



Pharmacodynamics of Depot-Medroxyprogesterone Acetate Side Effects and Complications Associated with Body Mass Index in Users of the Network of Healyh Establishments in Southern Morocco

Aslaou Fatima¹, Halima Ibrahimi², Chbabe milouda³, Barkat Amina¹

¹Research Team on Health and Nutrition of Mother and Child, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco.

²Higher Institutes for Nursing and Health Technology, and Higher Institutes of Nursing and Health Technology Professions, Ministry of health and social protection, Rabat, Morocco

³Higher Institute of Health Sciences, Hassan 1st Settat University, Morocco.

Abstract

Correctly practiced, the use of injectable hormonal contraceptive is one of the most effective popular methods as it contains progesterone and provides protection for a period of twelve weeks, suppressing ovulation. According to the latest WHO estimates, only 64% of women aged 15-49 who are married or in a consensual union are using any form of contraception. Designed for the treatment of endometriosis, precocious puberty and premature delivery, medroxyprogesterone acetate has been adopted as a long-term contraceptive drug. In Morocco, the recruitment rate of women of reproductive age reached 18.41 in 2021, with the Dakhla-Oued-eddhab region having the highest prevalence with a rate of 18.2. This is a cohort observational analytical study, conducted among 306 women, one of whom is obese and the other with normal bmi. Local ethics committees approved the investigation. The association between exposure to depot-medroxyprogesterone acetate in two cohorts, one with $bmi < 30$ and the other with $bmi > 30$, was analyzed by SPSS (version 23) for the different side effects and complications and by Epi-info for the epidemiological analysis. In terms of results, they show that the side effects related to dmpa exposure according to age, varies significantly ($p < 0.001$) between the age group under 24 years. In addition, dmpa users with $bmi > 30$ have a risk of weight gain 1.52 times that of dmpa users with $bmi < 30$. For complications, the incidence of ovarian cancer in obese women is higher than in women with $bmi < 30$, RR: 0.63 (0.7, 0.89), but dmpa use in obese women plays a protective role RR: 1.03 (0.7, 0.85).

Keywords: Women of reproductive age, obesity, side effect, complication, depot-medroxyprogesterone acetate

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1. Introduction

By its nature, pharmacodynamics is concerned with the mechanisms of action as well as the study of the physiological responses of all types of drugs. In fact, to protect themselves against unwanted pregnancies, women resort to short, medium and long term contraceptive methods depending on their needs, circumstances and medical indications. Hormonal contraception by injection of medroxyprogesterone acetate, whose prolonged protection (12 weeks) provides an effective means of fertility regulation, has become more popular as an important method of family planning [1]. There are several inherent advantages to the injectable: minor intestinal disturbances, no inhibition of lactation, few complications or effects due to estrogen. In addition, the inherent advantages of DMPA use in terms of

efficacy, which have been emphasized over the last few decades, are equal to or greater than that of oral contraception. The first systemic contraceptives developed in the mid 50's of the 20th century, were short-term progestin administered orally. The first systemic contraceptives developed in the mid-50s of the 20th century, were short-lasting progestins administered orally [2]. The first systemic contraceptives developed in the mid-50s of the 20th century, were short-lasting progestins administered orally [3].

In 1960, the United States administration approved it for use because of its safety, without much evidence on its effectiveness. Recall that medroxyprogesterone acetate was developed by the Upjohn Company in a clinical trial setting, for first time as a treatment for endometriosis. In June 1979, the WHO re-approved its safety after a series of studies during

a decade of toxicology evaluation on monkeys. In 1960, the United States administration approved it for use because of its safety, without much evidence on its effectiveness. Recall that medroxyprogesterone acetate was developed by the Upjohn Company in a clinical trial setting, for the first time as a treatment for endometriosis. In June 1979, the WHO re-approved its safety after a series of studies during a decade of toxicology evaluation on monkeys [4]. Note that as of 2018, both DMPA-IM and DMPA-SC are on the WHO Essential Medicines List. A list of medicines that address major health care needs of population and are selected based on their relevance to public health, availability of evidence to support their efficacy and safety, and their comparative cost-effectiveness [5]. Given their duration of effectiveness, their discreet nature and absence of an examination required at beginning of technique, injectable contraceptives preferred by some women and offer a number of advantages.

1.1. Structure and use

It is an acetate ester resulting from the formal condensation of the 17 α -hydroxy group of medroxyprogesterone with the carboxy group of acetic acid. A progestin widely used in menopausal hormone therapy and progestin-based contraceptives. It is a steroid ester, acetate ester, 20-oxo steroid, 3-oxo-Delta [6] steroid and a corticosteroid. It is derived from a medroxyprogesterone Depot medroxyprogesterone acetate is the most widely used injectable contraceptive (DMPA), with a perfect use failure rate of 0.2% over one year and a use failure rate normal 6%. US Food and Drug Administration (FDA US). First authorized DMPA in 1992 in the chemical form (C₂₄H₃₄O₄) of 150 mg for intramuscular administration (DMPA-IM). In 2004, a substitute subcutaneous formulation of 104 mg (DMPA-SC) was made available (Fig. 1). Both formulations have identical efficacy and safety characteristics, with effects lasting three months (13 weeks).

1.2. Pharmacology and mode of action

First, the World Health Organization's estimated need for family planning among married women of reproductive age (15-49) has reached 1.9 billion women, of whom 842 million are using contraceptive methods and 270 million have an unmet need for contraception. Notably, the proportion of family planning need met by modern methods increased from 55% to 58% in the Africa region according to indicator 3.7.1 of Sustainable Development Goals (SDGs) [7]. It should be noted that medroxyprogesterone acetate is prepared as a microcrystalline suspension for intramuscular injection in depot form, which produces a very prolonged release into the bloodstream. In addition, the Australian Committee for the Evaluation of Medicinal Products has indicated DMPA for indication, malignant neoplasia and precocious puberty; it is also prescribed in the management of Turner syndrome. In Morocco, family planning program was first launched in 1966. The PNPf has evolved over the years into a well-structured program adapted to WHO clinical guidelines. In addition, the program is called upon to meet challenge of promoting modern long-term methods, including Intrauterine Device and integrating early detection of breast and cervical cancers. The PNPf program continues to be among strategic axes at national and international level as it contributes to reduction of maternal mortality and morbidity (reduced maternal mortality by 26%) and infant mortality. Fatima et al., 2024

The MDGs have set a goal of ensuring, by 2030, universal access to sexual and reproductive health care services, including family planning, information and education, and the inclusion of reproductive health in national strategies and programs. It should be noted that medroxyprogesterone acetate prepared as a microcrystalline suspension for intramuscular injection in depot form, which produces a very prolonged release into the bloodstream.

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2. Material and Method

This is cohort study of female adopters of injectable contraceptive method with a body mass index greater than 30 using depot-medroxyprogesterone acetate and their peers adopting same method and of same age, with a BMI less than 30. From this cohort two subgroups were formed. For each adoptive DMPA having BMI > 30 kg/m², Two controls having BMI < 30 kg/m². The study involved the 306 women including 102 having BMI > 30 kg/m² and 204 women having BMI < 30 kg/m². For 4 years from March 2, 2018 to February 29, 2021, we recruited women aged 18 years or older, at any opportunity, who had an appointment at family planning service of four urban health centers of Dakhla, and who had received contraceptive counseling based on a medical consultation at maternal health service. Biomedical Research Ethics Committee of the Faculty of Medicine at the Mohamed V University and all local ethics committees approved study, which did not interfere with clinical management during consultation at family planning service. The written informed consent obtained from study participants in accordance with local requirements. The study adhered to the Declaration of Helsinki and the Good Clinical Practice Guidelines.

2.1. Data Management and Statistical Analysis

We used a centrally coordinated data management system developed combining the three software packages Epi-info, SPSS, and Jamovi. 10 associations between DMPA

exposure in two cohorts, one with $\text{bmi} < 30$ and the other with $\text{bmi} > 30$. Obesity diagnosis and side effect indices as binary outcomes were evaluated using Poisson models with a log link function and robust standard errors expressed as relative risk (RR) and 95% CI. Associations with various complications and side effects were assessed using negative binomial models with robust standard errors (expressed as incidence rate ratio and 95% CI). We set statistical significance at $P < 0.05$. Models for our primary outcomes were adjusted for month of study entry, maternal age, and maternal morbidity history (including, endocrine disorders, cardiac disorders, hypertension, and chronic respiratory diseases).

3. Results and discussion: evidence-based, and its application to the injectable contraceptive field.

The basic assumption is that the values of the independent variable, body mass index, are dispersed according to the normal distribution. The results of the K-S test prove that the first hypothesis is satisfactory as long as the K-S Z value is not significant at the $p < 0.05$ (0.072) threshold. The results confirm this in agreement with the skewness (Skewness = -0.037) and flattening (Kurtosis = -0.362) coefficients which are between -1 and 1. Finally, the histogram below shows normality of the dependent variables.

3.1. Side effects and complications

During the period from March 2, 2018 to February 29, 2021, three hundred and six women were followed to study the association of the body mass index effect in depot-medroxyprogesterone acetate users and exposure to risk factors and complications in two cohorts with similar characteristics, one of which is obese and the other normal. The characteristics of the two cohorts are summarized in Table 2. There is no difference between the two groups in our series regarding the majority of these data. Regarding DMPA exposure by age, there was a significant difference ($p < 0.001$) between under-24 age group and the married group ($P < 0.011$). Exposure to DMPA side effects varied significantly between the three smoking groups in favor of current smokers ($p < 0.011$). Moreover, difference was significant ($p < 0.001$) b/w 3 groups according to parity, particularly in multiparous women (4-6). The existence of a history of depression among DMPA users varied significantly ($p < 0.001$). For education level, an analysis of variance by one-factor Anova test was performed to compare the influence of four education levels on BMI. A post-hoc test indicated that group of illiterate subjects was different from those with secondary and higher levels of education, but there were no significant differences between the illiterate and primary level see table 3.

3.2. Side effects and complications

See Table 4.

4. Metabolic effects

4.1. Weight gain

The main side effect of all hormonal contraceptives is weight gain, which is regularly observed, although women who see it as a sign of good health can accept not all women gain weight. It favorably and this is the case of women in southern Morocco. According to the results of the study, dmpa users with $\text{bmi} > 30$ have a risk of weight gain 1.52 times that of dmpa users with $\text{bmi} < 30$. This is consistent with the results of a study conducted by the World Health Organization Fatima et al., 2024

in collaboration with the World Bank and the United Nations Development Fund. The criterion for selecting women for the study was: Gonadotropin (LH and FSH) and testosterone levels on screening should be within normal ranges of center, but gonadotropin levels may be below lower limit of normal ranges if overall endocrine profile and semen parameters are indicative of a normal reproductive state [9-10].

4.2. Glucose

According to the results of the study, obese women adopting dmpa show significant changes in carbohydrate metabolism as well as slight increases in fasting glucose and insulin levels and increased insulin response. The relative risk reported in the present study is well above 1 ($\text{RR} > 3$). The results are in good agreement with the findings of two studies that analyzed the effect of progesterone, which regulates glucose metabolism via the glucose transporter 1, in promoting endometrial receptivity. The results show that P4 increased glucose uptake at the cellular level. To better understand whether P4 activates glucose uptake and glycolysis, we measured three indicators of glycolysis, such as intracellular levels of pyruvate, lactate, and ATP at different concentrations of P4 [11-12].

5. Subjective side effects

5.1. Arterial pressure

The effects on blood pressure were generally minimal, with several investigators reporting a small decrease. Although changes in blood pressure are very difficult to study, whenever dmpa was administered, measurements indicated a twofold increase ($\text{RR}: 2.03$) in diastolic blood pressure in women with $\text{bmi} > 30$ than their peers with $\text{bmi} < 30$. The literature has endorsed an association by the effect of progesterone on blood pressure. In fact, the results of a study that found that there was an increase in weight gain and BMI in Depo-Provera users compared to non-users [13], a study has shown that pure progestogen contraceptives expose to the risk of hypertension, whatever its type and route of administration, is associated with a discrete increase in diastolic blood pressures [14-15].

5.2. Mood changes

Several reports indicate mood changes as a side effect of combined oral contraceptives. Some of these reports indicate that a disturbance in tryptophan metabolism can be demonstrated in over 90% of users. Synthetic estrogens have been found to be responsible for this abnormal condition, which can usually be normalized by high doses of pyridoxine. In the present study, obese users had higher rates of mood swings ($\text{RR} > 1$) than their peers with $\text{bmi} < 30$. Progesterone and progestins have shown to influence serotonin metabolism and it is possible that this is a contributing factor to mood changes. The high incidence of side effects reported for the placebo contraceptive studies is relevant to this issue [16].

5.3. Asthma

According to the study results, there are several reports of exposure to asthma, nausea, back pain, and loss of libido, but these are also found among IUD users. In relation to the study, asthma, the association is strongly positive ($\text{RR} > 3$), since obese women using dmpa are clearly exposed to the risk of asthma. It should be remembered that it could be a confounding factor as long as climate in the region is humid

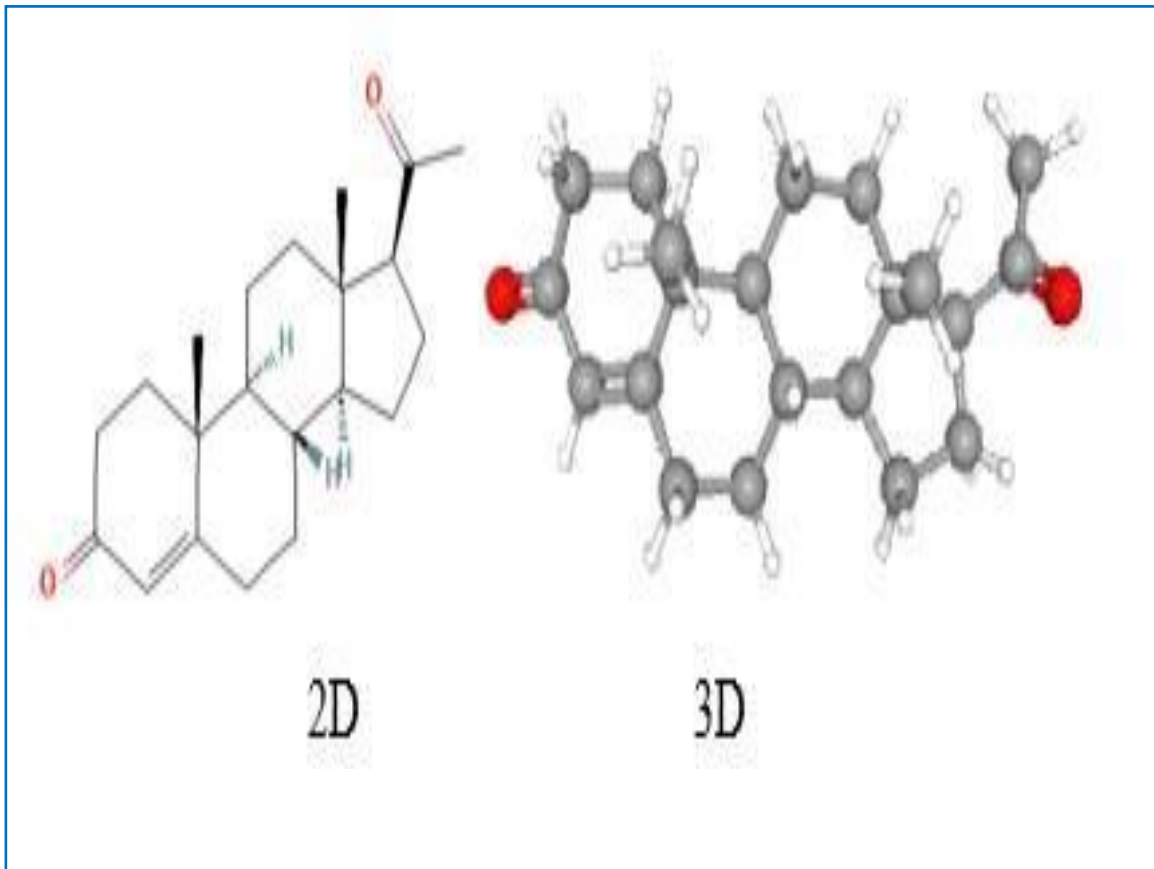


Figure 1: Depot-medroxyprogesterone acetate structure

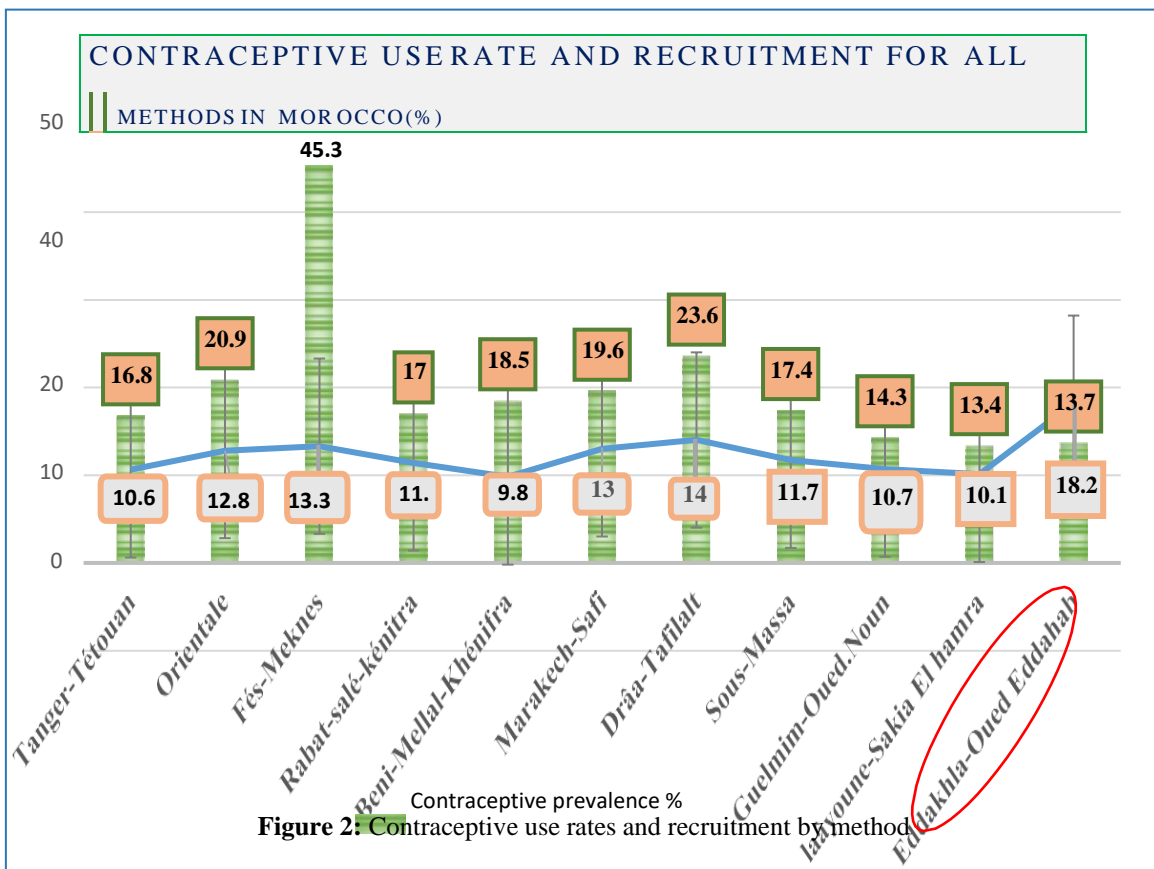


Figure 2: Contraceptive use rates and recruitment by method

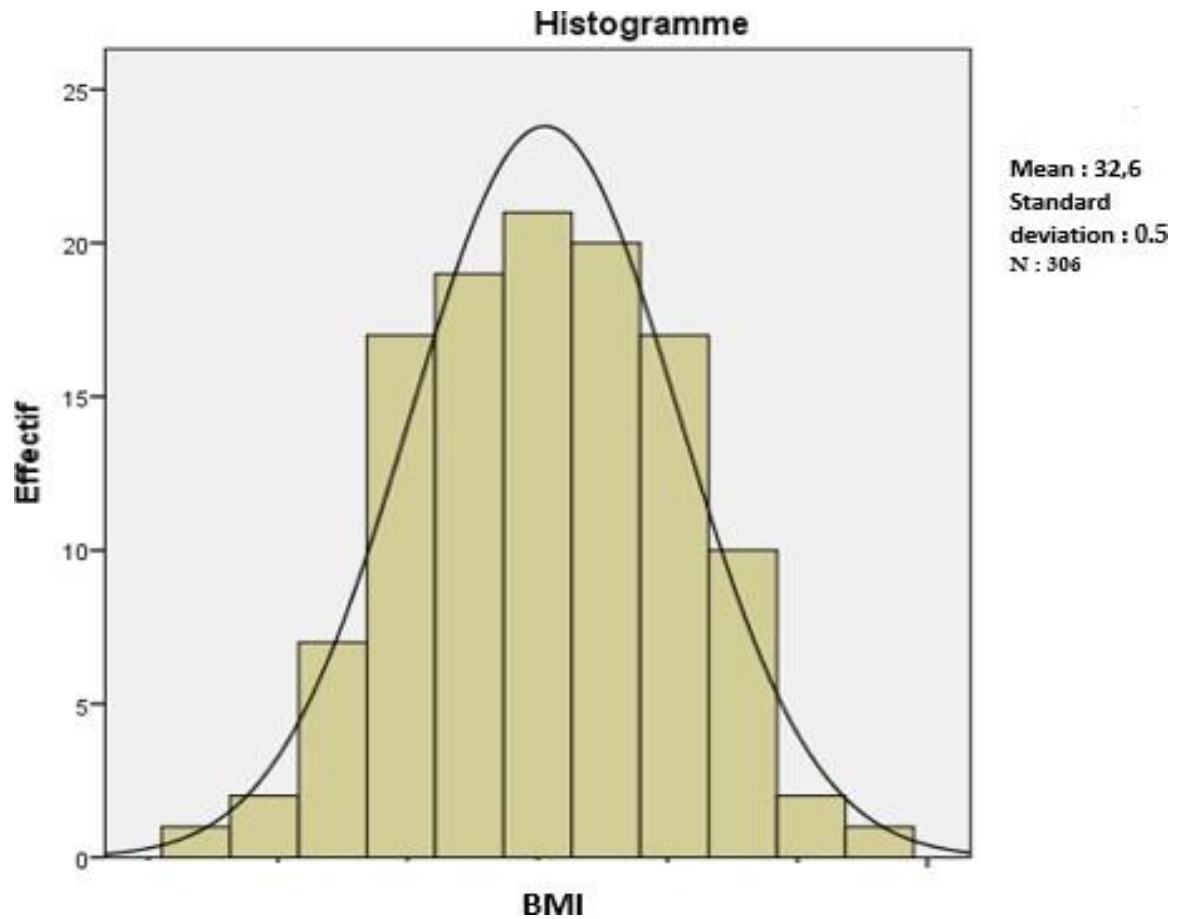


Figure 3: Test of normality

Table 1: Change in recruitment rate by year and contraceptive method [8].

	Method	2018	2019	2020	2021
Recruitment rate% MWRA 15-49	Pill	9,46	10,33	9,24	9,76
	DIU	1,21	1,24	1	1,22
	LT	0,01	0,01	0,01	0,62
	Condom	0,98	1,11	1,08	1,19
	DMPA	0,3	0,01	1,31	0,97
Rate of adoption of eachmethod % MWRA 15-49years	Pill	79,21	81,42	79,45	74,2
	DIU	10,1	9,77	8,61	9,25
	Condom	8,19	8,77	9,3	9,08
	LT	2,5	0,06	0,06	0,07
	DMPA	0,06	0,04	2,62	7,38
Rate of use		18,64	18,81	18,98	18,41

MWRA: Married women of reproductive

Table 2 : Socio-medical characteristics of the study population

Variable	Obese Cohort n=102 (%)	Healthy Cohort % n=204 (%)	Pearson chi2 (P .value)
•Age			
•16–24	65.32 (64)	52,42(25.9)	< 0.001
•25–34	13.21 (12.9)	83,46(40.9)	
•35–44	13.23 (12.9)	40,12(40.1)	
•45–49	10.24 (10.3)	28 (13.7)	
• Marital Status			
• Married	(89.21)	79(77.45)	< 0.011
• Divorced	11(10.78)	21(22.55)	
• Smoking			
• Never smoker	21(20.5)	46(22.5)	< 0.011
• Current smoker	56(54.9)	92(45.09)	
• Past smoker	25 (24.5)	66(32.6)	
• Parity			
• 0-3	25(24.5)	132(64.7)	< 0.001
• 4-6	54(95.2)	78(38.23)	
• >7	23(22.5)	6 (2.91)	
• Medical History			
• Covid-19	67(65.6)	170(83.3)	< 0.001
• Depression	23(22.5)	28 (13.7)	
• HIV	12(11.7)	6(2.9)	

Table 3: Post-hoc-test Bonferroni between BMI and level of instruction

level of education(i)	level of education(j)	Standard Error	Signification	Confidence interval à 95%	
				Lower terminal	Upper terminal
Illiterate	Primary	2.923E-02	.068	-,15195	3,1396E-03
	Secondary	2.219E-02	.000*	-,15681	-3,9071E-02
	Superior	2.510E-02	.000*	-,20224	-6,9054E-02
Primary	Illiterate	2.923E-02	.068	-3,14E-03	,15195
	Secondary	2.698E-02	1,000	-9,51E-02	4,8032E-02
	Superior	2,942E-02	,228	-,13928	1,6802E-02
Secondary	Illiterate	2,219 E-02	,000*	3,907 E-02	,15681
	Primary	2,698 E-02	1,000	-4,80 E-02	9,5098 E-02
	Superior	2,244 E-02	,562	-9,72 E-02	2,1813 E-02
Superior	Illiterate	2,510 E-02	,000*	6,905 E-02	,20224
	Primary	2,942 E-02	,228	-1,68 E-02	,13928
	Secondary	2,244 E-02	,562	-2,18 E-02	9,7225 E-02

Table 4 : Side effects and complications after depot-medroxyprogesterone acetate use

Characteristics	Cohort with BMI>30 (n =102) %	Cohort with BMI<30 (n=204) %	RR (CI95%)
•weight increase	59(57.8)	12(5.8)	1.52[1.32 , 1.67]
•Arterial pressure >14,6kPa	23(22.5)	6(2.9)	2.03 [1.15,1.67]
•Mood change	67(65.6)	35(17.1)	1.60 [1.07,2.53]
•Asthma	19(18.6)	3(1.47)	3.45 [1.16 ,1.34]
•Nausea	3(1.4)	2(0.9)	2.95 [1.34 ,3.45]
•Galactorrhea	8(7.8)	1(0.4)	1.30 [1.57, 3.4]
•Resumption of ovulation at 6months	30(29.4)	68(33.3)	1.03 [0.7, 0.85]
•Ectopic pregnancy	16(15.6)	6(2.9)	0.92 [0.87, 0.98]
•Glucose increase	47(46)	3(1.4)	3.78 [1.69, 2.19]
•Benign hepatic adenoma	7(6.8%)	1(0.4)	0.70 [0.85, 0.93]
•ovarian cancer	6(5.8)	3(1.4)	0.63 [0.73 ,0.89]

In this regard, a study was conducted in women of normal build, negating the difference in the incidence of asthma between pre-menopausal and post-menopausal women of the same age (Hazard Ratio 1.1 [0.8-1.3]). However, in overweight/obese women, the incidence of asthma was significantly increased in natural postmenopausal women and after bilateral oophorectomy [17].

5.4. Ectopic pregnancy

According to results of the study, it appears that the adoption of dmpa as a contraceptive method, constitutes a risk factor in women with BMI<30, as long as (RR<1). In same way, cases of ectopic pregnancy have been reported with dmpa; it seems that this risk exists but extremely low [18].

6. Complication

1). Resumption of ovulation

In this regard, obesity is a risk factor in women adopting dmpa than women with bmi<30. The incidence of amenorrhea and infrequent bleeding increased with the duration of injections in obese women (RR>1) than in women with BMI<30. Studies from several surveys indicate that regular menstruation is restored after the first injection within a year for 75% and within 18 months for 85%. Ovulation can be induced by treatment with human gonadotropins [19].

2). Benign hepatic adenoma

With respect to exposure, seven dmpa adoptive women with bmi>30, seven women manifested were suspected of having hepatic tumors. Angiography, radioisotope scan, and grayscale ultrasound were used for the diagnosis of liver adenoma, in addition to the systematic examinations: routine abdominal examination, globular sedimentation rate, and liver function tests were taken into consideration. As for the female dmpa user, screened for liver tumor, also has a history of using oral ester-progestin contraceptives more than nine years. It is concluded that contraceptive steroids are one of several factors that can influence development and the risk probably increases with steroid dosage and duration of use [20].

3). Ovarian cancer

In this regard, six users of dmpa for a period of 6 years with a bmi>30, were diagnosed for malignant adenoma by various biological and radiographic examinations, presented amenorrhea of grouping AB+, known for their susceptibility to this type of cancer. However, the results are insufficient to establish firm conclusions.

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