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Research

Comparison Effects of Giving Iron 60mg Folic Acid 0.4 mg Day And Iron 120 mg Folic Acid 2.8 mg Week On Hemoglobin Levels, Side Effects In Pregnant Women In Trimesters II-III And Fetal Welfare

Desiska Pricilia Tumatar*[1,2], Krisdiana Wijayanti[2], Bedjo Santoso[2], Ari Suwondo[2], Melyana Nurul Widyawati[2]

[1]*Lecturer, Muhammadiyah University of Manado, Pangiang, Pandu, Manado, North Sulawesi*
[2]*Postgraduate Program in Applied Health, Poltekkes Ministry of Health Semarang, Central Java, Indonesia*

*Author for Correspondence: Desiska Pricilia Tumatar
Email: desiskapricilia91@gmail.com

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Abstract

Background: Iron plays an essential role during pregnancy. However, pregnant women who use it daily may experience negative effects. There are suggestions that can be taken to reduce discomfort associated with iron consumption by administering weekly.
Destination: Researchers analyzed the difference between daily and weekly iron and folic acid administration on hemoglobin levels, side effects and fetal well-being.
Method: This study utilized a quasi-experimental, pretest-posttest, two-group design. 40 pregnant women in their second or third trimester were divided into two groups, each containing 20 participants: the group receiving iron 60 mg folic acid 0.4 mg per day and the group receiving iron 120 mg folic acid 2.8 mg per week. Examination of hemoglobin levels was performed once per month for three months during the intervention, while evaluation of side effects was done once per week and monitoring of fetal well-being was conducted at the beginning of the intervention and three months following the intervention.
Results: Result of hemoglobin level test using repeated measure ANOVA, administering 60 mg of folic acid 0.4 per day (0.012), and administering iron 120 mg of folic acid 2.8 mg per week (0.000), side effects using mcNemar test (0.125 nausea and vomiting 0.250 constipation) daily administration (0.625 nausea and vomiting 0.500 constipation) weekly administration, and fetal well-being using the Wilcoxon 0.000 test for daily administration, 0.000 for weekly.
Conclusion: Iron tablets can be administered weekly as an alternative to prevent oxidative stress and reduce digestive discomfort in pregnant women.

Keywords: Iron, Folic acid, Hemoglobin, Pregnant women.

INTRODUCTION

Iron is one of the numerous types of minerals that are essential for pregnant women. Iron is a vitamin that impacts the growth and development of the fetus and the health of pregnant women throughout pregnancy. Iron mineral is essential for maintaining hemoglobin. In which hemoglobin is essential for oxygen transmission and blood production.

Anemia is the scientific term for iron deficiency in women who are pregnant. If the hemoglobin level falls below 11gr/dL in the first and third trimesters, and there is a decrease of up to 0.5 gr/dL in the second trimester, the patient has anemia. Low hemoglobin levels can contribute to premature births, mother and newborn mortality, the incidence of infection, and intrauterine growth retardation (IUGR). The emergence of blood thinning in the body as a compensatory mechanism during pregnancy causes decreased hemoglobin levels so that the heart's workload does not increase with growing gestational age.

A decrease in hemoglobin levels can restrict the fetus from developing and growing as it should. This is induced by vasoconstriction of blood vessels, which reduces the blood flow responsible for transporting oxygen and nutrients. Growth and development of the fetus is one way to evaluate the fetus's well-being in the womb. A fetus is considered to be healthy if it receives the nutrients required for its growth, such as iron minerals that aid in cell division and the formation of hemoglobin.

Pregnant women's iron mineral requirements are not necessarily fulfilled by the food they consume. To prevent a decrease in hemoglobin levels during pregnancy, preventative measures are required, such as iron mineral supplementation, iron-enriched diets, nutrition education, parasite-borne infection prevention, and sanitation enhancement. Therefore, pregnant women require external vitamins and minerals to provide adequate levels of important minerals (iron). Pregnant women who are carrying one child require at least one thousand milligrams of iron. The division is necessary for the development of 500 to 600 milligrams of red blood cells and for the fetus to grow and create the placenta.

The World Health Organization (WHO) advises daily blood supplementation with 30-60 mg of elemental iron and 0.4 mg of folic acid. Thirty (30) grams of elemental iron, which is equal to 150 mg ferrous sulfate, 90 mg ferrous fumarate, or 250 mg ferrous gluconate3. As stated in Minister of Health Regulation Number 88 of 2014 about Standards for Blood Supplementation Tablets for Women of Childbearing Age and Pregnant Women, Indonesia also follows WHO recommendations to prevent anemia. The Minister of Health also regulates the dosage, which is one tablet per day or 90 tablets or more if necessary during pregnancy.

Pregnant women are sometimes adversely affected by the consumption of iron-containing blood supplements. The danger of oxidative stress resulting in digestive and pain disorders owing to excessive iron consumption exists. Constipation, black stools, diarrhea, loss of appetite, nausea, vomiting, and stomach pains are examples of potential disturbances.

Vernissa published in a journal the results of a study in which it was determined that pregnant women who were required to consume daily blood-added tablets containing 60 milligrams of iron and 0.4 milligrams of folate did not do so. The study found that pregnant women who received supplementation with added blood containing 60 milligrams of iron and 0.4 milligrams of folate did not comply. 50% of non-compliance was attributed to nausea, vomiting, and feeling uncomfortable, 28.1% to forgetfulness factors, and the remainder to boredom from having to eat iron every day and constipation, with the largest presentation occurring in roughly 54.5%.

Therefore, the World Health Organization (WHO) recommends weekly administration of tablets containing iron minerals and folic acid to prevent negative effects. 120 milligrams of elemental iron containing 600 mg ferrous sulfate, 360 mg ferrous fumarate, 1000 mg ferrous gluconate, and 2.8 mg of folic acid is administered. The suggested dosage for pregnant women without anemia is once per week; the prevalence of anemia is less than 20%.

Several foreign research, including those by Bouzari et al. (2011), Alaoddoleheiet al. (2013), Goonewardene and Senadheera (2016), and Ahankar et al. (2016), have examined the administration of blood-added pills given daily and weekly, but at a dose of 100 mg. The various amounts of iron are 50 mg, 60 mg, 100 mg, and folic acid 0.5 mg per day or per week and are determined by measuring the levels of hemoglobin, serum iron, and ferritin. It is difficult to discover papers that compare the delivery of iron and folic acid per day and per week, and there is only one journal that does so: Utari's research (2017). This study aims to examine side effects and fetal growth and development during pregnancy, in addition to continuing to measure hemoglobin as a basis for comparing the amount of blood-added tablets with a daily dose of 60 mg iron, 0.4 mg folic acid, and 120 mg iron, uric acid. 2.8 mg of folate per week as recommended by WHO.

METHOD

This research has been registered with the Sultan Agung Islamic University Semarang Research Bioethics Commission with the number 148/V/2021/Bioethics Commission. It research was conducted at the

Sagerat Health Center from April to December 2021.The purpose of this quasi-experimental study with a pretest-posttest and two-group design is to investigate the difference between iron administration on hemoglobin levels and side effects in second-trimester pregnant women and fetal health.

Using a random sampling technique, 40 samples were drawn from a population of 80 pregnant women using a random sampling technique. Respondents In this study, pregnant women were pretested in each intervention group. Twenty participants in the first group received 120 mg of elemental iron and 2.8 mg of folic acid per week for three months. After 30 days of the first month of treatment, hemoglobin levels were assessed or a posttest was administered in the first group, which was repeated every three months. In the second group of twenty participants, 60 mg of elemental iron and 0.4 mg of folic acid were administered before to the pre-test. In the second treatment group for three months, a posttest was administered 30 days after the first month of treatment. Monitoring of adverse effects was performed every week for three months, whereas interpretation of fetal weight was performed at the beginning of the intervention and three months later for fetal welfare. Data analysis utilizing repeated measure ANOVA for hemoglobin levels, McNemar for side effects, and Wilcoxon for fetal well-being

RESULTS AND DISCUSSION

Hemoglobin Examination Results

Table 1 shows the mean number of hemoglobin examinations in the three examinations in each group. The average daily hemoglobin examination result in the group showed that the first examination was 11.5 g/dL and decreased in the second examination by 11 g/dL. Then on the third hemoglobin examination, it also showed a decrease to 10.4 g/dL, the delta value was 1.1 g/dL. The second group, which was given weekly, showed a test result of 12.1 g/dL on the first examination, then decreased to 10.8 g/dL on the second examination and on the third examination it became 10.5 with a difference of decrease of 1.4 g/dL.

Table 1: The effectiveness of increasing hemoglobin levels by giving iron 60 mg folic acid 0.4 mg per day and iron 120 mg folic acid 2.8 mg per week

Inspection	*Mean* Hemoglobin (g/dL)	
	Daily Giving	Weekly Giving
Results I	11.5	12
Result II	11	10.8
Result III	10.4	10.6
result I-result III	1.1	1.4
p-value	0.012	0.000
Effect size	0.112	0.425

The calculations in table 1 show the difference in the mean values in each group before being compared after being given treatment. Where in the two groups there was no difference or it could be assumed that the results of the hemoglobin examination given daily and weekly had differences.

The mean value of the difference in hemoglobin examination results in the grouping of daily administration to the weekly administration group can be interpreted in the following chart 1 diagram.

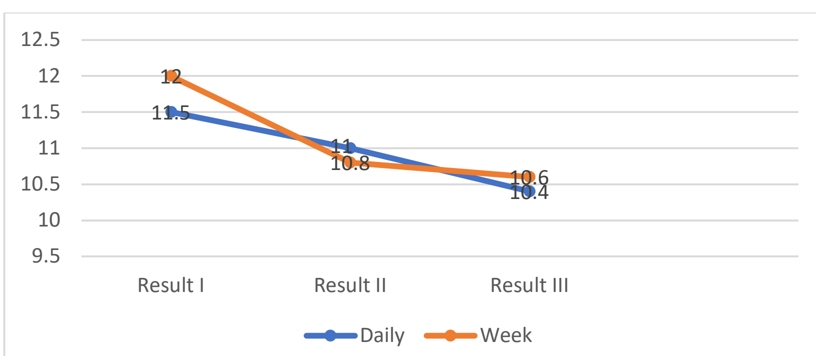

Fig 1: Changes in the average hemoglobin examination for each treatment group

Differences in Hemoglobin Examination Results for Each Intervention

Table 2: Differences in Hemoglobin Examination Results for Each Intervention

Group			*pretest-posttest*	*Mean difference*	*p-value*
Hemoglobin	Per day	Check 1	0.5	0.715	0.053*
		Check 2	1.1	0.925	0.013*
	Per week	Check 1	1.2	0.865	0.000*
		Check 2	1.4	1.375	0.000*

The results of the post hoc LSD follow-up test analysis are displayed in table 2 and demonstrate substantial differences across the groups. Exam table 1 in the daily group contains the first and second examinations with unimportant findings, as indicated by the p-value of 0.053>0.05. The p-value of 0.013 is greater than 0.05, indicating a significant difference between the first and third examinations in table 2 for the daily group.

Other data from the weekly group suggest that examination 1, consisting of the first and second hemoglobin tests, has a p-value of 0.000 0.05, indicating a significant difference between the first and second hemoglobin tests. Exam table 2 in the weekly group reveals a p-value of 0.000 0.05 between the first and third hemoglobin tests, indicating a significant change.

The repeated measures ANOVA test for the daily administration group yielded a p-value of 0.012, indicating that there was a significant difference between before and after the intervention was administered. In contrast, the weekly administration group had a p-value of 0.000, indicating that there was a statistically significant difference between the pre-intervention and post-intervention periods.

The partial eta squared test to determine the effect size revealed that the weekly administration group had a greater effect size with a value of 0.425 than the daily administration group with a value of 0.112, indicating that the weekly administration group had a greater impact on changes in hemoglobin levels.

Physiological changes that often occur in pregnancy are iron deficiency caused by hemodilution or blood thinning. Iron is needed for hemoglobin to be formed and for red blood cells to increase production. These two elements are most needed in the second and third trimesters because they are needed for the formation of the placenta and fetal development.

Iron derived from food and the breakdown of red blood cells (erythrocytes) by macrophages in the endothelium reticulum aids the iron metabolism system of the body. Iron minerals derived from food are split into two categories: heme and non-heme, with non-heme comprising 90% of the total and heme the remaining 10%. Meat, fish, poultry, shrimp, squid, and animal protein are sources of heme, as opposed to vegetables, fruit, beans, grains, and pasta, which do not contain heme.

Iron has essential metabolic activities in cells, but can be biochemically damaging. Iron is engaged in oxygen transport, ATP creation, nucleic acid synthesis, maintenance of mitochondrial fusion, protection of cellular structures against oxidative damage, pathways of action of placental development, cell growth and proliferation, and in several enzymes, among other functions. Iron is also a transition element, which makes it a catalyst for the Fenton and Haber-Weiss reactions. These processes result in the creation of free radicals, including hydroxyl radicals (OH) and Ferryl-2 ions ($FeO2+$), as well as lipid peroxidation, which, if excessive, can lead to oxidative stress and endothelial cell injury. It is hypothesized that oxidative stress plays a role in the pathophysiology of preeclampsia. As demonstrated by meta-analysis,

Zhuang et al. shown in their publication that iron as a transition metal has five oxidation states ($Fe2+$-$Fe6+$) in the basic stage, with $Fe2+$ $Fe3+$ being the most prevalent. Iron, which can create oxidative stress, will have a number of negative impacts on pregnant women, including DNA mutations and gestational diabetes. Several interventions were administered to experimental animals in order to induce DNA modifications. It was discovered that administering 300 mg/kg of iron to rats for one year increased the concentration of changed DNA bases in the liver. Iron can also promote GDM since it has been proven to enhance oxidative stress, which damages the pancreatic cells responsible for insulin production. However, serum iron levels support the existence of GDM as a biomarker.

Researcher obtained important outcomes from completed research. The intervention administered daily with a dose of 60 mg iron folic acid 0.4 mg resulted in a p-value of 0.012, indicating that the difference between the first, second, and third examinations was statistically significant. This conclusion was consistent with the hypothesis that hemoglobin levels will fall as a result of hemodilution. The treatment of 120 mg of iron and 2.8 mg of folic acid weekly demonstrated a statistically significant difference (p value 0.000). Based on the two interventions, both daily and weekly, there was a significant difference between the first, second, and third interventions within each intervention.

In the post hoc LSD follow-up test, the measurement findings between the first and second examinations on the daily administration intervention showed significant results with a drop of 0.5 and a p-value of 0.053, indicating that there was no meaningful change. In contrast to the weekly providing intervention, which witnessed a decrease of 1.2 on average with a p-value of 0.000, indicating a significant difference. The drop in hemoglobin levels observed in both therapies is consistent with the notion. Where, at the initial examination that began at 20 weeks of gestation, it was classified as non-anemic, namely 11.5 g/dL for the daily administration intervention and 12 g/dL for the weekly administration intervention. The anemia group includes the findings of the third examination conducted between 28 and 32 weeks of gestation on both types of intervention, daily and weekly. On the second examination in the second trimester, however, it did not fall into the category of anemia, with hemoglobin values ranging from 11 g/dL in the daily intervention to 10.8 g/dL in the weekly intervention. In theory, pregnant women are considered iron deficient if their hemoglobin levels were low that is below 10,5 g/dL16. Anemia in the third trimester is caused by the peak of blood thinning that occurs in the third trimester to minimize the heart's strain.

Of the third trimester, an imbalance between the quantity of plasma and the increase in red blood cells causes hemodilution, which impacts hemoconcentration, hematocrit, and erythrocytes. The research conducted by Aksari and Imanah on pregnant women in their third trimester provided noteworthy results that can be interpreted as typical characteristics of third-trimester pregnant women. This research confirms prior findings that anemia persists in the third trimester despite daily and weekly treatment.

The research of Rajoria et al. validates the research of researchers who compared daily iron delivery to intermittent iron administration (one or two times per week). The results indicated that the levels of hemoglobin, serum ferritin, and hematocrit were same. Research indicates that pregnant women who are not anemic may be given iron supplements twice per week to prevent iron deficiency anemia and iron deficiency during the third trimester.

Utari et al. conducted a study in Indonesia (Ciomas, Bogor) that compared weekly and daily iron treatment. However, the inclusion criteria for the study involving anemic pregnant women ranged from 9 to 10,9 g/dL. For both therapies, 60 mg of elemental iron and 0.4 mg of folic acid were administered. There were still substantial disparities between the two groups, with a rise of 0.5 g/dL between the initial and final examinations in the weekly administration group and a rise of 0.6 g/dL in the daily administration group. Where there is no significant difference between the results of daily and weekly administration tests for hemoglobin levels19. Even if pregnant women are anemic, it is permissible to give them iron tablets once a week, according to study undertaken by other scientists.

Results of monitoring side effects per day

Table 3: Monitoring Side Effects of Iron 60 mg Folic Acid 0.4 mg per day

Intervention	**Side effects**	
	Nauseous vomit	**Constipation**
	f	**f**
Before intervention	2	3
After intervention	6	6
after-before	4	3
p-value	0.125	0.250

Table 3 shows the results of monitoring the side effects of the intervention in the form of nausea, vomiting and constipation. The side effects of nausea and vomiting before the intervention were felt by 2 respondents. After the intervention, the side effects of nausea and vomiting were felt by 6 respondents. Monitoring of other side effects, namely constipation before the intervention was felt by 3 respondents after the intervention was felt by 6 respondents. The results of the different test on the two side effects showed insignificant values, meaning that the intervention given before and after the intervention had no difference.

Results of monitoring side effects weekly

Table 4: Monitoring Side Effects of Iron 120 mg *Folic Acid 2.8 mg Weekly*

Intervention	**Side effects**	
	Nauseous vomit	**Constipation**
	f	**f**
Before intervention	3	4
After intervention	6	6
after-before	3	2
p-value	0.625	0.500

Table 4 shows the results of monitoring for side effects of nausea, vomiting and constipation from the given intervention. The weekly intervention for nausea and vomiting was felt by 3 respondents before the intervention and 6 respondents after the intervention. Meanwhile, the side effect of constipation before the intervention was felt by 4 respondents and increased by 6 respondents after the intervention. The results of the different tests conducted on the two side effects caused by the given intervention showed insignificant results, which means that there was no difference from the intervention given to the perceived side effects.

The side effects studied in this study were nausea, vomiting and constipation. The first intervention that was given was the administration of iron on a daily basis where nausea and vomiting were initially felt by 2 respondents to 6 respondents after administration. Meanwhile, constipation which was initially felt by 3 respondents increased to 6 respondents after the intervention was given. The results of the test using McNemar to determine the relationship between side effects and daily administration got a p-value of 0.125 for the side effect of nausea and vomiting and 0.250 for the side effect of constipation. Both of these results are not included in the significant category. Although, there is no significant relationship but there is a twofold increase.

The second intervention given was the administration of 120 mg of iron per week. The results obtained that before the intervention nausea and vomiting were felt by 3 respondents and became 6 respondents after being given the intervention with a difference of 3. Meanwhile, the side effect of constipation which was initially felt by 4 respondents increased by 2 respondents to 6 respondents after being given the intervention. The results of the McNemar test to determine the relationship between weekly intervention and side effects showed insignificant results with a p-value of 0.625 for nausea and vomiting and 0.500 for constipation.

Supporting research that helps research conducted by Yaznil et al where the research conducted compared the side effects of daily and weekly iron administration. The results of this study showed that respondents who experienced nausea were felt by 17 respondents who received daily intervention while respondents who felt nauseated with weekly intervention were only 8 respondents out of a total of 42 respondents. Another side effect studied in this study was vomiting experienced by 8 respondents who received daily intervention and 3 respondents who received weekly intervention. The next side effect that supports the research is constipation where there is a difference between respondents who receive daily intervention and weekly intervention.

The side effects of nausea, vomiting and constipation in women in pregnancy included in this study were no different due to the form of iron obtained in the form of iron fumarate (Fe III) which according to the theory of iron (III) is absorbed more quickly by the body.

Fetal Weight Interpretation Examination Results

Table 5: Average Value of Fetal Body Weight Interpretation Iron 60 mg folic acid 0.4 mg per day and iron 120 mg folic acid 2.8 mg per week

Intervention	Interpretation of Fetal Weight (grams)	
	Per day	Per week
Before Intervention	305	384
After Intervention	1489	1544
after-before	1184	1160
p-value	0.000	0.000

Table 5 shows the difference in the mean interpretation of fetal weight in the intervention group per day and per week. The interpretation of fetal weight given the intervention showed a figure of 305 grams before the intervention and after the intervention was given to 1489 grams. Meanwhile, in the weekly intervention before the intervention, the fetal weight interpretation showed 384 grams and after the intervention, the fetal weight interpretation became 1544 grams. Different tests were carried out to see the difference in the mean interpretation of fetal weight in the two interventions. The results obtained by using the Wilcoxon test showed that the two interventions both daily and weekly showed the same significance value of 0.000, which means that there was no difference in the average value of the two interventions.

According to the findings of the research, fetal growth and development at the beginning of the pregnancy or before the intervention could be considered to be part of the category determined by gestational age. This category was defined as an average of 300 grams both per day and per week at 20 weeks of gestation, which was the point at which the inclusion criteria was applied. After that, the intervention was carried out over the course of three months, beginning at a gestational age ranging from 28 to 32 weeks. The results of monitoring for a period of three months showed appropriate results for the interpretation of fetal weight at gestational ages 28-32. These results were in accordance with the theory and ranged from 1000 grams to 1800 grams, with the average results of the interpretation of fetal weight ranging from 1500 grams per day and per week and being included in the welfare category.

Shankar et al. conducted a study in which they examined the effects of daily versus weekly administration of iron and folic acid on hemoglobin, hematocrit, MCV, and MCH as well as infant weight at birth in pregnant women who were either anemic or did not have anemia. The researchers were particularly interested in the baby's weight when it was first delivered. Whereas, there was not a significant difference found between the weight of the babies born to anemic pregnant women and those born to non-anemic pregnant women who got iron and folate supplements on a daily and weekly basis. The average birth weight of infants born to moms who did not have anemia was 2825 grams, whereas the average birth weight of infants born to mothers who did have anemia was 2819 grams.

CONCLUSION

Hemoglobin level examination results revealed no significant difference between daily and weekly iron administration. Daily use of blood-added tablets was associated with more severe negative impacts than weekly administration. Monitoring the interpretation of fetal weight following daily versus weekly delivery of blood-added tablets did not lead to different results. Pregnant women may be advised to take blood tablets per week as an alternative to iron to prevent oxidative stress and relieve stomach discomfort, although this has no impact on fetal growth and development.

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