Research Article

Profile Changes in Weight and Body Mass Index of Single Rod Levonorgestrel Implant Acceptor (Monoplant®)

Profil Perubahan Berat Badan dan Indeks Massa Tubuh Akseptor Implan Levonorgestrel Satu Batang (Monoplant®)

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Abstract

Objective: To finding out the change of weight and body mass index (BMI) of single rodlevonorgestrel implant acceptor (Monoplant®).

Methods: A cross-sectional descriptive study was conductedusing data changes of weight and BMI obtained from series of measurement which is recorded in patients' medical record in three years of Monoplant® placement in Raden Saleh Clinic, Jakarta. This method is the part of a research of a bigger phase two in clinical test.

Results: From 21 subjects of this research, the average weight and BMI before and after 3 years of Monoplant® placement is gained, i.e. 53.1 (SD 11,0) kg and 22.4 (SD 4.5) kg/m2, and 54.8 (SD 9.4) kg and 23.1 (SD 3.9) kg/m2. Despite the tendency of increasing, statistically the increasing of weight and BMI, however, is meaningless (p=0.09) and (p=0.08). There is a difference of weight in series of measurement, particularly after the 12th month (Repeated test ANOVA p=0.024). Even though there is no difference in BMI average, there is a difference in subject's proportion based on BMI categories before and after Monoplant® placement (Marginal homogeneity test p=0.046). The increasing of levonorgestrel level occurs in the 6th month and subsequently followed by the increase of BMI in the 12th month.

Conclusions: There is a tendency of increasing weight and BMI in Monoplant® users, specifically after one year despite statistically insignificant.

Keywords: levonorgestrel, monoplant®, weight, body mass index.

Abstrak

Tujuan: *Untuk mengetahui perubahan berat badan dan indeks massa tubuh pada akseptor implan levonorgestrel satu batang (Monoplant®).*

Metode: *Studi deskriptif dengan desain potong lintang mengambil data perubahan BB dan IMT diperoleh dari pengukuran serial yang tercatat dalam rekam medis pasien selama tiga tahun pemasangan Monoplant® di Klinik Raden Saleh, Jakarta. Penelitian ini merupakan bagian dari suatu penelitian uji klinis fase 2 yang lebih besar.*

Hasil: *Dari 21 subjek penelitian ini, didapatkan rerata BB dan IMT sebelum dan setelah 3 tahun pemasangan Monoplant®yakni 53,1 (SB 11,0) kg dan 22,4 (SB 4,5) kg/m2, serta 54,8 (SB 9,4) kg dan 23,1 (SB 3,9) kg/m2. Meskipun ada kecenderungan naik, tetapi secara statistik kenaikan BB dan IMT tersebut tidak bermakna (p=0,09) dan (p=0,08). Terdapat perbedaan berat badan dalam pengukuran serial, terutama setelah bulan ke-12 (Uji repeated ANOVA p=0,024). Walaupun tidak terdapat perbedaan rerata IMT, terdapat perbedaan proporsi subjek berdasarkan kategori IMT sebelum dan setelah pemasangan Monoplant® (Uji Marginal homogeinity p=0,046). Peningkatan kadar levonorgestrel terjadi pada bulan ke-6 yang kemudian diikuti oleh kenaikan IMT pada bulan ke-12.*

Kesimpulan: *Terdapat kecenderungan peningkatan BB dan IMT pengguna Monoplant®, khususnya setelah satu tahunmeskipun secara statistik tidak bermakna.*

Kata kunci: *berat badan, indeks massa tubuh, levonorgestrel, monoplant®.*

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INTRODUCTION

Indonesia is a developing country that has many problems, including the high rate of population growth, making it challenging to create the improvement of public welfare distribution. Survey results from Indonesian Demographic and Health (IDHS) in 2007 showed a stagnation of family planning programs that can be seen from the low increase in the contraceptive prevalence rate of 60.3% in the period 1997-2003 to 61.4% 2003-2007. By creating the nation's contraception that is comfortable, and affordable, hopefully, it can be accepted and widely used as a method of contraceptive choice for family planning acceptors in Indonesia. [1-4]

One of the contraceptives in Indonesia is an implant that can be used for a long term, it is highly effective and reversible, known as implantable contraceptives implant contraception or Alat Kontrasepsi Bawah Kulit (AKBK) in Indonesia. These implants have been widely used in the world by millions of women over the last three decades. In comparison with another contraceptive, the implant has the lowest failure rate in the first year of use. [5-7]

Norplant® is a contraceptive implant used in Indonesia; it was studied for the first time in 1981 and had been approved its use by the Ministry of Health in 1986. The birth control implant consists of a package of six capsules containing the active ingredient of levonorgestrel(LNG). [8,9] Nowadays, Indonesia has developed Monoplant®; it is an implant comprising the same hormones with Norplant® with only single rod packaging. It is expected that Monoplant® can be one of more desirable contraceptives for family planning acceptors.

In society, some complaints in selecting contraceptives are associated with the side effects of its use. One of the concerns from this study is about the weight gain associated with the use of hormonal contraceptives. The side effects usually occur in the early month of use. [10] There is no study of weight change during use Norplant® in Indonesia until now. From the previous studies on the use of other contraceptive methods, etonogestrel, in the United States, 12% of the users complained about weight change, Croxato et al found 20% of its users experienced an increase in BMI more than 10% of baseline BMI prior installation. Populations in China who use Norplant® was experiencing 0.8 kg weight gain in the first year and gained 3.1 kg more in the fourth year, in line with the findings in the population of New York.[11,12]In contrast with the finding, there were no differences in body weight after one year of using levonorgestrel implants.[13] Another study in the UK found that around 5% of users decided not to continue the implant because the weight gains issue. [11]

This concern about body weight can prevent the continuation of the use of contraceptives and lead to discontinuation of the use at the beginning. From those various studies, the researcher wanted to know the purpose of Monoplant®, is there any increasing of weight and BMI and the relationship between the levels of levonorgestrel with the change, so that it can be used as the basic data in considering contraceptives for family planning acceptors in Indonesia.

THEORETICAL OVERVIEW

Implants are one of the most effective methods of contraceptives that are available. The implant consists of a silicone rod for releasing progestin into the woman's body from its insertion under the skin through a minor surgical process. The implant is safe, effective and it can be used for long term. The period of duration of protection depends on the specific progestin and the type of polymer implants.[14-16] Implant containing levonorgestrel can prevent pregnancy in several ways, including to prevent ovulation, thicken the cervical mucus and reduces the thickness of the endometrium. [15,16]

Progestin is a synthetic compound that mimics the effects of natural progesterone but has a slightly different chemical structure. This progestin effect interacts not only with the progesterone receptor but also with other steroid hormone receptors that are androgen receptor, estrogen or glucocorticoid mineralocorticoid. All of the progestin would bind the progesterone receptor, and it has an effect on the endometrium, but each type of progestin will have its own profile against the other targets. [16,17]

Norgestrel is a progestin hormone that is a part of a group of 19-nortestoteron which has

a mixture of isomers dextrorotation and levorotary. Dextrorotation is known as d-norgestrel and levorotary is known as l-norgestrel, namely levonorgestrel. From 19-nortestosterone derivative directly binds to the receptor, namely levonorgestrel and norethindrone, whereas desogestrel and etonogestrel require bioactivating in the liver before becoming an active metabolite.[16] LNG is a hormone that can be active biologically for the anti-fertility effectsand biologically active progestin synthesis if given subcutaneously, there is no effect on the liver, and its bioavailability is almost 100 percent.[17-19]

LNG is a progestin agonist that has more powerful androgen agonist than other types and has no anti mineralocorticoid effect. Progesterone receptor is generally binding in reproductive tissues, but unfavourable effects have much correlation with receptors in tissues non-reproduction. The increase of blood pressure, weight gain and risk of cardiovascular disease caused by a lack of receptor antagonist of receptor mineralocorticoid in the intestine and kidney. Aldosterone which is a ligand of mineralocorticoid receptor functioning in the absorption of sodium in the distal renal tubular. It is useful for the regulation of blood pressure, improving and preventing the retention of sodium, increasing the retention of aldosterone in a secondary way to trigger H_2O osmotic retention so that the extracellular fluid volume increases and causes weight gain. [20-22]

Monoplant® is the latest generation of a contraceptive implant consisting of a single rod implant that has 43 mm length, 2.5 mm diameter and containing 160 mg of LNG. This single rod system is projected to have efficacy for up to three years. Monoplant® is applied to the acceptor at Raden Saleh Clinic in Jakarta for approximately three years.

Weight is the amount of protein, fat, water and bone in the body that can be measured in kilograms. In normal adults, there is an increasing trend of accumulation of fat with age, along with the decreasing of muscle protein. Such changes can be seen by determining body fat or fat-free mass. Weight can only be used to measure the nutritional status of the subject without oedema, ascites, starvation, dehydration, massive tumour growth because it can provide an assessment that is less precise in measurement.[23,24]

To measure the change in body weight, the actual weight, and the weight should be acquired. Intake depends on the food consumption which is influenced by many factors such as financial situation, eating habit, appetite, culture, the ability to consume and absorb nutrients.[23-26]Nutritional needs are also influenced by various factors such as infections, acute or chronic illness, fever, trauma, normal growth, pregnancy, rehabilitation, psychological stress. Nutritional status is also an important factor in the prediction of the main causes of death, including cardiovascular disease, hypertension, cerebrovascular, and diabetes.[23-25]

An evaluation of the size of the human body known as anthropometry to measure body composition can be done in order to measure the nutritional status. Furthermore, to evaluate the nutritional status of individuals in the dimensional measurement and body composition, it involves physical measurement associated with the standard links with the growth or development of the individual, or to monitor the effects of an intervention on the nutritional status. [23,24,27]

The Body Mass Index is a measurement widely used to measure the nutritional status. It has been validated by the measurements taken by body weight in kilograms and height in m^2. BMI does not distinguish between weight associated with muscle and weight associated with body fat; in some circumstances, higher value may be obtained from the increase in adiposity, muscles or oedema. BMI has its limit because it does not give a picture of the distribution of body fat, but the validity of body mass index as the index of body fat percentage in adults that have been assessed by connecting it with a body mass index of obesity. [25,26]This measurement can be an indicator of body fat used in a simple, inexpensive and noninvasive way, becoming good measurement methods for health screening and risk. BMI measurement is influenced by some factors such as age, sex, ethnicity and muscle mass. [27,28]

In the population groups in Asia-Pacific region as shown in Table 1. Has body mass index value < 18,5 kg/m2 for underweight, 18.5 – 22.9 kg/m^2 for normalweight, ≥ 23 kg/m^2 for overweight and ≥ 25 kg/m^2 for obesity. There is an increasing risk of

morbidity from type II diabetes and hypertension in body mass index between 23 to 24.9 kg/m^2.[29]

Weight gain is one of the factors that influence the selection of contraceptives or to continue to use contraceptives.[30] The weight gain can be caused by several factors: fluid retention increased muscle mass or body fat accumulation. LNG is a synthetic progestin that has a chemical derivative testosterone structure that has the most powerful androgenic effects. Mineralocorticoid's effect on LNG acceptor can increase body weight through fluid retention due to stimulation of the renin-angiotensin mechanism. Earlier research in 2004 suggested that an increase in weight associated with the accumulations of body fat. The measurement of body mass index is done to measure these indicators objectively.[31]

Based on Cochrane systematic review, there was a slight weight gain on users of progestin-only contraceptive as one of side effects complained of by the patient. The weight gain is estimated at only about 2 kg in the first year of use. But the systemic review had a difficulty relating to the lack of prospective studies with good quality because the existing research just reported subjective complaints of weight gain generally without objective evidence of the measurement before and after monitoring. [31]

METHODS

This study is part of a larger study conducted by Gunardi ER. The study aims to determine the effectiveness of a single rod implant levonorgestrel through LNG levels measurement on the subject of reproductive age (20-40 years) with three years of use. The study was a phase 2 clinical test. While this study is a cross-sectional descriptive study that used Gunardi ER's secondary data research to determine the profile of changes in subject's body weight and body mass index after three years of LNG single rod implementation.[32]

Data collection was done through medical records of patients at the Raden Saleh Polyclinic. The target population is women who use single rodlevonorgestrel implants. Population achieved was the subject of phase 2 clinical test by Gunardi ER. The inclusion criteria were a mother who has measured her maternal weight and levels of its levonorgestrel regularly and routinely, and those who had medical records that are legible and clear. Did not have exclusion criteria. Consecutive sampling was done in this research, and it was taking all of the acceptor subjects to be a sample of the data until the data are met.

The research was started by doing a preparation to conduct discussions with the supervisor, and then collect data from medical records, processing data with data verification, editing and coding and data analysis will be performed using SPSS (Statistical Package for the Social Sciences, Chicago., Inc.) version 22 with the characteristics descriptive data presentation of the subject study, weight changes over time, significant changes to the subject of serial measurements of body weight in three years, mean comparison of weight and BMI pairing variable before and after three years of Monoplant® installation, and the BMI data presentation as categorical data.

RESULTS

This study has successfully collected 21 medical records of patients who became the subject of phase 2 clinical test previously. Researchers then extract the subject characteristics data and the weight data and calculated BMI of all subjects. All of the subjects then included in this analysis.

Table 1. Characteristics of Research Subject

Characteristics	V	%
Age (year), Mean (SD)	31.4 (5.6)	
Parity (median, min-max)	2 (1-5)	
1	7	33.3
2	5	23.8
> 2	9	42.9
Wants to have more children?		
Yes	6	28.6
No	15	71.4
Contraception that is used before		
Pill	4	19.0
Implant	2	9.5
Injection	12	57.1
AKDR	2	9.5
Never use any	1	4.8
Weight, Mean (SD)	53.1 (11.0)	
Height, Mean (SD)	153.86 (3.6)	

The mean age of reproductive women who is the subject of this study was 31.4 with SD (5.6) years. Most of the subjects already have more than 2 children (9 subjects, 42.9%). Furthermore, 71.4% of the subjects did not want more children. From the history of the contraceptive modalities before, 12 subjects (57.1%) using injectable hormonal contraceptive before following this study as shown in Table 1.

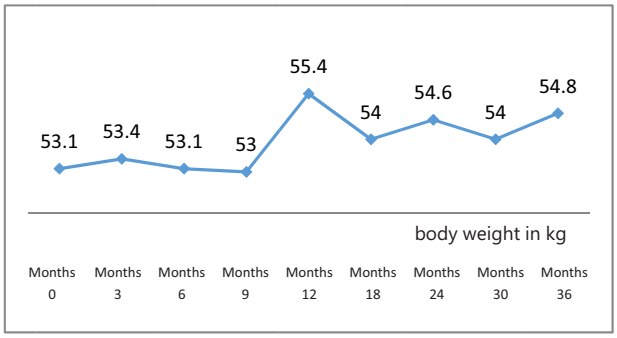

Figure 1. Mean weight subject from time to time during the three years of Monoplant® installation (n = 21)

The researcher found the trend change in the weight of all the research subjects. Prior to the Monoplant® installation, the average weight subjects were 53.1 (SD 11.0) kg. From time to time, there was a tendency for weight gain as seen in Figure 1. The biggest change occurred in the 12th month whereas previously (at 9th month) the average weight of all subjects was 53 kg, then changed to 55.4 kg. Mean weight in the third year was 54.8 (SD 9.4) kg.

ANOVA repeated test results with all of nine serial measurements of weight variables showed a significant change in the body weight during the three years of research period (p = 0.024). In particular, the results of paired-wise comparison of repeated ANOVA test showed significant differences in early weight with 12th month weight (p = 0.004), the 3rd month with 12th month (p = 0.006), 6th months with 12th month (p = 0.002), 9th month 12th month (p = 0.001) and 12th month with 18th month (p = 0.02).

Table 2. The Differences between Body Weight and BMI before and after Three Years of Monoplant®Installation

Variable	Before installation	After installation	*P-value*
Weight (kg),Mean (SD)	53.1 (11.0)	54.8 (9.4)	0,09
BMI(kg/m^2),Mean (SD)	22.4 (4.5)	23.1(3.9)	0,08

The increasing of weight and BMI prior to installation and after three years of Monoplant® use as shown in Table 2. Shows the average subject weight gain was 1.7 kg.

Table 3. Subject Frequency Distribution Based on Weight Change

Characteristics of weight change	V	%
Gaining	6	28.6
Constant	14	66.7
Losing	1	4.8

Total of six subjects (28.6%) experienced a weight gain while only one subject (4.8%) experienced weight loss as shown in Table 3.

Table 4. Test Result of BMI Change Marginal Homogeneity

		BMI after installation			Total	*P-value*
		Underweight	Normoweight	Over-obese		
BMI before installation	Underweight	2	2	0	4	0.046
	Normoweight	0	7	2	9	
	Over-obese	0	0	8	8	
Total		2	9	10	21	

There are differences in BMI categories subject before and after Monoplant® installation (p = 0.046). From the table 4 there is a trend of BMI increase based on the categorization of BMI subject.

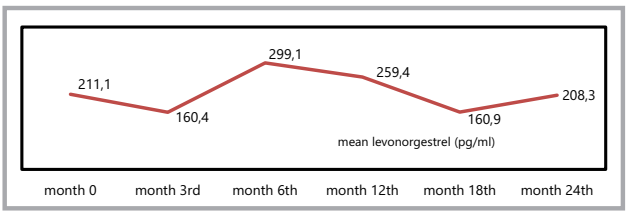

Figure 2. Mean Subject Levonorgestrel Level from Time to Time with Monoplant® Installation (n=21)

There are differences in BMI categories subject before and after Monoplant® installation (p = 0.046). From the table 4, there is a trend of BMI increase based on the categorization of BMI subject.

The levels of levonorgestrel subject of this study as seen in figure 2. Analysis of the correlation of LNG level at each measurement by weight found that there were negative correlation LNG levels on the 12th month with 12th-month weight (r = -0.611; p = 0.005) and BMI in the 12th month (r = -0.54; p = 0.016). This negative correlation remained visible until the 18th month with the acquisition of a significant negative correlation between the LNG levels on the 18th month with 18th-month weight (r = -0.52; p = 0.019) and BMI on the 18th month (r = -0.52; p = 0.018).

DISCUSSION

The main objective of this study is to assess weight and BMI change of patients with a single rod Monoplant® implant. The main result obtained is a weight gain based on serial measurements, especially after the 12 months since installation. In addition, there was an increased BMI subject based on classification comparison of BMI subjects before and after Monoplant® installation.

For data distribution of research shown in Table 1. The obtained reproductive age who are the subject of this study mean was 31.4 (5.6) years, with the majority already have more than 2 children (9 subjects, 42.9%) and 71, 4% of the subjects did not want more children. Therefore, we can see that from the subjects who wanted to use these implants expecting good contraception and enough to be used in the long term. For a history of the contraceptive modalities before, 12 subjects (57.1%) using injectable hormonal contraceptive before participating in the study. From previous studies, it was found that the subjects did not use hormonal contraception in the last six months so it should be stricter in selecting their hormonal effect before participating in the study. [33]

There was no significant change linked to weight and BMI numerical variables before and after the installation as shown in Table 1. However, if the observed trend of weight changes serially, there was a significant difference in weight before and after the 12th month as seen in figure 1.

In 2005 women's weight data distribution of the US population in 1999-2002 according to the CDC (in kilograms) by the age range obtained tendency to the addition of the average weight of the age range population 20-29 to 40-49 and will tend to decline over the age range of 50-59 years and older. This can be one of the data about weight gain judged by the increasing age. Distribution of a woman's Body Mass Index by the age range there was an increased but declined to the above age range of 60 and older. [34] In normal adults, there is a trend of increasing fat accumulation along with the increasing in age and decreasing of muscle protein. [22]

Increased weight change category as shown in Table 2 can be measured as an increase in weight change of subject 28.6% and 66.7% were constant. It is assessed according to research with the definition of the weight gain = increase ≥ 2.3 kg weight; constant = change of less than 2.3 kg weight; ≥ weight loss = losing of 2.3 kg of weight. 33 However, this study has not been able to show data related to several factors, especially factors eating habit, physical activity, lifestyle and psychological. [22] Those data on the subject is a limitation because it cannot be shown in this study.

Based on BMI classification of the subject before and after installation, there was an increasing number of subjects with his class BMI rise as shown in Table 3. BMI is a simple, inexpensive and noninvasive anthropometric measurement correlated with body fat and can be connected to predict morbidity on health risks for the screening of nutritional status to know the results of this research, we get an idea that this initial study can be generalized to a larger population.

BMI measurement has the limitation that should be considered because it does not distinguish between fat, muscle or bone mass and does not give an idea of the fat distribution among individuals. The average older parents have more body fat than younger adults and trained athletes may have higher BMI because of the increasing muscle mass. [23,27,28]

Weight gain is one of important side effects that needs to be investigated observing from the previous study, body weight is one of the causes why women with childbearing age don't want to

continue a modality of contraception. [30,35]

Theoretically, weight gain can be caused by various factors, one of them is the use of contraception. The biological mechanisms of hormonal contraceptives increase the weight through their fluid retention due to mineralocorticoid effects of secondary process activates the renin-angiotensin-aldosterone. [36]

Other than a side effect, there is the opinion that the effectiveness of the implant can be influenced by better nutrition condition, namely in overweight and obese individuals. This is due to the inverse relationship between the levels of progestin that is released by the implant with someone's weight. Although there has been researching to prove it, but the results are still disputed.[37]The levels of etonogestrel reduced in obese women but does not necessarily reduce its effectiveness.[38] However, other unwanted effects of factors hormonal contraceptive use and the incidence of overweight / obesity is a risk of thrombosis, cardiovascular. With the results of this study, it is expected to be used as a consideration in choosing the right contraceptive in the future.

The existence of a significant increase in body weight after Monoplant® use on the 12th month onwards as seen in figure 1. Weight affect the circulation levels of LNG itself causing the low concentration on the use of Norplant® and Jadelle®. But the constant levels are needed to prevent pregnancy remain unfulfilled.[16]Researchers have not been able to explain why it happened in this population. Until now, there has been no similar study that explain it. In connection with the pharmacokinetic Monoplant® profile, this study found a negative correlation between the degree of significant moderate levels of LNG subject, weight and BMI of the 12th month (weight r = -0.611 p = 0.005 and BMI r = -0.54 p = 0.016) and 18th (weight r = -0.52 p = 0.019 and BMI r = -0.52 p = 0.018). When examined from graphs 1 and 2, the increase levels of LNG at 6th month precede the weight gain of the 12th month. A negative correlation between weight and levels of LNG. Other research also found a negative correlation between BMI and LNG levels (r = -0.39). [39]

This study also showed a significant change in body weight after one-year use of Monoplant®. Previous studies that compared the weight gain after the use of DMPA, levonorgestrel implants, or contraceptive pills showed no changes in body weight were significant in all three acceptors of contraception.[40] If seen at the effect of weight gain after three years, the average weight gain in this study was 1.7 kg, the weight gain of DMPA users after three years of use in the study was 5.1 kg while subjects with contraceptive pills do not experience significant weight gain. However, only 17% of the subjects who had complete weight data at the end of the study, there was a possibility of dropped out subjects when realizing the weight gain.[41] Based on the results of this study, the use of Monoplant® has lighter effects in terms of weight gain compared to DMPA users.

The advantages of this study were the serially analyzed body measurement of weight and BMI, not just complaints by implantusers. With the objective measurement of body weight, it is expected to give more accurate picture of the side effects of weight gain in the female population of Monoplant® users in Indonesia. Moreover, this is the first study to evaluate changes in body weight and BMI Monoplant® acceptor as a single rod implant.

The limitations of this research are still part of the phase 2 clinical test studies. It is expected that a bigger prospective cohort study will be done to know the changes in nutritional status of Monoplant® acceptor. Recruitment of the subject was still a purposive sampling.

This study also has limitations that is the absence of data on the factors that influence weight gain, namely the physical activity, eating habits, psychological, lifestyle of the subject. It is expected in the future that those factors can be examined for a better research results. Another limitation in this study, is the major cause weight gain could not be ascertained because the scale of measurement using the body mass index has not been able to represent the composition of the whole body, it is expected in the future that the study can be done with a better diagnosis, for example by using bioelectrical impedance analysis (BIA).

CONCLUSION

There was an increase in mean body weight, especially after one year but not statistically significant. There was an increase in mean BMI

and the proportion became a higher category, but statistically it is not significant. There was a correlation between levels of LNG to BMI on the 12th month and to 18th. The presence of elevated levels of LNG on the 6th month preceding the increase in BMI and body weight at month 12 after Monoplant® installation. But theoretically, it cannot be concluded that the levonorgestrel causes the weight gain of the BMI measurement results.

SUGGESTION

Further study with larger sample size is required so that the results can be generalized to the larger population in Indonesia, taking confounding factors that influence weight gain, for example, eating habits, physical activity, lifestyle and psychological, it should be considered to use other evaluation tools such as bioelectrical impedance analysis to determine weight gain in more detailed view of the composition of the body, it is also necessary to evaluate the long-term effects of levonorgestrel in increasing body weight and BMI at Monoplant® acceptor in Indonesia.

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