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A New Family Planning Single Rod Implant Has Been Born And Is Ready To Be Marketed

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ABSTRACT

Two-rod subdermal family planning implants containing levonorgestrel (Indoplant®) have been widely used as a method of contraception in Indonesia. Recently, single-rod family planning implants (Monoplant®) were introduced as an alternative to implants that are easier to attach and remove. There is no comparative study on the effectiveness and acceptance of this single-rod family planning implants in Indonesia. To compare the effectiveness and acceptability of Monoplant® and Indoplant® birth control implants among women in Indonesia. This study is a phase III, open, randomized, multicentre clinical trial in Indonesia. Subjects were adult Indonesian women who were randomized to get Monoplant® or Indoplant® as their contraception and were recruited from 5 major cities in Indonesia, such as Palembang, Jakarta, Semarang, Surabaya and Makassar. A total of 900 subjects, 450 in the Monoplant® group and 450 in the Indoplant® group were included in the study between May 2015 and November 2019. The mean age of the subjects was 28.5 years, which varied from 20 years to 35 years. The probability of getting pregnant per 100 menstrual cycles at the end of the first, second, and third years was comparable between Monoplant® acceptors (0.00; 0.02; 0.03) and Indoplant® (0.02; 0.01; 0.02). Continuation rates for Monoplant® in the first, second, and third years were 99%, 99%, and 92%; while Indoplant® was 99% in the first year, 99% in the second year, and 92% in the third year. The levonorgestrel (Monoplant®) single-rod contraceptive implant system exhibits the same efficacy as the two-rod contraceptive implant system (Indoplant®) in preventing pregnancy. They also share the same tolerability profile. Monoplant® is easier to install and remove than Indoplant®.

1. INTRODUCTION

Implant contraception is one method of contraception that has been effective in preventing pregnancy. With the development of synthetic polymers, it is possible to develop a hormonal delivery system over a long period of time and a continuation of the release of the drug. The advantage of long-term contraception implants is that it can reduce complaints of hormonal side effects and accelerate the return of fertility after withdrawal. Levonorgestrel (LNG) implant is the first contraception made in the 1960s. Whereas in Indonesia, the form or type of implant was first introduced in 1982, Norplant®, which is a 6-stem implant with progesterone LNG. In 1989, contraception single rod was first introduced through phase II clinical trial research in Indonesia [1- 3]. The limited variation in the choice of implants in Indonesia and for the implant of the new single rod known only Implanon®, it is very necessary to develop another single rod implant in Indonesia. PT Triyasa Nagamas Farma tried to develop single rod implants, at affordable prices without reducing the effectiveness and security that was named Monoplant®. Monoplant contains 160 mg of levonorgestrel (LNG), with a tube length of 42.50-44.50 mm and a diameter of 2.52-2.72 mm with effectiveness for 3 (three) years. It is expected that Monoplant® single rod implants can provide effectiveness, the same safety as other implants and easier installation. Phase III clinical trial study on Comparison of contraceptives studies in single rod Monoplant®, with implants of double rod Indoplant®, is a continuation of phase II clinical trials, namely Pharmacokinetic and Pharmacodynamic Study of Monoplant® carried out in 2010. Indonesian Food and Drug Administration recommends that before Phase III clinical trials be carried out from 2006 to 2010 Monoplant® Phase II Clinical Tests were carried out in the Jakarta centre on 30 female subjects with 36 months of observation. The results of this study show that LNG levels for 12 months using Monoplant® averaged above 200 pg / ml (260.81 + 97.25). This figure shows that Monoplant® has met the requirements set by BPOM RI, so Phase Clinical Tests III can be implemented [4- 8].

Considering that Monoplant® is a new type of family planning implant, according to the provisions of the Indonesian government, it is necessary to examine it through Phase III Clinical Trials to see the safety, effectiveness and public acceptance. As a new type of contraception, Monoplant® is expected to provide advantages in terms of easier insertion and extraction compared to other methods of contraception consisting of more than one stem, in addition to having a guaranteed safety, effectiveness and level of security. The one-rod family planning implant of Monoplant® in this Clinical Trial is compared with Indoplant®.

2. Materials and Methods

This study is a phase III clinical trial, 'Open' (‘open label 'Randomized Clinical Trial), conducted randomized and multicentre, comparing two types of contraceptive implants, namely Monoplant® and Indoplant® performed in Indonesian healthy women. Random blocks of tithe allocation and randomly assigned divided by 5 Monoplants and 5 Indoplants. The total sample observed in this study: 450 subjects of Monoplant® users and 450 subjects of women using Indoplant® in 5 (five) centre in Indonesia, namely Jakarta, Semarang, Surabaya, Palembang and Makassar. Each centre recruits 180 subjects (90 Monoplant® acceptors and 90 Indoplant acceptors). This research has passed the ethics review with the ethics number 639/PL.301/H4/2013/

Subjects included in this study have fulfilled all of the following criteria: women of childbearing age aged 20 - 35 years, physically and mentally healthy, not pregnant, still having active sexual relations so that they

still have the risk of becoming pregnant, not exposed to hormonal contraception in the last 3 months, already got an explanation and understood the purpose, risks and benefits of the research and signed the informed consent, willing to return to the clinic for a repeat visit, willing to only use implants during the study in the next 3 (three) years.

A woman is excluded as the subject of this study if she experiences one of the following histories or events: has a family history of all types of cancer, abnormal or undiagnosed genital bleeding, severe thromboembolism or cardiovascular, have mental illness, depression, epilepsy, tuberculosis, often severe headaches, having a history of diabetes mellitus, have a history of liver disease or active liver disease, in regular care or just with drugs that induce liver enzymes, such as: barbiturates, phenytoin, carbamazepine or rifampicin, hypertension (systolic more than 160 mmHg; diastolic more than 100 mmHg), heavy hirsutism, participate in other clinical research activities in the last three months. The sample is calculated statistically, with the sample size formula for comparison of the proportions between the two sample study groups (Pocock). By using the formula, the number of subjects for each treatment group is 399. Based on the consideration of a 10% drop-out possibility, the total sample required is 444 subjects for each treatment group and rounded to 450 subjects for each group.

After insertion implant, each subject was asked to come to the clinic for follow-up at month-1, month- 3, month-6, month-18, month-24, month-30 and month-36. Some of the things that were observed at each visit were: body weight, pulse rate, blood pressure (systolic and diastolic) and the complaints that might arise when using the implant of Monoplant® and Indoplant®.

3. Results

This progress report basically displays the results of phase III clinical trials and results of examination of LNG in the blood for 36 months using implants of Monoplant® and Indoplant®, because the return visit data that is complete and can be analyzed to date is data up to a 36-month return visit. Phase III clinical trials were carried out on 450 Monoplant® and 450 Indoplant® subjects, which were conducted in 5 (five) research centre.

Table 1. shows the results of the subject according to the research centre and type of implant. In the table, it can be seen that in approximately 18 months, each centre has collected 180 subjects or 900 total subjects in 5 (five) research centre.

Centre	**Implant Type**		**Total**
	Monoplant	Indoplant	
Palembang	90	90	180
Jakarta	90	90	180
Semarang	90	90	180
Surabaya	90	90	180
Makassar	90	90	180
Total	**450**	**450**	**900**

Nearly all centre cannot meet the number of subjects within the set time. Among the 5 centre, which are the fastest and according to the time of the initial recruitment, which for approximately 6 months is the Palembang centre (5,7 months). The recruitment time for the Jakarta centre is 13,2 months, Semarang is 15 months, Surabaya is 14 months and Makassar is 17 months. The extension of the subject recruitment time is

because implant services are now easily accessible to almost all government and private health facilities that work with BPJS and do not pay, making it difficult to get prospective subjects to participate in this clinical trial. Another reason is, besides the strict exclusion criteria such as having to be hormone free in the last 3 months and the narrow age limit set (Table 1).

There is no difference in systole or diastole between Indoplant® and Monoplant® groups, as well as between centre. The systole pressure in Semarang centre is the highest compared to other centre with a value between 117.0 + 10.0 mmHg for Monoplant and 117.9 + 10.6 for Indoplant. The lowest sistole was found in Makassar centre namely 109.4 + 11.4 (Monoplant) and 109.3 + 10.3 (Indoplant). The lowest diastole was found in Surabaya centre for Monoplant® and Indoplant® subjects (73.8 +7.6 mmHg and 74.6 + 8.2 mmHg).

Obstetric history seen from the results of visual inspection of acetic acid (VIA) test, number of parity, number of pregnancies, menstrual pattern, desire to have more children and breastfeeding. The results of the analysis showed that the subjects who received Monoplant® or Indoplant® had an average of children born alive between 2-4 children. The average number of children is found in Makassar centre, especially for Monoplant subjects while for Indoplant ®subjects in Palembang centre. The Semarang centre has the lowest average child described from Monoplant® or Indoplant®. There is no difference in the number of children born alive which means between Monoplant® and Indoplant® subjects, judging from the level of parity.

Most of the total subjects who took part in this study especially 4 research centre did not want to add more children; even Semarang centre are mostly 90 percent (Monoplant®) and 84.4 percent (indoplant®) already don't want to add more children.

To fulfill the inclusion requirements, the subjects were asked whether in the last 3 months they had used hormonal contraception. According to the history of hormonal use, most subjects had used hormonal contraception more than three months ago, especially the type of injection. Centre with the highest proportion did not use hormones in the past 3 months, for Monoplant® subjects namely Semarang and Surabaya centre, 86.7 percent and 80.0 percent. The same centre was also experienced for Indoplant® subjects, namely 85.6 percent and 87.8 percent.

Most of the subjects, both Monoplant® and Indoplant® said that they had no difficulty at the time of the implant placement. Only the Palembang and Semarang centre say there is a 1.1 percent difficulty for Monoplant®. As for the installation of Indoplant®, there was 1.1 percent difficulty in the Palembang centre, 2.2 percent found in Semarang and Surabaya centre. While this shows the level of difficulty of implant placement of Indoplant stem II is relatively more than Monoplant®. There was no significant difference seen from the length of installation of the two types of implants.

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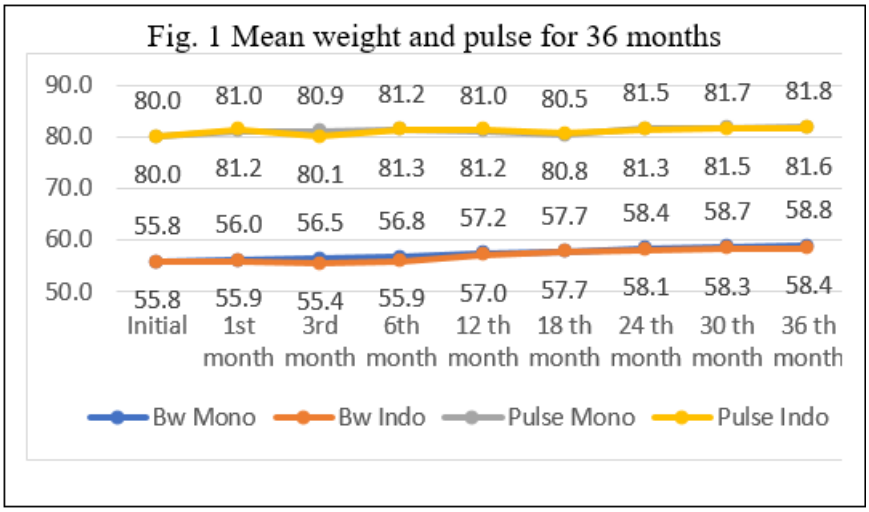

Figure 1 shows that from the start of the implant placement to the 36-month, there did not appear to be a change in the average body weight and pulse. There was a slight fluctuation in the two variables, but still within the normal range for the two study groups.

In addition to body weight and pulse, it turned out that changes in systolic and diastolic blood pressure in the two study groups also tended to be stable from the beginning to the 36- month (Fig 1).

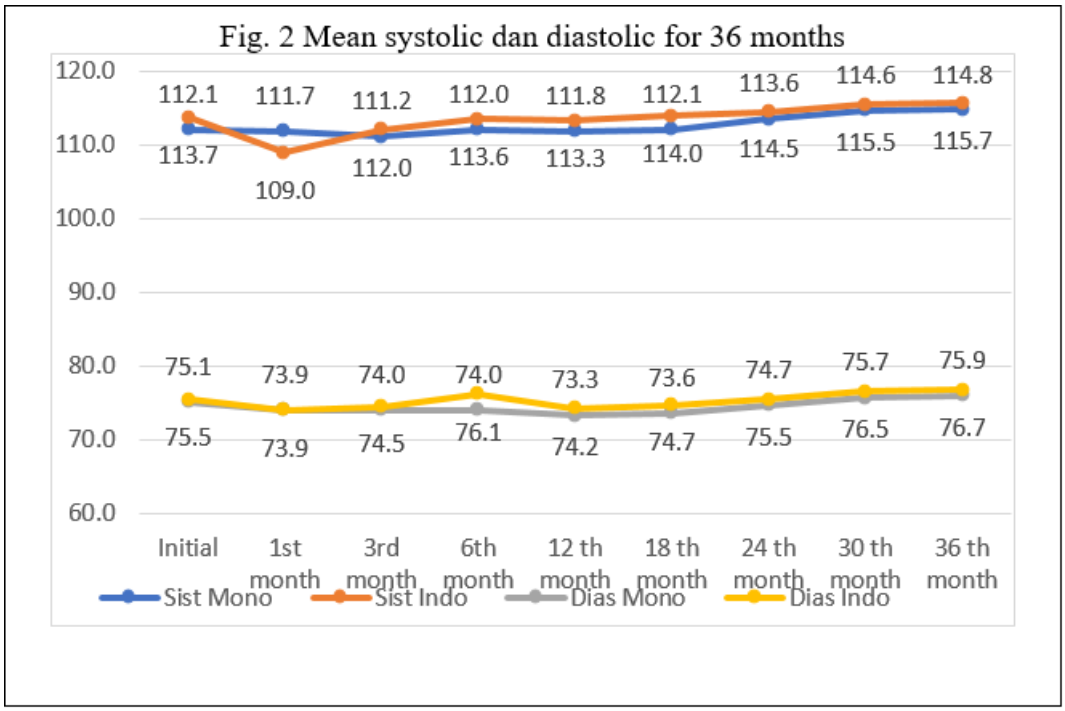

Figure 2 shows that the subject's systolic and diastolic blood pressure up to a 36-month did not show any significant changes, and is still in a normal condition.

The tendency of weight stability, pulse rate, and systolic and diastolic blood pressure shows a high level of security from the cardiovascular aspect for users of the two types of implants being studied. Cardiovascular disorders can be categorized as a systemic disorder that is quite serious and can trigger other organic disorders. (Fig 2)

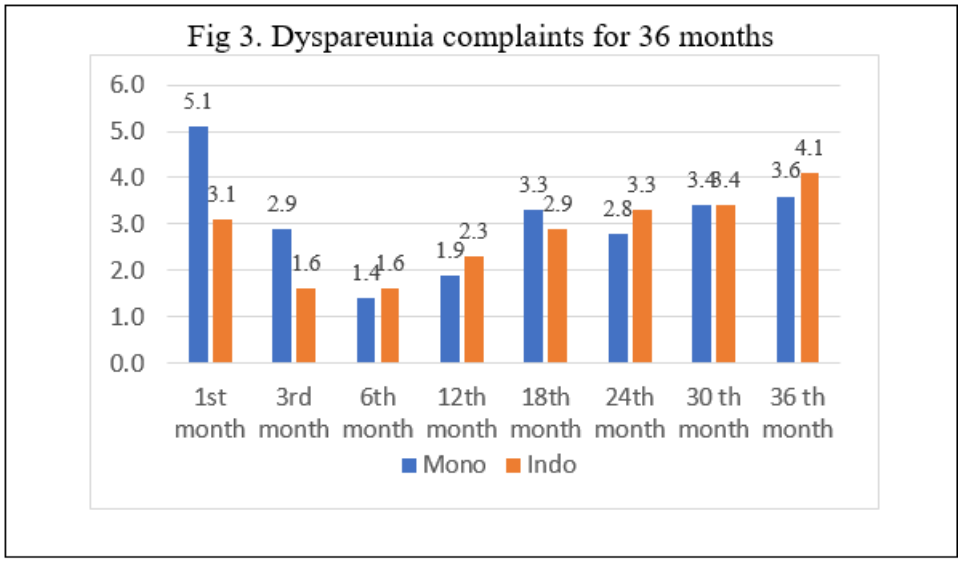

Fig 3. Dyspareunia complaints for 36 months

Subject complaints about health in the form of pain around the reproductive organs or known as dyspareunia after the use of Monoplant® and Indoplant® found in the 1st month - 36th month. Dyspareunia complaints tend to be higher in Monoplant® subjects than the Indoplant®. Within a period of 6 months, there was a noticeable decrease in complaints of dyspareunia for these both implants, however in the following months there were different complaints in the range of 3.3% to 3.6% for Monoplant® and between 2.9% to 4.3% for Indoplant®. The fluctuation of these complaints is still within normal limits (Fig 3).

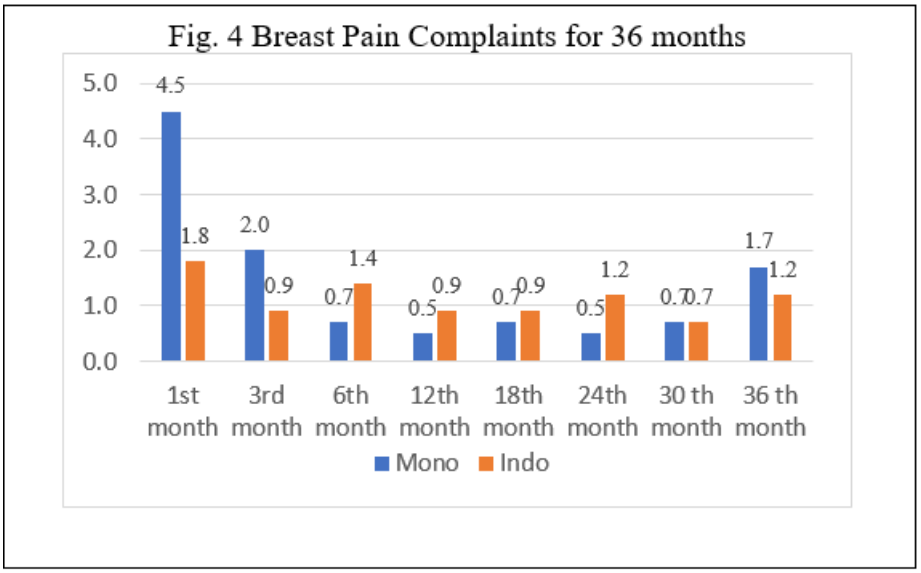

Fig. 4 Breast Pain Complaints for 36 months

Hormonal use for some subjects can cause complaints of breast pain. The same pattern with dyspareunia complaints also appears here. After observing for 36 months the use of implants of Monoplant® and Indoplant®, there was a decrease in pain complaints in the breast. In Monoplant® subjects, the incidence of breast pain dropped from 4.5 percent in the first month to 1,7 percent in the 36th month. For Indoplant® subjects, from 1.8 percent the subject fell to 1,2 percent in the 36th month (Fig 4).

The proportion of amenorrhea in Monoplant® subjects ranged from 44.9 percent (month 1) to 42.6 percent (month 3) and in month 6 to 41.7 percent then slightly decreased to 36.2 percent on month 12, and then continue to decline to the level of 9.2 percent in month thirty-six. Compared to Monoplant®, Indoplant® implants until the 6th month are relatively higher amenorrhea complaints; however, in the 12th month, amenorrhea complaints for Indoplant® decreased to 33.6 percent, so complaints of Indoplant® amenorrhea were slightly lower than Monoplant®. In the thirty sixth month, the level of complaints of amenorrhoea among Indoplant® acceptors was recorded at 8.5 percent. After entering the implant contraceptive use period for thirty-six months, most of the implant acceptors underwent an extraction process in each study center. In general, the implant removal process requires a longer time than the insertion time, for both Monoplant® and Indoplant® implants.

In addition to seeing the safety, effectiveness and acceptance of the Monoplant® and Indoplant® contraceptive implants in subjects for 36 months of use, follow-up up to 3 months after extraction was also carried out, especially for all subjects who had completed this study for 36 months of use. Of all subjects who have been released, 87% have been contacted by telephone to gather information about menstrual history, changes in body weight and the possibility of pregnancy and subsequent contraceptive use. In general, the disruption of the menstrual cycle pattern is getting smaller for the two types of implants. Amenorrhoea almost disappeared after three months, as well as complaints of excessive bleeding. Complaints about the small amount of menstrual blood were around 17% for both acceptors.

It appears that almost all subjects do not complain about changes in body weight. Only about 1% to 3% of former Monoplant® and Indoplant® acceptors complained of disturbing weight gain or loss. The return of fertility after the implantation of implant was assessed by the pregnancy rates experienced by former Monoplant® and Indoplant® acceptors after 3 months of withdrawal and not using contraception for various reasons. A total of 232 subjects who used Monoplant® did not use post- extraction contraception, while for Indoplant® was 237 subjects. The presence of pregnancy in 1.3% of former Monoplant® acceptors and 0.8% among former Indoplant® acceptors who can be contacted by telephone from the five study centers. This difference did not show a statistically significant difference ($p > 0.05$).

4. Discussion

There are currently several innovative contraceptive implant systems under development. Monoplant is a single rod contraceptive implant and it provides contraceptive protection for 3 years. Mechanism of action of monoplant® is by ovulation inhibition and increase in viscosity of cervical mucus. The most common side effects associated with Implanon® are irregular periods, weight gain, acne, headache and breast tenderness. Single rod implant will have the advantages of insertion and removal easily, the efficacy and safety are similar to Indoplant®. We had already performed research about the efficacy of Monoplant® and Indoplant® as contraceptive methods: a comparative study. Researchers want to determine the effectiveness, safety, and time of insertion between Monoplant® with Indoplant® to prevent pregnancy [9-11].

Subject complaints about health in the form of pain around the reproductive organs or known as dyspareunia after the use of Monoplant® and Indoplant® found in the 1st month - 36th month. Dyspareunia complaints tend to be higher in Monoplant subjects than the Indoplant® [6- 9]. Progestins cause changes in menstrual function, and can cause problems for users of the contraceptive implants. The results of this study indicate changes in the menstrual pattern of subjects who received both Monoplant and Indoplant® contraceptive implants. Both acceptor groups experienced changes in menstrual patterns, where quite a number of subjects experienced amenorrhea from the first month after use, up to 12 months of use, which

then decreased after entering contraceptive use in the following months. This was found both in the subjects who received the Monoplant® and Indoplant® implants. The conditions of oligomenorrhea and menorrhagia in the two groups using this contraceptive contraceptive tend to remain [12- 15].

Not all acceptors undergo the process of removal of the implant in the research center, because some of the acceptors who experienced withdrawal had actually removed the implant in other health facilities so the data on the difficulties experienced was not known. From the process of removal of the Monoplant® implant which was carried out directly at the research center, it turned out that the one experiencing difficulties was the Jakarta centre with a rate of 6.8 percent, followed by the Makassar centre with 2.3 percent while the other centre did not experience difficulties. The withdrawal of Indoplant® family planning contraceptives tended to experience difficulties except for the Palembang centre. The Makassar centre experienced complications by 5.8 percent, followed by the Jakarta centre with 5.6 percent, while the Surabaya and Semarang centre experienced complications, respectively, 2.2 and 1.1 percent. However, there was no significant difference ($p > 0.05$) in the complication of withdrawal between the two types of contraceptives [16], [17].

The highest cause for discontinuation reasons is menstrual cycle disorders which include amenorrhoea, prolonged menstrual bleeding and spotting outside the menstrual period. Withdrawals due to menstrual disorders reached 28 acceptors. Pregnancy that occurred in this study reached 8 acceptors consisting of 5 Monoplant® acceptors and 3 Indoplant® acceptors. Of the 5 Monoplant® acceptors who experienced this pregnancy after the investigation, it was found that one acceptor was simultaneously taking anti-tuberculosis drugs that were antagonistic with hormonal contraceptives, so this failure was more due to deviations from the protocol. One case of pregnancy in the Indoplant® group was detected at the first post-insertion visit, and was already 10 weeks pregnant so this was not a contraceptive failure [10], [15].

Based on the analysis, the level of possibility (probability) of the occurrence of the dropout rate caused by specific causal factors for each type of contraceptive implant has been calculated. The causes of discontinuation can be grouped into causal factors that are directly influenced by the hormonal quality of contraception, as well as groups of causal factors outside the hormonal quality of contraception. The groups of causes that can be directly related to contraceptive quality include pregnancy, changes in weight, disturbed menstrual patterns, and headache [16- 18].

The group of causes that are outside the hormonal quality factor of contraception is more expulsion due to incorrect implant insertion technique which tends to be less deep, pain or infection at the insertion site which can be due to unfavorable asepsis factors, as well as other causes such as divorce, wanting to become pregnant, dying, or systemic diseases that are not related to hormonal, or personal reasons [10], [15- 18].

The safety level of using the implant contraceptive in the study was indicated by the number of cases of dropouts due to complaints of changes in body weight, menstrual disorders and headaches. For implant contraceptive Monoplant® this figure was 0.90% due to changes in body weight, 3.46% due to menstrual disorders, and 0.23% due to headaches that resulted in withdrawal. Indoplant contraceptive implants® are generally slightly safer than Monoplant®, except for the onset of headache. The change in body weight of the Indoplant® acceptors which caused initial withdrawal reached 0.23%, while menstrual disorders reached 2.99%. Specifically for headaches that caused discontinuation of use of the Indoplant® acceptors, it reached 0.68% [17], [19].

In addition to seeing the safety, effectiveness and acceptance of Monoplant® and Indoplant® contraceptive

implants in subjects for 36 months of use, follow-up up to 3 months after extraction was also carried out, especially for all subjects who had completed this study for 36 months of use. Of all subjects who had been released, 87% had been contacted by telephone to gather information about menstrual history, changes in body weight and the possibility of pregnancy and subsequent contraceptive use. In general, the disruption of the menstrual cycle pattern is getting smaller for the two types of implants. Amenorrhoea almost disappeared after three months, as well as complaints of excessive bleeding. Complaints about the small amount of menstrual blood were around 17% for both acceptors [15], [17], [19].

The data obtained showed no significant difference in the effectiveness of both contraceptive methods. In addition, side effects such as menstrual disorders and weight gain did not differ significantly in those study groups. From that research, both implant have the same effectiveness, safety, no differences in weight gain and menstrual disorders during 1st until 36th months follow-up. However, the insertion of Monoplant® are faster than Indoplant®. Monoplant® can be used as a contraceptive method with the same effectiveness and safety as Indoplant®, yet with shorter insertion time [16- 20]. We believe that this advancement will bring a new hope to increase the efficacy of national contraception program.

The strength of this research is that it has gone through Phase III Clinical Trials to see the safety, effectiveness and public acceptance. This research was also conducted in 5 (five) research centers for Contraception and Reproductive Health using the Indoplant® (two-rod implant) comparison which has been widely used in the family planning program in Indonesia and has quite high efficacy and acceptance. As a new type of contraceptive family planning with one rod, Monoplant® is expected to provide advantages in terms of ease of insertion and removal compared to other family planning methods which consist of more than one rod, besides having a guaranteed safety, effectiveness and level of security. The weakness of this research is that the observation of this research is only until the third year, maybe for further researchers it can be continued and developed.

5. Conclusion

Based on the results of the analysis obtained at the thirty-sixth month re-examination, it can be considered as follows: the level of importance of the two types of implant contraceptives, for Monoplant® and Indoplant® is good, the contraceptive rate for implant family planning is good, the acceptor acceptance rate is high for both types of contraceptive implant, the side effects of pattern disorders that are dominated by amenorrhoea fluctuate, but are still within normal limits for contraceptive implants, other side effects of cycle disorders such as oligomenorrhea and menorrhagia tended to persist in both types of contraceptive implants. Based on the interim results, this can be concluded as follows, there is no significant difference the effectiveness, safety, and time in levonorgestrel levels between single rod implant monoplant® and double rod implant indoplant®. We believe that this advancement will bring a new hope to increase the efficacy of national contraception program.

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