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ORIGINAL ARTICLE

Effects of repeated administration of paracetamol in pregnant rats during pregnancy on newborn's lung, kidney and liver

Gebe ratlarda gebelik esnasında tekrarlayan dozlarda parasetamol uygulamasının doğacak ratların akciğer, böbrek ve karaciğer dokuları üzerine etkileri

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Summary

Objectives: Paracetamol is one of the most widely used analgesics and antipyretics in the world. It is the most commonly used analgesic and antipyretic agent in pregnancy. Paracetamol is known to have toxic effects on the liver, lung, and kidney. In this study, we investigated the effects of long-term chronic paracetamol exposure on the lung, liver, and kidney in newborn rats at different trimesters of pregnancy.

Methods: In our study, we formed control (group C), first trimester (group A), and third trimester (group B) groups. Group A had the first seven days of pregnancy and group B had days 15–21. Paracetamol was given orally during the specified periods. On the third postnatal day, pups were euthanized by applying 50 mg/kg ketamine intraperitoneally, and then lung, liver, and kidney tissues were kept under appropriate conditions for examination. A total of 70 pups underwent histopathological examination.

Results: The lung revealed congestion ($p<0.0001$), and erythrocytes ($p<0.0001$), the liver revealed significant histopathological findings in terms of the presence of inflammation ($p<0.0001$), vacuolar degeneration ($p<0.0001$), and sinusoidal dilatation in groups A and B compared to the control group under light microscopy. MDA and free radical metabolism enzyme activities, CAT, GSH, and SOD were evaluated. While there were no significant differences between the groups in lung and kidney tissues, oxidant parameters were significant in liver tissues.

Conclusion: Our data point out that subacute doses of paracetamol used chronically in different trimesters caused damage to the lung, liver, and kidney tissues of pups.

Keywords: Kidney; liver; lung; newborn; paracetamol; rat.

Özet

Amaç: Dünyada yaygın olarak kullanılan analjezik ve antipiretiklerin başında gelen parasetamol, gebelik döneminde en sık kullanılan analjezik ve antipiretik ajandır. Parasetamolün karaciğer, akciğer ve böbrek üzerine toksik etkisi olduğu bilinmektedir. Çalışmamızda gebeliğin farklı trimesterlerinde uzun dönem kronik parasetamol maruziyetinin yeni doğan ratlarda akciğer, karaciğer ve böbrek üzerine etkilerini araştırdık.

Gereç ve Yöntem: Çalışmamızda kontrol (grup C), birinci trimester (grup A), üçüncü trimester (grup B) grupları oluşturuldu. Grup A'ya gebeliğin ilk yedi günü, grup B'ye ise 15–21. günleri arasında parasetamol oral yoldan verildi. Doğum sonrası üçüncü günde yeni doğan ratlara 50 mg/kg ketamin intraperitoneal uygulanarak sakrifiye edildi ve sonrasında akciğer, karaciğer ve böbrek dokuları inceleme için uygun koşullarda alınarak saklandı. Toplam 70 yavru dokularında histopatolojik ve biyokimyasal inceleme yapıldı.

Bulgular: Işık mikroskopisi incelemesinde akciğer dokusu konjesyon ($p<0.0001$), eritrosit varlığı ($p<0.0001$) açısından, karaciğer dokusunda ise inflamasyon ($p<0.0001$), vakuoler dejenerasyon ($p<0.0001$) ve sinüzoidal dilatasyon A ve B gruplarında kontrol grubuna göre anlamlı farklılık bulundu. Böbrek doku incelemesinde anlamlı fark saptanmadı ($p>0.05$). MDA ve serbest radikal metabolizmasında etkin olan enzimlerden CAT, GPx, SOD aktiviteleri değerlendirildi. Akciğer ve böbrek dokularında gruplar arasında anlamlı farklar saptanmazken, karaciğer dokusunda oksidan parametreler anlamlı olarak farklı bulundu.

Sonuç: Farklı trimesterlerde subakut dozda kronik kullanılan parasetamolün yenidoğan ratların akciğer, karaciğer ve böbrek dokularında hasara neden olduğunu tespit ettik.

Anahtar sözcükler: Akciğer; böbrek; karaciğer; parasetamol; rat; yenidoğan.

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Introduction

The use of over-the-counter drugs is common in pregnancy, and the most commonly used analgesic and antipyretic agent is paracetamol. The use of prescription or over-the-counter drugs during pregnancy varies between countries in Europe (26% in France, 93% in Serbia) compared to 88.8% in the United States.[1] At least two-thirds of women use paracetamol during pregnancy, and half of these women use it in the first trimester of pregnancy.[2–4] Paracetamol is prescribed by physicians at all stages of pregnancy because of its analgesic and antipyretic effects. It is therefore widely accepted that paracetamol is a 'safe' drug in pregnancy. The drug and its metabolites can cross the placental barrier and affect fetal development.[5] It is not known exactly what the effects of exposure to paracetamol during different trimesters of pregnancy are on the offspring.

While paracetamol has a good safety profile when used at therapeutic levels, it can cause severe liver toxicity and even fatal acute liver failure (ALF) when used (intentionally or unintentionally) at supratherapeutic doses.[6] The main target organs of paracetamol toxicity are the liver and the kidneys, but studies have also shown that the lungs can also be affected, both in cases of overdose and at effective doses.[7–10] In recent years, both animal studies and clinical trials have shown that the use of paracetamol during pregnancy increases the incidence of asthma and wheezing in children and has adverse effects on liver function.[11–16] Recent experimental evidence has shown that the toxic paracetamol metabolite N-acetyl-p-benzoquinone imine (NAPQI) is produced in the lungs of mice after the administration of non-toxic low doses of paracetamol.[17]

The US Food and Drug Administration's (FDA) pregnancy category for paracetamol is B, which in brief means that there is no risk to the fetus in animal studies, but there are not enough studies in humans and therefore the benefits in pregnant women are acceptable despite the potential risks.[3]

Chronic exposure to paracetamol during pregnancy carries risks for both the mother and the fetus, but each trimester of pregnancy is a period in which different physiological conditions are prominent for the mother and the fetus. For this reason, our study aimed to evaluate the effects of repeated doses of paracetamol on the lungs, liver, and kidneys of the offspring during different trimesters of pregnancy, but not during the entire pregnancy.

Material and Methods

The protocols of this experimental study were approved by Gazi University Animal Ethics Committee on 11.07.2019 (G.Ü.ET-19.045). All animals received human care in accordance with the "Principles of Laboratory Animal Care" formulated by the National Association for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication no. 85-23, revised 1985).

Eighteen adult female Wistar albino rats, weighing between 190 and 220 g, were used in this study. Rats were housed in special cages at an average temperature of 20–21 °C in a controlled light/dark environment with free access to food and water.

Before the procedure, female rats were randomly divided into 3 groups (n=6/group). The estrus (ovulation) phase of the female rats was determined by vaginal smear sampling, and each 3 female rats and one male rat that were suitable for mating were placed in the same cage for one night to ensure mating. The morning after the female rats met the male rats was considered as the 1st day of pregnancy. The gestation period in rats lasts 21 days; therefore, days 1–7 were defined as the first trimester, days 8–14 as the second trimester, and days 15–21 as the third trimester.

In the study, a ready-to-use suspension of 250 mg/5 ml paracetamol (Calpol Suspension, GlaxoSmith-Kline 120 mg/5 ml) was added to the rats' drinking water at room temperature and administered to the groups at the appropriate dose.

The female rats in the control group (group C) were given standard care during pregnancy, with no additional treatment given after pregnancy was achieved. The first trimester group (group A) was given paracetamol 500 mg/kg orally during the first trimester (between the 1st and the 7th day of pregnancy) after the pregnancy was achieved. The third trimester group (group B) was given paracetamol

Table 1. Histopathologic findings of lung and liver tissues

	Group C (n=18) Mean±SD	Group A (n=34) Mean±SD	Group B (n=18) Mean±SD	p**
Lung congestion	0.33±0.16	1.58±0.13*	1.33±0.18*	<0.0001
Intraalveolar erytrocyte	0.00±0.00	0.58±0.09*	0.33±0.11	<0.0001
Liver ınflamation	1.33±0.11	2.00±0.13*	2.00±0.00*	<0.0001
Liver vacuolar degeneration	1.00±0.00	1.76±0.10*	2.11±0.28*	<0.0001
Liver sinusoidal dilatation	0.00±0.00	0.76±0.18*	1.44±0.20*,&	<0.0001

SD: Standard deviation; P**: Significance level p<0.05 by ANOVA test; *: P<0.05: Compared with Group C; & p<0.05: Compared with Group A.

500 mg/kg orally during the third trimester (between the 15th and the 21st day of pregnancy) after the pregnancy was achieved.

Sex segregation of rat pups was performed using the anal distance method on the third postnatal day. Group C consisted of three male and three female pups from 3 mothers, totaling 18 pups. Group A consisted of three male and three female rats from 4 mothers, 2 male and 3 female rats from 1 mother, and 3 male and 2 female rats from 1 mother, totaling 34 pups. Group B consisted of three male and three female pups from 3 mothers, totaling 18 pups. Pups were sacrificed on the third day of birth by intraperitoneal (ip) administration of 100 mg/kg ketamine. After sacrifice, liver, kidney, and lung tissues were removed in a manner that did not disrupt or traumatize their integrity. The right kidney, right lung, and right lobe of the liver were frozen in liquid nitrogen and stored at -80 °C for biochemical examination. The left kidney, left lung, and left lobe of the liver were placed in 10% formalin for histopathological examination and stored until the day of evaluation.

The left kidney, left lung, and left lobe of the liver of the offspring were fixed in 10% neutral formalin for histopathological examination. These tissues were embedded in paraffin and sectioned at 5 µm, stained with haematoxylin and eosin (H&E), and examined by light microscopy.

For biochemical analysis, tissue samples were weighed on a precision balance and homogenized in phosphate buffer (PBS) pH 7.4. The homogenized tissue samples were then centrifuged at 3000g for 20 minutes. After centrifugation, the supernatants were separated and transferred to new Eppendorf tubes and stored at +4 °C until analysis. All samples were simultaneously thawed and analyzed with an enzyme-linked immunosorbent assay device (Biotek, USA) using rat superoxide dismutase (SOD), rat catalase (CAT), rat glutathione peroxidase (GPx), and rat malondialdehyde (MDA) enzyme-linked immunosorbent assay kits (Bioassay Technology Laboratory, China).

Rat Superoxide Dismutase Kit: intra-assay coefficient variability CV<8% and inter-assay coefficient variability CV<10%.

Rat Catalase Kit: intra-assay coefficient variability CV<8% and inter-assay coefficient variability CV<10%.

Rat Glutathione Peroxidase Kit: intra-assay coefficient variability CV<8% and inter-assay coefficient variability CV<10%.

Rat Malondialdehyde Kit: intra-assay coefficient variability was CV<8% and inter-assay coefficient variability was CV<10%.

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 computer program, and p<0.05 was considered significant. Results are presented as mean±standard error of the mean (SEM). Data were analyzed using the ANOVA test. Significant variables were evaluated using the Bonferroni test.

Results

In light microscopy, lung tissue congestion level was found to be significantly different between the groups (p<0.0001). Congestion was observed more in groups A and B compared to the control group (p<0.0001, p=0.001, respectively). Congestion was similar in groups A and B (p=0.753) (Table 1, Fig. 1–3).

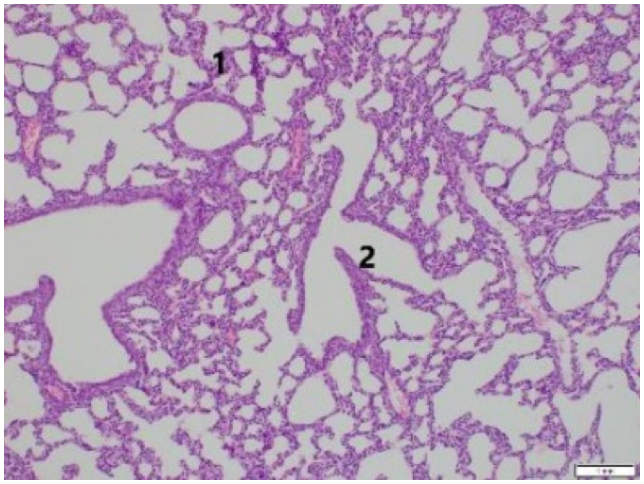

Figure 1. Normal lung structure in the control group (1: normal alveolar area, 2: normal bronchial area) (H&E x100).

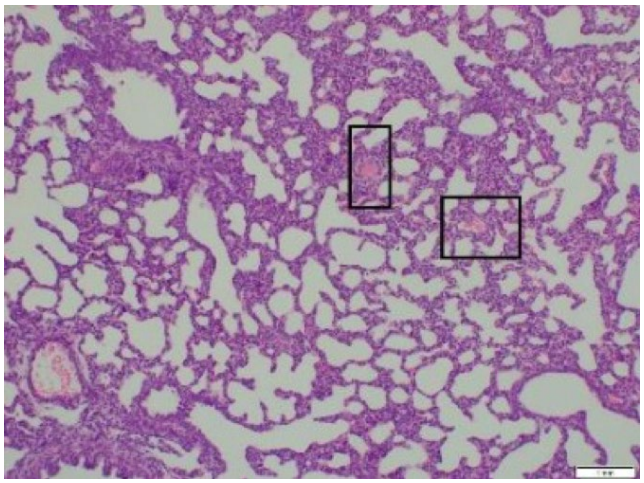

Figure 2. Group A lung areas of mild congestion (surrounded areas) (H&E x100).

The presence of intraalveolar erythrocytes was significantly different between the groups (p<0.0001). The presence of intraalveolar erythrocytes was similar in the control group and group B and in group A and group B (p=0.067, p=0.134, respectively) (Table 1, Fig. 1–3).

Light microscopy showed that the level of inflammation in liver tissue was significantly different between the groups (p<0.0001). Inflammation was observed to be more pronounced in groups A and B than in the control group (p<0.0001 and p=0.003, respectively). The level of inflammation in the liver tissue was similar in groups A and B (p=1.000) (Table 1, Fig. 4–8).

There was a significant difference in the vacuolar degeneration of liver tissue between the groups (p<0.0001). Vacuolar degeneration was more pronounced in groups A and B compared to the control group (p=0.001, p<0.0001, respectively). Vacuolar degeneration in the liver tissue was similar in groups A and B (p=0.298) (Table 1, Fig. 4–8).

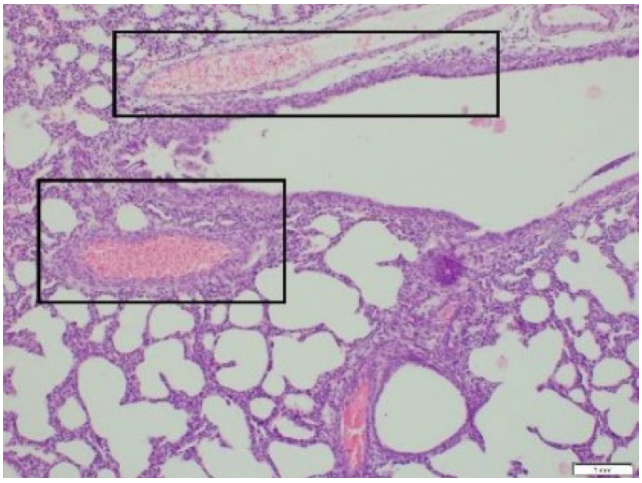

Figure 3. Group B lung severe congestion (surrounded areas) (H&E x100).

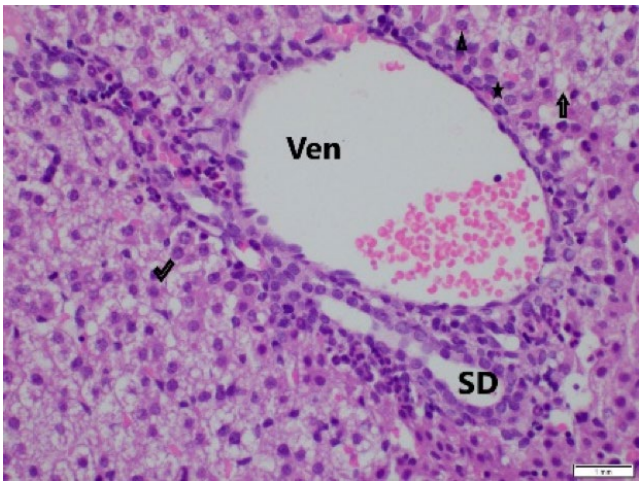

Figure 4. Control group normal liver area (SD: bile duct, arrowhead: vacuoles, star: neutrophils, apex of triangle (Δ): normal hepatocytes, tick mark: sinusoids). Mild inflammation is seen in the whole liver area (H&E x400).

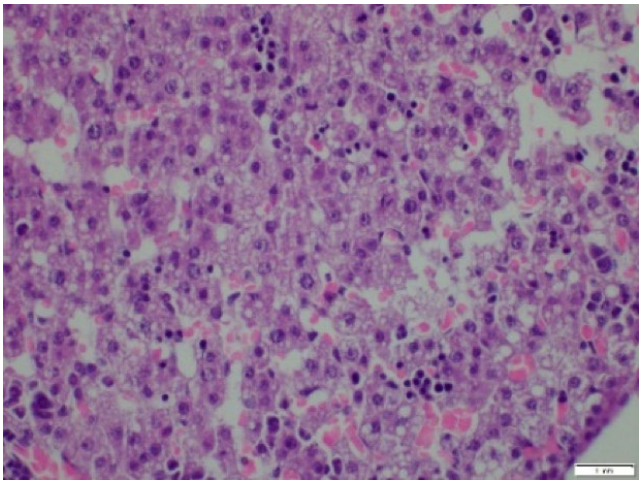

Figure 5. Group A liver mid vacuolar degeneration (H&E x400).

Table 2. Liver tissue oxidant status parameters

	Group C (n=18) Mean±SD	Group A (n=34) Mean±SD	Group B (n=18) Mean±SD	p**
SOD (ng/ gram tissue)	103.10±11.11	69.27±4.80*	59.47±6.12*	<0.0001
GPx (U/gram tissue)	3221.26±420.88	3081.90±262.18	1752.01±151.49*	0.002
MDA (nmol/gram tissue)	91.56±10.75	135.97±11.03*	121.78±14.48	0.031
CAT (ng/ gram tissue)	1575.88±187.37	1579.94±161.08	1137.73±125.69	0.106

SD: Standard deviation; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase; P**: Significance level p<0.05 by ANOVA test; *: P<0.05: Compared with Group C; p<0.05: Compared with Group A.

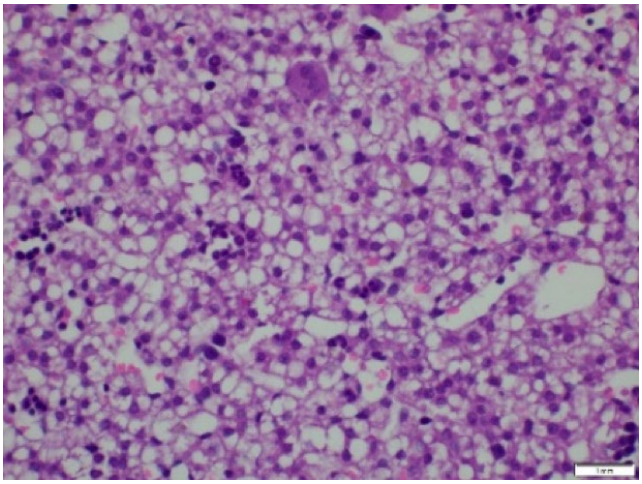

Figure 6. Group B liver severe vacuolar degeneration (H&E x400).

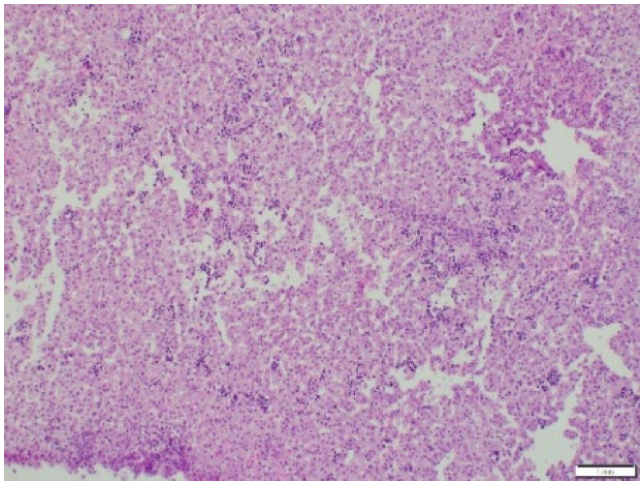

Figure 8. Group B liver marked sinusoidal dilatation (H&E x100).

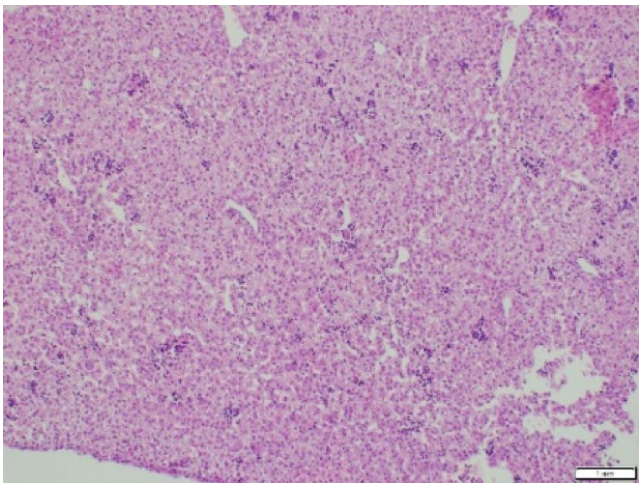

Figure 7. Group A liver mild sinusoidal dilatation (H&E x100).

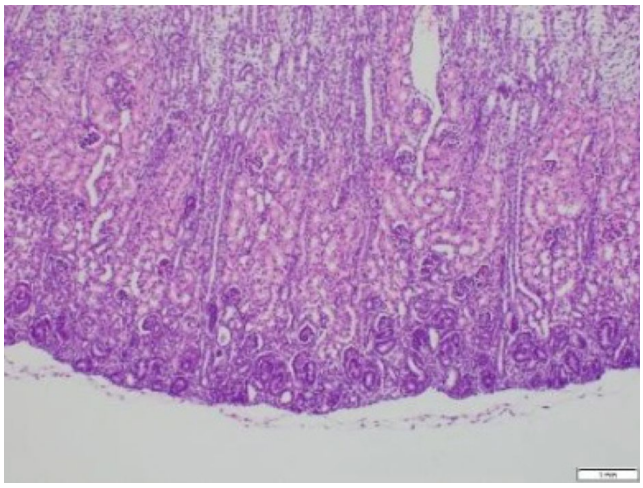

Figure 9. Kidney structure.

The sinusoidal dilatation and congestion of the liver tissue were found to be significantly different between the groups (p<0.0001). Compared to the control group, sinusoidal dilatation and congestion were more pronounced in groups A and B (p=0.006, p<0.0001, respectively). In addition, sinusoidal dilatation and congestion in liver tissue were significantly higher in group B than in group A (p=0.014) (Table 1, Fig 4–8).

Light microscopic findings of kidney tissue were similar between groups (p>0.05) (Fig. 9).

When the groups were compared regarding GPx enzyme activity in liver tissue, there was a significant difference between them (p=0.002). GPx enzyme activity was significantly higher in groups C and A compared to group B (p=0.001, p=0.002, respectively) (Table 2).

Table 3. Lung tissue oxidant status parameters

	Group C (n=18) Mean±SD	Group A (n=34) Mean±SD	Group B (n=18) Mean±SD	p*
SOD (ng/ gram tissue)	131.13±7.97	123.67±10.05	113.84±4.54	0.320
GPx (U/gram tissue)	8321.47±1320.78	8527.70±1924.02	5241.65±380.85	0.273
MDA (nmol/gram tissue)	153.90±13.34	154.08±10.84	181.68±19.96	0.327
CAT (ng/ gram tissue)	2064.03±159.50	2103.98±142.83	1887.52±101.29	0.532

SD: Standard deviation; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase; P*: Significance level p<0.05 with ANOVA test.

Table 4. Kidney tissue oxidant status parameters

	Group C (n=18) Mean±SD	Group A (n=34) Mean±SD	Group B (n=18) Mean±SD	p*
SOD (ng/ gram tissue)	1298.03±113.57	1266.56±97.81	1104.31±71.47	0.355
GPx (U/gram tissue)	74957.42±6839.10	66827.38±5170.85	61753.44±4543.97	0.283
MDA (nmol/gram tissue)	1861.40±170.49	1902.75±138.43	1672.99±103.61	0.486
CAT (ng/ gram tissue)	9457.49±786.22	8012.68±596.10	9046.08±974.08	0.375

SD: Standard deviation; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase; P*: Significance level p<0.05 with ANOVA test.

When the groups were compared regarding liver tissue CAT enzyme activity, it was found to be similar between them (p=0.106) (Table 2).

When the groups were compared regarding MDA levels in liver tissue, there was a significant difference between them (p=0.031). Group A was found to have significantly higher MDA than group C (p=0.009) (Table 2).

When the groups were compared regarding SOD enzyme activity in liver tissue, there was a significant difference between them (p<0.0001). The SOD enzyme activity was found to be significantly higher in group C than in groups A and B (p=0.002 and p<0.0001, respectively) (Table 2).

Oxidation status parameters of lung and kidney tissues were similar between groups (Table 3, 4).

Discussion

This study showed that subacute chronic administration of paracetamol to pregnant rats resulted in pulmonary congestion and increased the presence of red blood cells in the lungs of offspring. It has also been shown to cause inflammation, vacuolar degeneration, sinusoidal dilation, and congestion in liver tissue. The fact that the effects and damage may be different in different trimesters is evidenced by the fact that dilation and congestion in liver tissue were significantly higher in group B than in group A. When evaluated in terms of oxidative parameters, it was found that the level of MDA and the activity of CAT were higher in group A, while the level of GPx was lower in group B. These results show that oxidant parameters vary with gestational age.

The majority of paracetamol is metabolized in the liver by conjugation with glucuronic acid and sulfate. It is then excreted by the kidneys.[18] After large doses of paracetamol, these pathways are saturated. Approximately 10% of paracetamol is metabolized by cytochrome P450 (CYP450) isoenzymes to the highly reactive metabolite NAPQI. NAPQI is detoxified by conjugation with GSH via glutathione S-transferase and can accumulate and cause further damage in disease, drug use, chronic alcohol use, or when GSH is depleted.[18–20]

Although the exact mechanism of paracetamol-induced kidney injury is not known, studies suggest that active metabolites, lipid peroxidation, and oxidative stress may be involved in the injury to the liver.[21]

Roy et al.[22] reported renal glomerular degeneration, increases in urea, creatinine, SGOT, SGPT, and MDA, and decreases in GSH, SOD, and CAT in rats after 14 days of administration of 550 mg/kg paracetamol ip. In a study conducted by Ucheya and Igweh in pregnant Sprague-Dawley rats, reduction in glomerular dimensions (hypoplasia) and enlarged capsular areas, vascular congestion, hemorrhage, and tubular and glomerular damage were found in the mothers after paracetamol administration at a therapeutic dose (7.3 mgx3/kg/day) in the perinatal period. The same study reported that damage was more pronounced at high doses (1500 mg/kg) and that postpartum kidney problems in pregnant women may be related to paracetamol use during pregnancy.[23] Neto et al.[24] found liver and kidney damage in both the mother and the offspring from the administration of paracetamol in the perinatal period. No significant differences in histopathological and oxidative parameters were found in the kidney tissues of rat pups in our study.

Sandoval et al.[25] reported that in a toxicity study in non-pregnant rats, necrosis, inflammation, and sinusoidal dilatation increased in the liver, hepatic total GSH decreased, and the GSSG/GSH ratio increased. In the study conducted by Karimi et al.,[26] pregnant and non-pregnant rats were exposed to a non-toxic dose of paracetamol. An increase in serum AST, ALT, and bilirubin levels and a decrease in GSH levels were found to be more significant in pregnant rats compared to non-pregnant rats. In the same study, fetuses were examined and it was reported that the number of fetal liver cells, the number of liver stem cells, and the number of multipotent progenitor cells were lower in rat pups exposed to paracetamol. In a mouse study conducted by Wu et al.,[27] when the pups sacrificed on postnatal day 21 were examined, they found that there was no statistical significance in the body weight, liver mass, and associated liver index of the pups. In the same study, an increasing trend was observed in the liver index and alanine aminotransferase (ALT) of the pups, but there was no significant difference compared to the control mice.

In our study, we found that inflammation, vacuolar degeneration, sinusoidal dilatation, and hepatic congestion were significantly higher in paracetamol-treated groups compared to the control group. Karimi et al.[26] showed that a single dose of paracetamol 250 mg/kg ip gd 12.5 caused an increase in the SGOT, SGPT, and bilirubin levels in both groups, but this increase was more pronounced in pregnant mice than in non-pregnant mice. The same study also reported that severe centrilobular necrosis was observed in the liver histopathology of pregnant mice, whereas mild centrilobular necrosis was found in non-pregnant mice. This study demonstrates that pregnancy increases susceptibility to paracetamol toxicity. In our study, while evaluating the effect of liver damage on neonates, we found that prenatal chronic exposure to paracetamol could cause liver damage in neonatal rat liver. Compared with the first trimester, vacuolar degeneration in the liver caused significant damage in the third trimester. In our study, we found that the level of GPx was significantly lower in the third trimester group as compared to both the control group and the first trimester group. It is suggested that paracetamol may cause different levels of damage in different trimesters based on histopathological and oxidative parameters.

Wu et al.[27] showed that glucose metabolism was impaired in the offspring of pregnant mice exposed to paracetamol. In that study, paracetamol was administered orally to pregnant mice on gd 13–14 and assessed its effects on liver glucose metabolism in the offspring on postnatal day 21. In the aforementioned studies, paracetamol was administered to pregnant mice between gd 12–14. This is because the differentiation of the fetal liver starts at gd 10 and the hematopoiesis of the fetal liver starts at gd 12.[28,29] In our study, the first and third trimesters were evaluated to assess whether the activity of the fetal liver in paracetamol toxicity causes more damage to the liver of the offspring rats. The fact that liver GPx levels and sinusoidal dilation were significantly different in the third trimester suggests that the third trimester is more sensitive. However, we think that this should be studied in detail.

Sandoval et al.[25] reported that paracetamol was a cause of distal lung damage and that this damage was associated with liver toxicity. They also reported that the damage to the lungs was in the form of inflammation and emphysematous changes in the distal lung fields. They reported that the increased number of inflammatory cells in bronchoalveolar lavage (BAL) fluid was consistent with histopathological findings and that there was a decrease in the amount of GSH in

lung tissue. In our study, we found more congestion in the lung tissue and the presence of intraalveolar erythrocytes in the two paracetamol-treated groups compared with the control group, although no significant difference was found in terms of oxidant parameters. This will give us important results about the damage to the lungs caused by paracetamol.

Conclusion

We believe that chronic use of paracetamol at subtoxic doses during pregnancy may cause hepatotoxicity and alveolar damage in newborns. Further research is needed to understand the mechanism of this damage caused by paracetamol and to determine the doses that are safe for pregnancy in terms of the health of future generations.

Ethics Committee Approval: The Gazi University Animal Experiments Ethics Committee granted approval for this study (date: 11.07.2019, number: G.Ü.ET-19.045).

Conflict of interest: The authors and/or their family members do not have any relationship with any scientific or medical committee membership or membership, consultancy, expertise, employment status in any company, shareholding or similar situation that could pose a potential conflict of interest in relation to this study.

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