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Clinicopathological and Reproductive Studies on The Use of Ivermectin in Ewes

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ABSTRACT

This study aimed to investigate the effect of Ivermectin (IVM) on the reproductive hormones and hemato-biochemical parameters of twenty apparently healthy ewes weighing 30-40 kg and 2-3 years old. Ewes were randomly divided into two groups (ten for each). The first group was left without treatment (control group), and the second was treated with the recommended therapeutic dose of IVM (0.2 mg/kg, S/C) one day after parturition (treated group). The study continued for three months. Blood samples were collected from the two groups at the 1st, 30th, 60th, and 90th days after IVM treatment. The current study revealed that IVM injection delayed estrous for up to 3 months (absence of estrous signs and no ovarian structures were observed by sonar examination). There was a significant decrease in hemoglobin concentration (Hb), red blood cells (RBCs) count, and packed cell volume (PCV), with a significant increase in total leukocytic count (TLC) at 30th and 60th days post-treatment (p.t.). In addition to a significant decreased at ($P<0.05$) in the activity of glutathione peroxidase (GSH) and concentrations of total antioxidants (TAC), copper (Cu), phosphorus (P), estradiol, triiodothyronine(T_3), and tetraiodothyronine (T_4) for up to 3 months. In contrast, a significant increase in concentrations of calcium (Ca), progesterone and cortisol, and activity of malondialdehyde (MDA), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) enzymes were recorded at 30th and 60th days p.t. It has been concluded that IVM delayed estrous in ewes for three months via disturbing the female reproductive hormones and the hemato-biochemical parameters. Therefore, it is recommended that IVM not be injected at least three months before the reproductive season.

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INTRODUCTION

Ivermectin (IVM) is an anthelmintic drug widely used to control both internal and external parasites in humans and animals **(Makhlouf *et al.*, 2020)**. IVM is a form of insecticide Ivermectin, abamectin, eprinomectin, and doramectin are among them. IVM consists of two compounds; dihydro-avermectin B1a (H2B1a) and dihydro-avermectin B1b (H2B1b), similar to macrolide antibiotics but it does not seem to have any antibacterial or antifungal properties. IVM is approved for use in 46 countries and is being used to treat cattle, sheep, horses, and pigs worldwide. On the other hand, IVM has a wide range of action against gastrointestinal, lung nematodes, and ectoparasites in domestic animals **(Suarez *et al.*, 2013)**. Sheep is a highly prized animal; its meat is much relished, and it is very easy to market; it allows the farmer to meet unexpected expenditure quickly **(Sania *et al.*, 2016)**. Its raising has a social role which takes many forms as performing some religious rites, in Muslim ceremonies, in marriage feasts, slaughtered to honor a respected visitor or parent.

The fertility study results revealed unfavorable effects of Ivermectin on fertility and blocked the pregnancy **(Al-jassim *et al.*, 2015)**. The endocrine disruptor resulted from the excess production of free radicals, and it is very clear that

Ivermectin attends to accumulate in fatty tissues, particularly ovarian tissues. **Shkolnik *et al*., (2011)** found that Ivermectin has a negative impact on female reproductive efficacy, especially during ovulation.

In cows, Ivermectin affects fertility, healthy status, immunity, estrous and reproduction via delaying the estrous, disturbing the female reproductive hormones, and calcium/phosphorus homeostasis. Others believe that, IVM has a positive impact on animal reproductive production **(Kadry and Hazem, 2015)**. This study aimed to investigate the effect of Ivermectin (IVM) on the reproductive hormones and hemato-biochemical parameters of twenty apparently healthy ewes

MATERIALS AND METHODS

Experimental Study

In this experiment, ewes weighing 30-40 kg and aged 2-3 years were used. Two weeks prior to the experiment, all ewes were kept under observation and were subjected to fecal examinations to ensure they are free from any parasite. Twenty mature apparently healthy ewes and free from any diseases, especially parasitic ones, were randomly divided into two groups, comprising ten animals. The first group was left without treatment and considered as a control group. The second was treated with the recommended therapeutic dose of IVM one day after parturition (treated group) (1% W/V solution of IVM, VMD Ltd, Arendonk, Belgium, 0.2 mg/kg, S/C). The experiment continued for three months **(Garg *et al*., 2007)**. All ewes were examined by ultrasound scanner (200 pie Medical Co – Netherlands - Holland).

Hematological Studies

Blood samples (10 ml) were collected via jugular venipuncture at the 1st, 30th, 60th, and 90th days p.t. The first blood sample was anticoagulated using dipotassium salt of ethylene diamine tetra-acetic acid (EDTA); It was used for the evaluation of RBCs count, Hb concentration, PCV and TLC according to **Feldman *et al*., (2000)**.

Biochemical And Hormonal Assays

The second blood sample was collected in a clean centrifuge tube and was allowed to clot. Sera were extracted from blood samples by centrifuging them at 3000 rpm for 15 minutes, and clear non-hemolyzed supernatant serum was harvested and stored at -20 °C until carrying the biochemical analysis. All biochemical parameters were analyzed using commercially available kit methods. The biochemical analysis measures the following parameters: reduced glutathione peroxidase (GSH) **(Sedlak and Lindsay, 1968)**, total antioxidant capacity (TAC) **(Cortassa *et al*., 2004)** and malondialdehyde (MDA) **(Zhang, 1992)**. Estimation of serum calcium and copper **(Ahmad *et al*., 2007)**. Serum transaminases, including (AST) and (ALT) were measured according to the method described by **Kaneko *et al*., (1997)**. All the before-mentioned parameters were measured colorimetrically using commercial kits supplied by Biodiagnostic® company, Egypt. Concentrations of estradiol, progesterone, cortisol, T_3 and T_4 were measured by using enzyme-linked immunosorbent assay (ELISA) according to **Maxey *et al*., (1992)** using commercial diagnostic ELISA kits (Nova Tec. Immudiagnostica GmbH, WaldstraBe 23 A6, D-63128 Dietzenbach, Germany)

Statistical Analysis

All data were subjected to statistical analysis (ANOVA) according to **Sendecor and Cochran, (1982)** using a computer program "COSTAT."

RESULTS

General signs

Estrous signs including redness and swelling around the vulva, were absent. The expression of estrous in ewes is not as easily detected when she has been separated from the ram for a period of time. When mature ewes are in heat, they will seek out the ram and stand still for him to mount them. Ultrasound examinations revealed no ovarian structures (follicular and luteal structures) were observed for three months post IVM injection.

Effects of IVM's on hematological parameters

By comparing the treated group results with those of the control group, normocytic normochromic anemia was observed in treated ewes at the 30th and 60th days p.t. This anemia was manifested by the significant decrease ($P<0.05$) in RBCs count, Hb concentration, and PCV% associated with the insignificant changes in MCV and MCHC values. However, a significant increase ($P<0.05$) has been recorded in TLC in treated ewes at 30th and 60th days p.t. compared with the control group. At the 90th day p.t., all these results were changed toward control values (Table 1).

Effects of IVM's on antioxidants and oxidant parameters

By comparing the mean values of the treated group with those of the control group, serum activity of GSH, and concentration TAC were significantly decreased (P<0.05) at days 30th and 60th p.t. Moreover, it was returned to control values at the 90th-day p.t. Significant increase (P<0.05) has been indicated in MDA activity in treated ewes at the 30th and 60th days. These values were directed toward the control values at the 90th-day p.t. (Table 2).

Table 1: IVM's effects on hematological parameters in ewes

Groups		RBC_S ($X10^6/\mu L$)	HB (G/DL)	PCV (%)	MCV (FL)	MCH (PG)	MCHC (G/DL)	TLC ($X10^3/\mu L$)
Control		10.58 ± 0.12[a]	10.87 ± 0.27[a]	32.91 ± 0.52[a]	31.81 ± 0.37[a]	10.27 ± 0.31[a]	33.03 ± 0.16[a]	7.34 ± 0.41[a]
Treated	1st day	10.45 ± 0.18[a]	10.85 ± 0.35[a]	33.51 ± 0.11 [a]	32.16 ± 0.13[a]	10.12 ± 0.17 [a]	32.37 ± 0.32 [a]	7.21 ± 0.64[a]
	30th day	8.70 ± 0.18[b]	8.76 ± 0.089[b]	25.28 ± 0.22[b]	29.06 ± 0.41[a]	10.06 ± 0.24 [a]	34.65 ± 0.37[a]	16.93 ± 0.03[b]
	60th day	8.55 ± 0.13[b]	9.01 ± 0.01[b]	25.88 ± 0.19[b]	30.35 ± 0.15[a]	9.93 ± 0.27 [a]	34.25 ± 0.33[a]	14.15 ± 0.12[b]
	90th day	10.55 ± 0.11[a]	10.81 ± 0.01[a]	33.61 ± 0.27 [a]	31.28 ± 0.23 [a]	10.24 ± 0.17[a]	32.16 ± 0.16[a]	7.68 ± 0.13[a]

Different letters (a or b) in the same line indicate differences according to (p< 0.05).

Table 2: IVM's effects on antioxidants and oxidant parameters in ewes

Groups		GSH (µmol /g)	TAC (mmol/L)	MDA (nmol/ml)
Control		8.25 ± 1.21[a]	1.95± 0.22[a]	2.96 ±0.56[a]
Treated	1st day	8.04 ± 1.22[a]	1.91 ± 0.11[a]	2.98 ±0.13[a]
	30th day	4.25 ± 0.41[b]	0.61 ± 0.17[b]	3.83 ±0.47[b]
	60th day	5.06 ± 0.32[b]	0.79 ± 0.28[b]	4.67±0.22[b]
	90th day	8.15 ± 1.11[a]	1.92 ± 0.12[a]	2.94 ±0.15[a]

Different letters (a or b) in the same line indicate differences according to (p< 0.05).

Effects of IVM's on serum biochemical parameters

By comparing the obtained results of the treated group with those of the control group, there was a significant increase (P<0.05) in the concentration of Ca and activity of AST and ALT enzymes in treated ewes at days 30th and 60th days p.t. Significant decrease (P<0.05) in concentrations of P and Cu in treated ewes at day 30th and 60th days p.t. were recorded while, these results were returned to normal control values at the 90th-day p.t. (Table, 3).

Table 3: IVM's effects on serum biochemical parameters in ewes

Groups		Ca (mg/dl)	P (mg/dl)	Cu (mg/ml)	AST (IU/L)	ALT (IU/L)
Control		8.19 ± 0.32[a]	5.53 ± 0.19[a]	0.87 ±0.11[a]	19.81±0.16[a]	23.71±0.25[a]
Treated	1st day	8.33 ± 0.04[a]	5.37 ± 0.22[a]	0.84 ±0.33[a]	19.05±0.31[a]	23.21±0.23[a]
	30th day	9.38 ± 0.21[b]	4.19 ± 0.26[b]	0.71±0.015[b]	33.8±0.41[b]	35.44 ± 0.61[b]
	60th day	9.69 ± 0.21[b]	4.24 ± 0.23[b]	0.75±0.013[b]	37.1±0.27[b]	37.51±0.21[b]
	90th day	8.21 ± 0.43[a]	5.61 ± 0.21[a]	0.88 ± 0.01[a]	17.1±0.18[a]	24.62 ± 0.41[a]

Different letters (a or b) in the same line indicate differences according to (p< 0.05).

Effects of IVM's on serum reproductive hormones

By comparing the results of this treated group with those of the control one, a significant decrease (P<0.05) has been encountered in estradiol concentrations, T_3 and T_4 at the 30th and 60th days p.t and returned to its normal values at 90th. On the other hand, serum progesterone and cortisol concentrations show a significant (P<0.05) increase in treated ewes at the 30th and 60th days p.t. which towered to normal control concentration at the day 90th p.t. (Table, 4).

Table 4: IVM's effects on serum reproductive hormones in ewes

Groups		Estradiol (pg/ml)	Progesterone(ng/ml)	Cortisol (ng/ml)	T_3 (ng/L)	T_4 (µg /dl)
Control		58.11 ±0.66[a]	0.91±0.05[a]	7.79 ± 0.36[a]	1.24±0.05[a]	8.04±0.42[a]
Treated	1st day	54.31 ±0.42[a]	0.93±0.03[a]	7.55 ± 0.31[a]	1.35±0.03[a]	8.25±0.31[a]
	30th day	22.31 ± 0.45[b]	2.74±0.12[b]	16.81 ± 0.78[b]	0.56±0.07[b]	5.60±0.51[b]
	60th day	29.42 ± 0.13[b]	2.12±0.18[b]	15.99 ± 0.00[b]	0.64±0.07[b]	6.20±0.12[b]
	90th day	56.21 ± 0.73[a]	0.94±0.16[a]	8.17 ± 0.62[a]	1.13±0.02[a]	8.06±0.24[a]

Different letters (a or b) in the same line indicate differences according to (p < 0.05).

DISCUSSION

Since Ivermectin is a lipophilic substance, it tends to settle in fatty tissue, especially in the ovaries, which is an essential reservoir for the medication. This may affect how long it lasts in the body and how it acts pharmacologically. Ivermectin's lipophilic nature also speeds up its distribution from the bloodstream to various tissues **(Al-jassim *et al*., 2015)**.

Effect of Ivermectin on erythrogram parameters revealed normocytic normochromic, manifested by the significant decrease in RBCs count, Hb concentration, PCV%, and insignificant changes in MCV MCHC values. A change in hematopoiesis may cause this anemia due to hepatic degenerations or decreased bile salts in the small intestine. This suggestion confirmed by **(Abdou and Sharkawy, 2004; Ashraf and Ausama 2007** and **Saqib *et al*., 2015)**. According to **Gad, (1998)** and **Zaied, (2004)**, a therapeutic dose of Ivermectin caused hepatic degeneration, cloudy swelling lymphocytic infiltration,

coagulative necrosis, and congestion of the hepatic blood sinusoids.

On the other hand, the significant increase in TLC of the treated animals is consistent with previous findings and is most likely the result of underlying stress **(Saqib *et al*., 2015)**. Treatment with IVM appeared to substantially increase the number of leukocytes as compared to the control group. This increase may have resulted from body response to any injury **(Wanji *et al*., 2017)**.

As the demand for calcium grows, the parathyroid gland secretes parathormone into the blood, raising calcium levels and causing hypercalcemia **(Schmitz DG 2007)**. At the 30th and 60th days after drug injection, there was a significant increase in calcium and a significant decrease in phosphorus levels, implying that IVM disrupted calcium/phosphorus ratio and its long duration of action contribute to this effect **(Kadry and Hazem, 2015)**.

The investigated ewes' liver enzymes (AST, ALT) were elevated at the 30th and 60th-day post-treatment; this may be attributed to the liver having the most IVM residues. **Ashraf and Ausama (2007)** reported that the level of these enzymes is increased, an increase in AST and ALT levels may be attributed to hepatic cell damage caused by the drug's direct effect resulting in the escape of these enzymes into the plasma. ALT and AST are generally assessed clinically to assess liver health as part of a hepatocellular injury diagnostic assessment **(Wang *et al*., 2012)**.

Asmaa and Mohamed, (2020) concluded that, the use of Ivermectin for the treatment of camel mange has some adverse effects on liver function tests due to oxidative stress that could last for a long time. Antioxidant administration with Ivermectin was highly suggested to reduce the drug's side effects.

The copper concentration of the treated group at 30th and 60th days p.t. was decreased than the control group. This deficiency has been related to bone disorders, diarrhea, infertility, and tachycardia, and susceptibility to anemia in ruminants **(Mohamed *et al*., 2014)**. These diseases are linked to Cu-containing enzymes' functions in cellular respiration, immune function, and erythropoiesis formation. As a result, there was a potential connection between low Cu levels and the anemia seen in sheep. The biological significance of copper deficiency and abundance in the mammalian system has piqued researchers' interest. Various diseases are caused by abnormally high copper levels in the liver. The reciprocal rivalry between Zn and Cu in sheep may be affected by a genetic factor **(Abdou and Sharkawy, 2004)**.

Oxidative stress induced by the injection of the treated group with IVM resulted in a significant decrease in the concentrations of both TAC and GSH and increased MDA **(Mahmoud *et al*., 2014)**. Ivermectin causes damage and lowers antioxidant enzyme activity, and produces free radicals. **Behera *et al*., 2011** and **Turkan *et al*., 2018** mentioned that, IVM affects the balance between oxidants and antioxidants and significantly suppresses the release of GSH, with an inhibitory effect on the antioxidant's enzymes.

The effects of IVM on several reproductive hormones in ewes were studied. The current findings indicate that, after IVM injection, concentrations of estradiol, triiodothyronine, and tetra-iodothyronine hormones were decreased at the 30th and 60th-day p.t., and then return to normal values at the 90th-day p.t. Furthermore, because of the detrimental impact on the animals' fertility criteria, IVM should not be used in breeding bucks and rams. There was a substantial increase in serum progesterone levels when IVM was given to ewes during the breeding season **(Seri *et al*., 2000)**. The cause of the rise in progesterone level is unclear, but it may stem from the ovary or adrenal glands **(Kadry and Hazem, 2015)**.

Reduced FSH and LH, and as a result, reduced estrogen associated with delayed estrous after IVM injection may be due to progesterone's hypothalami-hypophyseal negative feedback as observed in the current study **(Kadry and Hazem, 2015)**. In the meantime, the cortisol hormone was elevated in Rabbits. Cortisol is a steroid hormone released by the adrenal cortex's zona fasciculata. Cortisol levels elevated in IVM treated rabbits indicate that, those animals are stressed **(Muehlenbein *et al*., 2010** and **El-Sawy *et al*., 2016)**.

Mejía *et al*., (1999) reported that, IVM treatment in dairy heifers might increase growth rate during development, advance the onset of ovarian function (earlier puberty), and positively affect the yearling pelvic region. When heifers were given IVM at weaning, the number of animals in estrous at the end of the feeding period increased. The same authors predicted that, any change in reproductive success would lead to an increase in fertility.

In heifers, antiparasitic therapy tends to be linked to early puberty and increased fertility **(Purvis and Whittier, 1996)**. Cortisol is a steroid hormone generated by the zona fasciculata of the adrenal cortex in response to stress. Although it serves to restore homeostasis, prolonged cortisol secretion, whether due to excessive secretion or chronic stress, causes significant physiological changes, suppressing immune and reproductive functions **(Muehlenbein and Watts, 2010)**.

Hormones are required for the normal growth, development, and metabolism of cells **(Yen, 2001** and **Puri, 2011)**. Hormones are produced in the blood via several glands for example, the thyroid gland; is the

largest gland that produces two principal hormones: tetraiodothyronine hormone (T_4) and triiodothyronine hormone (T_3) **(Puri, 2011)**. Both T_3 and T_4 are bio-indicators of the hypothalamus and pituitary glands activities **(Kirsten, 2000** and **Mebis *et al*., 2008)**. These hormones have an important function in the body, specifically the stimulation of metabolism **(Puri, 2011** and **Quraishi *et al*., 2015)**. T_3 and T_4 help acquire the element iodine and convert it into the biologically available **form (Granner, 2003)**. Abamectin significantly decreases the content of both T_4 and T_3 hormones compared to control. Oxidative stress has an impact on thyroid physiologies **(Omidi *et al*., 2015)**. Ivermectin's free radicals, according to some researchers, can cause oxidative stress, which can lead to sperm or ovum damage, deformity, endometriosis, preeclampsia, miscarriage, intrauterine growth retardation, and infertility **(Bansal and Bilaspuri, 2011** and **Al-Jassim *et al*., 2015)**.

When Ivermectin was given during the hormone decline process, there was no effect. **Sania and colleagues, (2016)** showed that, Ivermectin is an effective insecticide that enhanced the reproductive efficiency of ewes in her trials, as ovulation occurred at the drug's highest dosage. This result may be due to a change in hormones triggered by an endocrine disruptor as a result of free radical synthesis, resulting in reproductive toxicity.

Reactive oxygen species (ROS) could be generated directly from oocytes and embryos or from their surroundings, which leads to mediating the processes of embryonic development. This ROS could cause multiple physiological processes from oocyte maturation to fertilization and pregnancy **(Agarwal *et al*., 2005)**. This study provides first-hand information on adverse reactions of Ivermectin on ewes' reproduction.

CONCLUSION

This study's results identify adverse reactions of Ivermectin on ewe's reproduction via fertility troubles, alteration in hemato-biochemical parameters, and reproductive hormones. IVM delayed estrous in ewes for three months. As a result, IVM should not be injected after delivery. Moreover, the drug induced some degree of harm in the liver. So, we should use Ivermectin carefully to avoid possible adverse effects, especially during the reproductive season. We believe that more research is required to understand the relationship between IVM and reproductive hormones fully.

Declaration of Competing interest

On behalf of all authors, I hereby declare that no conflict of interest may interfere with the publication of the manuscript.

REFERENCES

ABD-ELHADY, H.K. AND ABOU-ELGHAR G.E., 2013. Abamectin induced biochemical and histopathological changes in the albino rat, *Rattus norvegicus*. Journal of Plant Protection Research 53: 263-270. http://dx.doi.org/10.2478/jppr-2013-0039.

ABDOU, K.A. AND SHARKAWY, A.A., 2004. Some toxicological studies on Ivermectin in goats. Proceeding of the 20 Annual meeting of the Egyptian Society of toxicology. Bibliotheca Alexandria.

AGARWAL, A., GUPTA, S. AND SHARMA, R.K., 2005. Role of oxidative stress in male reproduction. Repro Biol. Endocrinol. 3(1):28.

AHMAD T., M BILAL, S., UALLAH, Z.U., RAHMAN AND MUHAMMAD, G., 2007. Impact of mastitis severity on mineral contents of buffalo. Pak J Agric Sci, 44: 176-178.

ALA AL- DEEN, H. J. AND EMAN, A.A., 2015. Adverse effects of repeated doses of Ivermectin alone or with the combination of vitamin C on reproductive system of female rabbits. Indian journal of applied research volume: 5 | Issue: 9 | September 2015 | ISSN - 2249-555X.

AL-Hizab, F.A. and Hassieb, M.M., 2010. Histopathologic studies on the effect of repeated doses of Dectomax on some genital organs of female guinea pigs. 207-215.

ARASH O, MASOUMEH KHEIRIE AND HADI SARIR, 2015. Impact of Vitamin C on Concentrations of Thyroid Stimulating Hormone and Thyroid Hormones in Lambs Under Short-Term Acute Heat Stress. http://creativecommons.org/licenses/by-nc/3.0/ DOI 10.4081/vsd.2015.5965

ASHRAF, A., EL-GHONEIMY AND AUSAMA, B.E., 2007. some hematological and biochemical alterations consequent to concurrent administration of Ivermectin and rafoxanide in rams. Kafrelsheikh Vet. Med. J. Vol. 5 No. 1 (154-174).

ASMAA ABDALLAH DARWISH AND MOHAMED FAHMY ELDAKROURY, 2020. The effect of Ivermectin injection on some clinicopathological parameters in camels naturally infested with scabies.
DOI :http://dx.doi.org/10.17582/journal.aavs/2020/8.s2.34.40

BANSAL, A.K. AND BILASPURI, G.S., 2011. Impact of oxidative stress and antioxidants on semen function. Vet. Med. Int.:1-7.

BASUDDE C.D., 1989. Clinical signs and biochemical changes in calves caused by injection of Ivermectin. Vet Q. 11(1):29–32.

BEHERA, S.K., DIMRI, U., SINGH, S.K. AND MOHANTA, R.K., 2011. The curative and antioxidative efficiency of Ivermectin and Ivermectin + vitamin E-selenium treatment on canine *Sarcoptes scabie*i infestation. Vet. Res. Commun., 35: 237-244. DOI: 10.1007/s11259-011-9468-8.

CELIK-OZENCI, C., TASATARGIL, A., TEKCAN, M., SATI, L., GUNGOR, E.E., ISBIR, M. AND DEMIR, R., 2011. Effects of abamectin exposure on male fertility in rats: Potential role of oxidative stress-mediated poly (ADP-ribose) polymerase (PARP) activation. Regulatory Toxicology and Pharmacology

61: 310–317. http://dx.doi.org/10.1016/j.yrtph.2011.09.001.

CORTOSSA, S., AON, WASTON, M.A. AND ´ROURKE, R.L.B., 2004. A mitochondrial oscillator is dependent on reactive oxygen species. Biopysic. J, 87: 2060.

EL-SAWY, M.A.; M.E. EL-SPEIY; M.A., TONY, AND SADAKA1,T.A., 2016. Comparative studies on reproductive male rabbits as affected by therapeutic of Ivermectin or both of garlic and cinnamon oils treatments. b. biochemical blood, hormones and semen characteristics in male rabbit. Egyptian Journal of Rabbit Science, 26(1): 57- 87.

FELDMAN., ZINKL, J.G. AND JAIN, N.C., 2000. Schalm′s Veterinary Hematology. 5th ed., Lea and Febiger, Philadelphia, USA.

GAD, G. N. A., 1998. Effect of Ivermectin on female fertility. MVSc. Thesis, Pharmacol. Dep., Fac. Vet. Med., Zag. Univ.

GARG, R.G., UMAR, R.R., YADAY, C.L. AND BANERJEE, P.S., 2007. Duration of anthelmintic effect of three formulations of Ivermectin (oral, injectable and pour-on) against multiple anthelmintic resistant Haemonchus contortus in sheep. Vet. Res. Commun., 31 (6): 749-755.

GRANNER, D.K., 2003. the Diversity of the Endocrine System. In: Harper's Illustrated Biochemistry. Twenty-sixth edition. R.K. Mur-ray, D.K. Granner, P.A. Mayes, and V.W. Rodwell. Lange Medical Books/McGraw-Hill. Medical Publishing Division. Ch 42.

KADRY, M.S. AND HAZEM, M.S., 2015. The biochemical effects of Ivermectin on reproductive hormones and mineral homeostasis in Baladi cows post parturition. VETERINARSKI ARHIV 85 (1), 95-103.

KANEKO J.J., HARVEY J.W. AND BRUSS M.I., 1997. (Eds.) Clinical Biochemistry of Domestic Animals. San Diego: Academic Press, 932p. Revue Méd. Vét., 2000, 151, 7, 601-605

KHAWLA, B.A., ALAA ALDEEN, HASSAN, J. AND EMAN A.A., 2015. Adverse effects of repeated doses of Ivermectin alone or with the combination of vitamin C on reproductive system of female rabbits. Medical Science Volume: 5 | Issue: 9 | September 2015 | ISSN - 2249-555X Volume: 5 | Issue: 9 | September 2015 | ISSN - 2249-555X.

KIRSTEN, D., 2000. the thyroid gland: physiology and pathophysiology. Neonatal network: J Neonat Nurs 19: 11. http://dx.doi.org/10.1891/0730-0832.19.8.11.

MAKHLOUF C., KHALDOUN OH., BOKRETA, S., TARZALI, D.B., ASMA1, B.M., DAOUDI, Z.N., 2020. Beneficial effects of ascorbic acid on Ivermectin repeated high-dose therapy in rabbits: biochemical and histopathological investigations. European Journal of Biological Research ISSN 2449-8955.

MAXEY, K.M., MADDIPATI, K.R. AND BIRKMEIER, J., **1992.** Interference in enzyme immunoassay. Clin. Immunoassay 15, 116-120.

MEBIS, L., L. LANGOUCHE, AND G. VAN DEN BERGHE, 2008. Changes within the thyroid axis during the course of critical illness. In: Van den Berghe, G (Ed.). Contemporary Endocrinology: Acute Cause to Consequence. Humana Press, NY. http://dx.doi.org/10.1007/978-1-60327-177-6.

MEJÍA, M., GONZALEZ-IGLESIAS, AGS., DÍAZ-TORGA, P., VILLAFAÑ, N., FORMÍA, C., LIBERTUN, BECÚ- VILLALOBOS, DIM AND LACAU-MENGIDO, 1999. Effects of Continuous Ivermectin Treatment from Birth to Puberty on Growth and Reproduction in Dairy Heifers. J. Anim. Sci. 77, 1329-1334.

MOHAMMED, M., CAMPBELL, AND YOUSSEF, F.G., 2014. Serum Copper and Haematological Values of Sheep of Different Physiological Stages in the Dry and Wet Seasons of Central Trinidad. Hindawi Publishing Corporation Veterinary Medicine International Volume 2014, Article ID 972074, 7 pages. http://dx.doi.org/10.1155/2014/972074.

MUEHLENBEIN, M.P. AND WATTS, D.P., (2010. The costs of dominance: testosterone, cortisol and intestinal parasites in wild male chimpanzees. Biopsychosocial Med., 9:4–21.

MUHAMMAD SAQIB, GHAZANFAR ABBAS1, AND MUDASSAR NIAZ MUGHAL, 2015. Successful management of Ivermectin-induced blindness in an African lion (Panthera Leo) by intravenous administration of a lipid emulsion. BMC Veterinary Research (2015) 11:287

DOI 10.1186/s12917-015-0603-6.

PULLIAM JD AND PRESTON J.M., 1989. Safety of Ivermectin in target animals. In: Campbell WC, editor. Ivermectin and Abamectin. New York: Springer; 1989. p. 149–57.

PURI, D., 2011. Textbook of Medical Biochemistry, 3rd Edition. Elsevier, A division of Reed Elsevier India Private Limited. ISBN 978-81-312-2312-3.

PURVIS, HTJ AND WHITTIER, C., 1996. Effects of ionophore feeding and anthelmintic administration on age and weight at puberty in spring-born beef heifers. J. Anim. Sci. 74, 736-744.

SANIA A.I. SHADDAD, A.K. MUDDATHIR, I. B. ELTAYEB, O.Z. BARAKA, A.E.D. ABDALLA AND DINNAR, A., 2016. Effect of Ivermectin on reproduction of ewe. World Journal of Pharmaceutical Research. Vol 5, Issue 3, 2016.

SCHMITZ D.G., 2007. Toxins affecting the urinary system. Vet Clin North Am Equine Pract 23:677–690. doi:10.1016/j. cveq.2007.09.001

SEDLAK, J. AND LINDSAY, R.H.C., 1968. Estimation of total, protein-bound and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal. Biochem., 25: 192-205.

SERI, H., I. HUSNA, M. ELBASHIR, O. P. IDRIS, T. HASSAN, O. Z. AND BARAKA, 2000. Effect of Ivermectin on progesterone profile in the camel (*Camelus dromedarius*). The Sudan J. Vet. Res. 16, 17-22.

SHKOLNIK, K., TADMOR, A., BEN-DOR, S., NEVO, N., GALIANI, D AND DEKEL, N., 2011. Reactive oxygen species are indispensable in ovulation.

SNEDECOR, G.W. AND COCHRAN, W.G.. 1982. Statistical Methods. 7th Edition, Iowa State Press, Ames.

SUÁREZ, G., ALVAREZ, D. CASTELLS, CORREA, P. AND FAGIOLINO, 2013. Relative bioavailability and comparative clinical efficacy of different Ivermectin oral formulations in lambs. BMC Vet. Res. 9, 27-36.

TURKAN, F., HUYUT, Z. AND ATALAR M.N., 2018. The toxicological impact of some Ivermectin's on human erythrocytes glutathione S-transferase enzyme. J Biochem Mol Toxicol. Oct; 32(10).

WANJI, S., EYONG, EEJ., TENDONGFOR, N., NGWA, CJ., ESUKA, EN., KENGNE-OUAFO, AJ., DATCHOUA-POUTCHEU, FR., ENYONG, P., AGNEW, D., EVERSOLE, RR., HOPKINS, A AND MACKENZI C.D., 2017. Ivermectin treatment of Loa Loa hypermicrofilaraemic baboons (Papio anubis): Assessment of microfilarial load reduction, haematological and biochemical parameters and histopathological changes following treatment. PLoS Negl Trop Dis. 2017 l;11(7): e0005576.

WANIS, S. M., 1996. Some Pharmacological studies on Ivomec f, MVSc. Thesis, Pharmacol. Dep., Fac. Vet, Med., Alex. Univ., Egypt.

YEN, P.M., 2001. Physiological and Molecular Basis of Thyroid Hormone Action.
https://doi.org/10.1152/physrev.2001.81.3.1097.

ZAIED, G. M., 2004. Some pharmacodynamic properties of Ivermectin in comparison with dormactin in male rats. Ph D. Thesis, Pharmacol. Dep., Fac. Vet, Med., Alex. Univ.

ZHANG, XZ 1992. Crop Physiology Research Methods. China Agricultural Press Beijing, 131:207. DOI:10.4236/ajps.2012.36087

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