THE EFFECT OF SOME ANTI-INFLAMMATORY ON SOME BIOCHEMICAL AND SEXUAL HORMONES IN PREGNANT EWES

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ABSTRACT

The present study was delineated to asses the effects of some nonsteroidal anti-inflammatory (Flunoxin, meloxicam, phenylbutazone and Diclofenac) on some biochemical profiles and females sex hormones of pregnant ewes. This work was performed on 20 clinically healthy mature pregnant ewes. They were classified into five groups (4 animals for each). The first group was kept as control. The second group was injected (I/V) by Flunixin meglumine (1.1 mg/kg) for three successive days. The third group was injected (I/V) by meloxicam (20 mg/kg) for three successive days. While the forth group was injected (I/M) with diclofenac (1 mg/ml) for three succive days. The fives group was injected (I/M) by phenylbutazone (4.4 mg/kg) for three successive days).

Our data revealed that a significant decrease in total protein and albumen concentrations in G3 and group G5 after one day and significant decrease in total protein obtained in all treated groups after two days from injection of tested drugs. This decrease was also observed in G3, G4 and G5 after 3 and 7 days from the begging of the experiment and it was disappeared after 14 days of the experiment. While the significant decrease in albumen also recorded in G3, G4 and G5 after two days from the beginning while it was only recorded in G4 after three days and at the G3 at the 7^{th} day from the beginning of the experiment then it was decline at all tested group from the 14^{th} day to the end of the experiment. The globulin concentrations displayed a significant decrease in G2, G3, G4 and G5 after two and three days then it was disappeared at all tested groups to the end of the experiments.

The present study showed a significant increase in ALP concentration in G3 and G4 at the 7^{th} day from the beginning of the experiment. Meanwhile, the significant decrease in ALP was recorded at the G3, G4 and G5 at 21^{st} day from the beginning of the experiment. Moreover, a transient significant increase in AST concentrations in G2 was recorded after one day that completely disappeared at the second day till the end of the experiment. Meanwhile, a significant decrease in AST was observed in G4 com-

pared to G1 and G2 at 21st day. While there were no significant differences in ALT concentration in all treated groups. Our results reflected a significant increase on urea concentration in G2, G4 and G5 after one day. While after 14 day a significant decrease in urea concentration was recorded in G5.

The present study reveled a significant decrease in serum calcium concentration in G2, G4 and G5 at the first day, while at the second day it was recorded at G3, G4 and G5 and in all treated groups at 3rd day while at the 7th day it was recorded in G4 and G5 while at 14th day the significant decrease demonstrated at all treated groups and it was demonstrated in G4 and G5 compared to that of G3 at 21st day. At the 28th day the significant decrease in serum calcium concentration was recorded in G5 compared to that of G2. The significant decrease in serum phosphorus concentration in G2, G4 and G5 at the first day, in G5 after the second day, in all treated groups at the 3rd, 7th and 14th days and recorded in G4 and G5 at 21st day. Meanwhile, sodium concentration displayed a significant increase in G3, G4 andG5 at the first day, in G5 after two days and in all treated groups after 3 and 7 days. Moreover, a significant increase in potassium concentrations was recorded in G3, G4 and G5 at the first, 2nd, 3rd, 7th and 14th days from starting of the work.

Our study showed a significant decrease in estradiol concentration in G2, with a significant increase in its concentration in G3 and G4 at 28th day from the begging of the work. While, the progesterone concentrations exhibited a significant decrease in G2, G4 andG5 at the 7th day post starting the experiment.

INTRODUCTION

Non-steroidal anti-inflammatories (NSAIDs) reminiscent of carprofen, flunixin, ketoprofen, sodium salicylate, meloxicam and phenylbutazon are analgesic, antipyretic, and, as their name implies, anti-inflammatory drugs, which are widely used for the treatment of a variety of veterinary disease conditions in which control of pain and inflammation is desired **(Miksa, et. al. 2005)**.

Cyclooxygenases (COXs) are bifunctional hemoproteins that catalyze the bisoxygenation of arachidonic acid to prostaglandin H2, which serves as the common precursor for the synthesis of prostaglandins, prostacyclins, and thromboxanes, collectively known as prostanoids **(Chan et al. 1999)**. Two isoforms of COX have been identified COX-1 and COX-2 is induced by inflammatory conditions, growth factors, cytokines, and mitogens. It is primarily responsible for the prostanoid synthesis that mediates the propagation of inflammation, pain, and fever **(Smith and**

DeWitt 1998). Nonsteroidal anti-inflammatory drugs (NSAIDs) have different selectivity to inhibit cyclooxygenase-1 (COX-1) and COX-2 Nonsteroidal anti-inflammatory drugs (NSAIDs) have different selectivity to inhibit cyclooxygenase-1 (COX-1) and COX-2. **(Warner, et. al. 1999)**.

Flunixin meglumine was increased the pregnancy rate in 15-month-old Holstein heifers that synchronized with single or double injections of prostaglandin F(2alpha) followed by an injection of gonadotrophin-releasing hormone (gnrh) 48 hours later **(Guzeloglu, et. al., 2007)** . Moreover the flunixine meglumine increased the pregnancy rates in cows that transported after 14 days from artificial insemination (AI) wherever the transportation increases the serum corusol concentrations **(Merrill, et. al., 2007)**.

The nonsteroidal anti-inflammatory drug meloxicam, a more selective cyclooxygenase-2 inhibitor will successfully inhibit labor consequently. It used as effective and safe drug to prevent preterm labor in late pregnant females of sheep **(Kaç, et. al., 2006)**. The COX-2 inhibitors exert significant relaxation in myometrium with a similar potency in nonpregnant and pregnant (before and after labor onset) tissues **(Slattery, et. al., 2001)**.

Our study was delineated to asses the effects of some nonsteroidal anti-inflammatory (Flunoxin, meloxicam, phenylbutazone and Diclofenac) on some biochemical profiles and females sex hormones of pregnant sheep.

MATERIAL AND METHODS

Drugs :

1: Diclofenac (Vetrophen®): injectable solution is a ready- to - used, clear and sterile solution (Arabcomed. Co. for Vetropharm. Co. Egypt) each ml contains 5 mg.

2: Flunixin meglumine (Flunoxin®): injectable solution is a ready- to - used, clear and sterile solution (Noorbrok. Co. England) each ml contains 50 mg.

2: Meloxicam (Metacam®) : injectable solution is a ready- to - used, clear and sterile solution (Boehringer Ingelheim. Co. Germany) each ml contains 20 mg.

3: Phenylbutazone (Butafenyl ®): injectable solution is a ready- to - used, clear and sterile solution (Laboratorios Tornel. Co. Mexico) each ml contains 200 mg.

Animals:

This work was performed on 20 clinically healthy mature pregnant ewes in a private farm. There relative body weight ranged between 60- 70 kg. They were fed on green fodder (Barseem).

wheat straw and concentrate ration ad-libitum. They were classified into five groups (4 animals for each). The first group was kept as control and injected (I/V) with saline solution. The second group was injected (I/V) by Flunixin meglumine (1.1 mg/kg) for three successive days **(Beretta, et. al., 2005)**. The third group was injected (I/V) by meloxicam (20 mg/ml for three successive days) **(Friton, et. al., 2004)**. While the forth group was injected (I/M) with diclofenac (1mg/kg) for three succive days. The fives group was injected (I/M) by phenylbutazone (4.4 mg/kg) for three successive days) **(Beretta, et. al., 2005)**.

Sampling:

The blood samples were collected from all tested groups prior the injection of tested drugs. Subsequently collected at the first, second and third days, one week, two weeks, three weeks and four weeks post injection of drugs from the beginning of the experiments. The blood samples were collected in clean centrifuge tube without anticoagulant and used for separation of clear serum. The sera were separated by centrifugation at 3000 r.p.m for 15 minutes and kept frozen at -20°C until assayed.

Analysis :

The serum samples were assayed for total proteins (TP) & Albumin **(Doumas, 1975)** alkaline phosphatase (ALP) **(John, 1982)**, creatinine (Cr) (Young et al., 1975), alanine aminotransferase (ALT) **(King, 1965)**, aspartate aminotransferase (AST) **(Reitman and Frankel, 1957)**, blood calcium **(Gindler and King 1972)**, blood phosphorus **(Drekh and Jung 1970)**, sodium **(Trinder, 1951)**, potassium **(Terri and Sesin 1958)**, esteradiol **(Abraham, 1979)** and progesterone levels **(Mcphee and Tiberghien 1987)**.

Statistical analysis: data were statistically analysed using SPSS computer program (1999).

RESULTS AND DISCUSSION

The effects of tested drugs on some biochemical parameters:

Our data revealed that a significant decrease in total protein concentration in meloxicam treated group (G3) and phenybutazon treated group (G5) after one day from their injection (Table: 1). Also the same results were obtained in all treated groups after two days from injection of tested drugs (Table: 1). This decrease was also observed in G3, G4 and G5 after 3 and 7 days from the begging of the experiment and it was disappeared after 14 days of the experiment (Ta-

ble: 1). Moreover, the significant decrease in albumen concentration was recorded in meloxicam treated group (G3) and phenybutazon treated group (G5) after one day from their injection (Table: 1). It also recorded in meloxicam treated group (G3), diclofenac treated group (G4) and phenybutazon treated group (G5) after two days from the beginning of the experiment (Table: 1). The significant decrease in albumen concentration was only recorded in G4 after three day from the injection and at the G3 at the 7th day from the beginning of the experiment then it was decline at all tested group from the 14th day to the end of the experiment (Table: 1). The significant decrease in total protein and albumen concentrations were recorded with some anti-inflammatory for instance carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs **(Luna, et. al. 2007)**. The decreases in serum protein and albumin concentrations in dogs that received carprofen were caused by altered mucosal permeability of the gastrointestinal tract. **(Raekallio, et. al. 2006)**. Moreover, the phenylbutazone alone and its combination with flunixin meglumine were induced a significant decrease in serum total protein, albumin, and globulin of treated horses **(Reed, et. al, 2006)**.

The significant decrease in globulin concentrations was recorded in G2, G3, G4 and G5 after two and three days post the injection then it was disappeared at all tested groups to the end of the experiments (Table: 1). That supported by a results obtained by **Reed, et. al (2006)** who suggested a significant decrease in globulin concentration with phenylbutazone alone and its combination with flunixin meglumine in horses.

The significant decrease in plasma total protein might be attributed to the effect of tested drugs on the albumen and globulin concentrations.

The effects of tested drugs on some liver and kidney functions parameters:

The present study revealed that, there is a significant increase in ALP concentration in meloxicam and deciophenic treated groups (G3 and G4) at the 7th day from the beginning of the experiment. Meanwhile, the significant decrease in ALP was recorded at the G3 (meloxicam treated group), G4 (diclofenac treated group) and G5 (phenylbutazon treated group) at 21 day from the beginning of the experiment compared to non treated group (G1) (Table: 2). The decrease in ALP might be attributed to the activity of the tested anti-inflammatory on cyclooxygenase (COX)-2 predominantly that appeared in regression of hepatocellular carcinoma in diseased patients **(Dohmen , et. al. 2006)**.

Regarding the effect on the AST our study revealed a transient significant increase in AST concentrations in flunoxin treated group (G2) after one day from the beginning of the injection that completely disappeared at the second day till the end of the experiment (Table: 2). Mean

while, a significant decrease was observed in diclofenac treated group (G4) compared to non treated control group (G1) and flunoxine treated group (G2). While there were no significant differences were recorded in ALT concentration in all treated groups (Table: 2). Regarding the effects of tested drugs on urea concentration our results reflected a significant increase on urea concentration in flunoxin, diclofenac and phenybutazon treated groups (G2, G4 and G5) compared to other test groups (G1 and G3) after one day from the beginning of the experiment (Table: 2). While after 14 day a significant decrease in urea concentration was recorded in phenybutazon treated group (G5) (Table: 2). Meanwhile, renal dysfunction, hepatic events and gastroduodenal as well as large- and small-bowel effects are considered the mean problem of the nonsteroidal anti-inflammatory drugs **(Simon, 1994)** .

Our data reflected a significant increase in creatinine concentration in phenylbutazon treated group (G5) after one day from beginning of the work. The same result was recorded at flunoxin treated group (G2) and diclofenac treated group (G4) at the 14^{th} day from the beginning of the experiment and also recorded in G2 at the 21^{st} day (Table: 2). Under normal conditions, NSAIDs have relatively little effect on the kidney because of low renal production of prostaglandins **(Wen, 1997)**. On the other side of view, the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) may induce marked side effects, especially on renal function. Some of these side effects are the consequence of inhibition of prostaglandin (PG) synthesis that indispensable to maintain renal function **(De Torrenté, 1983)**. Acute renal failure with the transient use of nonsteroidal anti-inflammatory drugs (NSAIDs) is described **(Tsubol, et. al. 1997)**.

The effects of tested drugs on some electrolytes:

The present study reveled a significant decrease in serum calcium concentration flunoxin, diclofenac and phenylbutazon treated groups (G2, G4 and G5) at the first day from starting of the work, while at the second day the significant decrease was recorded at meloxicam, diclofenac and phenylbutazon treated groups (G3 , G4 and G5) (Table: 3). At the 3^{rd} day it was recoded in all treated groups compared to control group G1 and at the 7^{th} day it was recorded at G4 and G5 while at 14^{th} day the significant decrease demonstrated at all treated groups and it was demonstrated in G4 and G5 compared to that of G3 at 21^{st} day. At the 28^{th} day the significant decrease was recorded in G5 compared to that of G2 (Table: 3).. The significant decrease in plasma calcium level might be consequent to rapid increase in its renal execration that resulted from renal disturbance by inhibition of prostaglandin (PG) synthesis that indispensable to maintain renal function **(De Torrenté, 1983)**. Moreover, the change in the Ca2+ influx pathway properties induced by anti-inflammatory may involve changes in the metabolism of phosphoinositides but

not of the arachidonate metabolism (**Varecka, et. al. 1997**).

Our data reflected a significant decrease in serum phosphorus concentration in flunoxin, diclofenac and phenylbutazon treated groups (G2, G4 and G5) at the first day from starting of the work. The decrease was recorded in and phenylbutazon treated group (G5) after at the second day from the beginning or the experiment (Table: 3). At the 3rd, 7th and 14th days the significant decrease was recoded in all treated groups compared to control group (G1). While it was recorded in G4 and G5 compared to G1 and G3 at 21st day from the beginning of the work (Table: 3). The significant decrease was disappeared at 28th day. These results might be discussed in the same manner of that of serum calcium concentration which mirrored the rapid renal execration of phosphorus (**De Torrenté, 1983**).

Regarding the effects of tested drugs in sodium concentration the present data revealed a significant increase in sodium concentration in meloxicam, diclofenac and phenylbutazon treated groups (G3, G4 andG5) at the first day from starting of the work, it also recorded in phenylbutazon treated groups (G5) after two days (Table: 3). The significant increase was demonstrated in all treated groups (G2, G3, G4 andG5) after 3 and 7 days from the beginning of the experiment then it was diminished till the end of work (Table: 3). The significant increase in sodium concentration might be attributed to impairment of renal permeability to the sodium ions that elevate the plasma sodium levels (**Wen, 1997**).

Our data mirrored a significant increase in potassium concentrations in meloxicam, diclofenac and phenylbutazon treated groups (G3, G4 and G5) at the first, 2nd, 3rd, 7th and 14th days from starting of the work (Table: 3). This increase was completely disappeared at 21st and 28th day from the beginning of experiment. Although the clinical benefits and safety of nonsteroidal anti-inflammatory drugs are well established, the drugs may adversely affect renal perfusion, electrolyte balance, and blood pressure in susceptible patients. Hyperkalemia is the most frequently observed adverse effect (**Zipser and Henrich 1988**).

The effects of tested drugs on female reproductive hormones:

Our study showed a significant decrease in estradiol concentration in flunoxin treated group (G2), with significant increase in its concentrations in meloxicam and diclofenac treated groups (G3 and G4) at 28th day from the begging of the work (Table: 4). This increase not induced any clinical singes resembling create abortion as a consequent of PGF (2alpha) synthesis inhibitory effect of nonsteroidal anti-inflammatory (**Scenna, et. al. 2005**).

Regarding the effect of tested drugs in progesterone concentrations the present data reflect a

significant decrease in progesterone concentrations in flunoxin, diclofenac and phenylbutazon treated groups (G2, G4 andG5) at the 7^{th} day post starting the experiment (Table: 4). Our results is supported by the results obtained by **Hinrichs and Watson (1991)** who suggested that, the phenylbutazon reduce the progesterone level in treated mars after 5 days post ovulation that antagonized by intramuscular injection of progesterone (250 mg). On the other hand, phenylbutazon not interfere with the function of corpus luteum in treated mares **(Archbald, et. al. 1983)**. Furthermore, the transient decrease and subsequent recovery in progesterone concentrations was observed during early pregnancy in llamas after injection of flunixin meglumine **(Aba, et. al. 2000)**. Moreover, nonsteroidal anti-inflammatory drugs successfully inhibit labor consequently it used as effective and safe drug to prevent preterm labor in late pregnant females of sheep **(Rac, et. al., 2006)**.

Table (1): The effects of flunixin meglumine (1.1 mg/kg), meloxicam (20 mg/ml), diclofenac (1 mg/ml) and phenylbutazone (4.4 mg/kg) on plasma proteins of pregnant sheep. Mean ± S.E n=4

Variable	Time (Day)	Group				
		G_1	G_2	G_3	G_4	G_5
Total protein (gm/dl)	0	6.77 ± 0.18^{a}	6.55 ± 0.38^{a}	6.22 ± 0.80^{a}	7.77 ± 0.41^{a}	6.48 ± 0.62^{a}
	1	6.92 ± 0.59^{a}	6.61 ± 0.29^{a}	4.38 ± 0.46^{b}	6.59 ± 0.22^{a}	4.94 ± 0.26^{b}
	2	7.37 ± 0.79^{a}	4.83 ± 0.60^{b}	4.08 ± 0.49^{b}	4.46 ± 0.23^{b}	4.38± 0.28^{b}
	3	6.94 ± 0.56^{a}	6.07 ± 0.93^{a}	4.40 ± 0.37^{b}	3.66 ± 0.20^{b}	4.13 ± 0.19^{b}
	7	7.16 ± 0.28^{a}	6.78 ± 0.39^{a}	5.37 ± 0.34^{b}	5.61 ± 0.38^{b}	5.26 ± 0.46^{b}
	14	6.67 ± 0.88^{a}	5.86 ± 0.58^{a}	5.52 ± 0.24^{a}	6.14 ± 0.42^{a}	5.05 ± 0.47^{a}
	21	6.77 ± 0.49^{a}	6.01 ± 0.62^{a}	6.23 ± 0.71^{a}	6.73 ± 0.59^{a}	5.73 ± 0.46^{a}
	28	6.2.9 ± 0.40^{a}	6.76 ± 0.49^{a}	5.36 ± 0.58^{a}	5.95 ± 0.56^{a}	6.37 ± 0.33^{a}
Albumen (gm/dl)	0	3.78 ± 0.22^{a}	3.44 ± 0.24^{a}	3.86 0.34^{a}	3.9 ± 0.21^{a}	3.74 ± 0.30^{a}
	1	4.55 ± 0.49^{a}	3.76 ± 0.28^{ab}	2.70 ± 0.54^{b}	4.48 ± 0.26^{a}	3.14 ± 0.31^{b}
	2	4.29 ± 0.68^{a}	3.07 ± 0.41^{ab}	2.65 ± 0.38^{b}	3.02 ± 0.18^{b}	2.69 ± 0.30^{b}
	3	3.77 ± 0.30^{ac}	4.07 ± 0.73^{a}	2.76 ± 0.25^{bc}	2.42 ± 0.20^{b}	3.08 ± 0.14^{ab}
	7	4.08 ± 0.16^{a}	4.0 ± 0.26^{a}	2.70 ± 0.28^{b}	3.51 ± 0.54^{ab}	3.13 ±0.25^{ab}
	14	4.28 ± 0.35^{a}	3.85 ± 0.64^{a}	3.86 ± 0.23^{a}	3.97 ± 0.13^{a}	3.87 ± 0.17^{a}
	21	4.0 ± 0.25^{a}	3.49 ± 0.34^{a}	3.92 ± 0.34^{a}	3.92 ± 0.3^{a}	3.71 ± 0.13^{a}
	28	4.11 ± 0.14^{a}	4.03 ± 0.17^{a}	3.24 ± 0.30^{a}	3.55 ± 0.23^{a}	3.55 ± 0.21^{a}
Globulin (gm/dl)	0	2.98 ± 0.10^{a}	3.04 ± 0.20^{a}	2.54 ± 0.26^{a}	3.26 ± 0.27^{a}	4.03 ± 0.36^{a}
	1	2.30± 0.46^{a}	2.85± 0.66^{a}	1.67± 0.17^{a}	2.11± 0.10^{a}	1.80± 0.13^{a}
	2	3.07± 0.16^{a}	1.76± 0.23^{b}	1.39± 0.11^{b}	1.43± 0.15^{b}	1.71± 0.27^{b}
	3	2.84± 0.25^{a}	1.66± 0.24^{b}	1.63± 0.19^{b}	1.23± 0.11^{b}	1.05± 0.15^{b}
	7	2.83± 0.25^{a}	2.78± 0.22^{a}	2.92± 0.36^{a}	2.07± 0.24^{a}	2.18± 0.30^{a}
	14	2.64± 0.25^{a}	2.51 ± 0.32^{a}	1.61± 0.26^{a}	2.17± 0.36^{a}	1.67 ± 0.34^{a}
	21	2.76± 0.24^{a}	2.49± 0.14^{a}	2.30± 0.23^{a}	2.65± 0.31^{a}	1.80± 0.35^{a}
	28	3.18± 0.38^{a}	3.13± 0.24^{a}	2.07± 0.18^{a}	2.37± 0.24^{a}	2.18 ± 0.17^{a}

The different letters at the same raw means that there was a significant change ($P< 0.05$).

Table (2): The effects of flunixin meglumine (1.1 mg/kg), meloxicam (20 mg/ml), diclofenac (1mg/ml) and phenylbutazone (4.4 mg/kg) on some liver and kidney functions of pregnant sheep. .Mean ± S.E n=4

Variable	Time (Day)	Group				
		G1	G2	G3	G4	G5
ALP (µ//dl)	0	41.34 ± 4.71	44.14 ± 4.13	51.38 ± 4.32	42.61± 4.63	41.60± 1.93
	1	47.21 ± 3.33	49.86 ±2.34	41.21 ± 2.4	50.0 ± 2.21	46.45 ± 3.54
	2	40.13 ± 3.59	60.79 ± 2.64	41.46 ± 3.47	41.34 ± 2.30	41.52 ± 3.66
	3	45.15 ±1.76	45.50 ± 2.84	43.50 ± 4.86	49.75 ± 3.40	46.25 ± 1.62
	7	37.66 ± 2.72	40.90 ± 2.13	45.98 ± 2.95	44.32 ± 1.55	39.83 ± 1.88
	14	45.96 ± 1.09	41.70 ± 1.94	41.53 ± 1.79	42.42 ± 1.74	44.79 ± 0.62
	21	51.96 ± 3.85	46.98 ± 0.61	42.73 ± 2.84	37.83 ± 0.85	40.73 ± 1.91
	28	43.17 ± 4.21	41.15 ± 0.87	38.57 ± 1.48	43.26 ± 2.83	41.78 ± 4.15
AST (µ//dl)	0	46.77± 6.8	47.19 ± 3.84	46.52 ± 5.99	35.48 ± 3.55	42.24 ± 6.48
	1	44.94 ± 3.92	80.62 ± 6.72	60.9 ± 5.65	67.42 ± 1.10	57.78 ± 2.8
	2	55.53 ± 3.66	48.91 ± 3.03	41.65 ± 3.05	56.70 ± 6.3	53.56 ± 4.28
	3	58.08 ± 5.59	45.08 ± 3.41	59.03 ± 6.55	46.58 ± 5.83	52.98 ± 1.97
	7	54.87 ± 5.41	54.10 ± 3.73	44.05 ± 3.02	46.68 ± 2.33	44.58 ± 3.43
	14	45.21 ± 3.8	44.74 ± 3.35	43.77 ± 2.47	40.63 ± 2.93	41.54 ± 5.25
	21	54.25 ±5.22	58.18 ± 2.51	53.1 ± 2.97	41.69 ± 1.78	44.75 ± 2.87
	28	46.83 ±2.61	42.5 ± 2.13	42.31± 2.04	47.81. ± 2.66	51.39 ± 1.7
ALT (µ//dl)	0	36.17 ± 3.68	30.79 ± 3.84	36.42 ± 5.99	35.52 ± 4.86	33.70 ± 3.81
	1	40.92 ± 1.84	46.82 ± 3.83	42.34 ± 2.03	39.52 ± 4.49	43.55 ± 1.47
	2	40.75 ± 1.90	39.95 ± 1.81	38.92 ± 1.69	40.33 ± 2.93	40.04 ± 1.41
	3	43.16 ± 2.33	46.31 ± 2.49	39.08 ± 2.22	39.27 ± 0.30	43.13 ±3.56
	7	45.39 ± 3.62	45.52 ±3.32	44.59 ± 3.04	41.47 ± 1.89	41.0 ± 2.89
	14	42.43 ± 2.48	36.32 ± 3.77	40.85 ± 1.87	44.83 ± 2.83	45.02 ± 3.26
	21	42.34 ± 2.0	40.61 ± 1.38	44.56 ± 0.71	44.12 ± 1.11	41.48 ± 2.33
	28	44.06 ±3.66	45.34 ± 3.6	38.97 ± 2.41	41.34 ± 1.93	45.25 ± 3.21
Urea (mg/dl)	0	41.26 ± 2.13	39.21 ± 3.5	37.36 ± 2.4	39.10 ± 2.87	43.7 ± 3.74
	1	38.01 ± 2.33	45.56 ± 2.33	35.5 ± 2.25	40.5 ± 1.19	47.75 ± 1.1
	2	45.25 ± 1.25	46.5 ± 3.92	39.0 ± 4.54	38.5 ± 4.09	40.0 ± 2.79
	3	38.0 ± 0.57	42.2 ± 1.1	41.75 ± 2.05	38.5 ± 1.55	41.75 ± 1.43
	7	39.00 ± 2.04	39.5 ± 1.32	42.25 ± 3.35	40.5 ± 1.54	39.0 ± 2.04
	14	39.5 ± 2.39	44.5 ± 3.47	39.5 ± 1.19	40.5 ± 1.04	36.50 ± 1.04
	21	39.25 ± 2.83	42.26 ± 1.47	41.83 ± 4.68	37.07 ± 4.62	40.32 ± 0.34
	28	35.45 ± 2.83	39.75 ± 2.25	39.02 ± 3.44	39.55 ± 1.17	41.64 ± 2.0
Creatinin (mg/dl)	0	0.95 ± 0.08	0.71 ± 0.021	0.70 ± 0.022	0.75 ± 0.03	0.92 ± 0.05
	1	0.53 ±0.029	0.86 ± 0.14	0.89 ± 0.025	0.69 ± 0.02	0.95 ± 0.029
	2	0.80± 0.10	0.65± 0.19	0.95± 0.022	0.70± 0.11	0.62± 0.10
	3	0.74 ± 0.24	0.65 ± 0.027	0.75 ± 0.10	0.74 ± 0.023	0.75 ±0.042
	7	0.84 ± 0.02	0.88 ± 0.027	0.76 ± 0.028	0.66± 0.02	0.79 ± 0.04
	14	0.63. ± 0.07	0.88. ± 0.04	0.74. ± 0.03	0.86. ± 0.05	0.79± 0.07
	21	0.74. ± 0.10	1.09 ± 0.11	0.83 ± 0.04	0.74. ± 0.03	0.78. ± 0.04
	28	0.81 ± 0.026	0.76. ± 0.023	0.84. ±0.029	0.85. ± 0.018	0.79. ± 0.024

The different letters at the same raw means that there was a significant change ($P< 0.05$).

Table (3): The effects of flunixin meglumine (1.1 mg/kg), meloxicam (20 mg/ml), diclofenac (1mg/ml) and phenylbutazone (4.4 mg/kg) on some electrolytes of pregnant sheep. Mean ± S.E n=4

Variable	Time (Day)	Group				
		G_1	G_2	G_3	G_4	G_5
Calcium mg/dl	0	11.10 ± 1.60 ^{a}	12.01± 0.85 ^{a}	10.89 ± 1.82 ^{a}	11.39 ± 0.79 ^{a}	11.95 ± 2.01 ^{a}
	1	12.50 ± 1.01 ^{a}	15.66± 0.54 ^{b}	12.76 ± 0.62 ^{a}	6.83 ± 0.63 ^{c}	3.66 ± 0.32 ^{d}
	2	13.61 ± 1.30 ^{a}	11.55 ± 0.50 ^{ab}	10.02 ± 0.78 ^{b}	5.85 ± 0.70 ^{c}	4.04 ± 0.26 ^{c}
	3	16.62 ± 0.81 ^{a}	13.83 ± 0.69 ^{b}	13.40 ± 0.74 ^{b}	9.19 ± 0.38 ^{c}	8.24 ± 0.52 ^{c}
	7	14.44 ± 0.62 ^{a}	14.35 ± 0.33 ^{a}	15.90 ± 0.69 ^{a}	11.26 ± 0.41 ^{b}	9.88. ± 0.54 ^{c}
	14	14.80 ± 0.67 ^{a}	12.59 ± 0.51 ^{b}	12.59 ± 0.50 ^{b}	10.52 ± 0.45 ^{c}	8.12 ± 0.41 ^{d}
	21	14.66 ± 0.41 ^{ab}	14.86 ± 0.85 ^{ab}	15.55 ± 0.85 ^{a}	12.55 ± 0.62 ^{b}	12.82 ± 1.01 ^{b}
	28	13.27 ± 0.93 ^{ab}	15.52 ± 0.73 ^{a}	13.80 ± 0.64 ^{ab}	14.85 ± 0.85 ^{ab}	13.15 ± 0.50 ^{b}
Phosphorus (mg/dl)	0	7.72. ± 0.20 ^{a}	8.24. ± 0.81 ^{a}	8.09 ± 0.63 ^{a}	8.12 ± 0.21 ^{a}	9.89. ± 0.37 ^{a}
	1	10.45± 0.92 ^{a}	7.52± 0.65 ^{b}	10.11± 0.55 ^{a}	6.11± 0.14 ^{b}	7.22± 0.38 ^{b}
	2	9.69 ± 2.21 ^{abc}	11.18 ± 1.38 ^{bc}	12.29 ± 0.68 ^{b}	8.16± 1.02 ^{ac}	6.80± 1.08 ^{ad}
	3	11.91 ± 1.57 ^{a}	6.94 ± 0.22 ^{b}	5.80 ± 0.61 ^{b}	5.51 ± 0.48 ^{b}	5.100 ± 0.72 ^{b}
	7	12.40 ± 1.22 ^{a}	9.36 ± 0.47 ^{b}	7.30 ± 0.69 ^{b}	4.80 ± 0.59 ^{c}	4.36 ± 0.33 ^{c}
	14	14.60 ± 0.53 ^{a}	10.44 ± 0.63 ^{b}	9.77 ± 0.63 ^{b}	6.61 ± 0.44 ^{c}	10.80 ± 0.33 ^{b}
	21	15.62 ± 1.23 ^{a}	13.55 ± 1.20 ^{ac}	15.19 ± 0.43 ^{a}	11.34 ± 0.66 ^{bc}	10.52 ± 0.55 ^{b}
	28	12.77 ± 1.20 ^{a}	13.34 ± 0.44 ^{a}	11.19 ± 1.12 ^{a}	10.79 ± 0.81 ^{a}	12.16 ± 1.0 ^{a}
Sodium (mg/dl)	0	150.36± 7.98 ^{a}	156.44 ± 10.39 ^{a}	152.72 ± 9.54 ^{a}	147.01± 4.85 ^{a}	167.37 ± 12.17 ^{a}
	1	149.18 ± 6.62 ^{a}	173.80 ± 4.60 ^{ab}	198.50 ± 1.40 ^{b}	244.75 ± 14.3 ^{c}	233.75 ± 8.81 ^{c}
	2	134.27 ± 4.50 ^{a}	173.85 ± 11.02 ^{a}	196.49 ± 3.44 ^{ab}	173.32 ± 15.32 ^{a}	261.0 ± 6.62 ^{b}
	3	152.69 ± 6.84 ^{a}	194.45± 17.17 ^{b}	197.55 ± 13.04 ^{b}	279.75 ± 14.64 ^{c}	302.5 ±15.64 ^{c}
	7	147.25 ± 7.46 ^{a}	190.00± 10.0 ^{b}	213.0 ± 11.54 ^{bc}	243.75 ± 12.45 ^{c}	283.5 ± 22.03 ^{d}
	14	146.25± 13.06 ^{a}	144.25 ± 8.19 ^{a}	166.50 ± 7.80 ^{a}	178.5 ± 15.91 ^{ab}	173.25 ± 10.90 ^{a}
	21	144.75 ± 4.92 ^{a}	140.50 ± 5.69 ^{a}	160.5 ± 9.93 ^{a}	152.50 ± 8.02 ^{a}	156.5 ± 12.66 ^{a}
	28	136.75 ± 7.59 ^{a}	152.00 ± 6.98 ^{a}	146.75 ± 4.06 ^{a}	148.50 ± 10.2 ^{a}	158.5 ± 12.05 ^{a}
Potassium (mg/dl)	0	4.04 ± 0.27 ^{a}	5.11 ± 0.46 ^{a}	4.33 ± 0.58 ^{a}	4.85 ± 0.59 ^{a}	5.67 ± 0.36 ^{a}
	1	5.23 ± 0.12 ^{a}	7.77 ± 0.66 ^{ab}	9.60 ± 1.81 ^{b}	11.10 ± 1.91 ^{b}	11.09 ± 0.48 ^{b}
	2	5.62 ± 0.48 ^{a}	8.03 ± 0.64 ^{ab}	9.61 ± 0.65 ^{b}	9.85 ± 1.32 ^{b}	14.36 ± 0.86 ^{c}
	3	5.90 ± 0.56 ^{a}	7.73. ± 0.28 ^{a}	13.12 ± 0.49 ^{b}	14.34 ± 0.77 ^{bc}	15.99 ± 1.09 ^{c}
	7	7.20 ± 0.97 ^{a}	9.81 ± 0.62 ^{ab}	12.5 ± 0.81 ^{b}	10.08 ± 1.48 ^{ab}	11.67 ± 0.72 ^{b}
	14	7.91 ± 0.73 ^{a}	9.29 ± 0.47 ^{a}	12.25 ± 1.06 ^{b}	9.59 ± 0.57 ^{ac}	11.84 ± 0.91 ^{bc}
	21	7.59 ± 0.55 ^{a}	8.13 ± 0.43 ^{a}	9.13 ± 0.20 ^{a}	9.61. ± 0.72 ^{a}	8.23. ± 0.56 ^{a}
	28	9.24 ± 0.37 ^{a}	8.95 ± 0.40 ^{a}	8.98 ± 0.58 ^{a}	7.01 ± 0.95 ^{a}	9.01± 1.62 ^{a}

The different letters at the same raw means that there was a significant change ($P< 0.05$).

Table (4): The effects of flunixin meglumine (1.1 mg/kg), meloxicam (20 mg/ml), diclofenac (1mg/ml) and phenylbutazone (4.4 mg/kg) on some reproductive hormones of pregnant sheep. Mean ± S.E n=4

Variable	Time (Day)	Group				
		G_1	G_2	G_3	G_4	G_5
Estrodiol (ng/ml)	0	26.80 ± 1.82 [a]	43.77 ± 7.125 [a]	33.61 ± 9.25 [a]	44.33 ± 6.86 [a]	47.77 ± 4.28 [a]
	7	40.57 ± 2.16 [a]	39.90 ± 2.36 [a]	39.88 ± 2.58 [a]	42.75 ± 0.95 [a]	34.60 ± 4.01 [a]
	14	39.80 ± 2.46 [a]	33.11 ± 5.02 [a]	33.23 ± 4.87 [a]	38.49 ± 1.92 [a]	40.77 ± 1.56 [a]
	21	35.38 ± 0.68 [a]	35.11 ± 1.0 [a]	36.31 ± 3.65 [a]	40.13 ± 1.51 [a]	42.26 ±4.82 [a]
	28	39.58 ± 0.84 [abc]	36.98 ± 0.83 [b]	43.29 ± 1.34 [c]	42.79 ± 0.68 [c]	41.29 ± 0.84 [ac]
Progesterone (ng/ml)	0	20.63 ± 2.44 [a]	17.17 ± 3.87 [a]	16.40 ± 1.31 [a]	13.73 ± 2.58 [a]	16.91 ±1.18 [a]
	7	19.84 ± 0.86 [a]	13.50 ± 1.65 [b]	17.46 ± 0.92 [ac]	14.75 ± 1.19 [bd]	14.09 ± 0.81 [bd]
	14	17.05 ± 0.82 [a]	15.77 ± 0.50 [a]	16.31 ± 1.44 [a]	15.08 ± 0.78 [a]	16.28 ± 1.48 [a]
	21	16.05 ± 0.84 [a]	16.08 ± 0.82 [a]	17.80 ± 0.64 [a]	17.27 ± 0.38 [a]	16.34 ± 1.02 [a]
	28	18.04 ± 1.18 [a]	16.77 ± 0.95 [a]	17.03 ± 0.91 [a]	18.02 ± 0.63 [a]	16.35 ± 0.86 [a]

The different letters at the same raw means that there was a significant change ($P< 0.05$).

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الملخص العربى

تأثير بعض مضادات الالتهاب على بعض المؤشرات البيوكيميائية والهرمونات التناسلية فى إنـاث الأغنام الحوامل

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أجريت هذه الدراسة على عدد ٢٠ حيوان من إناث الأغنام الحوامل التى تم فحصها مسبقاً وذلك لدراسة تأثير بعض مضادات الإلتهاب مثل الفلونوكسين ميجلومين والميلوكسيكام والديكلوفينك والفنيل بيتازون على بعض المؤشرات البيوكيميائية والهرمونات التناسلية فى إناث الأغنام الحوامل.

تم تقسيم الحيوانات إلى خمس مجموعات (٤ حيوانات لكل مجموعة) أستخدمت المجموعة الأولى كمجموعة بينما تم إعطاء المجموعة الثانية) الجرعة العلاجية دواء الفلونوكسين ميجلومين (١ر١ ميللجرام / كجم) وكذلك تم إعطاء المجموعة الثالثة دواء الميلوكسيكام (٢٠ ميللجرام / كجم) كلاهما عن طريق الحقن الوريدى لمدة ثلاثة أيام متتالية، أما المجموعة الرابعة فلقد تم حقنها بدواء الديكلوفنيك (١ ملليجرام / كجم) وحقن الخامسة بدواء الفنيل بيتازون (٤ر٤ ميللجرام / كجم) كلاهما عن طريق الحقن العضلى لمدة ثلاثة أيام متتالية.

أوضحت الدراسة أنه قد حدث إنخفاضاً معنوياً فى نسبة البروتينات الكلية والإلبيومين فى المجموعات الثالثة، والرابعة والخامسة حتى اليوم ١٤ من بداية التجربة، كما تبين أنه حدث إنخفاضاً معنوياً فى نسبة الجلوبيلين فى كل المجموعات المعالجة فى اليومين الأول والثانى من بداية التجربة.

وبدراسة تأثير الأدوية على إنزيمات وظائف الكبد فقد تبين أنه حدث زيادة معنوية فى إنزيم الفوسفاتيز القلوى عند اليوم السابع فى المجموعتين الثالثة والرابعة ثم حدث إنخفاضاً معنوياً فى نفس الإنزيم فى المجموعات الثالثة والرابعة والخامسة عند اليوم ٢١. فى حين أنه ظهر زيادة معنوية مؤقتة فى إنزيم اسبرتات أمينو ترانس فيريز عند اليوم الأول فى المجموعة الثانية فى حين ظهر إنخفاضاً معنوياً فى نفس الإنزيم فى المجموعة الرابعة عند اليوم ٢١. فى حين أن نسبة البولينا قد زادت معنوياً عند اليوم الأول فى المجموعات الثانية، الرابعة والخامسة فى حين حدث إنخفاضاً معنوياً فى نسبة البولينا فى المجموعة الخامسة عند اليوم ١٤.

ولقد تبين أنه حدث إنخفاضاً معنوياً فى تركيز الكالسيوم والفسفور فى الدم فى حين اختفى ذلك الانخفاض فى المجموعة الثانية بعد اليوم الأول من التجربة، فى حين حدثت زيادة معنوية فى تركيز الصوديوم فى الدم فى المجموعات الثالثة والرابعة والخامسة حتى اليوم السابع كذلك حدثت زيادة معنوية تركيز البوتاسيوم فى الدم فى نفس المجموعات حتى اليوم ١٤ من بداية التجربة.

وقد أوضحت الدراسة حدوث إنخفاضاً معنوياً فى نسبة هرمون الاستروجين فى المجموعة الثانية فى حين حدثت زيادة معنوية فى نفس الهرمون فى المجموعات الثالثة والرابعة وذلك عند اليوم ٢٨ من بداية التجربة، وتبين من الدراسة حدوث إنخفاضاً معنوياً فى نسبة هرمون البروجيسترون فى المجموعات الثانية والرابعة والخامسة وذلك عند اليوم السابع من بداية التجربة.

ومماسبق يتضح أنه يمكن إستخدام مضادات الالتهاب (الفلونوكسين ميجلومين ، الميلوكسيكام والديكلوفينك والفنيل بيتازون) دون حدوث أى أثر ضار فى إناث الأغنام الحوامل.