# Lipopolysaccharide- induced

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# Lipopolysaccharide-induced pregnant mice had decreased serum iron while maintaining hepcidin level and Hamp1 mRNA expression

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## ABSTRACT

**Introduction:** Hepcidin is a hormone that regulates systemic iron homeostasis and is mostly produced in the liver. In pregnant women with inflammation, there are two opposing mechanisms in hepcidin expression: the suppression of hepcidin synthesis by pregnancy and the induction of hepcidin by inflammation. These conditions must receive special attention so clinicians can properly treat and manage pregnant women with inflammation. Therefore, this study aims to prove changes in hepcidin and serum iron levels in pregnant mice with inflammation.

**Method:** This study involved sixteen-second-week pregnant mice divided into two groups. Pregnant mice were injected with lipopolysaccharide (LPS) *Escherichia coli* serotype O111:B4 as much as 1 µg/g body weight intraperitoneally as the treatment group. In contrast, pregnant mice were injected with phosphate buffer saline (PBS) as a control group. Serum was measured using ELISA to determine hepcidin levels and colorimetry to determine serum iron. Mice livers were measured using Real-Time PCR to determine Hamp1 mRNA expression. The data obtained were analyzed using an independent t-test.

**Result:** Our results show that pregnant mice with inflammation show there was no difference in Hamp1 mRNA expression (p-value=0.163) and hepcidin level (p-value=0.789), but there was a significant difference in serum iron level (p-value=0.035).

**Conclusion:** This study demonstrates that inflammation in pregnancy does not affect changes in Hamp1 expression and hepcidin level but reduces serum iron, which could be caused by regulating hepcidin in the fetus.

**Keywords:** hepcidin, hamp1, inflammation; pregnancy, serum iron.
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## INTRODUCTION

Anemia is when the body experiences a shortage of red blood cells or due to red blood cells not functioning properly. According to the World Health Organization (WHO), iron deficiency is globally the most common cause of anemia.[1] Pregnant women are vulnerable to iron deficiency anemia because they experience an increased need for iron in the first trimester of 800 µg/day and increases up to 7500 µg/day with an estimated iron requirement during pregnancy of 1000 to 1200 mg.[2–4] This condition is the body's attempt to meet the mother's iron needs during pregnancy and to maintain and accommodate the developing fetus.

Hepcidin is a hormone that regulates systemic iron homeostasis and is mostly produced in the liver, the effect of hepcidin is to degrade ferroportin (Fpn) so that it has the effect of reducing iron absorption in enterocytes and releasing iron in cells that recycle and store iron. Hepcidin regulation is regulated by iron status, inflammation, erythropoiesis and sex hormones.[5,6] By regulating plasma iron hemostasis and systemic iron, hepcidin and ferroportin profoundly influence erythropoiesis.[7]

During pregnancy, there is a suppression of hepcidin production so that hepcidin levels decrease in the blood, this condition is the body's attempt to increase the absorption of dietary iron by the intestine because Fpn in enterocytes is not degraded by hepcidin.[8,9] The suppression mechanism is due to the increased E2 during pregnancy interacting with the ER (estrogen receptor) especially ERα in the cytoplasm, to form a complex that can bind half of the ERE (estrogen responsive element) site on the hepcidin gene promoter and inhibit hepcidin formation.[10–12]

Inflammation triggers increased hepcidin expression through the Janus kinase-Signal Transducer and Activator of Transcription (JAK-

STAT) and Bone Morphogenetic Protein - Small Mothers Against Decapentaplegic (BMP-SMAD) pathways which are mediated by pro-inflammatory cytokines. Induction of hepcidin via the JAK-STAT pathway requires interaction with the BMP-SMAD pathway. The protein complex formed will undergo translocation to the nucleus for transcription of Hamp1 mRNA.[13–16]

The problem is that two conflicting mechanisms exist for expressing hepcidin in pregnant women who experience inflammation. Therefore this condition must receive special attention so clinicians can provide treatment and attitude to pregnant women who experience infection. Thus, iron homeostasis and adequacy for the fetus can be maintained. So it is necessary to research to get an explanation of the level of hepcidin and serum iron in pregnant women who experience inflammation.

## MATERIALS AND METHODS

### Animal

Sixteen pregnant female mice (39±6g) in the second-week pregnancy were purchased from the Farma Veterinary Center (Surabaya, Indonesia). The day of the breeding day was taken as day 0 of pregnancy. Mice were housed under conventional conditions and given free access to food and drink. Pregnancy in mice was confirmed by the presence or absence of a fetus at the time of surgery. This research received ethical approval from the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, with certificate number 2.KE.111.11.2020.

Mice were randomly divided equally into two groups. Control pregnant mice were injected with phosphate buffer saline (PBS). As for the treatment group, pregnant mice were injected with lipopolysaccharide (LPS) Escherichia coli serotype O111:B4 (Sigma-Aldrich, Merck, Singapore) (1 µg/g body weight) intraperitoneally as the treatment group.

### Sample Collection

After four hours of treatment, the mice were sacrificed, and blood was collected intracardiacly using a syringe and transferred into a collection tube. The blood was allowed to clot for at least 1 hour, then centrifuged at 3000 rpm for 20 minutes to obtain serum. All sera were stored at -80°C until used for analysis.

Furthermore, the mice were dissected, and the uterus was checked to make sure the mice were pregnant by finding a fetus. After that, the liver was taken and washed using cold PBS until it was clean from blood. Subsequently, the liver was put into a container containing PBS and stored at -80°C until used for analysis.

### Enzyme-Linked Immunosorbent Assay

Serum was measured using an enzyme-linked immunosorbent assay (ELISA) to determine hepcidin levels (Cat. No. E1467Mo, Bioassay Technology Laboratory, Shanghai Korain Biotech Co., Ltd., Shanghai, China). Measurements were carried out according to the manufacturer's instructions.

### Iron serum measurement

For iron serum measurement, 50 µL of serum was pipetted and added to 450 µL of PBS. Then, serum iron was measured using a colorimetric assay (Elabscience Biotechnology Inc., Houston, TX, USA). Measurements were carried out according to the manufacturer's instructions. The serum iron concentration obtained was multiplied by 10 times.

### Isolasi RNA

RNA isolation was performed using the Total RNA Mini Kit (Cat. No. RT 100, Geneaid Biotech, Xizhi District, New Taipei City, Taiwan). Liver organs were weighed as much as 25 mg and then placed in a 1.5 ml microcentrifuge tube. Liquid nitrogen was added, and the liver was crushed using a micropestle. RNA isolation was carried out according to the manufacturer's instructions. RNA is stored at -20°C or used immediately.

### cDNA Synthesis

cDNA was synthesized using iScript™ cDNA Synthesis (Cat. No. 1708891, Biorad Laboratories Inc, Hercules, CA, US). The reagent components consisted of 5x iScript™ Reaction mix 4µl, iScript™ Reverse Transcriptase 1µl, Nuclease free water and RNA template 1µg. The reagent mix was incubated using a thermal cycler using the cycle program: Priming for 5 minutes at 25°C, Reverse transcription for 20 minutes at 46°C, and RT inactivation for 1 minute at 95°C. cDNA was analyzed quantitatively using an ND000 nanodrop (Thermo Fisher Scientific, Wilmington, DE, USA) and qualitatively using an electrophoresis gel.

### Real-Time PCR

mRNA expression was analyzed using the SensiFast SYBR™ No-ROX kit (Cat. No. BIO-98005, Bioline, Memphis, Tennessee, USA). β-actin was used as the positive control amplification using the following primers: F: 5'-ACC ATG TAC CCA GGC ATT GC -3' and R: 5'-CAC ACA GAG TAC TTG CGC TC-3', while the target gene used mouse Hamp1 primers as followings: F: 5'-AGA AAG CAG GGC AGA CAT TG-3' and R: 5'-CCC TGT TGC TGT AGC CGT AT3' [11]. Bio-Rad CFX96 Real-Time PCR System (Biorad Laboratories Inc, Hercules, CA, US) was used for amplification and analysis using the following cycles: Enzyme activation at 95°C for 2 minutes, followed by 40 cycles of denaturation at 95°C for 5 seconds, annealing at 55°C for 30 seconds.

### Statistical analysis

Data are shown as mean and standard deviation (SD). Statistical analysis was performed by t-test to determine differences between groups. All statistical tests used IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

## RESULTS

### Hamp1 expression and hepcidin level were maintained in LPS-induced pregnant mice

We observed hepcidin expression by measuring Hamp1 mRNA in hepatocytes and hepcidin protein in the blood. Hamp1 mRNA expression in LPS-induced pregnant mice (19.16 ± 8.65) compared to control pregnant mice (24.32 ± 7.84) showed no significant difference (p-value = 0.163). Blood hepcidin levels in LPS-induced pregnant mice (413.09 ± 87.07 ng/L) compared to control pregnant mice (424.34 ± 77.73 ng/L) also showed no significant difference (p-value=0.789).


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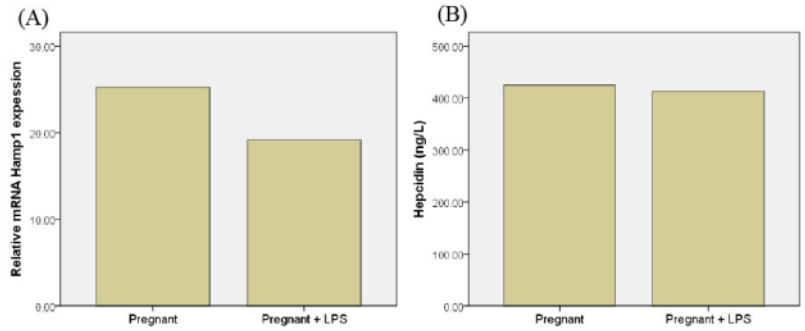


**Figure 1.** Comparison of hepcidin expression in non-LPS-induced pregnant mice and LPS-induced mice. (A) Hamp1 mRNA expression in hepatocytes. (B) Hepcidin expression in blood.

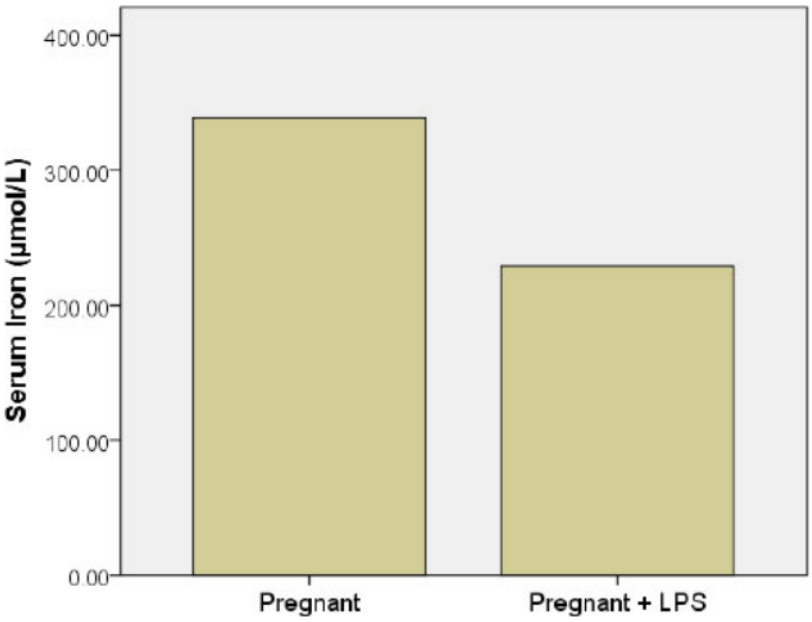


**Figure 2.** Induction of LPS in pregnant mice reduces serum iron levels.

Thus, hepcidin expression in pregnant mice was not affected by LPS (Figure 1).

### Decreased serum iron in pregnant mice after LPS injection

We also observed the response of serum iron, and our observations showed that LPS-induced pregnant mice (229.07 ± 80.63 µmol/L) had significantly lower serum iron levels compared to the control group (338.65 ± 115.11 µmol /L), with p-value 0.035 (Figure 2).

## DISCUSSION

This study showed that LPS induction in pregnant mice showed no significant increase in Hamp1 mRNA expression in the liver. We measured the hepcidin level in the blood to analyze the protein level. Our results also showed no significant increase in blood hepcidin levels. LPS-induced pregnant mice appear to maintain hepcidin expression at the same level to maintain iron homeostasis during gestation.

Several studies have shown that LPS is a protein that can induce hepcidin expression in hepatocytes.[17,18] LPS-induced hepcidin is also expressed in brain and heart cells.[19,20] However, the liver is the main source of hepcidin in vitro.[17] Increased hepcidin levels follow increased expression in hepatocytes in blood and reach a peak at 6 hours.[21,22] Intriguingly, our present study showed different results from the previous studies.

It is unknown what causes hepcidin to be retained in LPS-induced pregnant mice. LPS is a macromolecule that strongly mediates the inflammatory response, producing proteins, especially interleukin-6 (IL-6), as strong inducers of hepcidin expression.[23–25] Based on the available information, we speculate that estradiol (E2) may be the key to hepcidin regulation since there is an increase in E2 production during pregnancy.[26,27] E2 in the cytoplasm can form a complex with ER, which is then translocated into the nucleus and binds to the sequence estrogen-responsive element (ERE).[28] The hepcidin gene promoter region was identified as having half the ERE site. Therefore, the binding of the E2 complex to the hepcidin gene promoter will inhibit transcription and translation processes.[11,29,30]

Interestingly, in our study, LPS-induced pregnant mice showed decreased serum iron, even though the hepcidin level was maintained. Generally, decreased serum iron is accompanied by increased hepcidin.[25] It should be understood that the fetus also produces hepcidin and can regulate fetal iron content by controlling placental iron export.[10,31] We assume that serum iron is transported to the fetus in order to suppress the amount of serum iron levels in pregnant mice with inflammation and to keep up with iron in the fetus. Decreased serum iron is an immune mechanism to limit pathogenic microbes from accessing iron, further limiting their survival in the host.[32]

The previous studies demonstrated that cord blood hepcidin was associated with cord blood iron status, but no correlation was detected between cord blood hepcidin and pregnant women. However, maternal hepcidin correlated with parameters of newborn cord blood iron status.[10,31,33] The study by Sangkhae et al. (2020) reported that an increase in fetal hepcidin would decrease placental ferroportin (Fpn), thereby reducing the transfer of iron into the placenta. Meanwhile, decreased fetal hepcidin levels did not impact fetal iron. As a result, the hepcidin of pregnant women and the hepcidin of the fetus do not mix with each other. Besides being

regulated by the hepcidin of the pregnant woman, the Fpn of the placenta can also be regulated by the fetus. Ultimately, the fetus has a role in controlling the iron transfer from mother to fetus.[31]

A study by Kammerer et al. (2020) reported the autocrine role of hepcidin in regulating hepatic iron stores.[33] With this condition, autocrine impact on the liver as an iron storage organ will inhibit the release of iron in the blood, which results in a decrease in serum iron. If we look at Hamp1 and hepcidin in our study, LPS-induced pregnant mice did not show any autocrine role since Hamp1 mRNA expression and hepcidin level were not different from non-LPS-induced pregnant mice. Thus, it is suspected that decreased serum iron could probably be due to the increased transfer of serum iron to the fetus.

One of the limitations of our study is that we only examined Hamp1 expression, hepcidin and serum iron levels in the pregnant mice but not in the fetus. We also did not measure placental Fpn, which is used for iron transfer from mother to fetus. Therefore, the role of the fetus in controlling serum iron in pregnancy remains unclear.

## CONCLUSIONS

Our study shows that LPS-induced inflammation in pregnancy did not affect changes in Hamp1 mRNA expression and hepcidin level. However, it decreased serum iron in pregnancy, which could possibly be caused by hepcidin regulation in the fetus. Based on the insights gained from this study, further research is needed to study the involvement of the fetus in controlling iron hemostasis in pregnant women during inflammation.

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## CONFLICT OF INTERESTS

All authors declare that there are not any conflicts of interest.

## ETHICAL CLEARANCE

This research received ethical approval from the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, with certificate number 2.KE.111.11.2020.

## AUTHOR CONTRIBUTION

GN, conceptualization, methodology, investigation, validation, writing original draft; W, A, resources and investigation; W, A, HBN, methodology and supervision; W, A, CDKW, HN, WD, AS, HBN, PSR, methodology, writing, review, and editing; GN, W, A, supervision, conceptualization, project administration, and funding acquisition. All authors read and approved the final version of the manuscript

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