

Research Article

## Effects of Levonorgestrel Implants of One Rod and Two Rod on Lipid Profile, Follicle Stimulating Hormone (FSH), and Estradiol Levels in Acceptors

### Efek Implan Levonorgestrel Satu Batang dan Dua Batang terhadap Profil Lipid, Kadar Follicle Stimulating Hormone (FSH), dan Estradiol pada Akseptor

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#### Abstract

**Objective:** To find out the comparison of the effect of one-rod and two-rod levonorgestrel implants on FSH, estradiol levels and increase in acceptor lipid profile after a 3-month evaluation in the Mother and Child Hospital of Rika Amelia Palembang.

**Methods:** This study is a phase III clinical trial, "Open" (Open Randomized Clinical Trial), carried out randomization by comparing two types of implant KB, namely levonorgestrel implants, one rod with two rods. This research was conducted at the RSIA Rika Amelia Palembang. Research time is 6 months from November 2018 - April 2019 or until the number of samples is fulfilled.

**Results:** Based on the installation time, the average installation time using one rod LNG was  $1.54 \pm 0.11$  minutes and the LNG for the two rods was  $2.49 \pm 0.26$  minutes. Majority of patients having a normal blood pressure of 89.5% in one rod LNG and 68.4% in two rod LNG. The mean body mass index (BMI) of respondents using LNG implants one rod was  $24.19 \pm 3.93$  kg / m<sup>2</sup> and LNG for two rods was  $25.09 \pm 6.11$  kg / m<sup>2</sup>. Based on the menstrual pattern, it was found that 84.2% of the subjects had regular menstrual patterns in the one-rod LNG group, while there were 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there were no differences in cholesterol levels ( $p = 0.919$ ), HDL ( $p = 0.793$ ), LDL ( $p = 0.851$ ) and triglycerides ( $p = 0.679$ ). There were no differences in FSH levels between respondents using one rod and two rod LNG implants ( $p = 0.849$ ) and also on estradiol ( $p = 0.099$ )

**Conclusions:** There is no difference between the use of one-rod and two-rod levonorgestrel implants against FSH, Estradiol levels and increased lipid profile after 3 months of implant installation. The unpleasant effect in this study was the decline in HDL, but this was accompanied by a decrease in body weight, total cholesterol, LDL, HDL due to a decrease in all aspects.

**Keywords:** estradiol, FSH, implant contraception, levonorgestrel, lipid profile, one-rod, two-rod

#### Abstrak

**Tujuan:** Untuk mengetahui perbandingan efek implan levonorgestrel satu-batang dan dua-batang pada FSH, kadar estradiol dan peningkatan profil lipid akseptor setelah evaluasi 3 bulan di Rumah Sakit Ibu dan Anak Rika Amelia Palembang.

**Metode:** Penelitian ini adalah uji klinis fase III, "Open" (Open Randomized Clinical Trial), yang dilakukan secara acak dengan membandingkan dua jenis KB implan, yaitu levonorgestrel implan, satu batang dengan dua batang. Penelitian ini dilakukan di RSIA Rika Amelia Palembang. Waktu penelitian adalah 6 bulan dari November 2018 - April 2019 atau hingga jumlah sampel terpenuhi.

**Hasil:** Berdasarkan waktu pemasangan didapatkan rerata waktu pemasangan yang menggunakan LNG satubatangadalah  $1,54 \pm 0,11$  menit dan pada LNG dua batang adalah  $2,49 \pm 0,26$  menit. Mayoritas pasien memiliki tekanan darah yang normal 89.5% pada LNG satu batang dan 68.4% pada LNG dua batang. Rerata indeks massa tubuh (IMT) responden yang menggunakan implan LNG satu batang sebesar  $24,19 \pm 3,93$  kg/m<sup>2</sup> dan LNG dua batang sebesar  $25,09 \pm 6,11$  kg/m<sup>2</sup>. Berdasarkan pola haid, didapatkan sebanyak 84,2% subjek yang memiliki pola haid teratur pada kelompok LNG satu batang, sedangkan terdapat sebanyak 63,2% subjek yang memiliki pola haid tidak teratur. Dari uji statistik didapatkan bahwa tidak terdapat perbedaan kadar kolesterol ( $p = 0,919$ ), HDL ( $p = 0,793$ ), LDL ( $p = 0,851$ ) dan trigliserida ( $p = 0,679$ ). Tidak terdapat perbedaan kadar FSH antara responden yang menggunakan implan LNG satu batang dan dua batang ( $p = 0,849$ ) dan juga pada estradiol ( $p=0.099$ )

**Kesimpulan:** Tidak terdapat perbedaan antara penggunaan implan levonorgestrel satu batang dan dua batang terhadap kadar FSH, Estradiol serta peningkatan profil lipid setelah 3 bulan pemasangan implan. Efek yang tidak menyenangkan dalam penelitian ini adalah terjadinya penurunan HDL, namun hal ini disertai dengan penurunan berat badan, kolesterol total, LDL, HDL dikarenakan terjadi penurunan pada seluruh aspek.

**Kata kunci:** dua batang, estradiol, FSH, kontrasepsi implan, lenovorgestrel, profil lipid, satu batang.

## INTRODUCTION

Implant contraception is the most important contraceptive method in various contraceptive methods available today. High efficacy, lack of serious side effects, rapid reversibility, comfort in long-term use make implant method a form of contraception with a high level of acceptance.<sup>1</sup>Implants are hormonal contraceptives that are implanted under the skin (subdermal) and used for a long time. This contraception contains bioactive progestin levonorgestrel (LNG) ingredient, a steroid hormone that is a derivative of 19-nortestosterone. LNG has activities similar to progesterone with weak androgenic activity and has no estrogenic activity.<sup>1,2</sup>With the use of LNG implants, pregnancy is prevented through a combination mechanism as follows.<sup>3-5</sup>The primary mechanism is producing thick cervical mucus that prevents sperm penetration, and inhibits ovulation, at approximately 50% of the menstrual cycle. Secondary mechanisms, which can support the work of the primary mechanism include reducing natural progesterone production by the ovary during the luteal phase even in cycles when ovulation occurs and suppresses endometrial growth (hypoplasia).<sup>1-6</sup>

The most common impact on the use of implants is a change in menstrual bleeding patterns. Other impacts that can arise include headaches, changes in mood, depression, nausea, changes in body weight, changes in reproductive hormone status, changes in carbohydrate metabolism and affect lipid metabolism.<sup>1,6</sup>

The LNG implant is a testosterone derivative that has a mineralocorticoid effect that affects extracellular fluid minerals so that this contraception can also cause an increase in body weight.<sup>1,7-11</sup>Changes in lipid metabolism in the form of elevated triglyceride levels, total cholesterol, LDL and decreased HDL accompanied by an increase in excess body weight are diagnostic criteria for metabolic syndrome which can increase the occurrence of type II diabetes mellitus and cardiovascular disorders. The lipid profile itself is the best predictor of metabolic syndrome. Therefore a study of the effect of Levonorgestrel implant on one rod with two rods on lipid profiles in acceptors is important.<sup>1,6</sup>

There was an increase in body weight in the use of levonorgestrel implants for 6 months (1.3 kg) and use of 12 months (2.4 kg). There was an increase in body weight (2.5 kg) during the 5-year use of levonorgestrel implants.<sup>10</sup> Estrogen is cardioprotective (protecting the heart) and anti-atherogenic (anti-fat formation), while progesterone is anti-estrogen. Changes in fat metabolism occur because of the hormonal influence of progesterone which causes a disruption in the balance of lipid profiles in the body. Changes in serum lipid profile (triglyceride, total cholesterol, HDL and LDL) in long-term use of LNG are risk factors for atherosclerosis (accumulation of fat in the arterial wall) and cardiovascular.<sup>1-3,7-11</sup>Two-rod implant contraception, for example Jadena and Norplant 2 rods. Jadena is a type of LNG implant consisting of two flexible rods and inside each of them contains 75 mg of levonorgestrel. The implant rod is wrapped in a thin-walled silicone tube which at the ends is covered with medical-grade adhesive silastic (poly dimethyl-siloxane). His working period is 5 years. Whereas Norplant has 2 soft hollow silasticrods with a length of about 3.4 mm, and a diameter of 2.4 mm, which contains 36 mg of levonogestrel in the form of crystals which are placed in the interior of the capsule and the working period is 3 years.<sup>4,12-14</sup>One-rod implant contraception, for example Implanon is a single implant containing etonogestrel 68 mg wrapped in an ethylene vinyl acetate membrane. His working period is 3 years. On average in the first 6 weeks the hormone is released from 60 to 70 mcg / day, down to 35-45mcg / day at the end of the first year of use. The average hormone is released 30-40 mcg / day in the second year and at the end of the third year the hormone is released to 25-30 mcg / day.<sup>15</sup>

The advantage of a single-rod implant is the lower dose so that the level of levonorgestrel in syrodic circulation is lower, where the dose is expected to have a better effect than two-rod implants such as changes in lipid profile or side effects such as changes in menstrual pattern or blood pressure more beneficial to users but still can prevent the occurrence of pregnancy. This is similar to the effect of levonorgestrel in the vaginal ring and Mirena IUD which only contains 52 mg of levonorgestrel released in small doses (20 µg / day initially and decreases to around 10 µg / day after five years).<sup>14,15</sup>

## METHODS

This study is a phase III clinical trial, "Open" (Open Randomized Clinical Trial), carried out randomization by comparing two types of implant KB, namely levonorgestrel implants, one rod with two rods. This research was conducted at the RSAB Rika Amelia Palembang. Research time is 6 months from November 2018 - April 2019 or until the number of samples is fulfilled. The study sample was women of childbearing age and wanted to postpone or extend their pregnancies up to three years using implant contraception. The inclusion criteria in this study were couples of reproductive age 18-40 years and in good health, not pregnant, getting an explanation and understanding the objectives, risks and benefits of the study, and signing informed consent, subjects willing to return to the clinic, to make a repeat visit according to schedule and willing to only use implants as contraception during the study. The exclusion criteria in this study were a woman who had a history or event such as having experienced contraindications for long-term hormonal contraception including vaginal bleeding with unclear causes, bloody discharge from the nipple, breast cancer or other cancers that are related to hormone dependence, uterine bleeding with unclear causes, thromboembolic disorders or thrombophlebitis or there is a history of both diseases, acute liver disease or liver tumour, possible pregnancy, pregnancy, breastfeeding have a history of idiopathic intracranial hypertension, history of coronary heart disease, cerebral vascular disease, and hypersensitivity to levonorgestrel or other components of the drug. There is a history of hepatitis, diabetes mellitus, depression or other mental disorders and epilepsy.

Blood pressure more than 180/100 mmHg. The study subjects were suspected of being diagnosed as Pelvic Inflammatory Disease (PID). Severe hirsutism. Routine therapy with enzyme-stimulating drugs, such as barbiturates, phenytoin carbamazepine or rifampicin. Women with symptoms of amenorrhea total more than one year while using implants or other hormonal contraceptives. Have not experienced menstruation after giving birth. Have not had menstruation in the past 6 months after using injectable contraception or pills and are currently participating in other studies in the last 3 months.

## Work Procedures

The first step is identification of the patient including name, age, sex, address, diagnosis, education, occupation and income, special history (obstetric and gynecological history (parity, first day of last menstruation), history of previous illness, condition, blood pressure, pulse. The patient's next procedure is the determination of nutritional status by measuring the weight and height of the pretreatment and the third month, height and weight measured by researchers assisted by paramedics, standing position and using microtoire. The purpose of the study was briefed and informed to the patients. Patients who agreed to participate in the study were asked to sign the agreement provided for this study.

All patients who were included in this then get a random number, and they would get one of the treatment methods KB (one or two LNG implants) which was in accordance with the list of random numbers. The next step is the assessment of the working effect of one or two LNG implants in the acceptor's lipid profile. This was collected by recording the acceptors' body weight, menstrual patterns, total cholesterol, triglycerides, LDL and HDL after evaluation of blood serum examination from the lab. Finally, acceptors from both treatments were tested on their FSH and estradiol levels in the blood.

## RESULTS

Phase III clinical trials with Open Randomized Clinical Trial to determine the differences in the effects of one-rod and two-rod levonorgestrel implants on FSH and estradiol levels and increase in acceptor lipid profile after 3 months evaluation at RSAB Rika Amelia Palembang from October 2017 to April 2018. 38 people met the inclusion and exclusion criteria, 19 people received one-rod levonorgestrel implants (one rod LNG) and 19 others received two-levonorgestrel implants (two-rod LNG).

### General Characteristics of Research Subjects

The general characteristics of the research subject are shown in table 5. Based on the installation time, the average time of installation using one rod LNG implant was  $1.54 \pm 0.11$  minutes and the two-rod implant was  $2.49 \pm$

0.26 minutes. Based on age, it was found that the average age of respondents using LNG one implant was  $31.89 \pm 4.97$  years with the most age group being 20-35 years (68.4%) while the average age of respondents using two-rod.

LNG implants was  $30.79 \pm 4.43$  years with the most age group being 20-35 years (84.2%). The statistical test showed that there was no differ-

ence in age ( $p = 0.474$ ) or age group ( $p = 0.447$ ) between respondents who used LNG implants in one rod and two rods. In this study, the majority of parity respondents both using one rod of LNG implants (57.9%) and two rods (68.4%) were  $\geq 3$ . With statistical tests it was found that there was no difference in parity between respondents using one LNG implant and two rods ( $p = 0.737$ ).

**Table 1.** General Characteristics of Research Subjects

Variabel	Levonorgestrel		P-value
	One Rod	Two Rod	
<b>Installation Time</b>			
Mean $\pm$ SD	1.54 $\pm$ 0.11	2.49 $\pm$ 0.26	0.000 <sup>d</sup>
Median (Min-Max)	1.52 (1.48 - 2.00)	2.53 (1.49 - 3.00)	
<b>Age</b>			
Mean $\pm$ SD	31.89 $\pm$ 4.97	30.79 $\pm$ 4.43	0.474 <sup>a</sup>
Median (Min-Max)	31 (23 - 39)	32 (21-36)	
<b>Age, n(%)</b>			
20-35	13 (68.4)	16 (84.2)	0.447 <sup>b</sup>
> 35	6 (31.6)	3 (15.8)	
<b>Parity, n(%)</b>			
0	8 (42.1)	6 (31.6)	0.737 <sup>c</sup>
1-2	11 (57.9)	13 (68.4)	
<b>Education, n(%)</b>			
Low	11 (57.9)	12 (63.2)	1.000 <sup>c</sup>
High	8 (42.1)	7 (36.8)	
<b>Blood Pressure</b>			
Normal	17 (89.5)	13 (68.4)	0.111 <sup>e</sup>
Hypertension	2 (10.5)	6 (31.6)	
<b>Menstruation Cycle</b>			
Regular	16 (84.2)	7 (36.8)	0.007 <sup>b</sup>
Irregular	3 (15.8)	12 (63.2)	
<b>Body Mass Index</b>			
Mean $\pm$ SD	24.19 $\pm$ 3.93	25.09 $\pm$ 6.11	0.965 <sup>d</sup>
Median (Min-Max)	23.2 (19.3 - 35.9)	23.1 (17.8 - 39.3)	
<b>Body Mass Index, n(%)</b>			
Underweight	0 (0)	1 (5.3)	0.595 <sup>e</sup>
Normoweight	9 (47.4)	8 (42.1)	
Overweight	5 (26.3)	3 (15.8)	
Obese	5 (26.3)	7 (36.8)	

<sup>a</sup>Independent T Test,  $p = 0.05$ , <sup>b</sup>Uji Fisher Exact,  $p = 0.05$ , <sup>c</sup>Chi Square test,  $p = 0.05$ , <sup>d</sup>Mann Whitney test,  $p = 0.05$ , <sup>e</sup>Pearson Chi Square test,  $p = 0.05$

Based on education, it was found that the majority of patients had a low level of education both in the one implant LNG group (57.9%) and two rods (63.2%). Based on statistical tests the results showed no difference in education between respondents using one rod LNG implants and two rods ( $p = 1.000$ ). Based on blood pressure, the majority of patients had normal blood pressure of 89.5% in one rod LNG and 68.4% in two-rod LNG, with statistical tests showing no relationship between blood pressure and type of implant ( $p = 0.111$ ). Based on the menstrual pattern, it was found that 84.2% of subjects had regular menstrual patterns

and 15.8% had irregular menstrual patterns in one LNG group, whereas 36.8% of subjects had regular menstrual patterns and 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there was a correlation between menstrual pattern and implant type ( $p = 0.007$ ).

The mean Body Mass Index (BMI) of respondents using LNG implants in one rod was  $24.19 \pm 3.93$  kg / m<sup>2</sup> with the highest BMI category being normoweight (47.4%) while the BMI average of respondents using two-implant LNG was  $25, 09 \pm 6.11$  kg / m<sup>2</sup> with the highest

BMI category normoweight (42.1%). With statistical tests, it was found that there was no difference in BMI ( $p = 0.965$ ) or BMI category ( $p = 0.595$ ) among respondents who used one-rod implant and two LNG implants.

### Laboratory Characteristics of Research Subjects

The laboratory characteristics of the research subject can be seen in table 6. Based on statistical tests there were no differences in lipid profiles before treatment of both cholesterol ( $p = 0.260$ ), HDL ( $p = 0.989$ ), LDL ( $p = 0.791$ ) and triglycerides ( $p = 0.447$ ) between the two group of respondents.

**Table 2.** Laboratory Characteristics of Research Subjects

Variabel	Levonorgestrel		P-value
	One Rod	Two Rod	
<b>Total cholesterol</b>			
Mean $\pm$ SD	234.4 $\pm$ 30.9	246.7 $\pm$ 35.00	0.260 <sup>a</sup>
Median (Min-Max)	235.4 (191.1-308.9)	240.5 (196.1 – 326.2)	
<b>HDL</b>			
Mean $\pm$ SD	66.10 $\pm$ 10.63	66.05 $\pm$ 13.94	0.989 <sup>a</sup>
Median (Min-Max)	67.3 (44.9 – 88.4)	65,7 (44.1 – 94.7)	
<b>LDL</b>			
Mean $\pm$ SD	103.5 $\pm$ 20.88	105.28 $\pm$ 19.38	0.791 <sup>a</sup>
Median (Min-Max)	98.9 (68.1 – 150.4)	101.1 (75.1 – 137.6)	
<b>Triglycerides</b>			
Mean $\pm$ SD	31.89 $\pm$ 4.97	30.79 $\pm$ 4.43	0.737 <sup>b</sup>
Median (Min-Max)	31 (23-39)	32 (21-36)	
<b>FSH</b>			
Mean $\pm$ SD	4.93 $\pm$ 2.63	5.28 $\pm$ 3.45	0.673 <sup>a</sup>
Median (Min-Max)	5.11 (0.81 – 12.0)	4.94 (0.87 – 15.1)	
<b>Estradiol</b>			
Mean $\pm$ SD	33.52 $\pm$ 37.77	19.74 $\pm$ 9.99	0.215 <sup>b</sup>
Median (Min-Max)	18.91 (13.42 – 163.9)	17.7 (10.18–49.84)	

<sup>a</sup>Independent T Test,  $p = 0,05$ , <sup>b</sup>Mann Whitney test,  $p = 0,05$

Likewise with the levels of FSH and estradiol before treatment, it was found that there were no differences in FSH levels ( $p = 0.673$ ) or estradiol ( $p = 0.215$ ) between respondents using one-rod implant and two LNG implants.

### Difference in Effectiveness of Use of One-Rod and Two-LNG LNG Implants on Lipid Profiles

The study found a significant reduction in

cholesterol after 3 months both after the use of one rod of LNG ( $p = 0.000$ ) and two rods ( $p = 0,000$ ), there was a significant decrease in HDL after 3 months both after the use of one rod LNG ( $p = 0.000$ ) or two ( $p = 0.000$ ), there was a significant reduction in LDL after 3 months both after the use of one rod LNG ( $p = 0.040$ ) and two rods ( $p = 0.000$ ), and a significant increase in triglycerides after 3 months after the use of one rod LNG ( $p = 0.687$ ) or two rods ( $p = 0.543$ ).

**Table 3.** Effectiveness of the Use of One-Rod and Two-LNG LNG Implants on Lipid Profiles

Variable	One Rod			Two Rod			
	before	after	p-value	before	after	p-value	p-value
Cholesterol	234.4 $\pm$ 30.9	155.9 $\pm$ 30.9	0.000 <sup>a</sup>	246.7 $\pm$ 30.9	159.3 $\pm$ 32.9	0.000 <sup>b</sup>	0.919 <sup>c</sup>
HDL	66.1 $\pm$ 10.6	45.9 $\pm$ 8.8	0.000 <sup>a</sup>	66.0 $\pm$ 13.9	47.4 $\pm$ 12.5	0.000 <sup>b</sup>	0.793 <sup>c</sup>
LDL	103.5 $\pm$ 20.9	92.9 $\pm$ 23.7	0.040 <sup>a</sup>	105.3 $\pm$ 19.4	94.2 $\pm$ 16.6	0.000 <sup>a</sup>	0.851 <sup>d</sup>
Triglycerides	94.5 $\pm$ 53.9	946 $\pm$ 34.2	0.687 <sup>b</sup>	95.4 $\pm$ 45.5	99.3 $\pm$ 35.9	0.543 <sup>a</sup>	0.679 <sup>d</sup>

<sup>a</sup>Paired T Test,  $p = 0,05$ , <sup>b</sup>Uji Wilcoxon,  $p = 0.05$ , <sup>c</sup>Mann Whitney test,  $p = 0.05$ , <sup>d</sup>Independent T Test,  $p = 0.05$

In addition, it was found that there were no differences in cholesterol levels ( $p = 0.919$ ), HDL ( $p = 0.793$ ), LDL ( $p = 0.851$ ) and triglycerides ( $p =$

0.679) among respondents using one rod implant and two LNG implants.



### The difference in the Effectiveness of Using One-Rod LNG Implants and Two-Rod LNG Implants on FSH and Estradiol

The results showed that there was no

significant decrease in FSH levels before and 3 months after using one rod of LNG ( $p = 0.063$ ), but it was found that there was no significant decrease in estradiol levels before and 3 months after using one rod of LNG ( $p = 0.059$ ).

**Table 4.** Effectiveness of the Use of the One-Rod and Two-Rod LNG Implants against FSH and Estradiol

Variable	LNG One-Rod			LNG Two-Rod			p-value
	before	after	p-value	before	after	p-value	
FSH	4.93 ± 2.63	4.15 ± 1.96	0.063 <sup>a</sup>	5.28 ± 3.45	4.43 ± 2.14	0.117 <sup>b</sup>	0.849 <sup>c</sup>
Estradiol	33.52 ± 37.77	21.86 ± 12.07	0.059 <sup>b</sup>	19.74 ± 9.99	18.32 ± 10.79	0.295 <sup>b</sup>	0.099 <sup>c</sup>

<sup>a</sup>Paired T Test,  $p = 0.05$ , <sup>b</sup>Wilcoxon test,  $p = 0.05$ , <sup>c</sup>Mann Whitney test,  $p = 0.05$

In addition, it was found that there was no significant decrease in FSH levels before and 3 months after using two rods of LNG ( $p = 0.117$ ), other than that there was a significant decrease in estradiol levels before and 3 months after the use of LNG in two rods ( $p = 0.295$ ). In this study, it was also found that there were no significant differences in FSH levels between respondents using one-rod and two-rod LNG implants ( $p = 0.849$ ), respondents who used two-rod LNG had higher FSH levels than respondents using one-rod LNG but not meaningful. In addition, it was found that there were no significant differences in estradiol levels between respondents using one-rod and two-rod LNG implants ( $p = 0.099$ ), respondents who used two-rod LNG had lower estradiol levels than respondents using one-rod LNG but were not significant.

## DISCUSSION

Contraception is efforts made to prevent pregnancy, both temporary and permanent. Implants are hormonal contraceptives that are implanted under the skin (subdermal) and used for a long time. This contraception contains bioactive progestin levonorgestrel (LNG) ingredient, a steroid hormone that is a derivative of 19-nortestosterone. LNG has activities similar to progesterone with weak androgenic activity and has no estrogenic activity.<sup>1,2</sup>

Levonorgestrel is a progestin hormone which is a derivative of 19-nortestosterone. As an active contraceptive implant substance, levonorgestrel is a steroid hormone with strong progesterone activity and weak androgen activity, the chemical formula of the hormone. There are two types of Levonorgestrel implant contraceptives, one LNG rod and two rods. In this study, several samples were taken at different times. A total of

21 samples were implanted with implants on 15 December 2018 and 17 samples were installed on January 5, 2019. Sampling was carried out at the RSAB Rika Amelia Palembang. There were 21 samples that met the research criteria and were willing to take part in the study from 50 samples. The second sample was taken in a different place and 17 samples that met the study criteria were obtained.

In this study, it was found that the average installation time required for one rod LNG was  $1.54 \pm 0.11$  minutes and for LNG two rods was  $2.49 \pm 0.26$  minutes. From the data above we can see that the installation of one rod of LNG is faster than with two LNG. If viewed from the cost, LNG one rod only requires local anesthetic in the form of one ampoule lidocaine, while LNG for two rods requires two ampoules of lidocaine. There are no other differences either from the use of alcohol cotton, plaster, or syringes between the one rod LNG group and the two rod LNG. From this study it was also found that there was no difference between changes in blood pressure in the LNG group of one rod and LNG in two rod.

Implanted KB acceptors in the study were approximately 31 years old with the majority of the age categories 20-35 years (76.3%). The results of showed the percentage of implant KB acceptors aged 20-35 years was 54.8%. Study in 2017 showed an average age of patients using implants of approximately 34.3 years. The type of contraception used should be adjusted to the stage of reproduction.<sup>16</sup>Age 20-35 years is a period of reproductive life so the choice of contraception used is oral contraception or implant.

The majority of implantable KB acceptors parity  $\geq 3$  (63.2%) with a mean parity of 3.07

$\pm 1.02$ . This result is not much different from the research in 2017 where the implant parity acceptor implies a mean of  $3.0 \pm 2.0$ . The more often a woman gives birth to a child, the more risks she will have in childbirth. This means that the number of children will greatly influence the choice of mothers to choose contraception.<sup>16</sup> In couples with a small number of children (3 children or less) there is a tendency to use low-effectiveness contraceptives, namely pills and condoms, whereas if the child is felt quite a lot, a higher effectiveness contraceptive device will be used such as implants.

Based on blood pressure, the majority of patients had a normal blood pressure of 89.5% in one rod LNG and 68.4% in two rod LNG, with statistical tests showing that there was no correlation between blood pressure and implant type ( $p = 0.111$ ). Based on the menstrual pattern, it was found that 84.2% of subjects had regular menstrual patterns and 15.8% had irregular menstrual patterns in one LNG group, whereas 36.8% of subjects had regular menstrual patterns and 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there was a correlation between menstrual pattern and implant type ( $p = 0.007$ ).

In this study, it was found that LNG was associated with changes in menstrual patterns, both the use of one rod of LNG and two rods. Descriptively, there were 63.2% of subjects who had irregular menstrual patterns. The possibility of side effects that can occur is irregular menstruation. This is because LNG does not contain estrogen, which causes disruption of the menstrual cycle. Most women can know some variations in menstrual patterns. The use of Jadelle contraception has almost the same side effects as the use of Norplant contraception in the form of irregular menstrual bleeding, prolonged bleeding or spots (longer than a woman usually experiences), heavy bleeding, bleeding or spots between periods, no bleeding at all for several months, or a combination of these patterns. Hypertension can occur in 1.0% - 9.9% of women who use LNG contraception. However, this study did not show a significant relationship between hypertension and use of LNG contraception.<sup>6,17,18</sup>

In the distribution of subjects according to implant type and BMI, there was a mean BMI

in one rod of LNG before and after implant placement at  $24.16 \pm 3.97$  kg / m<sup>2</sup> and  $23.79 \pm 4.09$  kg / m<sup>2</sup>. While the mean BMI for LNG in the two rods before and after implant placement was  $25.21 \pm 6.01$  kg / m<sup>2</sup> and  $26.21 \pm 6.60$  kg / m<sup>2</sup>. Descriptively, LNG of two rods showed an increase in body weight of 1 kg / m<sup>2</sup> where one rod of LNG decreased BMI by 0.37 kg / m<sup>2</sup>. This result is different from the results of a study that there was a weight loss of 0.33% in the use of 2 rod LNG. Although there was an increase in BMI on 2-rod LNG, did not find any significant differences. The results of this study on IMT cannot be concluded, because the increase in BMI was influenced by dietary patterns not assessed in this study.<sup>6,19</sup>

In the distribution of subjects according to implant type and cholesterol, there was a mean cholesterol in the type of LNG 1 rod before and after implant placement was  $234.42 \pm 30.99$  mg / dL and  $155.86 \pm 30.94$  mg / dL. While the mean cholesterol in 2 rod LNG before and after implant placement was  $246.68 \pm 35.01$  mg / dL and  $159.32 \pm 32.85$  mg / dL. In this study there was a significant reduction in cholesterol levels in the group that received one rod and two LNG but there was no difference between the two groups. Descriptively, one rod LNG showed a decrease of 78.56 mg / dL, while LNG for two bars showed a decrease of 87.36 mg / dL. Two more LNG trunks show a larger decrease compared to one rod LNG. Research in 2017 showed an increase in total cholesterol levels after 6 and 12 months of implant placement, but decreased after 24 months. The difference obtained is probably because in this study the follow-up was carried out for 3 months. There was a decrease in cholesterol after LNG use after 3 months with a p value of  $<0.05$  and a mean cholesterol value of  $141.17 \pm 14.67$  mg / dL.<sup>18,20</sup>

In the distribution of subjects according to implant type and HDL in the blood, there was a mean HDL in LNG rods before and after implant placement was  $66.10 \pm 10.62$  mg / dL and  $45.94 \pm 8.79$  mg / dL. While the mean HDL in 2-rod LNG before and after implant placement was  $66.05 \pm 13.95$  mg / dL and  $47.40 \pm 12.53$  mg/dL. Descriptively, one rod of LNG showed a decrease in HDL of 20.16 mg / dL, while LNG of two rods showed a decrease in HDL of 18.65 mg / dL. One rod LNG showed more levels of HDL decrease. In the distribution of subjects according to implant

type and LDL in the blood, there was a mean LDL in implant type 1 rod before and after implant placement was  $103.54 \pm 20.88$  mg / dL and  $92.92 \pm 23.68$  mg / dL. While the mean LDL in the 2-rod implant type before and after implant placement was  $105.28 \pm 19.38$  mg / dL and  $94.18 \pm 16.56$  mg / dL. Descriptively LNG one rod showed a decrease of 10.62 mg / dL, while LNG for two rods showed a decrease of 11.1 mg / dL. Two more LNG LNG showed a decrease in LDL compared to one rod LNG.

There was a significant reduction in HDL and LDL in the group that received one rod and two LNG LNG but there was no difference between the two groups. In 2017 LDL reduction was found after 6, 12 and 24 months but there was an increase in HDL levels, this is different from the results of this study. Dash's research found that there was a significant decrease in HDL after the installation of 2-rod LNG within 3 months with a value of  $p = 0.02$  and an average HDL level of  $40.00 \pm 8.65$  and a significant decrease in LDL after installation of 2-rod LNG within 3 months with  $p = 0.05$  and the mean LDL level was  $92.33 \pm 11.60$ .<sup>18,20</sup>

In the distribution of subjects according to implant and triglyceride types, there were mean triglycerides in LNG 1 rod before and after implant placement were  $94.46 \pm 53.87$  mg / dL and  $94.58 \pm 34.23$  mg / dL. While the mean of triglycerides in 2 rod LNG before and after implant placement was  $95.38 \pm 45.48$  mg / dL and  $99.33 \pm 35.93$  mg / dL. Descriptively, one rod LNG showed an increase of 0.12 mg / dL, while LNG for two bars showed an increase of 3.95 mg / dL. LNG of two rods showed an increase in triglycerides compared to one rod LNG. In this study there was an increase in triglyceride levels both in the group that received one rod and two LNG LNG but the increase that occurred was not statistically significant. The increase in the LNG group of two rods was greater than that in the one-rod LNG group but was not significant. These results are in line. Study in which triglyceride levels increased after administration of implants for 6, 12 and 24 months. There was a significant decrease in triglycerides after the installation of 2-rod LNG within 3 months with a  $p$  value of  $<0.01$  and the average triglyceride level was  $76.65 \pm 19.95$ .<sup>18,20</sup>

Changes in fat metabolism in hormonal

contraceptive use are caused by estrogen and progesterone, each of which has a different effect. Estrogen is cardioprotective (protecting the heart) and antiatherogenic (anti-fat formation), while progesterone is anti-estrogen. The use of a single estrogen will reduce the activity of the lipoprotein lipase enzyme, increase HDL cholesterol levels and reduce LDL cholesterol levels. The effect of progesterone is precisely inversely proportional to the effect of estrogen, and this effect depends on the potential of the androgen. The stronger the androgen potential, the greater the adverse effect on fat metabolism.<sup>3,7-9,11</sup>

The mineral corticoid effects of LNG implants can cause weight gain. Weight gain is one of the causes of an increase in triglyceride levels and a decrease in HDL levels that occurred in this study, but it is different with decreasing total cholesterol and LDL levels.

Some of the results of this study are different from previous studies. Research in Ghana shows that hormonal contraception can increase BMI, diastolic blood pressure, total cholesterol levels, LDL cholesterol levels and reduce HDL cholesterol levels in the blood. Where this change is a potential risk factor for developing cardiovascular disease.<sup>8</sup> Research at the Benin Teaching Hospital, Nigeria showed that Implanon had an effect on lipid metabolism, there was a significant decrease in HDL and an increase in LDL levels in the 6th and 12th months.<sup>10</sup> The differences that occur in this study are likely because the patient's follow-up time is too short.

In the distribution of subjects according to implant type and FSH, there was a mean FSH for implant types 1 rod before and after implant placement was  $4.93 \pm 2.63$  and  $4.15 \pm 1.96$ . While the mean FSH for 2-rod implant types before and after implant placement was  $5.29 \pm 3.46$  and  $4.44 \pm 2.14$ . Descriptively, one rod LNG showed a decrease in FSH of 0.78, while LNG of two rods showed a decrease in FSH of 0.85. Two more LNG LNG showed a decrease in FSH compared to one rod LNG. From the results of the analysis, it was found that there was a significant decrease in FSH levels after the installation of one rod LNG implant or two rods for 3 months. In the distribution of subjects according to implant and estradiol types, there were Estradiol meanings on the type of implant 1 rod before and after implant



placement  $33.52 \pm 37.77$  and  $21.86 \pm 12.07$ . While the Estradiol mean on the 2-rod implant type before and after implant placement was  $19.74 \pm 9.99$  and  $18.32 \pm 10.79$ . Descriptively, one rod LNG showed a reduction in Estradiol of 11.66 while the LNG of two rods showed a decrease in Estradiol of 1.42. There is a greater decrease in one-rod LNG with Estradiol levels. From the results of the analysis it was also found that there was no significant decrease in estradiol levels after the installation of one rod LNG implant or two rods for 3 months.

In two-rod implants that are effective for 5 years, levonorgestrel will be released as much as 50-80  $\mu\text{g}$  / day for the first year of installation and release the following year until the 5th year of use is 30-35  $\mu\text{g}$  / day.<sup>4,5</sup> Whereas on one rod implant the average in the first 6 weeks of the hormone is released from 60 to 70 mcg / day, down to 35-45mcg / day at the end of the first year of use. The main working mechanism of LNG is to inhibit ovulation in about 50% of the menstrual cycle. A small amount of LNG released from the implant continuously will work in the hypothalamus and anterior pituitary gland. Furthermore, there is a decrease in FSH secretion (follicle stimulating hormone) and LH (lutening hormone). LNG will inhibit or reduce LH surge in the middle of the cycle. The anterior pituitary sex hormone, Follicle Stimulating Hormone (FSH) is secreted in response to hypothalamic hormones. FSH functions to stimulate the ovaries to produce steroids. Steroid hormones have a large effect on the menstrual cycle, where estrogen is produced in the follicular and progesterone phases during the luteal phase of the ovary. Estrogen has a strong effect on inhibiting LH and FSH production. The effect of inhibiting estrogen will increase if there is progesterone, although the progesterone itself has only a small effect.<sup>16-18,20,21</sup>

Whereas on one rod implant the average in the first 6 weeks of the hormone is released from 60 to 70 mcg / day, down to 35-45mcg / day at the end of the first year of use. The main working mechanism of LNG is to inhibit ovulation in about 50% of the menstrual cycle. A small amount of LNG released from the implant continuously will work in the hypothalamus and anterior pituitary gland. Furthermore, there is a decrease in FSH secretion (follicle-stimulating hormone) and LH (lutening hormone). LNG will inhibit or reduce LH surge in

the middle of the cycle. The anterior pituitary sex hormone, follicle-stimulating hormone (FSH) is secreted in response to hypothalamic hormones. FSH functions to stimulate the ovaries to produce steroids. Steroid hormones have a large effect on the menstrual cycle, where estrogen is produced in the follicular and progesterone phases during the luteal phase of the ovary. Estrogen has a strong effect on inhibiting LH and FSH production. The effect of inhibiting estrogen will increase if there is progesterone, although the progesterone itself has only a small effect.

## CONCLUSION

There is no difference between the use of one-stem and two-stem levonorgestrel implants against FSH, Estradiol levels and increased lipid profile after 3 months of implant installation with a value of  $p = 0.673$ ,  $p = 0.215$ ,  $p = 0.260$ ,  $p = 0.989$ ,  $p = 0.791$ . The unpleasant effect in this study was the decline in HDL, but this was accompanied by a decrease in body weight, total cholesterol, LDL, HDL due to a decrease in all aspects.

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