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Original article

Effects of intramuscular injection of artemether® on the histology of the uterus and ovaries of pregnant wistar rats

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ABSTRACT

This experiment was aimed at studying some of the histological effects of Artemether® on the uterus and ovaries of pregnant Wister Rats. Twelve pregnant rats were divided equally into treated and control groups. The rats in treated group received Artemether® while those in control group received phosphate buffered saline. Administration was intramuscular. Macroscopically, no significant differences were observed in the organs extracted in the treated and control rats. Microscopically, there is thick uterine mucosa with edematous gland and stroma with developed follicle in the ovaries of treated rats as observed 72 hours after intramuscular administration of Artemether®. The results of this study showed that administration of Artemether® intramuscularly to pregnant Wistar rats caused embryo loss.

1. Introduction

Artemether® and it derivatives have been shown in many studies to be effective in the treatment of both acute uncomplicated and severe malaria. They induce more rapid reduction of parasetaemia than other antimalarial drugs (vanVugt *et al*, 2000) with good results being obtained with intramuscular artemether, arteether and artesunate given in multidrug resistant areas and in severe malaria (Newton and White, 1999).

Different animal studies in various parts of the world have shown that artemisinin and its derivatives given in high doses have neurotoxic effect by causing an unusual pattern of selective damage to certain brainstem nuclei (Piola *et al*, 2005; Brewer *et al*, 1994; Akinlolu *et al*, 2006). Artemisinin are clinically safe and effective but are not

recommended during first trimester of pregnancy (Longo *et al,* 2006). Studies in animals have shown that administration of different derivatives of artemisinin during pregnancy produced toxic effects and congenital malformation in embryo (Clark, 2009; El-Dakdoky, 2009). Single oral doses of artesunate, arteether, artemether and dihydroartemisinin to rats during a sensitive period of organogenesis caused embryo death and malformations, and extended oral dosing of monkeys also caused embryo death (Clark, 2009). Administration of artemether orally to rats in organogenetic phase of pregnancy resulted to complete fetal resorption at higher dose and resorption in few of the implants at lower dose with low incidence of skeletal retardation and reduced fetal weight (El-Dakdoky, 2009). The use of plants and plant products for medicinal purposes has been well recorded over many years of study. Plants derived medicines have been a part of the evolution of human healthcare for many years. At present, there are a huge number of medicinal plants that have already been promoted for use in primary health care (Jeeva and Mathangi, 2011), example of this includes *Qinghaosu* (Rang *et al*, 1995). Although, the use of *Qinghaosu* and its derivatives have been effective in treating acute attacks of vivax and *falciparum* yet several unwanted effects have been reported. Some of the unwanted side effects include; transient heart blocks, reduction in the populations of neutrophils in the blood, gait disturbances, loss of spinal cord and pain response mechanisms in animals (Dayan, 1998; Genovese *et al*, 1995; Rang *et al*, 1995). Artemether® is an antimalarial drug used in the treatment of all forms of malaria. The strong efficacy of artemether® to various forms of malarial parasites made its introduction and use in malarial chemotherapy globally accepted (Raji *et al.,* 2005). Despite the increasing research and control efforts, malaria still remains one of the world's most deadly diseases (Curtis, 1993). According to Li *et. al.* (2002), the evidence of toxicity from the use of artemether® is overwhelming. Exposed laboratory animals suffer brain lesions and neurobehavioral disorders. Despite these, artemether® has been declared safe for combating malaria. With all of these in mind, this present study was undertaken to elucidate some of the short term effects of artemether® on the histology of the uterus and ovaries of pregnant Wistar rats.

2. Materials and methods

2.1. Animal care and experimental design

Twelve female Wistar rats weighing between 170g and 220g were obtained from the Department of Zoology, University of Ilorin, reared under standard laboratory conditions in the Animal House of the Department of Anatomy of the University and were fed with standard rat diet (Adeshewa-Adeshola Feeds, Ede, Osun State, Nigeria) and water *ad libitum*. They were randomly divided into two groups; A and B and were super-ovulated with 0.001mg/g body weight of oral Clomiphene citrate (Gunjikar,1977) before being exposed to male rats by mass mating for 48 hours (Ludwig and Walsh, 2008). Pregnancy was confirmed with vaginal smear for sperm cells on the first day of pregnancy. 0.09mls of intramuscular Artemether® (British National Formulary, 2008) was given as a stating dose to rats in groups A while 0.09mls of phosphate buffered saline was given as a stating dose to rats in group B. All the rats were sacrificed on day 3 of pregnancy by cervical dislocation. Uterus and ovaries were excised and fixed in 10% formol saline for 24 hours, the uteri ovaries were observed macroscopically under magnifying lens and the tissues were processed and stained with hematoxylin and eosin (Lillie, 1965) for histological study.

3. Results and discussion

Physical observations made under the magnifying lens, no significant alterations were observed in the ovaries and uteri extracted in the treated and control rats. Histological study of the ovaries of the treated rats (Fig. 1a) under the light microscope showed the ovaries in different stages of ovarian cycle with follicular cysts and immature follicles while the ovaries of the rats the control group (Fig. 1b) were predominant of corpus luteum devoid of follicular atresia. According to Osman (1985), a follicle was considered to be undergoing atresia or to regressing whenever two or more pyknotic granulosa cells would be found in a single section or whether the oocyte showed signs of degeneration, or thinning of cumulus oophorus as purposed (Osman, 1985). Most of the follicles of the rats in the treated section were atretic and viable oocytes were histologically few in the remaining follicles. Thin layer of granulosa cells were sometimes maintained in the remaining follicles. However, the number of corpus luteum was considerably fewer than in the control.

The ovaries of rats which were administered with 0.09 mls of intramuscular injection of artemether® (Fig. 1a), Graafian follicles and atretic follicles were increased. Treatment with 0.09mls of intramuscular artemether® caused

a significant decrease in the number of healthy follicles with concomitant significant increase in the number of atretic follicles and accordingly the corpus luteum area was enlarged. Plowchalk *et al*. (1993) reported that the quantitative assessment of follicle number is an indicator of the normal function as well as toxic responses in the ovary. Follicles are the principle functional units of the mammalian ovary.

The uteri of the rats in group A (Fig. 2a) showed thin uterine mucosa with short and straight uterine glands when compared with the thick mucosa with edematous uterine stroma and glands as observed in group B rats (Fig 2b). The present study revealed that healthy follicles were significant decreased with concomitant significant increase atretic follicles and corpus luteum in the sections of the ovaries of the rats treated with 0.09 mls of intramuscular injection of artemether®. Similar finding have been reported on the reduction of different types of healthy follicular stages with concomitant increase in the atresia in rats and mice treated with different pesticides. The outcome of this study is similar to the outcome of the studies of Iranloye and Owokunle (2008), Koc *et al*, (2009) and Al-Attar (2010).

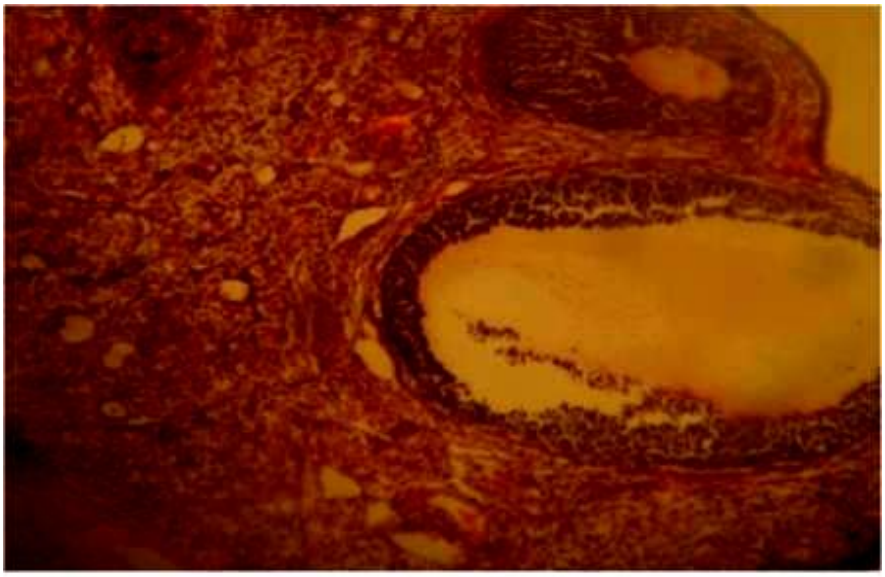

Fig 1a: Section of the ovary of the animals treated with artemether in pregnancy showing ovarian follicles in different stages of maturations (H&E x520)

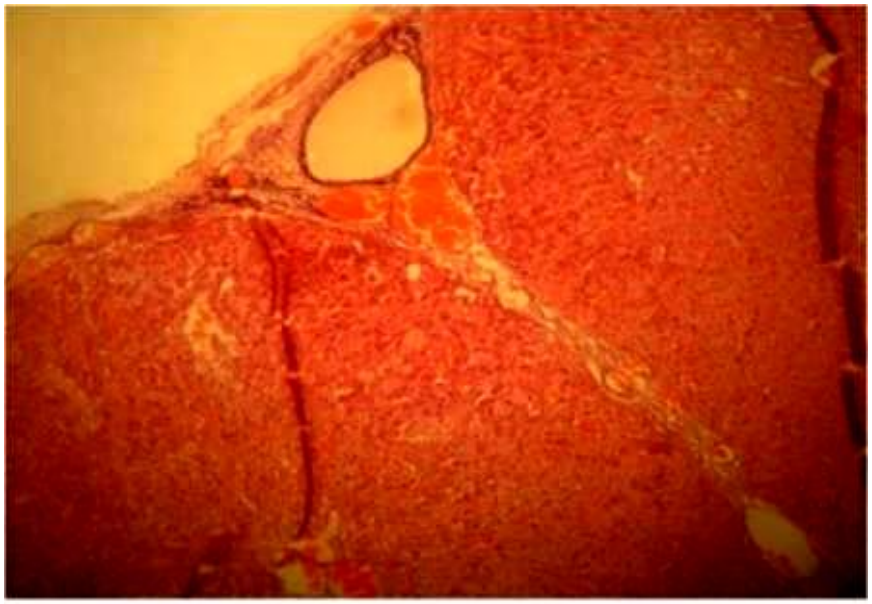

Fig 1b: Section of the ovary of the pregnant animals in the control group showing corpus luteum of pregnancy (H&E x520)

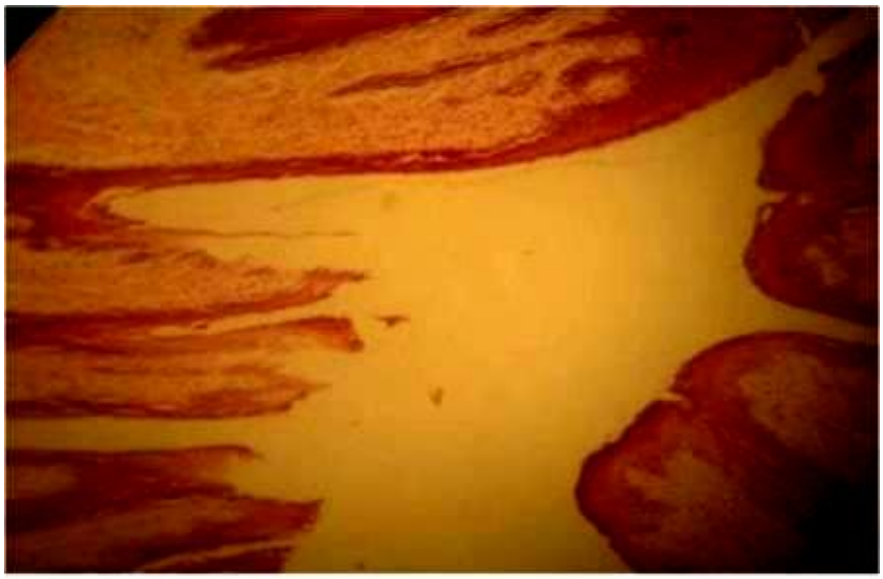

Fig 2a: Section of the uterus of the pregnant animals treated with artemether showing thin endometrium with straight endometrial glands (H&E x520)

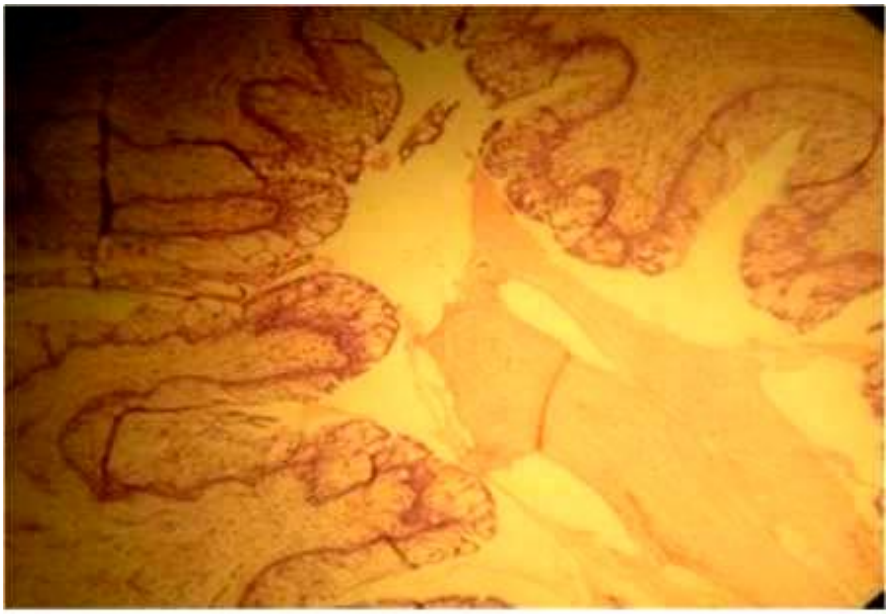

Fig 2b: Section of the uterus of the pregnant animals in the control group showing thick endometrial layer with tortuous endometrial glands (H&E x520)

4. Conclusion

It was observed in this study that the intramuscular injection of 0.09 ml of artemether® confers histotoxic effects on the histological profile of the uterus and ovaries of pregnant Wistar rats and as such may disrupt the functional characteristics of the studied organs in the pregnant rats.

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