

## Literature Review

## Monoplant<sup>®</sup> the Indonesian Implant: The Overview of Implant and Its Development

### Monoplant<sup>®</sup> Susuk KB Indonesia: Gambaran tentang Implant dan Perkembangannya

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#### Abstract

Norplant<sup>®</sup>, as a first-generation levonorgestrel implant and containing six capsules, has been shown to be effective as long-term contraception since more than 25 years ago. In the process, then the number of implants was reduced to two rods called Norplant-2<sup>®</sup>, which is then updated into Jadena<sup>®</sup> (in Indonesia) or Jadelle<sup>®</sup> (in America).

As a country with the largest implant acceptors in the world, Indonesia has developed its own implant method consisting of two rods called Indoplant<sup>®</sup>. Currently being developed implant that consists of single rod called Monoplant<sup>®</sup>. Monoplant<sup>®</sup> is expected to be the best option because it only consists of a single rod implant that is easy to insertion and remove, effective and safe for at least three years.

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#### Abstrak

Norplant<sup>®</sup>, sebagai susuk levonorgestrel generasi pertama dan berisi enam kapsul, telah terbukti efektif sebagai kontrasepsi jangka panjang sejak lebih dari 25 tahun yang lalu. Dalam perkembangannya, selanjutnya jumlah susuk dikurangi menjadi dua batang disebut Norplant-2<sup>®</sup>, yang kemudian diperbarui menjadi Jadena<sup>®</sup> (di Indonesia) atau Jadelle<sup>®</sup> (di Amerika).

Sebagai negara dengan jumlah akseptor susuk terbesar di dunia, Indonesia mengembangkan sendiri metoda susuk KB yang terdiri dari 2 batang yang disebut Indoplant<sup>®</sup>. Saat ini sedang dikembangkan susuk KB yang terdiri dari satu batang yang disebut Monoplant<sup>®</sup>. Monoplant<sup>®</sup> diharapkan akan menjadi pilihan yang terbaik karena hanya terdiri dari satu batang susuk sehingga mudah memasang dan mencabutnya, efektif dan aman untuk setidaknya tiga tahun.

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#### INTRODUCTION

Implant is a contraceptive device that is placed under the skin, containing steroid hormones and are used for a long time; one of them is the levonorgestrel implants.

Levonorgestrel (hereinafter abbreviated as LNG) is a progestogen and is a bioactive material which is currently widely used for contraceptive development, both for the contraceptive pill, injection, IUD (Intra Uterine Device), and implant.<sup>1,2</sup>

#### History of Implant History of Implant in the World

In 1964 Folkman and Long published their findings about silastic tube containing a drug that can slowly release it for long periode of time. Two years later, Dziuk and Cook found silastic capsules that can release the drug in vitro with a constant concentration. Segal and Croxatto incorporated these principles by

inserting some steroid hormones into the tube. Apparently silastic capsule containing a steroid hormone inserted under the skin can release the hormone more than one year. The results of this preliminary research into the basic concept of the development of long-term contraception under the skin (implant).<sup>3-5</sup>

First subdermal implant clinical trial began in 1968 in Santiago, Chile. This implant tube contained polydimethylsiloxane (silastic or silicon), which was filled chlormadinon acetate, a synthetic gestagen or progestin. But clinical trials have failed and no longer continued because chlormadinon acetate turned out to be toxic in animal experiments.<sup>6</sup>

Subsequently, from 1970 to 1978 series of clinical trials of single rod implant up to six rods containing megestrol acetate were carried out in Chile, India and Brazil. The emphasis of study was about how long the implant worked and how many implants should be inserted. However, these clinical trials was not continued because of contraceptive failure of ectopic pregnancy in some subjects. Pregnancy was suspected

because the levels of megestrol acetate was not strong enough to inhibit ovulation. Megestrol acetate was also associated with higher incidence of adnexal tumor and fetal heart abnormalities in the use of high doses for the treatment of abortion.<sup>4,7</sup>

In 1974 implant containing noretindron, norgestrienon, and levonorgestrel was used. Experiments using the implant that contained four to six implants noretindron were also not encouraging either. 21 pregnancies from 112 women in one year the use of implants were reported. Instead the six-implant clinical trials using levonorgestrel and norgestrienon could prevent pregnancy better with retention rates higher usage, because after the implant was inserted anovulatory menstrual cycle for several months would be obtained.<sup>4,7-8</sup>

Phase 3 clinical trials of LNG implant consisting of six capsules compared with the IUD was first performed in 1975 in six countries, Brazil, Chile, Denmark, Dominican Republic, Finland, and Jamaica. The results of this clinical trial demonstrated a low pregnancy rate (0.6 per 100 women a year), good received and high used survival rate (75 - 80%).<sup>9,10</sup> The results report of the first 5 years of research in the early years 1980 indicated that the LNG implants were well received and very few side effects.<sup>11</sup> Later in the year 1980 - 1982 conducted further phase 3 clinical trials in eight countries Colombia, Ecuador, Egypt, India, Indonesia, Sweden, Thailand, and USA.<sup>12</sup>

In 1982 a preliminary study comparing six LNG implant with two LNG implants was conducted in the Dominican Republic, Sweden, Chile, Finland, and USA. This research was delayed because of problems in the manufacture of implant. In 1983, Leiras Pharmaceuticals, Huhtamaki Oy, Turku, Finland was appointed to make and market the LNG implant Norplant<sup>®</sup>. Norplant<sup>®</sup> consists of six capsules. Each 36 mg capsule LNG as an ingredient, with capsule diameter 2.4 mm and 3.4 cm long. Finland is the first country to receive and use Norplant<sup>®</sup> as a method of contraception.<sup>13</sup>

In 1984 - 1985 Norplant<sup>®</sup> was studied in Bangladesh, China, Nepal, Philippines, Singapore, Sri Lanka, Ghana, Kenya, Nigeria, Haiti, and Zambia. In 1985, Sweden is the second country to receive and use Norplant<sup>®</sup>. Furthermore, in 1986 Indonesia, Thailand, Ecuador and the Dominican Republic also using Norplant<sup>®</sup> for Family Planning.<sup>14</sup>

Actually, 1980 was the start of the development and testing of the implant LNG mainly to the number of implants that will be installed. At that time implant was developed which consisted of two rods (Norplant-2<sup>®</sup>). Each rod implant was 1 cm longer than Norplant<sup>®</sup> capsules and contain the LNG is almost two times more. Norplant<sup>®</sup> capsule contains 36 mg of LNG while each rod Norplant-2<sup>®</sup> contains 75 mg of LNG.<sup>15</sup>

In early 1983, basic research on Norplant<sup>®</sup> has been completed but the research on the system 2 sticks (Norplant-2<sup>®</sup>) should be continued, because at that time the manufacture of elastomeric implant 2 sticks was not available in the market. A few years later (mid 1990) rod implant with a new elastomer that is softer and is known by the name Jadelle<sup>®</sup> (in America) or Jadena<sup>®</sup> (in Indonesia) became available.

Later clinical trials comparing implant capsule and implant 6 - 2 sticks, continued. As a result, Jadelle<sup>®</sup> has been recognized by the FDA in 1996,<sup>15,16</sup> and Leiras-Finland started to market in 2001.

Implant technology has been changed since this contraceptive method was first introduced in 1983. Implant tubes in use today are made from silicone elastomers, making it softer and more flexible, because a lower silicone content.<sup>17</sup> The progress of these technologies led to improve effectiveness as a contraceptive implant and affect long-term lower pregnancy rates.<sup>18</sup> This depends on the type of contraceptive progestins and type of polymer used.<sup>19-21</sup>

Since 2002 Norplant<sup>®</sup> is not used anymore in the United States. Wyeth has discontinued distribution of Norplant<sup>®</sup> for prosecution issues related to technical difficulties in extraction due to the lack of trained health personnel, although still used in other countries.<sup>22</sup> Outside the United States, Schering still distributing Norplant<sup>®</sup> to the world. It is still used by millions of women in developing countries and China.

Instead of Norplant<sup>®</sup>, there is a second-generation implant, Jadelle<sup>®</sup>, which consists of two rods. Jadelle<sup>®</sup> also developed by the Population Council and manufactured by Leiras Oy, and now by Schering AG, with the aim of reducing the number of implants placed. The system is made of elastomer with enhanced drug release capability. Therefore, two rods Jadelle<sup>®</sup> implants have the same ability in a release of LNG as the six capsule Norplant<sup>®</sup>. Jadelle<sup>®</sup> has been approved for use for five years in the USA and Europe; in Indonesia is used for three years,<sup>18,23-25</sup> with a cumulative pregnancy rate over the past five years is 1%.<sup>26</sup> Both the Norplant<sup>®</sup> and Jadelle<sup>®</sup> has the same work mechanism to prevent ovulation and thick the cervical mucus.<sup>27</sup>

By the year 2000 an Organon (Oss, The Netherlands) developed a new technology that is the only implant contain one rod, containing a different progestin that is Etonogestrel (ENG), with the name of Implanon<sup>®</sup>. This implant into the international market in 1998 and received by the FDA in 2004. Implanon<sup>®</sup> effective for three years, with the main mechanism of action is inhibition of ovulation.<sup>28</sup> Until 2006, Implanon<sup>®</sup> is registered in more than 40 Asian and European countries as well as in the United States and has been used by more than 2.5 million women. Currently, Implanon<sup>®</sup> is the only implant that is still used in USA.<sup>22,29,30</sup>

Other implant types, such as implant Nestorone<sup>®</sup> (Elkometrine<sup>®</sup>), Uniplant<sup>®</sup>, and Capronor<sup>®</sup>, or other implant that consists of a different progestin, biodegradable rod, pellets, and the microcapsules are still under development. Nestorone<sup>®</sup>, and Uniplant<sup>®</sup> (containing nomegestrol acetate), is a non-estrogenic progestin and non-androgenic inactive when given orally but is more potent than LNG when given by way of non-oral.<sup>31</sup> Capronor<sup>®</sup>, an implant of a biodegradable capsule LNG (non silastik). This implant, release of LNG over 12 - 18 months.<sup>32-34</sup>

In summary, various methods such implants are used by many women who want to delay pregnancy for several years or have enough children and do not plan to become pregnant again. The main advantage of this method is the high level of success and the

long period of usage without any compliance issues. However, the need for availability of skilled health services and trained for insertion and removal of implants and the issue of frequent side effects of bleeding, are the main disadvantages of this implant contraceptive method.

### History of Implant in Indonesia

Norplant<sup>®</sup> was first introduced and studied in Indonesia in May 1981. Early clinical trials done in Jakarta and Bandung. Later in September 1982 they conducted in eleven research centers spread across Indonesia with a total sample of 8681 subjects. The results are quite safe as Norplant<sup>®</sup> contraceptive. In 1986 Norplant<sup>®</sup> is accepted and used as one method of contraception in Indonesia.<sup>4</sup>

About 10 years later, in March 1992 there have been more than 1.25 million users of Norplant<sup>®</sup> acceptors throughout Indonesia, and until March 1999 increased to 2,882,889 acceptor implant or a 10.8% of all contraceptive acceptors in Indonesia totaling 26,729,030 acceptors. On the other hand, in foreign countries, up to August 1997 Norplant<sup>®</sup> has been approved and used as one of choice of contraceptive methods by about 60 countries, and today more than 70 million women worldwide have used Norplant<sup>®</sup> as a contraceptive.<sup>35,36</sup>

First-generation implant, Norplant<sup>®</sup>, developed by Population Council, New York, USA, and originally produced by Leiras Oy in Finland, consists of six capsules containing LNG in a matrix of silicone elastomer. Second-generation implant, Jadelle<sup>®</sup> or Jadena<sup>®</sup>, consisting of two sticks were also developed by the Population Council and manufactured by Leiras Oy, but now manufactured by Schering AG, with the aim of reducing the number of implants placed. Jadena<sup>®</sup> Clinical Research in Indonesia is carried out in 1998 with the same effectiveness and acceptance of Norplant<sup>®</sup>, but is faster and easier to insert and remove it out.<sup>37</sup>

Implanon<sup>®</sup>, a single rod implant with bioactive materials Etonogestrel (3-keto-desogestrel), was investigated in Indonesia in 1998. The result was quite effective as a contraceptive for three years, was safe and well received.<sup>38,39</sup>

### Overview of Implant

Since the first discovery of a progestin as a contraceptive implant and scientifically published by Croxatto 1969, and recognition of first-generation implant Norplant<sup>®</sup> in Finland in 1983, then the next several types of implants KB has been developed, researched and some have been registered and marketed. Until now it is estimated that implant has been used as a method of contraception in some 60 countries. More than 70 million women worldwide have used the implant as their contraception.<sup>40</sup>

Today implant research and development are aimed at 4 different types of progestin: levonorgestrel, etonogestrel, nesterone, and nomegestrol acetate, and 2 types of non-biodegradable polymer mixtures and biodegradable. Some of these implants have been marketed and the others were still in the research.<sup>27</sup> Im-

plant was placed under the skin on the inner arm between the biceps and triceps through the puncture trokar after previously cleaned and given a local anesthetic. Furthermore, the active ingredient progestin released slowly, little by little until the end of life, 6 months to 5 years depending on the type of implant.<sup>27</sup>

### Implant Levonorgestrel

LNG is a progestin that is widely used as active ingredients implant, Norplant<sup>®</sup> and Jadelle<sup>®</sup> Norplant<sup>®</sup> capsule and comprises six Jadelle<sup>®</sup> comprises 2 rods. Implant containing a mixture of steroids and polymer, and capsules containing crystalline steroid implants only. Both two types of implants are releasing LNG in the same amount for a period of 5 years. LNG levels in the blood rises rapidly within the first month after insertion, and then declined slowly until the end of useful life. The number of LNG levels depending on body weight acceptors.<sup>41,42</sup> At the end of the fifth year of usage, LNG levels still remains about 31%. After the implant removed, within 120 days of LNG is not found again in circulation.<sup>27</sup>

The first time capsule Norplant<sup>®</sup> was developed in 1983, using a rigid tube. Since 1991 capsules have been modified to be more delicate so as to release of LNG per day a little more and were significantly lower pregnancy rates.<sup>29</sup>

Effectiveness of Norplant<sup>®</sup> contraceptive and Jadelle<sup>®</sup> has been proven to be used up to 5 years<sup>43</sup>, but clinical data suggests Norplant<sup>®</sup> was still effective until year seven.<sup>44</sup> Sino-implant<sup>®</sup>, LNG implant made in China, similar Norplant<sup>®</sup> and Jadelle<sup>®</sup>, also showed similar effective to the original.<sup>45</sup>

### Implant Etonogestrel

Implanon<sup>®</sup> is a single rod implant containing etonogestrel and effective used for 3 years. Etonogestrel (3-keto-desogestrel) is the active metabolite of desogestrel. This implant is made from a mixture of steroids with polymer ethylene vinyl acetate (EVA) to form a rigid tube and wrapped by a thin membrane of EVA on the outside. Etonogestrel maximum levels are reached on day four after insertion, then levels are declined slowly until the third year of use. Etonogestrel levels are also associated with weight, and etonogestrel is not immediately detected within one week after implant removal.<sup>46</sup>

### Implant Nestorone

Nestorone<sup>®</sup> implant (ST1435) consist of one rod, developed by the Population Council in the USA, and is planned to be effective for 2 years. The same progestin studied in Brazil with the name Elcometrine<sup>®</sup> is one capsule with a silicone implant effectiveness for 6 months.<sup>27</sup>

### Implant Nomegestrol Acetate

Uniplant a silicone implant a capsule containing nomegestrol acetate with an approximate effective for one year. But until now it has not been marketed implant.<sup>27</sup>

## Drug Release System of Implant

In the past three decades a research was developed to determine the drug release control system in particular to determine the effective levels of drugs in pharmacology. Drug release system control technology already very advanced, especially for oral medications and transdermal. Especially for drugs that must be given within a period of time with technology insertion into the body, emerging issues of rejection of the body (biocompatibility), especially about tissue rejection (tissue compatibility). The reaction is usually a reaction of biocompatibility toxic, carcinogenic, immunogenic, and inflammation.<sup>47</sup> Biocompatibility of the body is related to implant materials (biomaterials) used.<sup>48</sup> Silicon, whether or methylvinylsiloxane dimethylsiloxane copolymer, has been used since 1950, and is the most compatible biomaterials.<sup>47</sup>

Silastic tube (medical grade polydimethylsiloxane) has been used in humans as an implant or implants and other surgical equipment, and placed permanently in the body, since 1950. For example, 200,000 cases of hydrocephalus have been using tube silastik as cerebrospinal fluid drainage throughout his life without any serious reactions against foreign substances. Similarly, medical glue (silicone type A) has been long and widely used during surgery.<sup>47</sup>

After the implant is placed under the skin, tissue rejection reaction (tissue compatibility) is triggered by tissue damage during insertion. Local inflammatory reaction occurs in the form of a series of rejection reaction of neutrophil cells, polimorfonukleus, eosinofil and macrophages. Next place the repair process of damaged tissue in the form of granulation tissue. Because the silastic tube is not digested by macrophage cells, the body through perivascular fibroblast cells tend to isolate the tube to form a sheath or connective tissue capsule around tube. Fibrous capsule formation around the tube affects drug release process, in addition to resulting in the tube is not easily driven and difficult to be separated at the time of implant removal.<sup>47</sup>

Since Folkman and Long (1964) found that silastic tube can be used for distribution of drugs because it can release the contents little by little; and Dziuk and Cook in vitro proved that the drug is removed from the tube silastic always in a constant concentration, so Segal and Croxatto (1966) first tried to use that silastic tube implanted under the skin as a system to distribute the steroid hormone. This research became the basis and concept development of long-term contraceptive that then we know as the implant or implants.<sup>4,49,50</sup>

The first generation of implant Norplant®, consisting of six capsules, containing LNG in a matrix of silicone elastomer. Once inserted, Norplant® immediate release of LNG 50 - 80 µg/day. At the end of the first year of use, LNG will be released around 40 - 50 µg/day, then will go down slowly to about 25 - 30 µg/day in the fifth year of use. However, Norplant® showed success in preventing pregnancy for a period of up to seven years, with a cumulative pregnancy rate of seven years is 1%.<sup>18,51</sup>

Further developed the second generation implant is Jadelle® which only consists of two rods. Since using

the new elastomer technology to become more soft, flexible, with a lower silicon content, the ability to increase drug release. Therefore, two bars Jadelle® has the ability to remove the same LNG as six capsule Norplant®. Jadelle® in the first month of LNG released about 100 µg/day. Then dropped to about 40 µg/day until month 12 and settled about 30 µg/day at month 24. Jadelle® has been approved for use during the five-year cumulative pregnancy rate of five years is 1%.<sup>26</sup>

## Pharmacodynamic and Mechanism of Actions

### Inhibition of Ovulation

LNG is a synthetic progesterone which can prevent pregnancy through several mechanisms work. The main working mechanisms are inhibiting ovulation in approximately 50% of the menstrual cycle.<sup>19,21,52</sup> A small amount of LNG that is released from the implant will continuously work on the hypothalamus and anterior pituitary gland. Furthermore, a decline in the secretion of FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone). LNG will inhibit or reduce wave surge of LH (LH surge) in mid-cycle so that ovulation is disturbed.<sup>53,54</sup>

Depend on the daily levels of LNG were released, LNG cause follicle growth and ovulation processes, ranging from ovulation or anovulation does not occur until there luteal phase insufficiency. LNG is not completely suppressing the secretion of estrogen. Ovulation can be prevented or hindered only, so its influence on the secretion of estrogen per cycle vary widely.<sup>53</sup> The mean levels of estrogen may still be within the normal range of 280 pmol/ml, but some of them could reach 1.5 nmol/ml.

Luteal phase of activity is generally not visible in the first year of implant use, but began to increase in the years following. If the activity seen luteal phase, progesterone levels remained low was significantly below normal levels. Luteal phase insufficiency is due to the influence of FSH and LH pre-ovulatory and mid-cycle LH surge is generally low and short. Use of Norplant® progesterone levels lower than women who did not use hormonal contraceptives. Low levels of progesterone is due to mechanism of action of LNG that suppress secretion of progesterone.<sup>53</sup>

### Thickness of Cervical Mucus

Mechanism of action of LNG is another cause of cervical mucus becomes cloudy and thick (within 24 - 48 hours after installation), making sperm penetration disturbed,<sup>54-56</sup> despite normal endogenous estrogen levels or above normal.

Under the influence of endogenous or exogenous progesterone, cervical mucus will become cloudy viscous inelastic and non-transparent or opaque. This situation is similar to cervical mucus after menstrual period ends, the exsternum ostium of uteri covered by a thick mucus and acidic, making it impossible for sperm to enter the uterus. The quality of mucus is different from the circumstances surrounding the time

of ovulation. At that time the mucus produced is more watery and elastic because it has a higher water content, more transparent or translucent, and less acidic.<sup>57</sup>

Croxatto (1993)<sup>58</sup> said that although the LNG implant of ovarian inhibition effect on several levels, including anovulation and luteal insufficiency, causing irregular endometrial thickness is not dependent on estrogen levels, but the main effect is to cause the cervical mucus becomes thick and slightly because antiestrogenic strong effect of LNG. Effect of sperm penetration of these barriers is the sole antifertility effect of Norplant®, even when circulating estradiol levels comparable to those seen in the late follicular phase of normal menstrual cycle or the cycle is still ovulating.<sup>59</sup>

### Suppress of Endometrium Growth

Mechanism of action of the other is to suppress endometrial growth (hypoplasia) because LNG inhibits progesterone work by occupying its receptors in the endometrium. This mechanism causes the endometrial cells lining the uterine cavity did not proliferate and the glands become smaller. As a result, the endometrium becomes thin layer so it is not friendly and complicate implantation.<sup>42,53,60</sup>

### Monoplant®, the New Indonesian Implant

#### The Indonesian Implant

Around the year of 1999 Biomedicine Programme Faculty of Medicine and Raden Saleh Clinic examined a prototype implant KB Indonesia in experimental animals. In the dorsal neck of an ape silicone-filled implants medroxyprogesterone acetate powder was implanted and the results were reported on a meeting at WHO consultation KB implant in 2001.<sup>61</sup>

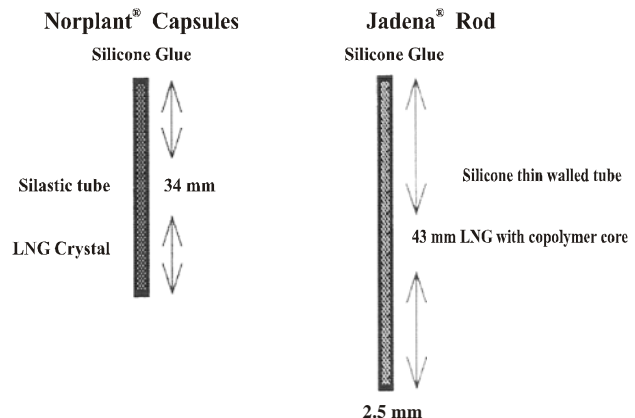
Indonesia always follows the development of this implant technology, even is eager to develop and create its own implant. Around the year of 2000 Indonesia developed and examined an implant which consists of 2 rods of LNG with an approximate effective for 3-year period called Indoplant®, but the implant has not been marketed because it is still in the research phase 3 clinical trials.<sup>62,63</sup>

### Monoplant®, the Single Rod Implant

Although some type of implant method in the world has been marketed, but each type has advantages and disadvantages, both effectiveness and side effects. Therefore, efforts were made in finding the best kind of kept doing particularly difficult to reduce complaints and duration of insertion and removal. It was attempted to develop implant comprising only one bar that is named Monoplant®.

Indoplant® and Monoplant®, developed and produced by Indonesian Pharmacy, also uses the same silastic elastomer tube with Jadelle®, contain 150 mg of LNG to Indoplant® and 160 mg for Monoplant®.

Monoplant® implant only contains progestin in the form of levonorgestrel. This implant consists of only one flexible rod and in contains a mixture of the same amount of LNG with silicone elastomer. Stem silicone



**Figure 1.** Norplant® capsules and Jadena® rod (and Monoplant®).

implant was wrapped with thin-walled tube (same as used in Jadelle® or Jadena®), and on the edges closed with a Silastic (polydimethyl-siloxane) Medical Grade Adhesive. Each implant stem 43 - 44 mm long with a diameter of 2.5 to 2.6 mm and contains 160 mg of LNG as shown in Figure 1.<sup>15,64</sup>

The materials used to make implants Monoplant® is not a new drug. LNG has been used for more than 30 years in both the pill for contraception (combination pills and minipil) and in the implant.<sup>64</sup>

Monoplant® is estimated to have effectiveness as a contraceptive for 3 (three) years. Because of this device is produced in Indonesia, the benefits to be obtained is very effective for 3-year pairs, does not require routine control, the price is cheaper so it is relatively easy affordable and widely available in the Center for Health Services, in addition to easy insertion and removal as compared with the method Another implant that consists of more than one rod.

### CONCLUSIONS

Implant began researched since 1966. It consists of silicon as a tube, and contains a progestin elastomers as bioactive materials. Since 1983 the first generation implant Norplant® 6 capsule, containing LNG, marketed. As a long-term contraceptive method that is placed under the skin, silicone tube and progestin are used up to now has been proven safe.

Although there has been researches on development of several implants with a different progestin, WHO recommends that only next-generation implant Jadelle® two rods and Implanon® single rod to be marketed and used.

As a country with the largest number of implant acceptors, Indonesia is also developing Indoplant® 2 rods implant and the last Monoplant® single rod implant. Both implant is effective for at least 3 years.

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