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A Comparative Study of Allopregnanolone Levels and Depression Severity Among Woman Using Contraceptive Implant and Depot Medroxyprogesterone Acetate (DMPA)

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KEYWORDS

Allopregnanolone, Contraceptive, Depression, Implant, Depot Medroxyprogesterone Acetate

ABSTRACT:

Introduction: Hormonal contraceptive may influence neurosteroid pathways involved in mood regulation, particularly allopregnanolone, a positive modulator of γ-aminobutyric acid (GABA) receptors. Differences in progestin-only delivery contraceptive between implant and depot medroxyprogesterone acetate (DMPA) may result in variations in allopregnanolone levels and potentially influence depression severity.

Objectives: to compare allopregnanolone levels to depression severity among woman using contraceptive implant and DMPA.

Methods: This cross-sectional study included reproductive aged woman using contraceptive implants and DMPA. Allopregnanolone levels were measured, and depression severity were assessed using The Hamilton Depression Rating Scale (HDRS). Statistical analysis was performed using SPSS version 29.0.

Results: Allopregnanolone levels were higher in DMPA acceptors compared to implant (0.65 (0.12-2.62) vs 0.70 (0.44-2.37) (p=0.473). All participants were in the mild depression category, with no significant difference in HDRS scores between groups (p=0.423). The statistics showed that there was no significant correlation between allopregnanolone levels and depression severity in implant (p=0.053) and DMPA (p=0.600) users.

Conclusions: There were no significant differences in allopregnanolone levels or depression severity between implant and DMPA users, and no significant association was observed between allopregnanolone levels and depressive symptoms in either group.

1. Introduction

Based on data from the World Health Organization (WHO), more than 280 million people in the world experience depression [1]. Hormonal and endocrine function changes may play a significant role in the pathophysiology of depression [2]. Women are more at risk of experiencing depression than men [1] Progesterone and allopregnanolone, a neurosteroid derivative, have been linked to hormone-related mood disorders. At physiological doses, allopregnanolone functions as a positive allosteric modulator of GABAA receptors. GABA system dysfunction has been linked to depression and other mood disorders [3]. Currently, over 60% of couples of reproductive age globally utilize contraception. Hormonal and non-hormonal contraception are both options. There are several hormonal contraceptives available for women. Some include solely progesterone, while others have both estrogen and progesterone. Depression is listed as a potential negative effect of hormonal contraception [4].

Depot Medroxyprogesterone Acetate (DMPA) was the first non-oral hormonal contraceptive formulation accessible in the United States, and preliminary research suggested a link between DMPA and mood problems. Civic et al. (2000) did a multivariate longitudinal analysis and found that ongoing DMPA users and those who quit DMPA had more depression symptoms than non-users [5]. Another contraceptive device, the implant, was created in the 1980s. Initially, the implant consisted of six rods containing the stronger androgenic progestin levonorgestrel. A newer version with two rods initially releases 60-70 mcg/day of etonogestrel (ENG), a 3-keto derivative of desogestrel, before gradually dropping to 25-30 mcg by the end of the third year. Berenson et al. (2020) found that 33% of teenagers and 17% of adults experienced mood alterations 6 months after starting LNG [6]. Another study assessing the tolerability of LNG devices found that 3–9% of participants discontinued LNG due to mood changes [7].

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Clinical information regarding the effects of progestin-only hormonal contraceptives, particularly implants and DMPA, and which contraceptives are more susceptible to depression, is still lacking. Therefore, research is needed to support clinical evidence. Both contraceptives contain synthetic progesterone, but the levels of the hormone released by each type vary.

2. Objectives

The purpose of this study was to evaluate the comparison between allopregnanolone levels in women experiencing depression who used implants and DMPA.

3. Methods

Study design

This is a comparative, cross-sectional study. It was conducted at all educational centers, public hospitals in Makassar City, and community health centers that provide contraceptive services. The laboratory will be located at the Hasanuddin University Medical Research Center (HUMRC FK UNHAS).

Research Sample and Research Criteria

The sample in this study were all women of childbearing age who used the Implant and DMPA contraceptives, who met the sample inclusion and exclusion criteria. Inclusion criteria: 1) Implant and DMPA acceptors aged 21–49 years; 2) Implant and DMPA acceptors who met the criteria for depression based on the HDRS questionnaire; 3) Subjects were willing to participate in the study; 4) Not on antidepressant therapy. Exclusion criteria: 1) Subjects were unwilling to continue the study series; 2) Subjects died.

Operational Definition

1) **Age**
   The age of the research subjects was assessed at the time of data collection and classified into <20 years, 20-35 years and >35 years.
2) **Education**
   Education is assessed based on the highest level of education completed and is classified into elementary, middle, high school, and college.
3) **Occupational**
   The employment status of research subjects is classified into unemployed and employed.
4) **Parity**
   Parity is assessed based on the number of live births and is classified into primipara and multipara.
5) **Labor**
   Delivery methods are classified into pervaginal and sectio caesarea.
6) **Body Mass Index (BMI)**
   BMI is assessed using the formula weight (kg)/height (m^2). Results are classified as Underweight <18.5; Normal 18.5–22.9; Overweight 23–24.9; Obese ≥ 25.
7) **Allopregnanolone levels**
   Allopregnanolone levels were examined on all study subjects using the ELISA technique.
8) **Depression Score**
   Depression score assessment was carried out on each research subject using the Hamilton Depression Rating Scale (HDRS) score with an interpretation of scores of 0-7 (not depressed), scores of 8-16 (mild depression), scores of 17-23 (moderate depression) and scores ≥24 (severe depression).

Research Ethics

Every action taken in this study has obtained the approval of the patient/patient's guardian by signing an informed consent. This study has obtained research permits in accordance with research ethics from the Human Biometric Research Ethics Commission and the Faculty of Medicine, Hasanuddin University, with Number: 996/UN4.6.4.5.31/PP36/2024.

Data Analysis

The Statistical Package for Social Sciences (SPSS) version 29.0 was utilized to examine the data. Univariate analysis was performed for subject characteristics (age, education, occupation, parity, childbirth, and BMI in the form of frequencies and percentages. Bivariate analysis was performed to compare allopregnanolone levels and HDRS scores in implant and DMPA recipients. The Shapiro-Wilk test was used to determine whether allopregnanolone levels and HDRS scores were normal. If the data were normally distributed, the comparison test employed an independent t-test. If the data did not follow a normal distribution, the Mann-Whitney test was applied. To analyze the link between allopregnanolone levels and depression, Pearson correlation was employed for normally distributed data and Spearman correlation for non-normally distributed data. The confidence interval was 95%. A p-value of <0.05 is considered significant.

4. Results

Basic Characteristics of the Subject

A total of 88 women met the study criteria. Subjects were divided into two groups: 44 women who used the implant for ≥12 months and 44 women who used DMPA for 2 injections (≥6 months). The characteristics of the subjects in both groups are presented as follows:

Table 1. Characteristics Subject Study

Characteristics	Implant (n = 44)	DMPA (n = 44)	p-value
	n (%)	n (%)	
Age			
20-35 years	34 (77.3)	30 (68.2)	0.338
> 35 years	10 (22.7)	14 (31.8)	

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Education			
Elementary/Middle School	22 (50.0)	22 (50.0)	
Senior High School	19 (43.2)	16 (36.4)	0.533
College	3 (6.8)	6 (13.6)	
Occupation			
Working	12 (27.3)	6 (13.6)	0.113
Not Working	32 (72.7)	38 (86.4)	
Parity			
Primipara	4 (9.1)	6 (13.6)	0.502
Multipara	40 (90.9)	38 (86.4)	
Labor			
Pervaginal	37 (84.1)	40 (90.9)	0.334
Sectio caesarea	7 (15.6)	4 (9.1)	
BMI			
Underweight/Normal	21 (47.7)	21 (47.7)	
Overweight	10 (22.7)	9 (20.5)	0.956
Obesity	13 (29.5)	14 (31.8)	

Chi square test

Comparison of Allopregnanolone Levels between the Two Groups

Allopregnanolone levels were compared between the two groups using the Mann-Whitney test. Table 2 shows that serum allopregnanolone levels in implant users were not significantly different from those in DMPA users (p = 0.473). Thus, neither progestin-only contraceptive method exhibited significant variations in allopregnanolone levels in this population.

Table 1. Comparison of allopregnanolone levels in implant and DMPA acceptors

	Implant (n = 44)	**DMPA (n = 44)**	**p-value**
	Median (min-max)	**Median (min-max)**	
Allopregnanolone levels (nmol/L)	0.65 (0.12-2.62)	0.70 (0.44-2.37)	0.473

Mann Whitney Test

Comparison of Depression Levels between the Two Groups

In this study, all women, both implant and DMPA users, experienced mild depression, so a comparison was conducted using the Hamilton Depression Rating Scale (HDRS) depression scores. The results of the comparison test for depression scores between implant and DMPA users are presented below.

Table 2. Comparison of depression levels based on HDRS scores in implant and DMPA acceptors

	Implant (n = 44)	**DMPA (n = 44)**	**p-value**
	Median (min-max)	**Median (min-max)**	
Depression score	9.00 (8.00-11.00)	9.00 (8.00-11.00)	0.423

Mann Whitney Test

Table 3 shows that depression scores based on the HDRS indicated that all participants were in the mild depression category. Implant users had the same median depression score as DMPA users. There was no difference in depression levels between implant and DMPA users (p = 0.423).

The relationship between allopregnanolone levels and depression levels

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The results of the relationship test between allopregnanolone levels and depression scores in implant and DMPA acceptors are presented as follows.

Table 3. The relationship between allopregnanolone levels and depression levels based on HDRS scores in implant and DMPA acceptors

	r	*p-value*
Implant	0.291	0.053
DMPA	0.080	0.600

Spearman correlation test

Table 4 shows that there was no significant relationship between allopregnanolone levels and depression scores in women using implant acceptors or DMPA acceptors.

Discussion

There was no difference in the study's subjects' characteristics between the two groups. Allopregnanolone levels and depression levels in implant and DMPA patients were compared in this study. The allopregnanolone levels of implant and DMPA recipients did not differ significantly, according to the results. An essential neurosteroid derived from progesterone, allopregnanolone functions as a positive agonist at the GABA-A receptor, which is involved in anxiety, emotional stability, and mood control. A woman's cognitive reactions may be impacted by changes in allopregnanolone levels [8]. Decreased allopregnanolone may lead to decreased GABA-A modulation and increased susceptibility to mood fluctuations, meanwhile, DMPA and implants have lower androgenic activity. Furthermore, continuous progestin exposure, as with implants and DMPA, tends to result in stable, rather than fluctuating, levels [9,10]. In a clinical context, these results provide the important implication that choosing between a progestin-only contraceptive implant and DMPA is unlikely to result in a significant difference in risk for potential allopregnanolone-mediated mood changes.

The results of this study also showed no difference between the HDRS depression scores of implant recipients and DMPA recipients. However, several studies support a greater risk of depression from DMPA use. A study by Ryan et al. (2022) reported that after 6 months of DMPA and implant use, estradiol levels in women using DMPA were 53% lower than those in women using the implant. This greater decrease in estradiol levels in women using DMPA compared to the implant has implications for psychological side effects [11]. . Estradiol has neuromodulatory effects on brain areas involved in mood and behavior. The high rate of depression in implant users is related to hormonal effects. Progestogen-only agents in implant contraceptives can affect neurotransmitter pathways such as serotonin by activating the hypothalamic-pituitary-adrenal (HPA) axis, resulting in mood disturbances that impact depressive symptoms. The hormonal effects of implants can affected neuroendocrine pathways and potentially exacerbate depressive symptoms [12].

In both groups, there was no significant association between allopregnanolone levels and depression levels as measured by the HDRS. This finding is consistent with previous research indicating that the effects of hormonal contraceptives on mood are not necessarily linear and are highly reliant on individual responses and biological factors. Enzymes like 5α-reductase and 3α-HSD play a significant role in the regulation of neurosteroid biosynthesis, including allopregnanolone. Variations in their expression may impact emotional responses [3]. The study by Rapkin et al (2019) also stated that there is no evidence to suggest that excess or deficiency of allopregnanolone acting on GABAA receptors causes depressive symptoms [13].

However, these results differ from the study by Almeida, Nin, and Barros (2020), which found a consistent decrease in allopregnanolone levels in the limbic brain area of rodents exposed to stress-induced depression models, such as social isolation and chronic stress. Allopregnanolone decreased due to a deficit in 5α-reductase type I (5α-RI) expression in Brodmann area 9 (BA9) of the prefrontal cortex, and in women, due to a decrease in the 3α-hydroxysteroid dehydrogenase enzyme [14]. The discrepancy in these study results can be explained by several factors. First, allopregnanolone levels were measured once, thus failing to capture dynamic neurosteroid fluctuations: literature suggests that neurosteroid levels can fluctuate temporally and are influenced by stress, the reproductive cycle, and enzymatic variability. Second, individual responses to progestins can differ, both pharmacokinetically and neurobiologically. Therefore, both the implant and DMPA can be considered safe in the context of depression risk, and allopregnanolone levels are not a primary determinant of depressive symptoms in users of these contraceptive methods.

The main strength of this study lies in its novelty, providing new evidence through a controlled comparison between two progestin-only contraceptives, the implant and DMPA, by combining objective neurosteroid measurements with depression assessment using a validated instrument. However, the study has several limitations. Subjects were homogeneous across depression categories and had a low range of scores. Furthermore, the study did not evaluate other factors that may contribute to variations in mood symptoms and could potentially be confounding variables, including neurotransmitter dysregulation, HPA axis dysfunction, neuroinflammatory processes, other medical comorbidities, psychosocial stress, relationship problems, or genetic variability and GABAA receptor sensitivity.

5. Conclusion

There was no significant difference between implant and DMPA acceptors in allopregnanolone levels or depression levels based on HDRS scores, and no significant correlation was found between allopregnanolone levels and depression levels in both groups.

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Conflict Of Interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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