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Effect of Depot-Medroxyprogesterone Acetate (DMPA) on Ovary and Uterine Tube of White Albino Rat a Histopathological Study

Sharma S[1*], Bajracharya M[1], Koirala S[2], Baral P[2] and Shakya T[3]

*[*1]Department of human anatomy, people's dental college and hospital (Trivhuwan University), Nepal*

[2]Department of Human Anatomy, B.P. Koirala Institute of Health Sciences, Nepal

[3]Department of Human anatomy, patan Academy of health sciences, Nepal.

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ABSTRACT

Even though, progesterone is a hormone naturally produced by ovary, but whether the external progesterone is as beneficial as the natural for female? What alterations come in which organ of female reproductive tract due to their use? We aimed to observe the histopathological changes brought by the long term use of Depot-medroxyprogesterone acetate (DMPA) "sangini sue", which is the highly popular and promoted contraceptive in developing countries, in reproductive tract of female rat particularly in ovary and Uterine tube. There was significant change in the morphology of ovary and uterine tube of experimental group rat compared to the control group. Such as, follicular atresia, medullary hemorrhage and atrophy of uterine epithelium were seen in experimental group rat only. In conclusion, long- term use of exogenous progesterone, such as DMPA for contraception has adverse impact in Female which outweighs the merits. Instead of promoting this hormonal product, which in long period attenuates the health of female, other non-hormonal methods of contraception should be publicized along with their efficacy.

Keywords: Follicular atresia, Atrophy, Deciliation, Medullary hemorrhage

Abbreviations: DMPA: Depot-Medroxyprogesterone Acetate; HRT: Hormone Replacement Therapy; POP: Progesterone Only Pill

INTRODUCTION

Unintended pregnancies in low-and middle-income countries remain a serious obstetric problem and awareness and promotion of all types of family planning methods are inevitable in those areas [1]. Family planning has been an important subject for population planners, couples and individuals because it aims for better health and because of its sociocultural benefits [2]. Depot medroxyprogesterone acetate (DMPA) is one of the most effective reversible contraceptives yet its use is not a without side effect which was developed in 1954 as a treatment for endometriosis and to prevent habitual or threatened abortions [3]. In cases where women are at an increased risk of estrogen complications progestin-only hormonal contraception is often prescribed as the method of choice [4]. The benefit of DMPA relates to the fact that; it is 99% effective at preventing pregnancy when used properly, requires only one injection every 3 months; and offers extended protection due to the crystallized progestin that slowly dissolves into the bloodstream [5].

Due to these merits it has been used as a contraceptive agent by millions of women in more than 90 countries since 1967 and was approved for use in several developing countries in 1992 [6]. Medroxyprogesterone acetate (17-acetoxy-6-methylpregn-4-ene-3,20-dione; MPA), a synthetic progesterone analog, is used in conception and hormone replacement therapy (HRT) by millions of women worldwide which contraception mechanism is the inhibition of ovulation [7].

Corresponding author: Sharma S, Department of human anatomy, people's dental college and hospital, 4 nayabazar Kathmandu, Nepal, Tel: +97714390692; Fax: +977-143-906-92; Email: sam2shree@gmail.com

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Compared to other progestin-only contraceptives, DMPA contains substantially higher levels of progestin [8]. A 90 day dosage of DMPA adds up to 150 mg, significantly higher than the 90-day dosages of the progestin-only pill (POP) (31.50 mg), Mirena IUD (1.8 mg) and Implanon/Nexplanon (etonogestrel implant) (6.3 mg) [9]. Consequently, DMPA is associated with more side effects, including irregular menstruation, anxiety, headaches, weakness, fatigue, bloating, abdominal pain and weight gain [10]. Recent data revealed an increased risk of fracture caused by the DMPA-induced lack of estrogen over extended periods of time, particularly in women who have not yet attained peak bone mass [11]. Additionally, many users experience delays in fertility following discontinuation [12]. DMPA usage is also directly linked to amenorrhea in 70% of users after 2 years [13]. So this study intend to observe the structural changes in the ovary and uterine tube to reveal the association between the long term use of DMPA and pathological changes in the ovary such as decrease ovarian follicles, follicular atresia as well as epithelial atrophy in the uterine tube, which may contribute for the delay return of fertility, in DMPA users.

MATERIALS AND METHODS

60 healthy female Wistar Albino female rats weighing 150-200 g were obtained from the animal house of BPKIHS, Dharan. They were given standard pellet diet and drinking water ad libitum. They were maintained in a well-ventilated room at controlled ambient temperature (25°C) with a 12 h in alternating light-dark cycle. They were housed in polypropylene cage (40 cm × 25 cm × 15 cm) with the paddy husk bed, which was changed on every 4-5 days [13].

Preparation of the depot-medroxyprogesterone acetate solution

DMPA vials sold as 'Sangini' in Nepal are manufactured by Pfizer pharmaceuticals group. One vial containing 150 mg/ml suspension was diluted in distilled water to make the required concentration for experiment. The experimental groups were given DMPA in the doses of 2.4 mg intramuscularly per week for 8 weeks.

While the control group rats were treated with 0.25 ml of normal saline intramuscularly for 8 weeks. The doses were converted from human dose to rat dose by using multiplication factors for dose conversion between different species by Paget and Barnes as follow [14].

Drug to be given for rat = 0.018 × Human dose

Experimental design and treatment regimen

Animals were divided into 2 groups, with in each group n=15 rats, Total number n=30 **(Table 1)**.

Table 1. Experimental design.

Group	Sample size	Duration of dose
Control	15	8 weeks
Case	15	8 weeks

Experimental group rats were sacrificed one day after the completion of 8 weeks. The rats were anesthetized with Ether soaked in cotton. Ovaries and uterine tubes were fixed by *in vivo* perfusion method. After completion of perfusion, the organs were isolated from the body with help of scalpel and forceps and post fixed for 24 h with Bouin's Fluid. Thus obtained organs were cut into pieces of 3 mm to fix in neutral buffered formalin for 7 days and processed for making paraffin blocks. The blocks were trimmed, sectioned at 4 µm thicknesses and stained by routine H&E (Hematoxylin and Eosin) staining. All sections were examined under light microscope.

Ethical clearance was taken as per the guideline of Institutional Ethical Review Board (IERB no. 143) of BPKIHS, Dharan, Nepal.

RESULTS

The microscopic observation was done with the help of light microscope, where all the slides of case and control group rat were compared, taking the appearance of follicle and the medulla of ovary in consideration. While the uterine tube observation was mostly focused to observe the appearance of uterine epithelium.

There were remarkable differences in the follicular and medullary appearance between the normal and the experimental rat. For instance, in the case group rat's ovarian follicular atresia as well as the medullary hemorrhage was noticeable compared to the placebo which is shown in **Figures 1 and 2**, respectively. Similarly, the distinguishable distortion of uterine epithelium was seen in case group rats compared to the normal group rats as demonstrated in **Figures 3 and 4**, respectively.

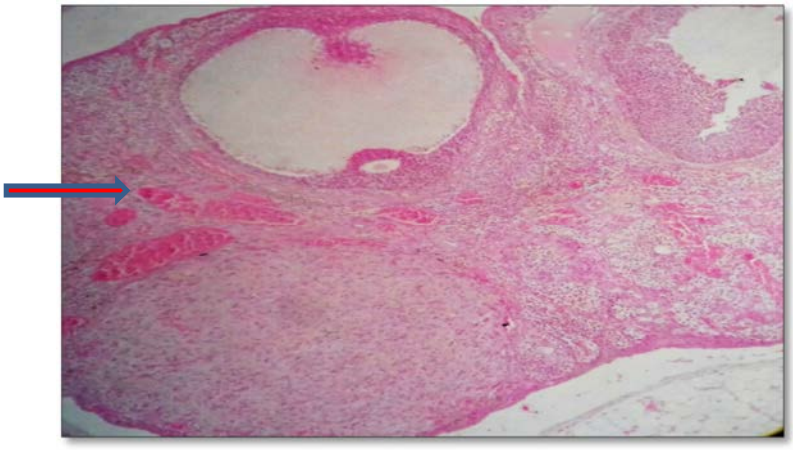

Figure 1. T.S of ovary of case group rat showing the medullary hemorrhage and follicular degeneration (H & E x10). *Red arrow showing hemorrhage. Blue arrow showing follicular atresia and degeneration*

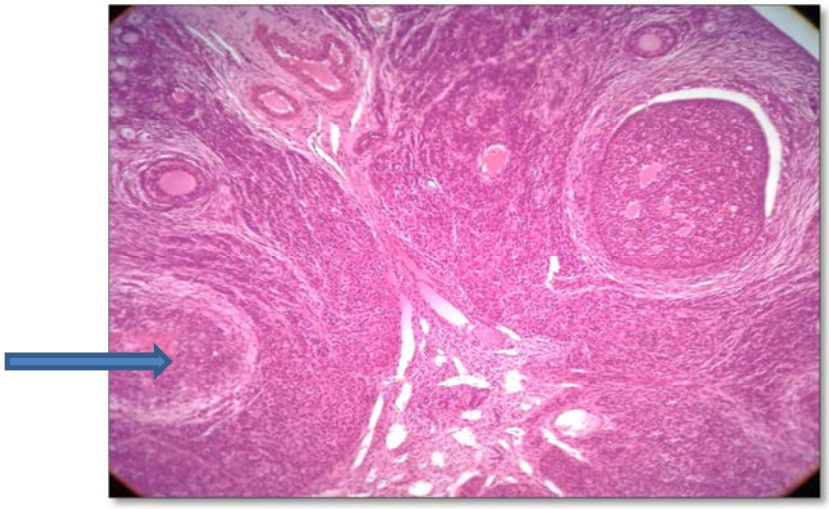

Figure 2. T.S of ovary of normal group rat ((H&E x10).

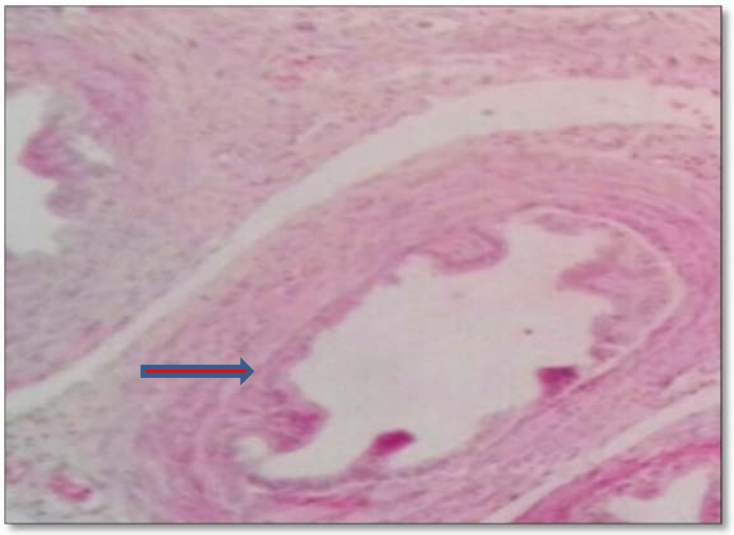

Figure 3. T.S of uterine tube of case group rat, arrow showing the epithelial atrophy (H&E x10).

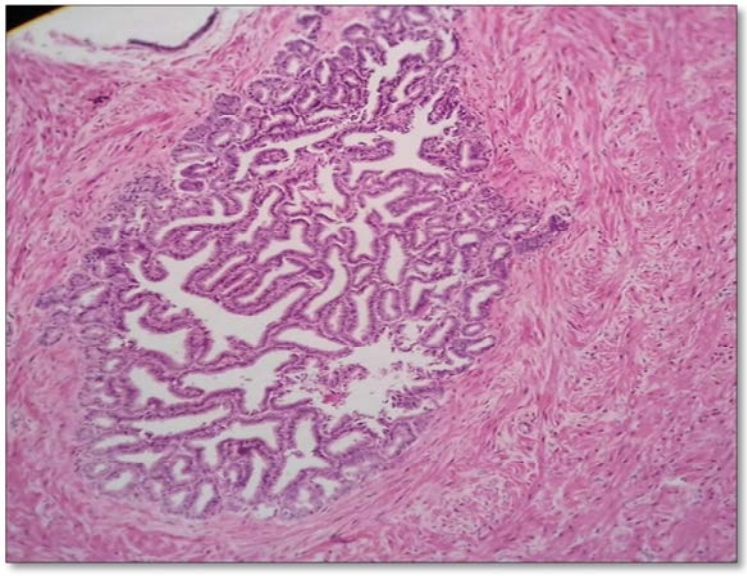

Figure 4. T.S of uterine tube of normal group rat (H&E x10).

DISCUSSION

DMPA has been used for many purposes but it is mostly used for contraception by many females without any specific medical supervision particularly in developing countries. With increased popularity, this drug has been also in attention for the peaking osteoporosis, obesity and delayed fertility return problem in the users. Present study about the effects of DMPA in ovary and uterine tube of rat found distinguishable distortion in the respective viscera which might attribute for the delayed fertility return.

The medullary hemorrhage and follicular atresia was significant in the ovary of the DMPA treated rat compared to the untreated rat which is shown in photomicrograph 1 and 2 respectively. Similar findings were reported by a study conducted in rats by Bhowmik and Mukherjea [15] who found the degeneration of ovarian follicle along with follicular atresia in DMPA treated rat which can be due to the apoptotic effect of progesterone on the ovarian follicle. While the hemorrhage can be due to the toxic effect of DMPA [15].

Another study conducted by Sivakumar and Kamakshi [16] revealed significant decrease in the number of follicles as well as increased follicular atresia with massive size corpus luteum in DMPA treated rat.

In this study, severe atrophy of uterine epithelium was observed in the experimental group rat compared to the control group as shown in photomicrograph 3 and 4 respectively which can be due to the anti-estrogenic effects of progesterone in the oviduct where progesterone blocks estradiol-inducible secretory proteins and induces deciliation and cessation of secretory activity of the oviductal epithelium. It can be further aggravated by the disturbance in the cell growth and differentiation due to the effect of steroid hormone.

Another study conducted by Gordon et al. [17] observed the similar findings, where deciliation and cessation of epithelial growth in the oviduct of progesterone treated Rhesus monkeys was reported.

Many other studies have found the association of progesterone with the morphological and functional alteration of uterine tube. For example, a study conducted by Hegazy and Hegazy [18]. WHO also reported the reduced mucosa and ciliary activity of uterine tube in DMPA treated rat [18].

CONCLUSION

It is believed that DMPA is the most effective contraceptive which has been popular around the world. However, many issues are ensued these days in the health of injectable contraceptive user female, such as obesity, loss of bone mineral density, etc., which are considered to be due to the adverse effect of the injectable contraceptive. This study also revealed some severe alteration in the uterine tube as well as in the ovary of rat which could pose massive impact on fertility of female. To conclude, there is dire need of more rigorous study about the impacts of DMPA in the health of the users as well as promoting the better option for contraception than the hormonal.

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CONFLICT OF INTEREST

No conflict of interest among the authors.

REFERENCES

1. Bakry S, Ahmed HA, Al-otaibi ML (2010) Prenatal exposure to medroxyprogesterone acetate. Am Eurasian J Toxicol Sci 2: 1-12.
2. WHO (1993) Facts about once-a-month injectable contraceptives: Memorandum from a WHO meeting. Bull World Health Organ 71: 677-689.
3. Speroff L, Darney PD (2005) Injectable contraception. A Clinical Guide for Contraception. 4th Edn. Philadelphia, PA: Lippincott Williams & Wilkins, pp: 201-220.
4. Hatcher R (2004) Depo-Provera injections, implants and progestin-only pills (minipills). In Hatcher RA, Trussell JS, Felicia H, et al. Contraceptive Technology. 18th Rev. Edn. New York, NY: Ardent Media, pp: 461-494.
5. Spevack E (2013) The long-term health implications of Depo-Provera. Integr Med 12: 27-34.
6. Zhang JW, Liu Y, Zhao JY, Wang LM, Ge GB, et al. (2008) Metabolic profiling and cytochrome P450 reaction phenotyping of medroxyprogesterone acetate. Drug Metab Dispos 36: 2292-2298.
7. Ratchanon S, Taneepanichskul S (2000) Depot medroxyprogesterone acetate and basal serum prolactin levels in lactating women. Obstet Gynecol 96: 926-928.
8. Pfizer (2018) Depo-Provera Contraceptive Injection, US patient labeling. Available from: http://www.pfizer.com/pfizer/download/ppi_depo_provera_contraceptive.pdf
9. Mosher WD, Martinez GM, Chandra A, Abma JC, Willson SJ (2004) Use of contraception and use of family planning services in the United States. Adv Data 350: 1-36.
10. Stacey D (2011) Depo Provera: The birth control shot. Available from http://contraception.about.com/od/prescriptionoptions/a/depoprovera.htm
11. Walsh JS, Eastell R, Peel NF (2008) Effects of Depot medroxyprogesterone acetate on bone density and bone metabolism before and after peak bone mass: A case-control study. J Clin Endocrinol Metab 93: 1317-23.
12. Tolaymat LL, Kaunitz AM (2009) Use of hormonal contraception in adolescents: skeletal health issues. Curr Opin Obstet Gynecol 21: 396-401.
13. Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR (2010) Use of depot medroxyprogesterone acetate and fracture risk. J Clin Endocrinol Metab 95: 4909-4916.
14. Paget G, Barnes J (1964) Interspecies dosage conversion scheme in evaluation of results and quantitative application in different species. In: Laurence D, Bacharach A, editors. Evaluation of drug activities: Pharmacometrics. London and New York: Acamemic Press, pp: 160-162.
15. Bhowmik T, Mukherjea M (1988) Histological changes in the ovary and uterus of rat after injectable contraceptive therapy. Contraception 37: 529-538.
16. Sivakumar G, Kamakshi K (2012) Study of oestrous cycle and histomotphometry of ovary in DMPA and a polyherbal drug treated adult female albino rats. Int J Curr Res Rev 4.
17. Niswender GD, Juengel JL, Silva PJ, Rollyson MK, McIntush EW (2000) Mechanisms controlling the function and life span of the corpus luteum. Physiol Rev 80: 1-29.
18. Hegazy R, Hegazy A (2015) DMPA-induced changes in estrogen and progesterone receptors of ampulla of rat-oviducts: An immunohistochemical study. Univers J Med Sci 3: 33-40.