C-reactive protein and lipid profile among depot-medroxyprogesterone acetate injections users

Wahda B. Al-Youzbaki
Department of Pharmacology, College of Medicine, University of Mosul.

ABSTRACT

Objective: To study the effect of depot-medroxyprogesterone acetate (DMPA) injections on C-reactive protein (CRP) and lipid profile and to find the predictors (body weight, body mass index (BMI), blood pressure (BP) and lipid profile) that significantly predict the risk of cardiovascular disease (CVD) among DMPA injections users.

Method: A prospective cohort study was performed during the period from March 2009 to March 2010 included thirty apparently healthy married women, their age ranged between 20-35 years, who were attending Al-Batool and Al-Khansa Family Planning Centers in Mosul and started (for the first time) to use DMPA injections (150 mg medroxyprogesterone acetate), called "Depo-Provera" as contraceptive. These (DMPA users group) were compared to another 30 healthy married women who did not use any hormonal contraceptives (non users group). Both groups were followed for one year, during which blood samples were obtained from both groups, before starting to use DMPA, after 6 months and after 12 months. Sera were used for the estimation of the biochemical studied parameters using commercial kits except serum low density lipoprotein (LDL) and atherogenic index (AI) which were calculated by special equations.

Results: DMPA injections caused a non significant increase in body weight but a significant increase in BMI after 12 months. There was a significant increase in the mean diastolic blood pressure (DBP) of DMPA users according to the duration of use. The DMPA caused non significant changes in the CRP levels. There was a significant increase in serum triglycerides (TG) after 6 months of DMPA uses with respect to the duration of use. But there were non significant changes in mean serum total cholesterol (TC), high density lipoprotein (HDL), LDL and AI. Among all variables that were studied, only body weight and BMI showed a significant positive correlations with CRP. Using a stepwise multiple regression analysis, it was found that the predictors that significantly predict the risk of CVD among DMPA users were AI, DBP and TG.

Conclusion: This study found that there is a significant positive association between CRP and CVD risk factors in DMPA injections users as contraceptive. Furthermore AI, DBP and TG were found to be significant predictors for the risk of CVD among DMPA users. This study confirmed the safety of DMPA use as contraceptive medication, but that special care should be directed for patients with CVD and other patients who were more sensitive to the harmful effects of lipid in the blood.

Key words: Depot-medroxyprogesterone acetate, CRP, lipid profile.

الخلاصة

الهدف: لدراسة تأثير حقن مخزن ميدروكسي بروجيستيرون أسيتيت على البروتين التفاعلي نوع ج ودهون الدم وإيجاد المتنبآت (وزن الجسم، مؤشر كثافة الجسم، ضغط الدم ودهون الدم) التي تتنبأ معنويا بأمراض القلب الوعائية لدى مستعملات مخزن ميدروكسي بروجيستيرون أسيتيت.

الطريقة: دراسة جماعة أجريت خلال الفترة من آذار ٢٠٠٩ إلى آذار ٢٠١٠ تضمنت أخذ مجموع ٣٠ امرأة سليمة (لمجموعة مستعملات DMPA) تتراوح أعمارهن بين (٢٠ – ٣٥) سنة مراجعات لمركزي تنظيم الأسرة في مستشفى البتول والخنساء في الموصل وممن بدأن بأستعمال حقن مخزن ميدروكسي بروجيستيرون أسيتيت والتي تسمى "Depo-Provera"(بتركيز ١٥٠ ملي غرام ميدروكسي بروجيستيرون أسيتيت) كمانع حمل كل ثلاثة أشهر وقد تم مقارنتهن مع ٣٠ إمرأة سليمة أخرى (مجموعة الضبط) ممن لايستعملن موانع الحمل الهرمونية. كلتا المجموعتين تمت متابعتهن لمدة سنة واحدة وخلالها تم سحب دم من كل إمرأة من كلا المجموعتين وعلى ثلاث فترات وهي قبل البدء بالمتابعة واستعمال حقن مخزن ميدروكسي بروجيستيرون أسيتيت وبعد ٦ أشهر ثم بعد ١٢ شهرا. تم إستخدام عينات مصل الدم المأخوذة من نماذج الدم لقياس الفحوصات الكيمياوية المدروسة باستعمال العدد اليدوية التجارية ماعدا مؤشر كثافة الجسم، كوليسترول الدهن واطئ الكثافة في مصل الدم ومؤشر التصلب العصيدي باستعمال معادلات خاصة.

النتائج: حقن مخزن ميدروكسي بروجيستيرون أسيتيت سببت زيادة غير معنوية بوزن الجسم ولكن زيادة معنوية بمؤشر كثافة الجسم بعد ١٢ شهر. كان هناك زيادة معنوية في ضغط الدم الواطئ لدى مجموعة مستعملات DMPA بالنسبة لمدة الأستعمال. إن حقن مخزن ميدروكسي بروجيستيرون أسيتيت سببت تغيرات غير معنوية في البروتين التفاعلي نوع ج في مصل الدم. كان هناك زيادة معنوية في مستوى ثلاثي الكليسيرايد في مصل الدم بعد ٦ أشهر من استعمال حقن مخزن ميدروكسي بروجيستيرون أسيتيت وبالنسبة لمدة الإستعمال. بينما كان هناك تغيرات غير معنوية في معدل مستوى الكولسترول الكلي، كولسترول الدهن عالي الكثافة، كولسترول الدهن واطئ الكثافة ومؤشر التصلب العصيدي. بين كل المتغيرات المدروسة، فقط وزن الجسم ومؤشر كثافة الجسم أظهرا علاقة ايجابية معنوية مع البروتين التفاعلي نوع ج. بإستعمال التحليل التدريجي المتعدد الترددي وجد أن المتنبأت ذات الدلالة والتي تتنبأ بخطورة حدوث أمراض القلب الوعائية لدى مستعملات حقن مخزن ميدروكسي بروجيستيرون كانت: مؤشر التصلب العصيدي، ضغط الدم الواطئ، ثلاثي الكليسيرايد.

الاستنتاج: هذه الدراسة وجدت أن هناك مرافقة إيجابية ومعنوية بين البروتين التفاعلي نوع ج وعوامل الخطورة لأمراض القلب الوعائية بين مجموعة مستعملات DMPA كمانع للحمل. بالإضافة الى أن مؤشر التصلب العصيدي، ضغط الدم الواطئ وثلاثي الكليسيرايد قد وجدوا بأنهم من المتنبأت المعنوية بخطورة أمراض القلب الوعائية لدى مستعملات DMPA. هذه الدراسة أكدت أمانة استخدام حقن مخزن ميدروكسي بروجيستيرون أسيتيت كموانع للحمل ولكن عناية خاصة يجب أن توجه لمرضى القلب الوعائية وغيرهم من المرضى الذين يكونون أكثر حساسية لتأثير أضرار الدهون في الدم.

مفتاح الكلمات: مخزن ميدروكسي بروجيستيرون أسيتيت، البروتين التفاعلي نوع ج ودهون الدم.

D epot-medroxyprogesterone acetate (DMPA) is a highly effective, convenient non-daily hormonal contraceptive option that has been available worldwide for many years. It is approved by the US Food and Drug Administration (FDA) since 1992 and used worldwide by more than 90 million women[1]. Long term use of DMPA injections may cause a reduction of menstrual blood loss, decreasing the risk of endometrial cancer and suppression of endogenous estrogen secretion which leads to reversible reduction in bone density and changes in plasma lipids associated with increased risk of atherosclerosis[2].

Since atherosclerosis may in part, be an inflammatory disease[3], circulating factors related to inflammation may be predictors of CVD in general population[4]. CRP, a marker of low grade chronic inflammation, has been identified for both men and women as an independent predictor for CVD[5,6] and has recently been shown to provide additional prognostic information to LDL[7], TC and HDL in women[8]. Recent data also indicate that level of CRP adds to the predictive value of lipid parameters in determining risk of a first myocardial infarction[8] and screening based on lipid levels may provide an improved method of identifying women at risk of CVD[9].

C-reactive protein is not simply a short term marker for risk, as has previously been demonstrated in patients with unstable angina[10], but a long term marker for risk, even

for events occurring six or more years later[5]. The relationship between inflammatory factors and coronary heart disease (CHD) suggests that subclinical chronic inflammation may have a major role in the development of atherosclerosis[11]. It is now well established that atherosclerosis originates in early life, and that its risk factors track to adulthood[4].

The relative CVD risk associated with elevated TG levels is greater in women than in men[12] and the threshold for increased risk from low HDL is higher[13]. HDL is atheroprotective as evidenced by a strong inverse association between HDL levels and coronary heart disease (CHD) risk[12]. Beside that, HDL levels greater than 60 mg/dl (1.55 mmol/l) which are more commonly found in women than in men, are so protective as to essentially negate the effect of one of other CHD risk factors[14].

Inflammatory processes, along with plasma lipids and lifestyle behaviors, play a pivotal role in the pathogenesis of cardiovascular diseases[7,15]. In both men and women, several epidemiological studies now indicate that the relationship between the inflammatory biomarker of high-sensitivity C-reactive protein (hsCRP) and future vascular events is strongly independent of other risk factors and the association of hsCRP with vascular events provided a strong argument for screening in the primary prevention population[7].

The relationship between CRP and the risk of CHD has been shown in adults[4]. Despite its widespread use, the cardiovascular effects of DMPA in young women are unclear, so the current study was conducted to investigate the association of serum CRP with body weight, BMI, BP and lipid profile among young DMPA injections users as contraceptives and to find the significant predictors of the risk of CVD among these users.

Subjects and methods

The approval of the study protocol by an ethical committee was obtained from local health committee of Ministry of Health, and College of Medicine, University of Mosul. This study included 30 apparently healthy married, not pregnant, not lactating women, were fertile at the time of study, having regular menstrual cycle, who were attending Al-Batool and Al-Khansa Family Planning Centers in Mosul. A written consents were taken from the women after explanation.

The following inclusion criteria were put: age 20-35 year, BMI < 25, hemoglobin not less than 10.5 g/dl, and no hormonal contraceptives before, or any medications during the period of the study. No history of allergy or any disease that interferes with the immune system, non smokers, and not alcoholics. They were just started to receive (for the first time) 150 mg DMPA injection (called "Depo-Provera" of Pharmacia NV/SA Puurs-Belgium) every 3 months. These women were called DMPA users group. The non users group included another 30 apparently healthy volunteer women who have the same inclusion criteria as the DMPA users group except that they were not using any hormonal contraceptives, instead, they used either a barrier method or mechanical methods. Anthropometric measures (blood pressure (mmHg), body weight (Kg) and height (cm)) were taken. Ten ml venous blood were withdrawn into plain tube, using a disposable syringe at about 8.30-10.00 am (after 12 hours fasting) from the DMPA injections users group at the beginning before they start taking the injection, after 6 months, then after 12 months of use, and from the non contraceptive users group using the same schedule. The blood was allowed to clot, then serum was separated by centrifugation at 3000 rpm for 10 minutes and then kept frozen at – 20°C to be analyzed:

1- Serum CRP was measured by slide agglutination using Biokit, Spain.
2- Measurement of serum TC and TG concentration was done by the enzymatic colorimetric method, using (BioMerieux kits, France) for each.
3- Serum HDL was measured by the precipitation method, using HDL Cholesterol/ Phospholipids kit (BioMerie-ux, France).
4- Serum LDL was calculated by using Friedewald equation[16]:
   LDL (mmol/l) = TC-HDL- (TG/2.19)
5- Atherogenic index (AI) was calculated by the following equation: AI = TC / HDL[17].

Standard statistical methods were used to determine the mean, standard deviation (SD) and the range. Paired t-test was used to compare the results of various biochemical parameters among the two groups. Linear regression analysis (Pearson correlation coefficient ®) was performed for finding the degree of association between different parameters. ANOVA test (analysis of variance) was used to identify the variation in the different variables in relation to the duration of DMPA users group. Duncan's test was used to identify groups responsible for statistical difference through comparison. Linear Stepwise Multiple Regression Technique was applied to detect the significant independent (predictors) variables that predict CVD risk among DMPA users. All values quoted as the mean ± SD and a P-value of ≤ 0.05 was considered to be statistically significant.

Results

The obligatory use of DMPA injections every 3 months led the users women to visit the Family Planning Center regularly and eventually every 3 months to take the injection, so all women enrolled in this study can be followed up with less possibility of loss to follow up.

There was no significant difference between mean ± SD of age of the DMPA users (28.36 ± 4.14 years) and of the non users (27.40 ± 4.71 years). There was no significant difference between mean ± SD height of the DMPA users (157.57 ± 3.33 cm.), and that of the non users (159.30 ± 3.25 cm.).

This study indicates that DMPA caused a non significant increase in body weight among DMPA users in comparison with non users after 6 and 12 months. Although DMPA use caused an increase in BMI of the DMPA users in comparison with non users after 6 and 12 months, only the increase after 12 months was significant. However ANOVA analysis of the DMPA users group revealed a non significant (F=1.67, p=0.207) increase in the mean BMI of the DMPA users in relation to the duration of usage (table 1).

Table (1): Comparison between mean BMI of DMPA users and non users.

Period of use (Months)	(Mean ± SD) BMI (kg/m^2)		P-value
	DMPA Users (n=30)	Non Users (n=30)	
0	22.186 ± 1.986 a	22.25 ± 1.94	0.946
6	23.24 ± 2.54 a	21.95 ± 2.11	0.255
12	24.36 ± 3.28 a	21.83 ± 2.33	0.042

- (a, b) different letters (vertically), means significant difference.

This study demonstrated that the use of DMPA injection causes a non significant increase in SBP and DBP among DMPA users in comparison with the non users after 6 and 12 months. ANOVA analysis among the DMPA users group indicated a non significant increase in the mean SBP of the DMPA users from non users, but a significant (F=3.41, p=0.048) increase in the mean DBP of DMPA users according to the duration of DMPA injections use.

There were no significant changes in the mean serum CRP among DMPA users in comparison to the non users after 6 and 12 months. ANOVA analysis of the DMPA users indicated that there were non significant changes in serum CRP among DMPA users in relation to the duration of DMPA injections usage.

Table (2) demonstrates that there was a significant increase in serum TG after 6 months in the DMPA users in comparison with the non users. There was no significant difference in the mean serum TG of the DMPA users and non users at the baseline time (0 month). ANOVA analysis among the DMPA users group indicated a significant (F=5.27, p=0.012) increase in the mean serum TG according to the duration of DMPA injections use.

Table (2): Comparison between mean serum TG of DMPA users and non users after 6 & 12 months.

| Period of use (Months) | (Mean ± SD) Serum TG (mmol/l) | | P-value |
	DMPA Users (n=30)	Non Users (n=30)	
0	0.97 ± 0.402 a	1.324 ± 0.732	0.430
6	1.82 ± 0.79 a	1.025 ± 0.57	0.017
12	1.913 ± 0.66 b	1.66 ± 0.84	0.226

- (a, b) different letters (vertically), means significant difference.

There were non significant changes in the mean serum TC, HDL, LDL, and AI among DMPA users in comparison to the non users after 6 and 12 months. ANOVA analysis of the DMPA users group indicated that there were non significant changes in serum TC, HDL, LDL and AI among DMPA users in relation to the duration of DMPA injections usage.

This study demonstrated that among all variables that were studied, only body weight and BMI showed a significant positive correlations with CRP (r=0.733, P=0.016 ; r= 0.612, P=0.057 respectively). By using linear stepwise multiple regression to account for any co depended effects of different biochemical parameters (using CRP) and other biochemical parameters (variables), the predictors that increase the risk of CVD significantly among DMPA users are AI, DBP and TG serum levels. (table 3).

Table (3): Linear multiple stepwise regression model for predictor of CVD in the DMPA users after 12 months.

Variable Xi (Predictors)	Regression Coefficient	Standard Error (SE)	P-value
AI	-2.700	0.394	0.021
DBP	-0.312	0.053	0.028
TG	-2.000	0.677	0.038

Discussion

This study found that there is a significant positive association between CRP and CVD risk markers in DMPA injections users as contraceptive, also CRP can be used as independent risk factor to predict other risk factors by using linear stepwise multiple regression to account for any co depended effects of different biochemical parameters (variables). It is found that the predictors that increase significantly the risk of CVD among DMPA users are AI, DBP and TG serum levels. To the best of our knowledge no previous study done to investigate such theory in DMPA injections users as contraceptive.

This study found that DMPA caused a non significant increase in body weight among the DMPA users in comparison with the non users after 6 and 12 months but caused a significant increase in BMI after 12 months in comparison to non users. This is not of clinical importance since comparison of changes with their respective pretreatment values were not statistically significant. This is in agreement with some studies[15,18], while other studies found that prolonged use of DMPA for 1-2 years in Navajo women[19] and for 3-5 years[20] caused a significant increase in body weight.

This study demonstrated that among all variables that were studied, only body weight and BMI showed significant positive correlations with CRP, but neither body weight nor BMI were significant predictor for the risk of CVD among DMPA users. Studies performed among different ethnic groups showed diverse results, but all these studies confirmed a relationship between serum CRP and both generalized and abdominal obesity[21].

Among men and women with CHD, CRP was correlated with traditional risk factors and to a lesser degree to manifestation of CHD and BMI is the main contributor to CRP variability, explained by these factors among women[22]. Another study found a significant positive association between CRP and atherosclerotic risk factors in healthy young people, as well as an increase in these markers in the upper quartiles of waist circumference, but not BMI [23].

In this study there was a non significant increase in SBP and DBP among DMPA users in comparison with the non users after 6 and 12 months. Non significant increase in the mean (SBP) but a significant increase in the mean (DBP) of DMPA users in comparison of changes with their respective pretreatment values was found. The study of Mia et al., [20] found that long term use of DMPA caused insignificant increase in SBP and DBP, but a significant increase in body weight, while the study of Al-Banna[24] found that the use of hormonal contraception cause a non significant changes in body weight, SBP and DBP.

This study revealed that DBP is one of the significant predictors for the risk of CVD among DMPA users by using CRP as the co depended variable. Hashimoto et al., [25] found that in hypertensive patients being managed by drug therapy or lifestyle modification, CRP is an equivalent or superior independent predictor of the progression of carotid atherosclerosis than the pulse pressure or systolic blood pressure.

This study found that there were non significant changes in mean serum CRP level among DMPA users in comparison to the non users after 6 and 12 months and in relation to the duration of use. This is in agreement with the study of Goldstein et al., [26] who found that the CRP was not significantly altered by the use of DMPA for 12 months.

This study also revealed that the use of DMPA injections as contraceptive in young women caused a significant increase in serum TG after 6 months in the DMPA users in comparison with the non users and according to the duration of use. However there were non significant changes in mean serum TC, HDL, LDL and AI among DMPA users in comparison to the non users after 6 and 12 months nor in relation to the duration of use. This is in agreement with the study of Garza-Flores et al., [27] who found that the use of DMPA for 5 years causes a moderate increase in the serum TG, but a moderate non significant decrease in TC and HDL, with unchanged LDL. Fahmy et al., [28] found that after 3 months use of DMPA, there were no significant changes in TC and TG, while there was a significant decrease in HDL, and a significant increase in LDL. After 15 months there was a significant increase in TC and LDL and a significant decrease in HDL. The study of Faddah et al., [29] although demonstrated that neither mean serum TC nor TG were affected by DMPA use, only AI was gradually but non significantly increased in comparison to control group as in this study.

Controversial results from different studies were found of the metabolic effects of long term DMPA use. Some studies found that there are non significant changes in lipid profile parameters[29,30,31] including AI[32] after one year use of DMPA, and concluded that DMPA may be considered as a safe contraceptive medication as the overall data indicate that acute and/or chronic DMPA use at the dose currently employed for contraception does not induce major abnormalities in serum lipoproteins. While other studies found that long term use of DMPA injections as contraception causes significant increase in the mean serum TC, TG and LDL levels, but a non significant decrease in HDL in comparison to that of the control group[33]. Other studies found that DMPA use for 12 weeks[34] or for one year[35] caused significant decrease in HDL level, and suggested that DMPA should not be prescribed to women with abnormally high risk for atherosclerosis such as heavy smokers and women with adiposity and /or diabetes mellitus.

This study found that one of the predictors that significantly predicts the risk of CVD among DMPA users were AI and TG. Despite extensive research, it has not yet been determined whether TG represent an independent risk factor for CHD. The association has been obscured by imprecision in TG measurements, individual variability, and complex interactions between TG and other lipid-nonlipid parameters. Although current guidelines do not mandate screening for elevated TG levels in the general population, obtaining TG levels in those with known CHD or with other risk factors can provide valuable prognostic information and therefore be of aid

in therapeutic decisions[36]. Models incorporating both hs-CRP and lipid parameters have significantly greater ability to model using lipid alone[37].

Conclusion

In the present study, the predictors that predict significantly the risk of CVD (represented by CRP) among DMPA users were AI, DBP and TG serum levels. This means that incorporating both CRP level, lipid parameters and blood pressure have a significantly greater ability to predict CVD risk among DMPA users than model using lipid profile alone.

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