Indonesian Journal of Pharmacy

VOL 33 (1) 2022: 128–134 | RESEARCH ARTICLE

Investigation of the Possible Toxicological Effects of Paracetamol on Lung in the Trimesters; an Experimental Study

İlyas Uçar[1]*, Seher Yılmaz[2], Muhammet Değermenci[3], Adem Tokpınar[2], Şükrü Ateş[2], Ayşe Yeşim Göçmen[4], Mehtap Nisari[1], and Erdoğan Unur[1]

1. Department of Anatomy, Faculty of Medicine, Erciyes University, Turkey
2. Department of Anatomy, Faculty of Medicine, Yozgat Bozok University, Turkey
3. Department of Anatomy, Faculty of Medicine, Ordu University, Turkey
4. Department of Medical Biochemistry, Faculty of Medicine, Yozgat Bozok University, Turkey

Info Article

Submitted: 27-01-2022
Revised: 06-03-2022
Accepted: 23-03-2022

*Corresponding author
İlyas Uçar

Email:
ilyas.ucar@erciyes.edu.tr

ABSTRACT

Paracetamol (PAR) is an analgesic and antipyretic drug that is frequently used during pregnancy in many countries of the world. Although the fetal and maternal effects of toxic or long-term therapeutic doses used during pregnancy are known, the data on fetal effects during trimesters are insufficient. In this study, the possible effects of PAR exposure on both maternal and fetal tissues were investigated during pregnancy and in different trimester periods. Pregnant rats were exposed to different doses of PAR (low dose: 50 mg/kg and high dose: 500 mg/kg) in first trimester (1-7th days), second trimester (8-14th days) and third trimester (15-21st days) of pregnancy. On the 21st day, fetuses were removed by cesarean section under anesthesia. Maternal and fetal lung tissues samples were taken for biochemical analysis. PAR exposure decreased antioxidants levels and increased oxidative stress parameters levels in maternal and infant lung tissues. TBARS and TOS values increased compared to the control group, and it was statistically significant in all groups except the 1LD group ($p < 0.05$). SOD, CAT, GPX, TAS, and GSH parameters decreased compared to the control group, which was statistically significant in maternal lungs ($p < 0.05$). In infant lungs, it was also statistically significant for all groups in SOD, CAT, and TAS parameters. This experimental study demonstrates that exposure to PAR during pregnancy caused toxic damage to both maternal and fetal lung organs, especially in long-term usage during pregnancy, and in the third trimester.

Keywords: paracetamol; prenatal exposure; lung; rat; toxicity

INTRODUCTION

PAR, preferred as a short-term pain reliever and antipyretic in every pregnancy period, is the most extensively used drug globally and available without a prescription (Atteya *et al*., 2019). It is reported that 40-50% of pregnant women use PAR at least once during pregnancy. Therefore, PAR overdose during pregnancy ranks first in cases of overdose use (Blecharz-Klin *et al*., 2021).

After oral ingestion, PAR is rapidly absorbed from the gastrointestinal tract and metabolized mainly in the liver and partially in the intestine and kidneys (Dargan *et al*., 2003; Asirvatham *et al*., 2017). Although PAR is known as one of the safest drugs that can be used during pregnancy, some recent studies have drawn attention to PAR use (Ashafaq *et al*., 2020). It is emphasized that PAR overdose may cross the placenta and lead to fetal and maternal toxicity (Nitsche *et al*., 2017). Human studies claim that exposure to PAR in the intrauterine period increases asthma risk in childhood or adolescence (Shaheen *et al*., 2005; Fan *et al*., 2017), and associated with the child's current wheeze at age 5 (Perzanowski *et al*., 2010). Also, a recent cohort study showed that PAR exposure during pregnancy was associated with childhood asthmatic symptoms (Liew *et al*., 2021). An experimental animal study demonstrated that toxic PAR exposure was associated with a shift in pulmonary metabolism away from glycolysis with increased oxidative phosphorylation (Dobrinskikh *et al*., 2021). These findings support concerns about whether PAR can still be recommended as a safe treatment during pregnancy.

In the literature review, we could not find any research about which trimester PAR causes more toxicity on maternal and fetal lung tissues. The present study aimed to determine antioxidants and oxidative stress parameters in the lung tissues to determine whether the possible toxic effects of PAR use in pregnant rats on both maternal and fetal tissues.

MATERIALS AND METHODS

All experimental protocols were approved by Erciyes University Animal Experiments Local Ethics Committee (Decision no: 19/002) and funded by Erciyes University Scientific Research Projects Unit (Project no: TSA-2020-9161).

Experimental animals and mating

Sixty-three 8-week-old virgin female Wistar Albino rats weighing 185-200 g, which had not been used in any study, were obtained from Erciyes University, Experimental Research and Application Center (DEKAM). The animal rooms were well ventilated and kept at room temperature at 27°C and relative humidity of 70% with 12 hours natural light-dark cycle and were allowed free access to food and water. Female rats were placed in the same cage with male rats for mating (1 male to 2 females) at 05.00 pm. Vaginal smear samples of the female rat were used as a positive indication of pregnancy and were taken daily between 07:00 and 08:00 am. by lavage with physiological saline (0.9% NaCl) and examined under a microscope. The day when the presence of the sperm in the vaginal smear was considered the first day of pregnancy and those rats were kept in separate cages.

Experimental groups and administration of PAR

Sixty-three pregnant female Wistar albino rats were randomly divided into nine groups (n=7) and placed into labeled cages. Powdered PAR (Atabay Pharmaceuticals and Fine Chemicals Inc., Istanbul) was dissolved with 1 ml saline solution (SF) and administered orally by gavage at 4.00 pm. The optimal doses for the experimental groups (Saleem *et al*., 2019) and the trimesters of rat pregnancy (Galea *et al*., 2000) were determined in the literature, so pregnant rats' body weight was measured every three days to adjust the dose.

Control group (Control): Only SF (1 ml/day) was administered to the pregnant rats by gavage on the day 1 – 21 of pregnancy.

In the first trimester, low dose (1LD): 50 mg/kg PAR was administered to the pregnant rats by gavage on day 1 - 7 of pregnancy.

In the first trimester, high dose (1HD): 500 mg/kg PAR was administered to the pregnant rats by gavage on day 1 – 7 of pregnancy.

In the second trimester, low dose (2LD): 50 mg/kg PAR was administered to the pregnant rats by gavage on day 8 – 14 of pregnancy.

In the second trimester, high dose (2HD): 500 mg/kg PAR was administered to the pregnant rats by gavage on day 8 – 14 of pregnancy.

In the third trimester, low dose (3LD): 50 mg/kg PAR was administered to the pregnant rats by gavage on day 15 – 21 of pregnancy.

In the third trimester, high dose (3HD): 500 mg/kg PAR was administered to the pregnant rats by gavage on day 15 – 21 of pregnancy.

During the whole pregnancy, low dose (WLD): 50 mg/kg PAR was administered to the pregnant rats by gavage on day 1 – 21 of pregnancy.

During the whole pregnancy, high dose (WHD): 500 mg/kg PAR was administered to the pregnant rats by gavage on day 1 – 21 of pregnancy.

Removing the fetuses and obtaining lung tissues

On the day 21 of pregnancy, rats were anesthetized with ketamine (75 mg/kg) + xylazine (10 mg/kg), and the abdominal area was cleaned with 70% ethyl alcohol to prevent fur from sticking. Then, the anterior abdominal wall was removed with a transverse incision. The fetuses in the uterus were dissected together with their placenta. The gender of each fetus was confirmed, and the male fetuses were used in the study. Tissue samples from the maternal and fetal organs (e.g., heart, liver, lung, stomach, intestine, kidney, brain) were quickly removed and stored at -80 degrees.

Biochemical analysis

Lung tissues from both maternal and fetal organs were removed and stored at -80° C. The tissue samples stored at 80° C were used for the biochemical analysis. Lungs were homogenized on ice and centrifuged (5 minutes at 5000 g) to remove supernatant. All the supernatant was used to measure superoxide dismutase (SOD; ab65354, Abcam, Cambridge, United Kingdom), catalase (CAT; E-BC-K031-S, Elabscince, Houston, US), glutathione peroxidase (GPx; ZB-GPX-96A, ZellBio GmbH, Ulm, Germany) total antioxidant status

(TAS; Rel Assay Diagnostics, Gaziantep Turkey), total oxidant status (TOS; Rel Assay Diagnostics, Gaziantep Turkey), glutathione content (GSH; E-BC-K 030-S, Elabscince, Houston, US), and the activity and level of malondialdehyde (TBARS MDA; E-BC-K025-S, Elabscince, Houston, US).

Statistical analysis

SPSS version 22 was used for descriptive statistics and frequency distributions of biochemical parameters. All data were assessed for normality by Kolmogorov and Smirnov's test and homogeneity by Levene test. Data in all experiments were analyzed for statistical significance using variance analysis (one-way ANOVA). Post hoc analyzes, and Tukey's HSD test was performed to compare the parameters of different groups. P <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Biochemical results of maternal lungs

The mean values of the lung tissue parameters in the maternal organs and the statistical analysis between the groups are summarized in Table 1. Accordingly, the minimum values in the TBARS and TOS parameters were measured in the control groups, and the maximum values were measured in the WHD groups. The maximum values for the SOD, CAT, GPX, TAS, and GSH parameters were calculated in the control groups, but the minimum values were found in the WHD groups. There was a statistically significant difference in the lung tissues between the control group and the WLD and WHD groups in all parameters (p <0.05; Figure 1 and Figure 2).

When the data on lung tissues were examined on a trimester basis, it was determined that TBARS and TOS values increased compared to the control group, and it was statistically significant in all groups except the 1LD group (p <0.05). SOD, CAT, GPX, TAS, and GSH parameters decreased compared to the control group, which was also statistically significant (p <0.05; Figure 1 and Figure 2).

Biochemical results of infant lungs

The mean values of the lung tissue parameters in the infant organs and the statistical analysis results between the groups are shown in Table 2. The minimum values in the TBARS and TOS parameters were measured in the control groups, and the maximum values were measured in the WHD groups. On the contrary, the maximum values for the SOD, CAT, GPX, TAS, and GSH parameters were calculated in the control groups, and the minimum values were in the WHD groups. A statistically significant difference was found between the control group and the WLD and WHD groups in all parameters of lung tissues (p <0.05; Figure 1 and Figure 2).

When the lung tissue parameters were addressed on a trimester basis, it was determined that TBARS and TOS values increased in the control group, which was statistically significant in all groups except the 1LD group for TBARS parameters (p <0.05). The SOD, CAT, GPX, and TAS parameters decreased in the control group, and it was statistically significant for all groups in SOD, CAT, and TAS values. The GPX parameters were meaningful for the control group and the third-trimester groups (p <0.05). In terms of GSH parameters, there was an increase in 1LD and 2LD groups compared to the control group, which was statistically similar (p> 0.05). A statistically significant decrease was measured in the 1HD, 2HD, and third-trimester groups compared to the control group (p <0.05; Figure 1 and Figure 2).

The current research is the most comprehensive study investigating PAR's toxic effects during pregnancy on maternal and fetal organs on a trimester basis. Researchers explored PAR's possible toxic damages on maternal and fetal tissues in terms of different trimesters. The study data indicated that PAR could have various toxic effects on the lung tissues. PAR is in the "B" group in the FDA risk factor category and the safest and the most frequently used drug by patient populations, including children, the elderly, and pregnant women (Brune *et al*., 2015; Gokkaya *et al*., 2021). However, some recent research studies have focused on PAR recently (Gou *et al*., 2019). The exclusion of pregnant women from clinical trials due to ethical reasons also limits the data on the safe use of PAR during pregnancy (Lupattelli *et al*., 2014). Therefore, experimental animal studies are of great importance in clarifying the current issue.

Although a voluntary high dose of PAR during pregnancy is not very common, it is reported that PAR is the most used drug with or without prescription (Lupattelli *et al*., 2014). An excessive PAR dose is transferred to the fetus through the umbilical cord, crossing the placental barrier. Rollins *et al*. showed that PAR is converted into a hepatotoxic metabolite in fetal liver cells and reported that the fetus would be at risk if the drug enters the fetal circulation (Rollins *et al*., 1979).

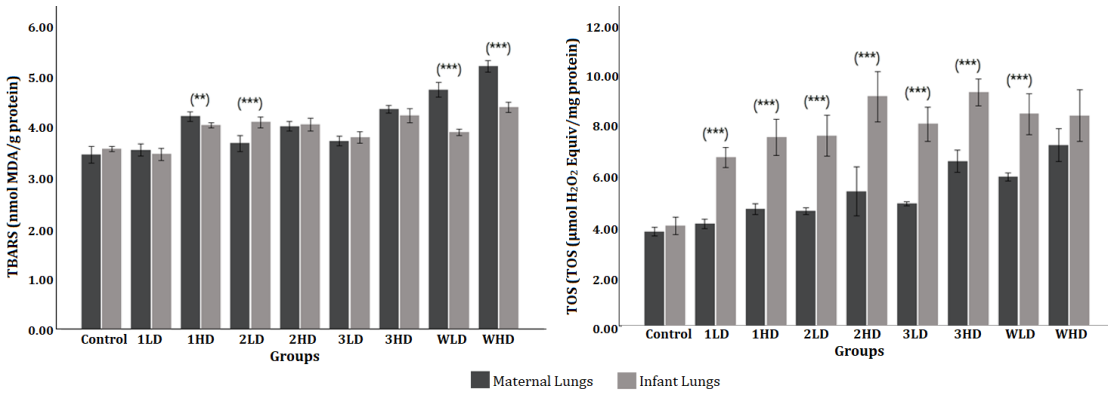

Figure 1. TBARS and TOS levels in maternal and infant lungs. *Represents the significance of p<0.05, ** Represents the significance of p<0.01, ***Represent the significance of p<0.001 compared to control.

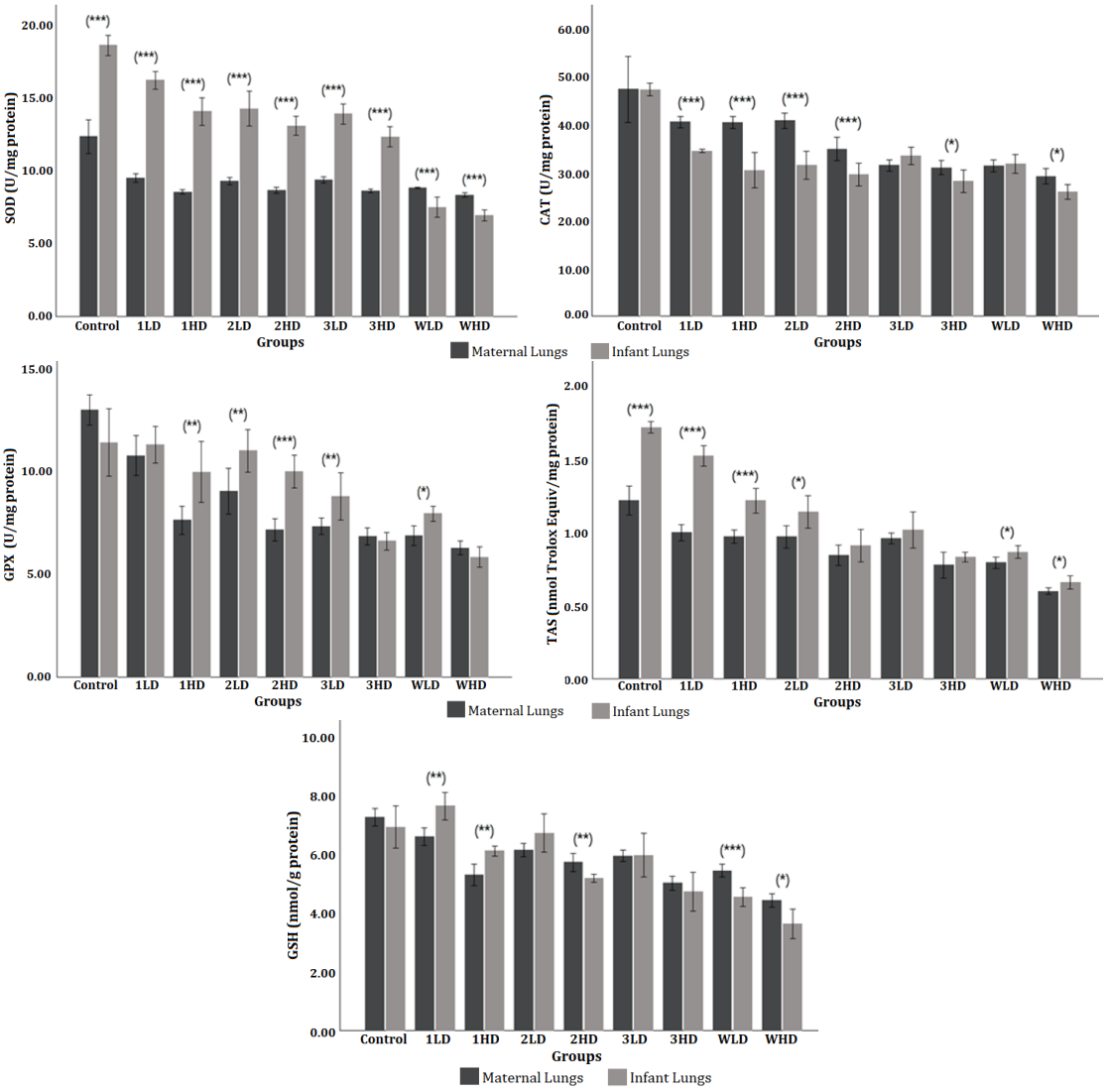

Figure 2. SOD, CAT, GPX, TAS and GSH levels in maternal and infant lungs. *Represents the significance of p<0.05, ** Represents the significance of p<0.01, ***Represent the significance of p<0.001 compared to control.

Table I. Biochemical parameters of maternal lung tissue

Organ	Groups	TBARS MDA	SOD	CAT	GPX	TAS	TOS	GSH
	Control	3.43±0.17^{a}	12.33±1.25^{a}	47.13±7.41^{a}	12.98±0.77^{a}	1.21±0.10^{a}	3.74±0.18^{a}	7.22±0.32^{a}
	1LD	3.52±0.12$^{a.b}$	9.49±0.33^{b}	40.34±1.23^{b}	10.76±1.05^{b}	0.99±0.06^{b}	4.06±0.19$^{a.b}$	6.56±0.31^{b}
	1HD	4.18±0.10^{c}	8.53±0.14$^{c.d}$	40.25±1.39^{b}	7.62±0.73^{c}	0.96±0.04^{b}	4.66±0.22$^{b.c}$	5.27±0.39$^{c.d}$
	2LD	3.65±0.16^{b}	9.29±0.28$^{b.c}$	40.64±1.73^{b}	9.03±1.21^{d}	0.96±0.08^{b}	4.57±0.15$^{b.d}$	6.11±0.25$^{b.e}$
Lung	2HD	3.99±0.10^{c}	8.63±0.22$^{c.e.f}$	34.77±2.57^{c}	7.16±0.60$^{c.e}$	0.84±0.07$^{c.d}$	5.35±1.05$^{c.d.e.f}$	5.70±0.33$^{c.e.f}$
	3LD	3.70±0.10^{b}	9.36±0.22$^{b.e.g}$	31.31±1.31$^{c.d}$	7.32±0.43$^{c.f}$	0.95±0.04$^{b.c}$	4.85±0.09$^{b.e}$	5.92±0.20$^{e.f}$
	3HD	4.32±0.07^{c}	8.61±0.11$^{c.g.h}$	30.89±1.63$^{c.d}$	6.84±0.43$^{c.f}$	0.77±0.09^{d}	6.55±0.48$^{f.g}$	4.99±0.25^{d}
	WLD	4.71±0.15^{d}	8.82±0.05$^{b.c.i}$	31.20±1.37$^{c.d}$	6.87±0.51$^{c.f}$	0.79±0.04^{d}	5.92±0.16^{f}	5.42±0.23$^{d.f}$
	WHD	5.16±0.12^{e}	8.32±0.17$^{d.f.h.i}$	29.07±1.74^{d}	6.27±0.36$^{e.f}$	0.59±0.02^{e}	7.19±0.70^{g}	4.41±0.24^{g}

Table II. Biochemical parameters of infant lung tissue

Fetus Organ	Groups	TBARS	SOD	CAT	GPX	TAS	TOS	G
	Control	3.48±0.13$^{a.e}$	18.89±0.99^{a}	46.73±1.70^{a}	11.33±1.76^{a}	1.71±0.06^{a}	4.03±0.40^{a}	6.59±
	1LD	3.41±0.11^{a}	16.88±1.88^{b}	34.60±1.33^{b}	11.19±1.19^{a}	1.49±0.10^{b}	6.50±0.78^{b}	7.51
	1HD	4.08±0.19^{b}	14.27±1.27^{c}	30.06±4.32$^{c.d.e}$	9.98±1.72$^{a.b}$	1.19±0.10^{c}	7.39±0.86$^{b.c}$	6.02±
	2LD	4.16±0.27$^{b.c}$	14.42±1.35^{c}	31.76±3.51$^{b.c.d}$	11.70±2.95^{a}	1.11±0.14$^{c.d}$	7.76±0.85$^{b.c}$	6.73±
Lung	2HD	3.91±0.30$^{b.d}$	12.92±0.93$^{c.d}$	29.51±3.89$^{c.f}$	9.66±1.62$^{a.b.c}$	0.91±0.12$^{e.f}$	9.06±1.15^{d}	5.11±
	3LD	3.76±0.13$^{d.e.f}$	13.75±0.87^{c}	32.91±3.32$^{b.c}$	8.61±1.60$^{b.c}$	0.99±0.15$^{d.e.g}$	7.75±1.08$^{b.c}$	5.64±
	3HD	4.09±0.30$^{b.c}$	11.95±1.24^{d}	28.41±2.85$^{d.f}$	6.41±0.55$^{c.d}$	0.82±0.03^{f}	9.24±0.64^{d}	4.57±
	WLD	3.92±0.14$^{b.f}$	7.23±1.09^{e}	32.24±2.26$^{b.c.d}$	7.50±1.16$^{c.d}$	0.86±0.04$^{f.g}$	8.43±0.92$^{c.d}$	4.48±
	WHD	4.37±0.12^{c}	6.69±0.65^{e}	25.88±1.85$^{e.f}$	5.56±0.62^{d}	0.66±0.04^{h}	8.35±1.11$^{c.d}$	3.52

Different letters mean statistically significant differences at $p<0.05$, $p<0.01$ and $p<0.001$. The same letters indicate the statistically similarity between the groups ($p>0.05$).

Therefore, it is essential to evaluate the severity of fetal damage stemming from PAR use in different doses and trimesters.

The global increase in the prevalence of asthma and PAR use instead of aspirin has raised doubts about the potential roles of PAR in the pathogenesis of asthma (Varner *et al*., 1998). Recent epidemiological studies reported that PAR might be a putative risk factor for asthma, based on the evidence that asthma risk may increase due to PAR exposure in intrauterine environment, infancy, late childhood, and adult life (Rebordosa *et al*., 2009). Besides, a review of case-control studies showed that prenatal PAR exposure might increase asthma incidence in the fetus (Fan *et al*., 2017; Farquhar *et al*., 2010). Rebordosa *et al*. (2008) reported that prenatal exposure to PAR, especially in the first trimester, increased the risk of asthma and wheezing in unborn babies. Shaheen *et al*. (2005) claimed that prenatal PAR exposure at the end of pregnancy might trigger persistent wheezing in early childhood, and thus childhood asthma begins in the prenatal period. However, they stressed that the highest risk occurred due to the first-trimester exposure. There are conflicting data in the literature regarding that PAR exposure leads to lung damage but at which trimester the risk is higher (Rebordosa *et al*., 2008; Shaheen *et al*., 2005), and experimental studies are limited (Özkoç *et al*., 2020). We found that MDA and TOS values increased in both maternal and fetal lung tissues due to PAR exposure during pregnancy and that SOD, CAT, GPX, TAS, and GSH values decreased. Compared on a trimester basis, we found that PAR in the late gestation period and the increase in dose had a very toxic effect on both maternal and fetal lung tissues. These findings indicated that PAR could also be metabolized in the lungs, and the changes in oxidant/antioxidant parameters could be the most likely mechanism between PAR use and asthma. A decrease in GSH level may affect the capacity of NAPQI, which is released due to metabolizing PAR, to resist the toxic effects and response to oxidative stress (Rebordosa *et al*., 2008). Also, previous studies indicated that measurable toxic effects of PAR on oxidant,

inflammatory, and endoplasmic reticulum might be an indicator of PAR-lung interaction (Sandoval *et al*., 2019).

In conclusion, crucial biochemical evidence has shown that PAR exposure during pregnancy may cause dose-dependent toxic effects on maternal and fetal organs, which is noticeable especially during pregnancy and the third trimester. There may be two reasons for this situation. First, although the lungs have no known function during fetal life, the lungs complete all the essential components towards the late stages of pregnancy. Second, a recovery mechanism may have developed against oxidative stress in the early stages of pregnancy. However, in the final stages, there may not be enough time for this recovery. In this sense, we believe that limiting the use of PAR, available without a prescription during pregnancy or under the supervision of a physician, will be necessary for both the mothers and future generations. Furthermore, alternative drug trials should be developed that offer a possible therapeutic alternative for the clinical management of pain during pregnancy.

ACKNOWLEDGMENT

This project was funded by the Erciyes University Scientific Research Projects Unit (grant number TSA-2020-9161).

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