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Original Research Paper

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COAGULATION ASSAYS AND AT-III ON LEVONORGESTREL IMPLANT ACCEPTORS

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ABSTRACT

***Background*:** Indonesia is the fourth most populous country in the world, so the government has focused Family Planning Program using contraception. Implants and IUDs are two most effective reversible contraceptive methods and often used in Indonesia. Implant releases progestin, with most common reported side effect of abnormal bleeding. Specifically for levonorgestrel implants, changes in menstrual intervals, duration, volume of menstrual flow can occur. Progestins are believed to cause changes in platelet and blood vessel, leading to hypercoagulability state, which can be assessed through coagulation assays (PT, TT, aPTT) and level of AT-III.

***Objective*:** This aims to determine the differences in coagulation assays and AT-III levels between levonorgestrel implant versus IUD acceptors.

***Methods*:** This study was an observational analytic study with retrospective cross-sectional design. The population were case population (levonorgestrel implant acceptors) and control population (IUD). A total of 74 respondents were chosen by consecutive sampling. Characteristics data were obtained by interview, anthropometric measurements, and medical records; PT, TT, aPTT, and AT-III data were obtained from blood samples by ELISA method. An independent T-test was used to analyze the data.

***Results*:** Mean PT was the same for implant and IUD users, 13.11 seconds (SD=0.81 seconds) (p=0.1,000). Mean TT of implant users was 14.78 seconds (SD=1.18 seconds) and IUD 14.58 seconds. (SD=1.18 seconds) (p=0.75). Mean aPTT for implant users was 30.22 seconds (SD=4.65 seconds) and IUD 30.55 seconds (SD=2.79 seconds) (p=0.200). Mean of ATIII in implant users was 92.18% (SD=9.72%) and IUD 84.79% (SD=14.74%) (p=0.250).

Conclusion: No significant mean differences for PT, TT, aPTT, and AT-III between groups of levonorgestrel implant and IUD acceptors (p value> 0.05).

KEYWORDS : Acceptors, AT-III, Coagulation assays, Contraception, Implant, IUD, Levonorgestrel

1. INTRODUCTION

Menstruation is a manifestation of cyclic physiological uterine bleeding due to shedding of endometrial lining following the hypothalamic-pituitary-ovarian axis hormonal interactions [1,2]. Menstruation can be caused by estrogen-progesterone withdrawal at the end of the ovulation cycle. However, this is not the only steroid hormone signaling pathway to induce endometrial bleeding. Bleeding can also be caused by estrogen withdrawal, estrogen breakthrough, progestogen withdrawal, and progestogen breakthrough. Continuous treatment of exogenous or synthetic progesterone causes intermittent bleeding, usually in the form of spotting. Clinical examples of bleeding due to breakthrough progestogens are often found in women who are using contraception, namely hormonal contraception [2, 3]. Indonesia is the fourth most populous country in the world with a number of 270,626,000 people [4]. In order to overcome this problem, the government focuses the Family Planning (*Keluarga Berencana*) program by utilizing contraception [5]. There are wo known contraception methods, namely non hormonal contraception, and hormonal. Non-hormonal contraception consists of the Lactation Amenorrhea Method (LAM), condoms, intrauterine contraceptive devices (IUDs), abstinence. and permanent contraception. As for hormonal contraception consists of Progestins (pills, injections & implants), combination pills, and combination injections [6]. According to the data from National Population and Family Planning Department (Badan Kependudukan dan Keluarga Berencana Nasional/BKKBN), implants and IUDs are one of the most effective and reversible contraceptive methods most often used in Indonesia [7].

Implants are contraceptives placed in the subdermal part of the upper arm. Subdermal implants release progestin hormones that work for long time and controlled. There are three main implant systems, namely Implanon, Norplant, and Jadelle. Implanon and Norplant contain etonogestrel, while Jadelle contains levonorgestrel [8]. The mechanisms of action of levonorgestrel are inhibiting ovulation temporarily, thinning the lining of the uterus, and thickening the cervix mucus to prevent sperm movement to the uterus [9,10].

The most common reported side effect of using implants is abnormal bleeding. Specifically with levonorgestrel implants, some changes in menstrual patterns (including intervals between bleeding, duration and volume of menstrual flow, and spotting) can occur during the first year in 80% of users and it reduces to 33% of users in the fifth year. Changes of coagulation state occur 6 months after usage [8]. The use of progestins increases the amount and aggregation of platelets, thus predisposing to hypercoagulability state. These agents also have antiplasmin and antithrombin activity [11].

There are two types of Intrauterine Contraception (IUD), namely hormonal and non-hormonal IUDs. The hormonal type IUD, known as the Mirena brand, contains levonorgestrel. Meanwhile, non-hormonal IUDs under the brand name of Paragard are coated by copper and are often referred to as copper-bearing IUDs (AKDR-Cu). The latter is a long-term contraceptive method that works by inducing an inflammatory reaction so that implantation cannot take place. The most common side effects of IUD use are dysmenorrhea and Abnormal Uterine Bleeding (AUB) especially menorrhagia and intramenstrual bleeding [2]. A study by Grigoryan et al. comparing oral contraceptives and the IUD to the hemostasis system in diabetics showed that subjects who received oral combination contraceptives had lower activated partial thromboplastin time (aPTT) and Thrombin Time (TT) values after intervention for 12 months, while the subjects who used the IUD had a neutral effect on the hemocoagulation system and fibrinolysis [13].

Progestogens play an important role as one of many factors affecting the hemostasis parameters [14]. The function of hemostasis can be examined through several biochemical examinations to assess blood clotting factors in the body, namely coagulations assays [15]. The most common coagulation test performed for coagulation assays are aPTT, PT , and TT [14].

A decrease in factor VIII is associated with the use of ovulation inhibitors such as progesterone contraception and can be determined by the prolongation of aPTT [15,16]. Shortening of PT causes hypercoagulation so that it can be used as a sign of an ongoing systemic thrombosis. TT is the time required in the reaction of changes in fibrinogen to fibrin and can evaluate abnormalities in the formation of fibrin from fibrinogen and the inhibition of thrombin [14,15].

The coagulation process aims to overcome vascular injury so that there is no excessive bleeding, but the process must be localized only in the area of injury, it must not spread to other places because it will endanger the blood circulation and cause thrombus. There are two important systems as natural anticoagulants, namely antithrombin III (ATIII) and protein C [11,17,18].

There are 2 types of ATIII examination, the first is AT III activity which is often done in clinical setting to assess the functional levels of ATIII and ATIII antigen assay to confirm hereditary antithrombin deficiency abnormalities. ATIII deficiency can be acquired or hereditary, and has a clinical correlation with an increase risk of thrombosis, thromboembolism, and related complications associated with a state of hypercoagulation [15].

Based on the description above, up to this day there have been no studies in Indonesia which assess the coagulation assays and ATIII on the use of levonorgestrel implants and researchers aim to know the differences in coagulation assays and ATIII levels between levonorgestrel implant users compared to IUD (non hormonal contraception) users, and so that this research can be the basis for providing appropriate management to prevent complications if there is a hemostasis disorder due to the use of implant.

2. MATERIALS AND METHOD

This study was an observational analytic study with cross-sectional retrospective study design held at Helvetia public health centers. This study involved 74 respondents chosen by consecutive sampling based on inclusion and exclusion criterias and consisted of two groups, namely the case group (levonorgestrel implant acceptors) and the control group who did not use hormonal contraception (IUD acceptors). Respondents in this study had received an explanation about the purpose of this study and had signed an informed consent. This study was approved by the Health Research Ethical Committee Medical Faculty of Universitas Sumatera Utara/H. Adam Malik General Hospital. Characteristics data of the respondents taken in this study include age and parity history which were obtained through interviews, body mass index obtained obtained through anthropometric measurements, while data about menstrual frequency, menstrual duration, use of levonorgestrel implants, and use of copper-bearing IUDs (AKDR-Cu) obtained through medical records. After entry and tabulation process, then the data was processed with SPSS software. Univariate analysis will be presented in table and narrative form to determine the frequency distribution based on the characteristics of the respondents. Categorical data are presented in the form of frequency n (%) and numerical data are presented in the form of mean ± SD or median (minimum-maximum). Bivariate analysis was used to determine the relationship between the independent variable and the dependent variable. Data analysis was performed to compare the effect of using levonorgestrel implants with an IUD on the coagulation assays and AT-III levels. The normality test used is Kolmogorov Smirnov. The hypothesis test used is the independent T test for normal distribution data or the Mann-Whitney test will be performed otherwise. The results are significant if the p value <0.05.

3. RESULTS

Table 1. Characteristics of respondents

Characteristics		Frequency (n)	Percentage (%)	Mean ± SD
Age (Year)	20- 29	26	35.1	30.93 ± 4.09
	30– 39	47	63.6	
	≥ 40	1	1.3	
Parity	Primipara	11	14.9	2.28 ± 0.79
	Secondipara	28	37.8	
	Multipara	35	47.3	
	Grande multipara	0	0	
BMI (Kg/m^2)	Underweight	1	1.3	24.01 ±1.82
	Normal	50	67.6	
	Overweight	23	31.1	
	Obese	0	0	
Cycle of Menstruation (days)	21-35	74	100	28.23 ± 1.54
	< 21	0	0	
	> 35	0	0	
Duration of Menstruation (days)	3-8	74	100	4.96 ± 1.12
	<3	0	0	
	>8	0	0	
Total		74	100	

A total of 74 respondents participated in this study; 63.3% aged 30-39 years. Most of the study subjects were from the multipara group (47.3%). In terms of Body Mass Index (BMI), the majority of respondents had a normal BMI (67.6.7%). Based on the menstrual cycle/frequency, all 74 study respondents had a cycle of 21-35 days and menstrual periods of 3-8 days.

Table 2. Differences in characteristics of respondents

Characteristics	Implant (n=37)	IUD (n=37)	p
Age			
20 – 29 years	16 (43.2)	10 (27)	0.237[a]
30 – 39 years	21 (56.8)	26 (70.3)	
≥ 40 years	0	1 (2.7)	
Parity, n (%)			
Primipara	6 (16.2)	5 (13.5)	0.099[a]
Secondipara	13 (35.1)	22 (59.5)	
Multipara	18 (48.6)	10 (27)	
BMI, n (%)			
Underweight	1 (2.7)	0	0.057[a]
Normoweight	29 (78.4)	21 (56.8)	
Overweight	7 (18.9)	16 (43.2)	
Menstrual Frequency			
Mean	28.30	28.16	0.572[b]
SD	1.63	1.46	
Min – max	25 – 31	25 – 30	
Menstrual Duration			
Mean	4.57	5.35	0.003[b]
SD	1.12	0.98	
Min – max	3 – 7	4 – 7	

[a]Kruskal Wallis, [b]Mann Whitney

Table 2 presents the differences in respondent characteristics in the two study groups. Statistical tests showed that there were no differences in characteristics between the two study groups based on age, parity, BMI, and menstrual frequency (p>0.05), but there were significant differences in the mean of duration of menstruation between the two groups (p=0.003).

Table 3. Differences in coagulation assays and ATIII levels between the two groups

Coagulation assays	Implant(n=37)	IUD (n=37)	*p*
PT, mean (SD), seconds	13.11 (0.81)	13.11 (0.64)	1.000[a]
TT, mean (SD), seconds	14.78 (1.18)	14.58 (1.18)	0.715[a]
aPTT, mean (SD), seconds	30.22 (4.65)	30.55 (2.79)	0.200[b]
ATIII, mean (SD), %	92.18 (9.72)	84.97 (14.74)	0.250[b]

[a]T Independent, [b]Mann Whitney

Table 3 presents and compares the complete mean coagulation assays and ATIII levels of the two study groups. The mean of PT in the implant users dan control group were 13.11 (SD=0.81 seconds) seconds and 13.11 seconds (SD=0.64 seconds) respectively and there were no significant mean differences (p=1.000). The mean of TT in the implant users and control group were 14.78 seconds (SD=1.18 seconds) and 14.58 seconds (SD=1.18 seconds) and there were no significant mean differences (p=0.715). The mean of aPTT in the implant users and control group were 30.22 seconds (SD=4.65 seconds) and 30.55 seconds (SD = 2.79 seconds) and there were no significant mean differences (p = 0.200). The mean of ATIII in the implant users and control group were 92.18% (SD = 9.72%) and 84.79% (SD = 14.74%) and there were no significant mean differences (p = 0.250).

4.DISCUSSION

Formerly, it was believed that oral contraceptives that contain progestogens with androgenic characteristics could cause atherosclerosis, in which a correlation between levonorgestrel dosage and a decrease in HDL levels and arterial disease was found, so that potent progestogens with less androgenic effects have been developed. Some studies indicate oral contraceptives that contain ethinylestradiol (estrogen) have a protective effect against atherosclerosis, through the inhibition of LDL oxidation mechanism induced by free radicals. Clinical experiences and experiments in animals and in vitro indicate that progesterone and synthetic progestogens have vasoconstrictive effects that can predispose the process of arterial thrombosis. In contrast to estrogen, which has a positive inotropic effect, progestogens are believed to reduce contractility of the left ventricle. [19]

A study by Diaz et al in 1990 states that prolonged bleeding and irregular bleeding are often the reason women stop using Norplant implants. Prolonged bleeding was reported in 1/3 of Norplant users during the first 90 days of use and about 1/5 of Norplant users at the end of the first year of use. The pathophysiology of irregular bleeding and prolonged bleeding in Norplant users still can not be explained, but several studies have found that irregular bleeding is associated to a drastic increase in sporadic estradiol accompanied by estradiol withdrawal.[20]

This study was a retrospective cross sectional study involving 74 women, namely 37 levonorgestrel implant acceptors and 37 IUD acceptors as controls. In this study, the mean duration of menstruation in the implant user group was shorter, which was 4.57 ± 1.12 days compared to the control group (IUD), which was 5.35 ± 0.98. The results of the analysis using the Mann Whitney test found a significant difference (p = 0.003) between the two. Different results from this previous study could be due to levonorgestrel implants used in the two studies which were different, where the study by Diaz used Norplant implants (6 capsules containing 36 mg of levonorgestrel; 85 mcg of circulating levonorgestrel per day at the beginning of use, decreased to 50 mcg/day in the ninth month, to 35 mcg/day in the eighteenth month, and thereafter up to 30 mcg/day) which is no longer available by the FDA. Whereas in this study, the levonorgestrel implant users group used Jadelle (2 rods containing 75 mg levonorgestrel; 100 mcg circulating levonorgestrel per day in the first month, followed by a decrease of up to 40 mcg/day in the twelveth month, 30 mcg/day in the second year and so on. [19]

Based on the Virchow's triad, the pathogenesis of thromboembolic disease is affected by the involvement of three venous stasis factors, increased coagubility and endothelial lesions, so as to assess the effects of progestogens on hemostasis parameters; platelets, endothelium, vascular walls and blood flow must be considered. [19]

A study of progesterone derivatives, 30 g oral levonorgestrel did not cause significant changes in fibrinogen, factors II, V, VII, VIII, IX, X, ATIII, coagulation time, aPTT, platelet aggregation, plasminogen, and fibrinolytic activity. Oral contraception increases fibrinolytic activity and vitamin K dependent factors (except protein C), but long-term continuous levonorgestrel administration can reduce fibrinolytic activity and synthesis of vitamin K dependent coagulation factors in the liver. Levonorgestrel can promote platelet activation, but the unchanging level of fibrinogen-fibrin degradation products indicates that there is no increase in the coagulation process.[19]

In 1992, Singh et al examined the effect of levonorgestrel implants on the coagulation assays of acceptors. The prospective study for 5 years investigated various hemostasis parameters in 100 women using Norplant-2, namely PT, aPTT, ATIII, fibrinogen coagulation factors, factors II, V, VII, VIII, and X, fibrinolysis activity (plasminogen activator), fibrin degradation products and plasminogen, and examination of platelet function (platelet count and platelet aggregation). It was then concluded that prolonged administration of Norplant-2 does not cause a hypercoagulable state, but an increase in the rate of platelet aggregation is worth considering.[12]

Most studies do not explain the effect of progestogen-only oral contraceptives on platelet aggregation, but in contrast long-term levonorgestrel implant contraception can cause

accelerated platelet aggregation as in the study by Singh et al 1992. Endothelium also participates in regulating thrombin formation, platelet aggregation, fibrinolysis, and function and growth of smooth muscle cells. Endothelium is known as a metabolic organ that produces tissue plasminogen activation (t-PA) and plasminogen activator inhibitor 1 (PAI-1) and vasodilatation components (Endothelium-derived Relaxing Factor and Nitric Oxide, prostacyclin, endothelin-1 vasoconstrictors, and thromboxane). Prostacyclin causes vasodilation and inhibition of platelet aggregation, whereas thromboxane produces platelets and has a vasoconstrictive and platelet proagregation effect. Steroid sex hormones appear to have an influence on the release of hemostasis activators and inhibitors in response to thrombin or platelet aggregation. [19]

A 1984 study by Shaaban et al investigated the effect of levonorgestrel Norplant implants on blood coagulation, comparing 47 Norplant users with 55 users of various types of combined contraceptive pills. In the study, changes in several hemostasis parameters in the Norplant group were found to be insignificant compared to the combination contraceptive pill group. However there was a significant increase in factor VII activity and a significant decrease in ATIII concentration after 6 months of implant use. [21]

In this study, the mean PT in the implant group was 13.11 (SD=0.81 seconds) seconds and in the control group (IUD acceptor) the same mean was found, 13.11 seconds (SD = 0.64 seconds). The analysis showed that there was no significant difference (p = 1.000) between the two. An insignificant difference (p=0.200) was also found in the examination of aPTT parameters, with the average aPTT in the implant group was 30.22 seconds (SD=4.65 seconds) and 30.55 seconds in the control group (SD=2.79 seconds). The mean PT and aPTT results in this study are still in the normal range (11.0-12.5 seconds for PT and 30-40 seconds for aPTT), which is consistent with previous research. [21] An insignificant mean difference (p=0.715) was also found in the TT parameters, the mean TT in the implant group was 14.78 seconds (SD=1.18 seconds) and 14.58 seconds in control group (SD=1.18 seconds).

In a study by Shaaban et al (1984), ATIII concentrations decreased significantly after 6 months of Norplant placement (17.2±4.7 vs changes -2.6±4.8 mg/dL; p<0.001). The decreasing effect of ATIII was also found in some combination contraceptive pills but some otherwise. This can be due to the type and dosage of hormones in those combination pills. However, changes in ATIII levels can be interpreted as a state of pretrombosis only if it drops to 40-50% from normal levels. [21] In this study, the mean of ATIII levels obtained in the implant group was 92.18% (SD=9.72%) while the control obtained a mean of 84.79% (SD=14.74%). The analysis show no significant difference (p=0.250) between the two groups.

Egberg et al in 1998 investigated the effect of Norplant (levonorgestrel) and Implanon (etonogestrel) for 6 months on caogulation assays and liver function. In the Norplant group, a significant decrease in aPTT -0.13 (p = 0.041) was found, a significant decrease in prothrombin/PT -5.81 activity (p<0.001), a significant increase in ATIII activity +0.03 (p=0.021) were also found. In addition, there was also a significant decrease in FVII activity, PAI-I activity and protein C activity, as well as a significant increase in fibrinogen, plasminogen and bilirubin (mean bilirubin increased ± 21.33%). It was concluded that the use of progestogen-only preparations is recommended in women who are more at risk of VTE (age> 35 years and smokers) because the effect on hemostasis parameters is less significant.[22]

The use of low-dose progestogen-only oral contraceptives has no significant effect on hemostasis, but at higher doses it causes some minor changes that are influenced by progestogen andogenic or antiandrogenic characteristics. An exception is the long-term use of levonorgestrel implants which causes accelerated platelet aggregation. In veins, progestogens can increase distensibility and capacitance and cause a decrease in blood flow. In women with predisposing factors, this can lead to venous stasis and cause thrombosis. In arteries, progesterone and some synthetic progestogens have a vasoconstrictive effect and can neutralize the vasodilation action due to estrogen. [19]

Article review by Skouby & Sidelmann in 2018 demonstated that progestogens have no effect or have very minimal effect on hemostatic proteins, but progestogens can intervene normal hemostasis by two mechanisms (increasing platelet aggregation and decreasing bleeding time). However, further research is still needed to be carried out by using various progestogen formulations to ascertain the role of progestogens in platelet function in humans. The potential role of progestogens in the hemostasis system needs to be discussed in detailed studies, particularly regarding the effects of progestogens on various components involved in tissue factor induced pathway in the coagulation mechanism.[23]

5. CONCLUSION

The mean duration of menstruation in samples using implants and the IUD is 4.57 and 5.35 days. Significant differences were found in menstrual periods between the implant user group and the control group (p value=0.003). The mean values of PT, aPTT, TT and ATIII obtained for implant users were 13.11 seconds, 30.22 seconds, 14.78 seconds and 92.18%, respectively. The mean values of PT, aPTT, TT and ATIII respectively in the control group were 13.11 seconds, 30.55 seconds, 14.58 seconds and 84.97%. There were no significant mean differences for PT, aPTT, TT and ATIII in the implant and control user groups. (p value > 0.05).

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