Tropical Journal of Obstetrics & Gynaecology
ISSN-Print: 0189-5117
Online: 2543-148X
Official Publication of Society of Obstetrics & Gynaecology of Nigeria

■ Original Research Article

The Effect of Depo-Medroxyprogesterone Acetate (DMPA) on Serum Proteins: Total Protein, Albumin and Globulin in Women

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Abstract:

Objectives: To determine the effect of DMPA on serum proteins: total proteins, albumin and Globulin among Nigerian women over a period of three months. **Methods:** This was a longitudinal cohort study of fifty consenting women in the reproductive age group who were undergoing administration of DMPA for contraception. Women received a recommended dose of 150mg of DMPA, given as deep intramuscular injection. Blood samples were collected at baseline (0), 1 and 3 months after injection. Information on the sociodemographic, obstetric, clinical characteristics and serum levels of total proteins, albumin, IgA, IgM and IgG was collected. Data was analysed using SPSS version 22. **Results:** The mean levels of IgG increased from pre-injection level of 1381.86mg% (± 92.60mg%) to 1444.00mg% (± 94.79mg%) at three months, $p< 0.05$. There was no significant change in the mean serum levels of IgA, IgM and total proteins during three months of DMPA use. There was an increase in DBP, weight and BMI. **Conclusion:** The raised mean serum levels of IgG may suggest an improved humoral immunity among women on DMPA which has potential health benefits. The increase in DBP, weight and BMI underscore the need for proper patient selection and counselling before DMPA uptake.

Key Words: Depo-medroxyprogesterone acetate, DMPA, DMPA protein metabolism, progestin protein metabolism, immunoglobulins, serum proteins
Conflict of Interest: Nil

Introduction:

Depo-medroxy-progesterone acetate (DMPA) is a highly-effective hormone-based contraceptive; it is a 19-nor progesterone derivative which is a long acting, reversible and discrete method of contraception. [1–3] DMPA is available in over eighty developed and developing countries including Nigeria, and used by over 90million women globally. [1,2,4] There is an increase in the uptake of DMPA globally and this is attributed to the ease of use, privacy, minimal side effects and non-interference with coitus. It has a low failure rate of 0.3 per 100 women in perfect users [1,2,5]; hence its high efficacy and uptake among women. In Nigeria, the contraceptive prevalence rate is 17% among currently married women aged 15-49 years. Injectable contraceptives and implants are the most commonly used modern contraceptive method[6]. This suggests that a sizeable proportion of women on contraceptives are using injectable contraceptives such as DMPA. It is also a commonly used method in the United States. [7,8]

DMPA inhibits gonadotropin-releasing hormone (GnRH) pulsatility and gonadotropin secretions with LH being more affected than FSH, prevents follicular development, and ovulation, alters the cervical mucus thickness thus blocking sperm penetration and thinning of the endometrium, hence it impairs implantation. [8] It is detected in the serum within thirty minutes after an injection of 150mg of DMPA. Serum concentration of DMPA vary between individual women but usually plateaus at about 1.0ng/ml for about three months after which there is a gradual decline.[9]

DMPA binds to the plasma proteins mainly albumin but not the sex-hormone-binding globulins. It is metabolized in the liver with an elimination half-life of about 50days [5] for both the intramuscular and subcutaneous routes of administration; it is excreted through the urine as glucuronide conjugates and minimally as sulfate. [10] DMPA has a low failure rate but may be associated with side-effects or alteration in the body metabolism. Some of the associated side effects include headaches, dizziness, weight gain, menstrual irregularity – amenorrhea or abnormal bleeding, delayed return of fertility, bone demineralization and tendency to fracture. [5]

There are few studies on the effect of DMPA on protein metabolism and the findings from previous studies on the effect of DMPA on protein metabolism have been conflicting. A study by Lali et al found no change in the levels of total proteins and albumin over a period of three months following administration of 150mg of DMPA. IgA and IgM remained unchanged while IgG levels increased. [11] In another study, there was an increase in the serum levels of albumin, alpha 1 acid glycoprotein, alpha-2 macroglobulin, haptoglobin IgG; with a reduction in the levels of alpha-1 antitrypsin, transferrin, C3c, and C4. However, there was no change in serum IgA, IgM, C-reactive protein and ceruloplasmin. [12]

Due to the increase in DMPA uptake globally among women, there is a need to update the current knowledge of its effects on protein metabolism. Furthermore, there is paucity of literature on the effect of DMPA on serum proteins among Nigerian women. This study aims to assess the effect of DMPA on total protein, albumin and globulin among women receiving DMPA at the family planning clinic of Adeoyo Maternity Teaching Hospital, Ibadan.

Materials and Methods:

Study Design:
This study was a prospective longitudinal cohort study conducted in the family planning clinic of Adeoyo Maternity Teaching Hospital, Ibadan, Oyo state, South-west Nigeria. The study site is in Ibadan North Local Government Area and serves as the referral centre for the Primary health centres and private health facilities in the environment.

Fifty healthy consenting females in the reproductive age group (15-49 years) who opted for DMPA as a contraceptive choice and have not been on any hormonal contraceptive were selected and enrolled into study. Non-consenting women, clients with metabolic disorders and chronic medical diseases were excluded from the study. The sample size was estimated using the formula ($N= 2 (u+v)^2 a^2/d^2$) based on double means.[13] Therefore, assuming a statistical power of 90%, serum protein level of 60mg % and an attrition rate of 10%; a minimum sample size of 36 patients was calculated. A total of 50 women were enrolled into the study.

Blood samples were taken between 8.30am and 10.00 a.m. by venipuncture of the antecubital vein, at recruitment (baseline (0), one (1) and three (3) months after DMPA injection respectively.

Samples were collected into non-heparinized bottles; thereafter allowed for clot formation and clot retraction. These were spun at 3000 rpm for five minutes, then stored at -20^{0}C and analyzed after the third month.

Total serum protein level was estimated using the standard Buiret method [14]; while the serum albumin level was measured by the Bromocresol green method.[14] Serum immunoglobulins were analysed using the turbidimetric method by the clinical chemistry analyzer HA-1900 manufactured by Hawskey. [14] Data was entered, and statistical analysis was done using the IBM SPSS Statistics version 22. Univariate analysis was done using frequencies and means. Analysis of normal variance test (ANOVA) was done to compare means and a post hoc analysis was done using Bonferonni T-test. The level of significance was set at 0.05.

Ethical approval was obtained from the Oyo State Research Ethical Review Committee Ministry of Health, Secretariat, Ibadan.

Results:

A total of fifty patients were recruited for the study. Five patients were lost to follow up and thus excluded from the analysis. A total of 45(90%) participants completed the study. Table 1- shows the Demographic distribution of the participants. The median age of the participants was 32.0 years (range 25-42). Majority of the participants were Muslims (57.8%) and mostly traders (53.3%). More than half had no formal or primary school education. Participants with 3- 4 parous experience were the ones with the highest number.

Table 2 shows changes in Weight, Basal Metabolic Index (BMI), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). There were minimal but significant changes in the weight between one and three months, (P=0.001); p value at 1 month was not significant. (P=0.27). The mean BMI ranged between 23.33Kg/m^2 pre-injection, 24.43Kg/m^2 at one-and 23.85Kg/m^2 at three-months post-injection respectively. These changes were significant at the third month post-injection (F=22.72, P<0.001). The mean SBP ranged between 113.36 to 121.56 mmHg. At one month, this change was not significant p=0.71 but became significant at three months (F=4.13, p=0.04). The DBP ranged between 72.62 and 77.02mmHg. The change in DBP at the first month post injection was not significant, (p=0.41) but was significant at three months (F=14.65, p<0.05).

Table 1: Demographic distribution of Participants

Variables	**Frequency (%) (n=45)**
Religion	
Islam	26 (57.8)
Christianity	19 (42.2)
Occupation	
Trading	24 (53.3)
Artisan	8 (17.8)
Teaching	7 (15.6)
Housewife	6 (13.3)
Parity	
1-2	7 (15.6)
3-4	31(68.9)
5-6	7 (15.6)
Educational level	
None/Primary	25(55.6)
Secondary	16 (35.6)
Tertiary	4(8.9)
Tribe	

Yoruba	34 (75.6)
Igbo	6 (13.3)
Hausa	5 (11.1)

In table 3, changes in the Protein levels at baseline, one and three months is shown. The mean levels of the Total Proteins, Albumin and the Globulins over the 3 months period are shown. The total proteins show a minimal increase in the mean values which was not statistically significant. The pre-injection level was 6.94±0.26g/dl; 7.12±0.25g/l, at one month and 7.02±0.26g/dl, at three months respectively, (F = 250.53; P>0.05). There was a slight but insignificant increase in the mean values of Albumin; pre-injection 3.80 (±0.19) to 3.87 (±0.18g/dl) in the first month, to 3.97 (±0.54g/dl) in the third month, (F=4.19, p>0.05). However, the levels of IgG increased from pre-injection levels in the first- and third-month post-injection. When compared to the pre-injection level 1381.86 (± 92.60mg %); there was a significant increase in the mean values of IgG at one month 1494.71(±84.53 mg%), (p<0.001) and three months 1444.00 (±94.79mg %), (F=268.59, p<0.001). The mean values of IgA and IgM were both slightly reduced during the period of study.

Table 2: Changes in Blood Pressure, Weight, and Body Mass Index

Variables	**Month 0 (Mean +SD)**	**Month 1 (Mean +SD)**	**Month 3 (Mean +SD)**	**F-test (p value)**
Systolic BP (mmHg)	116.43±9.83	116.19±10.58	118.33±10.34*	4.13 (<0.05)
Diastolic BP (mmHg)	72.62±7.01	73.33±5.70	77.02+6.90*	14.65 (<0.05)
Weight (Kg)	56.33±7.67	56.57±7.96	57.57±7.64*	22.45 (<0.05)
BMI (Kg/m^2)	23.33±2.58	23.43±2.71	23.85±2.58*	22.72 (<0.05)

*P< 0.05 at three months post injection

Table 3: Changes in the Mean Levels of Total Proteins, Albumin and Globulin

Variables	**Month 0**	**Month 1**	**Month 3**	**F-test (p value)**
Total Protein (g/dl)	6.94 ± 0.26	7.12 ± 0.25	7.02 ± 0.26	250.53 (p>0.05)
Albumin (g/dl)	3.80 ± 0.19	3.87 ± 0.54	3.97 ±0.26	4.19 (p>0.05)
IgG (mg %)	1381.86 ± 92.62	1494.71 ± 84.53	1444.00 ± 94.79	268.59(p<0.001)
IgA (mg %)	150.29 ± 16.42	146.82 ±16.44	144.20 ±15.84	65.35(p<0.05)
IgM (mg %)	1467.16 ±106.59	1459.34 ± 106.52	1454.29 ± 107.41	76.21(p<0.05)

Posthoc test: Bonferonic T test: P<0.05.

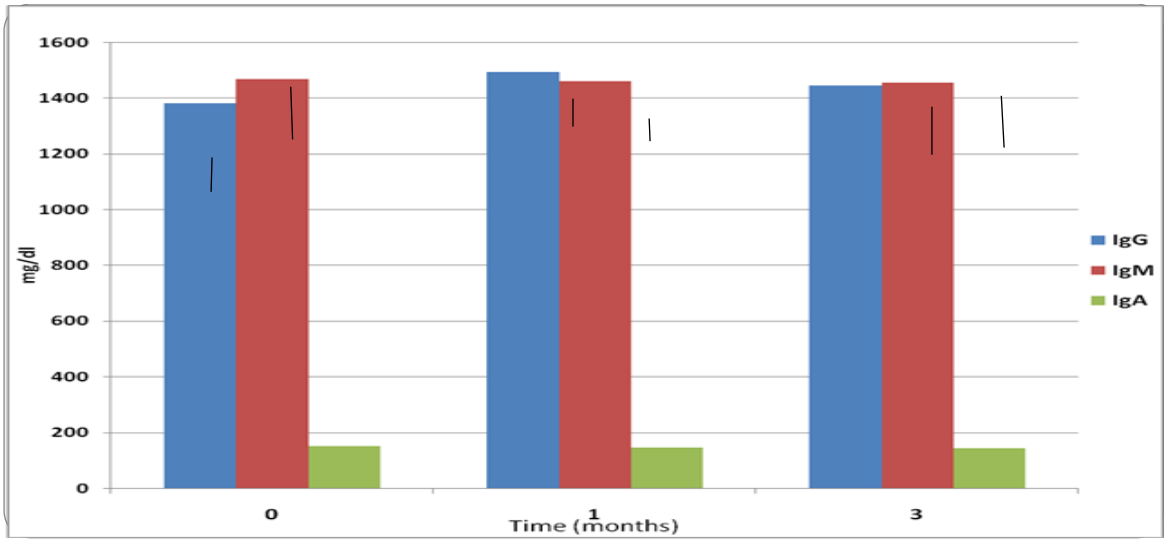

Figure 1: Pattern of immunoglobulin levels over 3 months of DMPA injection.

These reductions were significant at both one month and three months. IgA level pre-injection was 150.29 (±16.42 mg%), at 1month post-injection was 146.8 (±16.44mg%) ($p<0.05$) while 3 months post-injection was 144.20 (±15.84mg%), ($F=65.35$, $p<0.05$). IgM level pre-injection was 1467.16 (±106.59mg %), 1-month post-injection was 1459.34 (±106.52 mg%), ($p<0.05$) and 3-months post-injection was 1454.29 (±107.41mg%), ($F=76.21$, $p<0.05$).

Discussion:

The study evaluated the influence of DMPA on Total proteins, Albumin and Globulin on women in Adeoyo Maternity Teaching Hospital The participants in this study were a homogenous group of women in terms of socio-demographic characteristics. The study revealed a significant increase in immunoglobulin G level; but a significant decrease in immunoglobulin A and M, Total protein and Albumin were however not significantly changed.

There was a slight increase in the mean levels of serum total proteins and Albumin over three months of use which was found not to be statistically significant. This is in concordance with earlier studies done by Lali et al [11], Otolorin et al [15] and Adekunle et al [16]. Obisesan et al, however found a significant increase in total proteins, globulin but a non-significant difference in albumin in women on combined oral contraceptives. [17] There was a significant increase in the mean level of IgG at the first and third month which is in concordance with previous studies. [11,15,16] An in vivo study in humans also demonstrated the immune enhancing effect of steroid hormone and demonstrated steroids as having immuno-stimulatory factors. [18] Another study also found that low doses of MPA did not increase immunoglobulin secreting cells but it enhances the capacity of individual cells to produce specific immunoglobulins including IgG. [19] This possibility of improved humoral immunity in the recipient of DMPA as seen in this study which is in tandem with previous studies is an added advantage that can accrue to patient especially the immunocompromised ones. Other immunoglobulins IgA, IgM were both observed to have a decrease in mean values which had a statistical significance after three months of use.

An increase in mean body weight as well as mean BMI from the pre –injection level to the first and third month respectively was found in this study. This result is in keeping with the finding of Lopez et al in a systematic reviews which found an average weight gain of less than 2kg in the first year of DMPA use.[20] It was concluded that DMPA users do not all follow the same pattern of weight gain; about twenty five percent will gain weight excessively but certainly not all users. [21] The parity of the DMPA users have also been seen to be a risk factor for weight gain. [22] A positive association between number of children and obesity has been established in a

previous study [1], women with more than one parous experience tend to have weight gain with DMPA use. Sixty nine percent of the participants in this study were multiparous women and this could contribute to the significant weight gain observed. Another study found that the weight gain was time dependent, also an increase in protein intake can protect against gains in weight and body fat among women who choose DMPA [23]. In another study by Mia et Al on 200 women, the study shows a significant weight increase in DPMA users after three years compared to the controls. [24] DMPA also has glucocorticoid like activity which can enhance fluid retention in users [25], however weight gain in DMPA users have been attributed more to fat deposition rather than fluid accumulation. The amount and pattern of weight change is not well defined. Proper client selection is key. Dietary advice and modification will be given to selected clients.

There was also a significant increase in the mean value of the systolic and diastolic blood pressure in this study at three months of use. This difference calls for concern but may be due to a shorter duration of this study and the blood pressure changes may be time dependent. This means that the significant increase observed after three months use of DMPA in this study is likely to be temporary and reversible if study is conducted for a longer period.

In conclusion, this study shows that DMPA has no effect on the Total serum proteins and Albumin but has effect on the immunoglobulins. These changes have been shown to have beneficial

humoral effects on the users. All these can be used in better counseling as well as recruiting eligible clients after taking an informed consent. Thus, increasing the patronage of DMPA with all the added advantages of being long acting, reversible, discrete use, less frequent hospital visits as well as low failure rate.

The limitation of this study is the short duration. A longer duration for up to a year might have shown a different pattern. The study requires more time to allow one to study a pattern in the changes in the body protein levels both on short- and long-term basis. Participants dietary pattern were not modified as the variations in dietary habits could influence the weight gain and cholesterol contents, Participants

were not advised to abstain from herbs that could contain phytoestrogens and other hormones. It is recommended that a community-based study may be conducted to give a better information on the picture compared to this facility-based study. A larger sample size with the study done over a longer period will also be beneficial. There should also be a control for seasonal changes, baseline bodyweight and dietary intake.

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