The combined use of erythropoietin and iron preparations for the management of postpartum anemia: a systematic review and meta-analysis

Сочетанное применение эритропоэтина и препаратов железа для коррекции постгеморрагической анемии у родильниц: систематический обзор и метаанализ

N.A. Barkovskaya[1, 2, *], E.M. Shifman[3, 4], D.N. Protsenko[4, 5]

[1] *Privolzhsky Research Medical University, Nizhny Novgorod, Russia*
[2] *Dzerzhinsk Perinatal Center, Dzerzhinsk, Nizhny Novgorod Region, Russia*
[3] *Moscow Regional Research and Clinical Institute, Moscow, Russia*
[4] *Pirogov Russian National Research Medical University (RNRMU), Moscow, Russia*
[5] *Moscow's Multidisciplinary Clinical Center "Kommunarka", Moscow, Russia*

Н.А. Барковская[1, 2, *], Е.М. Шифман[3, 4], Д.Н. Проценко[4, 5]

[1] *ФГБОУ ВО «Приволжский исследовательский медицинский университет», Нижний Новгород, Россия*
[2] *ГБУЗ НО «Дзержинский перинатальный центр», Дзержинск, Россия*
[3] *ГБУЗ МО «Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского», Москва, Россия*
[4] *ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, Москва, Россия*
[5] *ГБУЗ «Московский многопрофильный клинический центр Коммунарка» Департамента здравоохранения города Москвы, Москва, Россия*

Abstract

INTRODUCTION: There are limited data on the effectiveness of erythropoietin in combination with oral ferrotherapy for the management of postpartum anemia. **OBJECTIVE:** To evaluate the efficacy of erythropoietin in combination with oral iron compared with oral ferrotherapy in puerperas with postpartum haemorrhage. **MATERIALS AND METHODS:** MEDLINE, Scopus, EBSCOhost and 5 other databases (January 1980 to February 2023) were searched for articles on the use of oral iron in combination with and without erythropoietin for the treatment of post-hemorrhagic anemia in puerperas. Primary outcomes: hemoglobin level, hemoglobin increase, hematocrit, number of blood transfusions, secondary outcomes: ferritin level, serum iron, lactation capacity. The analysis was carried out in accordance with the PRISMA guidelines, 2020. **RESULTS:** 4 studies were analyzed, 198 women were included. When using erythropoietin in combination with oral ferrotherapy, the cumulative value of the increase in hemoglobin concentration after 5 days, 2 weeks of treatment was significantly higher compared with the control group (mean difference [MD]: 11.83 g/L, 95% CI 4.43–19.23; $p = 0.002$, MD 10.13 g/L, 95% CI 4.97–15.29; $p = 0.0001$), respectively.

Реферат

АКТУАЛЬНОСТЬ: Относительно эффективности эритропоэтина в сочетании с пероральной ферротерапией для коррекции послеродовой анемии имеются ограниченные данные. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Оценить эффективность эритропоэтина в сочетании с пероральными добавками железа по сравнению с пероральной ферротерапией у родильниц, перенесших послеродовое кровотечение. **МАТЕРИАЛЫ И МЕТОДЫ:** В MEDLINE, Scopus, EBSCOhost и 5 других базах (с января 1980 г. по февраль 2023 г.) проведен поиск статей о применении пероральных препаратов железа в комбинации с эритропоэтином и без него для лечения постгеморрагической анемии у родильниц. Первичные конечные точки: уровень гемоглобина, прирост гемоглобина, гематокрит, число гемотрансфузий, вторичные: уровень ферритина, сывороточного железа, способность к лактации. Анализ выполнен в соответствии с руководством PRISMA, 2020. **РЕЗУЛЬТАТЫ:** Проанализировано 4 исследования, 198 женщин. При использовании эритропоэтина в сочетании с пероральной ферротерапией накопленное значение прироста концентрации гемоглобина через 5 дней, 2 нед. от начала лечения значимо

The cumulative mean hemoglobin concentration after 40 days of treatment was significantly higher in the erythropoietin group (MD 11.00 g/L, 95 % CI 1.70–20.30; $p = 0.02$). The cumulative mean hematocrit after 2 weeks of treatment was significantly higher in the erythropoietin group (MD 3.35 %, 95 % CI 0.31–6.39; $p = 0.03$). The use of erythropoietin in combination with oral iron reduces the likelihood of blood transfusion (relative risk 0.12, 95 % CI 0.02–0.95; $p = 0.04$). **CONCLUSIONS:** A faster hematological response was shown with the combined use of erythropoietin with oral ferrotherapy compared with monotherapy with iron preparations in the management of postpartum anemia. Further studies with sufficient sample sizes are required.

KEYWORDS: postpartum period, iron deficiency anemia, iron preparations, erythropoietin, blood transfusion, systematic review, meta-analysis

* *For correspondence*: Natalya A. Barkovskaya — PhD in medicine, Teaching Assistant, Department of Anaesthesiology, reanimatology and transfusiology, Privolzhsky Research Medical University, Nizhny Novgorod, Head of the department of Anaesthesiology and Intensive care, Russia; e-mail: bar-natalya@mail.ru; teh@arfpoint.ru

For citation: Barkovskaya N.A., Shifman E.M., Protsenko D.N. The combined use of erythropoietin and iron preparations for the management of postpartum anemia: a systematic review and meta-analysis. Annals of Critical Care. 2023;4:72–89. https://doi.org/10.21320/1818-474X-2023-4-72-89

Received: 18.06.2023
Accepted: 04.09.2023
Published online: 31.10.2023

выше по сравнению с контролем (разность средних, mean difference [MD] 11,83 г/л, 95 %-й доверительный интервал [95% ДИ] 4,43–19,23; $p = 0,002$; MD 10,13 г/л; 95% ДИ 4,97–15,29; $p = 0,0001$) соответственно. Накопленное среднее значение концентрации гемоглобина через 40 дней значимо выше в группе эритропоэтина (MD 11,00 г/л, 95% ДИ 1,70–20,30; $p = 0,02$). Накопленное среднее значение гематокрита через 2 нед. значимо выше в группе эритропоэтина (MD 3,35 %, 95% ДИ 0,31–6,39); $p = 0,03$). Применение эритропоэтина в комбинации с пероральной ферротерапией снижает вероятность гемотрансфузии (относительный риск 0,12, 95% ДИ 0,02–0,95; $p = 0,04$). **ВЫВОДЫ:** Показан более быстрый гематологический ответ при сочетанном применении эритропоэтина с пероральной ферротерапией по сравнению с монотерапией препаратами железа при коррекции постгеморрагической анемии у родильниц. Требуются дальнейшие исследования с достаточными объемами выборок.

КЛЮЧЕВЫЕ СЛОВА: послеродовый период, железодефицитная анемия, препараты железа, эритропоэтин, гемотрансфузия, систематический обзор, метаанализ

* *Для корреспонденции*: Барковская Наталья Александровна — канд. мед. наук, ассистент кафедры анестезиологии, реаниматологии и трансфузиологии ФГБОУ ВО «Приволжский исследовательский медицинский университет», Нижний Новгород; ОАР ГБУЗ НО «Дзержинский перинатальный центр», Дзержинск, Россия; e-mail: bar-natalya@mail.ru; teh@arfpoint.ru

Для цитирования: Барковская Н.А., Шифман Е.М., Проценко Д.Н. Сочетанное применение эритропоэтина и препаратов железа для коррекции постгеморрагической анемии у родильниц: систематический обзор и метаанализ. Вестник интенсивной терапии им. А.И. Салтанова. 2023;4:72–89. https://doi.org/10.21320/1818-474X-2023-4-72-89

Поступила: 18.06.2023
Принята к печати: 04.09.2023
Дата онлайн-публикации: 31.10.2023

DOI: 10.21320/1818-474X-2023-4-72-89

Introduction

Postpartum anemia, defined by hemoglobin < 100 g/L, is a common issue in obstetrics. Despite the anticipatory activation of erythropoiesis in the late third trimester, postpartum patients may not respond adequately to iron therapy. In many cases postpartum anemia is characterized by posthemorrhagic anemia occurring in the presence of pre-existing iron-deficiency anemia (IDA).

Back in 1992, in a study conducted by A.Huch et al. [1], it was demonstrated that recombinant human erythropoietin (EPO) combined with oral iron therapy in postpartum IDA enhanced endogenous erythropoiesis beyond the physiological rate of recovery. The same authors also suggested that for postpartum patients with hemoglobin levels between 70 and 85 g/L, signifying moderate to severe anemia, there is a possibility to avoid blood transfusions by incorporating EPO into a comprehensive treatment plan. Thus,

combining EPO with iron medications can be considered blood-conserving methods. Currently, there is a rising incidence of postpartum hemorrhages requiring blood transfusions in obstetric patients. Yet, most women typically require just a single dose of erythrocyte concentrate [2]. In many instances blood transfusions (with their potential risks and complications) can be avoided by employing alternative methods, including the use of EPO in the comprehensive treatment of posthemorrhagic anemia in postpartum women.

In the meta-analysis conducted by V.Markova et al. [3], an evaluation of the efficacy/harm of available treatment methods for postpartum IDA was performed. These methods included oral and parenteral iron, EPO and blood transfusion. However, the authors were unable to fully assess the efficacy of EPO medications due to the lack of evidence.

Our previous meta-analysis [4] showed a significant increase in hemoglobin levels (ΔHb) within 2 weeks when EPO was combined with intravenous iron therapy in these patients. Nevertheless, the impact of EPO on the need for blood transfusion could not be assessed due to extremely limited data.

Clinical question: does the combined administration of EPO and oral iron supplements increase treatment efficacy and reduce a number of blood transfusions in postpartum women with pathological/massive postpartum haemorrhage?

Purpose of the study

To evaluate the efficacy of erythropoiesis-stimulating agents in combination with oral iron supplements compare with oral iron therapy alone in women with postpartum hemorrhage.

Materials and methods

Data sources and search strategy

The review is presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from 2020 [5] and updated criteria for assessing the quality of systematic reviews using Assessment of Multiple Systematic Reviews-2 (AMSTAR-2) [6]. We did not register a review protocol. Ethical approval is not required as the analysis involves the examination of previously published data.

To be included in the review, there must have been studied the following treatment regimens for managing IDA in postpartum women: EPO (administered via any route) + oral iron. The comparator considered acceptable for inclusion in the review was oral iron therapy. Studies that used a different comparator (including intravenous iron therapy with subsequent transition to oral iron) were excluded. The combined use of vitamin and/or mineral supplements was not considered an interfering factor capable of affecting treatment outcomes significantly.

Types of studies included in the review: Published randomized controlled trials (RCTs) and interventional studies with comparable control groups reporting the use of oral iron medications, either with or without EPO, for managing postpartum IDA. There are no language restrictions.

Inclusion criteria:

- Studies must report on at least one of the following outcomes: hemoglobin (Hb), hematocrit (Ht) at relevant observation time points, a number of blood transfusions, iron metabolism parameters, clinical signs of anemia, lactation capacity, and adverse reactions to the studied medications.
- Time frame: Up to 42 days postpartum.
- RCTs published as abstracts were considered acceptable if they provided sufficient information.

Exclusion criteria: observational studies, absent control group, clinical case descriptions, low methodological quality.

Participants/Study Population:

- Inclusion criteria: postpartum women with moderate or severe IDA[1] with previous postpartum hemorrhage[2].
- Exclusion criteria: anemia unrelated to iron deficiency, hypertensive disorders during pregnancy, red blood cell transfusion, sepsis, bone marrow disorders, oncopathology, informed refusal of blood transfusion.

Primary outcomes of the meta-analysis:

- Hematologic response (Hb concentration in groups in 5, 14, and 40 days from the beginning of therapy; ΔHb and Ht concentration at 5 and 14 days from the beginning of therapy). Data presentation format: mean values and standard deviations (M [SD]).
- Number of blood transfusions/number of events (time frame: 14 days).

Secondary outcomes of the meta-analysis:

- Serum ferritin (SF) and serum iron (SI) concentrations in 5 days from the beginning of therapy.
- Number of patients with lactation/number of events (time frame: 40 days).
- Number, type, and outcome of side effects and adverse reactions of iron and EPO.

[1] Postpartum anaemia (WHO definition) — Hb < 110 g/L at one week post-delivery and Hb < 120 g/L in the first postpartum year.

[2] Early postpartum hemorrhage 500 mL of blood loss in natural childbirth and 1000 mL of blood loss in operative delivery, or any clinically significant volume of blood loss leading to hemodynamic instability within 24 hours after vaginal delivery or cesarean section.

Search strategy. A search was conducted in MEDLINE, Scopus, EBSCOhost (Academic Search Premier), WoS Core Collection, LILACS (www.bireme.br), and IBECS (from January 1, 1980 to February 2023). Search strategy was adapted for each database, and the following English queries were used: "anemia OR anaemia", "erythropoietin", "epoetin", "rHuEPO", "rhuepo", "iron", "oral iron", "postpartum OR postnatal OR puerperium anaemia". A search was conducted in the ClinicalTrials.gov registry. There were no language or publication year restrictions. Additionally, searches were done in Russian-language databases: eLIBRARY.RU and Google Scholar (from January 1, 1980 to February 2023). The following Russian queries were used: «эритропоэтин», «ЭПО», «препараты железа», «послеродовая анемия».

Previous systematic reviews related to the research question [3, 7] were checked, and reference lists were searched. The titles and abstracts of the studies identified in the search were assessed for relevance by two reviewers. On the third stage, two independent reviewers evaluated the full texts for eligibility. Any disputes were resolved through discussion, with the involvement of a third reviewer.

Data extraction and management

Information about the interventions subject to extraction included: type of medication, combination therapy (EPO + oral iron), monotherapy with oral iron, dosage, route of administration, treatment duration, and observation period. Graphical data were digitized using WebPlotDigitizer software [8]. Hemoglobin (Hb), serum ferritin (SF), and serum iron (SI) (along with their deviations) were extracted in the units specified by the authors and subsequently converted into g/L, μg/L, and μmol/L, respectively. The results presented by the authors as median and interquartile ranges (concentrations of Hb, Ht [1, 9], SF, and SI on the 5th day of treatment [9]) were transformed into means (SD), enabling us to conduct the meta-analysis. The rationale for the missing data transformation for the meta-analysis were based on:

1. Selection of Hb and Ht exhibits an approximately normal distribution (analyzed using numerous archival databases from previous studies).
2. In a random variable that follows a normal distribution, the mean (mathematical expectation) and the median values are equal. In such cases, the sample median can be used as an unbiased estimate of the variable's mean.
3. A nearly identical coefficient of variation for Hb and Ht within the same sample.
4. By analyzing databases of obstetric patients, it was possible to roughly associate the range of variation values coefficient with the "hematological" characteristics of the sample. When the study pertains to issues unrelated to blood loss, the coefficient of variation falls within the range of 7–9 %. For studies involving antepartum and postpartum hemorrhages, among which near-misses are a small fraction or entirely absent, the coefficient of variation is 12–14 %. In cases of severe massive hemorrhages, the coefficient of variation for Hb and Ht exceeds 20 % (22–24 %).
5. According to one of the theorems concerning the properties of the normal distribution, the sum (or difference) of two normally distributed random variables also follows a normal distribution.
6. According to one of the theorems regarding the statistical parameters of normally distributed random variables, the mathematical expectation (average) of the sum (or difference) of two normally distributed random variables is equal to the sum (or difference) of the mathematical expectations of these variables.

Based on the six reasons outlined above, the data for the meta-analysis were supplemented as follows:

- if both the baseline mean value and the mean value of delta by the 5th day or in 2 weeks were known, summing these two values could provide the absolute values of Hb and Ht at those time points;
- the coefficient of variation for this patient was assumed to be 14 % (there are haemorrhages, but they are not near-miss);
- if the mean value of Hb or Ht was known (or estimated), but its standard deviation was not provided, this parameter was estimated as 14 % of the known mean value.

For dichotomous outcomes, the number of events and participants in each group was extracted.

Assessment of study quality and risk of bias

Methodological quality and risk of bias assessment in each of the included studies was conducted by two independent experts using the updated Cochrane tool for assessing systematic error risk in RCTs (Risk-Of-Bias 2 [ROB-2]) [10, 11]. Risk for bias was evaluated as "low", "some concerns", or "high risk" across 5 domains (D1–5): D1 — risk of bias in the randomization process; D2 — risk of bias due to deviations from the intended interventions; D3 — risk of bias due to incomplete outcome data; D4 — risk of bias in outcome measurements; D5 — selective reporting.

For each study, an overall assessment of bias risk was made, and data were visually presented using the online statistical environment tool R (Risk-of-bias VISualization (robvis)) [12]. Responses to signaling questions, assessment algorithms and expert explanations are available in Supplementary File S1: https://data.mendeley.com/datasets/gx2pdpts36/1

Statistical analysis

The classical pairwise meta-analysis of the results obtained from 4 available studies was conducted. Analysis and synthesis of extracted data were performed using the RevMan v5.4.1 software [13]. Presentation format of the results included forest plots with a 95% confidence interval (95% CI). Cumulative effect assessment is presented as:

- difference in the cumulative mean Hb concentrations at the baseline and after 5, 14, and 40 days of the therapy;
- cumulative mean ΔHb between the baseline and after 5 and 14 days of the therapy;
- difference in cumulative mean Ht concentrations at the baseline and after 5 and 14 days of the therapy;
- difference in cumulative mean SF and SI concentrations after 5 days of the therapy.

The cumulative estimates (mean differences, MD) were accompanied by their 95% confidence intervals (CIs). Statistical significance of heterogeneity in the pooled samples was assessed using Cochrane's Q-test. The I^2 index was used for quantitative assessment of heterogeneity. Relative risk (RR) estimates with 95% CIs were calculated for the analysis of dichotomous outcomes (blood transfusions, lactation capability).

Results

Study selection

In the process of a database search, 865 records were identified. Once duplicates had been removed, 739 records underwent screening, with 715 being excluded based on title and abstract analysis. Of the 24 potentially eligible studies, 23 full-text documents were assessed, and 19 were subsequently excluded with reasons provided [14–32] (see File S2: https://data.mendeley.com/datasets/gx2pdpts36/1). Exclusion reasons: inappropriate study design, duplicate data, treatment regimens not matching the review question, low methodological quality. One full-text report was not obtained [33].

Differences in the methods of EPO administration (subcutaneous/intravenous) were not taken into account because we assumed that this would not have a significant impact on the studied outcomes. Publication selection was conducted following the 2020 PRISMA guidelines [5] (Figure 1), resulting in the inclusion of 4 studies into the qualitative and quantitative analysis.

Description of the studies

Four studies have been included in the review: A.Huch et al., 1992 [1], G.Makrydimas et al.,1998 [9], J.Danko et al., 1990 [34], T.Hatzis et al., 2003 [35], two studies were conducted in Switzerland [1, 34], and two in Greece [9, 35] (see Table 1). The study by T.Hatzis et al., 2003 [35], was supported by Janssen-Cilag company, while the funding sources for the other three studies were not specified.

Study designs included 2 RCTs (A. Huch et al., 1992 [1], G.Makrydimas et al., 1998 [9]), 1 pilot study (J. Danko et al., 1990 [34]). In one study (T. Hatzis et al., 2003 [35]), a matched pairs design was used: each patient in the intervention group was matched with a control patient who gave birth on the same day (an interventional study with comparable control groups). Controls were selected based on age, pre-delivery Hb levels, and gestational age.

All studies were open-label, prospective, single-centered. The number of patients in the groups ranged from 5 to 37. Average age, parity, and gestational age were comparable between the groups. On the 5th day of observation, 198 postpartum women with IDA were assessed, with 99 oreceiving EPO with oral iron and 99 undergoing oral iron monotherapy.

Dropout was recorded in the study by A.Huch et al., 1992 [1] on the 14th and 42nd days (see Table 1), the reason for dropout was failure to attend for laboratory control. In two studies (A. Huch et al., 1992 [1] and T.Hatzis et al., 2003 [35]), there is information about an equal ratio of vaginal deliveries to cesarean sections, while the data in the studies [9, 34] are not specified.

Hb concentrations at the beginning of a study did not differ significantly between the groups. In the study by J.Danko et al., 1990 [34], the initial Hb level in the intervention and control groups was 67.8 (2.9) g/L versus 74.8 (4.7) g/L. In the study by A.Huch et al., 1992 [1], it was 81.0 (10.0) g/L versus 88.0 (8.0) g/L. T.Hatzis et al., 2003 [35] reported values of 84.2 (1.7) g/L versus 81.0 (14.0) g/L. Data presented by G.Makrydimas et al., 1998 [9] as median and interquartile range were converted to M (SD): 71.6 (10.0) g/L versus 70.3 (9.8) g/L.

Protocols for postpartum IDA management used in the included studies are presented in Table 1. The timing of the initial dose of EPO varied as follows: in the study by T.Hatzis et al., 2003 [35], it was administered immediately after delivery; G.Makrydimas et al., 1998 [9] administered within the first day after delivery, while A.Huch et al., 1992 [1], and J.Danko et al., 1990 [34], administered on the second day after delivery. Epoietin alfa, Eprex®, was used as the EPO drug in three studies [1, 34, 35]. G.Makrydimas et al., 1998 [9], did not specify the trade name or the international non-proprietary name of the drug. However, considering the fact that this study was conducted in 1998, it implies the use of a first-generation drug with similar therapeutic capabilities in any case.

It is worth noting the differences in the course dose of EPO, which were 210,000 IU in the study by G.Makrydimas et al., 1998 [9] versus 20,000 IU in the other three studies [1, 34, 35]. Various methods of EPO administration were used in the cumulative studies, includ-

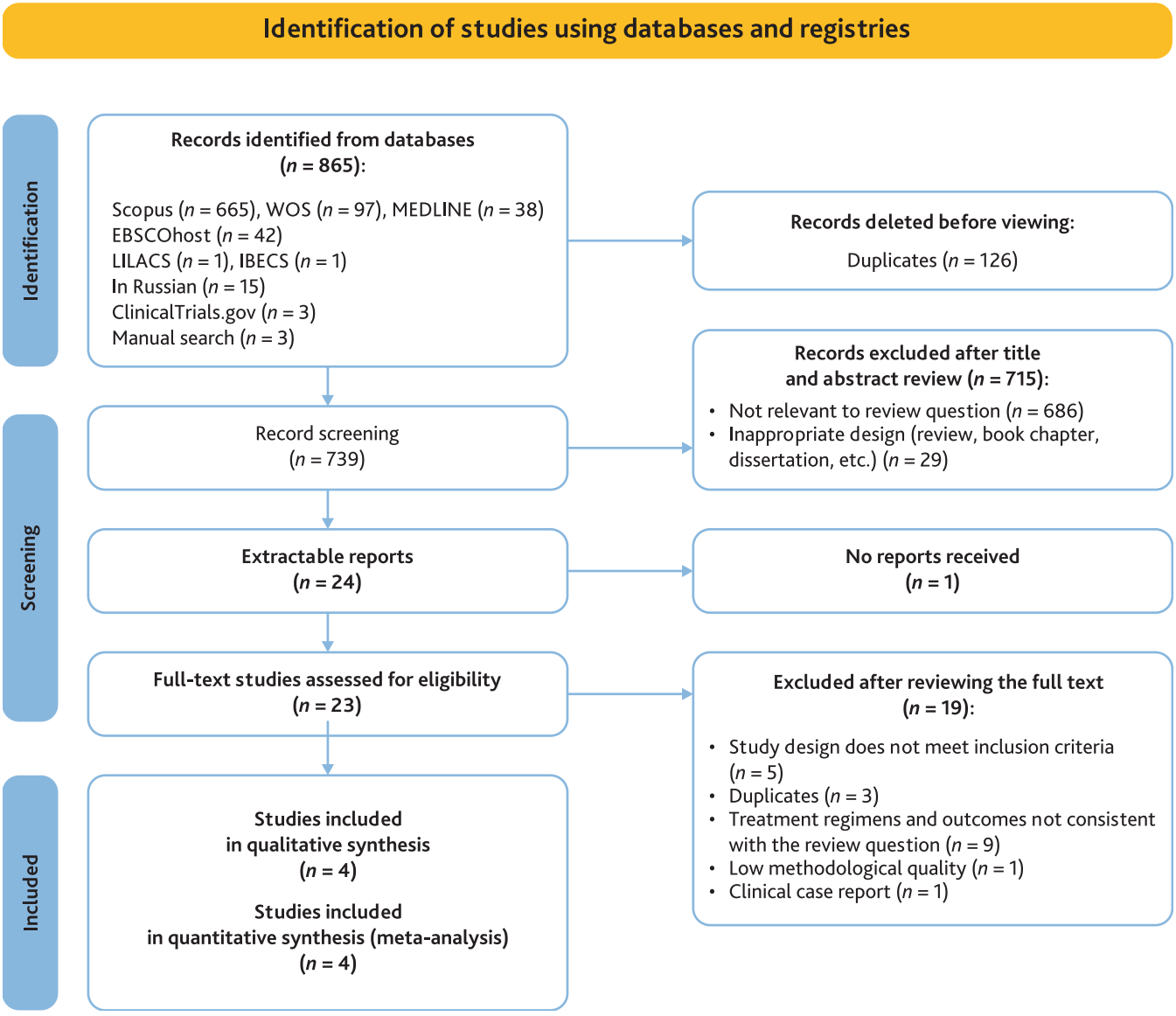


Fig. 1. Study flow diagram (PRISMA, 2020)

ing subcutaneous [9], intravenous [35], and combined [1, 34] (see Table 1). In the control groups, oral iron was taken in monotherapy (see File S3: https://data.mendeley.com/datasets/gx2pdpts36/1). Differences were observed in the types of iron supplements and the total dosages (ranging from 800 to 8,000 mg). In two studies [1, 34], iron sulfate (II), Gyno-Tardyferon (Robapharm), was taken, while in the study by T.Hatzis et al., 2003 [35] – iron protein succinylate (Legofer: Elpen). G.Makrydimas et al., 1998 [9] mentioned the use of "oral iron supplements with folic acid" and a high total dosage was administered (8,000 mg).

The studies did not provide information regarding treatment compliance. The follow-up period in two studies was 40 days [9, 35], in one study it was 42 days [1], and in the pilot study by J.Danko et al., 1990 [34] it was 14 days. The authors did not specify any side effects or adverse events associated with the therapy involving EPO and oral iron.

Regarding the haematological response: the results of all four studies are unidirectional. A.Huch et al., 1992 [1], demonstrated a more significant ΔHb in the EPO group compared to the control group on the 5th, 14th, and 42nd days (9.4 g/L vs. 5.0 g/L; 28.6 g/L vs. 21.0 g/L; 47.0 g/L vs. 31.6 g/L, respectively).

According to G.Makrydimas et al., 1998 [9], ΔHb on the 5th day was 22.0 g/L in the EPO group versus 7.0 g/L in the control group. T.Hatzis et al., 2003 [35] demonstrated that a single intravenous dose of 20,000 IU EPO immediately after delivery significantly increases the Hb levels, and this effect persists for at least 40 days. J.Danko et al., 1990 [34] also determined a more pronounced increase in Hb levels in women taking EPO.

Table 1. Characteristics of included studies

First author, year, country	Study design	Randomized (number)	Analyzed (number)	Time between delivery and the first dose of EPO	Inclusion criteria	Exclusion criteria
J. Danko et al., 1990, Switzerland [34]	Pilot	10	10:5/5	From the 2nd day postpartum	Women with postpartum IDA	Not specified
A. Huch et al., 1992, Switzerland [1]	RCT	74	74:37/37 (on the 5th day) 39:23/16 (on the 16th day) 15:10/5 (on the 42nd day)	From the 2nd day postpartum	1. Hb < 100 g/L (on the 1st, 2nd, or 3rd day postpartum). 2. Age 20–32 years. 3. Absence of serious illnesses, including preeclampsia	Not specified
G. Makrydimas et al., 1998, Greece [9]	RCT	40	40:20/20	On the 1st day postpartum	1. Hb < 100 g/L on the 1st day postpartum. 2. Age 19–44 years. 3. Absence of serious illnesses, including preeclampsia	Not specified
T. Hatzis et al., 2003, Greece [35]	Interventional with comparable control groups	74	74:37/37	Right after delivery	1. Hb < 110 g/L at the time of delivery. 2. Uncomplicated obstetric and medical history. 3. Equal number of C-sections in both groups	Not specified

AEs — adverse events; C-section — cesarean section; eEPO — endogenous erythropoietin; Hb — haemoglobin; Ht — hematocrit; IDA — iron-trial; rHuEPO — recombinant human erythropoietin; SF — serum ferritin; SI — serum iron; TIBC — total iron-binding capacity.

Regarding the need for blood transfusion: in the study by T.Hatzis et al., 2003 [35], 6 women (16%) in the control group received a blood transfusion, while in the EPO group, no blood transfusion was required. G.Makrydimas et al., 1998 [9] reported two blood transfusions in the control group. In the studies [1, 34], blood transfusions were not required.

In the study by G.Makrydimas et al., 1998 [9], 19 out of 20 women in the EPO group were able to lactate compared to only 10 out of 20 in the control group. The same trend is observed in the study by T.Hatzis et al., 2003 [35], with lactation issues occurring in 4 out of 37 women in the EPO group versus 18 out of 37 in the control group. A.Huch et al., 1992 [1] did not reveal any lactation problems in any of the patients. Data on lactation are not provided in the study by J.Danko et al., 1990 [34].

Thus, regarding the haematological response to EPO therapy, the results in all included studies were consistent.

Intervention group, *n*	Control group, *n*	Primary outcomes	Secondary outcomes	Follow-up period
Group 1 (*n* = 5) received epoetin alfa (Eprex, Cilag, Schaffhausen) at a dose of 60 IU/kg for 5 days (IV on the 1st day, then subcutaneously) + oral iron (Gyno-Tardyferon) 160 mg/day	Group 2 (*n* = 5) received oral iron (Gyno-Tardyferon) at a dose of 160 mg/day	Hb and Rt on the 1st, 2nd, 5th and 14th days postpartum	1. Blood pressure dynamics 2. Side effects of EPO	14 days
Group 1 (*n* = 37) epoietin alfa Eprex, Cilag, Schaffhausen 4000 IU daily for 5 days (1st dose IV, remaining 4 doses subcutaneously) + oral iron (Gyno-Tardyferon) 160 mg/day for 5 days postpartum	Group 2 (*n* = 37) oral iron (Gyno-Tardyferon) 160 mg/day for 5 days postpartum	Rt, Hb, Ht, PLT, SF on the 5th, 14th, and 42nd days postpartum	1. Clinical symptoms of anaemia (5th, 14th, and 42nd days). 2. Side effects of EPO, oral iron. 3. Lactation capability. 4. Need for blood transfusion	42 days
Group A (*n* = 20) rHuEPO subcutaneously 200 IU/kg/day for 15 days + oral iron 200 mg/day for 40 days	Group B (*n* = 20) oral iron 200 mg/day for 40 days	1. BP, t °C, ECG (1st, 15th, 40th days). 2. Hb, Ht, PLT, SI, SF, TIBC, B_{12}, eEPO, Creatinine (on the 1st, 3rd, 5th, 10th, 15th, 40th days postpartum). 3. Need for transfusion	1. Symptoms of anaemia, Lactation capability. 2. EPO side effects. 3. Psychological well-being. 4. Hospital stay duration. 5. Maternal mortality	40 days
Group EPO (*n* = 37) Epoietin alfa (Eprex) 300 IU/kg once intravenously + Legofer: Elpen (80 mg Fe+++) orally daily for 40 days postpartum	Control group (*n* = 37) Legofer: Elpen (80 mg Fe+++) orally daily for 40 days postpartum	1. Hb in 4 and 40 days postpartum. 2. Frequency of postpartum blood transfusions	1. Clinical signs of anemia. 2. Frequency of PPH. 3. Lactation issues. 4. Blood pressure (2 hours postpartum, on the 4th and 40th days). 5. Side effects and AEs of EPO and oral iron	40 days

deficiency anaemia; IU — international units; IV — intravenously; PLT — platelets; PPH — postpartum haemorrhage; RCT — randomised controlled

However, with regard to the need for blood transfusion and lactation capability, the results from the analyzed trials do not align.

Given the low statistical power of the included studies, inevitable differences in the magnitude of the observed effect and inconsistencies across several outcomes, there is a need to obtain a comprehensive estimate of the effect size through conducting a meta-analysis.

Methodological quality and risk of bias assessment

Risk of bias was assessed using the updated Cochrane ROB-2 tool [11] (see Figure 2, 3; see Supplementary File S4: https://data.mendeley.com/datasets/gx2p-dpts36/1). When assessing deviations in the randomisation process (domain 1), two studies (pilot study by J.Danko et al., 1990 [34] and the study by T.Hatzis et al., 2003 [35] with comparable comparison groups) showed a "high" risk

of bias, while the other two trials were graded as "some concerns".

High risk of bias due to deviations from intended interventions was revealed in the study by J.Danko et al., 1990 [34], while in the other three trials, the grading for this domain is reported as "some concerns". In all four studies, the risk of bias for domains 3, 4, and 5 (which consider the completeness of outcome data, measurement bias and selective reporting) was assessed by us as "low".

The overall judgment of the risk of bias for each included study was determined according to the ROB-2 algorithm [36]. The studies by J.Danko et al., 1990 [34] and T.Hatzis et al., 2003 [35] were classified as having a "high risk of bias" since at least one domain exhibited a "high risk". In the other two studies, A.Huch et al., 1992 [1] and G.Makrydimas et al., 1998 [9] there are "some concerns" regarding bias, considering a similar interpretation of risk across the first two domains.

Thus, we have established the clinical and methodological appropriateness of statistically combining the results of all four studies included in the systematic review.

Quantitative synthesis

For the synthesis of the results, we selected a random effects model, despite the small number of studies (n = 4) and identical participant characteristics. We relied on the following arguments:

- methodological: concerning the design — significant differences in the study design were identified among the accumulated studies, with one of them not being an RCT (pairwise control) and one being a pilot study with a very small sample size;
- clinical: different routes of EPO administration were used in the included studies (subcutaneous, intravenous, and combined use). Additionally, differences in treatment duration and dosages of EPO and oral iron were observed (see Table 1), Supplementary File S3: https://data.mendeley.com/datasets/gx2pdpts36/1

Subsequently, the model selection was confirmed by calculated statistics for each analyzed parameter ($p < 0.05$ in the χ^2 test, $I^2 > 40\%$).

Meta-analysis of primary outcomes

Analysis 1.1. Baseline hemoglobin levels before treatment (g/L)

The cumulative mean value of Hb concentration before the origin of treatment (Figure 4) was found to be slightly higher in the control group, with no statistically significant differences compared to the EPO group (MD −2.51 g/L, 95% CI −7.96–2.95; p = 0.37). The included studies are in agreement, with roughly equal weight assigned to all studies.

Analysis 1.2. Difference in haemoglobin concentration (ΔHb) after 5 days (g/L)

Meta-analysis results showed that the cumulative mean value of ΔHb after 5 days of the therapy (Figure 5) is higher in the group receiving EPO (MD 11.83 g/L, 95% CI 4.43–19.23), which is statistically significant (p = 0.002).

Analysis 1.3. Absolute hemoglobin after 5 days of the therapy (g/L)

When using EPO in combination with oral iron, the cumulative mean hemoglobin concentration after 5 days (Figure 6) was higher in the EPO group (MD 6.89 g/L, 95% CI −3.07–16.85), but without statistically significant differences compared to the control group (p = 0.18). The studies are in good agreement, and the confidence intervals overlap.

Analysis 1.4. Difference in hemoglobin concentration after 2 weeks of treatment (g/L)

Meta-analysis results showed that the cumulative mean ΔHb value after 2 weeks (Figure 7) was higher in the EPO group (MD 10.13 g/L, 95% CI 4.97–15.29), which is statistically significant (p = 0.0001).

Taking only 2 studies included in this analysis, a fixed effects model was tested that yielded similar results.

Analysis 1.5. Absolute hemoglobin after 2 weeks of the therapy (g/L)

When using EPO in combination with oral iron, the cumulative mean Hb concentration after 2 weeks of treatment (Figure 8) was higher in the EPO group (MD 7.55 g/L, 95% CI −5.58–20.67) but without statistically significant difference compared to the control group (p = 0.26). In this case, the appropriateness of using a random effects model is confirmed by calculated statistics ($p < 0.05$ in the χ^2 test, I^2=76%).

Analysis 1.6. Absolute hemoglobin concentration after 40 days of the therapy (g/L)

When using EPO in combination with oral iron, the cumulative mean concentration of Hb after 40 days of treatment (Figure 9) was statistically significantly higher in the EPO group (MD 11.00 g/L, 95% CI 1.70–20.30; p = 0.02).

Analysis 1.7. Baseline hematocrit levels before treatment (%)

Cumulative mean value of Ht before therapy (Figure 10) was slightly higher in the control group, with no statistically significant differences compared to the EPO group (MD −0.88%, 95% CI −3.62–1.86; p = 0.53). The weights of both studies are approximately the same. Only 2 studies were included in this analysis, but there is a correlation with the baseline cumulative hemoglobin value.

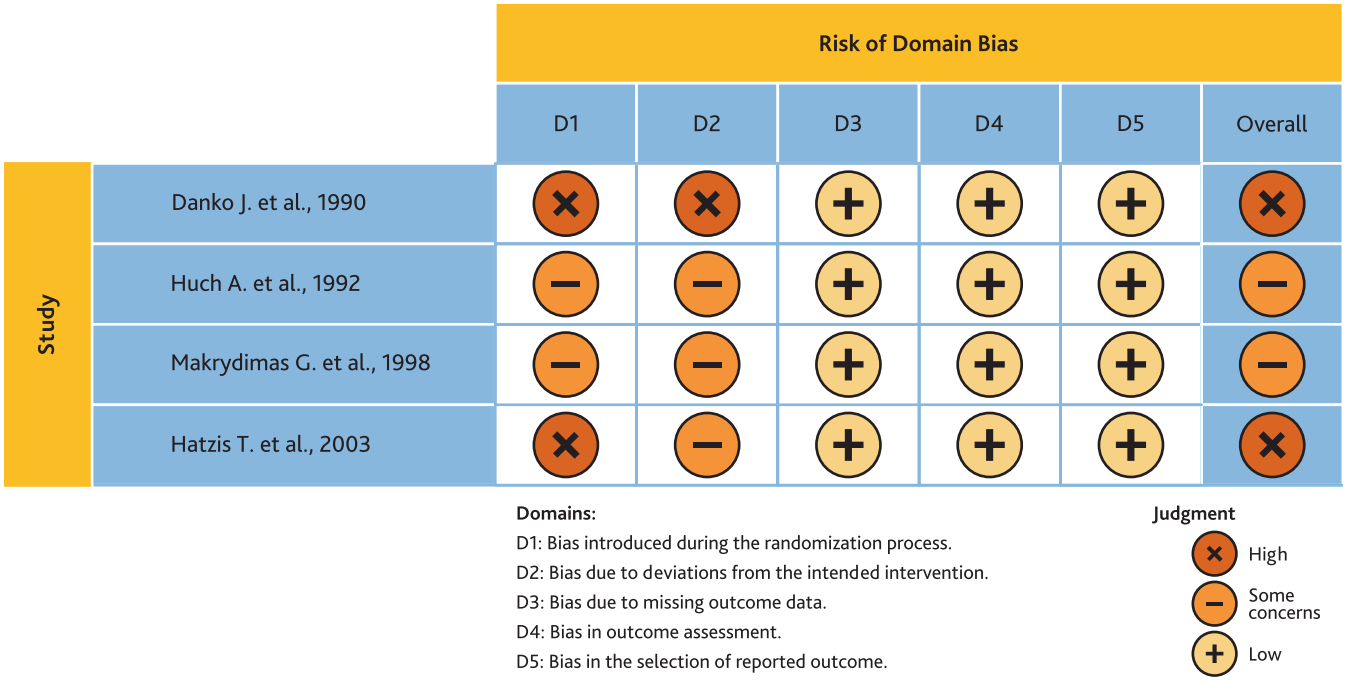


Fig. 2. Traffic light plot (ROB-2)
This plot displays the authors' judgments on each domain of bias risk for all included studies.

Analysis 1.8. Hematocrit levels after 5 days of treatment (%)

When EPO was used in combination with oral iron, the cumulative mean Ht after 5 days of the therapy (Figure 11) showed no significant difference compared to the control group (MD 1.02%, 95% CI −2.51–4.54; $p = 0.57$).

Analysis 1.9. Hematocrit levels after 2 weeks of treatment (%)

Meta-analysis results showed that the cumulative mean Ht levels after 2 weeks of treatment (Figure 12) were higher in the EPO group (MD 3.35%, 95% CI 0.31–6.39), which was statistically significant ($p = 0.03$).

Analysis 1.10. Need for blood transfusion

We obtained very limited information regarding the frequency of blood transfusions in the groups of patients when comparing EPO in combination with oral iron to treatment with only oral iron in the management of IDA in postpartum women. Four studies with 198 participants were included in the analysis. In two out of the four studies, blood transfusions were not conducted. In the meta-analysis of this event (Figure 13), risks ratio (RR) was 0.12; 95% CI 0.02–0.95; $p = 0.04$. The CI does not include the value of one, indicating the statistical significance of the obtained result. An RR value less than one indicates

Fig. 3. Summary plot (ROB-2)
Risk of bias is based on the authors' judgments for each domain and is expressed as a percentage of all included studies.

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l)	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Danko J. et al., 1990	67.8	2.9	5	74.8	4.7	5	25.2 %	–7.00 (–11.84, –2.16)	1990
Huch A. et al., 1992	81.0	10.0	37	88.0	8.0	37	26.6 %	–7.00 (–11.13, –2.87)	1992
Makrydimas G. et al.,1998	71.6	10.0	20	70.3	9.8	20	22.5 %	1.30 (–4.84, 7.44)	1998
Hatzis T. et al., 2003	84.2	1.7	37	81.0	14.0	37	25.8 %	3.20 (–1.34, 7.74)	2003
Total (95% CI)			**99**			**99**	**100.0 %**	**–2.51 (–7.96, 2.95)**	

Heterogeneity: Tau² = 24.72; Chi² = 15.27, df = 3 (*p* = 0.002); I^2 = 80 %

Test for overall effect: Z = 0.90 (*p* = 0.37) 0,002); I^2 = 80 %

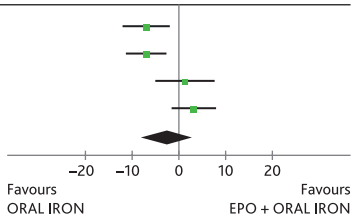


Fig. 4. Analysis 1.1. Baseline hemoglobin levels before treatment (g/L). Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l)	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Danko J. et al., 1990	14.0	8.4	5	4.0	8.5	5	20.8 %	10.00 (–0.47, 20.47)	1990
Huch A. et al., 1992	9.4	11.4	37	5.0	10.8	37	30.6 %	4.40 (–0.66, 9.46)	1992
Makrydimas G. et al.,1998	22.0	14.6	20	7.0	10.3	20	25.5 %	15.00 (7.17, 22.83)	1998
Hatzis T. et al., 2003	25.0	17.4	37	5.2	20.4	31	23.1 %	19.80 (10.69, 28.91)	2003
Total (95% CI)			**99**			**93**	**100.0 %**	**11.83 (4.43, 19.23)**	

Heterogeneity: Tau² = 39.97; Chi² = 10.70, df = 3 (*p* = 0.01); I^2 = 72 %

Test for overall effect: Z = 3.13 (*p* = 0.002)

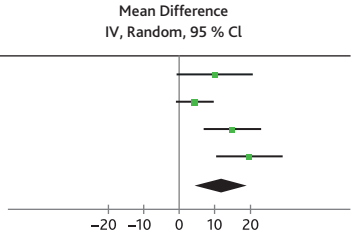


Fig. 5. Analysis 1.2. Hemoglobin increment (ΔHb, g/L) after 5 days. Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l)	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Danko J. et al., 1990	81.8	11.5	5	78.8	11.0	5	20.0 %	3.00 (–10.95, 16.95)	1990
Huch A. et al., 1992	90.4	12.7	37	93.0	13.0	37	29.6 %	–2.60 (–8.46, 3.26)	1992
Makrydimas G. et al.,1998	84.1	11.8	20	77.1	10.8	20	28.3 %	7.00 (–0.01, 14.01)	1998
Hatzis T. et al., 2003	109.2	25.0	37	86.2	26.0	31	22.1 %	23.00 (10.81, 35.19)	2003
Total (95% CI)			**99**			**93**	**100.0 %**	**6.89 (–3.07, 16.85)**	

Heterogeneity: Tau² = 78.39; Chi² = 14.93, df = 3 (*p* = 0.002); I^2 = 80 %

Test for overall effect: Z = 1.36 (*p* = 0.18)

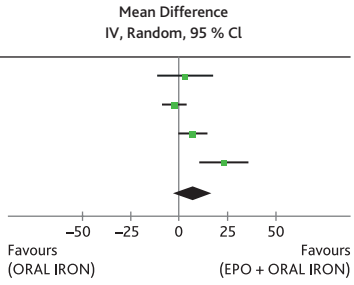


Fig. 6. Analysis 1.3. Absolute hemoglobin concentration (g/L) after 5 days of treatment. Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l)	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Danko J. et al., 1990	0.0	0.0	0	0.0	0.0	0		Not estimable	1990
Huch A. et al., 1992	28.6	12.3	23	21.0	10.7	16	50.4 %	7.60 (0.34, 14.86)	1992
Makrydimas G. et al.,1998	31.4	12.4	20	18.7	11.2	20	49.6 %	12.70 (5.38, 20.02)	1998
Hatzis T. et al., 2003	0.0	0.0	0	0.0	0.0	0		Not estimable	2003
Total (95% CI)			**43**			**36**	**100.0 %**	**10.13 (4.97, 15.29)**	

Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (*p* = 0.33); I^2 = 0 %

Test for overall effect: Z = 3.85 (*p* = 0.0001)

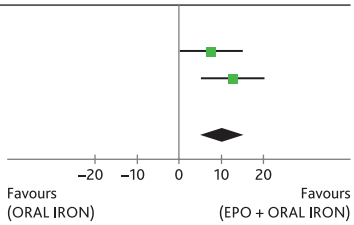


Fig. 7. Analysis 1.4. Difference in hemoglobin concentration (ΔHb, g/L) after 2 weeks of treatment. Random effects model

that the use of EPO in combination with oral iron in the intervention group reduced the likelihood of blood transfusions compared to the control group.

Meta-analysis of secondary outcomes

Analysis 2.1. Serum ferritin levels after 5 days of treatment (μg/L)

When using EPO in combination with oral iron, the cumulative mean value of SF levels after 5 days treatment (Figure 14) was statistically significantly lower in the group receiving EPO (MD −14.83 μg/L, 95 % CI −20.61 to −9.06; $p < 0.00001$).

Analysis 2.2. Serum iron concentration (μmol/L) after 5 days of treatment

Cumulative mean concentration of serum iron (Figure 15) after 5 days of treatment was higher in the EPO group but without statistically significant differences compared to the control group (MD 1.30 μmol/L, 95 % CI 0.01–2.58; $p = 0.05$).

Analysis 2.3. Lactation capability

This analysis includes 3 studies, 3 comparisons and 188 participants. In the meta-analysis of this event (Figure 16), RR was 1.48; 95 % CI 0.42–5.27; $p = 0.54$. A very wide CI of 95 % is observed, including the value of one, indicating the lack of statistical significance of the obtained result.

Publication bias assessment and sensitivity analysis were not conducted due to the limited number of studies ($n = 4$). It is generally considered that for a relatively reliable assessment of publication bias using a funnel plot, a meta-analysis should include at least 5–10 primary studies [37].

Discussion

The results of our meta-analysis showed that the use of EPO in combination with oral iron for managing anaemia in postpartum women allows to obtain a more pronounced haematological response and reduce the likelihood of blood transfusions compared to the control group.

Haematological response:

1. Quantitative synthesis of the data showed a statistically significant increase in Hb concentrations in the EPO group after 5 days of treatment as well as after 2 weeks of treatment.
2. Cumulative mean absolute Hb concentration within the same time intervals were higher in the EPO group, but without statistical significance compared to the control group, reaching statistical significance in favor of EPO by the 40th day of therapy. Despite a significant dropout of patients in the study by A.Huch et al., 1992 [1] (on the 40th day of observation, 10 and 5 participants were analyzed in the EPO and control groups, respectively), it was decided to include the results obtained by the authors in the meta-analysis.
3. There is likely a long-term effect when using EPO in combination with oral iron in postpartum women. The study with the most significant weight in the combined effect estimate (50 %) was the one by G.Makrydimas et al., 1998 [9], where EPO was administered subcutaneously for 15 days, with a total dose of 210,000 IU. Adequate supplementation of oral iron (200 mg/day for 40 days) was provided. Given the increased iron requirements during lactation, this treatment regimen is likely to be the most appropriate.
4. It is necessary to note the initially higher levels of Hb in the control group at the onset of the treatment, thus ΔHb in the groups over the specified time intervals should be considered more reliable.
5. A similar trend is observed in hematocrit levels: after 2 weeks of treatment, the levels were significantly higher in the EPO group.

On a similar topic, two pairwise meta-analyses had been previously conducted based on the studies [3, 38]. In the study by J.M. Dodd et al., 2004 [38], 6 RCTs (411 women) were analyzed and a greater increase in Hb levels was observed in the EPO groups. Thus, a similar trend was identified by the authors, and the lack of statistical significance may be related to the smaller number of participants in the analysis.

In the study by V.Markova et al., 2015 [3], the assessment of clinical signs of IDA in postpartum women was conducted. Our meta-analysis focuses more on the evaluation of laboratory parameters. Although the latter are commonly considered "surrogate" outcomes, it is important to note that the transfusion threshold (hemotransfusion trigger), determining the indications for blood transfusion invariably takes into account laboratory criteria. One of our outcomes was the frequency of blood transfusions in the comparing groups of postpartum women.

In the study by A.C. Kotto-Kome et al., 2003 [7], focused on assessing the efficacy of EPO in managing postpartum anaemia, there was a trend toward a quicker haematological response among postpartum women in the EPO groups. However, the high heterogeneity of the included trials prevented the authors from conducting a quantitative synthesis of results.

If we broaden our focus beyond the obstetric patients, the systematic review by L.Kaufner et al. in 2020 [39] presented results indicating the efficacy of using high doses of EPO (500–600 IU/kg) in combination with iron medications in adult patients undergoing non-cardiac surgeries. The authors demonstrated a significant increase in Hb concentration (MD 18.7 g/L, 95 % CI 12.6–24.9; $p < 0.00001$) and a reduction in the need for allogeneic red blood cell transfusions (RR 0.55; 95 % CI 0.38–0.80). The subgroup

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l))	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. et al., 1992	109.6	15.3	23	109	15.3	16	48.2 %	0.60 (–9.16, 10.36)	1992
Makrydimas G. et al.,1998	103.0	14.4	20	89	12.5	20	51.8 %	14.00 (5.64, 22.36)	1998
Total (95% CI)			**43**			**36**	**100.0 %**	**7.55 (–5.58, 20.67)**	

Heterogeneity: Tau² = 68.29; Chi² = 4.18, df = 1 (*p* = 0.04); *I*² = 76 %

Test for overall effect: Z = 1.13 (*p* = 0.26)

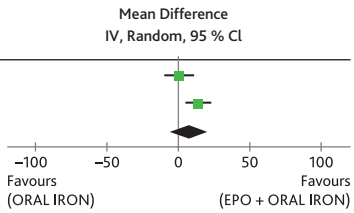


Fig. 8. Analysis 1.5. Absolute hemoglobin concentration after 2 weeks of the therapy (g/L). Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	SD (g/l)	Total	ORAL IRON Mean (g/l)	SD (g/l)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. et al., 1992	128.0	17.9	10	119	16.6	5	21.6 %	9.00 (–9.30, 27.30)	1992
Makrydimas G. et al.,1998	122.0	17.1	20	116	16.2	20	50.0 %	6.00 (–4.32, 16.32)	1998
Hatzis T. et al., 2003	118.3	28.0	37	97	35.5	31	28.4 %	21.30 (5.89, 36.71)	2003
Total (95% CI)			**67**			**56**	**100.0 %**	**11.00 (1.70, 20.30)**	

Heterogeneity: Tau² = 17.28; Chi² = 2.64, df = 2 (*p* = 0.27); *I*² = 24 %

Test for overall effect: Z = 2.32 (*p* = 0.02)

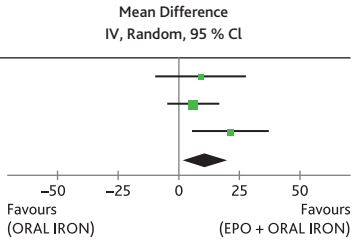


Fig. 9. Analysis 1.6. Absolute hemoglobin concentration (g/L) after 40 days of the therapy. Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (%)	SD (%)	Total	ORAL IRON Mean (%)	SD (%)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. et al., 1992	24.6	3.20	37	26.8	2.50	37	52.8 %	–2.20 (–3.51, –0.89)	1992
Makrydimas G. et al.,1998	21.6	3.02	20	21.0	2.94	20	47.2 %	0.60 (–1.25, 2.45)	1998
Total (95% CI)			**57**			**57**	**100.0 %**	**–0.88 (–3.62, 1.86)**	

Heterogeneity: Tau² = 3.25; Chi² = 5.88, df = 1 (*p* = 0.02); *I*² = 83 %

Test for overall effect: Z = 0.63 (*p* = 0.53)

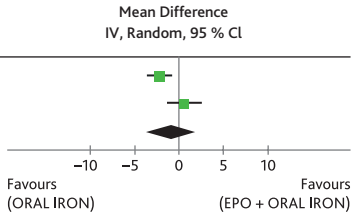


Fig. 10. Analysis 1.7. Baseline hematocrit before treatment (%). Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (%)	SD (%)	Total	ORAL IRON Mean (%)	SD (%)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. et al., 1992	27.3	3.90	37	28	3.10	37	52.3 %	–0.70 (–2.31, 0.91)	1992
Makrydimas G. et al.,1998	26.9	3.77	20	24	3.36	20	47.7 %	2.90 (0.69, 5.11)	1998
Total (95% CI)			**57**			**57**	**100.0 %**	**1.02 (–2.51, 4.54)**	

Heterogeneity: Tau² = 5.51; Chi² = 6.66, df = 1 (*p* = 0.010); *I*² = 85 %

Test for overall effect: Z = 0.57 (*p* = 0.57)

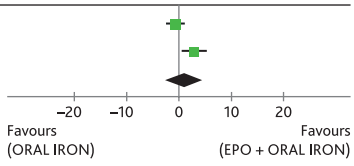


Fig. 11. Analysis 1.8. Hematocrit levels after 5 Days of Treatment (%). Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (%)	SD (%)	Total	ORAL IRON Mean (%)	SD (%)	Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. et al., 1992	32.9	2.50	23	31.1	3.7	16	50.0 %	1.80 (–0.28, 3.88)	1992
Makrydimas G. et al.,1998	32.0	2.88	20	27.1	3.8	20	50.0 %	4.90 (2.81, 6.99)	1998
Total (95 % CI)			**43**			**36**	**100.0 %**	**3.35 (0.31, 6.39)**	

Heterogeneity: Tau² = 3.67; Chi² = 4.24, df = 1 (*p* = 0.04); *I*² = 76 %

Test for overall effect: Z = 2.16 (*p* = 0.03)

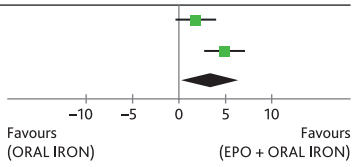
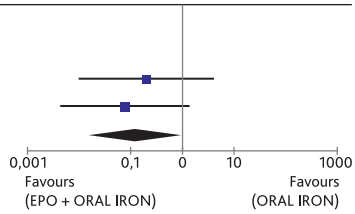


Fig. 12. Analysis 1.9. Hematocrit levels after 2 weeks of treatment (%). Random effects model

Study or Subgroup	EPO + ORAL IRON Events	EPO + ORAL IRON Total	ORAL IRON Events	ORAL IRON Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Danko J. et al., 1990	0	5	0	5		Not estimable	1990
Huch A. et al., 1992	0	37	0	37		Not estimable	1992
Makrydimas G. et al.,1998	0	20	2	20	47.7 %	0.20 (0.01, 3.92)	1998
Hatzis T. et al., 2003	0	37	6	37	52.3 %	0.08 (0.00, 1.32)	2003
Total (95% CI)		**99**		**99**	**100.0 %**	**0.12 (0.02, 0.95)**	
Total events	**0**		**8**				

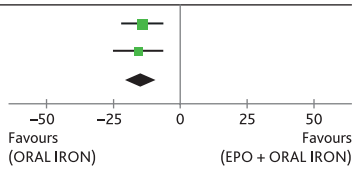


Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (*p* = 0.64); I^2 = 0 %

Test for overall effect: Z = 2.01 (*p* = 0.04)

Fig. 13. Analysis 1.10. Red blood cell transfusion. Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (µg/l)	EPO + ORAL IRON SD (µg/l)	EPO + ORAL IRON Total	ORAL IRON Mean (µg/l)	ORAL IRON SD (µg/l)	ORAL IRON Total	Weight	Mean Difference IV, Random, 95% CI	Year
Huch A. et al., 1992	23.1	17.7	37	37.30	15.2	37	59.1 %	–14.20 (–21.72, –6.68)	1992
Makrydimas G. et al.,1998	21.5	16.3	20	37.25	12.6	20	40.9 %	–15.75 (–24.78, –6.72)	1998
Total (95% CI)			**57**			**57**	**100.0 %**	**–14.83 (–20.61, –9.06)**	

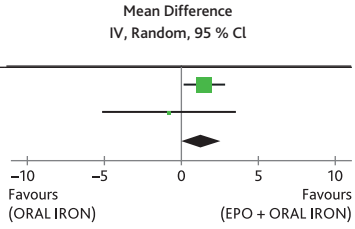


Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (*p* = 0.80); I^2 = 0 %

Test for overall effect: Z = 5.03 (*p* < 0.00001)

Fig. 14. Analysis 2.1. Serum ferritin levels (µg/L) after 5 days of treatment. Random effects model

Study or Subgroup	EPO + ORAL IRON Mean (g/l)	EPO + ORAL IRON SD (g/l)	EPO + ORAL IRON Total	ORAL IRON Mean (g/l))	ORAL IRON SD (g/l)	ORAL IRON Total	Weight	Mean Difference IV, Random, 95 % CI	Year
Huch A. , et al., 1992	8.5	3.1	37	7.0	2.5	37	91.1 %	1.50 (0.22, 2.78)	1992
Makrydimas G. , et al.,1998	10.5	6.5	20	11.3	7.3	20	8.9 %	–0.80 (–5.08, 3.48)	1998
Total (95% CI)			**57**			**57**	**100.0 %**	**1.30 (0.01, 2.58)**	

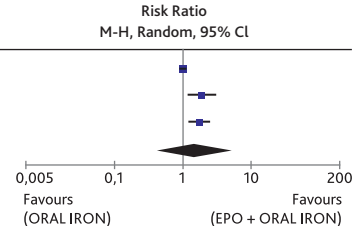


Heterogeneity: Tau² = 0.04; Chi² = 1.02, df = 1 (*p* = 0.31); I^2 = 2 %

Test for overall effect: Z = 1.98 (*p* = 0.05)

Fig. 15. Analysis 2.2. Serum iron concentration (µmol/L) after 5 days of treatment. Random effects model

Study or Subgroup	EPO + ORAL IRON Events	EPO + ORAL IRON Total	ORAL IRON Events	ORAL IRON Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Huch A. , et al., 1992	37	37	37	37	34.0 %	1.00 (0.95, 1.05)	1992
Makrydimas G. , et al.,1998	19	20	10	20	32.7 %	1.90 (1.21, 2.98)	1998
Hatzis T. , et al., 2003	33	37	19	37	33.3 %	1.74 (1.24, 2.42)	2003
Total (95% CI)		**94**		**94**	**100.0 %**	**1.48 (0.42, 5.27)**	
Total events	**89**		**66**				



Heterogeneity: Tau² = 1.23; Chi² = 130.24, df = 2 (*p* < 0.00001); I^2 = 98 %

Test for overall effect: Z = 0.61 (*p* = 0.54)

Fig. 16. Analysis 2.3. Lactation capability. Random effects model

analysis was conducted to assess haematological response based on different EPO doses (low dose: 150–300 IU/kg, high dose: 500–600 IU/kg) administered either subcutaneously or parenterally.

It is important to note that the mentioned study included studies regardless iron doses and administration routes. This is likely due to the limited number of direct comparisons when categorizing iron supplements, which prevented the authors from conducting quantitative synthesis. As for orphan comparisons are concerned, for some clear reasons, they provide no value within the scope of the meta-analysis. Extrapolating this situation to the obstetric patients, there are grounds to attempt the use of both direct and indirect comparisons for further analysis and ranking concerning the combined use of EPO and various iron supplements (including the type of supplement, dose, and administration route).

In the meta-analysis by J.M. Dodd et al., 2004 [38], no significant impact on the need for blood transfusion was found when comparing EPO in combination with iron supplements to the treatment with iron supplements alone in anaemic postpartum women (2 RCTs, n = 100; RR 0.20; 95% CI 0.01–3.92). The authors assumed that the included RCTs were of insufficient size to exclude important clinical differences. In the meta-analysis by V.Markova et al., 2015 [3], concerning this outcome, only the study by G.Makrydimas et al., 1998 [9], which was also included in our meta-analysis, is mentioned.

The results of our meta-analysis for this outcome showed that the combined use of EPO with oral iron in postpartum women with IDA in the intervention group reduced the likelihood of blood transfusion compared to the control group. However, these results should be interpreted with caution because:

- the magnitude of the observed effect is small, RR 0.12; 95% CI 0.02–0.95; p = 0.04;
- information regarding the frequency of blood transfusions is limited: in two of the four studies included in the review, blood transfusions were not performed/not required.

Regarding the secondary outcomes of the meta-analysis: when EPO was used, the cumulative mean SF concentration after 5 days of treatment was statistically significantly lower in the EPO group, indicating erythropoiesis stimulation and increased iron requirements (secondary iron deficiency due to erythropoiesis stimulation). Treatment with EPO is recommended when iron deficiency is either ruled out or managed [40].

However, the SF levels in the postpartum period (during the first 6 weeks after delivery) differ from the levels in pregnant women and have a limited value — they can be overvalued and/or unreliable. Therefore, it is necessary to treat the results of this analysis with caution, and we included this parameter in the secondary outcomes of the meta-analysis.

Cumulative mean SF concentration levels after 5 days of therapy were higher in the group of women receiving EPO but without statistically significant differences between the compared groups.

It is important to note that SF is an unstable parameter that can change depending on food intake and/or iron-containing supplements.

Our meta-analysis did not reveal any improvements in lactation capability with the combined use of EPO and oral iron. In the study by J.M. Dodd et al., 2004 [38], it was shown that the use of EPO compared to monotherapy with iron supplements increased the likelihood of lactation at discharge from the hospital (1 RCT, n = 40; RR 1.90; 95% CI 1.21–2.98). However, in this case the authors relied on the results of only one RCT — G.Makrydimas et al., 1998 [9], which was also included in our analysis. In the meta-analysis by V. Markova et al., 2015 [3], despite the stated (in the protocol as well as in the review) outcome of "breastfeeding", the results are not presented due to a lack of data.

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE):

- Body of evidence — the quality is reduced due to the absence of blinding in the included studies, all studies are open-label.
- Inconsistency — the quality is reduced due to high heterogeneity, including clinical, methodological and statistical heterogeneity.
- Indirectness — no specific problems related to indirectness have been identified.
- Imprecision — the quality is reduced due to small sample sizes and, consequently, wide confidence intervals, which decrease our confidence in the results.
- Selective reporting — the quality is reduced because study protocols are missing.

Thus, the quality of evidence according to GRADE can be determined as low.

The strengths of our review lie in the methodological quality of the search, selection, and analysis of the data conducted in accordance with Cochrane standards for systematic reviews of interventions [41], see Files S5, S6: https://data.mendeley.com/datasets/gx2pdpts36/1

Study limitations

The conducted meta-analysis has several methodological limitations:

- Small number of included studies (n = 4), considering the extremely limited information available on this clinical question.
- Two included study designs were not RCTs.
- The compared groups differed in terms of ethnic composition (studies were conducted in Switzerland and Greece) and socio-economic status.

Therefore, the obtained results should be interpreted with caution. To provide a more precise answer to the clinical question posed, further well-planned randomized controlled trials with sufficient sample sizes and coverage of different patient populations are necessary.

Conclusion

The results of the conducted meta-analysis have shown a faster haematological response with the combined use of erythropoietin and oral iron therapy compared to monotherapy with oral iron for the management of post-hemorrhagic anemia in postpartum women. The use of erythropoietin helps to reduce the likelihood of blood transfusions in these patients.

No side effects or adverse events of EPO and oral iron in the included studies were reported by the authors. Further carefully planned randomized controlled trials with sufficient sample sizes are needed to address this issue.

Disclosure. The authors declare that they have no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. Not required.

Funding source. This study was not supported by any external sources of funding.

Data Availability Statement. The data that support the findings of this study are openly available in repository Mendeley Data at https://doi.org/10.17632/gx2pdpts36.1

Author's ORCID:

Barkovskaya N.A. — 0000-0002-2360-0805
Shifman E.M. — 0000-0002-6113-8498
Protsenko D.N. — 0000-0002-5166-3280

References

[1] *Huch A., Eichhorn K.H., Danko J., et al*. Recombinant human erythropoietin in the treatment of postpartum anemia. Obstet Gynecol. 1992; 80(1): 127–31.

[2] *Vander Meulen H., Strauss R., Lin Y., et al*. The contribution of iron deficiency to the risk of peripartum transfusion: A retrospective case control study. BMC Pregnancy Childbirth. 2020; 20(1). DOI: 10.1186/s12884-020-02886-z

[3] *Markova V., Norgaard A., Jørgensen K.J., Langhoff-Roos J*. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database of Systematic Reviews. 2015; 2015(8). DOI: 10.1002/14651858.cd010861.pub2

[4] *Барковская Н.А., Шифман Е.М., Каткова Н.Ю.* Эффективность эритропоэтина в сочетании с препаратами железа для внутривенного введения в лечении постгеморрагической анемии у родильниц. Систематический обзор и метаанализ РКИ. Анестезиология и реаниматология. 2023; 2: 15–26. DOI: 10.17116/anaesthesiology202302115 [*Barkovskaya N.A., Shifman E.M., Katkova N. Yu*. Efficacy of erythropoietin combined with intravenous iron therapy for postpartum anemia: A systematic review and meta-analysis of randomized controlled trials. Russian Journal of Anaesthesiology and R eanimatology = Anesteziologiya I Reanimatologiya. 2023; 2: 15–26. DOI: 10.17116/anaesthesiology202302115 (In Russ)]

[5] *Page M.J., Moher D., Bossuyt P.M., et al*. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021; 372: n160. DOI: 10.1136/bmj.n160

[6] *Квашнина Д.В., Полибин Р.В., Саперкин Н.В. и др*. AMSTAR 2 — инструмент оценки качества систематических обзоров. Эпидемиология и Вакцинопрофилактика. 2022; 21(3): 80–9. DOI: 10.31631/2073-3046-2022-21-3-80-89 [*Kvashnina D.V., Polibin R.V., Saperkin N.V. et al*. A Russian version of AMSTAR 2: Validation and guidance. Epidemiology and Vaccinal Prevention. 2022; 21(3): 80–9. DOI: 10.31631/2073-3046-2022-21-3-80-89 (In Russ)]

[7] *Kotto-Kome A.C., Calhoun D.A., Montenegro R., et al*. Effect of administering recombinant erythropoietin to women with postpartum anemia: A meta-analysis. J Perinatol. 2003; 24(1): 11–5. DOI: 10.1038/sj.jp.7211017

[8] *Rohatgi A*. WebPlotDigitizer — copyright 2010–2022 Ankit Rohatgi. Accessed July 24, 2023. https://apps.automeris.io/wpd/index.de_DE.html

[9] *Makrydimas G., Lolis D., Lialios G., et al*. Recombinant human erythropoietin treatment of postpartum anemia. Eur J Obstet Gynecol Reprod Biol. 1998; 81(1): 27–31. DOI: 10.1016/s0301-2115(98)00158-4

[10] *Higgins J.P.T.*, *Thomas J.*, *Chandler J.*, *et al*. (eds) Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from: www.training.cochrane.org/handbook

[11] *Sterne J.A.C.*, *Savović J.*, *Page M.J.*, *et al*. Rob 2: A revised tool for assessing risk of bias in randomised trials. BMJ. Published online 2019:l4898. DOI: 10.1136/bmj.l4898

[12] *McGuinness L.A*, *Higgins J.P.T*. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2020; 12(1): 55–61. DOI: 10.1002/jrsm.1411

[13] Review Manager (RevMan) [Computer program]. Version 5.4.1, The Cochrane Collaboration, 2020. Accessed: Apr. 23, 2023. [Online]. Available: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download/download-and-installation

[14] *Krafft A.*, *Breymann C.*, *Hüttner C.*, *et al*. Erythropoietic quality of maternal milk. The Lancet. 1999; 354(9180): 778. DOI: 10.1016/s0140-6736(05)76022-0

[15] *Zimmermann R.*, *Breymann C.*, *Richter C.*, *et al*. rhEPO treatment of postpartum anemia. J Perinat Med. 1995; 23(1–2): 111–8. DOI: 10.1515/jpme.1995.23.1-2.111

[16] *Bisbe Vives E.*, *Moltó L*. Aproximación Terapéutica a la anemia postoperatoria. Revista Española de Anestesiología y Reanimación. 2015; 62: 41–4. DOI: 10.1016/s0034-9356(15)30006-2

[17] *Belfort M.*, *Kofford S.*, *Varner M*. Massive obstetric hemorrhage in a jehovah's witness: Intraoperative strategies and high-dose erythropoietin use. Am J Perinatol. 2010; 28(03): 207–10. DOI: 10.1055/s-0030-1266158

[18] *Malinova M*. Human recombinant erythropoietin in the treatment of the severe anemia following labor (a preliminary report). Akush Ginekol. (Soffia). 1999; 38: 13–5.

[19] *Vora M.*, *Gruslin A*. Erythropoietin in obstetrics. Obstetrical & Gynecological Survey. 1998; 53(8): 500–8. DOI: 10.1097/00006254-199808000-00023

[20] *Danko J.*, *Svirohva V.*, *Visnovsky V*. Treatment of postpartum anaemia using recombination human erythropoietin. Gynekolog (Czech Rep). 1992; 1: 4–7.

[21] *Delzanno G.*, *Falcone M.*, *Gaudiano L.*, *et al*. Impiego dell'eritropoietina umana ricombinante in stati anemici di interesse ostetrico-ginecologico. Valutazione dell'utilità di tale trattamento in alternativa all'emotrasfusione [Human recombinant erythropoietin in the treatment of anemia in obstetric-gynecologic patients. Evaluation of such treatment as an alternative to blood transfusion]. Minerva Ginecol. 1996; 48(3): 115–8. (In Italian)]

[22] *Коноводова Е.Н.*, *Бурлев В.А.*, *Орджоникидзе Н.В. и др*. Лечение дефицита железа у родильниц рекомбинантным эритропоэтином. Акушерство и гинекология. 2010; 3: 35–8. [*Konovodova E.N.*, *Burlev V.A.*, *Ordzhonikidze N.V.*, *et al*. Treatment of iron deficiency in puerperas with recombinant erythropoietin. Akusherstvo i Ginekologiya. Obstetrics and Gynecology. 2010; 3: 35–8. (In Russ)]

[23] *Айламазян Э.К.*, *Тарасова М.А.*, *Зайцев А.А.*, *Самарина А.В.* Роль эритропоэтина в патогенезе и лечении железодефицитной анемии при беременности и в послеродовом периоде. Журнал акушерства и женских болезней. 2003; 4(52): 17–22. [*Ailamazyan E.K.*, *Tarasova M.A.*, *Zaitsev A.A.*, *Samarina A.V.* Rol' eritropoetina v patogeneze i lechenii zhelezodefitsitnoi anemii pri beremennosti i v poslerodovom periode. Zhurnal akusherstva i zhenskikh boleznei. 2003; 4(52): 17–22. (In Russ)]

[24] *Айламазян Э.К.*, *Самарина А.В.*, *Тарасова М.А.* Рекомбинантный эритропоэтин в лечении анемии беременных и родильниц. Акушерство и гинекология. 2003; 2: 68–70. [*Ailamazyan E.K.*, *Samarina A.V.*, *Tarasova M.A.* Rekombinantnyi eritropoetin v lechenii anemii beremennykh i rodil'nits. Akusherstvo i ginekologiya. Obstetrics and Gynecology. 2003; 2: 68–70. (In Russ)]

[25] *Бурлев В.А.*, *Коноводова Е.Н.*, *Нерсесян Р.А. и др*. Эритропоэтин у родильниц с анемией. Проблемы репродукции. 2002; 5(8): 53–6. [*Burlev V.A.*, *Konovodova E.N.*, *Nersesyan R.A. et al*. Eritropoetin u rodil'nits s anemiei. Problemy reproduktsii. 2002; 5(8): 53–6. (In Russ)]

[26] *Breymann C.*, *Zimmermann R.*, *Huch R.*, *Huch A*. Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anaemia. Eur J Clin Invest. 1996; 26(2): 123–30. DOI: 10.1046/j.1365-2362.1996.109261.x

[27] *Breymann C.*, *Richter C.*, *Hüttner C.*, *et al*. Effectiveness of recombinant erythropoietin and iron sucrose vs. iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. Eur J Clin Invest. 2000; 30(2): 154–61. DOI: 10.1046/j.1365-2362.2000.00605.x

[28] *Lebrecht A.*, *Häberlin F.*, *Eberhard J.* Anämie im WOCHENBETT; Parenterale Eisensubstitution Macht erythropoetin-Therapie Entbehrlich. Geburtshilfe und Frauenheilkunde. 1995; 55(03): 167–70. DOI: 10.1055/s-2007-1022798 [*Lebrecht A*, *Häberlin F*, *Eberhard J*. Anemia in puerperium; parenteral iron substitution renders erythropoietin therapy dispensable. Geburtshilfe Frauenheilkd 1995; 55: 167–70. DOI: 10.1055/s-2007-1022798 (In Deu)]

[29] *Meyer J.W.*, *Eichhorn K.-H.*, *Vetter K.*, *et al*. Does recombinant human erythropoietin not only treat anemia but reduce postpartum (emotional) distress as well? J Perinat Med. 1995; 23(1–2): 99–110. DOI: 10.1515/jpme.1995.23.1-2.99

[30] *Zimmermann R.*, *Breymann C.*, *Huch R.*, *Huch A*. rHuEPO in the treatment of postpartum anemia: subcutaneous versus intravenous administration. Clin Investig. 1994; 72: 25–30.

[31] *Wågström E.*, *Åkesson A.*, *Van Rooijen M.*, *et al*. Erythropoietin and intravenous iron therapy in postpartum anaemia. Acta Obstet Gynecol Scand. 2007; 86(8): 957–62. DOI: 10.1080/00016340701446157

[32] *Krafft A.*, *Breymann C.* Iron sucrose with and without recombinant erythropoietin for the treatment of severe postpartum anemia: A prospective, randomized, open-label study. J Obstet Gynaecol Res. 2010; 37(2): 119–24. DOI: 10.1111/j.1447-0756.2010.01328.x

[33] *Gordon M.S.* Erythropoietin and intravenous iron therapy in postpartum anaemia. Yearbook of Oncology. 2008; 2008: 364–5. DOI: 10.1016/s1040-1741(08)79135-8

[34] *Danko J.*, *Huch R.*, *Huch A*. Epoetin Alfa for treatment of postpartum anaemia. The Lancet. 1990; 335(8691): 737–8. DOI: 10.1016/0140-6736(90)90860-8

[35] *Hatzis T.*, *Cardamakis E.*, *Tsapanos V.*, *et al*. The effects of recombinant human erythropoietin given immediately after delivery to women with anaemia. Curr Med Res Opin. 2003; 19(4): 346–9. DOI: 10.1185/030079903125001802

[36] A revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Accessed July 23, 2023.URL: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

[37] Principles and practice of systematic reviews and meta-analysis. SpringerLink. Accessed July 24, 2023. https://link.springer.com/book/10.1007/978-3-030-71921-0

[38] *Dodd J.M.*, *Dare M.R.*, *Middleton P*. Treatment for women with postpartum iron deficiency anaemia. Cochrane Database of Systematic Reviews. 2004; 2015(9). DOI: 10.1002/14651858.cd004222.pub2

[39] *Kaufner L.*, *von Heymann C.*, *Henkelmann A.*, *et al*. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. Cochrane Database of Systematic Reviews. 2020; 2020(8). DOI: 10.1002/14651858.cd012451.pub2

[40] *Goodnough L.T.*, *Maniatis A.*, *Earnshaw P.*, *et al.* Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic Surgical Patient: NATA guidelines. Br J Anaesth. 2011; 106(1): 13–22. DOI: 10.1093/bja/aeq361

[41] MECIR manual. MECIR Manual Cochrane Community. Accessed July 24, 2023. https://community.cochrane.org/mecir-manual