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Correlation Between The Use of Depot Medroxyprogesterone Acetate (DMPA) For 12 Months and Coagulation Factors

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Abstract
Background: *Of safe motherhood initiative program, Keluarga Berencana (KB) is expected to reduce fertility rate in Indonesia. Injectable hormonal contraceptive, known as DMPA is believed to have failure rate of <0.5%. One of DMPA side effects is irregular bleeding in term of coagulation factors disruption.*
Objective: *To assess the effects of DMPA for 12 months on coagulation factors.*
Methods: *The design of study was cross sectional, conducted at primary health care Medan Johor, on July 2017. Forty women using DMPA for 12-16 months were selected by consecutive sampling. Data were analyzed using T-paired test.*
Results: *Characteristics of the study mostly often encountered were 30-39 years of age group (72.5%), multiparous (82.5%), overweight (37.5%) and abnormal menstruation cycle (72.5%). The mean values of PT, TT and APTT were 13.19±0.64 s, 17.17±1.28 s, and 0.65±4.19 s respectively. Eventually, no significant correlation between the use of DMPA for 12 months and coagulation factor (p=0.948).*
Conclusion: *There was no significant correlation between the use of DMPA for 12 months and coagulation factor (p>0,05).*
Keywords: *Depot Medroxyprogesterone Acetate, bleeding, coagulation factors.*

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I. Introduction

Data of population reference bureau 2016 demonstrated that worldwide population has reached 7.4 billion people, considering Indonesia as the fourth most populous country in the world after the People's Republic of China, India and the United States. The total population in Indonesia reached 237.6 million people in 2010 with a population growth rate of 1.49 percent.[1]

Data of SKDI 2012 demonstrated that the estimated maternal mortality ratio from 2008-2012 reached 359 maternal deaths per 100,000 live births. This ratio is quite high, considering Millennium Development Goals (MDGs)) expected 102 per 100,000 live births by 2015.[2] As one of the safe motherhood initiative programs, program of Keluarga Berencana in Indonesia is expected to reduce fertility rates.[3] Based on Riskesdas 2013, the use of contraceptives in Indonesia is dominated by injectable contraception (34.3%).

Injectable contraception as the main method in developing countries, dominated by injectable contraceptive depot medroxyprogesterone acetate (DMPA) has a failure rate of <0.5%. DMPA causes irregular bleeding (spotting, breakthrough bleeding), weight gain, decreased bone density, late fertility returns.[5,6]

Through these all, we need to further examine the correlation of using DMPA for 12 months to coagulation factors in order to minimize and anticipate unwanted side effects.

II. Methods

The design of this study is an observational analytic, cross-sectional study, conducted at primary health care of Medan Johor in July 2017. The sample of this research is DMPA acceptors as long as 12 months at Johor Puskesmas which met inclusion criteria, such as women aged 20-40 years who routinely receive DMPA injection for at least 12 months, BMI <30 kg/m2, are not currently on anticoagulant treatment, and there is no history of systemic diseases such as diabetes mellitus, hypertension, liver disease, and others. Damaged blood samples during the process were not taken. Forty women were selected by consecutive sampling.

Data was collected through primary and secondary data. Primary data was the value of PT, TT, aPTT on DMPA acceptor conducted in July 2017, while secondary data was medical record at primary health care of Medan Johor. Characteristics of age, parity, body mass index, cycle and duration of menstruation, and hemorrhaguc screening test (HST) were distributively tabulated.

The data will be analyzed descriptively to see the frequency distribution based on the characteristics. The data will be analyzed differently by using T-paired test. If the normal data distribution (p>0.05) will be tested Kolmogorov-Smirnov normality, whereas if the data distribution is not normal will be tested Mann-Whitney. Data analysis was performed to see the correlation of coagulation factor disruption in case of using of DMPA for 12 months.

All participants included here would be informed of the objectives, benefits, advantages and disadvantages, and examination procedures of the research undertaken. The participation of research subjects is voluntary based. For research permission, approval was obtained from Ethics Committee of Faculty of Medicine, University of Sumatra Utara.

III. Results And Discussion

The characteristics of samples shown below.

Table 1. Characteristics of samples

Characteristic	n	Percentage (%)
Age		
20 –29	11	27,5
30 –39	29	72,5
≥40	0	0
Parity		
Primipara	1	2,5
Secundipara	6	15,0
Multipara	33	82,5
BMI		
Underweight	0	0
Normal	14	35
Overweight	15	37,5
Obesitas I	11	27,5
Obesitas II	0	0
Menstrual Cycles		
Normal	11	27,5
Abnormal	29	72,5
Total	40	100,0

From table 1. above, DMPA acceptors most often found at 30-39 years old (n=29; 7.5%), no acceptor that is ≥40 years old age, considering acceptors will come into menopause phase. Based on the results of the BKKBN (2013) survey, younger women (15-19 years old age) and older (45-49 years old age) were fewer using contraceptives compared to women of middle age (20-44 years old age). In older women (30-44 years old age), consumption of pills and long-term contraceptive methods such as IUDs, implants and sterilization of women would be higher than in younger women.[7] These results were similar to those of this study.

Seen from parity, mostly found in multipara of 33 women (82,5%). This was certainly aimed at preventing subsequent pregnancies so that many women chose this method of contraception. Based on BMI, mostly found in overweight of 15 women (37,5%), followed by normal as of 14 women (35%), and obesity I of 11 women (27,5%). Weight is estimated to increase due to weight gain side effects of DMPA, although no weight gain difference exists between DMPA users.[8]

Table 2. Result of coagulation factor parameters.

Coagulation Factor Parameter	n	*Mean*	SD	Min	Max	References
PT	40	13,192	0,6395	11,9	14,7	11,9–14,4
TT	40	17,168	1,2825	15,5	21,7	14–21
aPTT	40	30,655	4,1862	23,2	40,5	26,4–37,6

Through table 2. DMPA acceptors demostrated mean value of PT was 13.19±0.64 seconds; the minimum and maximum values were 11.9 and 14.7, respectively. The mean value of TT was 17.17±1.28 seconds; the minimum and maximum values were 15.5 and 21.7, and mean value of aPTT was 30.65±4.19 seconds; the minimum and maximum were 23.2 and 40.5 .

Table 3. Correlation between PT, TT, and aPTT values and menstrual cycles

PT	Siklus dan Lama Menstruasi		*p*
	Normal	Abnormal	
Normal	11 (27,5%)	29 (72,5%)	
Abnormal	0 (0%)	0 (0%)	
TT			
Normal	11 (27,5%)	29 (72,5%)	
Abnormal	0 (0%)	0 (0%)	

aPTT			0,948
Normal	9 (31%)	20 (69%)	
Abnormal	2 (18%)	9 (82%)	
Total	11 (27,5%)	29 (72,5%)	

It can be seen from table 3. above that those with normal PT and TT values had most abnormal menstrual cycle were of 29 women (72.5%), whereas those with normal menstruation cycle were of 11 women (27.5%). None known had elongated or shortened PT and TT values. Based on the results above, the correlation between PT and TT values and mesntrual duration and cycle could not be measured because PT and TT values on all DMPA acceptors were normal.

Those with normal aPTT value had abnormal menstruation cycle were of 20 women (69%), while those who had normal menstrual cycle were of 9 women (31%). DMPA acceptor with aPTT value extended as many as 1 women (50%) in each normal and abnormal menstrual cycle group. DMPA acceptor with aPTT value shortened mostly had abnormal menstrual cycle as many as 8 women (88,9%), while normal as much as 1 woman (11,1%). Based on the results above, there is no significant correlation between aPTT value and menstrual cycle and length (p> 0,05).

The result of this study was similar to Goldstein's (2007) in which aPTT levels in the 12 month DMPA usage were 34.2±0.8, which decreased 6% of aPTT levels with a decrease of <0.05 from baseline.[9] In Obaidy and Youzbaiki (2014), no decrease in PT levels in DMPA users for 12 months (14,66±1,34), >12 months (14,621,33), and no significant correlation was found (p>0,05).[10]

The disorder of menstrual bleeding is an imbalance of hemostasis factor, i.e. procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic. Tissue factor (TF) and thrombin plays an important role in the cessation of bleeding so that coagulation factors are important to assess in assessing bleeding disorders.[11] There are several mechanisms that explain the effects of progestin on endometrial blood vessels, such as angiogenic disorders, tissue factor changes, and matrix metalloproteinase (MMP).[12,13] In progestin long-term use, decreased blood flow induces local hypoxia, decidualization, and increased angiogenic expression factor, and inhibits the proliferation and migration of vascular smooth cell muscles (VSCMs). This causes a vascular maturation disorder, resulting in blood vessels produced thin-walled, hyperblending, and brittle resulting in leakage and abnormal uterine bleeding.[14]

Women using long-term progestin are found to damage extracellular matrix, associated with unrestricted controlled activity of multiple MMP locally and decreased TMP expression. So, the balance between MMP and TIMP (tissue inhibitors of metalloproteinases) has a role in regulating bleeding that occurs in the use of progestin.[15]

TF expression is upregulated by progesterone during the luteal phase. TF is the primary initiator of endometrial hemostasis through factor VIIa, factors of Xa/Va that produce potent thrombin and mediator for angiogenesis. The thrombin resulting from activation of the TF/VII complex is central to the occurrence of coagulation and thrombus formation, and interacts with the endothelium for vasoconstriction mediation.[16]

IV. Conclusion

The majority of the study subjects were 30-39 years old age group, multiparous, overweight and had abnormal menstrual cycles. Most of the subjects had mean PT value of 13.19±0.64 seconds, TT of 17.17±1.28 seconds and aPTT of 0.65±4.19 seconds after 12 months of use of DMPA.

There was no significant correlation between the use of DMPA for 12 months and coagulation factor disruption (p <0,05).

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