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Der Pharma Chemica, 2015, 7(4):234-236  
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X  
CODEN (USA): PCHHAX

## Effects of pioglitazone on improving the quality and fertility of ewes during the breeding season

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### ABSTRACT

Pioglitazone is the oral anti-diabetic drug and it needs insulin to exert its effects and it reduces insulin resistance in environment. This drug is a potent and specific agonist for PPAR. The purpose of this study is testing the effect of different doses of pioglitazone on the ovulation hormones. This experiment is done in a completely randomized block design and compared with Duncan test. In this experiment 16 sheep with an average of 3 to 4 years and weighing about 60 kg were used. Ewes were randomly divided into 4 groups. The control group received no treatment, treatment 1 received 10mg of pioglitazone, treatment 2 received 20 mg of pioglitazone, treatment 3 received 30 mg of pioglitazone. The pioglitazone treatment was given orally for 42 days. The first blood sampling was performed 2 times first blood sampling was before treatment and the second was after the forty-second days after ram up. In this study, serum concentrations of LH, FSH, estrogen, progesterone, insulin, leptin, cholesterol and triglycerides were measured. The results of this study shows that serum levels of estrogen, progesterone, 1, 2 and 3 compared to control treatments were significantly different ( $P < 0.05$ ). Treatment 1 of FSH was significantly different compared to control group ( $P < 0.05$ ). Treatment 1 insulin was significantly different compared to control group ( $P < 0.05$ ). Treatments 1, 2 and 3 of leptin were significantly different compared to control group ( $P < 0.05$ ). The results of this experiment showed that pioglitazone may have significant effects on hypothalamic-pituitary and ovarian hormones.

**Keywords:** Pioglitazone, Quality, Productivity, Ewe

### INTRODUCTION

Pioglitazone is an oral anti-diabetic drug. The mechanism of anti-diabetic effect of pioglitazone is on insulin resistance in peripheral tissues and the liver. This drug is a potent agonist for the receptor in insulin-sensitive tissues, such as adipose tissue, skeletal muscle and liver and pharmacologically derived from the thiazolidinediones. Pioglitazone needs insulin to exert its effects. The drug reduces their distance to insulin. Thiazolidinediones pioglitazone derivatives, a relatively new drug approved for the treatment of type II diabetes [1], and improves sensitivity to Hirsute and insulin and lowers bloods grand causes ovulation in patients with polycystic ovary syndrome [2]. A study that examined the effect of pioglitazone on monkeys has shown that pioglitazone has a role in normal men stroll cycles, Insulin resistance and mechanical role in maintaining the lack of ovulation in most female monkeys [3]. In women with polycystic ovary syndrome that treated with metformin significantly improved spontaneous ovulation and response to gonadotropins and ovulation and reduced androgen levels and increased fertility have been shown [4]. Pioglitazone decreases insulin resistance in adipose tissue, liver and muscles. The present study was examined the effect of different doses of pioglitazone on hormones and other factors affecting ewe ovulation.

## MATERIALS AND METHODS

In this experiment 16 sheep with an average age of 3-4 years and weighing about 60 kg were used. Ewes were randomly divided into 4 groups and in each group 4 experimental units (ewe) was located. The control group received no treatment, treatment 1 received 10mg of pioglitazone, treatment 2 received 20 mg of pioglitazone, and treatment 3 received 30 mg of pioglitazone. The pioglitazone treatment was given orally for 42 days. 2 times the blood sampling was performed; first one was before treatment and second one was after the forty-second days after ram up. In this study, serum concentrations of LH, FSH, estrogen, progesterone, insulin, leptin, cholesterol and triglycerides were measured. In this experiment, 30 mg pioglitazone tablets of pharmaceutical company model were prepared. All experimental groups received the are mixed and had free access to water. Forty days after the second operation was performed ram and 4 were healthy and reproductively.

### - Blood manner, separating the serum samples and measured variables:

Blood samples were taken from the jugular vein by using a 20 mL syringe. Serum samples were removed and tested until the ELISA was placed at -20° C. Serum samples sent to the laboratory and diagnostic tests were performed on the hormonal and immune Quality. In this study, serum concentrations of LH, FSH, estrogen, progesterone, insulin, leptin, cholesterol and triglycerides (a corporate kit, drag, Germany) was to measure. Detection the levels of hormones in this study was performed by Immune enzymatic as say and by using a photometer (ELISA Reader Stat fax303 making America).

### - Statistical Analysis:

Data were analyzed by using SAS statically software. The data from this study, design in completely random block and normally distributed data Citizen Sheep (Ryan Boehner) and compared with a multiple range test Duncan.

## RESULTS

The results of this study, show that serum levels of estrogen, progesterone, LH 1, 2 and 3 that compared to control treatments were significantly different ( $P < 0.05$ ) (Table 2.1).

FSH treatment 1 was significantly different compared to control ( $P < 0.05$ ) (Table 2). Insulin treatment 1 was significantly different compared to control ( $P < 0.05$ ) (Table3). 1, 2 and 3 in leptin treatment compared to the control group was significantly different ( $P < 0.05$ ) (Table3).

**Table 1: Comparison of estrogen and progesterone**

Treatment 3	Treatment 2	Treatment 1	control	variables
45.9662 <sup>b</sup> ± 0.28825	45.5338 <sup>b</sup> ± 0.28352	45.9212 <sup>b</sup> ± 0.7460	43.8162 ± 0.49359 <sup>a</sup>	E <sub>2</sub> (nmol/L)
1.6762 <sup>b</sup> ± 0.00999	1.6912 <sup>b</sup> ± 0.00441	1.6787 <sup>b</sup> ± 0.00718	1.6462 ± 0.00981	P <sub>4</sub> (nmol/L)

*Dissimilar letters are significantly different ( $P < 0.05$ )*

**Table 2: Comparison of LH and FSH**

Treatment 3	Treatment 2	Treatment 1	control	variables
0.88888 <sup>b</sup> ± 0.015530	0.87950 <sup>b</sup> ± 0.012700	0.88100 <sup>b</sup> ± 0.005871	0.85100 <sup>a</sup> ± 0.007008	LH (mlu/mL)
0.57525 <sup>ab</sup> ± 0.002477	0.57538 <sup>ab</sup> ± 0.005669	0.58012 <sup>b</sup> ± 0.003889	0.566500.004844 <sup>a±</sup>	FSH (mlu/mL)

*Dissimilar letters are significantly different ( $P < 0.05$ )*

**Table 3: Comparison of Insulin and leptin**

Treatment 3	Treatment 2	Treatment 1	control	variables
28.5100 <sup>a</sup> ± 0.28642	29.7188 <sup>bc</sup> ± 0.32444	30.448 <sup>c</sup> ± 0.27920	29.962 <sup>ab</sup> ± 0.29874	Insulin (mol/L)
6.57662 <sup>c</sup> ± 0.025415	6.57238 <sup>bc</sup> ± 0.015003	6.54513 <sup>b</sup> ± 0.019751	6.45200 <sup>a</sup> ± 0.016694	Leptin (ng/mL)

*Dissimilar letters are significantly different ( $P < 0.05$ )*

## DISCUSSION

The present study showed that the effect of pioglitazone on serum estrogen at level of 0.01 was highly significant and Treatments 1, 2 and 3 were significantly different compared to the control group. Mesbah study that evaluates the 30 mg / kg / day of metformin in rats has shown that estradiol levels were significantly increased that was consistent with this study [5]. The study of Rao Zhou and colleagues, which examines the 3 mg/Kg pioglitazone for 7 months in monkeys, has been demonstrated that pioglitazone reduces serum estradiol level that was not match to this

study[6].The present study showed that the effect of pioglitazone on serum progesterone at levels of 0.01was very meaningful and treatments 1, 2 and 3were significantly different compared to the control group. The results of Glueck study (2002), which examines the 45 mg of pioglitazone plus metformin for 10 months in humans, has shown that pioglitazone in with metformin increases the sex hormones, and was consistent with the present results [7].

The present study showed that the effect of pioglitazone on serum FSH level was pointless at level of 0.05. FSH in treatments 2 and 3 showed no significant difference compared to control group and treatment 1compared to control group was significantly different. The study showed that' serum levels of insulin in treatment 1was significantly different compared to the control. The results of Ziaie et al study showed that the rate of 30 mg of pioglitazone for 12 weeks in humans has been resulted in significant changes of fasting insulin levels [8].

The present study showed that the effect of pioglitazone on serum leptin at levels of 0.01was very significant and treatments 1, 2 and 3 compared to control group were significantly different. The results of Brannian and colleagues (2008) study showed that pioglitazone caused a decrease in serum leptin levels. Leptin is essential for a function of the reproductive system in balancing the body's energy reserves. The presence of high levels of leptin receptor in the hypothalamus-pituitary-gonadal axis indicates all levels of leptinin the regulation of reproduction, including a set of complex functions. Leptin not only acts through the hypothalamus- pituitary but also directly effects on the target organs such as the uterus, placenta, and mammary gland. Experiments show that leptin is produced by the ovaries and estradiol stimulates leptin production [9]. Hypothalamus causes leak age of gonadotropins to the pituitary, control secretion of gonadotropin from the hypothalamus is done by release of GnRH. Gonadotropins (LH, FSH) release from the pituitary gland and in the early follicular phase, FSH secretion is increased ovarian estrogen and increased LH during the luteal phase caused increasing of progesterone. The Leptin increases pulse of LH is increased (hormones Applied Animal [10, 11]. Pioglitazone increased secretion of gonadotropins and stimulates ovulation and reduces the effectiveness of contraceptives [12]. Pioglitazone is a potent agonist on insulin receptors and has direct effect on insulin, it increases insulin and caused a decrease in blood sugar.

#### CONCLUSION

The results of this experiment showed that pioglitazone may have significant effects on hypothalamic- pituitary and ovarian hormones.

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