

**Role of metformin, spironolactone
treatment and their combination
in estradiol valerate induced polycystic
ovarian female rats.
(*Rattus norvegicus*).**

**A Thesis
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By

Muhsin Sagheer Ghalib AL-Mozie'l

BVMS(1989) /DVM(2005)/MSc/2009)

Supervised by

Asst.Prof. Dr. Jassim.M.A. Alkalby Prof. Dr. Alaa A. Sawad

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Summary

The current study was conducted at the College of Veterinary Medicine, University of Basrah in the period extended from 9/2/2012 of 1/9/2013; in order to study the physiology impact accompanied polycystic ovary syndrome (PCOS) induced virgin female rats. One hundred twenty virgin female rats and twenty five adult male rats were used and three experiments were done:

First experiment (induction of PCOS): This experiment was designed to investigate the effects of estradiol valerate (EV) induced PCOS rats on some physiological, biochemical parameters and histological changes. One hundred twenty virgin females rats included in this experiment. Rats were divided into two control and treatment groups: Control (30 female rats) were injected with single i.m dose (0.2ml/rat) of pure corn oil. Treated group (90 female rats) were injected with single i.m dose (4mg/rat) of EV dissolved in (0.2ml/rat) of corn oil. Vaginal smear examination of all female rats was done to detect persists estrus cycle to ensure the occurrence of PCOS. After 63 days of injection, 10 females from each group were weighed and sacrificed. Blood samples were obtained from inferior vena cava of each rat and sera were separated for physiological and biochemical tests and tissue samples were obtained from ovaries, uterus, liver and pancreas for histopathological study. The results of the present experiment revealed the following:

1. Significant increase ($P \leq 0.05$) of body weight gain of virgin female rats treated with EV (PCOS) compared with control.

2. Significant increase ($P \leq 0.05$) of serum, Insulin, Resistin, insulin like growth factor-I(GF-I), Free testosterone(FT) and Dehydroepiandrosterone

Summary

Sulfate (DHEA-S) concentrations in PCOS-induced group compared with control and significant decrease ($P \leq 0.05$) in serum sex hormone binding globulin (SHBG) in PCOS induced group compared with control.

3-Significant increase ($P \leq 0.05$) of serum concentrations of Luteinizing hormone (LH), estradiol (E_2) progesterone (P_4) and prolactin (PRL) in PCOS group compared with control.

4-Significant increase ($P \leq 0.05$) of serum glucose, cholesterol(Chol), triglyceride(Tg), low density lipoprotein(LDL-C), and very low density lipoprotein(VLDL-C) concentrations and significant decrease of serum high density lipoprotein concentrations in PCOS group compared with control.

5-Significant increase ($P \leq 0.05$) in serum ALT enzyme level in PCOS group compared with control.

6-Significant increase ($P \leq 0.05$) of serum Iron and Zinc concentrations and significant decrease of Copper concentration in PCOS group compared with control.

7-Significant increase ($P \leq 0.05$) of relative weight of liver, pancreas, ovaries and uterus in PCOS-induced group compared with control.

8-Histopathological examination revealed arrested folliculogenesis, small atretic follicles, hyperthecosis and follicular cysts in the ovary of PCOS group compared with control. Uteri of PCOS rats showed thin uterine epithelium and enlarged uterine glands. Liver sections showed vacuolated hepatocytes and pyknotic nuclei and whereas pancreatic sections from PCOS rats revealed hyperplasia of islet of Langerhans.

Second experiment (treatment): This experiment was designed to evaluate the role of metformin, spironolactone and their combination therapy in amelioration the changes of EV-induced PCOS female rats.

Summary

The remainder animals from the first experiment were used in this experiment as follow:

Twenty rats from the control group of the 1st experiment were daily administrated with (0.2ml) /rat of D.W by oral gavage and 80 rats from PCOS-induced rats group were divided into four equal subgroups (20 PCOS-induced rats per each), daily administrated by oral gavage with 0.2ml/rat D.W(PCOS-induced subgroup), 50mg/kg b.wt of metf (PCOS-Metf subgroup), 2.5mg/kg b.wt of SPL (PCOS-SPL subgroup), and combination of metf 50mg and 2.5mg/kg b.wt of SPL (PCOS-Metf-SPL subgroup). The treated was extended for 15 days. At the end of the treatment period 10 rats from each subgroup were sacrificed to obtain internal organs and serum to study the same parameters as in 1st experiment. The results revealed the following:

1-Significant improvement ($P \leq 0.05$) of serum insulin, resistin, IGF-I, SHBG, DHEA-S and FT concentrations in PCOS rats treated with metf, SPL and their combination compared with PCOS non treated female rats.

2-Significant increase ($P \leq 0.05$) in serum FSH concentration and significant decrease of serum LH, E₂, P₄ and PRL concentrations in PCOS female rats treated subgroups compared with PCOS non-treated subgroup and the metf subgroup appeared the best among other treated subgroup.

3-Significant improvement ($P \leq 0.05$) of serum glucose concentration and lipid profile in PCOS female rats treated subgroups compared with PCOS non-treated subgroup.

4-Significant increase ($P \leq 0.05$) of serum AST and ALT enzymes concentration in PCOS treated subgroups compared with PCOS non-treated subgroup.

Summary

5-Significant improvement ($P \leq 0.05$) of serum Fe, Zn and Cu concentrations in PCOS treated subgroups compared with PCOS non-treated subgroup.

6-Significant decrease ($P \leq 0.05$) of body weight in PCOS treated subgroups compared with PCOS non-treated subgroup. On the other hand significant decrease ($P \leq 0.05$) of the relative weight of ovaries, uteri, liver and pancreas were observed in PCOS treated subgroups compared with PCOS non-treated subgroup.

7-The histological study revealed normal architectures of the ovaries in the PCOS female rats treated with metf, SPL and their combination with some old follicular cysts compared with PCOS non-treated subgroup. Whereas, uteri of PCOS treated female rats showed active uterine glands and thick myometrium. Also, the liver of PCOS treated female rats appeared in normal architecture compared with control non-treated. The pancreas sections appeared in normal limit in all treated subgroups compared with control.

Third experiment (mating): This experiment aimed to evaluate the fertility efficiency of PCOS-induced female rats after treatments. Remainder animals from 2nd experiment were mated with 25 healthy adults' males each 2 females were coupled with one male. The results revealed that the fertility rates of the females treated with metf, SPL and both metf-SPL were 80%, 40% and 60% respectively compared with PCOS rats non-treated subgroups 0%, but still less than that of control 100%.