanism of action of all progestogen-containing contraceptives is inhibition of sperm penetration by changes in the cervical mucus. Inhibition of ovarian function during DMPA use causes the endometrium to become thin and atrophic. These changes in the endometrium could, prevent implantation [9].

Table 1: contraceptive injections

Common Trade Names	Formulation	Injection Type and Schedule
Progestin-Only Injectables		
Depo-Provera®, Megestron®, Contracep®, Depo-Prodasone	Depot medroxyprogesterone acetate (DMPA) 150 mg	One intramuscular (IM) injection every 3 months
depo-subQprovera 104® (DMPA-SC)	Depot medroxyprogesterone acetate (DMPA) 104 mg	One subcutaneous injection every 3 months
Noristerat®, Norigest®, Doryxas	®Norethisteroneenanthate (NET-EN)200 mg	One IM injection every 2 months

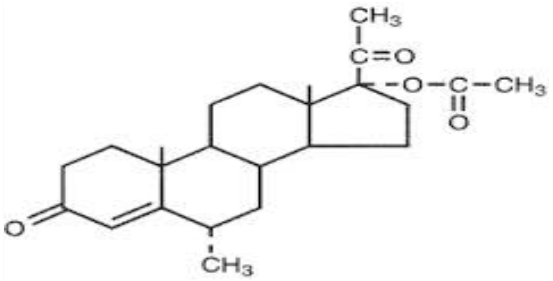

Figure 1: DepotMedroxyprogesterone acetate (Depo-Provera)chemical structure[10]

Depot medroxy-progesterone acetate (Depo-Provera) is an effective reversible contraception. It was developed in 1954 as a treatment for endometriosis and to prevent habitual or threatened abortion. In 1987, the US food and drug Administration (FDA) approved DMPA as a contraception and currently been used worldwide[11].

It's administered subcutaneously or intramuscularly every 3 months. DMPA can be administered up to 2 weeks early or 2 weeks late without the need for a protective back-up contraceptive method. If it is more than 2 weeks late, the injection can be used, but additional contraceptive protection should be used for the next 7 days [12]. There is other injectable contraceptive available is nor-ethisteroneenanthate (NET-EN) rarely used and only licensed for short-term use.[13]. It's side effects mainlyIrregular bleedingin 80% of women while70% women got amenorrhea after 12 months of use. Spotting and heavy bleeding can be developed. Counseling before administration improves tolerance for it's use[14]. There is conflicting evidence that Depo-Provera causes a reduction in bone mineral density [14]which is recovered when been stopped [15]. There is no evidence for long-term fracture risk and those with significant risk factors for osteoporosis should consider other methods of contraception. It's licensed for long-term use and the benefit/risk profile for women been re-evaluated if she wishes to continue using it for more than two years [15]. Other side effects cardiovascular disease ,changes in serum cholesterol (specially low-density lipoprotein) levels have been demonstrated [16]. Weight gain of up to 3 kg in one year may occur [14].

Fertility is returned within 10 months from the last injection so a woman should not be worried if she has not become pregnant after 12 months[17]. Other side effects; as nausea, dizziness, breast tenderness/engorgement, acne, insomnia, leg cramps, arthralgia, scalp hair loss, depression, decrease in libido due to decrease level of testosterone, greater risk of acquiring sexual transmitted infection, spreading gonorrhea and Chlamydia is seen with use of Depo-Provera compared to non-hormonal methods [18,19].Advantages include;Prevention or improvement of iron deficiency anemia. Reduction in severity of symptoms of endometriosis also reduction in severity of sickle cell crises among women with sickle cell anemia.There's no increased risk for cervical, ovarian cancer or liver tumors while risk of endometrial carcinoma is reduced. Inject-able contraceptiongives protection against ectopic pregnancy, pelvic inflammatory disease and functional ovarian cysts, because ovulation is

inhibited. Neither Depo-Provera nor Noristerataffects blood pressure. In women with epilepsy its use lessens the frequency of seizures. Disadvantagesof its use when given its effect cannot be removed , possible risks of long-term hypo-estrogenism,delay in the return to fertility, depression and other mood changes,galactorrhoea can occur, with a raised prolactin, androgenic effects such as acneand local complications as hematoma[20]. There are four UK Medical Eligibility Criteria for Contraceptive Use for progestogen-only inject-able use [21].The failure rate in perfect use of MPA is 0.3% while in typical use it is 3.1%.Triglycerols , fatty acids, cholesterol, and phospholipids are the major lipid components of the body. Many cells have the capacity for synthesisand degradation of these lipids to produce or convert them to another biologically important compound [22].TG used in the body mainly to provide energy for different metabolic processes they share it with carbohydrates. A lot of fat are stored in adipose tissue and liver until they are needed to provide energy elsewhere in the body. The fat cells can synthesize very small amounts of fatty acids and triglycerides from carbohydrates. Large quantities of lipases are present in the adipose tissue some of these enzymes catalyze the deposition of cell triglycerides from chylomicrons and lipoproteins. Others, when activated by hormones, cause splitting of triglycerides of fat cells to release free fatty acids. The principal function of the liver in lipid metabolism includes; degradation of fatty acids into small compounds that can be used for energy, synthesis of triglycerides' mainly from carbohydrates but to less extent from proteins, synthesize other lipids from fatty acids as cholesterol and phospholipids(23).Lipids in the body as Lipoproteins [23].Cholesterol,Triglyceride[33] Fatty acids[22], Phospholipids [23], Apo lipoproteins (Apo)[32], Progestins administered alone induced hepatic lipase activity,increasing the degradation of HDL;whereas, the addition of progesterone to oestrogens tend to attenuate the increase in serum HDL and the decrease in serum LDL. These effects of progestins upon lipid profile depend on their biochemical structures. Progestins with pure progesteronic effect do not alter the lipid metabolism[25]. Progestins with strong androgenic or anti-estrogenic effects decrease HDL2, selectively in premenopausal women , and this decrease associated with increase hepatic lipase activity. In women taken oral contraceptives containing mainly progestin increased plasma triglycerides and decreased plasma HDL especially HDL2[26].

The aim of study was to find the effect of Depot medroxy-progesterone acetate on serum lipids overthree months of contraceptive use.

Materials and Methods

The study design was approved by the scientific committee of Iraqi board for medical specialization in Obstetrics and Gynecology. It was prospective study carried out in Family Planning Clinic in Al-Imamein Al-Kadhemein medical city , from (15^{th} of July 2013) till (15^{th} of January 2014).The studied group consisted of 40 women selected out of the cases visiting Family Planning Clinic seeking contraception .They have chosen the Depot Medroxyprogesterone Acetate as a contraception after counseling the benefits and side effects of this method by the health care providers. Their serum lipids before injection of the Depot Medroxyprogesterone Acetate was assessed, then followed up and, re-

assessed their serum lipids three months after injection of the Depot Medroxyprogesterone Acetate. Inclusion criteria were; women accepted to participate in the study,their ages from (15-49) years, no history of previous use of hormonal contraception since marriage, BMI = (18-24) kg/m^2,base line investigations of serum cholesterol, serum triglyceride, serum HDL and serum LDL, are within the normal range, fasting women; 10-12 hours at time of presentation.Exclusion criteria included; current pregnancy or suspicion of early pregnancy, women who refused to participate, lactation amenorrhea, history of acute or chronic liver diseases, current use of chronic medications affect serum lipids history of chronic diseases (hypertension, diabetes mellitus,heart diseases),smokers, history of breast cancer, history of unexplained vaginal bleeding and a body mass index BMI $>25kg/m^2$.

A questionnaire was designed and reviewed by three obstetricians. It included; demographic measurements (age, parity, weight, height, residence, education and occupation), medical history, drug intake, menstrual history, obstetrical history and contraception history,smoking and history of breast feeding. The results of blood sample were obtained two hours later. Normal lipid profile results are a must for the case to be included in the study.

Difficulties were encountered regarding acceptance to participate in the study, the inclusion criteria, the type of contraception requested, the co-operation to re-attend back to the clinic three months later.

During the study period; number of women attended Family Planning Clinic during the 3months, were 250 women. After counseling, unfortunately; only ninety cases agreed to use the injectable contraception andto participate in the study. Sixty of them had initially the inclusioncriteria. Four ml of blood sample was obtained from each,after ١٠ - 12 hours fasting (morning specimen), which revealed a normal lipid profile in only forty–five cases who were considered as the study group. Their phone number wastaken, they were re-called 3 months later; 5 refused to come back to clinic and only 40 women continued till the end of the studied period.

After verbal consent, 4 ml of venous blood was collected from each case of 10-12 hours fasting (morning specimen) using a disposable syringe then put in tube without anticoagulant, left at room temperature for at least 15 minutes ,then the tube centrifuged to obtain serum using centrifuge device (universal 16 A, Hettichi, manufactured in Germany), then 500 microgram from this serum was aspirated by a pipette and put in a tube then introduced into the computerized auto-analyzer (Abbott, manufactured in USA) containing reagents specific for each type of lipid. After 10 minutes of chemical reactions between the serum samples and reagents the results of serum cholesterol , serum triglyceride and serum HDL appear on the computer screen .We had calculated serum VLDL from TG/5.We had calculated serum LDL from Friedewald' s equation : Serum LDL= Cholesterol - (HDL+VLDL).

Table 2: Normal values of serum lipids in Al-Imamein Al-Kadhemein medical city lab

S. cholesterol	150-240 mg/dl.
S.TG	70-160 mg/dl.
S HDL	More than 40 mg/dl.
S.LDL	70-160 mg/dl.
S.VLDL	Less than 40 mg/dl.

Then, women received a dose of medroxyprogesterone acetate (Depo-Provera) manufactured in Belgium of 150 mg/ml lasting for 3 months administered by deep intramuscular injection into the buttock or upper arm depending on client's preference by Z track technique and avoid massage or exercise. Injections started on or before the 5th day of the menstrual cycle. Three months after injection , re- evaluation of serum lipids (s. cholesterol, s. triglycerides, s.HDL. s.LDL) in 10- 12 hours fasting women was done , in a follow-up visit. Height and body weight was measured as a baseline in the first visit, then weight was measured 3 months after DMPA use, BMI was then measured by the following equation BMI= weight kg / height m^2. Overweight is considered when the body mass index is between 25.1kg/m^2 to 29.9kg/m^2, while a body mass index $\geq$ 30kg/m^2 is considered as obesity, both excluded in our study.

Statistical analysis performed by using statistical package or social sciences (SPSS) version 21. Categorical data were described as count and percentage while numerical data were described as mean and standard error o mean. Comparisons between groups were made by using chi-square test or categorical data and t-test or numerical data. The lowest level of probability to be accepted.

Results

Table 3: Descriptive statistics of age in study group.

Age (years)	Mean	Standard Error	Standard Deviation	Range	Minimum	Maximum
Study group	29.60	1.34	7.34	22	18	40

Table 4: descriptive statistics of BMI in study group.

BMI (kg/m^2)	Mean	Standard. Error	Standard Deviation	Range	Minimum	Maximum	P value
Pre-injection of DMPA	22.4	0.43	4.3	5.5	19	24.5	0.652
3 months after injection	21.63	0.66	3.60	6.00	18.00	24.00	

There was no significant difference in BMI between pre-injection and three months after injection of DMPA as p value >0.05 which is statistically not significant.

Table 5: Descriptive statistics of residency, occupation, education and previous use of non-hormonal contraception in the study group.

		Study group	
		Frequency	%
Residency	Rural	8	20%
	Urban	32	80%
	Total	40	100%
Occupation	Employed	19	47.50%
	Unemployed	21	52.50%
	Total	40	100%
Education	Higher education	6	15%
	Primary	13	32.50%
	Secondary	15	37.50%
	Illiterate	6	15%
	Total	40	100%
Previous non hormonal use of contraception	No	23	57.50%
	Yes	17	42.50%
	Total	40	100%

Table 6: show Mean ± Standard Deviation (SD) of serum lipids in the study group; pre-injection of DMPA and three months after DMPA injection.

	Pre-injection of DMPA Mean ±SD	**3 months after injection Mean ±SD**	**P value**
LDL	108.90±7.63	176.10±3.51	<0.001
HDL	52.10±1.98	30.03±1.85	<0.001
Cholesterol	169.60±7.11	217.90±4.23	>0.05
TG	102.80±5.79	109.20±6.05	>0.05
VLDL	20.56±1.16	21.84±1.21	>0.05

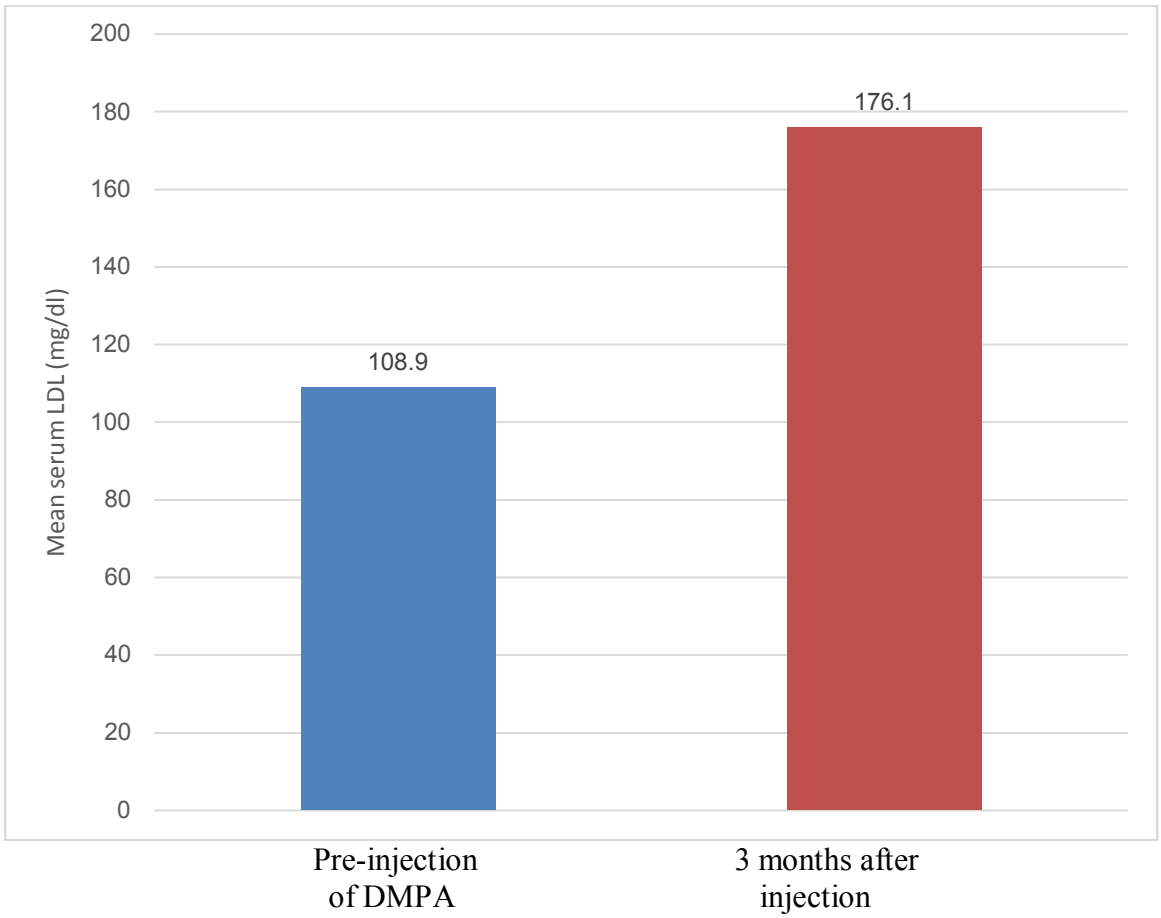

Figure 2: Mean serum LDL (mg/dl) in pre-injection of DMPA and three months after injection.

There was significant increase in serum LDL three months after DMPA injection as compared with pre-injection of DMPA as p value <0.00l which is statistically significant.

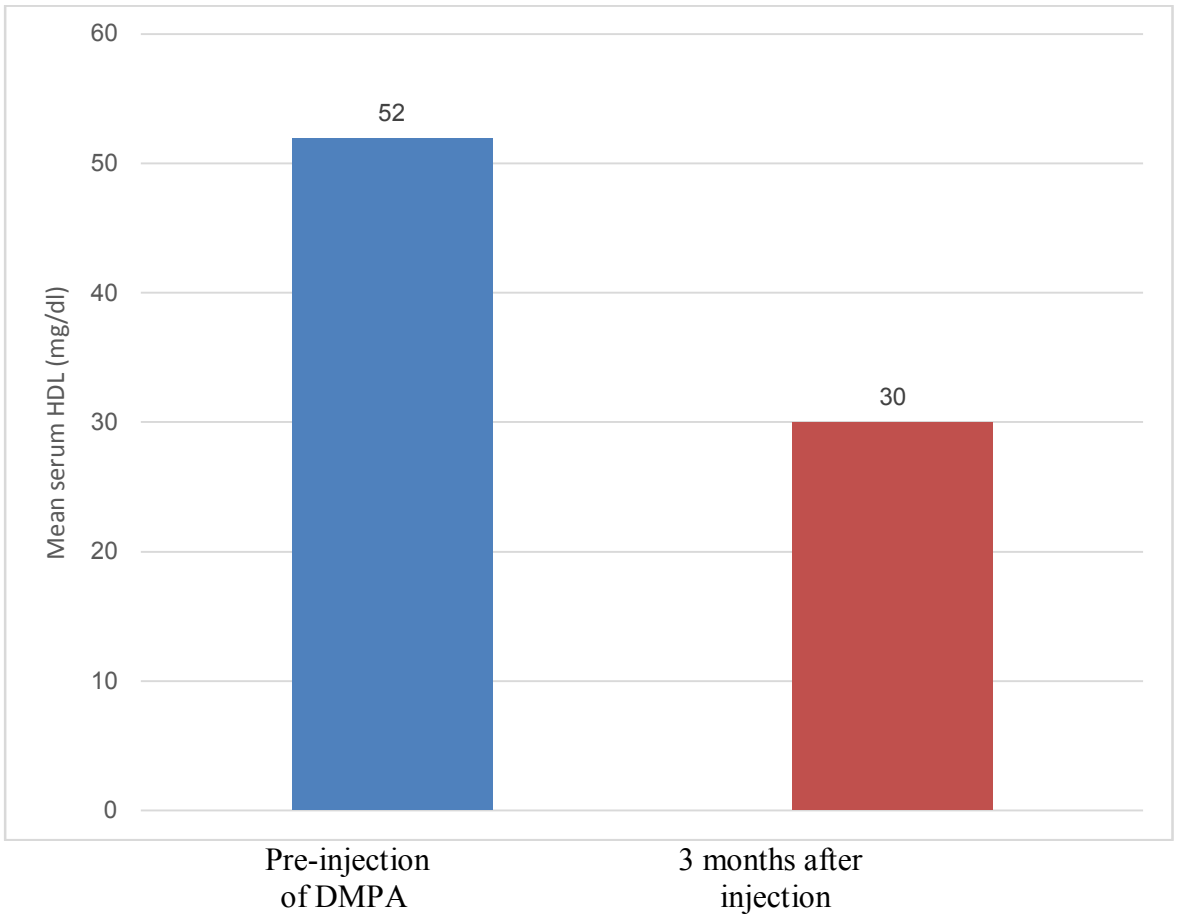

Figure 3: Mean serum HDL (mg/dl) in pre-injection of DMPA and three months after injection .

There was significant decrease in serum HDL three months after DMPA injection as compared with pre-injection of DMPA p value< 0.001 which is statistically significant.

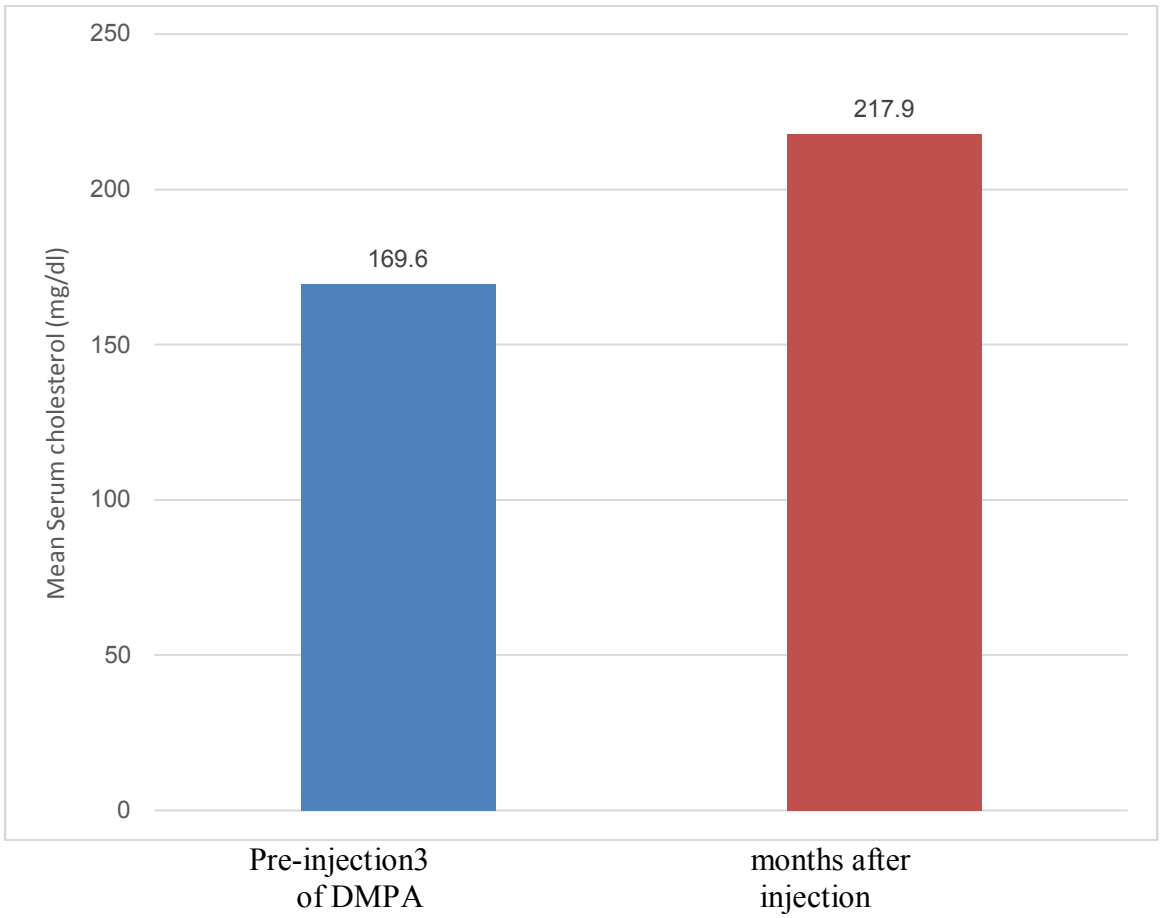

Figure 4: Mean serum cholesterol (mg/dl) in pre-injection of DMPA and three months after injection.

There was insignificant increase in serum cholesterol three months after DMPA injection as compared with pre-injection of DMPA p value> 0.05 which is statistically not significant.

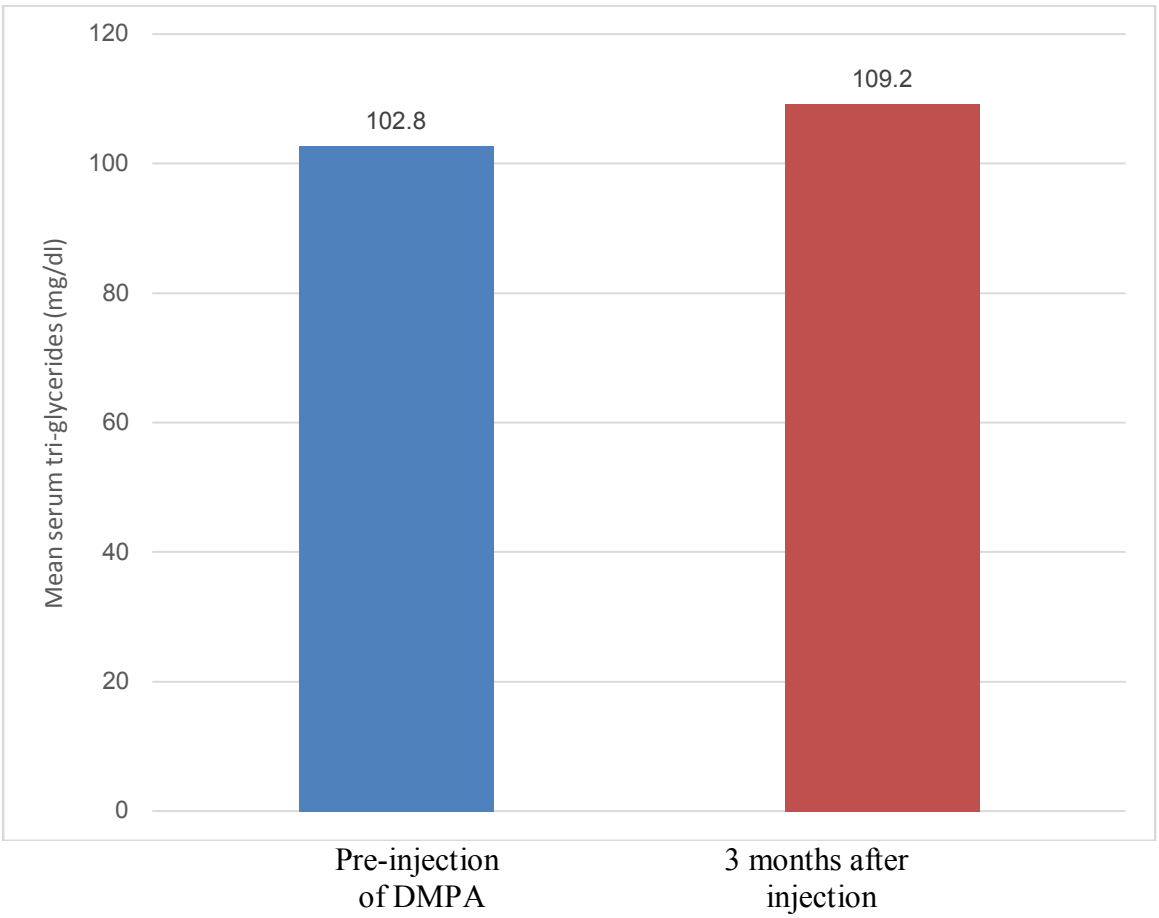

Figure5 : Mean serum triglycerides (mg/dl) in pre-injection of DMPA and three months after injection.

There was no changes in serum triglyceride three months after DMPA injection as compared with pre-injection of DMPA p value>0.05 which is statistically not significant.

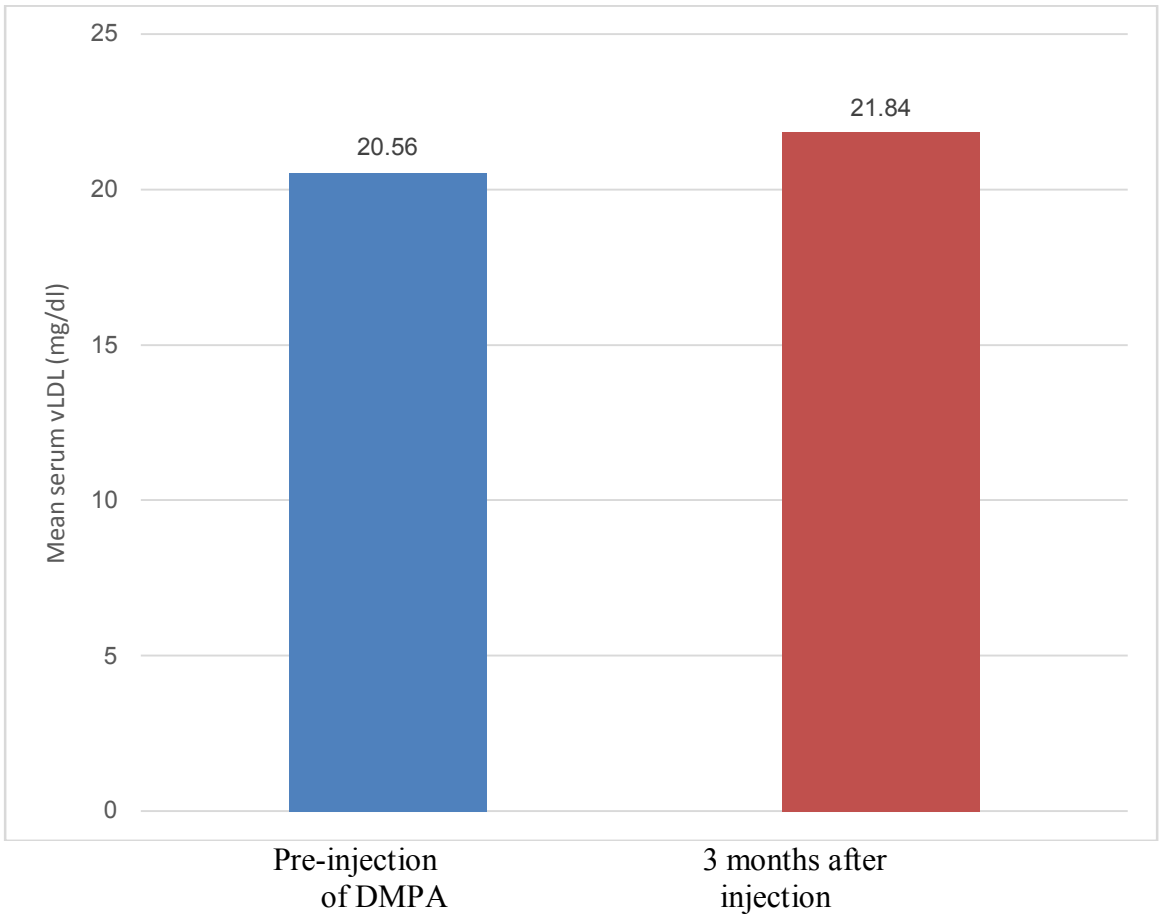

Figure 6: Mean serum VLDL (mg/dl) in pre-injection of DMPA and three months after injection.

There was no changes in serum VLDL three months after DMPA injection as compared with pre-injection of DMPA p value>0.05which is statistically not significant.

Discussion

In this study Depot-medroxyprogesterone acetate used which is highly effective contraceptive with a very low failure rate.There has been considerable debate about the effect of DMPA on lipid metabolism .[26]The level of s.HDL is inversely related to the incidence of cardiovascular diseases.Dyslipidemia is an important co-morbidity of obesity associated with a very high incidence of coronary and vascular events.[27]

Studies on lipid profile changes in DMPAusers were conducted in Arab countries as well as Muslim countries . One of those studies was performed in Eygpt , by Kamal Fahmy et al. in 1991.[28] He found that three months after injection of depot medroxyprogesterone acetate, there was a significant increase in serum LDL, a significant decrease in serum HDL but no changes in serum cholesterol or serum triglycerides. These findings were similar to the results obtained in current studied group, where a significant increase in serum LDL, a significant decrease in serum HDL. On the other hand; the current study revealed an insignificant increase in serum cholesterol with no changes in serum triglycerides.

Another study conducted in Pakistan, by UzmaFaryal et al. in 2013 [29-30].They found six months after injection of depot medroxyprogesterone acetate

there was a significant increase in serum LDL and serum triglycerides, significant decrease in serum HDL and no change in serum cholesterol.

Another study was conducted in Texas,USA; by Berenson et al. (2009)[27],who found that serum lipids measured every six month thereafter for three years in DMPA users, the serum LDL levels were significantly increased whereas the serum HDL was significantly decreased. The serum LDL to serum HDL ratio was raised during the first 6 months of DMPA use, but dropped back to baseline over the next 24 months, even if DMPA was continued.

He found that changes in appetite, total caloric intake and amount of protein, fat, and carbohydrate consumed per day did not predict any changes in serum lipids level or serum LDL to serum HDL ratio. On the other hand, he found that ; body fat and race both affect the lipid profile and a beneficial effect on serum TC and serum LDL with increased parity .

Another study in Sweden, by Enk L et al (1992)[30]. He found an increase in serum LDL and decrease in serum HDL in DMPA users which were considered as a risk factor for atherosclerosis and cardiovascular disease.

Yaday BK et al. (2011)[27] in Nepal showed no difference in age and weight between control group and DMPA users, with a significant increase in serum LDL and serum TG in DMPA users two years after injection compared to those of the control group, with no changes in other serum lipids.

Okeke et al(2011)[30] in Nigeria,showed a significant reduction in serum LDL ($p<0.05$), a significant elevation in serum HDL ($p<0.05$) which was reverse to the current study.No changes in serum TG. were detected .

Faddah LM et al(2005)[22] in Egypt demonstrated only the serum LDL/serum HDL ratio which was non-significantly increased in comparison to the control group. However; neither total cholesterol nor triglycerides (TG) were affected by the DMPA as serum lipids measured after one, two, three and four years of injection.

Mostafavi H. et al. (1999)[30] in Iran, showed that the LDL level were increased, while HDL level were decreased.Total cholesterol and TG were increased, with a significantlyincreased LDL/HDL ratio.

Mia (2005)[29] ,who conducted a study on clients using DMPA for 3-5 years uninterruptedly. The mean serum LDL level of DMPA users was significantly ($P<0.05$) elevated in comparison to that of the control groups.The mean serum HDL was decreased in DMPA users in comparison to that of the control group. The decrease was not significant ($P>0.05$).The mean serum total cholesterol and mean serum triglyceride levels of the DMPA users were significantly elevated in comparison to that of the non-users($P<O.05$ and $P<0.01$ respectively).

Garza-Flores J [29] in Mexico, were blood samples taken on the day of injection and 15, 29, 57 and 92 days after the i.m. administration of 150 mg of DMPA, the results demonstrated that the serum LDL remained unchanged, while there was a decreased in serum HDL and serum cholesterol. A moderate increase in the serum total TG concentrations on the expense of the VLDL fraction in the group of DMPA users, indicate that acute and/or chronic DMPA administration at the dose currently employed for contraception does not induce major abnormalities in lipoproteins in serum. In regards to the current studied group; the serum LDL levels were significantly increased after three months of DMPA injection as compared to that in pre-injection of DMPA ($p<0.001$). On the other hand ; serum HDL levels three months after DMPA injection were significantly decreased as compared to that in pre-injection of DMPA ($p<0.001$). Serum

cholesterol insignificantly increased three months after DMPA injection when compared to its level in pre-injection of DMPA (p value>0.05) ,while there was no change in s.TG. three months after injection. These changes in serum lipids could be contributed to differences in the duration of the studied period (short term or long term use of DMPA) or difference in the sample size.

Conclusion

Depot medroxyprogestrerone acetate used in women with reproductive age group as injectable contraception, can cause significant changes in lipid metabolism.

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