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Article

The Effect of Medroxy Progesterone Acetate Hormone Administration to Endometrial Thickness of the *Female Rattus norvegicus* Wistar *strain*

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A B S T R A C T

Many alternative contraceptives can be used as needed. The most effective type of contraception is injection contraception because it is relatively safe, effective, simple and inexpensive. Contraceptive users must be selective in choosing contraception because there is no method of contraception that is safe and effective for all acceptors. The side effects of Medroxy Progesterone Acetat injection include bleeding disorders such as amenorrhoea, weight gain, high blood pressure, acne, spotting. Medroxy Progesterone Acetat is a progestin contraceptive regimen that is often used and works long-term. The mechanism of action of Medroxy Progesterone Acetate injection is to inhibit gonadotropin secretion so that it will prevent the maturation of primary follicles in the ovary and also prevent ovulation and cause endometrial depletion.

The research design is the post test only control group design. The population in this research are the white rats species Rattus norvegicus Wistar strain. The samples are taken randomly from all populations that met the following sample criteria: Female rats, Aged 12-14 weeks, having a body weight of 150 - 200 grams.

The results showed that Medroxy Progesterone Acetate hormone affects the thickness of the endometrium, and there is a difference in the histological picture of endometrial thickness due to the administration of the Medroxy Progesterone Acetate hormone and without the administration of the Medroxy Progesterone Acetate hormone

I. INTRODUCTION

One way to reduce the rate of population growth is using contraception. Nowadays, many alternative contraceptives can be used as needed. There are several contraceptives commonly used including simple contraception (calendar method, interruptus coitus, cervical mucus, basal temperature, condoms, diaphragm cap, spermicide). Modern methods of contraception consist of hormonal methods, intrauterine devices (IUDs) and solid contraception. The most effective type of contraception is injection contraception because it is relatively safe, effective, simple and inexpensive. Injectable contraception is used in more than 90 countries and has been used for more than 20 years. Until now, the number of acceptors is around 5 million. In Indonesia, injection contraception is estimated to be used by nearly half a million couples (Hartanto, 2004).

Based on the National Population and Family Planning Agency (BKKBN) data in 2013, there were 8.500.247 couples of childbearing age who were new KB (family planning) participants with the following details: using contraceptive pills of 2,261,480 (26.60%), using injections of 4,128,115 (48.56%), using implants of 784,215 (9.23%), using IUD of 658,632 (7, 75% 0, using Condoms of 517,638 (6.09%), using MOW of 128,793 (1.52%), using MOP of 21,374 (0.25%) (Indonesian Ministry of Health data and information center, 2014).

The achievement of active KB (family planning) participants in all contraceptive methods in 2015 in West Sumatra province was 13,966 consisting of 5,701 (47.4%) injecting participants, 3,170 pill participants (26.4%), 611 (5.1%) contraceptive IUD participants, 744 (6.2%) implant participants, 591 (5%) MOP (Male Surgery) participants and MOW (Female Surgery) participants, 1,203 (10%) condom participants. The highest achievement is injection of (47.4%), and lowest achievement is MOP and MOW of (5%). (Profile of the Health Office of West Sumatra City, 2016).

Contraceptive users must be selective in choosing contraception because there is no method of contraception that is safe and effective for all acceptors. Each contraceptive has a different suitability and individual compatibility for each acceptor. Discrepancy and incompatibility can cause side effects on users of contraception. The side effects of Medroxy Progesterone Acetat injection include bleeding disorders such as amenorrhoea, weight gain, high blood pressure, acne, spotting. While the most common side effects are amenorrhoea, which is 50% of amenorrhea after 1 year of first use and 72% after 2 years of use (Hartanto, 2004).

Based on research conducted by Manne in 1997 on 100 acceptors using Medroxy Progesterone Acetat, at the end of the 6th month after the use of contraception only 10% had regular menstruation. After 6 months of follow-up Medroxy Progesterone Acetat, users complained of having amenorrhoea.Soetrisno (1993) in his research found: the side effects of using Medroxy Progesterone Acetate experienced amenorrhoea (50%), spoting (20%), menorrhagia (15%), nausea and headaches (15%). A high incidence of amenorrea complaints is considered to be related to endometrial depletion. Research conducted by Moghaddam (2006) states that, cell proliferation is influenced by hormones where medroxy progesterone acetate will inhibit cell proliferation. Medroxy Progesterone Acetat is a progestin contraceptive regimen that is often used and works long-term. Medroxy Progesterone Acetat is a synthetic analogue of the natural progesterone hormone that can suppress the secretion of pituitary gonadotropins so that the production of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) is also inhibited. The mechanism of action of Medroxy Progesterone Acetate injection is to inhibit gonadotropin secretion so that it will prevent the maturation of primary follicles in the ovary and also prevent ovulation and cause endometrial depletion (Mishell, 1996).

Based on the above phenomenon, researcher is interested in conducting research on the effect of the administration of Medroxy Progesterone Acetate hormone to endometrial thickness of the *Female Rattus norvegicus* Wistar *strain*

II. METHODS

The research design is the post test only control group design (Arief, M. 2008). The research is conducted at the Pharmacology Laboratory of Faculty of Pharmacy, Andalas Padang University for the maintenance and treatment of rats. As for the histological examination of endometrial thickness, it is conducted at the Pathology Anatomy Laboratory of Faculty of Medicine, Andalas Padang University.

The population in this research are the white rats species Rattus norvegicus Wistar strain. The samples are taken randomly from all populations that met the following sample criteria: Female rats, Aged 12-14 weeks, having a body weight of 150 - 200 grams.

Based on the calculation of the sample size by using the Abo Crombi formula, the sample size / number of animals r = 10 rats was obtained by taking into account the possibility of a trial animal that died / dropped out by 20%, thus the overall sample size for both groups both treatment and control were 20 female rats which included: Group 1 amounted to 10 rats that were not given the Medroxy Progesterone Acetat hormone as a control group, Group 2 consisted of 10 rats that given Medroxy Progesterone Acetat as a treatment group.

Research preparation stage;

1. Before treatment, rats are kept for ± 2 weeks to adjust to the environment and given food and drink.
2. To equalize the estrous cycle of rats, then prior to treatment, male urine is placed in female rat's cage that serves to stimulate estrus in female rats (Hill, M. 2006). Then the estrous rat is moved to another place and labeled.
3. Rats are grouped into 2 groups with details where each group consists of 10 rats. Group 1 (Control) was not given the Medroxy Progesterone Acetate hormone while Group 2 (P1) was given the Medroxy Progesterone Acetate hormone.
4. Each group of rat was placed in a separate cage made of plastic and treated for 6 weeks effectively.

Stage of research implementation:

1. The Medroxy Progesterone Acetat hormon at a dose of 0.05 ml is given to the treatment group by injecting Intra Muscular (IM) on the thigh muscles every 5 days. The treatment is given for 6 weeks.
2. On day 42, rats are sacrificed by dislocating the neck of the rat, the abdomen is then dissected, and the uterine tissue is taken. Uterine tissue that has been taken is immediately placed in a container containing 10% formaldehyde and directly examined the thickness of the endometrium (Endardjo, 2008).
3. Histological examination of endometrial thickness using the Olympus Microscope 4-TVO 5XC-3 Japan accompanied by measurement facilities in a micrometer (Fawcett, D. 2002)

The data obtained are processed and analyzed by using Anova test with a 95% confidence level, if significant results are obtained from the Anova test then followed by a Bonferroni Post Hoc Test (Multiple Comparisons) statistical test..

III. RESULT

The research results of 20 female rats, aged 12-14 weeks with body weight ranging from 150-200 grams are divided into 2 groups: the control group and P1. The control group is the group that is not given the treatment, while the P1 group is the group that is given the Medroxy Progesterone Acetat hormone at a dose of 0.05 ml. The results obtained in this research are as follows.

Table 1. **ANOVA Test Results for the Average Thickness of Endomterium Female Rattus Novergicus Wistar Strains**

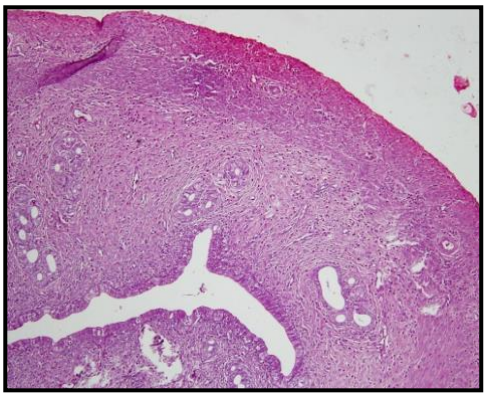
Group Control	Treatment Group	P
Control	P1 *(Medroxy Progesterone Acetat)*	0,023

From the ANOVA test table, the P value <0.05 means that there is a very significant difference in the average endometrial thickness between the control group and the treatment group. Thus, it can be continued with the *Post Hoc Bonfferoni Test*, to see more clearly a significant difference in the average thickness of the endometrium.

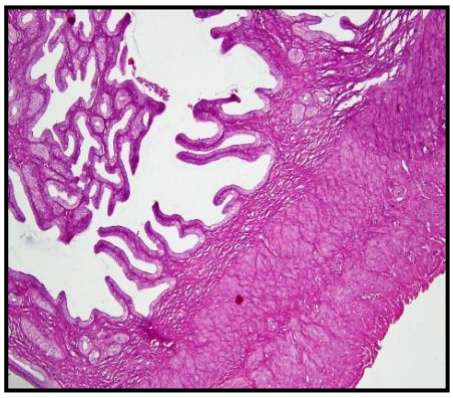
Table 2. Post Hoc Bonfferoni Test Results for Average Endometrial Thickness of Female Rattus Novergicus Wistar Strains

Group	Endometrial Thickness (µm) (Mean ± SD)	P
Control	1192,57 ± 428,94	
P1(*Medroxy Progesterone Acetat*)	493,17 ± 114,96	< 0,000

Based on the results of the Post Hoc Bonfferoni Test, it appears that the average endometrial thickness between Control and P1 shows a significant difference (P <0.05),



(A)
Control



(B)
Medroxy Progesterone Acetat (P1)

Fig 1: Histological features of endometrial thickness in Rattus novergicus Female starin Wistar

The comparison of histological features of endometrial thickness in female Rattus novergicus Wistar strains with magnification (10x10). In the control group (A) the endometrial stroma is seen looser, the surface of the endometrium is flatter. In the Medroxy Progesterone Acetat (B) group, the surface of the endometrium appears in the form of small protrusions such as papillae, the stroma is denser and less dense.

In the control group, microscopically the endometrial surface was flatter with the columnar surface epithelium. Glands in groups, tubules covered with cuboidal epithelium to columnar with a rather loose stroma. In the group of Medroxy Progesterone Acetate, it can be seen that the surface of the endometrium is shaped as small protrusions such as papillae, where the glands are denser and closer to the surface, the glands do not experience hyperplasia, some columnoid surface epithelium forms cuboid to columnar, the stroma is denser and smaller, some blood vessels hyperemic.

IV. DISCUSSION

The results showed the average endometrial thickness in the (P1) Medroxy Progesterone Acetate Hormone group was 493.17 µm ± 114.96, this result was lower than the control group 1192.56 µm ± 428.94. The results of this research were the same as Song Yu's (1995) research which states that progesterone influences endometrial morphology which varies from suppression of endometrial gland growth through decidua stroma and leukocyte infiltration to glandular atrophy and necrosis of the stroma.

This is because Medroxy Progesterone Acetat contains the hormone progesterone. This hormone will reduce the proliferation of the hormone estrogen in both the vaginal epithelium and change the uterine epithelium from the proliferation phase to the secretion phase. The Medroxy Progesterone Acetat hormone works to inhibit the secretion of gonadotropin so that it will prevent the maturation of primary follicles in the ovaries and also prevent ovulation and cause endometrial thinning. As an additional progestational effect, Medroxy Progesterone Acetat also causes changes in secretory abortive transformation in the endometrium, which will eventually become atrophy (Mishell, 1996).

Progesterone stimulates an inflammatory response in endometrial tissue so that the total number of leukocytes in the endometrium significantly increases up to 40% stroma. Inflammatory infiltrate from these leukocytes including neutrophils, eosinophils and macrophages or monocytes drawn by chemokines that are synthesized by endometrial cells, leukocytes produce various regulatory molecules including cytokines, chemokines and many enzymes that contribute to endometrium.

The progressive enzymatic degradation of the endometrium ultimately destroys the venous vascular system and sub-surface capillaries, causing intersisial bleeding from the surface membrane which allowing blood to exit into the endometrial cavity. Eventually, degeneration extends to the deepest functional layer where ruptured arterioles contribute to bleeding. Desquamation begins in the fundus and gradually extends toward the ismus. The final result is that the endometrium becomes thin and shallow (Speroff, 1996).

This result is the same as the research result conducted by Fraser (1995) showing that the use of steroid hormones especially progesterone can increase free radicals. An increase in free radicals is caused by the activation of macrophage cells as a reaction to the necrosis of endometrial tissue stimulated by progesterone.

Microscopically, it is seen significantly different between the P1 group and the control group. In the control group, it can be seen that the surface of the endometrium is flatter with the columnar surface epithelium. Glands in groups, tubules covered with

cuboidal epithelium to columnar with a rather loose stroma. When compared with P1, we can see that the surface of the endometrium is in the form of small bumps like papillae where the glands are denser and closer to the surface, the glands do not experience hyperplasia. Some columnar surface epithelium forms cuboid to columnar, hyperemic blood vessels with fewer stromas. Based on the research results obtained and the theory of the influence of the administration of the Medroxy Progesterone acetate hormone to the thickness of the endometrium which will have an impact on endometrial depletion.

V. CONCLUSION

Based on the analysis of research results and discussion, it can be concluded that: Medroxy Progesterone Acetate hormone affects the thickness of the endometrium, and there is a difference in the histological picture of endometrial thickness due to the administration of the Medroxy Progesterone Acetate hormone and without the administration of the Medroxy Progesterone Acetate hormone.

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BIOGRAPHY

Devi Yulita The researcher was born in Padang, May 23, 1980. The researcher graduated from SPK Kesdam 1 / BB Padang in 1998, graduated her D III (diploma) from Midwifery of *Health Polytechnic Ministry of Health of* Bukittinggi in 2001, graduated D IV from Educator Midwife of Institute of Health Science Ngudi Waluyo Unggaran in 2004, then the researcher completed her education in Biomedical Science Postgraduate Program in 2011. Since September 11, 2005, the researcher has taught as a permanent lecturer until now, as a provider of maternity care, childbirth care, breastfeeding and family planning.