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Abnormal uterine bleeding among injected depo-medroxyprogesterone acetate and levonorgestrel implant: a prospective cohort study

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ABSTRACT

Objective. This study aims to analyse the relationship between depo-medroxyprogesterone acetate (DMPA) injection and Levonorgestrel (LNG) implant toward abnormal uterine bleeding (AUB), a crucial aspect of women's health and contraceptive methods.

Materials and Methods. A rigorous cohort prospective study was conducted at several healthcare facilities from August 2023 to February 2024. The study included 122 women who underwent contraceptive methods such as DMPA or implants. It utilized a comprehensive observational method for assessing abnormal uterine bleeding (AUB) through questionnaires and the Pictorial Blood Assessment Chart (PBAC). Demographic and clinical data were meticulously extracted from medical records.

Results. In both groups, most samples had an incidence of AUB in six and nine months of use. The most common type of AUB was amenorrhea in six and nine months of use. However, there was no significant difference in AUB incidence between the DMPA injection and Levonorgestrel implant group at six months (ARR 0.632, 95%CI 0.265-1.506) and nine months of observation (ARR 0.081, 95%CI 0.360-1.786).

Conclusions. The use of DMPA injections and Levonorgestrel implants as contraceptives has a similar long-term side effect profile regarding the incidence of AUB. The present findings can serve as a basis for considering the appropriate contraceptive method for women of reproductive age.

INTRODUCTION

Injectable contraception is widely used in Indonesia, accounting for approximately 32% of contraceptive methods employed in the country. The most effective contraceptive injection is depo-medroxyprogesterone acetate (DMPA), which has a failure rate of only 0.2%. However, DMPA can lead to amenorrhea, and 90% of DMPA users experience abnormal uterine bleeding (AUB), often resulting in the discontinuation of the method. Disorders in menstrual bleeding patterns are the primary reason for discontinuation of progesterone-based contraception [1, 2].

Contraceptive implants are also very effective long-term progesterone contraceptives, with a failure rate of around 0.3-1.0% within 12 months of use. However, like DMPA, progestin-only contraceptives can also cause AUB. AUB often leads to discontinuing the DMPA method, which has been a significant obstacle to its widespread use. Menstrual bleeding pattern disorders can take the form of amenorrhea, irregular, frequent, and prolonged bleeding. Unpredictable menstrual disorders, such as hypomenorrhea, metrorrhagia, or a mixture of both patterns, are caused by the levonorgestrel contraceptive implant, affecting around 40-80% of users in the first year of use, particularly in the first two years. The use of levonorgestrel has discouraged women from starting contraception [3, 4].

Previous research has yielded inconsistent findings regarding the incidence of AUB associated with different types of contraception. A systematic review conducted by Moray *et al*. reported that users of etonogestrel implants experienced a higher frequency of abnormal menstrual events compared to those using levonorgestrel injections [5]. Conversely, a review by Foran indicated that amenorrhea rates were more prevalent among individuals utilizing injectable contraception *versus* implants, with figures of 50% *versus* 20% at the 12-month mark [6]. In contrast, a comprehensive study by Rezk *et al*. concluded that there were no significant differences in AUB patterns between the two contraceptive methods regarding abnormal bleeding or amenorrhea [7]. This research represents the first comparative analysis of AUB side effects between these two contraceptive methods conducted in Indonesia, where previous investigations primarily focused on detailing the side effects without performing direct comparisons. In international studies, there is a predominance of research focusing on the etonogestrel implant; however, this study emphasizes levonorgestrel, which is more commonly utilized in the country of investigation. The findings of this study aim to enhance the understanding of the comparative effects of these two contraceptive methods. A comparison of these two types of contraceptives can assist in selecting a hormonal contraception method by identifying which type carries a higher risk of causing uterine haemorrhage. Therefore, this study aimed to evaluate the relationship between the use of levonorgestrel implants and the hormonal injection of DMPA acetate concerning the incidence of abnormal uterine bleeding.

MATERIALS AND METHODS

Study design

This article was generated in accordance with STROBE 2007 (Strengthening the Reporting of Observational Studies in Epidemiology) [8]. A prospective cohort study was conducted at several healthcare facilities. The study included women who used contraceptives such as DMPA (Depot Medroxyprogesterone Acetate) or the levonorgestrel implant, and they were assessed for abnormal uterine bleeding (AUB) through questionnaires and the Pictorial Blood Assessment Chart (PBAC). The study period spanned from August 2023 to February 2024.

Population and samples

The eligibility criteria for the study included non-perimenopausal women aged between 20 and 40 who had used DMPA injections or levonorgestrel implants for 6 to 9 months during the postpartum period. Samples were excluded if participants had comorbid conditions (PALM-COEIN) that could cause abnormal uterine bleeding, such as polyps, adenomyosis, leiomyomas, malignancy, hyperplasia, coagulopathy, ovulatory dysfunction, or endometrial dysfunction. Additionally, those with a history of consuming medications that could increase bleeding risk (including antiplatelet or anticoagulant drugs, herbal medicines, or other similar substances) or a history of menstrual disorders or abnormal uterine bleeding prior to using contraception were also excluded.

AUB in this study was defined as a spectrum of vaginal bleeding problems including menstrual disorders based on the FIGO classification consisting of amenorrhoea (no bleeding), infrequent menstrual bleeding (> 38 days), frequent menstrual bleeding (< 24 days), prolonged menstrual bleeding (> 8 days), irregular menstrual bleeding (shortest to longest cycle variation: ≥ 8-10 days), light menstrual bleeding, heavy menstrual bleeding, random intermenstrual bleeding, cyclic intermenstrual bleeding, and presence of unscheduled bleeding on Progestrin ± Estrogen gonadal steroids [9, 10].

In this study, the DMPA injection was defined as a long-term contraceptive method containing the progestin hormone depot medroxyprogesterone

acetate (150 mg), administered once every three months. The levonorgestrel implant was defined as a long-term contraceptive consisting of two Silastic rods containing the progestin hormone levonorgestrel (150 mg), which is released continuously subcutaneously and can be used for up to three years.

Data collection

Demographic and clinical data were extracted from medical records. The questionnaire was developed based on the PBAC scale, incorporating key elements for diagnosing AUB. Patients completed the PBAC form, noting that a score greater than 100 indicates menorrhagia, necessitating immediate classification as AUB [11-13]. If the PBAC score is less than 100, patients are then asked whether they experience bleeding outside their normal menstrual cycle, including post-coital bleeding. If so, they may have amenorrhea, oligomenorrhea, or metrorrhagia, all of which are categorized under AUB. Aetiologies other than iatrogenic causes will be excluded from consideration.

Certain patients demonstrate inconsistencies in their completion of the PBAC data. Consequently, in incomplete scoring, efforts will be made to supplement the data with information derived from the Anamnesis results. However, if the scoring remains incomplete, it will be excluded from further analysis.

Sampling size

A purposive sampling method was employed to obtain the samples. The formula for calculating sample size for two independent population proportion studies was used. The sample size (n) was 61 for each group, based on distinct proportions: 50% for the levonorgestrel implant, 90% for the DMPA injection, and 25% for the low-risk group. A 95% confidence interval and a precision level of 20% were applied in the estimation.

Data analysis

Baseline data were summarized descriptively, and differences in each variable between groups were calculated using the Chi-Square test. Additionally, a multiple logistic regression analysis was performed, adjusting for age, parity, and body mass index (BMI) to assess the relative risk associated with different types of contraception concerning the incidence of AUB. Statistical significance was determined at a P-value of less than 0.05 using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM, USA).

RESULTS

Subject characteristics

A total of 122 patients who had recently used DMPA injections or levonorgestrel implants were included in the present study. The final analysis included 61 patients who met the eligibility criteria in both groups, with no dropout samples. **Table 1** presents the baseline characteristics of the study participants. Both groups exhibited similar characteristics, with the majority of participants aged between 20 and 35, having lower education levels, being unemployed, multiparous, and classified as non-obese.

Comparison of AUB incidence between DMPA injection and levonorgestrel implant at six and nine months of use

The comparative analysis of AUB incidence between groups at six and nine months of use is presented in **Table 2**. Both groups demonstrated a relatively high incidence of AUB at six months (incidence rate exceeding 70%) and nine months (incidence rate exceeding 67%). However, there was no statistically

Table 1. *Baseline characteristics of study participants.*

Variables	DMPA	LNG	Total	P-value
	n (%)	n (%)	n (%)	
Age (years old)				0.541
< 20 or > 35	15 (24.6)	18 (29.5)	33 (27.0)	
20-35	46 (75.4)	43 (70.5)	89 (73.0)	
Education				0.625
≤ 12 years	52 (85.2)	50 (82.0)	102 (83.6)	
20 (16.4)	22.7%	19.9-25.7%		
> 12 years	9 (14.8)	11 (18.0)		
Employment Status				0.346
Employed	9 (14.8)	13 (21.3)	22 (18.0)	
Unemployed	52 (85.2)	48 (78.7)	100 (82.0)	
Parity				0.161
Primipara	21 (34.4)	14 (23.0)	35 (28,7)	
Multiparous	40 (65.6)	47 (77.0)	87 (71.3)	
Body mass index				0.592
Non-obese	54 (88.5)	52 (85.2)	106 (86.9)	
Obese	7 (11.5)	9 (14.8)	16 (13.1)	

DMPA: Depo-Medroxyprogesterone; LNG: Levonorgestrel; n: number.

Table 2. *Comparison of AUB incidence between DMPA injection and LNG implant in six and nine months of use.*

Abnormal uterine bleeding	DMPA n (%)	Implant n (%)	ARR	95%CI	P-value
6-months use			0.632	0.265-1.506	0.300
Absent	13 (21.3)	17 (27.9)			
Present	48 (78.7)	44 (72.1)			
9-months use			0.801	0.360-1.786	0.588
Absent	18 (29.5)	20 (32.8)			
Present	43 (70.5)	41 (67.2)			

ARR: Adjusted relative risk (age, parity, and body mass index); DMPA: Depo-Medroxyprogesterone; LNG: Levonorgestrel; n: number.

significant difference in AUB incidence between the two groups at six months after adjusting for age, parity, and BMI (Adjusted Rate Ratio [ARR] 0.632, 95% Confidence Interval [CI] 0.265-1.506, p = 0.300) and at nine months of use (ARR 0.801, 95%CI 0.360-1.786, p = 0.588).

The comparative analysis of AUB symptoms between groups at six and nine months of use is shown in **Table 3**. Both groups exhibited similar AUB symptom patterns, with amenorrhea being the most common, followed by regular menstruation and light menstrual bleeding. However, no significant differences in AUB symptoms were reported between the two groups at six months of use (p = 0.088) and nine months (p = 0.239).

DISCUSSION

Subjects in this study were predominantly aged 20 to 35 years, multiparous, unemployed, of non-obese nutritional status, and had less than 12 years of education. A comparison of the independent variables – DMPA injection contraception and implants – with the dependent variables of age, parity, occupation, and education showed no significant differences, indicating homogeneous characteristics among the subjects [14].

There was no significant difference in the risk of abnormal uterine bleeding (AUB) between the age groups of 20-35 years and those under 20 or over 35 years. Analysis of a randomized clinical trial also found no association between age and amenorrhea [15]. Additionally, no significant differences were observed between subjects with primiparous and multiparous parity status who received DMPA injection contraception and implants. Research indicated that there was no relationship between the number of previous pregnancies and the duration of bleeding in AUB due to DMPA injection use. Furthermore, work status and education showed no significant differences among subjects who received DMPA injection contraception and LNG implants. No other studies have specifically assessed education and employment as risk factors for AUB.

The nutritional status (BMI) showed no significant differences between users of DMPA injection contra-

Table 3. *Comparison of AUB symptoms between DMPA injection and LNG implant in six and nine months of use.*

Menstrual pattern	Contraceptive		Total n (%)	P-value
	DMPA n (%)	Implant n (%)		
6-months use				0.088
Light menstrual bleeding	12 (19.7)	15 (24.6)	27 (22.1)	
Amenorrhoea	30 (49.2)	16 (26.2)	46 (37.7)	
Random intermenstrual bleeding	4 (6.6)	4 (6.6)	8 (6.6)	
Frequent menstrual bleeding	1 (1.6)	5 (8.2)	6 (4.9)	
Heavy menstrual bleeding	1 (1.6)	4 (6.6)	5 (4.1)	
Regular menstrual bleeding	13 (21.3)	17 (27.9)	30 (24.6)	
9-months use				0.239
Light menstrual bleeding	14 (23.0)	8 (13.1)	22 (18.0)	
Amenorrhoea	24 (39.3)	19 (31.1)	43 (35.2)	
Random intermenstrual bleeding	2 (3.3)	4 (6.6)	5 (4.1)	
Frequent menstrual bleeding	1 (1.6)	3 (4.9)	4 (3.3)	
Heavy menstrual bleeding	2 (3.3)	7 (11.5)	9 (7.4)	
Regular menstrual bleeding	18 (29.5)	20 (32.8)	39 (32.0)	

DMPA: Depo-Medroxyprogesterone; LNG: Levonorgestrel; n: number.

ception and those using implants. However, secondary data revealed significant weight gain among DMPA users from 6 to 9 months of use. Research indicates that weight gain associated with DMPA is linked to increased body fat and appetite regulation, influenced by the hormone progesterone, which stimulates the hypothalamic appetite control centre. This weight gain may deter some individuals from using this contraceptive method [2]. Observational studies report varying effects of DMPA on weight gain, which are complicated by natural weight gain over time, as well as differences in study design and subject characteristics [16].

Obesity is the most common risk factor for AUB, leading to prolonged estrogen exposure due to increased peripheral aromatization of adrenal androgens. This process can result in the development of polyps, leiomyomas, and endometrial carcinoma [17]. Obesity triggers pro-inflammatory conditions and increases cytokine production, which enhances estrogen synthesis by upregulating aromatase. Inflammatory mediators like tumour necrosis factor (TNF) and interleukin-6 (IL-6) significantly increase in the uterine tissue of mice on a high-fat diet, correlating with greater menstrual blood loss [18]. Fei *et al*. reported no significant difference in baseline BMI or changes in BMI between individuals with and without AUB after using subdermal implants. However, at 12 months, those with AUB tended to have a lower average BMI [19].

The main issues associated with DMPA use include irregular menstruation, bleeding, breast tenderness, weight gain, and depression. Irregular bleeding occurs in 70% of users during the first year, decreasing to 10% thereafter. Both bleeding and spotting tend to decrease with each reinjection, with 80% of users achieving amenorrhea after five years, compared to only 10% of implant users. Subcutaneous DMPA preparations exhibit similar bleeding patterns, with 55% achieving amenorrhea within the first year and 70% after two years. Irregular bleeding can be troublesome and may inhibit sexual activity, making amenorrhea preferable for many users.

Levonorgestrel implant users more frequently report weight gain than weight loss, although findings vary. Weight change assessments are confounded by factors such as exercise, diet, and age-related changes, and the increased appetite may be linked to the androgenic activity of levonorgestrel. The LNG implant is highly effective in overweight and obese women, although it is less effective in women weighing less than 70 kg [20, 21].

There was no significant difference in the history of AUB between subjects using DMPA injections and those using implants at 6 and 9 months of use. The most common type of AUB recorded was amenorrhea, and there were no significant differences in menstrual disorders between users of implants and DMPA [22].

Long-term hormonal contraceptive use, particularly progestins, suppresses the hypothalamus and pituitary glands, which in turn prevents ovulation. Approximately one-third of menstrual cycles are anovulatory during the first two years of use, increasing to over 50% within five years. Progestins also suppress estradiol-induced cyclic endometrial maturation, causing atrophy and preventing implantation. Pregnancy should be considered in women with amenorrhea who have a history of regular menstruation prior to the onset of amenorrhea [23, 24].

Progestins also alter cervical mucus and tubal motility, inhibiting sperm migration and fertilization. Progestins inhibit gonadotropin secretion, follicular maturation, and ovulation at high doses. This dual effect maintains contraceptive effectiveness even with inconsistent ovulation in implant users towards the end of the third year. Additionally, progestins suppress endometrial activity, rendering it non-receptive to implantation [25, 26]. The pathogenesis of bleeding in hormonal contraceptive users remains unclear; however, it is thought to result from the transition of the endometrium from a thick to a thin state due to the dominant progestin components. The endometrium forms a dense network of small, fragile veins and capillaries prone to focal bleeding. Changes in matrix metalloproteinase activity, endometrial perfusion, local vascular haemostasis, pro and antioxidant processes, and cell migration all contribute to this bleeding [27-29].

Secondary data indicated a significant increase in the risk of AUB after nine months of DMPA use compared to six months. The risk was 11 times higher for those who experienced AUB at six months. In contrast, no significant difference in AUB incidence was observed among implant users between six and nine months. All progestin contraceptive implants are associated with a variety of uterine bleeding patterns, ranging from amenorrhea to frequent and irregular bleeding. Users of the LNG implant report unpredictable bleeding patterns, with amenorrhea either not occurring or persisting. A tolerable bleeding pattern in the first three months

can predict subsequent patterns, with a 50% chance of improvement for those experiencing intolerable patterns [30-32].

At 6 and 9 months of use, most users of DMPA and LNG implants experienced amenorrhea, with no significant difference in the pattern of menstrual disorders between the two groups. A comprehensive study conducted by Rezk *et al*. demonstrated that there was no significant difference in the patterns of AUB between the two forms of contraception over six months, encompassing both abnormal bleeding and amenorrhea. However, the group receiving the DMPA injection exhibited a relatively higher incidence of AUB compared to those using etonogestrel (ENG) implants, with rates of abnormal bleeding at 34.6% *versus* 27.6% and amenorrhoea at 30.2% *versus* 21.2% [7]. Furthermore, another review by Foran corroborated these findings, indicating a higher incidence of amenorrhea in individuals using progestin-based contraception via the injection method compared to the implant method (50% *vs* 20% at 12 months) [6]. Conversely, a systematic review suggested that the prevalence of amenorrhoea associated with DMPA was greater than that observed with LNG implants over 12 months; however, LNG implant users reported prolonged menstrual bleeding or spotting more frequently than DMPA users [33-35]. Additionally, a systematic review by Moray *et al*. highlighted that abnormal menstrual incidents were more prevalent among users of etonogestrel implants compared to those receiving levonorgestrel injections. This review concluded that the most common menstrual-related side effects reported by users of progestin-based implants included heavy menstrual bleeding, followed by prolonged or frequent bleeding and amenorrhea [5].

Progestins suppress LH surges necessary for ovulation, leading to anovulatory cycles and reducing estrogen-induced endometrial maturation, which results in atrophy. These changes prevent implantation if fertilization occurs. Pregnancy should be considered in women with amenorrhea and a history of ovulation. Progestins also inhibit sperm migration and fertilization by altering cervical mucus and tubal motility. They suppress gonadotropin secretion, follicular maturation, and ovulation at high doses, maintaining contraceptive effectiveness even in cases of inconsistent ovulation. The pathogenesis of bleeding remains unclear; however, it is thought to result from the transition from a thick to a thin endometrium due to progestin components. Endometrial changes and matrix metalloproteinase activity may contribute to vascular fragility and bleeding [36-39].

Levonorgestrel implants and DMPA injections, both categorized as progestin-only contraceptives, have a significant impact on endometrial thickness. Levonorgestrel implants are associated with a more consistent reduction in endometrial thickness [40, 41], while the effects of DMPA may result in increased or decreased endometrial thickness, varying based on individual patient characteristics and duration of use [42]. Furthermore, the morphological alterations in the endometrium and the associated local mediators differ between LNG and DMPA, contributing to the patterns of AUB observed with each method. In the case of LNG implants, there is an upregulation of progesterone receptors, accompanied by dilation and thinning of the delicate vascular wall, increased vascular density, decreased levels of vascular endothelial growth factor (VEGF) in glandular cells, heightened expression of various angiogenic factors, and increased stromal matrix metalloproteinases (MMP-1 and MMP-3). These changes are implicated in the higher incidence of heavy or frequent menstrual bleeding commonly observed among LNG implant users. Conversely, DMPA injections lead to a downregulation of progesterone receptors, similar vascular wall alterations, reduced vascular density at elevated doses, and decreased tissue inhibitors of metalloproteinases (TIMP) across all endometrial compartments. These factors contribute to a higher prevalence of amenorrhea in users of DMPA injections [43].

The present study has several limitations. It includes only women who continued contraception for 6-9 months, excluding early discontinuers who may have stopped due to severe AUB. In this study, we did not evaluate women's satisfaction and quality of life using either method. Further examination of the underlying mechanisms is necessary. Moreover, it is important to categorize patients based on their symptoms following usage and to include a larger population and extended outcomes for a more comprehensive analysis.

CONCLUSIONS

There are no significant differences between the use of DMPA and LNG regarding the incidence of AUB. Both DMPA and LNG can lead to iatrogenic

AUB, resulting in changes to menstrual patterns. However, the changes caused by LNG implants are less variable compared to the expected menstrual pattern than those induced by DMPA. This difference is attributed to the hormonal mechanisms of action, with amenorrhea being the most common type of AUB observed.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
D.Z.H.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing – original draft, writing – review & editing. A.M.T.: Conceptualization, data curation, formal analysis. S.S.: Conceptualization, formal analysis, methodology, I.S.: Formal analysis, methodology. E.H., M.F.F.: Validation, writing – review & editing.

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Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
The research was ethically approved by the Human Biomedical Research Ethics Commission, Faculty of Medicine, Hasanuddin University (No. 197/UN6.4.5.31/PP36 /2023).

Informed consent
Patients signed the informed consent prior to participate.

Data sharing
Data are available under reasonable request to the corresponding author.

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