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***Research article***

# A Study of Embryological and Histopathological Effects of Levofloxacin Drug on Heart and Lung of Pregnant Albino Rats

**Ashraf Raoof Mohammed Ali**[1*]

[1] *Faculty of Science, University of Kufa, Najaf, Iraq.*

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***Corresponding:***

ashrafr.ali@uokufa.edu.iq

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**Abstract**

The study has been conducted in Animal House/Faculty of Sciences/University of Kufa between November 2024 and January 2025, fifteen female Albino Rats are used. levofloxacin drug is fluoroquinolone antibiotic. Particular emphasis is placed on the clinical efficacy of levofloxacin and its place in therapy. Compared with ciprofloxacin and the earlier quinolone agents, levofloxacin has an improved pharmacokinetic profile that allows convenient once-daily dosing in either an oral or parenteral formulation. The present study has been intended to show the effect of levofloxacin drug on determine the morphological changes of embryos and the chance of pregnancy and evaluate the possible histopathological effects on some maternal organs (heart and lung) in 20th day post coitum in female Albino Rats. The females Rats are randomly divided into two main groups, comprising five rats for control group and ten rats for treated group. The control group is given orally of physiological normal saline and the second group are given orally of levofloxacin doses 1.5 mg/kg/day for 20 days from the first day of pregnancy to the end of experimental allocated for each female. levofloxacin doses 1.5 mg/kg/day caused morphological changes of embryos and reduce the chance of pregnancy and on observed histopathological effects in heart but observed histopathological effects on maternal lungs such as congestion and hemorrhage compared with control group.

## 1. Introduction

Levofloxacin a fluoroquinolone antibiotic. Particular emphasis is placed on the clinical efficacy of levofloxacin and its place in therapy. Levofloxacin has an improved pharmacokinetic profile that allows convenient once-daily dosing in either an oral or parenteral formulation. Levofloxacin has enhanced activity against gram-positive aerobic organisms [1]. In a study conducted to determine the effect of levofloxacin, it was found that the penetration of levofloxacin and its accumulation in high concentrations in the tissues of the heart, liver, kidneys, spleen, muscles, and skin in humans, levofloxacin had good penetration into the liver, kidney, and spleen as well as other tissues in humans, levofloxacin penetrated the abdominal organs well, monitoring for adverse effects should also be carried out when using levofloxacin [2]. The pregnancy duration represent critical periods in which the pregnant mother is exposed to external impacts and the most likely effects are the period called the embryonic period, which extends in the human fertilized stage until the end of the eighth week of pregnancy, during this period the three germinal layers are formed which included ectoderm, mesoderm and endoderm and also neural crest cells, it is known that different body organs originate from these germinal layers [3]. In mammals, the peri-implantation is considered as a developmental period, implantation and signaling for pregnancy maintenance, which are a periods for floating time after zona pellucida hatch, but the cells growth and differentiation during embryonic development [4]. Implantation is defined as the process by which the embryo attaches to the endometrial surface of the uterus and invades the epithelium and then the maternal circulation to form the placenta [5]. Levofloxacin induces toxic effects on heart according to the dose of administration and duration of treatment, Some of the effects of levofloxacin on the heart were

moderate vascular congestion with intermuscular edema and inflammatory cell infiltration. Levofloxacin reduces lung injury for short and long periods, respectively, and at the same time inhibits endotoxins [6]. The antibiotic levofloxacin inhibits the proliferation of lung cancer cells and stimulates their death by causing a defect in the mitochondria [2]. Long-term administration the ECG pattern of rats of levofloxacin and ciprofloxacin produced deleterious effects on with/without AMI. The effect was generally baseline-dependent and therefore, rats with AMI showed greater ECG disturbances and increases in cardiac enzymes, these data make it advisable to monitor patients with a history of acute AMI requiring treatment with these antibiotics until data from human studies are available [7].

## 2. Materials and Methods

### 2.1. Animal Model

The present study will achieve on female albino rat *(Rattus norvegicus)* (fifteen) and selects rats most aged more than eight weeks and weights ranging from (190 $\pm$ 10) g. They should be in good health. The rats are placed in plastic cages with metal covers, 48 cm length, 15 cm wide and 7 cm height. The sawdust, which should be replaced three times a week, is considered in its care to clean the hatching of the special diet and plastic bottles can be used to make a watering tough with a cork equipped with metal pipes. The animals are placed under suitable laboratory conditions in terms of temperature 18-26 $^{\circ}C$ and light/dark cycle 10/14 and ventilation rate time/hour 10-15 and also the relative humidity 30-70 [8].

### 2.2. Drug used

In this study, levofloxacin is used in the form of tablets 500 mg, from Najaf Central Drug Store, MEDLAK PHARMA ITALI company which is used for orally administration in human, and also orally administration of experiment animals. The dose given to the animal is prepared as follows:

- levofloxacin concentration 500 mg
- Suggest human body weight is 70 k = 70000 g and Rats body weight = 190g

500 mg - 70000 g, X - 150 g, X=1.5 mg
500 mg tablet soluble in 10 ml N.S = 50 mg (stander solution).
$C1 \times V1 = C2 \times V2$
$50mg \times V1 = 1.5mg \times 100ml$
V1=3 ml + 97 ml N.S=100 ml

- Ingested of it 1 ml orally (1.5 mg/kg/day) [9].

### 2.3. Experiment Groups

**First Control group:** Included five female rats injected by normal saline (Nacl 0.9%) by the orally administration for twenty days, the group sacrifice it in the end of experiment.
**Second treated group:** Included ten female rats orally administration by dose 1.5 mg/kg/day of levofloxacin for twenty days, the group sacrifice it in the end of experiment, for knowledge of levofloxacin effect on embryos, pregnancy and detect the histopathological effects.

### 2.4. Animals sacrifice and collected of organs

The experimental animals of all groups were sacrificed after general anesthesia by combination of Ketamine: Xylazine (90mg/ kg: 10mg/ kg intra peritoneal), used ketamine 0.5 ml & xylazine 0.1 ml for each 250 g of body weight for anesthesia when sacrifice the female rats from the control and treated croups, after the anesthesia the heart and lungs of female rats removed by anatomical tools. Saved in containers contains 10% formalin [10].

### 2.5. Histological preparations

All samples fixed after remove them from animals in containers contains 10% formalin (38%100ml formalin in 900ml tap water) and then done series of processed in series steps [11].

### 2.6. Staining and mounting

Used the following special dyes for tissue differentiation:

**Harris Hematoxylin**

A general base color used to stain the nucleus in dark blue, components, hematoxylin solved in absolute alcohol then add to it the alum dissolved in warm distilled water and put the mixture on the fire until boiling then add to it red mercury oxide, and cold directly in cold water then add to it Glacial acetic acid [12].

**Eosin stain**

A general acid color used to stain the cytoplasm in red color, eosin solved in alcohol then add to it glacial acetic acid and filtered before used in second day [12].

# 3. Results and Discussion

## 3.1. Macroscopic Observations

### Macroscopic Features of Embryos and Placenta 20th Day Post Coitum (dpc)

In 20 th dpc, the embryos recognized in four main regions (cranial, dorsal, caudal and ventral), umbilical cord connect the embryo with placenta, the embryos weights from 3.8 to 4 g, the lengths of pups from 4 to 4.2 cm Figure 1 and Figure 2 control group of embryos (20th dpc) show normal body color while Figure 3 treated group of Levofloxacin1.5 mg/kg/day show embryos (20th dpc) abnormal body color.

The present study indicates that there is treated groups 1.5 mg/kg/day of Levofloxacin showed decrease pregnancy chances and changes in the color of embryos. This is caused may be by levofloxacin effects during the embryological development.

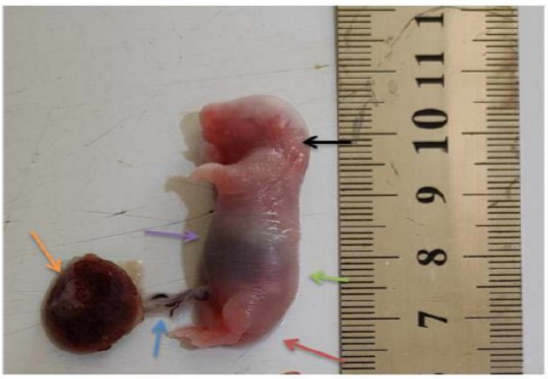

**Figure 1:** Photograph of Control group embryos (20th dpc) show the embroyos that cranian (→), dorsal (→), caudal (→), ventral (→), placenta (→) and umbilical cord (→)

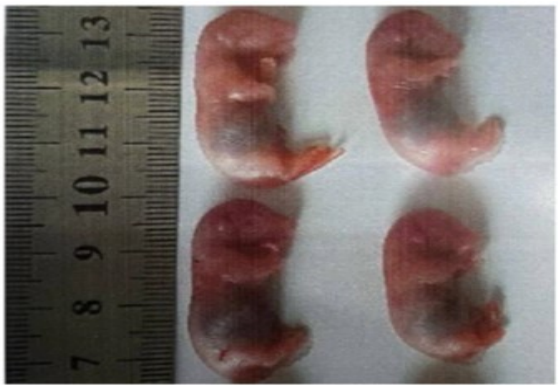

**Figure 2:** Photograph of control group of embryos (20th dpc) show normal Body Colour

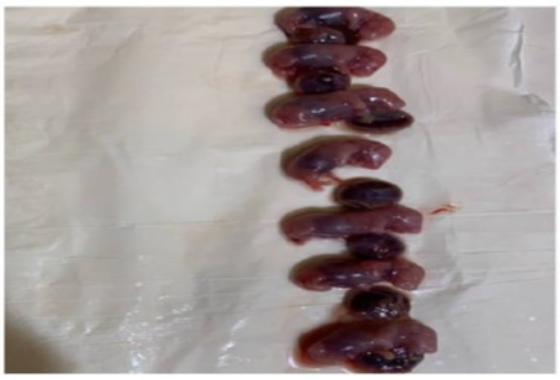

**Figure 3:** Photograph of treated group of levofloxacin 1.5 mg/kg/day show embryos (20th dpc) abnormal body color

The results of a study indicated that there was a significant decrease $(P < 0.05)$ in the numbers of total and the numbers of live embryos, while the numbers of absorbed and dead embryos were significantly increased $(P < 0.05)$ in groups of animals treated with the antibiotic levofloxacin at concentrations 500 g/kg and 750 g/kg of body weight for pregnancy periods (7,16,20) days respectively compared with the numbers of all embryos and for the three pregnancy periods (7,16,20) days respectively in the control groups, and the results pointed to significant differences in two groups treated with concentrations of (500,750) g/kg of body weight during the three pregnancy periods when comparing them [13].

## 3.2. Histological Sections Staining by Hematoxylin and Eosin

### Histological Sections of maternal heart 20th Day Post Coitum (dpc)

The walls of all four heart chambers consist of three major layers: the internal endocardium; the middle myocardium; and the external epicardium. The endocardium consists of a very thin inner layer of endothelium and supporting connective tissue, a middle my elastic layer of smooth muscle fibers and connective tissue, and a deep layer of connective tissue called the subendocardial layer that merges with the myocardium Branches of the heart's impulse-conducting system, consisting of modified cardiac muscle fibers, are Also located in the subendocardial layer. The thickest layer, the myocardium, consists mainly of cardiac muscle with its fibers arranged spirally around each heart chamber. Because strong force is required to pump blood through the systemic and pulmonary circulations, the myocardium is much thicker in the walls of the ventricles, particularly the left, than in the atrial walls. The epicardium is a simple squamous mesothelium supported by a layer of loose connective tissue containing blood vessels and nerves. The epicardium corresponds to the visceral layer of the pericardium, the membrane surrounding the heart. Where the large vessels enter and leave the heart, the epicardium is reflected back as the parietal layer lining the pericardium. During heart movements, underlying structures are cushioned by deposits of adipose tissue in the epicardium and friction within the pericardium is prevented by lubricant fluid produced by both layers of serous mesothelial cells Figure 4. Cross section of heart myocardium of pregnant rat (20th dpc) treated by dose 1.5 mg/kg/day of levofloxacin show, normal muscle fibers and cardiac myocyte Figure 5.

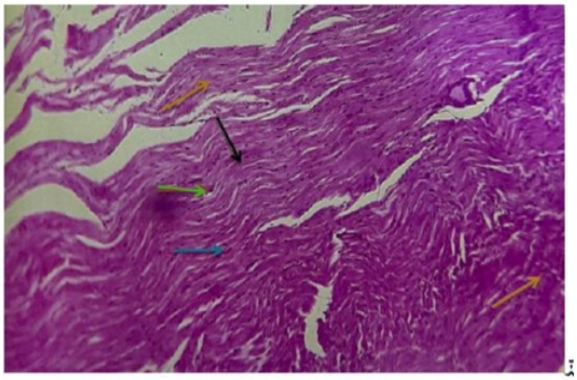

**Figure 4:** Cross section of heart myocardium in pregnant rat (20th dpc) control group show the muscle fibers (→), intercalated disc (→), nucleus (→), cardiac myocyte (→), H&E, 400X

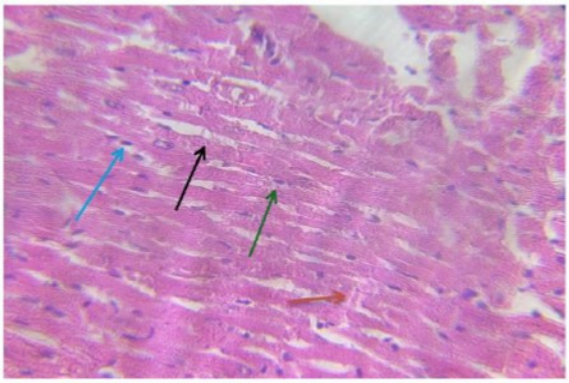

**Figure 5:** Cross section of heart myocardium in pregnant rat (20th dpc) treated by levofloxacin 1.5 mg/kg/day show Normal muscle fibers (→), intercalated disc (→), nucleus (→), cardiac myocyte (→), H&E, 400X

Levofloxacin (LFX), a broad spectrum fluoroquinolone antibiotic of third generation, is widely used to treat respiratory and genitourinary infections. Keeping in view the controversy about its toxicity, current study was conducted to assess the levofloxacin induced hepatotoxicity, nephrotoxicity and its likely noxious effects on spermatogenesis in mammals. Forty mice, randomly categorized into four groups (N=10) were administered orally with different concentrations of levofloxacin (0.00, 9.37, 18.75 and 37.50 $\mu$g/g BW of mice) for 30 days consecutively. Mice were sacrificed on 31st day (24 hours after last dose administered) under deep chloroform anesthesia. Blood was extracted through cardiac puncture and viscera were dissected out for further analysis. Levofloxacin induced reduction in body weight while caused a noticeable increase in liver, kidney and testis weights.

Significant increase in levels of total alkaline aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and bilirubin was observed in blood plasma. Urea level showed a remarkable decrease, whereas creatinine level increased but not significantly. Histological examinations exhibited pyknosis, necrosis, vacuolations, increased sinusoidal spaces, karyomegaly, glomerulosclerosis, glomerulonephritis, epithelium degeneration, spermatocytes exfoliation, tubular degeneration and aspermia in liver, kidney and testis respectively. Levofloxacin causes deleterious effects on liver, kidneys and testes of mice and alters normal functioning of vital organs [14]. So the levofloxacin generally effects on vital organs of rats.

**Histological Sections of maternal lungs 20th Day Post Coitum (dpc)**

The rat lung slide included on pulmonary alveoli, alveolar sacs, bronchioles, blood vessels. The tissue is columnar epithelia that surrounding the bronchioles, and also present smooth muscle. In the newborn is immature and contains no alveoli or alveolar ducts; instead, gas exchange occurs in smooth walled channels and saccules, and the prospective alveolar structures. Once the rat reaches 4 days old, a rapid restructuring of lung parenchyma occurs so that by day 7, the lung is morphologically more mature. Respiratory bronchioles are also absent at birth but by day 10 are easily identified. Rats have the thinnest pulmonary artery and the thickest pulmonary vein of all rodent species. In the conscious resting rat, blood flow preferentially distributes to the central and hilar regions of the lung lobes, with less blood flow to the peripheral regions. Precapillary anastomoses between the bronchial and pulmonary arteries have been demonstrated in the rat, as they have been in man and guinea pig, and are limited to the hilar region in the rat. Innervation of the lung is complex, with high neuronal density similar to the calf, mouse, and guinea pig. The rat and rabbit do not have an adrenergic nerve supply to the bronchial musculature, and bronchoconstriction is controlled by vagal tone. At least 10 morphologically distinct cell types have been identified in the intrapulmonary airways, and is thought to be responsible for the low-viscosity liquid layer found at all levels of the rat's respiratory tract Figure 6. Sections from lungs related to rats treated with dose 1.5 mg/kg/day of levofloxacin, shown congestion in blood Vessels Figure 7. Levofloxacin (LFX), a broad spectrum fluoroquinolone antibiotic of third generation, is widely used to treat respiratory and genitourinary infections. Keeping in view the controversy about its toxicity, current study was conducted to assess the levofloxacin induced hepatotoxicity, nephrotoxicity and its likely noxious effects on spermatogenesis in mammals. Forty mice, Levofloxacin causes deleterious effects on liver, kidneys and testes of mice and alters normal functioning of vital organs [14].

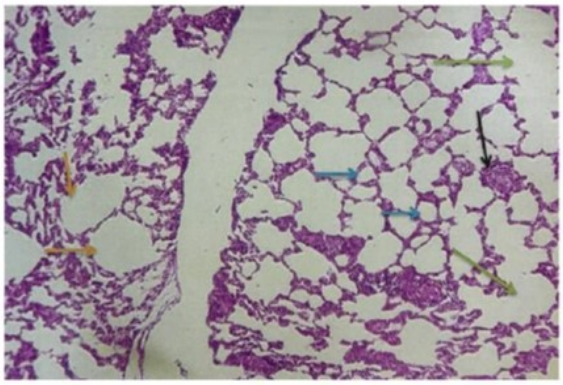

**Figure 6:** Cross section of lung in pregnant rat (20th dpc) control group show blood vessels (→), bronchi (→), pulmonary alveoli (→), alveolar sac (→), H&E, 100X

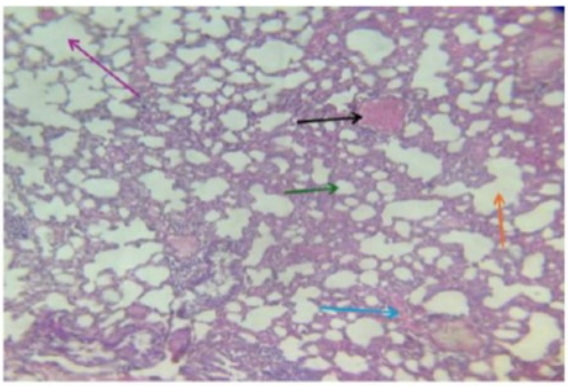

**Figure 7:** Cross section of lung in pregnant rat (20th dpc) treated by levofloxacin dose 1.5 mg/kg/day show blood vessels (→), hemorrhage (→),bronchi (→), pulmonary alveoli (→), alveolar sac (→), H&E, 100X

The hepatopulmonary syndrome (HPS) is characterized by liver disease, pulmonary vascular dilatation and arterial hypoxemia. Hypoxemia, a hallmark of this syndrome, has been mainly explained by pulmonary vascular and ventilation/perfusion mismatch due to the increased pulmonary vascular flow with a uniformly preserved ventilation. However, using an experimental model of common bile duct ligation (CBDL) in rats, we demonstrated important modifications on the respiratory system mechanics and lung structure, characterized by increased chest wall impedance; increased energy dissipation against lung viscoelastic properties and lung elastance with a concomitant reduction of tidal volume and minute ventilation; airway and vasculature remodeling with increased bronchial and vascular deposits of collagen and

elastic fibers; and perivascular edema, which indicates that other mechanisms contribute to the ventilation/perfusion mismatch [15]. lungs and histological changes were observed grossly. Untreated infected rat lungs demonstrated higher mRNA expression for inflammatory markers, cytokine levels, and microbial load compared to vehicle control [16].The gelatin microsphere allows for surface modification, and mechanically entrapped in endothelial capillary of the lung further increases affinity leading to higher levofloxacin concentration in lungs, which helps in optimizing the therapeutic efficacy in the treatment of pneumonia [17].

### Article Information

**Disclaimer (Artificial Intelligence):** The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

**Competing Interests:** Authors have declared that no competing interests exist.

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