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ABOUT COVER

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EDITORIAL

Use of iron in perinatal anaemia: Indications for women's health care policies and procedure

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Abstract

This paper reviews management of obstetric anaemia and the role of intravenous iron for the treatment of obstetric anaemia. Red blood cell transfusions are routinely used for haemoglobin restoration in anaemic women. The decision for red blood cell transfusion is made on a combination of haemoglobin level and clinical status, and it is suggested that transfusions are not necessary in those who are well compensated or when alternative therapy is available. To reduce the risk, intravenous iron infusion is proposed as a bloodless therapeutic approach. There are a variety of iron preparations. Intravenous iron infusion can reduce the requirement for blood transfusion in hemodynamically stable women with perinatal anaemia, especially in resource-scarce settings. It a cost-effective bloodless approach for the treatment of anaemia than can enhance patient outcomes. According to the literature, when haemoglobin is greater than 90 g/L, blood transfusion is not often required. In perinatal women with anaemia, the decision whether to administer blood or iron is based on patient preferences, haemoglobin levels, clinical symptoms, past and present medical conditions and the clinician's

judgement. Nevertheless, due to the lack of rigid criteria for blood transfusions in the majority of clinical settings, it is considered the default treatment for anaemia in perinatal women.

Key Words: Anaemia; Blood transfusion; Iron deficiency; Iron infusion; Postpartum haemorrhage; Pregnancy

Core Tip: Red blood cell (RBC) transfusions are routinely used for haemoglobin (Hb) restoration in anaemic women. However, unnecessary RBC transfusion is associated with adverse outcomes. Obstetrics patient blood management guidelines aims to reduce the use of RBC through utilisation of iron. Iron preparations can improve haematological parameters including Hb and ferritin. Iron infusion is a cost-effective bloodless approach for the treatment of anaemia.

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INTRODUCTION

Perinatal anaemia is a common health condition among women of reproductive age and is a public health concern[1]. The most common cause of anaemia is depletion of iron stores due to inability to maintain the balance between uptake and utilisation. Iron deficiency reduces the erythropoietic system followed by a reduction in haemoglobin levels and subsequent anaemia. Pregnancy-induced haemorrhage and birth-related haemorrhage are some of the risk factors[2].

Improvement of anaemia can alleviate the physical and psychological symptoms of anaemia and prevent or decrease the likelihood of obstetric morbidity and mortality[3]. For many years, the most common therapeutic approach to correct the obstetric anaemia has been blood transfusion. The use of blood transfusion during the coronavirus disease 2019 pandemic has, however, indicated that the obstetric emergency practice is not well-prepared to prevent the shortage of blood products for perinatal women who need correction of their anaemia. The gap the pandemic has revealed indicates the need to implement innovative approaches to protect obstetric patients from the side effects of the anaemia, such as intravenous iron infusion[4]. This paper reviews management of obstetric anaemia and the role of intravenous iron for the treatment of obstetric anaemia.

Antenatal anaemia

Antenatal anaemia is diagnosed when haemoglobin (Hb) is less than 110 g/L in the first trimester and less than 105 g/L in the second and third trimesters. There are a variety of reasons for antenatal anaemia one of which is due to iron deficiency. It is defined as severe if the ferritin level is less than 30 g/L or mild-moderate when the ferritin level is between 30-100 g/L[5]. Maternal iron demand is increased during pregnancy. Reasons are a rise in maternal plasma and blood volumes, the metabolic and oxygen delivery needs of the fetus, and large iron storage in placenta[6].

In high-income countries, annually 25% of pregnant women are diagnosed with anaemia[7]. In developing countries, antenatal anaemia ranges between 46% in urban areas and 52% in rural areas. Anaemia contributes to 20%-40% of maternal deaths in India and 80% of maternal deaths in South Asia[8,9]. In South Africa, the prevalence of anaemia among women of reproductive age is 22% to 44%, and the prevalence of antenatal anaemia is 29% to 42.7%[10]. A study from India reported that 68% of women who became pregnant during 2018-2019 had anaemia, out of whom 72.3% had mild anaemia, 24.6% had moderate anaemia and 8% had severe anaemia[11].

While anaemia can be resulted from various factors such as deficiency in vitamin B12 and folate, inflammation, infection and hemoglobinopathies[9], almost half of the antenatal anaemia is suggested to be due to iron deficiency, with various proportions among different population groups and regions[12]. The rate of antenatal iron-deficiency anaemia has been reported to be 6.9% in the first, 14.3% second and 28.4% in the third trimester of pregnancy[13].

Antenatal anaemia can cause or exacerbate maternal complications and increase perinatal morbidity and mortality. It can also result in fetal complications, such as premature birth, low birth weight, intrauterine growth restriction and neonatal mortality. A study from Northern Tanzania reported that out of 18% of pregnant women with anaemia, 10 women had stillbirths, 16 delivered low birth weight newborns, and two of them has preterm births[14]. Women who have anaemia during pregnancy are less likely to cope with childbirth-related haemorrhage and are more likely to contract infection or experience severe anaemia after birth[9]. According to the World Health Organization, iron-deficiency anaemia is responsible for more than one million maternal deaths globally each year[15].

Postpartum anaemia

Postpartum anaemia is usually diagnosed when the Hb is less than 100 g/L within 24 to 48 h after childbirth. Other recommendations define postpartum anaemia as a Hb less than 110 g/L at 7 d and less than 120 g/L at 8 wk postpartum [16,17]. Persistent postpartum anaemia in clinically stable women is a common complication of childbirth. The resultant

anaemia is principally iron deficient and is usually related to the degree of postpartum blood loss. Postpartum haemorrhage (PPH) occurs in 6.3% of all childbirths and is one of the primary causes of maternal mortality and morbidity [18]. Traditionally, PPH was defined as a blood loss of greater than or equal to 500 mL within the first 24 h after birth. A more recent definition of PPH indicates as bleeding of greater than 1000 mL. Persistent PPH is ongoing active bleeding of more than 1000 mL within 24 h after birth that continues despite the administration of initial treatments with uterotonic medications and uterine massage[19]. According to a recent large population-based study, the rate of PPH is 3.2%, 10.5% and 10.2% for low-, medium- and high-risk women, respectively[20]. Another clinical trial investigating maternal mortality in 20060 women with PPH after childbirth (including both vaginal birth and caesarean section), from 193 hospitals in 21 countries between 2010 and 2016[21] reported a maternal mortality rate of 3% in Africa and 1.7% in Asia.

PPH exceeding 500 mL is most commonly associated with moderate anaemia (Hb 90-100 g/L) and in some women is accompanied with severe anaemia (Hb ≤ 80 g/L)[22]. Postpartum haemorrhage and anaemia together account for 20% of maternal morbidity and mortality worldwide and the incidence is higher in developing countries than developed countries[16,22].

A study on women in Spain showed that almost 1 out of 3 childbearing women, or 29%, suffered from postpartum anaemia (Hb < 100 g/L) during the first 48 h after birth[23]. Another study showed that out of 2990 women who had vaginal birth, 45% had Hb < 11 g/dL, and 7.1% had Hb < 9 g/dL after birth[24]. Similarly, a study from northwest Ethiopia showed that postpartum anaemia occurred in 24.3% of women. This study also showed significant association between anaemia and less frequent antenatal care (less than 4 visits during pregnancy), antepartum haemorrhage, postpartum haemorrhage, instrumental birth and poor adherence to iron treatment during pregnancy[25]. Secondary analysis of multi-country data from Pakistan, Burkina Faso, Egypt, Turkey, Vietnam and Ecuador showed that postpartum anaemia occurs in 31% to 71% of women after birth. Higher prevalence of postpartum anaemia was also noted among women in Saudi Arabia (59%)[26] and in an Indonesian regency (60%)[27].

Acute anaemia manifests with fatigue, feeling ill, lethargy, decreased mental alertness, poor mental performance, physical weakness, disturbed cognition and emotion and difficulty with breastfeeding[28]. These symptoms interfere with a woman's ability to care for her newborn and may in turn impose negatively on the cognitive and behavioural development of the infant, and the woman's quality of life[29,30]. Women with anaemia are at a greater risk of postpartum depression, despite being of high socioeconomic status[29]. Severe postpartum anaemia (defined as Hb < 70 g/L) has been reported to be related to maternal death after birth[31].

MANAGEMENT OF OBSTETRIC ANAEMIA

Red blood cell transfusion

The standard approach for treating mild to moderate anaemia after PPH is the use of oral iron supplements, which help restore Hb and pre-pregnancy iron stores by 3 to 6 wk postpartum. The efficiency of oral treatment is slow because of limited gastrointestinal absorption, often complicated by poor adherence to treatment by the patients[29]. For women with severe PPH and symptomatic anaemia who require immediate Hb correction to increase tissue oxygen-carrying capacity, it is common to administer red blood cell (RBC) transfusions[32].

RBC transfusions are also used for Hb restoration in both emergency cases and other haemodynamically stable women. This facilitates early discharge and reduces clinician anxiety that patients will become unstable post-discharge or be lost to follow up[32]. However, the validity of this practice is not well-defined in the literature, and it is largely clinician-dependent[33]. According to Munoz *et al*[29], in the absence of active postpartum bleeding, RBC transfusion can be considered in women with a Hb of less than 60 g/L while taking clinical signs and symptoms into consideration.

Existing guidelines suggest that blood transfusion when Hb is between 70 g/L and 90 g/L is not associated with reduced mortality in haemodynamically stable women. Thus, the decision to commence RBC transfusion should be based on the need to relieve clinical signs and symptoms of anaemia and to prevent significant morbidity and mortality. The National Blood Authority of Australia and New Zealand recommends that a decision for transfusion be made on a combination of Hb level and clinical status, suggesting transfusions are likely to be appropriate in all patients with a Hb less than 70 g/L but not necessarily in those who are haemodynamically stable and well compensated, or when alternative therapy is available[34].

Despite the life-saving benefits of RBC transfusion in women with severe PPH, administration of RBC is not without a risk. These include transmission of blood-born infections, blood group mismatch, transfusion-associated circulatory overload, ischaemic events, multiple organ failure and acute lung damage[29]. Also, large observational studies show that transfusion is independently associated with higher mortality and morbidity, including septicaemia, severe haematological reaction, delayed wound healing and thromboembolism. These adverse outcomes occur in a dose-dependent fashion and are particularly concerning for the postpartum patient who may receive multiple transfusions[35]. The use of RBC transfusion has also been suggested to be an independent risk factor for postpartum thrombosis, followed by a longer length of hospital stay and a higher risk of admission to the intensive care unit[36,37]. The long-term benefits of RBC transfusion in postpartum women have not been established. High cost and resource scarcity are other practical considerations favouring the limitation of RBC transfusions[33]. While it is recommended that the use of RBC transfusion should be considered only when the advantages outweigh the risks, there is no clear recommendation for alternative therapies[33,38].

Patient blood management

Current management of haemodynamically stable women with acute postpartum anaemia remains highly variable. No

guideline or consensus exists to inform clinicians about exactly when to commence RBC transfusion and how to avoid the inherent risks associated with this practice. Several arguments support the limitation of RBC transfusions in stable women with postpartum anaemia. Consideration of alternative therapies to RBC transfusion in postpartum women is therefore entirely appropriate and is well aligned with the 2010 World Health Assembly resolution, which recognises the need for an international patient blood management scheme to limit the use of blood products on a global scale[33], and the 2017 World Health Assembly resolution, which also recognises the need to limit the use of blood products globally [15].

In 2005, an Australian haematologist, Prof. Isbister, recommended changing the focus of treatment away from transfusion of blood products to patients[39]. Subsequently, obstetrics patient blood management guidelines were developed in 2015 aiming for: (1) Timely identification and treatment of anaemia before or during pregnancy, (2) minimisation of peripartum blood loss, and (3) reduction of RBC administration through adequate hydration or volume replacement, infection treatment, infusion of iron replacement and finally RBC transfusion in accordance with best practice guidelines[34]. Successful blood management results in a faster recovery and less postoperative complications, hospital mortality and nosocomial infections in patients, and a shorter length of hospital stay[40,41]. A study from South Australia showed that maternity patient blood management and Clinical Practice Improvement can clinically optimise antenatal haemoglobin, and reduce the risk of pre-birth anaemia and subsequent blood transfusion[42]. Despite these, effective patient blood management has been practiced only in a few countries and its global implementation is significantly slow, driven by cultural behaviours and religious beliefs rather than scientific evidence[43,44].

Alternative therapy

Obstetrics is a clinical field with a substantially heightened morbidity and mortality rate in women who do not receive blood transfusions due to the unavailability of blood products or the patient's refusal to receive blood[44]. An observational study of obstetric outcome of women from the Jehovah's Witnesses over a 53-year period reported fifteen maternal deaths from haemorrhage due to the refusal to receive RBC[45].

While unnecessary RBC transfusion is associated with some adverse outcomes, not receiving treatment can be life-threatening[29]. Therefore, intravenous iron infusion has been proposed as a bloodless therapeutic approach. It has been shown to reduce the requirement for blood transfusion in a number of obstetric[3] and non-obstetric scenarios[46] and enhance patient outcomes[3].

INTRAVENOUS IRON PREPARATIONS FOR TREATMENT OF OBSTETRIC ANAEMIA

Until July 1999, high molecular-weight iron dextran (Dexferrum®) was the only available intravenous iron preparation. However, this formula is no longer available due to severe sensitivity reactions[47]. During recent decades, newer formulations of intravenous iron have been introduced for the treatment of anaemia with favourable results. Current intravenous iron preparations are iron sucrose, iron carboxymaltose, iron dextran, iron polymaltose, iron isomaltoside, ferumoxytol and sodium ferric gluconate (Table 1)[48]. These preparations are available worldwide. For example, ferumoxytol has been approved to be used only in the United States, and has been used mainly in studies of pregnant women and other non-obstetrics patients. Research on the efficacy and safety of ferumoxytol for the treatment of postpartum anaemia after PPH is scarce[49]. Iron isomaltoside has approval for administration in Europe only[50]. Three approved preparations of intravenous iron for use in Australia are ferric carboxymaltose (Ferinject®), iron polymaltose (Ferrosig®) and iron sucrose (Venofer®). Venofer® is used mainly for treating iron deficiency anaemia in patients with chronic haemodialysis or those on supplemental erythropoietin therapy. In cases when oral therapy is contraindicated or the patient is non-compliant or has persistent gastrointestinal intolerance, Ferrosig® is the most suitable treatment. Ferinject® is used when oral iron supplements are ineffective or the patient needs to rapidly receive iron supplement[51].

Calculating the required dose of iron for intravenous infusion

The total iron deficit for each patient is the collective dose of iron required to replenish iron stores in the body. It is different from the iron product's admissible dose per infusion. The required cumulative dose of the preferred iron preparation is calculated using two methods: (1) The Ganzoni formula[52], and (2) The simplified method[53]. Both methods are based on the patient's Hb and body weight.

Ganzoni formula

Total body iron deficit/cumulative iron dose (mg) = body weight (Kg) x (target Hb – actual Hb in g/L) x 0.24 + iron store (mg)[52].

'Body weight' for overweight patients is their ideal body weight, and for underweight patients is their actual body weight. The 'iron store' is 15 mg/Kg body weight for women whose weight is less than 35 Kg, and 500 mg for women who weigh greater than or equal to 35 Kg. Target Hb is generally considered as 150 g/L. For example, to calculate the iron deficit of a 65 Kg woman with Hb of 79 g/L:

765 × (150 – 79) × 0.24 + 500 = 1795 mg (usually rounded to approximately 1800 mg)

Clinicians need to remember that the target Hb may be different in various patient populations. According to the UK guidelines on the management of iron deficiency[30]:

"Parenteral iron should be considered from the 2nd trimester onwards and postpartum period in women with iron deficiency anaemia who fail to respond to or are intolerant of oral iron. The dose of parenteral iron should be calculated on the basis of pre-pregnancy weight, aiming for a target Hb of 110 g/L. The choice of parenteral iron preparation should

Table 1 Intravenous iron preparations

Name	Components	Trade name	Maximum dose and metabolism	Administration	Side effects	Contraindications and precautions
Iron sucrose[30,51,76,77]	Polynuclear iron (III) hydroxide in sucrose. Dose of elemental iron = 20 mg/mL	Venofer®	Maximum dose for a single infusion is 300 mg. The infusion can be repeated up to 3 times per week. After administration, it reaches peak level at 10 min after infusion. Half-life is about 6-20 h	Test dose is required if drug allergies present, only for the first dose administration and only in new patients. Intravenous infusion should be given within at least 15 min	Anaphylaxis phlebitis; Pain and swelling in the infusion area; Constipation; Blurred vision; Headache; Pruritus and rash; Drowsiness; Metallic taste; Slow or fast heartbeat; Sweating; Tingling of the hands or feet; Unusual tiredness or weakness	First trimester of pregnancy; Hypersensitivity to iron sucrose; Anaemia not caused by iron deficiency; Iron overload; Known or genetic tendency to haemochromatosis; Lactation (insufficient data)
Iron dextran[30,78]	Ferric hydroxide or ferric oxyhydroxide combined with partially hydrolysed low molecular-weight dextran; Dose of elemental iron = 50 mg/mL	INFeD® (IV or IM use); Cosmofer® (low molecular weight – both IV and IM routes of administration)	The intravenous dose is 100-200 mg (or 20 mg/kg), administered ≤ 3 times per week. Reticulocytosis may begin by 4th day after the intravenous infusion of the total dose. Peak level Reaches a maximum by about 10th day. Half-life is about 5-30 h	Test dose is required before every intravenous administration. Intravenous infusion should be given within 4-6 h. Intramuscular injection of 100 Cosmofer can be injected into alternate buttocks ≤ 3 times per week	Anaphylaxis; Arthralgia; Chills; Dizziness; Fever; Headache; Malaise; Myalgia; Metallic taste; Pain and swelling in the infusion area; Low blood pressure	Heart disease; Liver disease; Kidney disease; Rheumatoid arthritis; Bleeding or blood clotting disorder; Stomach bleeding; Asthma or allergies; Allergy; Using a beta-blocker medicine; Pregnancy
Iron polymaltose[57,79]	Iron (III) –hydroxide (trivalent iron, Fe3+) with the carrier polymaltose	FerrumH®; Ferrosig®	Each 2 mL ampoule contains 318 mg iron polymaltose equivalent to 100 mg iron III (50 mg per mL). It is used for postnatal women when the required dose of iron is > 1000 mg. Average total dose of iron polymaltose infusion is usually between 1000-2500 mg for adults. Maximum dose for a single infusion is 2500 mg	Total dose is administered within 5 h; The first 50 mL should be administered slowly (5-10 drops/min); The intravenous preparation should not be mixed with any other medication	Anaphylaxis; Itching; Mild erythematous or urticarial rash; Lower quadrant abdominal pain; Dizziness; Chest and back pain; Occasional arrhythmias; Dyspnoea; Flushing; Sweating; Injection/infusion site pain	First trimester of pregnancy; Iron overload; Chronic polyarthritis; Acute renal infection; Uncontrolled hyperparathyroidism; Hepatic cirrhosis; Infectious hepatitis; Liver infection; Bronchial asthma; Anaemia not caused by iron deficiency (*i.e.* microcytic anaemia); Iron overload; Anaemia not caused by iron deficiency (*i.e.* microcytic anaemia); Iron overload; Lactation (no data available)
Iron carboxymaltose[30,51,80]	Ferric carboxymaltose. Dose of elemental iron = 50 mg/mL.	Ferinject®; Ferrosig®	Each vial contains 50 mg/mL Ferric carboxymaltose and they come as 2 mL (100 mg) or 10 mL (500 mg) vials. Maximum dose for a single infusion for patients ≥ 35 kg is 1000 mg/wk, or a maximum of 15 mg/kg/wk can be administered. Administered IV dose is 1000 mg or up to 15 mg/kg/wk. Half-life is about 7-12 h	Test dose is not required before intravenous administration. It is administered within 30-45 min	Anaphylaxis (rare); Headache; Gastrointestinal symptoms; Nausea; Rash; Injection/infusion site reactions; Hypophosphataemia; Flushing; Dizziness; Hypertension	Anaemia not caused by iron deficiency (*i.e.* microcytic anaemia); Iron overload; Acute or chronic infection; Asthma; Eczema; Atopic allergies; Liver dysfunction; Children under 14 yr
Iron isomaltoside[30]	Dose of elemental iron (ferric derisomaltose) = 100 mg/mL	Monofer®	Administered IV dose is 100-200 mg up to 3 times a week. Half-life is about 1-4 d	Test dose is not required before intravenous administration. Doses up to 10 mg/Kg should be administered within at least 30 min. Doses larger than 10 mg/kg should be administered within at least one hour	Anaphylaxis; Infusion site complications; Myalgia; Phlebitis; Headache; Tachycardia; Hypotension; Hypertension; Chest pain; Dyspnoea; Bronchospasm; Abdominal pain; Vomiting; Dyspepsia; Constipation; Diarrhoea; Hypophosphataemia	Hypersensitivity to ferric substances; Non-iron deficiency anaemia; Iron overload; Unavailability of resuscitation facility; Liver dysfunction; Chronic infection; Asthma; Eczema; Atopic allergies; Ongoing bacteraemia; First trimester of pregnancy; Lactation (no data available)
Ferumoxytol[81]	Superparamagnetic iron	Feraheme®	Maximum dose for a single infusion	510 mg Ferumoxytol is	Anaphylaxis; Abdominal pain;	Hypersensitivity to ferric substances; Iron

	oxide comound linked to polyglucose sorbitol carboxy-methylether; Dose of elemental iron = 30 mg/mL		is 510 mg	Administered over within 15-30 min. Second dose of 510 mg is administered approximately one week later	Headache; Blurred vision; Confusion; Fever; Flush; Chest tightness; Back pain; Nausea; Nasal congestion; Itching; Scratchy throat and cough; Sweating; Hands or feet tingling	overload syndrome; Low blood pressure; Non-iron deficiency anaemia; Hypotension; MRI study; First trimester of pregnancy; Lactation (no data available)
Iron gluconate [48]	Dose of elemental iron = 12.5 mg/mL with Benxyl alcohol as preservative	Ferrlecit®	Maximum dose for a single infusion is 125 mg. Half-life is 1 h	Test dose is required if drug allergies present	Allergic reaction; Rash; Itching; Swelling; Severe dizziness; Difficulty breathing; Nausea; Vomiting; Diarrhoea; Loss of appetite; Stomach pain; Leg cramps; Swelling of extremities; Headache	Allery; Iron overload syndrome; Haemolytic anaemia; Ulcerative colitis; Stomach ulcers; Thalassemia; Receiving regular blood transfusions; First trimester of pregnancy; Lactation (no data available)

be based on local facilities, taking into consideration not only drug costs but also facilities and staff required for administration[13,30]".

Simplified method: Based on clinical practice and the published Australian drug guidelines[51,54], a simplified method that takes the Hb level and patient's weight into consideration can be used to estimate the required dose of iron to provide body iron stores. Similar to the Ganzoni formula, for overweight patients their ideal body weight should be considered when estimating their required dose of iron infusion. However, for underweight patients their actual body weight must be used. It is noteworthy to mention that this simplified method must be used with caution as the data are based on only a single clinical trial in adults with inflammatory bowel disease, whose median Hb was 104 g/L and body weight was greater than or equal to 35 Kg[53].

Efficacy of intravenous iron

The chemical makeup of the currently used iron formulas are all similar in the core but different in the type and size of the carbohydrate part adjacent to the core. That is why their pharmacokinetic and pharmacological properties are unique, and they may cause different adverse outcomes[55]. For example, iron sucrose, iron gluconate and iron isomaltosid require up to 3 visits for the administration of the required dosage in patients who need more than 200-250 mg of iron, due to the high risk of infusion reactions. Compared to other iron preparations, iron sucrose and iron isomaltosid have smaller carbohydrate cores and looser elemental iron binding. This structure increases the likelihood of the labile free iron and the demand for more iron administration as well an increased risk of infection[46,48,56]. Iron dextran and iron carboxymaltose can be administered as a complete single dose of 1000 mg. Iron polymaltose can be administered as a single dose of up to 2500 mg. Compared to other currently used iron products, iron polymaltose is the only established parenteral iron preparation that allows unrestricted maximum single dose administration[57]. All other preparations are limited to smaller single doses or multiple doses over days to weeks due to the potential for toxicity and thrombosis. A single-dosing property is important, as it is convenient and will not unnecessarily prolong postpartum hospital stay. Relatively low free-iron content in the iron polymaltose preparation also limits the potential for bacterial overgrowth thereby preventing infection[57,58]. Despite the comprehensive data evaluating the efficacy of intravenous iron sucrose in the UK, Europe and the US, iron sucrose is not routinely used in some other countries, such as Australia, in the absence of chronic kidney disease or known intolerance to iron polymaltose[57].

Several studies have investigated the effects of intravenous iron preparations; however, their outcomes of interest differed. One study evaluated the effect of iron on maternal fatigue[59], and some others used changes of Hb and haematocrit as their endpoint[60]. The recommendation from many of these studies is that intravenous iron is effective in alleviating symptoms of anaemia. For example, a systematic review and meta-analysis of 22 studies involving 3321

participants with renal, obstetric, surgical, oncology/haematology, cardiology and gastroenterology complications. Nineteen of these studies were randomised controlled trials in which they compared the effect of intravenous iron with either oral iron or no iron supplementation on antenatal and postpartum iron deficiency anemia. Litton *et al*[46] showed that intravenous iron therapy significantly reduced the need for further RBC transfusion. Another systematic review and meta-analysis of 13 studies compared the short-term benefits and safety of oral iron with intravenous iron dextran, iron sucrose and iron gluconate. Findings of this study showed that a non-dextran intravenous iron preparation may be more beneficial to patients compared to an iron-dextran formula. Also, they reported that despite a significant increase in the reticulocyte counts and ferritin stores after iron infusion, there was no significant difference between intravenous and oral iron in increasing Hb or haematocrit[60]. The researchers suggested that further randomised controlled trials are required to establish efficacy of intravenous iron.

However, there is only limited research comparing the effects of iron infusion with blood transfusion in women with acute postpartum haemorrhage and resulting anaemia. In a small randomised trial by Holm *et al*[61] 13 women who had PPH greater than 1000 mL and a Hb of 56 g/L to 81 g/L were randomised to 1500 mg intravenous iron isomaltoside or RBC transfusion. Results of their study showed no significant difference in fatigue or depression symptoms between the study groups. The Hb level was higher on day one in women who received RBC, but it was higher at 3 to 12 wk in women who receive iron infusion. Also, women who receive RBC had lower iron levels compared to the other group. As per the authors conclusion, despite being a small study, it showed that intravenous iron can replace the need for RBC transfusion in postpartum women with severe anaemia.

A number of arguments support the limitation of RBC transfusions in stable women with postpartum anaemia[37], and others have reported the superiority of intravenous iron to oral iron supplements in correcting anaemia symptoms[46, 48]. Some studies have investigated expectant management and intravenous iron as alternative therapies to treat postpartum anaemia in select women. For example, in the WOMB trial[62], 521 women with severe PPH and anaemia were randomised to expectant management (non-intervention) or RBC transfusion with an average of 2 units of RBC transfusion. They reported that women who received RBC transfusion had less fatigue symptoms at day 3 and one week postpartum. In the non-intervention arm, 33 women needed to receive RBC transfusion, due to anaemia symptoms[62].

Adverse outcomes of intravenous iron

While the positive effect of iron infusion on maternal and neonatal outcomes has been well-documented in the literature, a few *in vitro* studies have indicated that iron infusion is not without risks (Table 1)[30]. Research has suggested that administration of intravenous iron may negatively affect the pathophysiology of cellular immunity and exacerbate active infection or may potentiate bacterial growth. Nevertheless, this association remains inconclusive due to a paucity of human data specifically evaluating infection endpoints in patients receiving intravenous iron therapy[63].

Although the majority of the adverse outcomes are minor and self-limiting within a few days after infusion[30], it has been suggested that the risk may increase when iron is infused rapidly, because of the oversaturation of transferrin and the rapid release of free iron. Free iron has been reported to be associated with toxicity, hypersensitivity and vasomotor reactions[41]. The earliest side effects are pruritus or a burning sensation of the tongue. An initial test dose with a small amount of the preparation is warranted in some cases[64]. While some research has not followed the recommended infusion duration and has completed the infusion within a shorter period of time[61], there is no report of anaphylactic reaction after rapid infusion of all types of iron. For example, an interventional study of postpartum women with moderate and severe anaemia (Hb level of 50-99 g/L) showed that administration of 500 mg to 1000 mg iron carboxymaltose over 15 min was not associated with any major adverse events[65].

The risk of anaphylactic reaction is greater with the use of certain forms of iron preparations than others, as mentioned earlier[66,67]. Nevertheless, there are controversial reports in the literature on the safety of each iron preparation. Generally, intravenous iron can create oxidative stress, inflammation, endothelial dysfunction, and in severe cases, cardiovascular and renal damage. It is reported that the risk of these adverse events increases with the use of non-dextran iron. On the other hand, iron dextran, especially high molecular-weight iron Dexferrum®, has been shown to be associated with anaphylactic reactions[64]. A case report showed that iron dextran can cause dextran-induced anaphylactic reaction[66]. In contrast, more recent research that compared hypersensitivity reactions in patients who received ferric carboxymaltose with iron dextran from 2008 to 2017 showed the risk of hypersensitivity reaction was greater in patients that received ferric carboxymaltose than those who received iron dextran[68]. A case study reported the death of a young primigravida with no history of allergy after receiving iron sucrose to treat her severe iron deficiency anaemia[67]. however, the risk of anaphylactic reactions to iron sucrose can be considered rare and consists of generalised pruritus and a burning sensation in the tongue[64].

In a randomised controlled trial on women with postpartum haemorrhage, iron isomaltoside was used to treat fatigue. The study showed that compared to oral iron tablets, the intravenous iron infusion significantly reduced physical fatigue [59]. Iron polymaltose has a very good safety profile with no reported serious adverse effects[57]. However, there is limited data on the safety of other iron preparations used in the treatment of postpartum women. In a recent multicentre, randomised, double blind, placebo-controlled trial[69], the effect of intravenous iron Monofer® on blood indices and quality of life in people with anaemia and advanced cancer was investigated. Results of the study showed that compared to placebo, intravenous iron was more likely to increase haemoglobin and improve quality of life measures.

Adverse outcomes of six iron treatment comparisons were compared in a systematic review of 26 randomised clinical trial and 16 cohort studies involving 6062 patients[70]. The iron comparison included intravenous iron versus oral tablets, intravenous iron *vs* usual care/no iron, intravenous ferric carboxymaltose *vs* intravenous iron sucrose, erythropoiesis-stimulating agent plus iron *vs* control (placebo and/or no treatment), erythropoiesis-stimulating agent plus intravenous iron *vs* erythropoiesis-stimulating agent plus oral iron, and two different dosing regimens of erythropoiesis-stimulating agent plus intravenous iron versus. Results of the review showed that there is uncertainty about adverse outcomes of iron

treatment due to the high risk of bias, limitations in the study design, data collection and reporting.

CAN IRON INFUSION REPLACE BLOOD TRANSFUSION?

RBCs are responsible for supplying oxygen to the body. A low RBC level can cause a decreased oxygenation of the cells followed by undesirable outcomes. After PPH and iron deficiency anaemia, new RBCs cannot be produced quickly to replace older non-functioning RBCs[71]. According to the European Society of Anaesthesiology, in the presence of active haemorrhage, both Hb levels and serum lactate should be measured frequently to evaluate tissue perfusion and oxygenation.

For many years, RBC transfusion has been used as a quick way to increase the Hb level after acute haemorrhage. It provides an immediate treatment when anaemia is sudden and severe, and the patient needs immediate recovery[72]. According to the literature, when Hb is greater than 90 g/L, RBC transfusion is not often required. However, despite the higher costs and risks of RBC transfusion, and due to no rigid criteria for RBC transfusions, it is considered the default treatment for anaemia in postpartum women with acute PPH in the majority of clinical settings[71].

Several studies have attempted to comate the efficacy of iron infusion and blood transfusion in obstetric patients. Hye *et al*[73] from Bangladesh investigated the efficacy of intravenous iron sucrose versus blood transfusion in improving the haematological parameters in 44 hemodynamically stable postpartum women with moderate anaemia. Results of their study showed the use of iron sucrose infusion was as effective as blood transfusion in restoring the haemoglobin and serum ferritin levels at sixth week after the treatment. The researcher suggested that iron could be an efficient alternative to blood transfusion in treating haemodynamically stable women with postpartum anaemia, particularly in resource-scarce settings. Another study from Saudi Arabia[74] compared the effect of iron infusion and blood transfusion on the anaemia of 90 postpartum women. They reported that both groups showed similar increase in their mean Hb and serum ferritin levels after one week post intervention.

RBC transfusion needs to be considered only when Hb is less than 60 g/L or between 70 g/L and 90 g/L accompanied by severe symptoms of anaemia. In postpartum women without active bleeding who are symptomatic, the RBC transfusion should be limited and consist of administration of only one unit of RBC. After further follow-up measurements of Hb level and evaluation of the patient's clinical status, it can be decided whether more RBC transfusion is needed. Haemodynamically stable postpartum women with a Hb below 60 g/L or between 60 g/L and 80 g/L do not normally require RBC transfusion and can be managed by alternative treatments, such as iron infusion. The decision to opt for RBC transfusion or iron infusion in these women is made based on patient preferences, Hb levels, clinical symptoms, past and present medical conditions, lactation status and the clinician's judgement of the patient's current situation[71]. Haemodynamically stable women with a Hb of 80 g/L or above rarely need RBC transfusion. In the majority of these cases, RBC transfusion can be avoided, and replaced with intravenous iron infusion for a rapid recovery of Hb levels and mitigation of clinical symptoms[75].

Implications for the profession and/or patient care

Obstetrics patient blood management guidelines aims to reduce the use of RBC. Adherence to these guidelines and the sue of iron infusion as a bloodless approach can optimise health outcomes for the patients and alleviate the burden of unnecessary blood use in the healthcare system. However, once size does not fit all. Hospital protocols on iron infusion need to provide appropriate recommendations related to best practice for the safe intravenous infusion of iron. Nurses, midwives and other clinicians providing care to perinatal women need to be well-informed about features of different types of iron preparations, their indications and contraindications and their potential side effects on the mother and her unborn baby (when administered during pregnancy).

What does this paper contribute to the wider global clinical community?

Unnecessary RBC transfusion is associated with adverse outcomes. Obstetrics patient blood management guidelines aims to reduce the use of RBC. Iron infusion is a bloodless approach for the treatment of anaemia and can improve haematological parameters including Hb and ferritin.

CONCLUSION

Obstetric anaemia is an important condition, associated with potentially debilitating symptoms, that negatively affects women's health and experience of motherhood. Wide practice variations exist in the management of stable perinatal women with anaemia and blood products continue to be overused in some settings. Despite the effectiveness of RBC transfusion, its high cost, scarcity and potential risks or side effects necessitate seeking alternative treatments. Intravenous iron infusion has been proposed as a bloodless therapeutic approach in perinatal women with anaemia and has been shown to reduce the requirement for blood transfusion.

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CASE REPORT

Atypical eclampsia at primary health care in a remote area: A case report

Rifka Wangiana Yulia Putri, Rifda El Mahroos

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Abstract

BACKGROUND

Eclampsia is a generalized tonic-clonic seizure induced by pregnancy. It contributes to a high rate of maternal and neonatal morbidity and mortality worldwide. Eclampsia is characterised by classic signs such as elevated blood pressure, proteinuria, and seizures. However, it may occur in the absence of hypertension and/or proteinuria. The uncommon appearance of eclampsia makes it difficult to immediately assess and treat it. In addition, the occurrence of this case in a remote area makes it more challenging to handle. The objective of this case report is to increase awareness of uncommon manifestations of eclampsia, particularly in limited-resource settings.

CASE SUMMARY

A young primigravida experienced a generalised seizure without hypertension and/or proteinuria. Sudden hearing loss, blurred vision, and vomiting were complained about before the seizure attack. The patient was diagnosed with eclampsia. A loading dose of magnesium sulphate was administered immediately. The patient was referred from community healthcare to a hospital and discharged without any complications.

CONCLUSION

Atypical eclampsia may be a diagnostic challenge. However, other symptoms may be beneficial, such as awareness of eclampsia signs.

Key Words: Atypical eclampsia; Eclampsia; Hypertension-induced pregnancy; Case report

Core Tip: Generalized seizures are the hallmark of eclampsia, along with high blood pressure and proteinuria. However, in some women, eclampsia could develop in the absence of proteinuria and hypertension. A seizure in pregnancy without hypertension and/or proteinuria is considered atypical eclampsia. Here, we report an atypical presentation of eclampsia, the generalised seizure without prior hypertension and proteinuria, experienced by a young primigravida in a primary healthcare centre located in a remote area. We found neurological disturbances and gastrointestinal symptoms were present as impending eclampsia symptoms. Magnesium sulphate is administered as the first line of eclampsia treatment.

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INTRODUCTION

Eclampsia is an emergency obstetric complication that is characterised by seizures accompanied by hypertension and proteinuria that occur during antepartum (over 20 wk of gestation), intrapartum, or postpartum (48 h post-delivery) and can lead to maternal morbidity and death[1]. In a rare case, eclampsia can present as atypical, which refers to eclamptic seizures that happen without usual high blood pressure (BP) or proteinuria. A seizure that occurs < 20 wk after gestation or > 48 h after childbirth is another atypical feature of eclampsia[2].

Rural and remote communities often encounter more healthcare barriers that limit their access to the necessary healthcare services they need. Poor access to advanced healthcare facilities and limited resources in primary healthcare centres are two main reasons for inadequate healthcare delivery. Furthermore, this became a challenge for healthcare providers in order to provide appropriate diagnosis and treatment. Raising awareness of the uncommon presentation of eclampsia may enhance clinical management, especially in rural areas and other limited-resource primary healthcare services.

CASE PRESENTATION

Chief complaints

A 22-year-old, 39-wk-old primigravida (G1P0A0) Asian woman complained of vomiting followed by sudden visual and hearing disturbances, and a generalised seizure.

History of present illness

A young nulliparous woman was admitted to the primary healthcare centre due to true labour clinical manifestations, regular contractions, and a small amount of blood and mucus released from the vagina. During stage 2 of labour, an episodic tonic-clonic seizure was present for around 1 min. Sudden visual disturbances, vomiting, and hearing disturbances were complained about by the patient immediately before the seizure.

History of past illness

The patient had no history of seizures or hypertension before pregnancy and/or during antenatal care. Our patient had no past head trauma or illnesses such as hypertension, epilepsy, metabolic diseases, autoimmune disease, infection, stroke, severe headache, or cancer. A history of medication was also denied. The patient had routine antenatal care in a primary healthcare facility and vaccination for tetanus and coronavirus disease 2019. The patient's general conditions, vital signs, proteinuria, weight gain, and foetal conditions were examined through regular antenatal visits and showed no abnormalities.

Personal and family history

Relevant personal and family histories were denied. Family history of seizure, hypertension, eclampsia, and pre-eclampsia were absent.

Physical examination

At stage 1 of labour, the normal-weight patient was conscious and in good general condition; thus, a physical examination was performed. On admission, it was reported that her supine blood pressure (BP) was 112/70 mmHg, heart rate (HR) 76 beats/min, respiratory rate (RR) 20 breaths/min, temperature 36.8°C, and oxygen saturation 98% in room air. Cephalic proportion, normoregular foetal HR, 1 cm cervical dilatation, and adequate uterine contraction were also reported. Extremity and lung oedema manifestations were absent. Other physical examinations were normal. Vital signs, progress of labour, and foetal HR were monitored every 4 h. During monitoring, the partograph curve and vital signs were within normal ranges. Systolic BP was 110-124 mmHg, and diastolic BP was 72-80 mmHg.

The patient experienced a prolonged second stage of labour due to inadequate power, thus complaining of vomiting, blurred vision, and hearing disturbances followed immediately by a tonic-clonic seizure. Vital signs and foetal HR were re-evaluated. The latest supine BP was 128/72 mmHg, HR 80 beats/min, RR 18 breaths/min, temperature 36.9°C, and oxygen saturation 96% in room air. We found no abnormalities on physical and neurological examinations.

Laboratory examinations

This case was first found in a limited-resource primary healthcare setting where there was no laboratory facility, so only simple traditional laboratory examinations could be performed through strip tests. Stick haemoglobin 12.8 g/dL, stick random blood glucose 110 mg/dL, negative rapid test human immunodeficiency virus, and negative proteinuria (dipstick) were reported.

Imaging examinations

Imaging examinations such as brain magnetic resonance imaging (MRI) and brain computed tomography (CT) scan could not be performed because of absence of equipment.

MULTIDISCIPLINARY EXPERT CONSULTATION

Susanto Rahmad, MD, obstetrician and gynaecologist.

FINAL DIAGNOSIS

Eclampsia in primigravida patient.

TREATMENT

Treatment with 4 g intravenous $MgSO_4$ was given immediately as a loading dose, followed by 2 g intravenous $MgSO_4$ dissolved in 500 mL crystalloid (normal saline) at a rate of 28 drops/min. A urine catheter and 3 L/min oxygen *via* nasal cannula were administered. We did not give antihypertensive medication because the patient's BP was normal.

OUTCOME AND FOLLOW-UP

The seizure did not relapse after immediate treatment was given. Vomiting and visual and hearing disturbances were also relieved after treatment. Vital signs were re-evaluated after treatment: supine BP 110/75 mmHg, HR 75 beats/min, RR 21 breaths/min, temperature 36.9°C, and oxygen saturation 98% with 3 L/min oxygen administered by nasal cannula. Around 50 mL urine output and 1+ proteinuria (30-100 mg/dL) were present in the urine examination. The complete blood test was not carried out due to limited laboratory facilities. Subsequently, the patient was referred to the hospital in a conscious and stable condition. The patient's condition and vital signs were re-evaluated every 1 h after treatment was given until they arrived at the hospital: Systolic BP was 128-123 mmHg, diastolic BP 71-85 mmHg, HR 95 beats/min, RR 20-22 breaths/min, temperature 36.8°C, and oxygen saturation 97%-98%. The patient's follow-up during hospitalisation could not be obtained due to incomplete medical record documentation. The patient was discharged in healthy condition from the hospital 3 d later, and a healthy 2.8-kg baby was born by vaginal delivery. The complete timeline of the patient's condition is shown in Figure 1.

DISCUSSION

Elevated BP during pregnancy is considered one of the five leading causes of maternal mortality and morbidity worldwide. The global report that was analysed by the World Health Organization showed that around 343 000 maternal mortalities from 2003 to 2009 were caused by hypertension, and it was the second most common direct cause of maternal death (14%) after haemorrhage (26.1%). The incidence of pre-eclampsia and eclampsia was also higher in low- and low-to-middle-income countries. In Indonesia, the incidence of eclampsia was 128.753 per annum[3].

Eclampsia is defined as one of the hypertensive disorders related to pregnancy that is characterised by eclamptic seizures, an episodic general tonic-clonic seizure, followed by classic pre-eclampsia features such as hypertension (≥ 140 systolic BP and/or ≥ 90 diastolic BP), proteinuria (≥ 30 mg/dL), and/or organ damage (liver or renal dysfunction, low platelet, lung oedema, haemolysis, and unconscious) between 20-wk gestation and 48-h post-delivery. In rare, atypical cases, a pregnant woman may experience pre-eclampsia and/or eclampsia without either hypertension or proteinuria. However, other clinical manifestations such as severe abdominal pain, nausea, vomiting, blurred vision, mucosal bleeding, and severe headache may present in atypical pre-eclampsia eclampsia[4]. A systematic review also reported

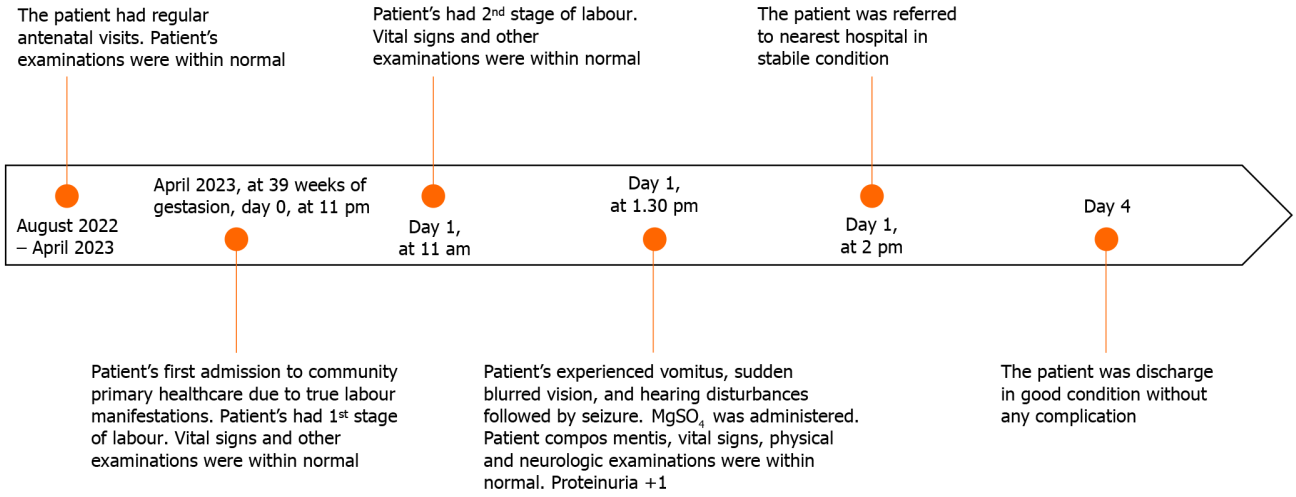

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Figure 1 Timeline of the case report.

that visual disturbance (27%), headache (66%), and epigastric pain (25%) are common symptoms, followed by eclampsia [5,6]. Our patient also experienced sudden persistent hearing loss, blurred vision, and vomiting without prior high BP and proteinuria.

New-onset seizures in pregnant women can be difficult and challenging to differentiate between eclampsia and other aetiologies. Eclampsia without classical signs may lead to unawareness of the diagnosis and delay in necessary treatment. Further examination, such as deeper physical examination, laboratory examination, and neuroimaging (head CT scan or MRI), should be carried out carefully to determine the underlying aetiology of the seizure attack, such as epilepsy, brain injury (ischemic or haemorrhagic), meningoencephalitis, hypoglycaemia, and posterior reversible encephalopathy syndrome[6]. In addition, a multidisciplinary approach may be required to diagnose appropriately. Our patient denied any history of trauma or past illnesses. In addition, physical and neurological examinations were also normal. Unfortunately, this case occurred in a remote area with limited resources, so required neuroimaging and laboratory work could not be performed.

Eclampsia can develop before, during or after delivery. Based on gestational age, it can occur at < 34 wk gestation (early) and ≥ 34 wk gestation (late). In a comparative study, pre- and antepartum eclampsia were found more often in young (< 25 years old) nulliparous rather than multiparous women[7]. Similarly, a 6-year cohort study also reported that anaemia, obesity, nulliparity, and history of heart disease may be potential risks for eclampsia development[8]. These findings were in line with the characteristics of the patient in this study, a 22-year-old primigravida.

Based on guidelines from the National Institute for Health and Care Excellence, women with a history of hypertensive disease during previous pregnancy, autoimmune disease, chronic kidney disease, chronic hypertension, and diabetes would have a higher risk of developing pre-eclampsia and eclampsia. In addition, other conditions such as obesity, nulliparity, age ≥ 40 years, ≥ 10 years pregnancy interval, and multiple pregnancies could also increase the risk of pre-eclampsia and eclampsia[9].

The mechanism underlying eclampsia has been widely studied. Early onset of pre-eclampsia eclampsia is suggested to develop from placenta abruption, while late onset of pre-eclampsia eclampsia is suggested to develop from placenta senescence and the mother's genetic predisposition to metabolic and cardiovascular diseases[10]. Disruption of placental blood flow causes a decrease in uteroplacental perfusion, thus inducing oxidative stress due to hypoxia and vascular endothelial dysfunction. The alteration of the placenta led to antiangiogenic factors and other inflammatory releases. In addition, the renin-angiotensin II axis, immune maladaptation, and genetics may also have roles in pre-eclampsia pathogenesis[11] (Figure 2).

Eclampsia is a life-threatening event during pregnancy or labour. Immediate treatment should be administered by a physician to prevent worse outcomes for both the mother and the baby. $MgSO_4$ is a first-line drug to control and/or prevent convulsions in pre-eclampsia eclampsia treatment. The loading dose of $MgSO_4$ is intravenous 4-6 g given in 15-20 min, followed by 1-2 g/h $MgSO_4$ administered by infusion. Patella reflexes, urine output, and vital signs should be well-monitored after magnesium treatment in order to detect its toxicity early[12]. Oxygen supplementation at 8-10 L/min can be administered to maintain oxygenation, particularly during convulsive episodes. In addition, antihypertensive agents must be given to treat hypertensive emergencies (systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg). Guideline recommendation of acute first-line antihypertensive medication includes labetalol 20 mg intravenously followed by 20-80 mg at 10-min intervals, hydralazine 5-10 mg intravenously followed by 10 mg at 20-min intervals, and nifedipine 10 mg orally and repeated every 30-min for 50 mg maximum dose in 1 h. The next step of eclampsia management is to deliver the baby within 24 h of eclampsia onset[6].

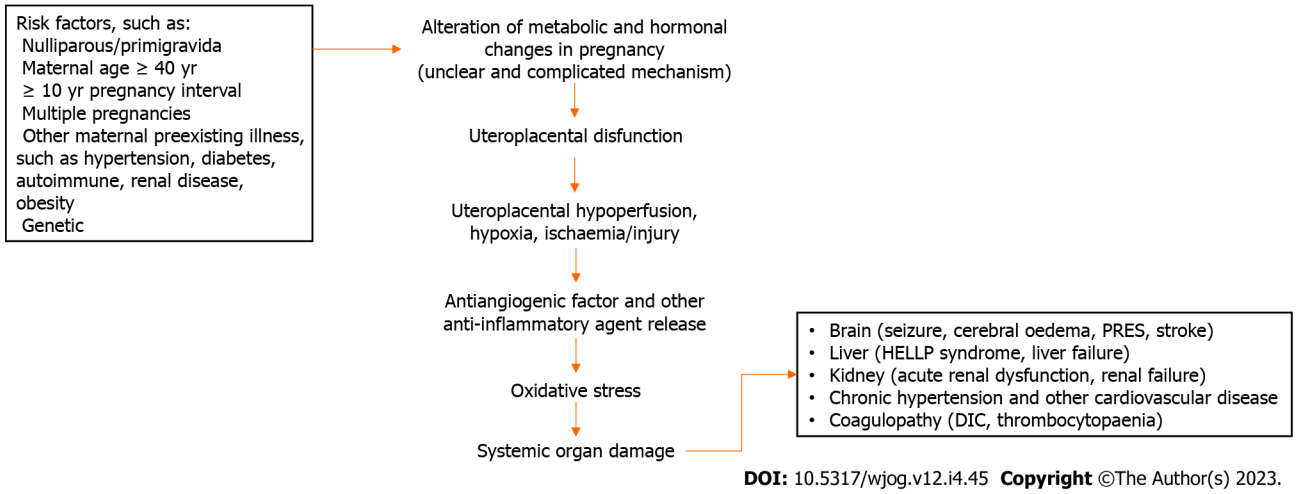

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Figure 2 Possible pathomechanisms of eclampsia.

CONCLUSION

Hypertension, proteinuria, and generalised seizures are the hallmarks of eclampsia. However, some pregnant women may experience atypical features of eclampsia, and eclamptic seizures without a prior history of high BP and proteinuria. The absence of these classic signs may lead to physician unawareness of pre-eclampsia eclampsia and become a diagnostic challenge. However, other symptoms, such as neural disturbances and gastrointestinal manifestations, may present as signs of impending eclampsia. In addition, deeper anamnesis and the required physical examination would be tremendously helpful for the physician in order to properly diagnose during work in a limited-facility setting.

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FOOTNOTES

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