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Original article

Teratogenic Effect of Ciprofloxacin in Albino Rats

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ABSTRACT

Aim. *The present study aims to evaluate the risk of the ciprofloxacin drug on the development of fetuses of the albino rat during pregnancy.* ***Method.*** *Pregnant rats were exposed orally to 206 mg kg-1 of coumatetralyl daily on days 5 through 20 of gestation. Animals were sacrificed on the 20th day of gestation for fetal examination.* ***Results.*** *Ciprofloxacin produced a significant elevation in the percentages of late resorption sites and dead fetuses compared with the control group. The mean fetal weights were significantly reduced. Visceral abnormalities were revealed in the form of dilated brain ventricles, hypertrophy of the heart, hypoplasia of the lung, dilated renal pelvis. Skeletal examination showed wide open fontanel, incomplete ossification of parietal and interparietal bones, incomplete ossification of the sternum, reduction in the number, or even complete absence of phalanges, sacral, and/or caudal vertebrae.* ***Conclusion****. The results indicate that ciprofloxacin has a teratogenic effect at lower doses. Therefore, further studies are necessary to evaluate its safety during pregnancy.*

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INTRODUCTION

Antibiotics are among the most generously prescribed medications during pregnancy and lactation [1]. Pregnancy can increase the susceptibility of urinary tract infections (UTIs) in women because of physiological changes [2]. Bacterial infections need effective treatment during pregnancy because they may be hazardous to the health of the mother and the unborn child [3,4]. Fluoroquinolones are one of the main classes of antimicrobials used in the treatment of urinary tract infections [5]. The original fluoroquinolone is norfloxacin; others in the group include ciprofloxacin, ofloxacin, clinafloxacin, ternofloxacin, levofloxacin lomefloxacin, and sparfloxacin [6]. All are entirely synthetic [7]. Ciprofloxacin is one of the most recent advancements of Fluoroquinolone derivatives in the field of synthetic antimicrobial agents, it has a greater intrinsic antibacterial activity and a broader antimicrobial spectrum than Nalidixic Acid, because of its high concentration in urine [8] However, experimental studies on animals and human experience dealt with the side effects of it, including teratogenicity and fetotoxicity [9-11]. Therefore, the aim of the work is to study the teratogenic effect of ciprofloxacin in the offspring of rats treated orally at a dose of 206 mg / kg during the period of organogenesis.

METHODS

Drug

Ciprofloxacin (CPX) (1-Cyclopropyl -6-Fluoro-1, 4-Dihydro -4-Oxo -7-(1-Piperazinyl) -3-Quinolonecarboxylic Acid). Its empirical formula is $C_{17}H_{18}FN_3O3$ and its molecular weight is 331.4 g/mol. It is a faintly yellowish to light

yellow crystalline substance. Obtained from the pharmacy (prescribed by doctors), Ciprofloxacin 500 mg, Bristol Laboratories Ltd.

Animals

The total number of 40 adult female albino rats weighing 200–220 g. All animals had access to laboratory Standard feed and tap water. The total number of 40 adult female albino rats weighing 200–220 g. All animals had access to laboratory Standard feed and tap water. The animals were left for a week to adjust to laboratory conditions before use. Each two adult virgin females in proestrus were caged overnight in an animal plastic cage with a normal mature male. Vagina was examined daily for suggesting pregnancy by a vaginal smear [fig.1], technique according to the method of Matthews and Kenyon [12]. Pregnancy was confirmed the following morning by the presence of sperms in the vaginal washing of each female and considered as the zero-day of pregnancy.

Experimental Design

The pregnant rats were divided into two groups each of 20 rats. The first group was kept without any treatment and served as a control. The second group was given Ciprofloxacin orally at a dose of 206 mg kg-1 (low dose) [13]. The dose of 206 mg/ kg for a mouse is comparable to the human daily therapeutic dose, following correction for interspecies differences with a dose-scaling factor daily on days 5-20 of gestation [14].

Procedures of teratogenic examination

External examination All treated and control female groups were killed by slaughter to the calculated date of delivery (at the 20th day of gestation). After that, an incision was made in the abdominal wall to expose the l viscera. The gravid uterus of each dam was exteriorized then the numbers of uterine implants, late resorptions, live and dead fetuses were counted. The fetuses were blotted dry, weighed, and examined for gross external abnormalities. The remained fetuses were divided into one-third kept in Bouin's fixative for at least one week, after which fetuses were sectioned using Wilson's free-hand razor blade sectioning technique as described by [15] searching for internal visceral malformations. The remaining two-thirds of the fetuses from each group were fixed in 95% ethanol, eviscerated then cleared with 2 % potassium hydroxide, and stained with alizarin red S – stain solution for examining the skeletal deformities.

Statistical analysis

Our data are recorded as percentages and means ± standard error (SE). Statistical significance of fetal weights was determined by one way ANOVA while Chi-square test was used for the comparison of the different morphological, visceral skeletal anomalies between treated and control groups (SPSS; statistical package for social sciences 10.0 for windows).

RESULTS

The pregnant rats were orally administered 206 mg kg-1 (Group B) of ciprofloxacin during the gestational period (5-20th day), There were no clinical signs nor mortality cases recorded and significant decreased the numbers of live fetuses per dam was observed. and the fetal body weights compared to the control (Fig. 2). The resorption (Fig. 3) and dead fetuses' number per dam were significantly increased in the treated group compared with the control group, as presented in Table (1).

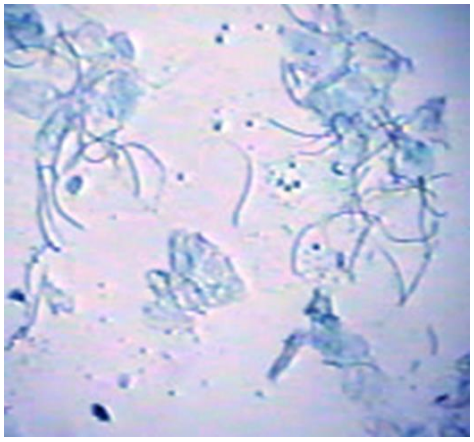

Fig1. Vaginal Smear of a Female Rat Showing Sperm.

Table 1: Morphological Examination of Rat Fetuses Obtained from Control and Treated Dams.

Groups	Parameters								
	No. of pregnant dams	No. of uterine implants	Late resorption		Dead fetuses		Live fetuses		**Mean fetal weights (g)**
			NO.	%	NO.	%	NO.	%	
Control	10	103	1	97	0		102	99	**4.05±0.03**
Ciprofloxacin	10	80	19	23.8*	50	13.8	50	62.5*	**3.01±0.07***

*Significant difference between control and treated groups at p ≤ 0.05.**

Table 2: Visceral malformations of rat fetuses obtained from control and treated dams.

Groups	Parameters								
	Total No. of fetuses examined	Dilated renal pelvis		Hydrocephaly		Heart hypertrophy		Lung hypoplasia	
		NO.	%	NO.	%	NO.	%	NO.	%
Control	34	0	0	1	0	0	0	0	0
Ciprofloxacin	21	9	42.9*	11	52.4*	12	57.1*	9	42.9*

*Significant difference between control and treated groups at p ≤ 0.05.**

Fig 2. Two rat fetuses the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing stunted growth (dwarfism).

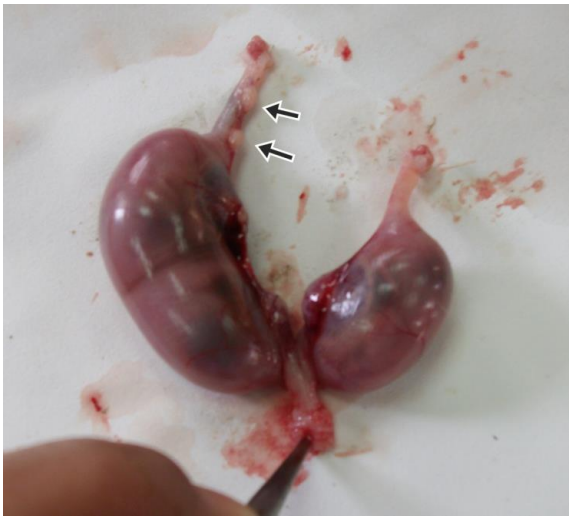

Fig 3. Uterus of a pregnant female rat exposed to ciprofloxacin exposure at 206mg kg^{-1} on days 5-20 of gestation showing resorption sites (Arrow).

The effects of ciprofloxacin exposure (orally at 206mg/ kg on days 5-20 of gestation) on the visceral organs of the obtained rat fetuses from exposed dams are shown in table (2) and fig. 4–7. Ciprofloxacin significantly increased the total fetuses with visceral anomalies compared to the control. The visceral anomalies recorded in the treated groups were in the form of dilated brain lateral ventricles (hydrocephaly) (Fig.4), heart and lung hypoplasia (Fig 5&6), dilated renal pelvis (Fig. 7).

Fig 4. Transverse sections in the head of two rat fetuses, the left one is control and the right one obtained from a a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing Dilation of the third ventricle of the brain.

Fig 5. Transverse sections in the chest of two rat fetuses the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing pulmonary hypoplasia(a) with cardiac enlargement (b)

Fig 6. Transverse sections in the chest of two rat fetuses the left one is control and the right one obtained from a a pregnant dam treated orally with 206 mg kg-1 ciprofloxacin daily on days 5-20 of gestation showing hypoplasia of the lung.

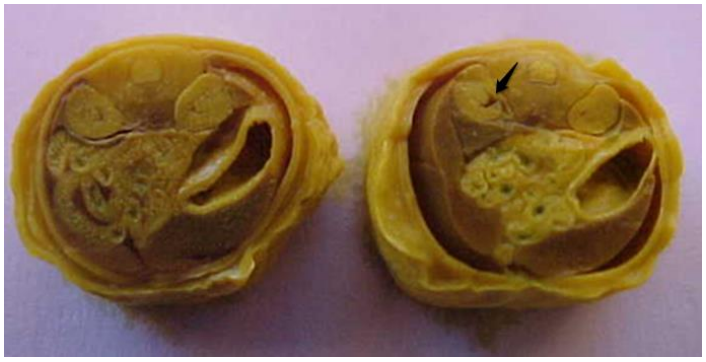

Fig 7. Transverse sections in two rat fetuses the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing dilated renal pelvis.

Many skeletal abnormalities in the examined fetuses from ciprofloxacin-treated dams are shown in table [3] and Figs 8–12. It was revealed that oral exposure of pregnant dams to ciprofloxacin induced a significant elevation in the percentages of the offspring that had skeletal anomalies compared to the control.

Table 3: Skeletal malformations of rat fetuses obtained from control and treated dams.

Groups	Parameters											
	No. of fetuses examined	Wide open fontanel		Incomplete ossification of parietal and/or interparietal bones		Sternum		Phalanges		Sacral vertebrae		Caudal vertebrae	
		N0.	%	No.	%	No.	%	NO.	%	NO.	%	NO.	%
Control	68	1	1.47	0	0	0	0	0	0	0	0	2	2.9
ciprofloxacin	40	14	35*	12	30*	11	27.5*	10	25*	9	22.5*	13	32.5*

*Significant difference between control and treated groups at p ≤ 0.05.**

Fig 8. Skeleton of two rat fetuses the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing wide open fontanel.

Fig 9. Skeleton of two rat fetuses, the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing incomplete ossification of parietal and interparietal bones.

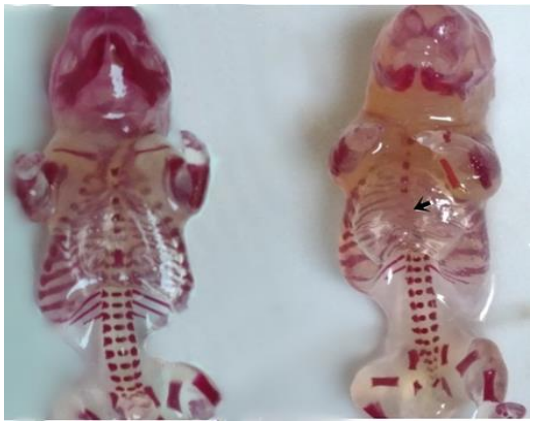

Fig 10. Skeleton of two rat fetuses, the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing reduced number of sternbrae.

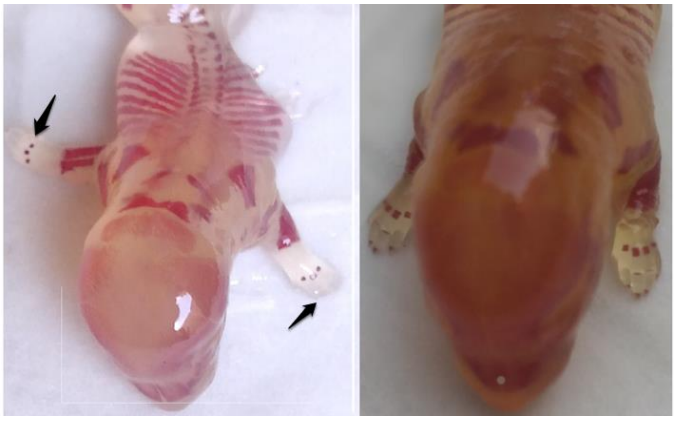

Fig 11. Skeleton of two rat fetuses, the left one is control and the right one obtained from a pregnant dam treated orally with 206 mg kg^{-1} ciprofloxacin daily on days 5-20 of gestation showing absence of hind limb phalanges.

DISCUSSION

Oral administration of ciprofloxacin to female pregnant rats during the period of organogenesis. induced a decrease in the number of fetuses and an increase in the number of resorbed fetuses either early or late when compared with that recorded value of the control group. This result was consistent with the data reported after administration of enrofloxacin, ciprofloxacin, ofloxacin, and norfloxacin to domestic animals, where very high doses of it in female monkeys led to a decrease in the number of fetuses [16,17]. there was a significant decrease in fetal body weight, fetal body length, and fetal tail length significantly decreased after ciprofloxacin administration in pregnant female rats. [10] reported that, ciprofloxacin significantly decreased litter size, and fetal weight and increased fetal resorption ratio and fetal loss when given to pregnant rats. These results are consistent with other studies of teratogenicity of ciprofloxacin in women exposed to ciprofloxacin during pregnancy. [18,19]. Also, other several studies [20-25] concluded that treatment with a rapamycin-induced decrease in the number of fetuses and fetal weight and increase in the number of resorbed fetuses.in another study, pregnant rats were found to be exposed to norfloxacin During the period of organogenesis, the weight and height of the fetus decreased significantly [10]. Chernoff al. showed a relationship between maternal toxicity and developmental toxicity [29]. Cassano, et al. and Giamarellouet al. found that the maternal serum levels of ciprofloxacin are several times lower than those in non-pregnant women [30,31].

The antibiotics having low plasma protein binding usually reach the highest concentrations in the fetal serum [27,28] as enrofloxacin and ciprofloxacin [32]. For this reason, the increase in the number of resorbed fetuses in the present study may be attributed to the interference of the tested drug with the placental transmission of leucine amino acid and magnesium as deficiency of leucine or magnesium produced a high incidence of a fetal resorption [33]. Also, it may be attributed to discontinued production of placental progesterone when hormone production switched from luteal to placental [34]. The reported decrease in fetal weight and height that resulted from the oral administration of the medication may be attributed to a nutrient deficiency Needed by embryos because female rats receive ofloxacin or, levofloxacin diarrhea may occur due to an imbalance in the intestinal bacteria as reported in a study [35,17] of the fluoroquinolones is mild at therapeutic doses, and generally consists of gastrointestinal disturbances such as nausea, vomiting, and diarrhea [36]. At slightly higher doses the central nervous system (CNS) signs of dizziness, restlessness, headache, depression, somnolence, or insomnia may be seen [37]. On the other hand, the quinolone group causes a detectable level of DNA damage in fetal tissues decreases the number of viable cells and increased embryo lethality [38-41].

Fluoroquinolones are known to act as DNA gyrase inhibitors as well as mitosis inhibitors. The complete damage of DNA could result in fetal loss or resorption, while partial damage could induce malformation [42,43]. On the other hand, DNA damage induced by CPX may be attributed to its ability to releasing oxygen free radicals [44] It is known that oxygen free radicals attack DNA [45].

Previous studies reported that ciprofloxacin caused chromosomal aberration and sister chromatid exchange when human lymphocytes were cultured in vitro where abnormalities appeared in the form of dilated cerebral ventricles, also the findings of (hydrocephalus), nasal dilation, cardiac hypoplasia, and intra-thoracic pelvic dilatation agreed with [47,21] The result is also similar to that reported by [48] in which about 4.7% of cases of congenital anomalies (hydrocephalus) were found in live-born babies exposed to ciprofloxacin during the first trimester of pregnancy. Diverticulum dilatation in the brain of fetuses might be attributed to the lack of placental transfusion of amino acid, arginine, metabolism in the fetus [33], the neurotoxic effect of norfloxacin [49], or some antibacterials that had a neurotoxic effect as levofloxacin and ciprofloxacin which easily cross the blood-brain barrier and compete with gamma-aminobutyric acid receptor [50]. Fluoroquinolones can block the cardiac potassium channel leading to cardiac arrhythmias and consequently cardiac enlargement [51]. Pulmonary hypoplasia might be attributed to extensive distribution into the lung and achieved higher concentration malformation in fetuses exposed to ciprofloxacin during the period of organogenesis. Some fetal skeletal malformations were recorded such as impaired ossification of the skull, absence of sternebrae, absence of digit's bone of fore and hind limb, and absence of some metacarpal and metatarsal bone, reduction or absence of caudal vertebrae. This result agrees with that reported by many investigators [52,53], Also, with the administration of ofloxacin to pregnant female rats and rabbits [35], administration of levofloxacin to rats [15,17], and administration of fluoroquinolones (DW-116) to the pregnant rats and rabbits, respectively [53, 54] These results can be explained by the association of fluoroquinolones with a wide range of musculoskeletal complications that include not only tendons but also cartilage, bone, and muscle. [54], and that these effects are associated with irreversible bone damage and growth inhibition. These effects may be explained by the magnesium-chelating properties of these drugs, leading to a deficit of functionally available magnesium and, subsequently, to radical formation and irreversible connective tissue lesions [55] also, Arora stated that bone and cartilage damage can be caused by fluoride accumulation with frequent administration of fluoroquinolones [56].

CONCLUSION

Through these results, it can be said that caution should be exercised when using ciprofloxacin during pregnancy, and future studies should be conducted to assess its toxic effects on the mother and fetuses at low doses.

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