

The Effect of Ferric Carboxymaltose Versus Iron Sucrose on Hemoglobin Levels in Pregnant Women with Anemia: Meta-Analysis

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ABSTRACT

Background: Anemia in pregnant women is one of the global health problems experienced by developed or developing countries affecting 1.62 billion world population, which corresponds to 24.8% of the population in the world. Anemia is a serious problem for maternal health because it is one of the five problems that becomes the target of solving the World Health Organization (WHO) in 2025. This study aimed to estimate the magnitude of the effect of Ferric Carboxymaltose on hemoglobin levels in pregnant women with anemia compared to Iron Sucrose.

Subjects and Method: This study was a meta-analysis study. The study was conducted by looking for data from the study results in the period 2010-2019. The data of this study was from Pubmed, DOAJ, Science Direct, Springer Link, Web of Science, Cochrane, Google Scholar, BMJ, BMC, Research Gate, J Stor, Wiley, Clinical Key, J Gate, SAGE, IEEE Xplore, ERIC Institute of Education Science, BASE, SciELO, WorldCat, Microsoft Academic, Index Copernicus, CABI, Cambridge, Nature, Oxford, ProQuest, and BJOG using the keyword "ferric carboxymaltose" AND "iron sucrose" AND "anemia in pregnancy" AND "randomized control trial" OR RCT, "ferric carboxymaltose" AND "iron sucrose" AND "hemoglobin in pregnancy" AND "randomized

control trial". The subjects of this study were pregnant women with anemia. The study used a Revman 5.3 application to analyze the article.

Results: The eight articles were reviewed using the meta-analysis technique in this study. Pregnant women who were given ferric carboxymaltose therapy had a higher mean hemoglobin level than those who were not treated carboxymaltose therapy and it was statistically significant (SMD= 1.11; 95% CI= 0.37 to 1.85; p= 0.003). The heterogeneity of the data showed I²= 98% so that the distribution of the data was stated to be heterogeneous (random effect model).

Conclusion: Ferric Carboxymaltose is effective in increasing hemoglobin levels in pregnant women with anemia.

Keywords: Ferric Carboxymaltose, Iron Sucrose, Randomized Controlled Trial.

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BACKGROUND

Anemia is one of the global health problems experienced by developed and developing countries. Anemia affected 1.62 billion people in the world, which corresponded to 24.8% of the world's population (Pavord et al., 2012).

Anemia is a serious problem for maternal health because anemia is one of the five problems that becomes the target of solving the World Health Organization (WHO) in 2025. Anemia is also a risk factor that

contributes to 50% of maternal mortality (Khaskheli et al., 2016). WHO targets to reduce the incidence of anemia by 50% in women of childbearing age around the world.

A study conducted by Stevens et al. (2013) stated that globally from 1995 to 2011 in 107 countries, pregnant women had a high-risk factor for anemia cases. Anemia in pregnant women is a health problem that requires special attention due to the high incidence rates and complications that can arise in both mother and fetus (Obizue et al., 2013). Research continued to perform to assess the prevalence of anemia. Several studies stated that the prevalence of anemia in India, Indonesia, Ethiopia, and China still had high rates in pregnant women, which were 73.1%, 37.1%, 32.8%, and 12.71% (Gogoi et al., 2016 and Bekele et al., 2015).

The most common cause of anemia worldwide was iron deficiency anemia which was estimated to be about 50% of the cases (Camaschella, 2015 and WHO, 2014).

Anemia is identified by low levels of hemoglobin and hematocrit in the blood. The lack of hemoglobin and hematocrit levels are caused by low production of red blood cells (erythrocytes), damage to erythrocytes (hemolysis), and loss of excessive blood. Pregnant women are the population that most susceptible to developing iron deficiency anemia. Health interventions had been carried out on a large scale, but the incidence of iron-deficiency anemia continued to increase in developing countries (Bilimale et al., 2010). Iron deficiency occurs when the amount of iron is not sufficient to meet the increasing body needs such as the condition of the mother during pregnancy, especially in the third trimester because it is used for fetal development (Tadesse et al., 2017).

A study conducted by Rahman et al., (2016) mentioned that anemia contributed to the incidence of LBW 25%, preterm delivery

44%, and perinatal mortality 21% in low-income countries. The effects of anemia suffered by mothers during pregnancy can increase the risk of malnourished infants.

According to WHO policy until 2025, anemia affects on nutritional deficiencies in infants, starting from the formation of the fetus, causing stunting and wasting.

The availability of Intravenous (IV) iron is quite promising, especially in severe anemia cases. Intravenous iron provides a greater and faster supply of iron than oral iron therapy without the gastrointestinal side effects from oral substitution and makes it possible to avoid blood transfusions with associated risks. To date, several studies had focused on the use of IV iron and its side effects and safety in pregnant women. Iron sucrose has been used for many years for the treatment of iron deficiency in pregnant women after the first trimester. However, the use of iron sucrose is limited to low doses because of local and systemic side effects at higher doses. Intravenous iron Ferric Carboxymaltose was then introduced in the scope of anemia management in the world of health.

Based on the route of administration, iron can be consumed by oral and intravenous (IV) injection. Intravenous iron is considered to be a useful option when prompt treatment is required (Qassim et al., 2017). Intravenous iron is considered to be a useful option when prompt treatment is required (Qassim et al., 2017). The fear of anaphylaxis (no formulation has the highest Food and Drug Administration or FDA safety level) the use of intravenous (IV) had no adverse side effects that had been reported for use in thousands of patients (Tolkien et al., 2015).

Based on the problems above, the researchers are interested in examining the effect of Ferric Carboxymaltose versus Iron Sucrose on hemoglobin levels in pregnant

women with anemia. The data obtained will be analyzed using meta-analysis.

SUBJECTS AND METHOD

1. Study Design

This study was a meta-analysis study. The study used data from the results of the previous studies in which the researcher presented the summary that corresponded the questions formulated by the researcher, namely the effect of Ferric Carboxymaltose. This study also used a systematic review which was useful in combining some results of the studies conducted separately and expected to reduce bias. Frequently, systematic reviews involved a meta-analysis process, namely statistical techniques to synthesize the data into one quantitative result to produce a measure of the effect summary (Lindsay, 2011).

2. Population and Sample

The articles were searched by considering the eligibility criteria which were determined using the PICO model. The population of the study was pregnant women with anemia with a sample of the intervention group and the control group.

3. Inclusion Criteria

The inclusion criteria were a full paper article with the randomized controlled trial. Articles were in English or Indonesian. The therapy given was ferric carboxymaltose and iron sucrose as the comparison. The subjects of the study were pregnant women with anemia.

4. Exclusion Criteria

The study was conducted with an observational study. The Articles published before 2010.

5. Operational Definition of Variables

Hemoglobin levels in pregnant women with anemia were conditions of mothers with Hb levels below 11 gr% in the first and third trimesters or <10.5 gr% in the second trimester. The study used laboratory examination instruments and a continuous measuring

scale. Ferric carboxymaltose therapy was a new iron complex consisting of an iron hydroxide core stabilized by a carbohydrate shell. The study used the instrument of the dose guideline program in the administration of therapy and a continuous measuring scale. Iron sucrose therapy was iron sucrose which stimulated erythropoiesis so it increased iron availability. The study used the instrument of the dose guideline program in the administration of therapy and a continuous measuring scale.

6. Data Analysis

The data processing was carried out by ReviewManager (RevMan5.3) by calculating the effect size and heterogeneity to determine which research models were combined and to form the final meta-analysis result.

RESULTS

The process of searching for the articles was through journal databases, included: PubMed, DOAJ, Science Direct, Springer Link, Web of Science, Cochrane, Google Scholar, BMJ, BMC, Research Gate, J Stor, Wiley, Clinical Key, J Gate, SAGE, IEEE Xplore, ERIC Institute of Education Science, BASE, SciELO, WorldCat, Microsoft Academic, Index Copernicus, CABI, Cambridge, Nature, Oxford, ProQuest, and BJOG. The keywords used included: "ferric carboxymaltose" AND "iron sucrose" AND "anemia in pregnancy" AND "randomized control trial" OR RCT, "ferric carboxymaltose" AND "iron sucrose" AND "hemoglobin in pregnancy" AND "randomized control trial". The article review process could be seen in the search flow as follows: The initial search process generated 411 articles, after the process of deleting published articles, there were 368 articles with 96 of them were eligible for a full-text review. The full-text articles were included in the exclusion criteria because of the following reasons:

1. Did not use RCT studies

2. The Intervention was not Ferric Carboxymaltose
3. The outcome was not the hemoglobin level in pregnant women with anemia.

The following is the flow of the review and the research map (Figure 1):

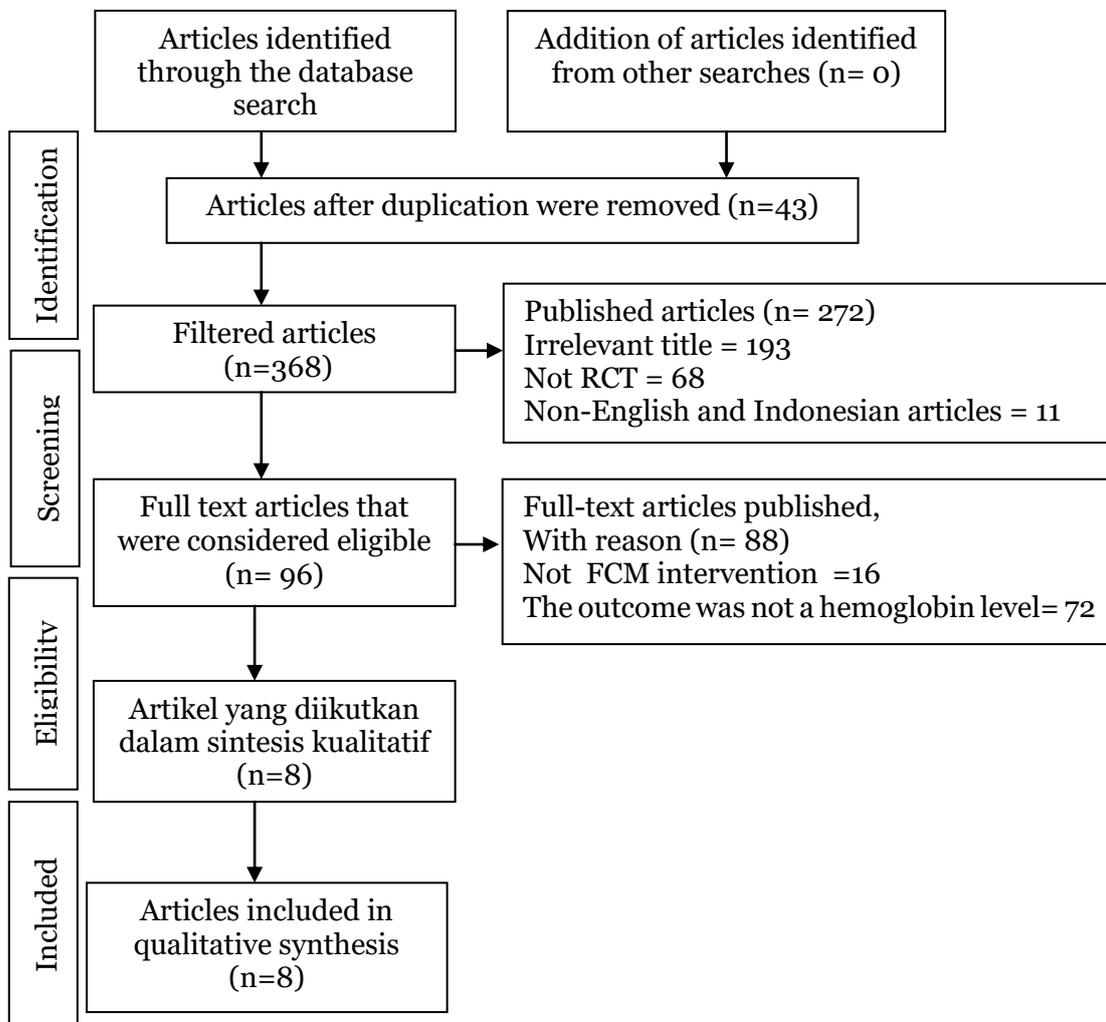


Figure 1. Review Flow Process

Table 1. The effect of ferric carboxymaltose versus iron sucrose on Hemoglobin Levels in Pregnant Women with Anemia

Author (years)	Title	Country	Study Design	Population and Sample	Intervention (I) and comparison (C)	Outcome
Jose et al. (2019)	Comparison of ferric carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy randomised controlled trial	India	RCT	The population of pregnant women with anemia. The intervention sample was 50 and the control sample was 50	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 11.53 gr / dL and hemoglobin levels in the Iron Sucrose group were 10.88 gr / dL
Mahajan et al. (2018)	A comparative study of efficacy and safety of intravenous ferric carboxymaltose versus iron sucrose in the treatment of iron deficiency anaemia of pregnancy in a tertiary care hospital	India	RCT	The Population of pregnant women with anemia. The intervention sample was 50 and the control sample was 50	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 10.29 gr / dL and hemoglobin levels in the Iron Sucrose group were 9.57 gr / dL
Mahaur et al. (2020)	Comparative study of iron sucrose versus ferric carboxymaltose in the management of iron deficiency anaemia in pregnancy	India	RCT	The population of pregnant women with anemia. The intervention sample was 50 and the control sample was 50	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin level in the Ferric Carboxymaltose group was 10.9 gr / dL and hemoglobin level in the Iron Sucrose group was 10.1 gr / dL
Maheshwari et al. (2017)	Evaluation of efficacy, safety and cost effectiveness of oral iron and injectable iron sucrose and ferric carboxymaltose in pregnant women in 2 nd and 3 rd trimester in anaemia	India	RCT	The population of pregnant women with anemia. The intervention sample was 100 and the control sample was 100	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 11.66 gr / dL and hemoglobin levels in the Iron Sucrose group were 10.4 gr / dL
Naqash et al. (2018)	Effectiveness and safety of ferric carboxymaltose compared to iron sucrose in women with iron deficiency anemia	India	RCT	The population of pregnant women with anemia. The intervention sample was 50 and the control sample was 50	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 13.25 gr / dL and hemoglobin levels in the Iron Sucrose group were 11.59 gr / dL

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Neogi et al. (2019)	Safety and effectiveness of intravenous iron sucrose, ferric carboxymaltose and standard oral iron therapy in pregnant women with moderate-to-severe anaemia In India	India	RCT	The population of pregnant women with anemia. The intervention sample was 1016 and the control sample was 983	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 8.1 gr / dL and hemoglobin levels in the Iron Sucrose group were 8.1 gr / dL
Patel et al. (2020)	A comparative study of ferric carboxymaltose and iron sucrose as a parenteral iron treatment in iron deficiency anaemia during pregnancy	India	RCT	The population of pregnant women with anemia. The intervention sample was 50 and the control sample was 50	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 11.4 gr / dL and hemoglobin levels in the Iron Sucrose group were 10.4 gr / dL
Rajwani et al. (2020)	Randomized clinical trial of IV iron sucrose and IV ferric carboxymaltose in the treatment of moderate iron deficiency anaemia in pregnancy.	India	RCT	The population of pregnant women with anemia. 80 intervention samples and 80 control samples	I: Ferric Carboxymaltose Therapy C: Iron Sucrose Therapy	Hemoglobin levels in the Ferric Carboxymaltose group were 10.15 gr / dL and hemoglobin levels in the Iron Sucrose group were 9.88 gr / dL

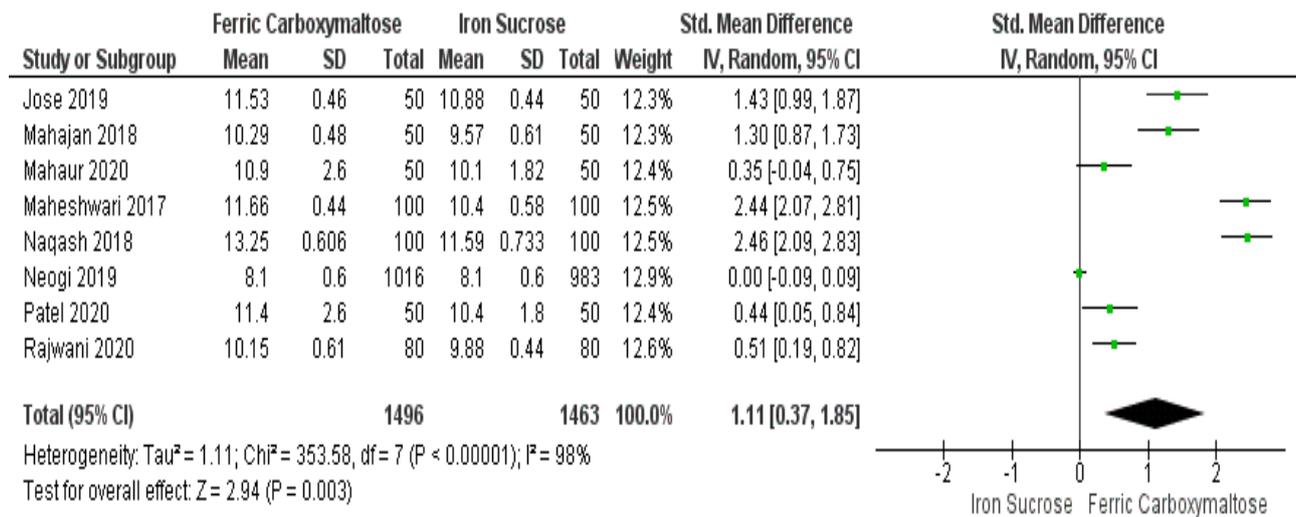


Figure 2. Forest plot of the effect of ferric carboxymaltose versus iron sucrose on hemoglobin levels of pregnant women with anemia

1. Forest Plot

The interpretation of the results from the meta-analysis process could be seen through a forest plot. Figure 4.3 showed that pregnant women who were given ferric carboxymaltose therapy had a higher mean hemoglobin level than those who were not

given ferric carboxymaltose therapy and it was statistically significant (SMD= 1.11; 95% CI= 0.37 to 1.85; p= 0.003). The heterogeneity of the research data showed the result of I²= 98% so that the distribution of the data was stated to be heterogeneous (random effect model).

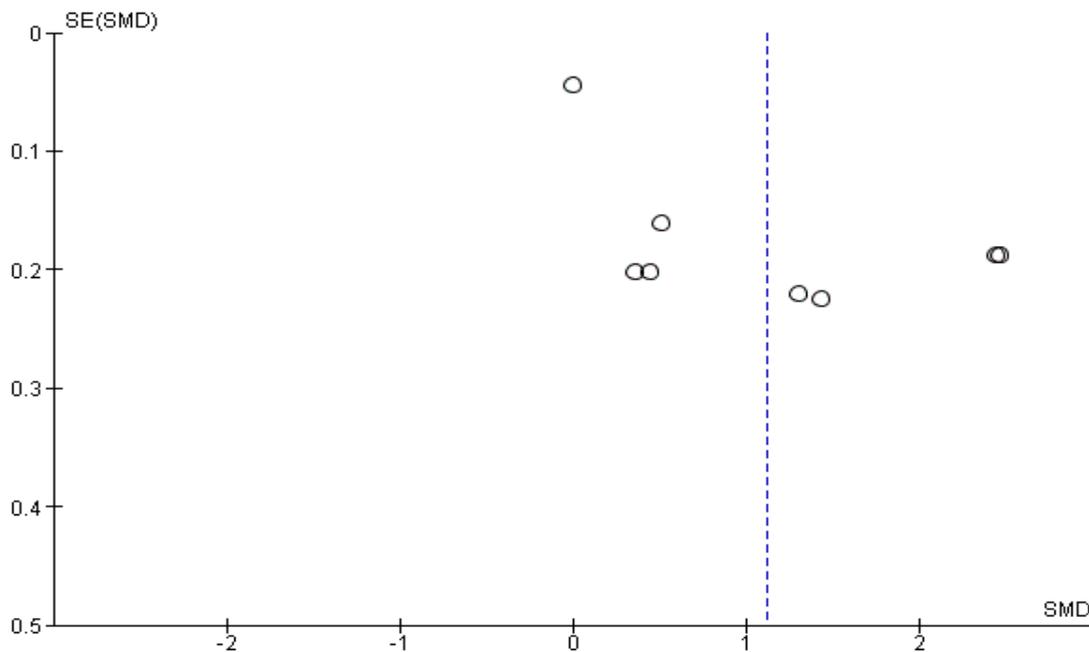


Figure 4. Funnel plot of the effect of ferric carboxymaltose versus iron sucrose on hemoglobin levels in pregnant women with anemia

2. Funnel Plot

A funnel plot was a plot that described the estimated effect size of each study on its estimate of accuracy which was usually the standard error.

DISCUSSION

Anemia is a serious problem for maternal health because anemia is one of the five problems that that becomes the target of solving the World Health Organization (WHO) in 2025. The most common cause of anemia worldwide was iron deficiency anemia which was estimated to be around 50% of cases (WHO, 2014).

The impact caused by pregnant women who experienced anemia was very diverse and dangerous for both mother and fetus, so it required proper treatment. The mainstay of treatment for iron deficiency anemia was iron supplementation either orally or intravenously. An indication for intravenous iron treatment was intolerance to oral iron. In some countries, intravenous iron preparations such as iron dextran, ferrous sucrose, sodium iron gluconate, and ferric carboxymaltose were recommended as alternative treatments for pregnant women who failed to respond to oral therapy (Revez, 2012).

Intravenous iron administration as an alternative treatment option for iron deficiency anemia in pregnancy and it had been recommended in various guidelines (Honegger, 2017). The data from observational studies on the efficacy and safety of these new treatments were essential to guide clinical management decisions, and to ensure the safety of pregnant women and their unborn fetuses (Christop, 2010).

Based on the result, this systematic and meta-analysis study raised the theme of the effect of ferric carboxymaltose versus iron sucrose on hemoglobin levels in pregnant women with anemia. The independent variables analyzed were ferric carboxymaltose and

iron sucrose. The study that discussed data on hemoglobin levels in pregnant women with anemia was considered important because of the small number of relevant studies published and accessible, and the data access problem (data duplication) (Murti, 2018).

The estimation of the effect of ferric carboxymaltose versus iron sucrose on hemoglobin levels in pregnant women with anemia was processed using the RevMan 5.3 application with the continuous method. This method was used if the outcome was continuous data.

The results of the systematic study and meta-analysis were presented in the form of a forest plot and a funnel plot. Forest plots showed visually the large variation in heterogeneity (Akobeng, 2005 in Murti, 2018). The funnel plot presented the relationship between the effect size of the study and the sample size of the various studies researched, which could be measured in some different ways (Murti, 2018). Funnel plots could be assessed from the asymmetry of the study, which included the number of dots on the right and left sides compared to the standard error and the balance of the number of studies on the right and left (D'Souza et al, 2002).

The results of the forest plot ferric carboxymaltose versus iron sucrose on hemoglobin levels in pregnant women with anemia showed that pregnant women who were given ferric carboxymaltose therapy had a higher mean hemoglobin level than those who were not treated with ferric carboxymaltose and it was statistically significant (SM= 1.11; 95% CI= 0.37 to 1.85; p= 0.003).

A study conducted by Naqash et al., (2018) aimed to evaluate the effectiveness and safety of Ferric Carboxymaltose compared to Iron Sucrose in pregnant women with anemia. The study stated that hemoglobin at week 4 was recorded as mean= 13.25 and SD= 0.606 in the Ferric Carboxymaltose

group. However, in the Iron Sucrose group the mean= 11.59 and SD= 0.733 with ($p < 0.001$). It proved that Ferric Carboxymaltose was better than Iron Sucrose in the management of anemia in pregnant women. Ferric Carboxymaltose and Iron Sucrose also showed an increase in ferritin levels, in that study Ferric Carboxymaltose showed a significant increase in ferritin levels. The detailed mean value of other laboratory parameters proved that Ferric Carboxymaltose was a better therapy for the management of anemia in pregnant women compared to Iron Sucrose. Based on observations from various research results, it is reasonable to state that Ferric Carboxymaltose is more effective than Iron Sucrose in the management of iron deficiency anemia in pregnant women.

AUTHOR CONTRIBUTION

Astika Candra Nirwana was the main researcher who selected the topics, explored, and collected the data. Yulia Lanti Retno Dewi and Bhisma Murti had a role in analyzing data and reviewing documents.

CONFLICT OF INTEREST

There was no conflict of interest in this study.

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This study used personal funds from the main researcher.

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