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# ASSOCIATION BETWEEN BLEEDING PATTERN AND ESTRADIOL LEVEL OF DEPOT MEDROXY PROGESTERON ACETATE USERS

## *HUBUNGAN POLA PERDARAHAN UTERUS DENGAN KADAR ESTRADIOL PADA AKSEPTOR KONTRASEPSI INJEKSI DMPA*

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## ABSTRACT

**Background:** Bleeding disturbances are the main complaint that cause most DMPA users discontinuing contraceptive use. Mechanism underlying the bleeding disturbances is not clear. It is presumed that the condition is related to fluctuation of estradiol level or to low persistent estradiol level

**Objective**: 1. To evaluate an association between bleeding pattern and estradiol level of DMPA users after 3, 6, 9, 12 months use. 2. To evaluate an association between estradiol level and length of use. 3. To evaluate an association between bleeding pattern and estradiol level, body mass index (BMI), age, parity, total cholesterol level of DMPA users.

**Design:** Observational study, secondary analysis nested on "Randomized Controlled Trial Planibu® and Depo Progestin®"

**Material and Method**: Seventy DMPA users received injection every 3 months for 12 months. Before injection was administered, venous blood was taken and examination of estradiol level was done using Enzyme Imuno Absorbent Assay (ELISA). In addition, in-depth interview was also done on bleeding pattern for the last reference period (90 days). Subject was classified according to their bleeding pattern into groups of amenorrhea, oligomenorrhea, spotting, and bleeding,

**Results**: All research subjects indicated low estradiol concentration with an average concentration less than 150 pg/ml. There was a correlation between length of usage and estradiol level; estradiol level after 12 months of usage was less than 100 pg/ml. There was no different between bleeding pattern and estradiol in month 3, 6, 9,12 using bivariate analysis with t-test with amenorrhea group as reference and $p > 0,05$. T-test and Chi Square analyses using amenorrhea group as reference stated that there was no association between bleeding pattern and age, BMI, and parity. Using multivariate analysis with Multinomial Logistic Regression, it was stated that correlation between estradiol concentration and bleeding pattern was not affected by age, body mass index, or total cholesterol level. There was an association between bleeding pattern and cholesterol level using bivariate and multivariate analyses.

**Conclusion**: 1. Estradiol level in various bleeding pattern after 3,6,9,12 month of usage was not different. 2. There was correlation between low estradiol level and length of usage. 3. Association between bleeding pattern and estradiol level was not influenced by age, parity and body mass index, and total cholesterol level.

***Keywords*:** bleeding pattern, estradiol, DMPA, injectable contraception

## INTRODUCTION

Uterus bleeding are the complaint most found on acceptor of DMPA injection contraception. Bleeding disturbance is a side effect that mostly results in acceptor that discontinues contraception and the rate of the bleeding disturbance is 52-68%.[1] Counseling is required by acceptor to prevent the discontinuity of contraception usage considering that side effect of bleeding disturbance is not harmful and usually is only seen in first year of the usage that will be better in next years.[2]

Mechanism or pathophysiology of irregular bleeding on user of injection contraception is still unclear. Many researhes mentioned that it was because of fluctuating estradiol level or estradiol on progesterone. Other researches also mentioned that it was because of low persistent estradiol level[3-5]. Basic mechanism involved here is that cyclical fluctuating estradiol or progesterone gave a stimulus for endometrial growth and menstruation. Bleeding disorder was caused by disturbaces in this cyclical fluctuating level.[6,7,8] Therapy bleeding disorder with estradiol or progestin was based on this basic.

Others findings said that acceptors experience amenorrhea had a low persistent estradiol level, Estradiol level wasn't different between amenorrhea

or bleeding group. Estradiol level, estradiol receptor level. and progesterone level wasn't different between amenorrhea and prolonged bleeding group.[3,9] Another research indicated that low persistent estradiol level could be correlated with amenorrhea, spotting, oligomenorrhea or prolonged bleeding.[10]

Based on that results, we need a study that evaluate association between bleeding pattern and estradiol level of depot medroxy progesterone acetate users.

## RESEARCH METHOD

This research used observational study design, with secondary data analysis nested on research "Double Blind Randomized Controlled Trial of Planibu® and Depo Progestin®". Primary research was conducted in Purworejo regency and Manado municipality from February 2006 to February 2007.

Population of primary research was married women in reproductive age desiring to delay or space pregnancy using injectable contraception in Purworejo regency and Manado municipality. The subject was women in childbearing age of 20-35 years old, being married, being healthy, being not pregnant, still getting menstruation, and getting injectable contraception of Planibu and Depo Progestin according to random allocation received.

Subject of 70 women meeting inclusion and exclusion criteria received DMPA injection every 3 months for 12 months given at the same time. Before injection administration, vein blood was taken from each acceptor and processed to be serum, packaged, sent and examined its estradiol level in laboratory according to standardized method. Examination of estradiol level was done with Enzyme-Linked Immunoabsorbent Assay (ELISA) by an analyst in the Clinical Pathology Laboratory of Dr. Sardjito Hospital in Yogyakarta. It was carried out to prevent bias of measurement result.

Data on bleeding pattern was collected with in-depth interview. The in-depth interview used familiar and mutual-trust principles. Subject was required to record menstrual pattern for last 90 days (referential period) in menstrual diary chart previously given. Subject that could not recall more than 10 days their menstrual pattern in reference period were included into exclusion criteria. It was to avoid recall bias. In-depth interview on bleeding pattern was done before injection. Subject was grouped into bleeding patterns: amenorrhea, oligomenorrhea, spotting and bleeding. In addition, monthly regular visit was done for counseling and preventing drop-out.

Bleeding group included frequent and prolonged bleeding. Oligomenorea group included infrequent and reguler bleeding. Spotting group included subjects experience bleeding and spotting pattern. Amenorea included subjects didn't experience bleeding and spotting pattern. Frequent bleeding is defined as subjects experience more than 4 episodes of bledings. Prolonged bleeding is defined as one episode of bleeding lasting more than 10 days. Irreguler bleeding is defined as bleeding free interval less than 17 days. Reguller bleeding is defined as bleeding free interval more than 17 days. Spotting is defined as subjects didn't need sanitary napkins. Reference period is defined as 90 days like WHO standard.

## RESULT AND DISCUSSION

Characteristic of each research group was homogenous (Table 1). So, it was expected that difference between variables that was seen in this research was not due to characteristic difference of each group of bleeding pattern as a dependent variable.

**Table 1. Characteristic of research subject in month 12**

| Variable | | Amenorrhea | Oligomenorrhea | Spotting |
|---|---|---|---|---|
| BMI (kg/m$^2$) | (Mean) | 23.39 | 20.97 | 23.84 |
| | (SD) | 3.58 | 3.02 | 4.02 |
| Age (year) | (Mean) | 28 | 31 | 29 |
| | (SD) | 5 | 5 | 5 |
| Cholesterol (mg/dl) | (Mean) | 165.27 | 136.85 | 139.34 |
| | (SD) | 37.07 | 24.91 | 35.57 |
| Estradiol (pg/ml) | (Mean) | 94.03 | 91.33 | 97.77 |
| | (SD) | 15.88 | 12.34 | 14.13 |
| Parity | | | | |
| 1 | | 23(42.6%) | 2(25%) | 2(25%) |
| 2-3 | | 28(51.9%) | 5(62.5%) | 6(75%) |
| ≥4 | | 3(5.6%) | 1(12.5%) | |

The result indicated that there occurred change in bleeding pattern on DMPA acceptors over time. Therefore, with longer contraception use, dominant bleeding pattern shifted from irregular and spotting bleeding to be amenorrhea (Table 3). Discontinuity rate will decrease over time because in the past 20 years, there have been changes in people's opinion about importance of monthly menstruation. Most acceptors were more comfortable with oligo/ amenorrhea condition compared with irregular or regular bleeding monthly. It was related to their sexual, social or religious activities.[11,12]

Entirely, estradiol level in the research subject was low with average level less than 130 pg/ml, while after 12-month use, estradiol level decreased to be <100 pg/ml (Table 3). The suppressed estradiol level suited follicular phase of menstrual cycle. Estradiol suppression agreed with previous research where concentration of estradiol on DMPA acceptor was low and kept beyond menopause women (<100 pg/ ml).[13,14] The research found estradiol level closing one in menopause women compared with follicular phase (18.9 pg/ml). It might be due to its reagent that has better sensitivity at low estradiol level.[15]

There was no association between bleeding pattern and age, parity, BMI (Table 2). It was also suggested in previous publications.[9,15] They presented that there is an inverse association between estradiol and duration of contraception usage, but there is not found association between estradiol level and age, body mass index, parity and existence of uterus bleeding. There was difference in cholesterol level between amenorrhea group and oligomenorrhea group (p=0.04).

Estradiol suppression was more significant with longer contraception usage (Table 3). For example, in amenorrhea group, there occur estradiol decrease from 134.420 in month 3, to 107.843 pg/ml, 100/898 pg/ml, 94.029 pg/ml in month 6, 9, and 12. The similar thing also occurred in oligomenorrhea and spotting group. Previous research also indicated that there was a reverse association between estradiol level and duration of use of DMPA contraception.[10,15]

Estradiol level in various bleeding patterns was not different on month 3, 6, 9, and 12. Estradiol level

**Table 2. Bivariate analysis: association of bleeding pattern and BMI, age, cholesterol level and parity**

**T-test**

| | Amenorrhea* | | Oligomenorrhea | | | | Spotting | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | T value | Sig/p | Mean | SD | T value | Sig/p |
| BMI (kg/m$^2$ | 23.9 | 3.58 | 20.97 | 3.02 | -1.82 | 0.07 | 23.84 | 4.02 | 0.33 | 0.75 |
| Age (year) | 28.20 | 4.83 | 30.88 | 4.76 | 1.46 | 0.15 | 29.25 | 5.12 | 0.57 | 0.57 |
| Cholesterol (mgdl) | 165.27 | 37.07 | 136.85 | 24.91 | -2.09 | 0.04 | 139.34 | 35.57 | -1.85 | 0.07 |

* Reference Significant: p<0.05

**Chi-Square**

| | Amenorrhea | | Oligomenorrhea | | Spotting | | $X^2$ | Sig/p |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | | |
| Parity 1 | 23 | (42.6) | 2 | (25.0) | 2 | (25.0) | 2.839 | 0.585 |
| 2-3 | 28 | (51.9) | 5 | (62.5) | 6 | (75.0) | | |
| ≥4 | 3 | (5.6) | 1 | (12.5) | 0 | (0) | | |

Significant: p<0.05

**Table 3. Bivariate analysis: association of bleeding pattern and estradiol level in month 3, 6, 9, and 12**

**T-test**

| Month | Bleeding pattern | Estradiol level | | t value | Sig/p |
|---|---|---|---|---|---|
| | | Mean | SD | | |
| 3 | Amenorrhea* | 134.420 | 18.696 | | |
| | Oligomenorrhea | 129.620 | 15.613 | -0.629 | 0.533 |
| | Spotting | 133.743 | 8.829 | -0.085 | 0.934 |
| | Bleeding | 130.225 | 13.194 | -0.587 | 0.563 |
| 6 | Amenorrhea* | 107.843 | 14.33 | | |
| | Oligomenorrhea | 112.531 | 7.607 | 1.234 | 0.223 |
| | Spotting | 107.554 | 16.232 | -0.057 | 0.954 |
| 9 | Amenorrhea* | 100.898 | 11.273 | | |
| | Oligomenorrhea | 97.177 | 17.844 | 0.895 | 0.375 |
| | Spotting | 100.564 | 8.127 | 0.087 | 0.931 |
| 12 | Amenorrhea* | 94.029 | 15.88 | | |
| | Oligomenorrhea | 91.333 | 12.34 | -0.457 | 0.649 |
| | Spotting | 97.769 | 14.13 | 0.590 | 0.558 |

* Reference Significant: p<0.05

in amenorrhea, oligomenorrhea, spotting or bleeding groups was not different to each other (Table 3). Bivariate analysis to view association was done with t-test using amenorrhea as reference. There was no association between estradiol level and bleeding pattern with p more than 0.05.

Multivariate analysis with multinomial logistic regression was done to view influence of body mass index, age, and total cholesterol level on association of bleeding pattern and estradiol level. The association between bleeding pattern and estradiol level after making control over age, BMI, total cholesterol factors was not found (Table 4). There was different cholesterol level between amenorrhea group and spotting group (p=0.03).

It showed that there was an association between bleeding pattern and cholesterol level that was consistent whether it used univariate, bivariate or multivariate analysis. In univariate analysis, the significance level was 0.03 (p=0.03); in bivariate analysis between amenorrhea group and oligomenorrhea group, the significance level was 0.04 (p=0.04); and in multivariate analysis between amenorrhea group and spotting group, the significance level was 0.03 (p=0.03) (Table 1, 2, 3). Ester cholesterol is precursor of steroid hormone and, cholesterol level will affect synthesis of endogen estradiol. It is known that increasingly suppressed and low estradiol level will result in change in bleeding pattern from irregular/spotting to be amenorrhea, so that low cholesterol intake may reduce endogen estradiol synthesis and decrease frequency of irregular bleeding/spotting. In addition, it is also known that cholesterol is one of important substances making up cell membrane determining integrity of cell membrane and vascular. Cholesterol is made up from nuclear ring system with hydrocarbon chain and has a main characteristic of amphipathic (hydrophobic and hydrophilic).[16] Mechanism related to endometrial bleeding in DMPA acceptor was endometrial vascular morphology, changes in vascular structure integrity, perfusion and endometrial oxygenation change, changes in endometrial response to steroid hormone, changes in endometrial vascular hemostasis and changes in immunocompetent cell.[3]

No association of bleeding pattern and estradiol level was also presented by other research indicating that estradiol level, estradiol receptor level and progesterone receptor level were not different in amenorrhea group and bleeding group. This research has similar methodology where blood sample and endometrial biopsy were done once in end of reference period.[9]

Bleeding mechanism on DMPA contraception acceptor may be due to fluctuation of estradiol and/or progesterone or persistent low estradiol level resulting in bleeding through progesterone breakthrough bleeding mechanism. Acceptor with amenorrhea underwent persistent low estradiol level that then fluctuated near menstruation.[3,11]

Other research stated that low estradiol level might relate to period of amenorrhea, oligomenorrhea, spotting or bleeding. It indicated that association between bleeding pattern and estradiol level was unclear; bleeding may occur or stop without any change in estradiol level. Existence of various bleeding patterns and low estradiol level indicate no

**Table 4. Multivariate analysis with multinomial Logistic regression: association of bleeding pattern and estradiol level by controlling BMI, age, total cholesterol factors in month 12**
**Dependent variable: bleeding pattern***

| Variable | $X^2$ Wald | Sig/p | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| - Oligomenorrhea Independent | | | | | |
| Estradiol | 0.030 | 0.862 | 0.995 | 0.939 | 1.054 |
| Age | 2.614 | 0.106 | 1.183 | 0.965 | 1.449 |
| BMI | 3.094 | 0.079 | 0.750 | 0.545 | 1.033 |
| Cholesterol | 2.543 | 0.111 | 0.975 | 0.945 | 1.006 |
| - Spotting Independent | | | | | |
| Estradiol | 0.826 | 0.363 | 1.032 | 0.964 | 1.105 |
| Age | 0.179 | 0.672 | 1.039 | 0.869 | 1.243 |
| BMI | 0.000 | 0.987 | 0.997 | 0.724 | 1.374 |
| Cholesterol | 4.686 | 0.030 | 0.967 | 0.938 | 0.997 |

* Reference: amenorrhea Significant: p<0.05

association between bleeding pattern and estradiol level.[10,17,18] No association between bleeding pattern and estradiol level is confirmed by other findings in a longitudinal study where women with the same hormonal condition may undergo different bleeding patterns. For example, low estradiol level and no luteal activity may cause amenorrhea, frequent bleeding, and prolonged bleeding. In contrary, women with regular bleeding may have ultrasonography image and estradiol and progesterone levels that agree with one in normal ovulation, luteinization, unruptured follicle, growing follicle without ovulation, and no growing follicle.[19]

Contradiction was presented by other research suggesting that prolonged bleeding, oligomenorrhea condition, or end period of amenorrhea were marked with the increase in estradiol level which was then followed by the decrease in estradiol level. Result of this research was supported by other research stating that the decrease in estradiol level happened in 72 hours before withdrawal bleeding occurred[20]. Other researchers stated that an incident of bleeding after increase in, which was followed by decrease in, estradiol level is found in long term injection contraception acceptor or Noretindrone enantat groups.[19]

In two other studies, one in Norplant acceptor[3] and another in Nestorone[10], Faudner et al stated that fluctuation of estradiol level did not influence bleeding pattern. Bleeding occur after increase in, which was followed by decrease in, estradiol or estradiol and progesterone levels. Bleeding period often started with decrease in estradiol level and end with increase in estradiol level[3,21]. Irregular bleeding was not always related to fluctuating estradiol level. It is supported with other research stating that subject with irregular/ frequent bleeding had persistent low estradiol level (<75pg/ml) without luteal activity and bleeding might occur without estradiol fluctuation.[3,15] On Nestorone acceptor, in anovulation cycle, duration of bleeding significantly was related directly to the highest estradiol level at previous 15 day.[10]

Lockwood et al[22] did a research by taking endometrial sample from bleeding location on women using DMPA and found that level of Tissue Factor (TF), an early initiator of homeostasis, decreased at the site and found a reduced level of estrogen and progesterone receptor at the site. Research taking endometrial sample at the same location in bleeding and not bleeding episode is still required. Other research indicated that there was no difference of estrogen and progesterone receptor level between amenorrhea and bleeding groups[9].

Other researches indicated that bleeding during the use of DMPA injectable contraception was related to condition of increase in and decrease in estradiol level or was related to persistent low estradiol level. Mechanism underlying bleeding at low estradiol level is progesterone breakthrough bleeding[3]. Both different hormonal conditions may relate to normal cycle condition, oligomenorrhea, amenorrhea, irregular/frequent bleeding or prolonged bleeding[3].

No association between bleeding pattern and estradiol level in this research might be due to some factors. First, pathophysiology of various researches stated that bleeding occurred due to fluctuation of estradiol and/or progesterone, while in amenorrhea estradiol level was persistently low till then fluctuated near menstruation. Therefore, it was possible that measurement of estradiol was done while it could not capture the changes. Single/infrequent measurement could not capture estradiol variability. Level of hormone suppression depended on time of sample taking[15]. Both bleedings occurred due to mechanism of progesterone breakthrough bleeding where persistent low estradiol level due to estradiol suppression was not equal to high progesterone condition[3].

Mechanism underlying effect of estradiol on endometrial bleeding is not clear. Some opinions suggest that it relate to histological change of endometrium or endometrial thickness measured with ultrasonography and change in vascular endometrium[9]. In Norplant acceptor, thin endometrium was found, which was not related to bleeding pattern and estradiol and progesterone levels. Some researchers reported positive association between endometrium thickness, peripheral estradiol level and amount of bleeding day in period of 90 days before endometrium biopsy. A study done for 18.5 years on Norplant acceptor by Darney et al[6] found that proliferative endometrium was related to abnormal bleeding.

In this research, a three-month period of free contraception before using injectable contraception was used to avoid loss of exogenous hormonal effect in acceptor blood. Washing period was determined 3 months according to washing period suggested by WHO.

A one month follow up period in early research agreed with recommendation. A period of one month is important to: (1) record information on service quality, (2) provide additional data on socio-demography, and (3) record side effects due to use of injecTable contraception.

**CONCLUSION**

There is no association between bleeding pattern and estradiol level after 3, 6, 9, and 12 months of use of DMPA injectable contraception. Estradiol level will decrease with longer time of use of contraception which suppressed estradiol level. An association between bleeding pattern and estradiol level is not influenced by age, parity, BMI and total cholesterol level

**SUGGESTION**

Further research with greater samples that measure estradiol level in a series of ways to see existence of fluctuation of estradiol level underlying mechanism of bleeding in DMPA acceptor is required. To understand progesterone breakthrough bleeding as mechanism underlying uterus bleeding on DMPA acceptor, a series of measurement of progesterone level is required.

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