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Histopathological and some biochemical effects of platinum drug on the liver and kidney of pregnant mice *Mus musculus* and their embryos

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Abstract

The current study was done to investigate the effects of two doses 3and 6 mg/kg B.w. of the Platinum drug on the structure of the liver and kidney of pregnant mice, and embryos in addition to the weight of the mothers, embryos, maternal liver and kidneys, as well as some biochemical parameters, were established. For this study, thirty pregnant mice were used, divided into three groups (10 mice/group) as follows; group I (control group); animals were injected intraperitoneally (IP) with distilled water on the days 7th, 12th, and 17th of gestation. The other both groups II, and III were injected intraperitoneally (IP) with the selected doses above of the Platinum at the days 7th, 12th, and 17th of gestation, respectively. Microscopically, maternal and fetal' liver sections of group II revealed vacuolation, swelling, apoptosis, infiltration of inflammatory cells, congestion, degeneration, and presence of the extramedullary hematopoietic cells, respectively. Previous lesions were increased in group III. Maternal and, fetal kidney sections of group II revealed degeneration, expansion of Bowman's space, inflammatory cells infiltration into interstitial tissue, and blood capillaries congestion. However, the previous lesions showed more severity in group III. The drug caused a reduction in the body weight of the mothers, selected organs, and embryos. Biochemical assessment of the maternal serum AST, ALT, and ALP levels showed an increase in both experimental groups II and III, but to varying degrees. Moreover, both groups II and III showed an increase in the levels of the maternal BUN and, urea. Whist, group III showed a significant increase of the creatinine compared to the control group. In conclusion, using anticancer drugs during pregnancy will harm both mothers and fetal organs. The risk of these medications represents their ability to cross the placenta and enters the fetal body. Therefore, the drug may affect the formation of the fetal organs. The drug also alters the regulatory antioxidant mechanism in the maternal body during the treatment duration. The drug should be used under medical follow up.

Introduction

Platinum is a metallic collaboration compound, belongs to the class of platinum-based antitumour drugs, these drugs are used in the treatment of many types of cancers such as germ cell tumours, ovarian cancer, cervical cancer, testicular cancer (1). Platinum is a water-soluble inorganic divalent agent (2), and classified as an alkylating - like factor. Platinum is given by injection into a vein (IV) or directly into the peritoneal cavity (IP), (3). Cancer is a time disease. The rate of cancer occurrence during gestation is increasing day after day. Treating pregnant women with drugs was considered one of the causes of cancer (4). Chemical treatment was used in cancer therapy during gestation because of its effective results. Furthermore, the safety of using it during this critical period has not sufficiently studied. Platinum is a good choice for treating cancer during gestation, except that the drug can kill rapidly proliferating

cells, and the fetus represented just as a rapidly proliferating cell mass (5), as well as the possibility of affecting the maternal organs and impairing fetal development (6). The drug promotes cytotoxicity by forming covalent bonds with nucleophile purine -N7 sites in DNA, it also affects DNA replication, transcription and induces cell death (7), nephrotoxicity, and hepatotoxicity (8), especially if high doses were used (9). The previous data confirmed that the use of anticancer drugs during pregnancy, especially during the first trimester may cause a structural, and a functional disturbance in both mother and fetus bodies (10-12), it also may cause early delivery, intracranial bleeding because the drug can be easily absorbed, and transferred to the fetus through the placenta. The drugs used to treat cancer, although they destroy cancer cells, they cause abnormal changes in the normal cells of the vital organs, especially those responsible for detoxification such as liver and kidney (13). Exposure to the high doses of anticancer gives rise to the rate of oxidative stress in both liver, and kidney of rodents, as well as promotes ovary problems in women (14,15). The drug accumulates in the mitochondria, and induces cellular mitochondrial damage that has a teratogenic effect on the mouse embryonic development (16,17). The current study aimed to investigate the toxic effects of the doses 3and 6 mg/ kg of b.w. of a Platinum drug on the liver, kidneys of both pregnant mice *Mus musculus* and their fetuses, in addition to the body weight of the mothers, selected organs, and the fetuses. The pregnant mice were injected with certain doses intraperitoneally (IP) on the days 7th, 12th, and 17th of pregnancy as a one single dose per day. Moreover, some biochemical variables were measured in the maternal serum to evaluate the sufficiency of both maternal liver, and kidney functions.

Materials and methods

Animal husbandry

Thirty pregnant mice *Mus musculus* weighted 29±3 gm at age 60±4 days were used in the current study. The study was conducted within 4 months. Animals were brought from the animal's house of the College of Veterinary Medicine, Mosul University, and Mosul, Iraq. All animals were housed in standard plastic cages with free access to their food and water. They were kept in the animals' house of the department of Biology, College of Education for Pure Science. They exposed to an equal day/night cycle, at 23±3℃. Animals were treated following the care and the use of laboratory animal guides. For mating, both males and females were caged together for overnight (one male / two female per cage) (18). The presence of a vaginal plug was examined early in the morning, and considered as the first day of pregnancy (19). Selected mice were isolated in separated cages. The drug used in the present study was the Platinum (Cis-diamminedichloroplatinum) injection

solution (50 mg /100 ml) produced by Kang Pharmacy, Haryana, India.

Experimental design

Pregnant mice were divided into three groups (each group consisted of 10 pregnant mice), as the following; group I: (control group) was injected intraperitonialy (IP) with 0.2 ml of distilled water at the days 7th, 12th, and 17th of pregnancy for once. Group II: injected (IP) with 3 mg/kg of b.w. of Platinum at the days 7th, 12th, and 17th of pregnancy for once. Group III: injected (IP) with 6mg/kg of b.w. of Platinum at the days 7th, 12th and 17th of pregnancy for once. The doses were withdrawn from the drug solution by insulin syringe (0.1 ml). The volume of the doses was determined to be appropriate for the weight of pregnant mice. The selected doses were chosen depending on the LD_{50} of the Platinum, which is 7.5mg /kg of b.w. for mice (20).

Specimens preparation and examination

Pregnant mice were euthanized, and dissected on the 17th day of pregnancy. Fetuses, liver, kidney of both mothers and fetuses were isolated, weighed, and washed with distilled water. All specimens were fixed with formalin 10% fixative for 48 hours. After fixation, the specimens were washed with distilled water for 2 hours, and the samples were processed routinely. Sections were stained with Delafield's Hematoxylin and Eosin. The slides were mounted with DPX (21). The histological examination was done using an optical microscope. For photography, a digital camera was used (type MDCE-5A, Japan). The camera was connected to the optical lens of the microscope. Blood samples were collected using a method of the retro-orbital plexus prior to dissection. Collected blood was kept in the anticoagulant tubes. The serum was prepared using the standard method used in the biochemical laboratories.

Biochemical evaluation of maternal liver and kidney functions

The activities of alanine transferase (ALT), alkaline phosphatase (AIP), and aspartate aminotransferase (AST) enzymes were measured using the antioxidant assay kit (Sigma-Aldrich, C50790) to evaluate the efficiency of the maternal liver function. Furthermore, Urea, uric acid, creatinine, and blood urea nitrogen (BUN) were measured using commercial kits (Biomerieux, France) to evaluate the competence of maternal kidney.

Data analysis

The current data including; weight changes in the body of mothers and fetuses, selected organs, and activities of maternal liver and kidney biomarkers were expressed as mean ± standard deviation (SD). The data were statistically analyzed using one -way ANOVA (one -way analysis of variance). Dunnett's test (multiple comparison method) was used to indicate the differences by comparing the means of

each experimental groups II, and III with the mean of the control group I. The statistical estimations of the current data were achieved using statistical software Graph Pad Prism 5.0 (San Diego, USA). The significance level was set at *P<0.05 is significant, **P<0.01; a highly significant, and *** P<0.001; a very highly significant.

Results

Histopathological observations of the maternal and fetal liver

Light microscopic examination of the control liver sections of pregnant mice showed normal liver tissue composed of central vein, and hepatocytes (Figure 1).

Liver sections of the mothers' group II showed; vacuolation of hepatocytes, congestion of the central vein (Figure 2). Moreover, apoptosis, and necrosis of some hepatocytes also were observed (Figure 3).
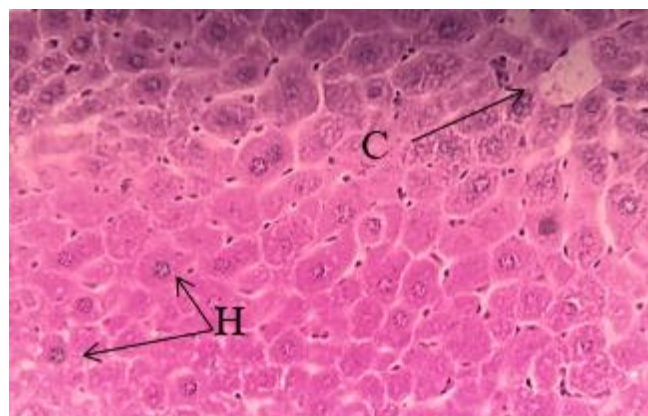
Figure 1: Cross-section of pregnant mice *Mus musculus* liver (control) showing; normal liver tissue composed of the central vein (C), and normal hepatocytes (H). (H&E, 400X).

At the dose of 6 mg /kg of b.w. of Platinum, the lesions were increased, and represented with the dilatation of sinusoids, an increase in the eosinophil's, and vacuolation of hepatocytes (Figure 4). Furthermore, congestion of the portal vein, and infiltration of the inflammatory cells were observed in the portal area (Figure 5).

The light microscope examination of the fetal liver of the control group I revealed; normal hepatic primitive tissue (Figure 6).
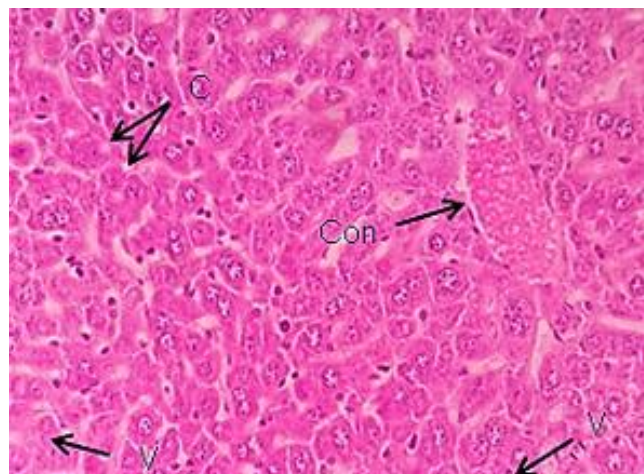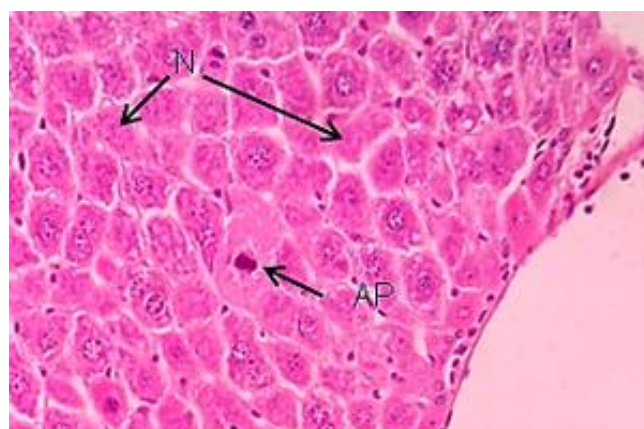

Figure 2: Cross-section of pregnant mice *Mus musculus* liver injected (IP) with a Platinum drug at the dose of 3 mg/kg of b.w. on the days 7th , 12th ,and 17th of pregnancy showing; vacuolation (V, C) of hepatocytes, and congestion (Con) of the central vein. (H&E, 400 X).

Figure 3: Cross-section of pregnant mice *Mus musculus* liver injected (IP) with a Platinum drug at the dose of 3 mg/kg of b.w. on the days 7th , 12th , and 17th of pregnancy showing; apoptosis (AP) , and necrosis (N) of some hepatocytes. (H&E, 400 X).

Fetal liver sections of mothers' group II showed; congestion of the blood capillaries between hepatocytes, presence of extramedullary hematopoietic cells, and mild degeneration of the primitive hepatocytes (Figure 7).

At the dose of 6 mg/kg of b.w. congestion was increased (Figure 8), and primitive hepatocytes showed severe degeneration (Figure 9).
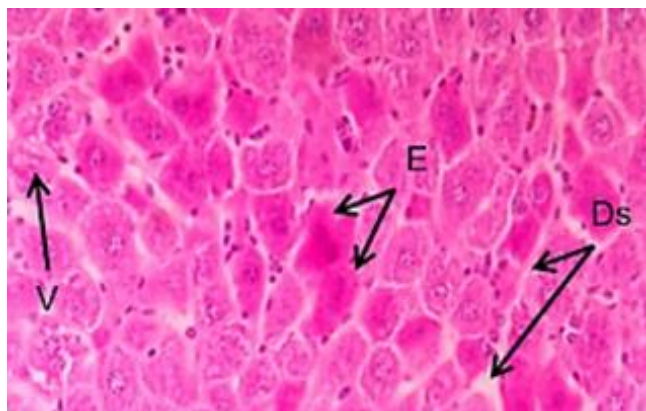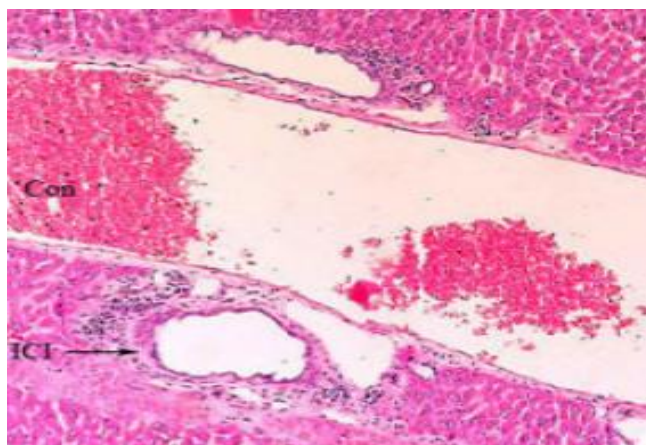
Figure 4: Cross-section of pregnant mice *Mus musculus* liver injected (IP) with a Platinum drug at the dose of 6 mg/kg of b.w. at the days 7th , 12th , and 17th of pregnancy showing; dilatation of sinusoids (DS), increase in the eosinophil's (E) ,and vacuolation (V) of hepatocytes. (H&E, 400X).

Figure 5: Cross-section of pregnant mice *Mus musculus* liver injected (IP) with a Platinum drug at the dose of 6 mg/kg of b.w. at the days 7th , 12th ,and 17th of pregnancy showing; congestion of the portal vein (Con), Inflammatory cells infiltration (ICI) in the portal area. (H&E, 400X).

Histopathological observations of the maternal and fetal kidneys

Light microscope examination of the maternal kidney sections of the control group I showed; normal renal tissue composed of glomerulus, and renal tubules (Figure 10).

Sections from mothers group II showed; degeneration of proximal convoluted tubules epithelium, and expansion of Bowman's space (Figure 11).

Moreover, kidney sections of mothers' group III showed; an increase in the inflammatory cells infiltration in the interstitial tissue, and severe degeneration of the proximal convoluted tubules epithelium (Figure 12).
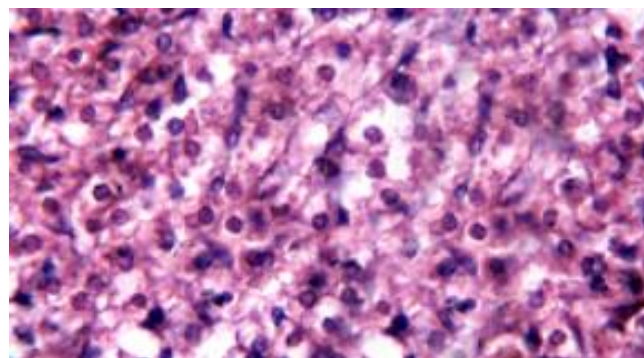

Figure 6: Cross-section of the fetal liver of pregnant mice *Mus musculus* (control) showing; normal hepatic primitive tissue. (H&E, 400 X).
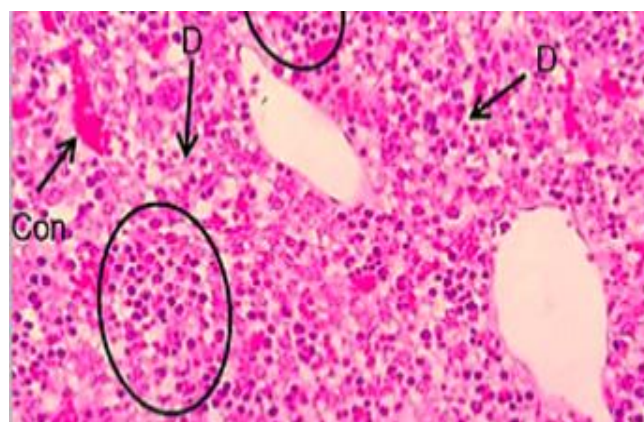

Figure 7: Cross-section of the fetal liver of pregnant mice *Mus musculus* injected (IP) with a Platinum drug at the dose of 3 mg/kg of b.w. on the days 7th, 12th, and 17th of pregnancy showing; congestion (Con), extramedullary hematopoietic cells (circles), and degeneration (D) of the primitive hepatocytes. (H&E, 400 X).
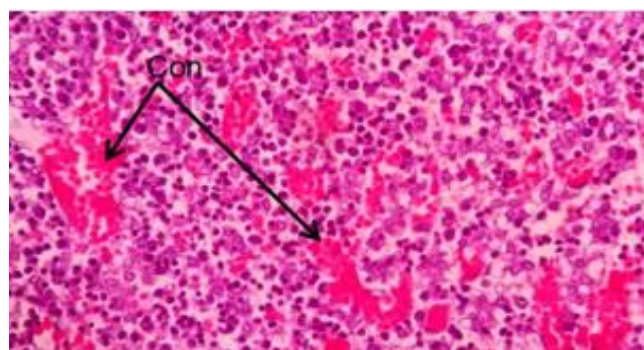

Figure 8: Cross-section of the fetal liver of pregnant mice *Mus musculus* injected (IP) with a Platinum drug at the dose of 6mg/kg of b.w. on the days 7th, 12th, and 17th of pregnancy showing; an increase in the congestion (Con). (H&E, 400X).
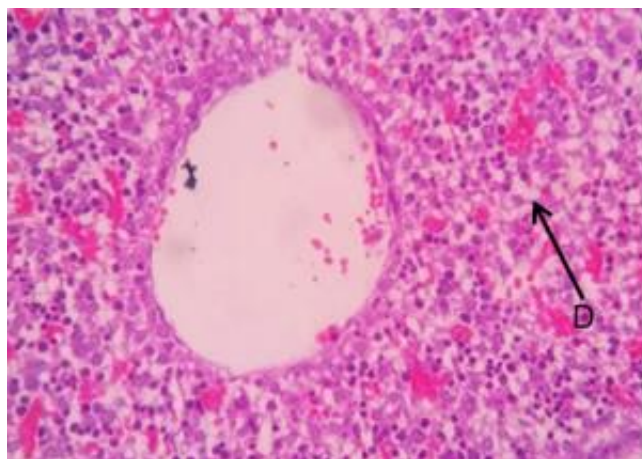
Figure 9: Cross-section of the fetal liver of pregnant mice *Mus musculus* injected (IP) with a Platinum drug at the dose of 6mg/kg of b.w. at the days 7th, 12th, and 17th of pregnancy showing; severe degeneration (D) of the primitive hepatocytes. (H&E, 400X)
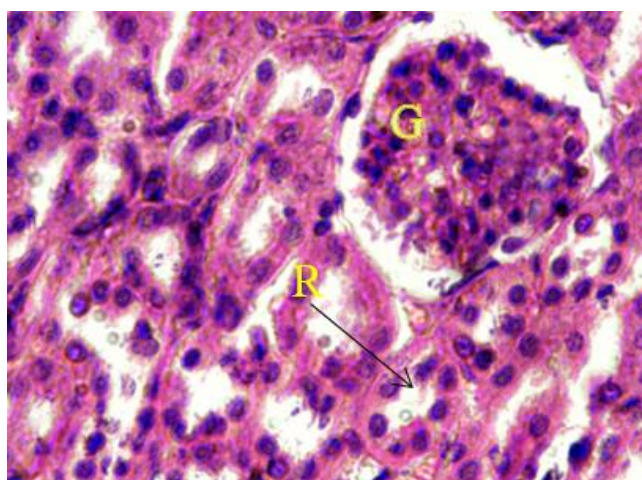

Figure 10: Cross-section of pregnant mice *Mus musculus* kidney (control) showing; normal renal tissue composed of glomerulus (G), and renal tubules (R). (H&E, 400X).

Microscopical examination of the fetal kidney of the control group I showed; normal renal primitive tissue composed of primitive renal tubules, and primitive glomerulus (Figure 13).

Sections from mothers group II showed; degeneration of the primitive tubules epithelium, and congestion of the blood capillaries within the interstitial tissue (Figure 14).

Sections of mothers group III showed; an increase in the degeneration of the primitive renal tubules epithelium, and an increase in the congestion of the blood capillaries within the interstitial tissue (Figure 15).
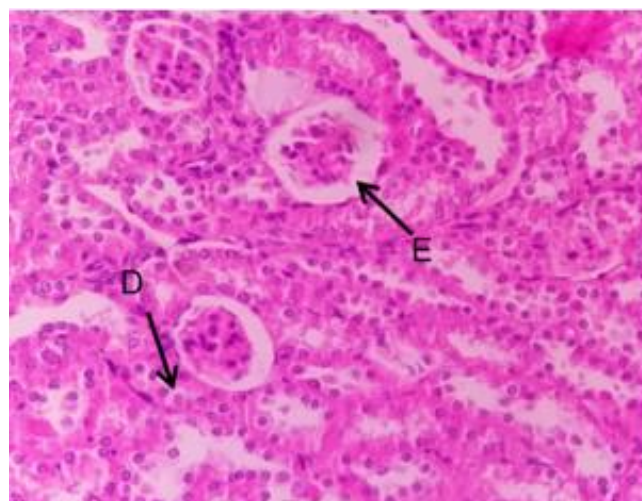

Figure 11: Cross-section of pregnant mice *Mus musculus* kidney injected (IP) with a Platinum drug at the dose of 3 mg/kg of b.w. on the days 7th, 12th, and 17th of pregnancy showing; degeneration (D) of proximal convoluted tubules epithelium , and expansion of Bowman's space (E). (H&E, 400X)

Figure 12: Cross-section of pregnant mice *Mus musculus* kidney injected (IP) with a Platinum drug at the dose of 6 mg/kg of b.w. on the days 7th , 12th , and 17th of pregnancy showing; an increase in the inflammatory cells infiltration in the interstitial tissue (ICI), and degeneration (D) of proximal convoluted tubules epithelium. (H&E, 400X).
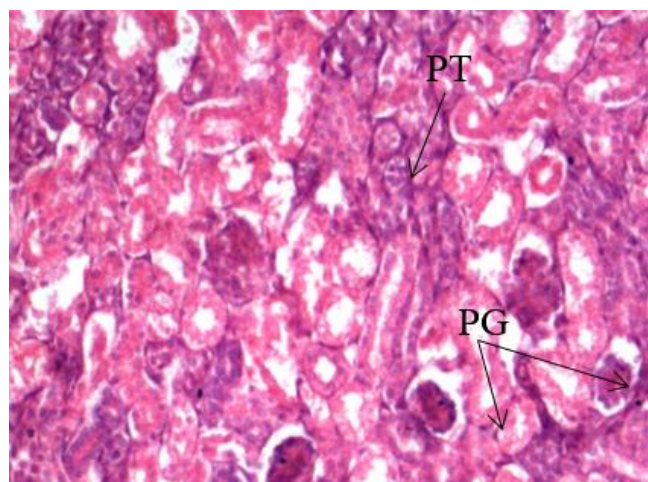
Figure 13: Cross-section of the fetal kidney of pregnant mice *Mus musculus* (control) showing; normal renal primitive tissue composed of primitive renal tubules (PT), and primitive glomerulus (PG).(H&E, 400X).
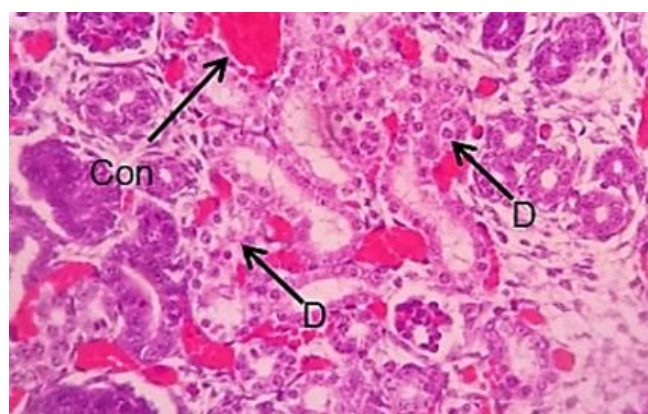

Figure 14: Cross-section of the fetal kidney of pregnant mice *Mus musculus* injected (IP) with a Platinum drug at the 3 mg/kg of b.w. on the days of 7ᵗʰ , 12ᵗʰ , and 17ᵗʰ of pregnancy showing; degeneration (D) of primitive renal tubules epithelium, and congestion (Con) of blood capillaries within the interstitial tissue. (H&E, 400X).
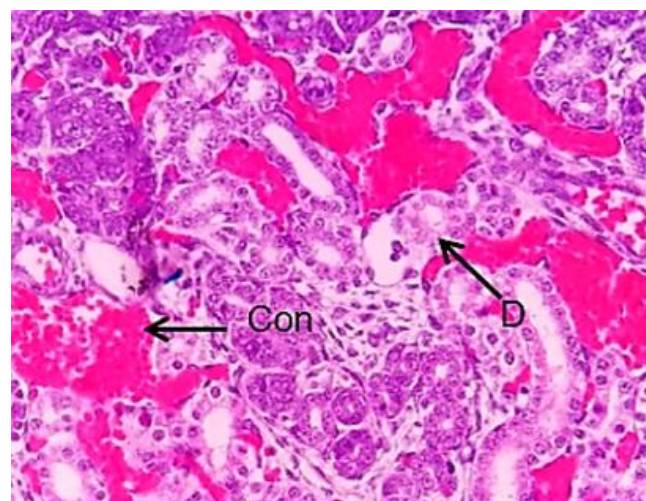

Figure 15: Cross-section of the fetal kidney of pregnant mice *Mus musculus* injected (IP) with a Platinum drug at the 6mg/kg of b.w. on the days of 7ᵗʰ , 12ᵗʰ , and17ᵗʰ of pregnancy showing; an increase in the degeneration (D) of the primitive renal tubules epithelium, and an increase in the congestion (Con) of the blood capillaries in the interstitial cells. (H&E, 400X).

Weight changes

Throughout the experimental period, all groups I, II and III were weighted twice in the days 7ᵗʰ and 17ᵗʰ of pregnancy. Both groups II, and III showed a significant reduction $P< 0.05$, and a highly reduction $P< 0.01$ in maternal body weight compared to the control group, respectively. Maternal liver of both groups II, and III did not show any change in their weight compared to the control group I, respectively. Group III showed a significant decrease $P< 0.05$ in the maternal kidney weight, but group II did not report any weight changes compared to the control group I, respectively. Furthermore, There had been a highly decrease $P< 0.01$, and a non-significant decrease in the fetal body weight of both groups II, and III compared to control group I, respectively (Table 1).

Table 1: Illustrates the effect of two doses 3 and 6 mg/kg b.w. of Platinum administrated to the pregnant mice at the days 7ᵗʰ, 12ᵗʰ, and 17ᵗʰ of gestation on the maternal weight of the body, liver, kidneys, and the fetal body weight

	Control	Group II	Group III
Mean Body Weight on the 7ᵗʰ day	26.54±0.45	27.1±1.07	27.04±0.21
Mean body Weight on the 17ᵗʰ day	29.91±0.94	27.56±1.06*	26.85±1.17**
Mean Liver Weight on the 17ᵗʰ day	2.14±0.21	2.09±0.73	1.79±0.43
Mean Kidney Weight on the 17ᵗʰ day	1.58±0.29	1.48±0.28	1.06±0.12*
Mean foetus Weight on the 17ᵗʰ day	1.32±0.06	1.22±0.16	0.96±0.11**

All values were expressed with mean ± standard deviation (SD), the significance level was estimated at; *$P< 0.05$; significant, and **$P< 0.01$; a highly significant. Dunnett's test was employed to determine the differences by examining each mean of groups II, and III with the mean of the control group I.

Effect of Platinum on the maternal liver and kidney functions

The biochemical estimation of the maternal serum of both groups II, and III showed; a highly significant increase P< 0.01, and non-significant changes in the activity of AST compared to the control group I, respectively. ALT levels of both groups III, II showed a very highly significant increase P<0.001, and a highly significant increase P<0.01 compared to the control group I, respectively. ALP activity showed a significant increase P<0.05 in the group III, while group II showed a non-significant increase compared to the control group I, respectively (Figure 16).
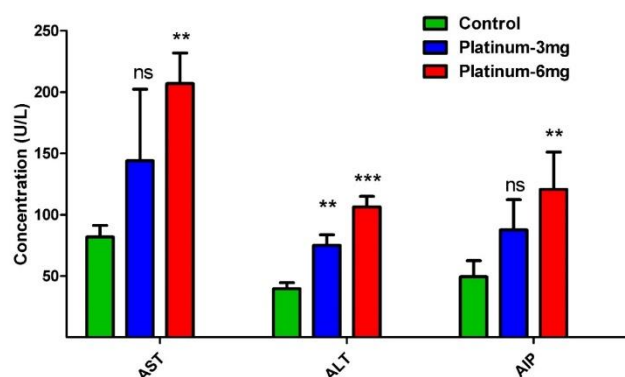

Figure 16: Explaining the impact of two doses 3 and 6 mg /kg b.w of Platinum administrated to the pregnant mice at the days 7th , 12th , and 17th of gestation on the levels of motherly serum enzymes including; AST, ALT, and ALP. The data were expressed as mean ± standard deviation (SD), and n=three. All values were considered significant at *P< 0.05, a highly significant at ** P < 0.01, a very highly significant at *** P < 0.001, and ns- non-significant compared to the control group I. Dunnett's test was employed to show the differences by comparing the mean of each enzyme of both experimental groups II, and III with the mean of control group I.

Biochemical testing of the maternal serum that performed to assess the competence of the kidney functions, clearly demonstrated; a highly significant increase of P < 0.01 in the BUN levels of both groups II, and III compared to control group I, respectively. Both groups II, and III revealed; a highly significant raise P<0.01, and non-significant changes in the levels of creatinine compared to the control group I, respectively. Furthermore, they also revealed; a significant raise P < 0.05, and a highly significant raise P < 0.01 in levels of urea compared to the control group I, respectively (Figure 17).
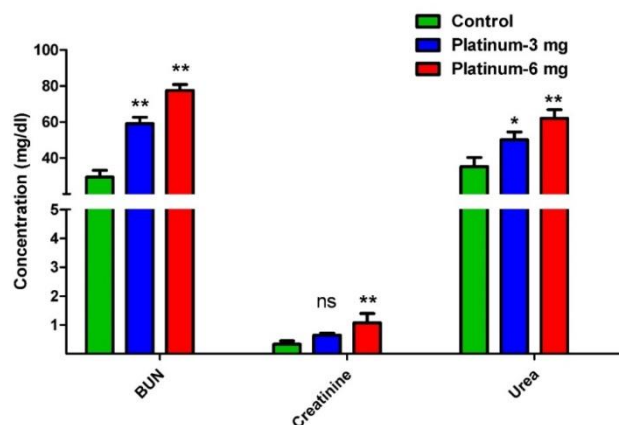

Figure 17: Explaining the effect of two doses 3and 6 mg /kg b.w. of a Platinum on the levels of motherly serum BUN, Creatinine, and Urea. The drug was administrated to the pregnant mice at the days 7th, 12th, and 17th of gestation. The results were expressed as mean ± standard deviation (SD), (n=3), ns - non-significant. The values were considered significant at *P< 0.05, and a highly significant at ** P<0.01 compared to the control group I. Dunnett's test was used to show the differences by comparing the mean of each concentration of experimental groups II, III to the mean of the control group I.

Discussion

The prevailing data revealed several lesions in the maternal liver of both groups II and III including ; vacuolation, apoptosis, an increase of the eosinophil's of some hepatocytes in the portal area, congestion of the central vein, and dilatation of the sinusoids. The current findings were comparable to the findings of those (22-27), how indicates that injecting rodents (rats) with the platinum- base anticancer at certain doses can induce programmed cell death, and some structural changes in the liver. The current findings were contrary to the findings of (25). The occurrence of previous lesions in the current study may due to the interaction of the drug with an antioxidant defense system that induces highly reactive oxygen species formation (28). Besides, the drug generates cellular toxic effects, including functional and structural mitochondrial damage, apoptosis induction, CA homeostasis disruption, and the participation of pro-inflammatory genes like COX-II, that play an important role in the Platinum hepatotoxicity process (29).

Microscopic examination of the fetal liver of both groups II, and III exhibited several lesions outlined with the congestion of blood capillaries, and degeneration of the primitive hepatocytes. The severity of histological injuries was dose-dependent -manner. The current findings were agreed with the findings of the authors (30-33), but they were

in contrast with the findings of (34). Previous lesions occurring in the current study may be explained by the fact that the selected drug is characterized with its low molecular weight, and its ability to cross the placenta. Thus, the medication enters the fetal body, and reaches the liver through the circulatory system. Therefore, the selected drug will be distributed and accumulated in the liver cells resulting in high oxidative stress, which in turn destroys the liver cells (35) or it may be attributable to doses, and duration of exposure. (36).

The maternal kidney of both groups II and III explained remarkable lesions including; degeneration of the proximal convoluted epithelium, expansion of Bowman's space, and inflammatory cells infiltration within interstitial tissue, respectively. The current findings were similar to those of (37,38). Whilst, the current findings were in contrast with the findings of those (39-41), where all authors confirmed that the drug cause loss of brush border, glomerular sclerosis, and interstitial fibrosis, respectively. Kidney lesions in the current study may due to the drug had a bad effect on sodium water transport, which may cause early renal tissue injuries (42). The drug molecule is uncharged, that made it freely flow through the glomeruli, and taken up by renal tubular cells, so the drug reaches its highest concentration in the outer part of the renal cortex (43).

The fetal kidney of group III showed degeneration of the primitive renal tissue, and congestion of the blood capillaries. The current findings were in agreement with the findings of (32), but they were indifferent with the findings of (6), who explained that the administration of cisplatin to the rats (therapeutic doses) throughout gestation induces dilatation of the renal pelvis, and several lesions in the lung and heart. The current findings also agreed with what confirmed by (44).u Lesions' occurrence in the current study may due to that platinum-based antitumour has three characteristics. These characteristics are as follows; low molecular weight, lipid-soluble, and they are nonionized (35). Thus, these drugs easily spread through the placenta by passive diffusion, and reaches the fetal body through the bloodstream. It is worth noting that the concentration of these drugs in the fetal blood circulation is lower than in the mother's blood (45).

The current study revealed a significant P>0.05, and a highly significant P<0.01 reduction in the maternal body weight of both groups II and III compared to the control group I, respectively. Maternal kidneys of group III showed; a significant reduction P<0.05 in their weight compared to the control group I. The findings also showed a highly significant reduction P<0.01 in the fetal body weight of group III. The current findings were agreed with those of (46-48), where all authors confirm the effect of the Platinum on the rodent's weight. Moreover, the weight reduction in the maternal bodies, liver, kidneys, and embryos in the current study may due to that Platinum alters lipid metabolism, and induce weight loss in both of the mothers, and fetuses (49).

Alternatively, may due to that Platinum increase the markers of lipolysis in the white adipose tissue (WAT), B-oxidation, and suppressed lipogenesis in the liver. Thus, these markers had regulated by other factors in a tissue-specific manner. On the other hand, maybe because of the decrease in the ability to concentrate urine resulting in papillary hypertonicity, that is considered the main reason for losing body weight (49,50).

Biochemically, the maternal serum of group III showed; a highly significant increase P<0.01 in the levels of AST, ALP, and a very highly significant increase P<0.001 in the level of ALT. Thus, the rise in the levels of these enzymes indicates disruption of liver function. Whilst, both groups II and III showed; a highly significant increase P<0.01 in the concentrations of BUN, creatinine, and urea, respectively. The current findings were similar to those of (51,52). The biochemical changes in the current study may be due to that the drug causes a reduction in the glutathione concentration (which plays an important role in removing many toxic metabolites) in the tissue of the maternal liver, kidneys, and that seems to have the main role in disturbing the cellular antioxidant regulation. The decrease in the glutathione levels leads to the accumulation of toxic materials in the living cells, which in turn cause cellular dysfunction (53).

Conclusions

Compared to the benefits of using anticancer drugs in cancer therapy at high doses, it might cause many adverse effects. Thus, the consequence of the drug depended on the doses, and the exposure period. The recent research established the toxic effect of the Platinum drug over both doses of 3 and 6 mg/kg b.w on pregnant mice administered at certain days of gestation. The medication had injured both mothers fetuses 'liver and kidneys, especially if used during delicate pregnancy stages including; the first trimester, the second trimester, and the third trimester. The selected drug alters the regulation of the antioxidant levels in the living body. Thus, the drug should be taken under special medical care, and the patient must adhere to the certain dose prescribed by the specialist.

Acknowledgment

Conflict of interest

The authors declare that there are no conflicts of interest.

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التغيرات النسجية المرضية وبعض التأثيرات الكيموحيوية لعقار البلاتينيوم على كبد وكلية الفئران الحوامل *Mus muscullus* واجنتها

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الخلاصة

أجريت الدراسة الحالية للتحري عن تأثير جرعتين هما ٣ و ٦ ملغم /كغم من وزن الجسم من عقار البلاتينيوم على تركيب كل من كبد وكلية الفئران الحوامل وأجنتها و تسجيل التغيرات الوزنية لكل من الأمهات الحوامل، الأجنة والأعضاء قيد الدراسة، فضلا عن إجراء بعض الفحوص الكيموحيوية. استخدمت ثلاثون فأر حامل في الدراسة الحالية وقسمت إلى ثلاث مجاميع (١٠ حيوانات /مجموعة) وكالاتي المجموعة الأولى (سيطرة) حقنت بالماء المقطر في الخلب في الأيام ٧، ١٢، ١٧ من الحمل. المجموعتين الثانية والثالثة في الخلب بالجرعتين ٣ و ٦ ملغم /كغم من وزن الجسم من البلاتينيوم في الأيام ٧، ١٢، ١٧ من الحمل وعلى التوالي. مجهريا، أظهرت مقاطع الكبد للمجموعة الثانية من الأمهات الحوامل تغيرات نسجية تمثلت بالتفجي، احتقان، الموت المبرمج، ارتشاح الخلايا الالتهابية، في حين تمثلت الآفات في كبد الجنين بالاحتقان وظهور الخلايا الدموية الأولية والتنكس وهذه الآفات ازدادت عند التركيز ٦ملغم /كغم من وزن الجسم في كبد الأمهات وأجنتها. وأظهرت مقاطع الكلية للمجموعة الثانية من الأمهات الحوامل وأجنتها عددا من الآفات تمثلت بالتنكس، توسع فسحة بومان، ارتشاح الخلايا الالتهابية في النسيج الخلالي واحتقان الشعيرات الدموية وازدادت هذه الآفات عند التركيز ٦ ملغم/كغم من وزن الجسم. سبب العقار انخفاض في وزن كل من الفئران الحوامل، الأجنة والأعضاء قيد الدراسة وكانت شدة الانخفاض مرتبطة بتركيز الجرعة المعطاة. وأظهرت نتائج الفحوص الكيموحيوية زيادة في مستوي أنزيمات مصل الدم ناقلة أمين الالنين وناقلة أمين الاسبارتيت والفوسفتاز القاعدي في المجموعتين الأولى والثانية، فضلا عن أن الزيادة في مستوي كل من نيتروجين اليوريا واليوريا في المجموعتين الأولى والثانية مقارنة بالمجموعة الأولى وعلى التوالي، بينما الزيادة في مستوي الكرياتينين كانت واضحة في المجموعة الثانية مقارنة بمجموعة السيطرة وبهذا يمكن القول ببساطة، أن استعمال مضادات السرطان خلال فترة الحمل يمكن أن يسبب تأثيرات ضارة في جسم كل من الأمهات الحوامل وأجنتها. ويكمن خطر هذه العقاقير في كونها تعبر الحاجز المشيمي وتصل إلى الجنين، وتؤثر على عملية تكوين الأعضاء. يسبب هذا العقار أيضا تحويرا في نظام عمل مضادات الأكسدة في جسم الأمهات الحوامل خلال فترة العلاج، وبهذا يجب اخذ هذا العقار تحت المتابعة والإشراف الطبي.