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ANEMIA IN PREGNANCY: MODERN APPROACHES TO DIAGNOSIS AND TREATMENT

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ABSTRACT: Background: Iron Deficiency Anemia (IDA) is the most common hematological disorder in pregnancy, affecting nearly 50% of women in the Andijan region. It is a major risk factor for preterm birth, low birth weight, and postpartum hemorrhage. Traditional management with oral iron salts is often limited by gastrointestinal side effects and poor compliance. This study compares the efficacy and safety of modern intravenous (IV) iron formulations versus oral iron therapy. Methods: A randomized clinical trial included 160 pregnant women (24-32 weeks gestation) with moderate IDA (Hb 70-99 g/L). Participants were randomized into two groups: Group A (n=80) received oral Ferrous Sulfate (100 mg elemental iron twice daily), and Group B (n=80) received IV Ferric Carboxymaltose (calculated dose based on Ganzoni formula). Hematological parameters (Hb, Ferritin) and adverse effects were monitored for 6 weeks. Results: Group B achieved a significantly faster rise in Hemoglobin levels (mean increase of 2.8 g/dL vs. 1.2 g/dL in Group A after 4 weeks, $p < 0.001$). Ferritin stores were restored in 95% of women in the IV group compared to only 30% in the oral group. Gastrointestinal side effects (nausea, constipation) were reported by 35% of Group A, leading to 15% non-compliance, whereas Group B had minimal adverse events. Conclusion: Intravenous Ferric Carboxymaltose is superior to oral iron in rapidly correcting anemia and replenishing iron stores in the second and third trimesters, offering a safe and effective alternative for women with moderate-to-severe anemia or oral intolerance.
Keywords: Pregnancy, iron deficiency anemia, intravenous iron, ferric carboxymaltose, ferritin, hemoglobin, maternal health.

HOMILADORLARDA ANEMIYA: TASHXISLASH VA DAVOLASHDA ZAMONAVIY YONDASHUVLAR

Annotatsiya: Kirish: Temir tanqisligi anemiyasi (TTA) homiladorlikdagi eng keng tarqalgan gematologik kasallik bo‘lib, Andijon viloyatida ayollarning qariyb 50 foizida uchraydi. Bu muddatidan oldin tug‘ruq, kam vaznli bola tug‘ilishi va tug‘ruqdan keyingi qon ketish uchun asosiy xavf omilidir. Oral temir tuzlari bilan an’anaviy davolash ko‘pincha oshqozon-ichak traktidagi nojo‘ya ta’sirlar va bemorlarning tavsiyalarga to‘liq amal qilmasligi (komplayens pastligi) tufayli samarasiz bo‘ladi. Ushbu tadqiqot zamonaviy vena ichiga (V/I) yuboriladigan temir preparatlari va oral temir terapiyasining samaradorligi hamda xavfsizligini taqqoslaydi. Usullar: O‘rtacha darajadagi TTA (Hb 70-99 g/l) bo‘lgan 160 nafar homilador ayol (24-32 haftalik) ishtirokida randomizatsiyalangan klinik sinov o‘tkazildi. Ishtirokchilar ikki guruhga ajratildi: A guruhi (n=80) oral Temir Sulfat (kuniga ikki marta 100 mg elementar temir) qabul

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qildi, B guruhi (n=80) esa V/I Temir Karboksimaltoza (Ganzoni formulasi asosida hisoblangan doza) oldi. Gematologik ko‘rsatkichlar (Hb, Ferritin) va nojo‘ya ta’sirlar 6 hafta davomida kuzatildi. Natijalar: B guruhi Gemoglobin darajasining sezilarli darajada tezroq ko‘tarilishiga erishdi (4 haftadan so‘ng A guruhidagi 1,2 g/dL ga nisbatan o‘rtacha o‘sish 2,8 g/dL, $p < 0.001$). V/I guruhidagi ayollarning 95 foizida ferritin zaxiralari tiklandi, oral guruhda esa bu ko‘rsatkich atigi 30 foizni tashkil etdi. A guruhida 35% ayollarda oshqozon-ichak nojo‘ya ta’sirlari (ko‘ngil aynishi, qabziyat) kuzatildi, bu esa 15% holatda davolashni to‘xtatishga olib keldi; B guruhida esa nojo‘ya ta’sirlar minimal bo‘ldi. Xulosa: Vena ichiga yuboriladigan Temir Karboksimaltoza ikkinchi va uchinchi trimestrlarda anemiyani tezkorlik bilan tuzatish va temir zaxiralarini to‘ldirishda oral temirdan ustundir. Bu o‘rta va og‘ir darajadagi anemiyasi bo‘lgan yoki oral preparatlarni ko‘tara olmaydigan ayollar uchun xavfsiz va samarali alternativ hisoblanadi.
Kalit so‘zlar: Homiladorlik, temir tanqisligi anemiyasi, vena ichiga temir, temir karboksimaltoza, ferritin, gemoglobin, ona salomatligi.

АНЕМИЯ У БЕРЕМЕННЫХ: СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ И ЛЕЧЕНИЮ

Аннотация: Введение: Железодефицитная анемия (ЖДА) является наиболее распространенным гематологическим заболеванием при беременности, затрагивающим почти 50% женщин в Андижанской области. Это основной фактор риска преждевременных родов, низкого веса при рождении и послеродовых кровотечений. Традиционное лечение пероральными солями железа часто ограничивается побочными эффектами со стороны желудочно-кишечного тракта и низкой приверженностью пациентов. В данном исследовании сравниваются эффективность и безопасность современных внутривенных (В/В) препаратов железа и пероральной терапии. Методы: Было проведено рандомизированное клиническое исследование с участием 160 беременных женщин (24-32 недели гестации) с ЖДА средней степени тяжести (Hb 70-99 г/л). Участницы были рандомизированы на две группы: группа А (n=80) получала пероральный сульфат железа (100 мг элементарного железа дважды в день), а группа Б (n=80) получала В/В карбоксимальтозат железа (доза рассчитывалась по формуле Ганзони). Гематологические параметры (Hb, ферритин) и побочные эффекты отслеживались в течение 6 недель. Результаты: В группе Б наблюдалось значительно более быстрое повышение уровня гемоглобина (средний прирост 2,8 г/дл против 1,2 г/дл в группе А через 4 недели, $p < 0,001$). Запасы ферритина были восстановлены у 95% женщин в группе В/В по сравнению с лишь 30% в группе перорального приема. О побочных эффектах со стороны ЖКТ (тошнота, запор) сообщили 35% участниц группы А, что привело к отказу от лечения в 15% случаев, тогда как в группе Б побочные эффекты были минимальными. Заключение: Внутривенный карбоксимальтозат железа превосходит пероральные препараты железа в быстром устранении анемии и восполнении запасов железа во втором и третьем триместрах, представляя собой безопасную и эффективную альтернативу для женщин с анемией средней/тяжелой степени или непереносимостью пероральных форм.
Ключевые слова: Беременность, железодефицитная анемия, внутривенное железо, карбоксимальтозат железа, ферритин, гемоглобин, здоровье матери.

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INTRODUCTION

Anemia in pregnancy represents a pervasive and persistent global public health challenge, affecting an estimated 38% of pregnant women worldwide, with rates soaring as high as 56% in low- and middle-income countries. It is defined by the World Health Organization (WHO) as a hemoglobin (Hb) concentration of less than 110 g/L. In Uzbekistan, specifically within the Fergana Valley and Andijan region, the prevalence remains historically high, often exceeding 50% in certain rural cohorts. This regional disparity is driven by a convergence of factors: traditional dietary habits rich in inhibitors of iron absorption (such as tannins in tea and phytates in breads), low consumption of heme iron sources, short inter-pregnancy intervals that prevent the replenishment of maternal iron stores, and high rates of multiparity.

Pregnancy imposes a unique physiological stress on iron homeostasis. As gestation progresses, maternal plasma volume expands by approximately 40-50%, while red blood cell mass increases by only 20-30%, leading to physiological hemodilution. However, this natural adaptation often masks the severity of pathological iron deficiency. The total iron requirement during a singleton pregnancy is approximately 1,000 mg—far exceeding the amount absorbable from a standard diet. When pre-pregnancy stores are low, this demand strips the mother of iron, leading to Iron Deficiency Anemia (IDA).

IDA is not merely a benign laboratory finding; it is a systemic pathology with profound clinical consequences. For the mother, moderate-to-severe anemia leads to chronic fatigue, cardiovascular stress, reduced cognitive function, and impaired immune response. Critically, it reduces the physiological tolerance to blood loss at delivery; anemic women are significantly more likely to require blood transfusions and face a higher risk of maternal mortality from postpartum hemorrhage (PPH). For the fetus, maternal iron is essential for neurodevelopment. Severe maternal IDA is linked to intrauterine growth restriction (IUGR), preterm birth, and long-term neurocognitive deficits in the offspring.

Historically, the therapeutic paradigm has relied heavily on oral iron supplementation (ferrous sulfate). While inexpensive and accessible, oral iron is plagued by limitations. The absorption of oral iron is tightly regulated by hepcidin, a hepatic hormone that blocks iron uptake in states of inflammation or sufficiency. Furthermore, gastrointestinal side effects (nausea, constipation, epigastric pain) affect up to 40% of users, leading to extremely poor adherence. Consequently, many women reach term with uncorrected anemia.

The advent of modern intravenous (IV) iron formulations, particularly Ferric Carboxymaltose (FCM), offers a paradigm shift. FCM allows for the rapid administration of high doses (up to 1,000 mg) in a single short infusion without the need for a test dose, bypassing the gut and the hepcidin block. Despite international guidelines advocating for IV iron in the second and third trimesters for moderate-severe anemia, its adoption in primary care settings in Uzbekistan remains inconsistent. This study aims to evaluate the comparative efficacy, safety, and feasibility of shifting from a "oral-first" to an "IV-preferred" strategy for moderate anemia in the pregnant population of Andijan.

LITERATURE REVIEW

Epidemiology and Etiology of Anemia While nutritional iron deficiency accounts for approximately 75% of anemia cases in pregnancy, other etiologies must be considered. In

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Central Asia, folate deficiency and hemoglobinopathies (like thalassemia trait) also contribute. However, the depletion of iron stores (ferritin) remains the primary driver. A study by *Khoshnood et al. (2018)* highlighted that the prevalence of anemia in Central Asian countries has not significantly declined despite mandatory flour fortification programs, suggesting that dietary interventions alone are insufficient to meet the high demands of pregnancy.

Pathophysiology - The Role of Hepcidin Understanding iron homeostasis is key to modern treatment. Iron absorption is controlled by hepcidin, which degrades the iron exporter ferroportin in enterocytes. During the first trimester, hepcidin levels are naturally low to facilitate absorption. However, in the second and third trimesters, or in the presence of even low-grade inflammation (e.g., urinary tract infections, obesity), hepcidin levels may rise, effectively locking the door to oral iron absorption. *Bain et al. (2012)* demonstrated that increasing the dose of oral iron triggers a hepcidin surge that blocks absorption for the next 24 hours, suggesting that traditional twice-daily dosing might be counterproductive compared to alternate-day dosing or IV administration.

Limitations of Oral Iron Therapy Oral iron (ferrous salts) has been the standard of care for decades. However, its effectiveness is strictly limited by biology and behavior. Biologically, the gut can only absorb a few milligrams of iron per day. Behaviorally, adherence is a major barrier. A systematic review by *Tolkien et al. (2015)* found that gastrointestinal side effects occur in up to 70% of patients taking ferrous sulfate. In the context of pregnancy nausea (morning sickness) or mechanical compression of the stomach in the third trimester, these side effects often lead to treatment discontinuation. This results in "therapeutic failure," where the patient is prescribed iron but remains anemic at delivery.

Intravenous Iron: From Dextran to Carboxymaltose Historically, IV iron (High-Molecular-Weight Iron Dextran) was associated with a high risk of anaphylactic reactions, leading to hesitation among clinicians. However, the landscape has changed with the development of "Type I" complexes like Iron Sucrose and Ferric Carboxymaltose (FCM). These newer formulations have a carbohydrate shell that tightly binds the iron, releasing it slowly to the reticuloendothelial system and minimizing the release of free toxic iron.

Ferric Carboxymaltose (FCM): This is a robust, stable complex that allows for the administration of large doses (500-1000 mg) in 15 minutes. The *FER-ASAP trial (Breymann et al., 2017)*, a multicenter randomized controlled trial, showed that FCM was significantly superior to oral iron in increasing Hb levels and correcting ferritin stores, with a safety profile comparable to placebo.

Safety Profile: Current data suggests that the risk of serious hypersensitivity reactions with FCM is extremely low (<1:100,000). Unlike Iron Sucrose, which requires multiple slow infusions over several days to deliver a full dose, FCM supports a "single-visit" correction approach, which is logistically superior for patients in rural areas of Andijan who may have difficulty attending frequent clinic appointments.

Guidelines and Gaps International guidelines (e.g., UK Guidelines on the Management of Iron Deficiency in Pregnancy, 2020) now recommend considering IV iron for women who present with anemia after 34 weeks, or those who are non-compliant/intolerant to oral iron at any stage. However, local protocols often lag, reserving IV iron only for severe cases (Hb <70 g/L). This study seeks to provide the local evidence base required to update these protocols for broader use in moderate anemia.

MATERIALS AND METHODS

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Study Design and Setting A prospective, randomized, open-label clinical trial was conducted at the Andijan Regional Perinatal Center and District Polyclinics (2023-2024). Participants 160 pregnant women (gestational age 24-32 weeks) diagnosed with moderate IDA were enrolled.
Inclusion Criteria: Singleton pregnancy, Hb 70-99 g/L, Serum Ferritin <30 µg/L.
Exclusion Criteria: Anemia of other etiologies (B12/Folate deficiency, Thalassemia), history of anaphylaxis to iron, active infection (CRP >10 mg/L).
Group A (Oral Iron, n=80): Prescribed Ferrous Sulfate 325 mg (100 mg elemental iron) twice daily. Compliance was monitored via pill counts.
Group B (IV Iron, n=80): Received Ferric Carboxymaltose (FCM). The total iron deficit was calculated using the Ganzoni formula:

$$TotalIronDeficit[mg] = Weight[kg] \times (TargetHb - ActualHb)[g/dL] \times 2.4 + 500$$

FCM was administered as a single dose (up to 1000 mg) or two divided doses over 15 minutes.
Monitoring Blood counts and ferritin levels were checked at baseline, 2 weeks, 4 weeks, and pre-delivery.

RESULTS

Hematological Response Group B (IV Iron) demonstrated a rapid and robust response.

Table 1: Changes in Hematological Parameters (Mean ± SD)

Parameter	Timepoint	Group A (Oral)	Group B (IV FCM)	P-value
Hemoglobin (g/L)	Baseline	84.5 ± 5.2	83.9 ± 4.8	0.45
	Week 2	89.1 ± 6.1	102.4 ± 5.5	<0.001
	Week 4	96.5 ± 7.2	112.8 ± 6.0	<0.001
Ferritin (µg/L)	Baseline	12.4 ± 4.5	11.9 ± 3.8	0.52
	Week 4	28.5 ± 12.1	145.6 ± 45.2	<0.001

By Week 4, 85% of women in Group B achieved the target Hb (>110 g/L), compared to only 32% in Group A.
Safety and Compliance In Group A, 28 women (35%) reported significant gastrointestinal distress. 12 women (15%) discontinued treatment or took less than 50% of the prescribed dose. In contrast, Group B reported zero GI side effects. Minor injection site reactions occurred in 2 cases (2.5%). No serious adverse events (anaphylaxis) were recorded.
Perinatal Outcomes Although the study was not powered for neonatal outcomes, the rate of blood transfusion at delivery was significantly lower in Group B (1.2% vs 6.2% in Group A).

DISCUSSION

The study results highlight the limitations of the traditional "oral iron for everyone" approach in the context of the Andijan region. Many women present with anemia late in pregnancy (late 2nd/3rd trimester). In this timeframe, oral iron works too slowly to replenish stores before delivery. The rate of Hb rise in the oral group (approx. 0.3 g/dL per week) is insufficient for a woman starting with an Hb of 80 g/L at 32 weeks.
In contrast, IV Ferric Carboxymaltose utilized the bone marrow's maximal capacity for erythropoiesis, raising Hb by nearly 3.0 g/dL in 4 weeks. Crucially, it replenished ferritin stores.

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This "iron bank" is vital for the fetus and protects the mother from postpartum fatigue and depression.
The economic argument against IV iron (high cost of the drug) is often countered by the reduction in hospitalizations, blood transfusions, and the hidden costs of treating complications of prematurity and maternal morbidity.

CONCLUSION

Modern obstetric care must move towards individualized anemia management based on gestational age and severity.
IV iron is the treatment of choice for moderate-severe anemia in the 3rd trimester due to rapid efficacy.
Diagnosis must include ferritin testing to distinguish true deficiency and monitor store replenishment.
Modern IV formulations are safe and well-tolerated, overcoming the compliance barrier of oral iron.
Establish Ferritin screening as a mandatory part of the first antenatal visit.
Revise local protocols to recommend IV iron as first-line therapy for Hb <90 g/L after 14 weeks gestation.

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