



## EFFECT OF DEXAMETHASONE ON LIVER AND KIDNEY IN PREGNANT RATS AND THEIR FETUSES

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Article history:		Abstract:
Received:	14 <sup>th</sup> April 2024	<b>Background:</b> A number of drugs have been used and are being studied for Covid-19 although they are primarily intended to treat other diseases, these drugs have the ability to prevent the spread of the virus, reduce morbidity and relieve symptoms for patients infected with Covid-19, including the drug dexamethasone. <b>Objective:</b> To evaluate effect Dexamethasone on liver and kidney of pregnant rats and ability to cause phenotypic abnormalities in their fetuses. <b>Materials and Methods:</b> 14 pregnant white rats, divided into 2 groups (Materials were given in day to day ,from days 5 to 20 of pregnancy).1 <sup>st</sup> group: treated with distilled water ,2 <sup>nd</sup> group: it was injected with Dexamethasone (0.2 mg/kg/day) . Animals were sacrificed 24 h after the last treated. Biochemical blood parameters like AST, ALT,ALP, creatinine , urea and glucose. histopathologic changes of liver and kidney were studied and the embryos were extracted and examined. <b>Results:</b> Giving dexamethasone led to rise in levels of ALT, AST, ALP, creatinine , urea and glucose compared to the control group .Histological changes in 2 <sup>nd</sup> group in liver were represented by congestion in central vein, bleeding ,degeneration , infiltration of inflammatory cells, and necrosis .In kidney,it happened bleeding, infiltration, glomerular atrophy , necrosis and sloughing of the lining of the renal tubules .Dexamethasone reduced the size of the fetuses in 2nd group, while they were healthy in 1 <sup>st</sup> group. <b>Conclusions</b> :Dexamethasone causes damage to the liver, kidneys, and the embryo formation process. It should not be used unless the benefits outweigh the harms, especially during pregnancy.
Accepted:	7 <sup>th</sup> May 2024	

**Keywords:** Satellite Channels, Displacement, Visual Media, Al-Iraqiya Channel.

### INTRODUCTION

The COVID-19 pandemic began in early December 2019 in Wuhan, the seventh most populous city in China .After the outbreak of Covid-19 pandemic, many medicines were used alone or in combination in many countries <sup>1</sup>.The RECOVERY trial in United Kingdom recently showed that dexamethasone is one of the drugs capable of reducing the death rate in severe Covid-19 disease <sup>2</sup> .Many studies have also shown that it significantly reduces the mortality rate in hospitalized COVID-19 patients who need oxygen<sup>3</sup>.Aim of this research is to determine effect of dexamethasone on liver , kidney and fetus of pregnant rats.

### MATERIALS AND METHODS:

Fourteen female white rats, *Rattus norvegicus*, were used in this experiment, obtained from the animal house of the College of Veterinary Medicine / Tikrit University. Approximately 12-14 weeks old and weighing between 225-275 grams and in good health .After collecting females with males and fertilization occurred, the females were isolated .Pregnant females were divided into two groups: 1<sup>st</sup> group (control group) was given distilled water, 2<sup>nd</sup> group was injected with dexamethasone at a concentration of 0.2 mg/kg from days 5<sup>th</sup> -19<sup>th</sup> of pregnancy and between one day and another. On 20<sup>th</sup> day of pregnancy, the animals were sacrificed and blood samples were taken to perform the required tests(AST, ALT, ALP, Creatinine, Urea and Glucose).The liver and kidneys were also taken for tissue sectioning. The embryos were isolated to observe the changes occurring in them.

**Statistical analysis:** Statistical analysis of the results was conducted using the Analysis of Variance test, and significant differences were determined according to Duncan's multiple ranges test with a significance level ( $P \leq 0.05$ ).

### RESULTS AND DISCUSSION

**Biochemical parameters:** It is noted from Table (1), in 2<sup>nd</sup> group a significant increase ( $P \leq 0.05$ ) in the levels of ALT, AST, ALP, Creatinine, Urea and Glucose compared with 1<sup>st</sup> group.

Table (1) levels ALT, AST, ALP, Creatinine, Urea and Glucose.

parameter s group	AST (IU/L)	ALT (IU/L)	AL P (IU/L)	Urea (mg/dl)	Creatinin (mg/dl)	Glucose (mg/dl)
G1	116.832±3.93 B	31.6571±0.404 b	41.1271±0.399 B	40.4457±1.265 b	0.8171±0.036 b	110.4857±9.582 b
G2	171.000±2.69 a	48.1429±1.056 a	58.7500±0.613 a	56.1814±1.005 a	1.7371±0.049 a	151.6286±9.015 a

Values represent the arithmetic mean ± standard error. Different letters vertically mean there is a significant difference at a significant level ( $P \leq 0.05$ ).

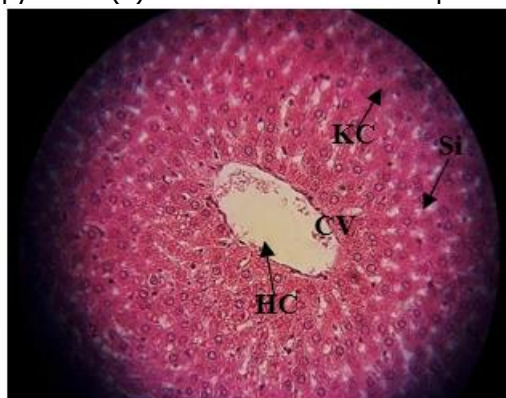
The results showed a significant increase in the three liver enzymes ALT, AST, and ALP when pregnant rats were treated with dexamethasone, and this result is consistent with the findings of Alkot (2022)<sup>4</sup>. Increased activity of these enzymes indicates the degree and type of liver damage<sup>5</sup>. Use of dexamethasone for a long period of time leads to an increase in the production of reactive oxygen species, which leads to mitochondrial dysfunction, elevated cytosolic calcium, and irreversible oxidative modifications of cellular lipids, proteins, and DNA, which ultimately leads to cell injury and damage<sup>6</sup>.

The result of a significant increase in the levels of creatinine and urea in 2<sup>nd</sup> group is consistent with the results Olufunto (2022)<sup>7</sup> conducted a study to test the use of dexamethasone on pregnant rats at a dose of 0.2 mg/kg in pregnancy days 14<sup>th</sup> -19<sup>th</sup>. The results showed an increase in creatinine, urea, free fatty acids, accumulation of lipid peroxide, an increase in the level of aminotransferase enzymes, and glutathione depletion. It also indicated that kidney damage caused by dexamethasone can be worsened by pregnancy.

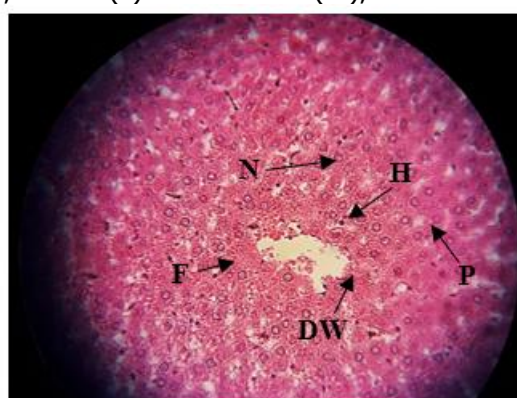
The current results show a significant increase in the blood sugar level of pregnant rats in 2<sup>nd</sup> group compared to the 1<sup>st</sup> group, and this result is consistent with the results of LV (2017)<sup>8</sup> in an experiment they conducted to determine the effect of dexamethasone on antioxidants and metabolism in broiler chickens. Many factors explain the causes of high blood Glucose after taking dexamethasone, such as decreased insulin sensitivity, impaired function of pancreatic alpha and beta cells, and increased gluconeogenesis in the liver<sup>9</sup>.

**Histological changes**

**Liver:** Microscopic examination of liver tissue in 1<sup>st</sup> group showed normal shape of central vein (Cv) surrounded by rows of hepatocytes (Hc), which are arranged around central vein in the form of ropes radiographically, separated by sinusoids (Si) that appeared normal in size with the proliferation of Kupffer cells (Kc) during the sinusoids, as indicated in the picture (1). It was observed in 2<sup>nd</sup> group that there was damage central vein wall (Dw), hemorrhage (H), thickening of pyknosis (P) of the nuclei of some hepatic cells, Fibrosis(F) and necrosis (N), as shown in the picture (2).



Picture (1) liver of a pregnant rat of 1<sup>st</sup> group showing central vein (CV), hepatic cells (HC), hepatic sinusoids (Si), and Kupffer cells (KC). stain: H&E, 400X.



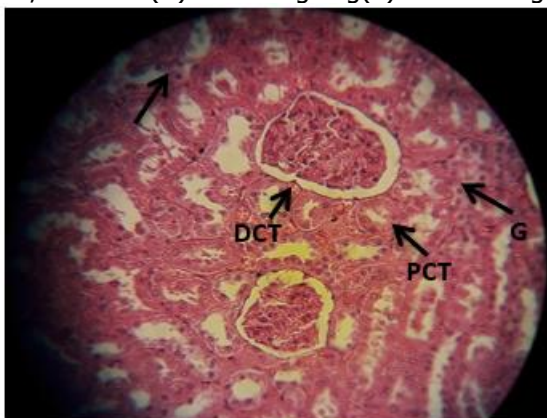
Picture (2): liver of a pregnant rat of 2<sup>nd</sup> group showing damage central vein wall (DW), hemorrhage (H), pyknosis (P) cell nuclei, Fibrosis (F) and necrosis (N). stain: H&E, 400X.

These results are consistent with what Jasim (2022)<sup>10</sup> mentioned regarding the effect of giving dexamethasone on liver of rabbits after taking its doses orally (0.25 mg/kg/day). Some evidence has indicated that glucocorticosteroids, including dexamethasone, gradually cause an increase in the fragility and weakness of intracellular organelles such as lysosomes, with a change in properties of the plasma membrane<sup>11</sup>, causing noticeable changes in the structures of mitochondria and a decrease in their number, thus reducing oxidative phosphorylation and active respiration<sup>12</sup>.

This leads to a decrease in the energy produced by the cell and may lead to a disturbance in the balance of electrolytes through the "sodium-potassium pump," because this is a mechanism that depends on energy, so the flow of potassium ions decreases in exchange for the accumulation of sodium ions, which leads to an increase in osmotic

pressure in the cytoplasm to change the function of the plasma membrane and thus attracts an increase of water molecules, as a result the cells swell and thus hydrolysis occurs<sup>13</sup>.

**Kidney:** Microscopic examination of prepared histological sections explain the glomerulus (G) in its normal size, the proximal convoluted tubule (PCT), and the distal convoluted tubule (DCT), picture (3). In 2<sup>nd</sup> group, microscopic examination shows the occurrence of hemorrhage (H), infiltration of inflammatory cells (If), atrophy (A) in the glomerular, necrosis (N) and sloughing (S) of the lining of the renal tubules, pictures (4).



Picture (3) section of kidney of a pregnant rat from 1<sup>st</sup> group, showing normal size of glomerulus (G), proximal convoluted tubule (PCT), and distal convoluted tubule (DCT). stain; H&E; 400X.



Picture (4) section of kidney of a pregnant rat from 2<sup>nd</sup> group, showing Atrophy of glomerulus (A), Hemorrhage (H), Infiltration (If), Sloughing (S) and Necrosis (N). stain; H&E; 400X.

This result is consistent with the findings of Danaiyan (2023)<sup>14</sup> in a study he conducted to determine the effect of dexamethasone on kidney. Long-term or high-dose exposure to dexamethasone leads to an increase in production of reactive oxygen species (ROS), which leads to a defect in the structure and function of mitochondria, an increase in calcium in the cytosol, and irreversible oxidative changes to cellular lipids, proteins, and DNA, which ultimately leads to cell degeneration and necrosis<sup>6</sup>.

**Embryos variations:** The fetuses in 1<sup>st</sup> group appeared in normal shapes and sizes, it was approximately 4 cm long, with clearly defined basic parts such as the head, front limbs, torso, and hind limbs, with a straight spine, picture (5). In 2<sup>nd</sup> group, it has been observed that the resorption of embryos occurs with a decrease in the size of some of them, picture(6).



Picture (5) shows a rat embryo at 20 days of gestation in 1<sup>st</sup> group, with a length of approximately 4 cm.



Picture (6) shows a rat embryo small in size at 20 days of gestation in 2<sup>nd</sup> group.

Studies conducted on rodents by giving dexamethasone during pregnancy have proven some of its harmful effects on embryonic development, such as an increase in the number of embryo resorption processes, and the implantation of non-viable embryos and affected embryos<sup>15</sup>. The reason for the small size of the fetus may be the small placenta, which limits the uterine blood supply to the fetuses, and thus is an important cause of delayed fetal growth and small size<sup>16</sup>.

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