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Contents

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MINIREVIEWS

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WJOG mainly publishes articles reporting research results and findings obtained in the field of obstetrics and gynecology and covering a wide range of topics including the diagnosis and treatment of infertility, family planning (including contraception and pregnancy termination), sexual medicine, pediatric and adolescent gynecology, menopausal gynecology, reproductive endocrinology and infertility, and female pelvic medicine and reconstructive surgery.

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MINIREVIEWS

What to do when it is breech? A state-of-the-art review on management of breech presentation

Afshin Azimirad

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Abstract

Any non-cephalic presentation in a fetus is regarded as malpresentation. The most common malpresentation, breech, contributes to 3%-5% of term pregnancies and is a leading indication for cesarean delivery. Identification of risk factors and a proper physical examination are beneficial; however, ultrasound is the gold standard for the diagnosis of malpresentations. External cephalic version (ECV) refers to a procedure aimed to convert a non-cephalic presenting fetus to cephalic presentation. This procedure is performed manually through the mother's abdomen by a trained health care provider, to reduce the likelihood of a cesarean section. Studies have reported a version success rate of above 50% by ECV. The main objective of this review is to present a broad perspective on fetal malpresentation, ECV, and delivery of a breech fetus. The focus is to elaborate all clinical scenarios of breech and to provide an evidence-based clinical approach for them. After discussing breech prevalence, risk factors, diagnosis, and management, an updated review of ECV is presented. Moreover, ECV indications/contraindications, alternatives, clinical techniques on how to perform ECV and breech vaginal delivery, and obstetrical considerations for the delivery of malpresentations are thoroughly discussed.

Key Words: Labor presentation; Breech presentation; Obstetric delivery; Cesarean section; External cephalic version; Fetal version

Core Tip: Breech presentation is a leading indication for cesarean surgery. However, external cephalic version (ECV), with a success chance of above 50%, can be performed at 36 wk of gestation or at 39 wk of gestation in order to convert a non-cephalic presenting fetus to a cephalic presenting. A trial of labor or cesarean delivery can be planned after an unsuccessful ECV. Fetus breech can be delivered by vaginal breech delivery or cesarean delivery. The main objective of this review is to present a broad perspective on fetal malpresentation, ECV, and delivery of a breech fetus.

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INTRODUCTION

The nearest anatomical part of the fetal body to the maternal pelvic inlet is defined as fetal presentation. The most desired presentation, with the lowest maternal and fetal risk, is the cephalic presentation[1,2].

Any non-cephalic presentation in a fetus is regarded as malpresentation. The most common malpresentation is breech, accounting for almost 80% of all malpresentation cases[3-6]. Other malpresentations include shoulder, compound, umbilical cord, face, and brow[4,5].

METHODS

Search strategy, search terms, and inclusion criteria

A literature search on the platforms Medline (*via* PubMed), Google Scholar, Scopus, and Web of Science, and Cochrane Database of Systematic Reviews was performed to find the published articles on the subject of this narrative review. The search time period was set to January 1995 to March 2022. The search terms are included in Table 1. The inclusion criteria included full texts, any article type, and English literature. This narrative review followed the steps proposed in SANRA tool-a scale for the quality assessment of narrative review articles[7].

Breech presentation

Breech is when the fetal buttocks or feet are the presenting parts. Breech can happen as frank (hips flexed, knees extended), complete (hips and knees flexed), and incomplete (not fully flexed hip; one-sided or both-sided). Most breech fetuses present as frank breech. Rarely, the foot advances into the birth canal, which is known as a footling breech presentation[4,6,8,9]. Please refer to Figure 1.

Prevalence of breech

Breech complicates around 3%-5% of at-term pregnancies. However, earlier in pregnancy, as the fetus is floating in the intrauterine cavity, it is more common. The prevalence of breech at 28 and 32 wk of gestation decreases from 20%-25% to 8%-16%. Naturally, as pregnancy advances, the fetus tends to rotate inside the uterus to present with the head in the maternal pelvis. The reason for this is not clear; however, 3%-5% of term fetuses fail to do so[10,11].

Pathogenesis of breech

The etiopathogenesis of breech is not very well understood. Many physicians regard it as an accidental phenomenon. Nonetheless, breech is more common when there is a concurrent fetal, uterine, or placental abnormality.

Almost one-quarter of fetuses at 28 wk of gestation are in the breech presentation, while only 4% are at-term. The transitional non-cephalic presentation is expected, especially earlier in pregnancy as a smaller fetus can easily rotate within a relatively large volume of amniotic fluid. However, as time goes forward, this becomes less plausible. The reasons why most fetuses assume cephalic presentation and why few do not are still disputed. However, the clinical implication here, when a fetal malpresentation is diagnosed at term in a singleton pregnancy, is to assess for underlying anomalies[3,12,13].

Risk factors

Various risk factors have been attributed to breech presentation. They can be categorized into three main groups: (1) Maternal (a history of breech in a previous pregnancy, multiparity as it results in a lax abdominal wall, primiparity, hypothyroidism, gestational diabetes, smoking, older or younger maternal age, delivery before term, and a personal history of being in breech); (2) Fetal (fetal neurologic deficit,

Table 1 Search terms used in platforms during course of the study

Search terms		
Fetal malpresentation	External cephalic version	Fetal presentation, breech
Fetal presentation	Fetal version	Frank breech presentation
Presentation, fetal	Version, external cephalic	Incomplete breech
Version, fetal	Breech presentation	Labor presentation
Presentation, breech	Complete breech	Breech
Labor presentation		

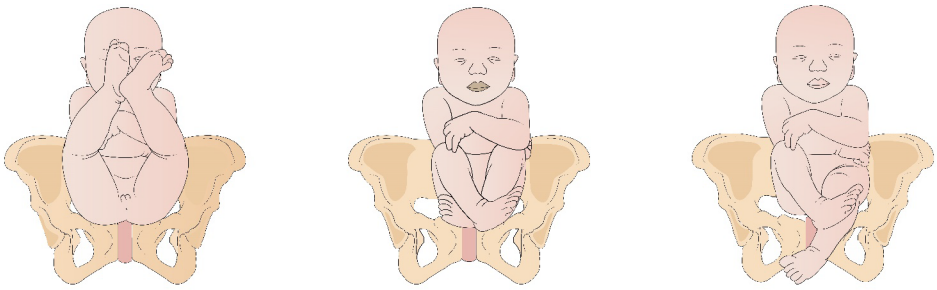

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Figure 1 Types of breech presentation.

anencephaly, hydrocephaly, macrosomia, fetal asphyxia, fetal growth restriction, multiple gestation, and female gender); and (3) Uteroplacental (oligohydramnios, polyhydramnios, uterine anomalies, bicornuate and unicornuate uterus, uterine didelphys, fibroids, and placenta previa) (Table 2)[14-17].

DIAGNOSIS

History and physical examination

Some women, in the third trimester, may complain of subcostal discomfort (fetal head in the fundus) or pain in the lower abdomen or groins (as the fetus kicks the cervix). However, these happen in normal pregnancies too, and are not considered specific or pathognomonic[8].

The physical examination includes inspection and transabdominal palpation of the fetus. The abdominal examination is performed through the Leopold maneuvers (Figure 2). The purpose of Leopold maneuvers is to determine the fetal lie, presentation, and engagement.

The physician should be at the right side of the patient, while she is placed in the dorsal recumbent position. The first step is a full inspection of the abdomen regarding its shape and size. The first maneuver is to measure the fundal height. Of note, the uterus, due to the pressure from the sigmoid colon, tends to rotate to its right. The dextrorotation of the uterus should be corrected before measuring the fundal height, which is an indicator of gestational age. The second maneuver is to determine the fetal lie (longitudinal, oblique, or transverse). The examiner assesses both lateral sides of the abdomen for that. Assessment of the upper and lower parts of the abdomen is the third maneuver or the Pawlik's grip. The goal is to locate the fetal head. The last step is to assess if the fetal leading part is engaged in the pelvis. The provider must stand near the mother's head, facing her feet, and with both hands assess the space between the fetus and maternal pelvis[18,19].

For assessment of the station, position, and attitude, a vaginal examination of the fetus is performed. The station is the location of the fetal leading part regarding the midpoint of the maternal pelvis (the ischial spines). The position or orientation is how the fetal leading part is situated in the anteroposterior axis of the maternal pelvis. For cephalic presentations, usually the occiput, and for breech presentations, the sacrum is a landmark to describe the position. The attitude describes the fetal head's flexion or extension status.

The clinically valuable point for the care provider is not to misidentify the fetal buttocks (palpating the ischial tuberosities, anus, genitalia, sacrum, or lower limbs) with fetal head, face, and facial features and orifices. This is clinically very important as cephalic and breech presentations have different plans. Although, history and physical examination are crucial parts of any clinical encounter. However,

Table 2 Risk factors for breech presentation

Maternal	Fetal	Uteroplacental
A history of breech in a previous pregnancy	Fetal neurologic deficit	Oligohydramnios
Multiparity	Anencephaly	Polyhydramnios
Primiparity	Hydrocephaly	Uterine anomalies (bicornuate and unicornuate uterus, uterine didelphys)
Hypothyroidism	Macrosomia	Uterine fibroids
Gestational diabetes	Fetal asphyxia	Placenta previa
Smoking		
Older or younger maternal age		
Delivery before term		
A personal history of being in breech		

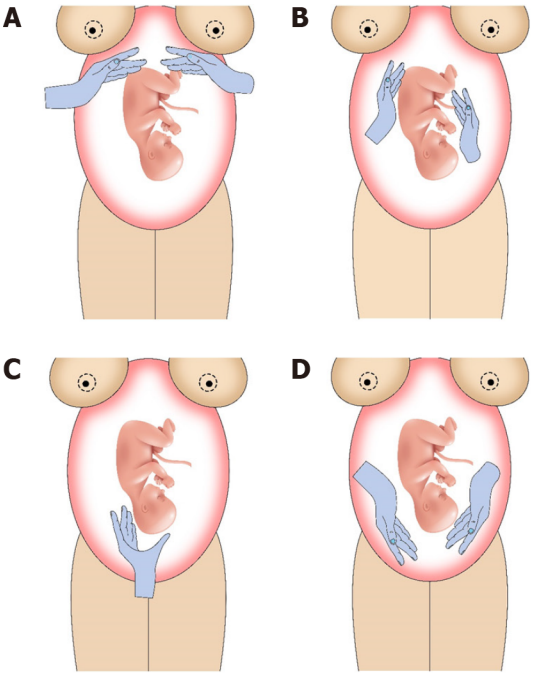

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Figure 2 Leopold's maneuvers. A: Measuring the fundal height; B: Determining the fetal lie; C: Locating the fetal head by assessing both ends of the uterus; D: Assessment of engagement of fetal leading part in the pelvis.

relying solely on them and not utilizing imaging techniques can lead to misdiagnosis or under-diagnosis of malpresentations[6,19,20].

Imaging assessment

The gold standard for the diagnosis of fetal malpresentation is transabdominal ultrasonography. The fetal presentation and flexion or extension of the hips and knees (types of breech) can be easily evaluated through ultrasound. It also enables the care provider to assess for other structures and factors, such as placenta, umbilical cord, amniotic fluid volume, and estimated fetal weight. The fetal or uterine contraindications of vaginal delivery such as hyperextension of fetal head or very large uterine fibroids can be visualized too. Other advantages of ultrasonography include its low cost, acceptability, accessibility, and no major adverse effects.

Abdominal χ-ray, Computed Topography scan, and Magnetic Resonance Imaging are other modalities that can visualize a non-cephalic presenting fetus; however, are not recommended for routine clinical use[16,20-22].

MANAGEMENT OF BREECH PREGNANCY

Introduction

Most guidelines recommend cesarean section as the desired approach for singleton breech pregnancies with gestational age at or after 39 wk. Two major studies, Term Breech Trial (TBT) in 2000 and Premoda in 2006, provided clinical evidence in favor of cesarean section.

TBT, a randomized controlled clinical trial in a multi-national setting, aimed to determine whether planned cesarean delivery or planned vaginal delivery benefits the breech-presenting fetuses more. This major study studied more than 200 singleton pregnancies in 26 countries. Perinatal and neonatal mortality and serious neonatal morbidity were the primary outcomes. Maternal mortality and serious maternal morbidity were regarded as secondary outcomes. The breech pregnancies undergoing cesarean section had significantly lower perinatal or neonatal mortality and serious neonatal morbidity, compared to the other cohort (risk ratio [RR] = 0.23, 95% confidence interval [CI]: 0.07–0.81, P = 0.01 and RR = 0.36, 95%CI: 0.19–0.65, P = 0.0003, respectively)[22,23].

Premoda, a prospective observational study of more than 800 term breech pregnancies, aimed to determine whether planned cesarean delivery or planned vaginal delivery benefits the breech-presenting fetuses more. The primary outcomes in Premoda included fetal or neonatal mortality and severe neonatal morbidity. This study assessed the babies up to one year after birth and based on its finding of no difference between the two groups, concluded that planned vaginal delivery is a safe approach for delivery of at-term breech pregnancies[24].

Basics and plans

Providing all the information to the mother and educating her on the advantages and risks of both vaginal and cesarean deliveries is an essential duty for any health care provider. The physician should stay away from biases, ambiguity, and coercing the mother or himself/herself to any plans against anyone's wishes, values, capabilities, or clinical judgment[25-29].

In general, six plans can be anticipated for persistent breech-presenting fetuses: (1) ECV at 36-37 wk of gestation and expectant management; (2) ECV at 39 wk of gestation and if successful, followed by a trial of labor; (3) ECV at 39 wk of gestation and if unsuccessful, followed by cesarean delivery for breech fetus; (4) ECV at 39 wk of gestation and if unsuccessful, followed by a trial of labor and vaginal breech delivery for selected individuals; (5) Planned cesarean delivery for breech fetus; and (6) Planned vaginal breech delivery for the low-risk group (Figure 3)[23,25-27,29].

Before any further elaboration on managing the scenarios, ECV shall be explained here.

External cephalic version

ECV refers to a procedure aimed to convert a non-cephalic presenting fetus to a cephalic presenting. This procedure is performed manually through the mother's abdomen by a trained health care provider, to reduce the likelihood of a cesarean section.

ECV is considered an elective manipulation when the labor process has not been initiated yet and should be indicated after a comprehensive evaluation of risks and contraindications, for both mother and fetus.

Overall, it is important to keep in mind that currently in the United States, a previous uterine surgery is the leading cause of cesarean-section, and non-cephalic pregnancies stand as the second[23,25-30].

Indications for ECV: ECV is indicated in any non-cephalic presenting singleton pregnancies in their late third trimester when there is no contraindication[23,26,27].

Contraindications for ECV: Any contraindication for labor or vaginal delivery is a contraindication for ECV. In addition to those regarded as the absolute contraindications for ECV, there are relative contraindications for ECV too. The contraindications can be due to maternal, uteroplacental, or fetal factors, including rupture of membranes, placental anomalies (placenta praevia, placenta accreta/increta/percreta, and vasa praevia), placental abruption, maternal cardiac disease, a history of classical (high vertical) hysterotomy, two or more cesarean sections, antepartum bleeding, cephalopelvic disproportion, abnormal cardiotocography, fetal descent, and multiple gestation. Relative contraindications for ECV include fetal growth restriction, oligohydramnios, preeclampsia/hypertension, fetal growth restriction, fetal macrosomia > 4000 g, maternal obesity, and hyperextended fetal head[23,26,27,29,31]. Table 3 provides an overview of this information.

Adverse events of ECV: Adverse events occur in < 1% of cases[23,25-27,29-30]. However, educating individuals on the risks of ECV is essential. Placental abruption, non-reassuring fetal tests, rupture of membranes, isoimmunization due to feto-maternal hemorrhage, and stillbirth are the most serious ones. Moreover, some subjects report it as uncomfortable[2,29,30].

Of note, ECV should be only performed in centers capable of performing emergency cesarean deliveries. After ECV fetus might experience tachycardia, bradycardia, decelerations, or instability in heart rate patterns, which may require an emergency cesarean delivery[23,25-27,29-30].

Table 3 Absolute and relative contraindications for ECV

Absolute contraindications (any contraindication for labor or a vaginal delivery)			Relative contraindications
Maternal	**Fetal**	**Uteroplacental**	**Fetal growth restriction**
Maternal cardiac disease	Abnormal cardiotocography (indeterminate fetal heart rate)	Rupture of membranes	Oligohydramnios
A history of classical (high vertical) hysterotomy	Fetal descent	Placental anomalies (placenta praevia, placenta accreta/increta/percreta, vasa praevia)	Preeclampsia/hypertension
A history of two or more Caeserean sections	Multiple gestation	Placental abruption	Fetal growth restriction
Cephalopelvic disproportion			Fetal macrosomia > 4000 g
Antepartum bleeding			Hyperextended fetal head
			Maternal obesity

ECV: External cephalic version.

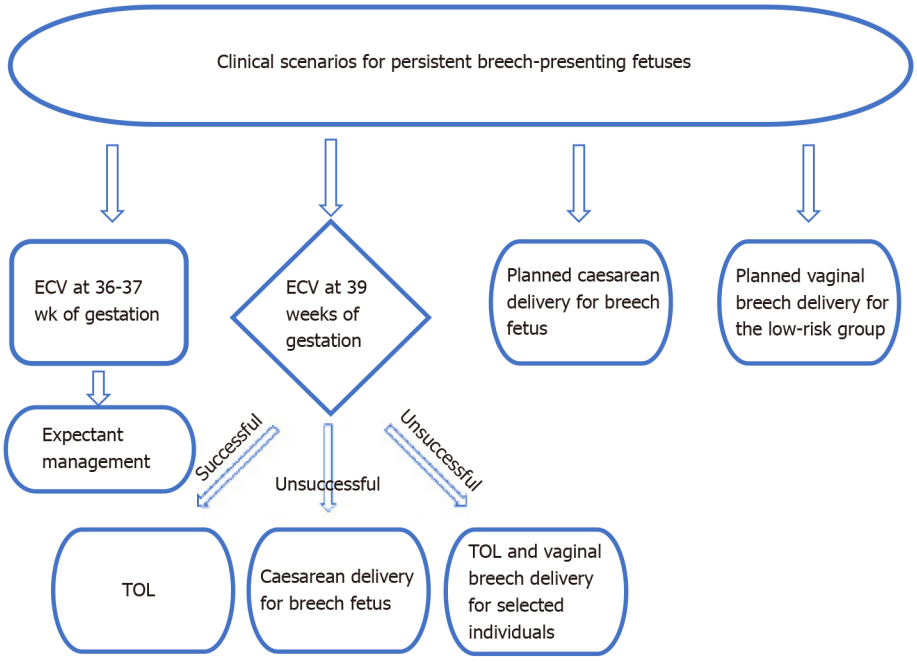

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Figure 3 Flow chart diagram for clinical scenarios for persistent breech-presenting fetuses. ECV: External cephalic version; TOL: Trial of labor.

Success rates of ECV: A meta-analysis revealed a success rate of 58% for ECV. However, many factors are associated with ECV success. These include earlier gestational age, higher parity, trained health care provider, higher body mass index in mother, tocolytics, and epidural analgesia[29,30].

Acceptability of ECV: Various studies report that one-third to two-thirds of eligible individuals rejected ECV. Young age and lower parity are associated with a more negative attitude toward ECV[32].

Technical considerations for ECV: The first step is to reconfirm that the fetus is still assuming a non-cephalic presentation.

Obtaining informed consent is the next step. The facility should be fully set up for an emergency cesarean delivery in case it is needed[25,29]. After a satisfactory biophysical profile or a reactive fetal heart rate documented by a cardiotocography was noticed, tocolytics might be administered. Most commonly, β2 agonists are administered: Subcutaneous terbutaline 250 μg, or intravenous salbutamol 250 μg/20 mL normal saline. Neuraxial blockade or regional analgesia both are accepted methods that increase the chances of a successful ECV[29]. However, the advantages of administration of systemic opioids, abdominal lubricants, and amnioinfusion are still a matter of research, according to a 2015

Cochrane systematic review[33].

Applying either lubricant gel or cornstarch powder to the abdomen will facilitate the process. First, above the maternal symphysis pubis should be examined to know how deep the fetus has been engaged into the maternal pelvis. To successfully convert, the breech should be disengaged using the non-dominant hand. Thereafter, there are two techniques to perform ECV: Forward somersault, and backward. To perform the forward, using the dominant hand, the fetal head may be pushed forward toward the maternal symphysis pubis. If this maneuver yields no success after a few tries, the backward somersault shall be attempted. While the fetal head is being pushed back towards the symphysis pubis, the breech, with the dominant hand, is pushed forward to the uterine fundus. The recommended time for ECV is 10 min.

Monitoring the fetal heart rate for at least 30 min afterward, and isoimmunization of Rh(D)-negative individuals is recommended[29,30]. Please refer to Figure 4.

Alternatives to ECV: There are three proposed alternatives for ECV: (1) Watchful waiting: There is a chance for a natural conversion of the fetus as gestational age advances; (2) Postural techniques: The knee-chest position and elevated pelvis in supine are the postures that have been proposed as alternatives for ECV. However, systematic reviews have not found sufficient evidence to support the idea[29,34,35]; and (3) Moxibustion: Moxibustion is a traditional Chinese therapy consisting of burning mugwort on specific parts of the body coupled with acupuncture. It is hypothesized that the inhaled medicinal herb increases fetal movements, resulting in conversion. A Cochrane systematic review, however, found that the state-of-the-art body of evidence is not sufficient to recommend[35].

Delivery of the persistent breech at term

Even though the findings of the TBT trials effectively disfavored breech vaginal delivery, low-risk individuals may benefit from vaginal deliveries in well-equipped centers[23]. Of note, the relative risk of perinatal morbidity and mortality is two to five times more for vaginal breech delivery than cesarean delivery. According to a 2015 Cochrane systematic review, planned vaginal breech delivery enhances both the perinatal/neonatal mortality rates and serious neonatal morbidity rates. Nevertheless, this study emphasized the importance of the mother's authority and individual risk-assessment of each case. Notably, after a breech vaginal delivery, about 90% of women stated that they would again consider breech vaginal delivery, according to an international survey[36,37].

Technical considerations for breech vaginal delivery

The first fetal parts that show up in the birth canal are lower limbs; however, traction of these parts is highly discouraged. This might result in fetal head extending or enhancing the risk of nuchal arms. Fetal lower limbs and buttocks usually are delivered without any traction or pressure from the accoucheur. Current guidelines mostly discourage performing episiotomy for vaginal breech delivery. Facilitation of delivery of hips may lower the risk of neonatal developmental dysplasia of the hip (odds ratio [OR] = 5.7, 95%CI: 4.4-7.4)[38-43]. The accoucheur, holding the bony pelvis in hands, should rotate the fetus to the sacrum anterior position, after hips are delivered. To deliver the rest of the body, persistent, smooth traction and 180 degrees clockwise and counterclockwise rotation, should be applied several times. This maneuver is called Løvset maneuver, which may reduce risk of nuchal arms. To deliver the arms the accoucheur may grasp them cross the body as soon as the scapulae appear[38-42].

Delivery of the head in vaginal breech delivery requires lots of experience. A popular maneuver for this is the Mauriceau-Smellie-Veit maneuver. Before that, the fetal head needs to be flexed, not extended. When arms are almost delivered, the body should be elevated. As soon as the face is approachable, the mouth should be suctioned to clear the airway. The maneuver includes insertions of two or three fingers inside the birth canal and putting them on the fetal face to support and flex the head. The other hand, also inside the birth canal, should be put on the fetal neck and occiput, and flexion of the head smoothened. Moreover, an assistant can facilitate the vaginal breech delivery by applying pressure external on the maternal abdomen. However, if with all these techniques, the head is not delivered, no traction should be applied. In this case, utilization of piper forceps is recommended. Therefore, the fetal body is elevated while covered in a towel. The two blades are placed on the lateral sides of the head while applying pressure to flex the fetal head, and it will be delivered[38-42].

A not common position that might occur is the sacrum posterior position. This position can be complicated when the fetal chin cannot pass through the maternal symphysis pubis. In this case, the clinician should perform the modified Prague maneuver. This includes holding the fetal body with one hand and elevating fetal lower limbs with another hand and rotating the baby around the maternal symphysis pubis[38-42].

Complications and how to manage them

Entrapment of fetal arms and head are the most serious complications in breech. To reduce the risk of the "nuchal arm", the Løvset maneuver (discussed earlier) should be performed.

Head entrapment is an obstetric emergency, as it can lead to asphyxia. The fetus will not get oxygenated through the umbilical cord, and the head trapped in the cervical canal cannot perfuse the brain. Pharmacologic therapy includes administration of β2 agonists, such as terbutaline or salbutamol,

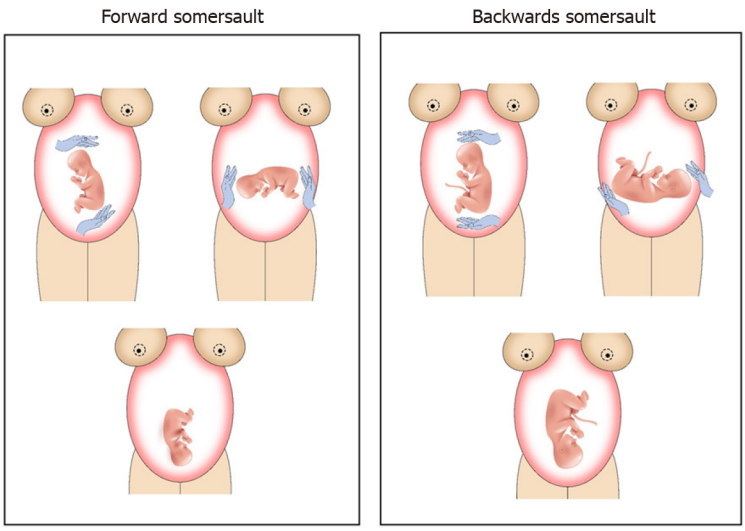

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Figure 4 Techniques for external cephalic version.

or nitroglycerine. The surgical approach includes making three incisions on the cervix, at 6, 2, and 10 o'clock. This approach is called Dührssen incisions. It especially benefits the preterm breech deliveries, as the fetus has a relatively larger head to the body, and the cervix is effaced while not dilated yet. First, the clinician should put two fingers inside the maternal cervix. This will help to separate the fetal body from the cervix. Then, they may incise the cervix at the three aforementioned points, utilizing bandage scissors. However, management of the incisions is challenging. Other less common approaches include general anesthesia and endotracheal intubation, the Zavanelli maneuver (reversing the delivery of fetal body and limbs and performing a cesarean section), and symphysiotomy on the mother[38-42].

Delivery of the preterm breech

It has been suggested that planned cesarean delivery, compared to vaginal delivery, is associated with lower perinatal morbidity and mortality (adjusted OR = 0.77, 95%CI: 0.63–0.93), lower neonatal mortality (30.2% *vs* 56.8%; P = 0.017), and higher maternal morbidity (anemia: 15.29% *vs* 10.04%, P = 0.005; wound infection: 0.001% *vs* 0.41%, P = 0.026)[44,45].

Cesarean delivery is considered the acceptable approach for delivery of the preterm breech fetus. In some specific cases, vaginal delivery is preferred, such as the delivery of a pre-viable fetus (earlier than 23 wk of gestation), a fetus with a non-compatible-with-life condition, and delivery of the breech twin B [25].

Neonatal outcomes

A higher rate of mortality and morbidity is observed in breech-presenting neonates. However, the causality relationship between the breech presentation and this phenomenon is not proven yet[46,47]. Sometimes there might be an underlying risk factor or condition that can develop both. Congenital anomalies, mild deformations, torticollis, and developmental dysplasia of the hip, without regard to the route of delivery, are more likely to present in neonates who were in breech[47,48].

CONCLUSION

Breech is a leading indication for cesarean surgery. ECV has a success chance of above 50%. ECV can be performed at 36 wk of gestation or at 39 wk of gestation. A trial of labor or cesarean delivery can be planned after an unsuccessful ECV. Fetus breech can be delivered by vaginal breech delivery or cesarean delivery. This review is proposing state-of-the-Art management for breech presentation.

FOOTNOTES

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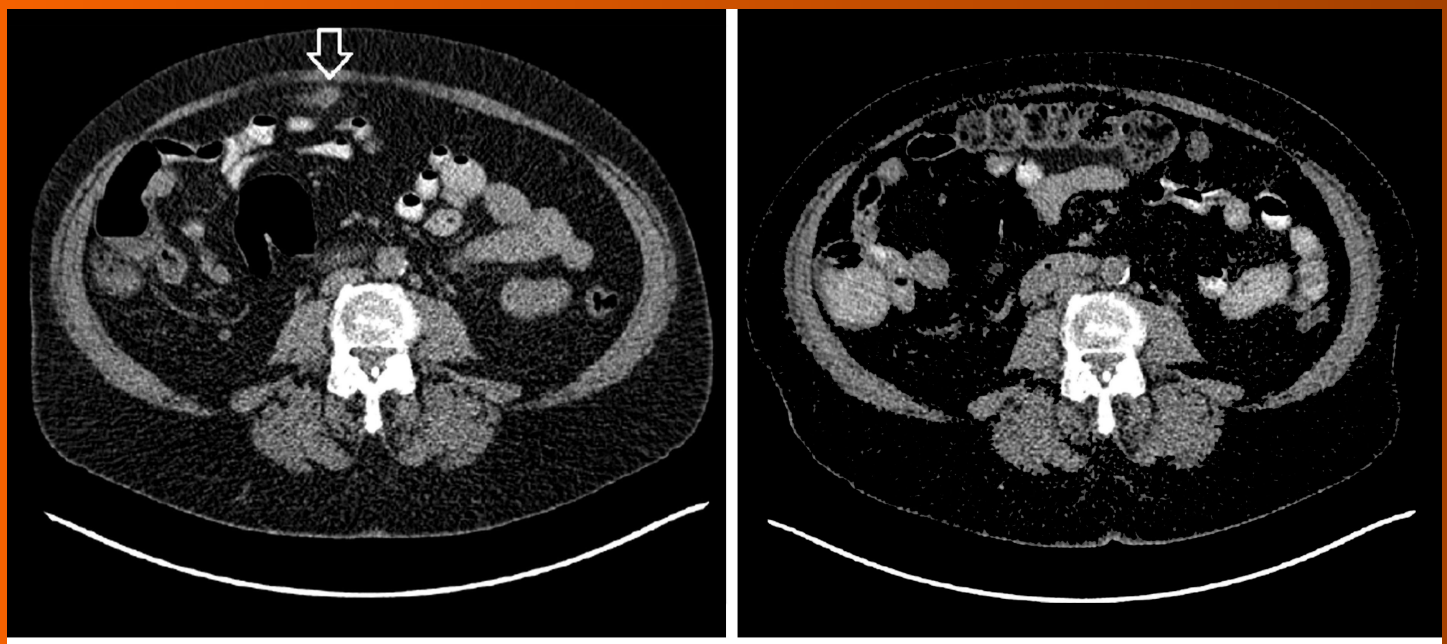

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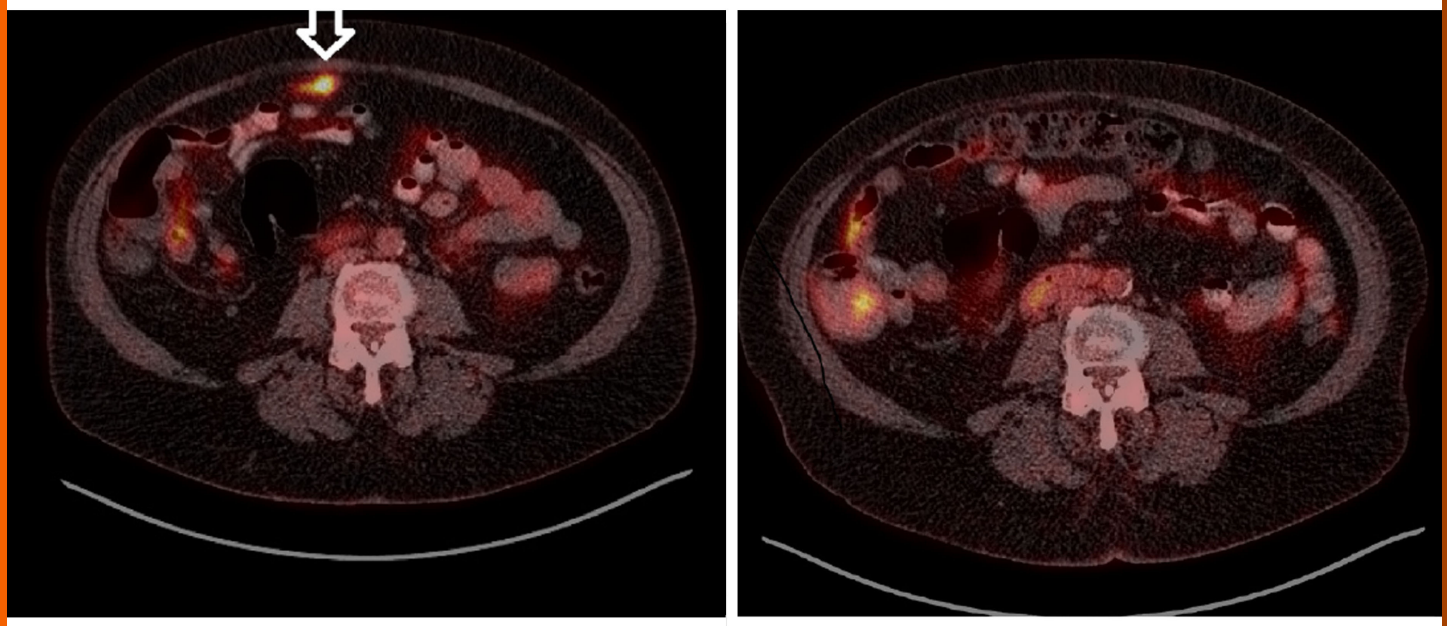

Comparison of fluorine 18 fluorodeoxyglucose position emission tomography with computed tomography.

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CASE REPORT

Spilled gallstone mimicking metastasis from cervix cancer on positron emission tomography – computed tomography

Kenneth L Chan, Martin Lord, Daniel McNamara, Étienne Désilets, Eric Bergeron

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Abstract

BACKGROUND

Spilled gallstones from previous cholecystectomy is not an uncommon situation. It may further mimic neoplastic disease and can be misled by fluorine 18 fluorodeoxyglucose position emission tomography with computed tomography ([18F]FDG PET/CT).

CASE SUMMARY

A 63 year-old patient was diagnosed with a cancer of the cervix. Pretreatment [18F]FDG PET/CT showed a peritoneal lesion suspicious for metastasis. Surgical exploration and histologic examination revealed the lesion to be a spilled gallstone from a previous cholecystectomy.

CONCLUSION

[18F]FDG PET/CT carries pitfalls since benign conditions such as intraperitoneal gallstones may be confused as malignant lesions. This case highlights the importance to be aware of the possible implications of dropped gallstones for the future, minimize its occurrence, and make all efforts to properly evaluate cancer staging, particularly for the cervix cancer.

Key Words: Cervix cancer; Dropped gallstones; PET/CT; Metastasis; Case report

Core Tip: Proper staging with imaging and fluorine 18 fluorodeoxyglucose position emission tomography with computed tomography ([18F]FDG PET/CT) is primordial for the management of cervical cancer. [18F]FDG PET/CT however carries pitfalls since benign conditions may be confused as malignant lesions. Spilled gallstones from previous cholecystectomy may be misdiagnosed as neoplastic disease with [18F]FDG PET/CT.

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INTRODUCTION

Fluorine 18 fluorodeoxyglucose (FDG) position emission tomography with computed tomography ([18F]FDG PET/CT) is nowadays a ubiquitous tool in the differentiation of benign from malignant tumors, in the staging of cancers, and in the follow-up of patients who have undergone surgery, radiation therapy, or chemotherapy[1,2]. It allows for the detection of metastases or recurrences of cancer which typically exhibit increased glucose metabolism[1]. However, pitfalls may occur with increased FDG uptake in some benign conditions[1,3].

We present a patient who has been diagnosed with a cervical cancer. A [18F]FDG PET/CT for staging showed a suspicious lesion for peritoneal metastasis was discovered. After surgery and pathologic examination, the lesion was diagnosed as a dropped gallstone from a previous cholecystectomy.

CASE PRESENTATION

Chief complaints

The patient suffered from a post-menopausal bleeding.

History of present illness

A 63-year-old caucasian female was referred with a history of post-menopausal bleeding. Vaginal bleeding was irregular with small quantity but increased with physical activities. She was not sexually active at the time. She had no fatigue or loss of weight. She did not report any abdominal or pelvic pain.

History of past illness

She had a laparoscopic cholecystectomy without known complications three years before. The gallbladder was fibrotic and sheared during dissection. There was no awareness of gallstones left unretrieved. She has no medical problem.

Physical examination

The patient looked in good shape. There was no abdominal pain. No abdominal mass was palpated. On gynecological examination, the exocervix appeared normal but necrotic tissue could be seen at the endocervix.

Laboratory examinations

Hemoglobin level was normal. There was no increase of tumor markers. Endocervical curettage and endometrial biopsy were performed. The biopsy revealed clear cell carcinoma.

Imaging examinations

A magnetic resonance imaging of the pelvis was performed which showed a 4.4 cm × 3.7 cm × 2.8 cm lesion in the cervix with extension to the lower third of the endometrium (Figure 1). The parametrium, vagina and adnexa were negative for cancer but a 9 mm lymph node was seen in the right iliac region. A CT scan of the thorax, abdomen and pelvis showed a suspicious intraperitoneal lesion besides and in front of the transverse colon (Figure 2A). No suspicious adenopathy was identified. [18F]FDG PET/CT revealed a hypermetabolic (SUV = 6) area 1 cm × 4 cm in size embedded in the peri-colic fat of the transverse colon in addition to a hypermetabolic cervical lesion (Figure 3A).

The patient underwent a diagnostic laparoscopy to investigate this unusual site of possible metastasis. At the same time, sentinel node biopsy was carried out. At surgery, a dark colored nodule

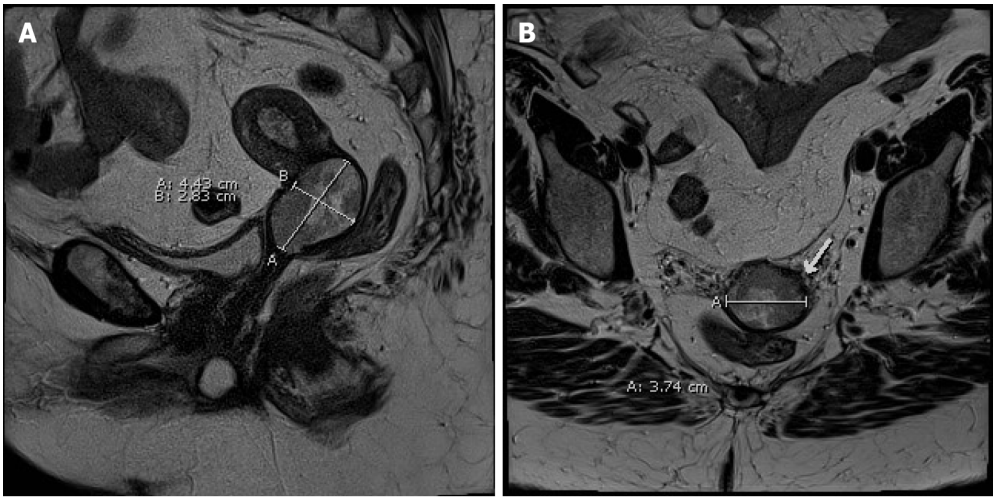

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Figure 1 Magnetic resonance imaging showing a 4.4 cm × 3.7 cm × 2.8 cm lesion in the cervix with extension to the lower third of the endometrium. A: Sagittal view; B: Transverse view.

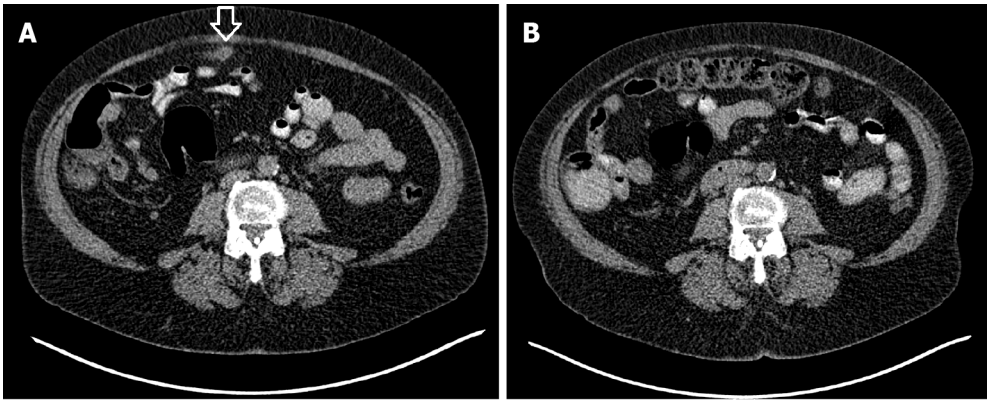

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Figure 2 Comparison of computed tomography-scans of the abdomen. A: A suspicious lesion is seen in front of transverse colon (arrow) before surgery; B: The lesion is not seen 4 mo after surgery.

was found close to but not adherent to the mid transverse colon (Figure 4). It was dissected completely without any bleeding and the surgery was completed with bilateral sentinel lymph node biopsy. A frozen section analysis was done which showed a hard calculus without signs of malignancy. The final pathology showed an 8 mm diameter calculus surrounded by acute and chronic inflammation with abscess formation and granuloma as well as negative sentinel nodes.

FINAL DIAGNOSIS

Clear cell carcinoma of the cervix, stage IB3. Dropped intraperitoneal gallstone with surrounding inflammation. Absence of peritoneal metastases.

TREATMENT

Combined chemotherapy and radiotherapy were prescribed.

OUTCOME AND FOLLOW-UP

CT scan and [18F]FDG PET/CT were performed 4 mo post treatment and showed no residual activity in

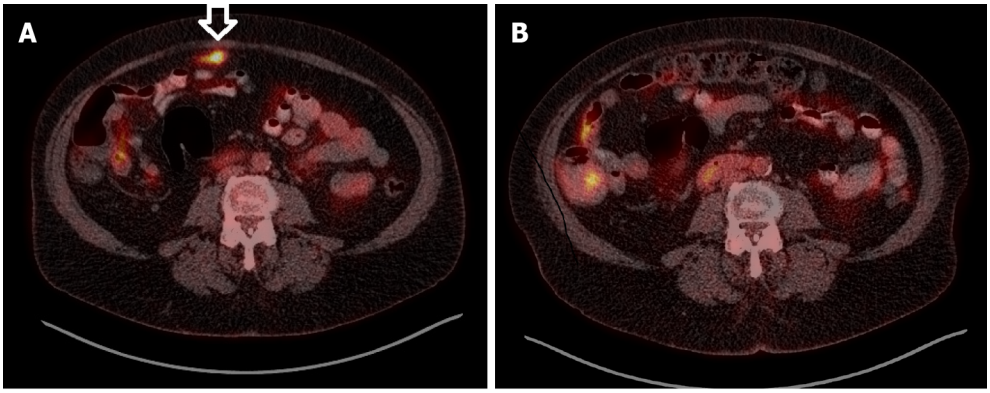

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Figure 3 Comparison of fluorine 18 fluorodeoxyglucose position emission tomography with computed tomography. A: A hypermetabolic intraabdominal lesion is demonstrated (arrow); B: The lesion has disappeared 4 mo after surgery.

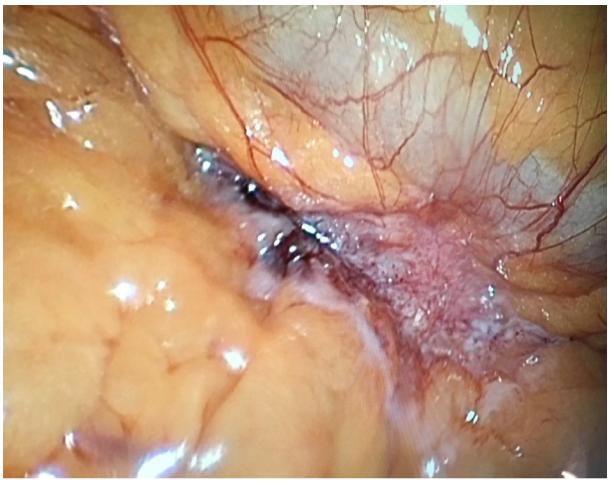

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Figure 4 Image of the intraperitoneal lesion besides the transverse colon during laparoscopic exploration.

the previous hypermetabolic site (Figures 2B and 3B). There was discrete activity in the uterus which was confirmed to be benign by magnetic resonance imaging. The patient currently has no evidence of disease at 20 mo after treatment. The case is summarized in Table 1.

DISCUSSION

Cervical cancer accounts for 1.3% of all new female cancers and 1.1% of all female cancer deaths in Canada[4]. Cervical cancer staging is based on tumor size, vaginal or parametrial involvement, bladder/rectum extension, and distant metastases[2]. [18F]FDG PET/CT is used for the evaluation of patients with cervical cancer[2,3]. Proper staging is mandatory in the planning of treatment of cancer of the cervix[2] and [18F]FDG PET/CT is nowadays used routinely in developed countries[2,5]. Sensitivity and specificity are respectively 53%-73% and 90%-97% for the detection of lymph node in cervical cancer[5].

Accidental gallstone spillage is often encountered during laparoscopic cholecystectomy[6]. Incidence of gallbladder perforation is 18.3%, gallstone spillage 7.3%, and unretrieved peritoneal gallstones 2.4% [7]. There is however no recent evaluation of the incidence of gallbladder perforation and spilled gallstones[8]. Despites better awareness of possible problems with dropped gallstones, incidence has probably not changed.

More than 90% of lost gallstones remain asymptomatic[9] with an estimate of 8.5% leading to a complication[10]. Such complications may occur such as localized infection or abscess, which are the most frequent[9-12], as well as inflammation, fibrosis, erosion or fistulization[6,9]. The occurrence of complication has been reported up to fifteen[9,13] and even twenty years[14] after cholecystectomy.

Table 1 Summary of history and investigation

History	History of post-menopausal bleeding, past laparoscopic cholecystectomy in a 63-year-old female
Examination	Exocervix normal; Endocervix showing necrotic tissue
Endometrial biopsy	Clear cell carcinoma
Magnetic resonance imaging	4.4 cm × 3.7 cm × 2.8 cm lesion in the cervix with extension to the lower third of the endometrium 9 mm right iliac node
Computed tomography	Suspicious intraperitoneal lesion in front the transverse colon
[18F]FDG PET/CT	1 cm × 4 cm hypermetabolic area in the peri-colic fat of the transverse colon; Hypermetabolic cervical lesion
Diagnostic laparoscopy and excisional biopsy	8-mm diameter calculus surrounded by acute and chronic inflammation with abscess formation and granuloma
Sentinel node biopsy	Negative
Treatment	Combined chemotherapy and radiotherapy
[18F]FDG PET/CT (after 4 mo)	No residual activity in the previous hypermetabolic site; Normal uterine activity
Follow-up	No recurrence after 20 mo

[18F]FDG PET/CT: Fluorine 18 fluorodeoxyglucose position emission tomography with CT.

Dropped gallstones can even mimic malignancies, lymph nodes, metastatic implants or carcinomatosis[1,6,9,12,15], so diagnosis is particularly challenging in the absence of histological confirmation [11]. False positive [18F]FDG PET/CT occurs in many conditions as a result of granulomatous disease or inflammation, foreign body reaction, and surgical changes[3]. In the present case, the lesion captured FDG, because of the inflammation surrounding the stone, not the stone itself[16,17]. CT scan also demonstrated a suspicious mass. In the presence of a cervical cancer, even without regional nodes, the occurrence of such a mass in the peritoneal cavity is, until proven otherwise, a metastatic lesion. Only removal and analysis of the mass could solve the diagnostic challenge and eliminate a peritoneal implant. Even at surgical exploration, the lesion appeared suspicious of neoplastic disease (Figure 4).

Some images of this case have been reported[18]. However, unlike what was showed, this report demonstrates the disappearance of the lesion on subsequent imaging studies (Figures 2 and 3) further proving that it has been removed. Moreover, the negative yet essential pathologic analysis definitively ascertains its benign nature. Consequently, the cancer was finally downstaged from stage IV to Stage IB3. In this patient with cervical cancer, optimal staging was mandatory as it drastically modified potential prognosis and management.

This case demonstrates that [18F]FDG PET/CT carries potential pitfalls since benign conditions may be confused as malignant lesions[1,3], as for intraperitoneal dropped gallstones from a previous cholecystectomy[1,6,15] which is not a so rare situation[7]. Even in case of known and documented dropped gallstones, diagnosis remains markedly challenging, and biopsy or even surgical exploration may become necessary for proper staging and management.

CONCLUSION

Staging is essential in order to properly manage cervical cancers and adequately evaluate prognosis. [18F]FDG PET/CT is the mainstay in the evaluation of patients with cervical cancer. However, it carries some pitfalls as in cases of previous dropped gallstones which could mimic neoplastic or metastatic disease.

FOOTNOTES

Author contributions: Chan KL managed the case, provided case presentation and surgical image. Lord M and McNamara D were involved in the provision of study material and reviewed imaging. Bergeron E and Désilets E participated in the writing of the manuscript and provided digestive and surgical expertise, and all authors critically reviewed and approved the final version of the article.

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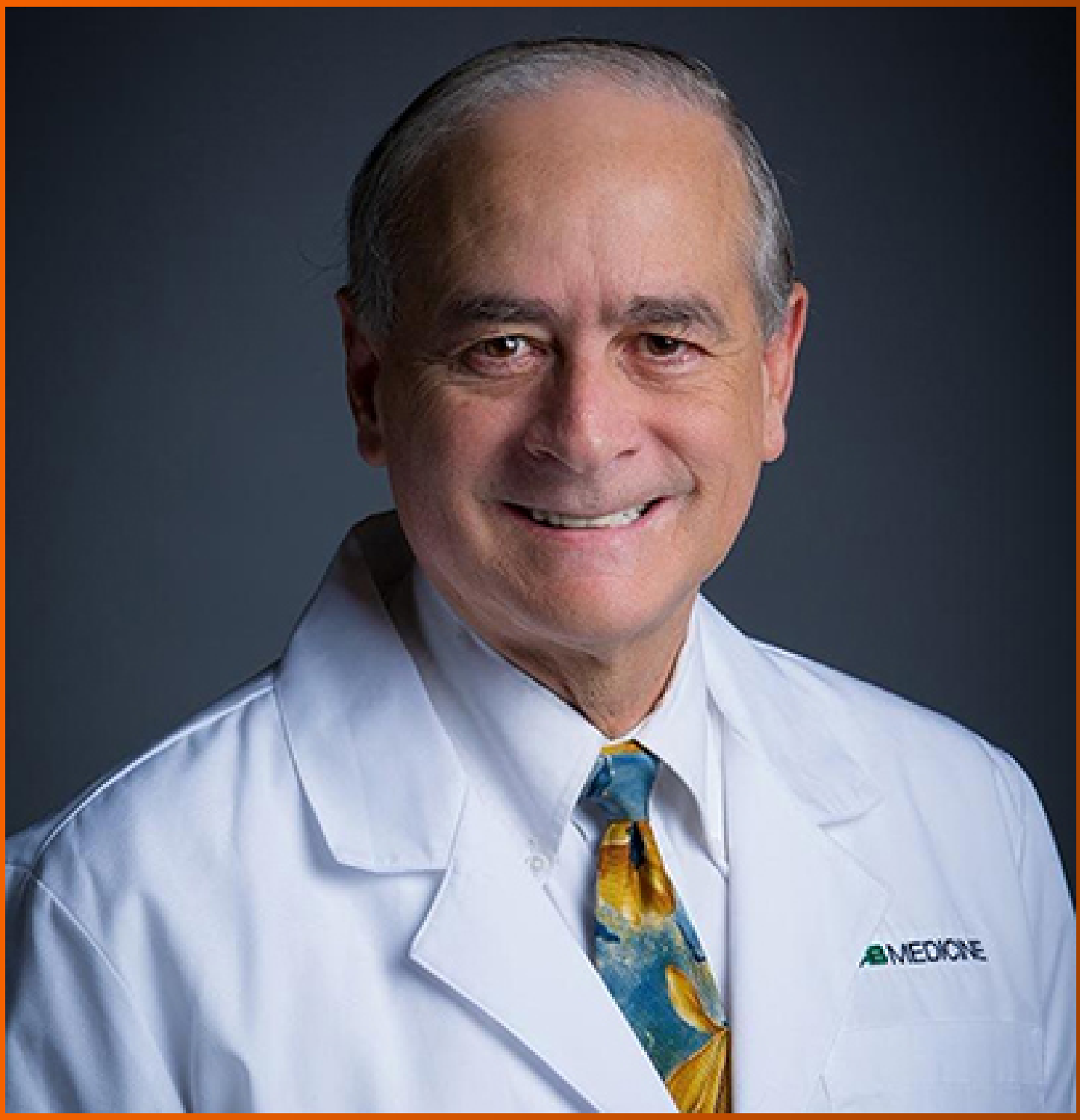

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ORIGINAL ARTICLE

Observational Study

Clinical implication of platelet to lymphocyte ratio in early onset preeclampsia: A single-center experience

Wisam Akram, Zina Abdullah Hussein, Mazin Hameed Humadi, Wassan Nori

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Abstract

BACKGROUND

Preeclampsia (PE) is a pregnancy syndrome of undetermined etiology; inflammation was one of the proposed theories for its development.

AIM

To examine the platelet to lymphocyte ratio (PLR), an inflammatory biomarker, as a marker to predict poor maternal-neonatal outcomes in early-onset PE (EoPE).

METHODS

A cross-sectional study enrolled 60 pregnant women with EoPE (at 32-30 wk of gestation) at a university hospital. Demographic criteria and hematological indices were collected, including platelet counts and indices (mean platelet volume and platelet distribution width), PLR, and the Doppler study, which calculated estimated fetal weight (EFW), amniotic fluid index (AFI), resistance index (RI), and pulsatility index (PI). Participants were followed until delivery, where maternal outcomes were recorded, including; delivery mode and reason for cesarean section, and neonatal outcomes, including fetal growth restriction (FGR), meconium-stained liquid, the 5-min Apgar score, and admission to the intensive care unit.

RESULTS

There was a trend of insignificant increases in cesarean sections. Sixty-one-point two percent (37/60) fetuses were admitted to the neonatal care unit; 70.0% of admitted fetuses were meconium-stained liquor, and 56.7% of them had FGR. PLR was positively correlated with AFI and EFW as r = 0.98, 0.97, P < 0.001; PLR showed negative correlations with PI and RI as r = -0.99, -0.98, P < 0.001. The Apgar score and the number of days admitted to the intensive care unit had a positive and negative correlation (0.69, -0.98), P < 0.0001, respectively. Receiver

operating characteristic calculated a PLR cutoff value (7.49) that distinguished FGR at 100% sensitivity and 80% specificity.

CONCLUSION

Strong, meaningful relationships between PLR and FGR parameters and a poor neonatal outcome with a significant *P* value make it a recommendable biomarker for screening EoPE-related complications. Further studies are suggested to see the impact on maternal-neonatal health.

Key Words: Preeclampsia; Early onset; Maternal complication; Adverse perinatal outcome; Apgar score

Core Tip: Women with preeclampsia (PE) suffer increased morbidity and mortality; their offspring endure higher risks in the early neonatal period and later life. Despite extensive research into PE, the only definitive treatment is to terminate the pregnancy. Many seek efficient prediction methods that may reduce expected risk. Platelet to lymphocyte ratio (PLR), an inflammatory biomarker, was studied in PE; however, little is known about its role in early-onset PE, a subtype with serious consequences for fetal and maternal health. Herein, we examine the role of PLR, which showed a strong, meaningful relationship between fetal growth restriction and poor neonatal outcome, making PLR a recommendable screening parameter.

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INTRODUCTION

Preeclampsia (PE) is identified as new-onset hypertension in formerly normotensive pregnant women, combined with proteinuria, after the 20th wk of gestation; it affects 7% to 10% of all pregnancies. PE is primarily a placenta disease that can be early-onset or late-onset PE according to its onset below or above 32 wk of gestation[1,2]. Early-onset PE (EoPE) is a severe form of PE with a 0.35%-0.50% prevalence caused by inadequate recasting of the uterine spiral arteries and poor placental implantation. The hypoxic placenta produces excessive inflammatory mediators in maternal circulation as the pregnancy proceeds. As a result, vascular integrity is disrupted, and endothelial dysfunction occurs. The latter leads to hypertension, proteinuria, and other PE-related symptoms. The decreased perfusion to the fetus will reduce fetal growth rates; indeed, PE is a major cause of fetal growth restriction (FGR)[2-4].

FGR is linked to adverse obstetric effects, including higher cesarean sections (C-sections), poor neonatal outcomes; such as low Apgar scores, admission to the neonatal intensive care unit (NICU), and meconium-stained liquor, in addition to long-term health effects such as delayed neurodevelopmental milestones and adult cardiovascular disease[5-7].

Diagnosing FGR is made *via* serial ultrasound examination, which needs follow-up and patient compliance[3,8]. As a result, there was a necessity for prediction modules to assess current placental activity. Inflammation is a proposed cause of PE, and numerous inflammatory markers were examined to define PE severity and its related consequences[9-11]. Platelet turnover increases in the maternal circulation of PE women, which eventually reduces their numbers along with alterations in platelet size, and functionality; lymphocytes, on the other hand, will be increased in PE cases[12] owing to a maladaptive immune response and a hyper-inflammatory state in PE[13]. Therefore, the platelet to lymphocyte ratio (PLR) will decrease in severe PE cases as the numerator (platelets) decreases when divided by the increased denominator (lymphocyte). PLR has been studied for prognostic and predictive roles in various diseases, including PE and cancer prognosis. However, they presented inconsistent and sometimes contradicting results[11-13]. Moreover, PLR was not tested in EoPE.

We hypothesized that the reduction in PLR would predict poor obstetrical and neonatal outcomes in early-onset PE. We aimed to predict FGR through biological and ultrasonic markers for patients with EoPE as a primary goal. The secondary aim was to examine the correlation of PLR with predictors of maternal-fetal outcome.

MATERIALS AND METHODS

At the University Hospital in Baghdad, Iraq, a longitudinal study with a cross-sectional design recruited 60 eligible participants in June 2019 and ended in October 2020. The ethical committee of Mustansiriyah University approved the study (IRB 160, February 2019). The Declaration of Helsinki was followed in the study; all participants gave informed consent after we explained the study aims and methods prior to enrollment. The study participants were women with early-onset PE (less than 34 wk). Only women with severe PE were recruited (Figure 1).

Inclusion criteria

Pregnant between the ages of 18 and 40, with a gestational age of 30-32 wk, as determined by history and/or confirmed by an early ultrasound scan. They should not have started treatment. We aimed to have a narrow window in recruitment to make the study's demographics more uniform.

Exclusion criteria

Pregnant women with gestational age outside reference gestational age (> 32 wk and < 30 wk). Medical disorders like kidney and liver diseases, a personal or family history of thyroid, diabetes, or cardiovascular diseases, a personal history of chronic hypertension, blood dyscrasias, and anemia**.** Those with twin pregnancies and congenital fetal anomalies. Smoking mothers and those on aspirin or steroids were also excluded. Non-severe PE cases have been excluded.

Our hospital is a tertiary center that receives many cases of PE in addition to referred cases from the periphery of Baghdad. Admission, assessment of fetomaternal wellbeing, blood pressure control, accelerated lung maturity, and close follow-up for any deterioration of a pregnant mom or her unborn baby necessitating pregnancy termination are all part of the policy for managing severe EoPE.

Maternal assessment

A detailed history and general and obstetrical exams were conducted on the day of admission. In every case, maternal age, weeks of gestation, and systolic and diastolic blood pressure (SBP, DBP) were recorded while the patients were at rest. Lab tests were ordered, including blood biochemistry (serum creatinine, blood urea, alanine aminotransferase, and aspartate aminotransferase); a complete blood count to assess hematological indices hematocrit (10%), platelet distribution width, mean platelet volume, platelet counts, lymphocyte count, where the PLR was created; and a urine sample for evaluating total protein excreted.

Fetal assessment

On the same day of admission, an ultrasound scan was arranged to assess fetal wellbeing [gestational age, amniotic fluid index (AFI), estimated fetal weight (EFW), signs of fetal growth resection (FGR)]. A color Doppler spectral study measured uterine artery pulsatility and resistance index (PI and RI).

Cases were followed until delivery, at which point the maternal outcomes, including; the mode of delivery and reason for a C-section, were recorded. In addition, the neonatal outcome included meconium-stained liquor, a 5-min Apgar score, and admission to the NICU. The information was saved on an Excel sheet so that it could be analyzed later.

Defining study parameters

PE was defined according to the ACOG technical bulletin No. 219 (American College of Obstetricians and Gynecologists), which includes patients with a systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg following 20 wk of gestation and albuminuria of > 300 mg or a sustained 1+ dipstick at 24 h. A gestational age of less than 32 wk defines EoPE[1].

Cases of severe PE had a systolic blood pressure of 160 mmHg or a diastolic blood pressure of 110 mmHg. In the absence of proteinuria, the diagnostic criteria for severe PE comprise hypertension plus thrombocytopenia, impaired liver function, pulmonary edema, new development of renal insufficiency, or new-onset cerebral or visual problems[2].

The early-onset FGR was defined as ultrasonic EFW or fetal abdomen circumference less than the 3rd percentile using a population chart, or EFW or fetal abdominal circumference less than the 10th percentile correlated with umbilical artery PI more than the 95th percentile, or cerebroplacental ratios less than the 5th percentile[3,8].

The sample size was calculated according to the following equation for a cross-sectional study with quantitative variables[14]: Z1-α/2 = is a standard normal variate which is equal to 1.96; SD = standard deviation of a variable calculated by earlier published works; d = the precision level decided by the operator; sample size = $(1.96)^2$ $(0.35)^2/(0.1)^2$ = (3.84 × 0.1225)/0.01 = 43 patients. So, the sample size is 43 patients; we recruited 60 cases.

Statistical analysis

The statistical analysis of the data was carried out through Microsoft Office Excel 2016 and the SPSS 26 program. The numerical data were expressed as mean, standard deviation. Categorical data were

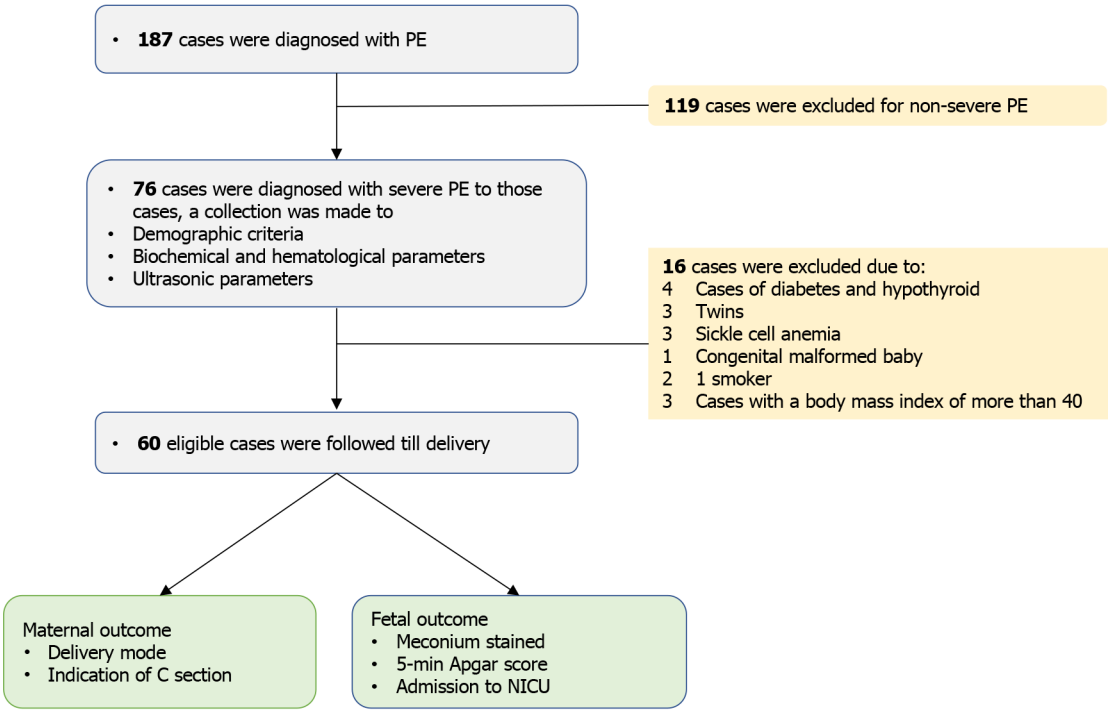

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Figure 1 Study flow chart. PE: Preeclampsia; NICU: Neonatal intensive care unit.

presented as numbers and percentages. Linear regression assessed the correlation between PLR and the study parameters, including maternal and neonatal outcomes. The receiver operating characteristic (ROC) curve was constructed to calculate the PLR that correlates with FGR at the highest sensitivity and specificity. All tests were considered significant when the *P* value was 0.05.

RESULTS

This study examined 60 pregnant women diagnosed with severe PE at a gestational age of 32-30 wk. Table 1 shows the primary criteria of the study. The mean maternal age was 27.0 years ± 2.6 years, the PLR ratio was 7.86 ± 1.75, the EFW was 1.30 ± 0.08, the days of admission to the NICU were 7.09 d ± 2.05 d, and the mean Apgar score was 6.54 ± 1.60. Table 2 describes the maternal outcome in terms of cesarean section (C-section), which showed a trend toward a higher percentage *vs* vaginal delivery with no statistical significance (65% *vs* 35%). Table 3 describes the neonatal outcome of the delivered newborn. Of the total fetuses studied, 37/60 (61.2%) were admitted to the NICU. Seventy percent of admitted fetuses were meconium-stained liquor. The occurrence of meconium-stained liquor was significantly higher among admitted cases. The FGR was reported in 56.7% of the admitted fetuses, which is significantly higher in admitted fetuses. The lowest Apgar scores were found in the admitted cases to the NICU. A statistically significant difference was confirmed in the admission to the NICU between different Apgar scores. The percentage of dead fetuses is not statistically significant between admitted and unadmitted fetuses in Table 4. PLR, taken as an independent variable, was correlated with the FGR parameters (AFI, EFW, PI, and RI). All correlations were strongly significant, as the correlation coefficients (*r*) were (0.98, 0.97, -0.99, -0.98), respectively, with $P < 0.001$. As for newborn parameters, the Apgar score showed a positive correlation of 0.69, while admission days to the NICU showed a strong inverse correlation of -0.98; both had a $P < 0.0001$. The ROC curve calculated a PLR cutoff value < 7.49, an AUC of 0.8, and $P < 0.001$, which was correlated at 100% sensitivity and 80% specificity with FGR, as described in Table 5.

DISCUSSION

Analysis showed a strong, meaningful correlation of PLR to parameters that define FGR, which indicates PLR reliability in FGR prediction. The strong link between PLR and neonatal outcomes, such as Apgar score and number of days in the NICU, suggests that PLR is a good predictor of neonatal outcome.

Table 1 Primary characteristics of the studied group

Maternal demographic and biochemical parameter, *n* = 60	
Maternal age in yr	27.0 ± 2.6
Mean systolic BP in mL/Hg	160.2 ± 5.2
Mean diastolic BP in mL/Hg	105.2 ± 4.7
Urine for albumin in gm/dL	2.89 ± 0.09
Serum creatinine in mg/dL	0.86 ± 0.52
Blood urea in mg/dL	29.38 ± 14.04
Alanine aminotransferase in U/L	27.43 ± 5.32
Aspartate aminotransferase in U/L	21.80 ± 4.49
Maternal hematological indices, *n* = 60	
Hematocrit, 10%	36.58 ± 2.81
Platelet count as × 10^9	182.40 ± 47.42
MPV in fL	10.52 ± 0.23
PDW in fL	16.68 ± 1.37
PLR ratio	7.86 ± 1.75
Fetal demographic criteria, *n* = 60	
Fetal AFI in cm	6.60 ± 1.19
Estimated fetal weight FW in kg	1.360 ± 0.08
PI UA Doppler	3.29 ± 0.59
RI UA Doppler	3.13 ± 0.55
Admission to NICU in d	7.09 ± 2.05
Mean Apgar score	6.54 ± 1.60

Data are mean ± SD. AFI: Amniotic fluid index; BP: Blood pressure; FW: Fetal weight; MPV: Mean platelet volume; NICU: Neonatal intensive care unit; PDW: Platelet distribution width; PI: Pulsatility index; PLR: Platelet to lymphocyte ratio; RI: Resistance index; UA: Uterine artery.

Table 2 Maternal outcome for the enrolled participants, *n* = 60

Parameter	Study participants presented	*n* (%)	*P* value
Mode of delivery	Vaginal delivery	21 (35)	< 0.407
	Cesarean delivery	39 (65)	
Indication for CS delivery	Previous scar	13 (22.5)	< 0.190
	Fetal distress	12 (20)	
	Failed induction	11 (17.5)	
	Malpresentation	3 (5)	

According to Mannaerts *et al*[15], PLR was low among the EoPE group compared to healthy controls. They confirmed that PLR tends to decrease after 20 wk of gestation in patients destined to have PE. Their results were in good agreement with the Yücel *et al*[16], which confirmed a lower PLR among severe PE cases compared to mild PE and healthy controls. Sisti *et al*[17] examined PLR in a case-control study involving cases of HELLP syndrome and healthy controls. Their analysis confirmed lower PLR among affected patients. They suggested that the ratio be included in the HELLP syndrome prediction mode.

Our results showed a strong positive link between PLR and AFI. Less blood flow to the placenta and ischemia cause less blood flow to the fetal kidneys, which lowers AFI[10].

The PLR showed a significant positive correlation with the EFW. Likewise, Can *et al*[18] investigated PLR and NLR in relation to birth weight in healthy and malnourished term babies. Both ratios were

Table 3 Neonatal outcome of the delivered newborn (*n* = 60) presented as numbers and percentage

Variable		Admitted, *n* = 37	Not admitted, *n* = 23	*P* value
Meconium	Meconium stain	26 (70%)	0 (0%)	0.000
	No meconium	11 (30%)	23 (100%)	
Occurrence of FGR	FGR	21 (56.7%)	0 (0%)	0.000
	No FGR	16 (43.3%)	23 (100%)	
Apgar score	> 7	0 (0%)	19 (51.3%)	0.000
	5-7	5 (21.7%)	18 (48.7%)	
	< 5	23 (78.3%)	0 (0%)	
Occurrence of dead fetus	Dead fetus	2 (5%)	0 (0%)	0.257
	Not dead fetus	35 (95%)	23 (100%)	

FGR: Fetal growth restriction.

Table 4 Correlation between the platelet to lymphocyte ratio and the studied variables

PLR *vs* variables	Correlation coefficient	*P* value
AFI	0.98	< 0.001
EFW	0.97	< 0.001
PI	-0.99	< 0.001
RI	-0.98	< 0.001
Apgar score	0.69	< 0.0001
Admission days to NICU	-0.98	< 0.0001

AFI: Amniotic fluid index; EFW: Estimated fetal weight; NICU: Neonatal intensive care unit; PI: Pressure index; PLR: Platelet to lymphocyte ratio; RI: Resistance index; UA: Uterine artery.

Table 5 Receiver operating characteristic curve defined the platelet to lymphocyte ratio cutoff value that discriminated fetal growth restriction with the utmost sensitivity and specificity

Parameter	Cutoff value	Sensitivity	Specificity	AUC	*P* value
PLR	< 7.49	100%	80%	0.9	< 0.001

AUC: Area under the curve; PLR: Platelet to lymphocyte ratio.

significantly high in the malnourished study division; they were recommended as reliable markers.

Akgun *et al*[19] investigated PLR with birth weight and gestational age. Their results show a significant correlation with birth weight. Furthermore, a significant correlation was found between infants' birth weight and gestational age. Kırmızı *et al*[20] examined PLR and NLR in late onset FGR in a case-control study. They did not recommend PLR as its levels were statistically insignificant compared to the NLR. Their study had a small sample size, which may explain the shortcomings of their results.

Both PI and RI were strongly correlated with PLR, which was consistent with previous research linking changes in PI and RI waveforms of uterine arteries to the development of PE and FGR[21]. A Cochrane review also showed that the use of a doppler can help reduce the number of C-sections, labor inductions, and perinatal deaths in FGR babies[22].

Platelet indices, along with PI and RI, were suggested by Abdel Razik *et al*[23] as a way to measure the severity of PE rather than predict its onset.

In terms of obstetric outcomes, 60.0% of cases were ended by C-section, 61.2% of fetuses were admitted to the neonatal care unit, 70.0% were meconium-stained, and 56.7% of the meconium-stained fetuses had FGR, which led to a lower Apgar score among admitted cases. Our results were in line with the study of Jha *et al*[24], where significant differences were seen in the PE groups they examined. In

addition to low Apgar scores at 1st and 5th min and on admission days to the NICU[24].

In the current study, the Apgar score showed a significant *P* value among newborns with a positive correlation to PLR. Okoye *et al*[25] discussed lower PLR in neonates of PE women, which correlates with hypertension severity. PLR has also been linked to poor birth outcomes, as evidenced by low Apgar scores. Their study examined PLR and other blood indices in the cord blood of neonates born to PE mothers. No meaningful association was seen between PLR and neonatal birth weight; it only correlated with 1st and 5-min Apgar scores in newborns.

Kim *et al*[26] discussed a considerably low PLR in women with severe PE. It was most strongly related to the time of admission to the delivery interval.

According to the Özdemirci *et al*[27], PLR in late-onset FGR cases did not show a significant increase. They suggested that an exaggerated inflammatory response was proposed to be a cause for FGR and to be absent in late-onset FGR cases, emphasizing our findings and forming the novelty of our study.

PE is a major risk factor for growth restriction; insufficient spiral artery penetration during early implantation has been blamed for early-onset FGR. To supply the fetus with nutrients, the diseased placenta will develop a mechanism to overcome increased resistance to blood flow and decreased placenta perfusion[5]. Since blood is a primary interface between the fetus and mother, any stressful event will cause blood parameters passing through the placenta to be altered. Therefore, many researchers addressed blood indices, searching for biomarkers that correlate with PE and consequent FGR[10,28].

Different pathophysiologic mechanisms underlie PE sub-types. EoPE is the result of impaired placenta development and improper innate immune system activation that trigger a systemic inflammatory response as early as the second trimester. The injured endothelial cells secrete many cytokines and inflammatory markers into the circulation that cause changes in the complete blood film parameters in PE cases[29,30].

Platelet numbers will be reduced due to consumption. Lymphocyte numbers, key players in systemic inflammation, will be increased. These changes are thought to be responsible for maternal and fetal complications[11]. Hence, PLR forecasts an impending or ongoing inflammatory pathology.

The current study result may have a clinical implication by preventing PE-related complications. Patients with known inflammatory biomarkers may benefit from prophylactic doses of low molecular weight heparin, which has immunomodulatory and anti-inflammatory properties. Low-molecular-weight heparin was recommended to prevent adverse obstetrical problems[31].

We have to acknowledge some of the inconsistencies in earlier studies regarding the value of PLR. Morisaki *et al*[32] technical report explained that different blood ratios were caused by different gestational ages, attributing these inconsistencies to different maternal criteria, gestational age, and inflammatory responses among pregnant women. Our findings clearly demonstrated that there was no statistical correlation between the PLR and the mode of delivery or the indication of the delivery, which was consistent with previous studies that criticized the insignificant role of blood ratios in predicting maternal outcomes[33,34]. Since delivery is the only treatment for PE progression, we must evaluate maternal risk against newborn problems. For that, early and accurate detection is necessary[35,36].

Study limitations

The cross-sectional nature of this study is one since the causal effect cannot be elucidated[37]. A case-control study may perform better in confirming the link between PLR and EoPE. We aimed to collect a higher sample size; however, the COVID-19 pandemic limited many work aspects. It is worth mentioning that risk analysis for the prevention of PE was not done; we think that the current analysis served our aim well. The fact that the current study was a single-center experience may limit the globalization of its results.

Study strengths

Although PLR was examined in late-onset PE, its role in EoPE was not addressed earlier. This paper emphasizes the significance of PLR in predicting early-onset PE associated with FGR[38-40]. PLR was intimately linked to FGR parameters; moreover, it correlated with important predictors of neonatal outcome; its significant correlation to FGR EoPE with high sensitivity and specificity (100%, 80%) and a significant AUC of 0.9, $P < 0.001$ makes it a valuable predictor. Since PLR was already validated for PE and its related co-morbidities, we needed no external validation. FGR is responsible for 50% of unexplained stillbirths. Its implications extend beyond postpartum, as it increases neonatal morbidity and the risk of cardiovascular diseases in the offspring[41]. PLR is simple, inexpensive, and can guide clinicians and assist with the timely referral of affected women to tertiary care centers to halt adverse fetal outcomes. Further studies are needed to explore the future implications of PLR on fetal and maternal health and their predictive value for early childhood and adult-onset diseases.

CONCLUSION

PLR is a reliable predictor of adverse fetal outcomes, including FGR parameters, a poor Apgar score,

and admission to the neonatal care unit among pregnant women with EoPE. PLR had high sensitivity and specificity with no added expanders, making it a recommendable marker in their prediction. In light of the promising role of anti-coagulant use in preventing obstetrical-related complications, PLR may be used in predicting, categorizing, and preventing early-onset PE-related complications.

ARTICLE HIGHLIGHTS

Research background

Preeclampsia (PE) is a pregnancy condition with an unknown origin that includes two subtypes based on 34 wk of gestation: Early and late onset PE; inflammation was postulated as an explanation. The platelet to lymphocyte ratio (PLR), an inflammatory biomarker, was investigated as a predictor of poor maternal-neonatal outcome in patients with early-onset PE (EoPE).

Research motivation

Much research has shown that inflammation may be an underlying pathology that triggers PE development. There is an increased need for new methods with enhanced predictive ability. Demonstrating changes in blood indices, PLR seems an appealing option given the promising results declared by earlier work.

Research objectives

To ascertain if PLR in cases with early-onset PE can be linked to essential predictors of fetomaternal wellbeing during the intrapartum period. The second goal is to analyze the reliability of PLR as a helpful marker for monitoring prenatal predictors in women with early-onset PE.

Research methods

Cross-sectional research at University Hospital involved 60 pregnant women with EoPE (at 32-30 wk of gestation). Platelet counts and indices (mean platelet volume and platelet distribution width), PLR, Doppler study, which produced estimated fetal weight (EFW), amniotic fluid index (AFI), resistance index (RI), and pulsatility index (PI) were all gathered. Participants were tracked until birth, when maternal outcomes such as delivery style and reason for cesarean section were documented, as well as newborn outcomes such as fetal growth restriction (FGR), meconium-stained fluids, five-minute Apgar score, and admission to the critical care unit.

Research results

A cesarean section trend has been noted. Sixty-one-point two percent (37/60) fetuses were hospitalized to the newborn care unit, 70% had meconium-stained liquid, and 56.7% had FGR. PLR was shown to be favorably connected with AFI and EFW (r = 0.98, 0.97, P < 0.001), and negatively correlated with PI and RI (r = -0.99, -0.98, P < 0.001). The Apgar score and the number of days admitted to the critical care unit had a positive and negative connection (r = 0.69, -0.98, P < 0.001), respectively. The PLR cutoff value derived by receiver operating characteristic (7.49) differentiated FGR with 100% sensitivity and 80% specificity.

Research conclusions

PLR had substantial P value associations with FGR measures and poor neonatal outcomes, making it a promising biomarker for screening EoPE-related problems. More research is needed to determine the influence on maternal-neonatal health.

Research perspectives

Defining reliable biomarkers that are antenatal clinics based with no added expense can be a promising option, especially for low-resource settings.

FOOTNOTES

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CASE REPORT

Stone accumulation overlying vaginal mesh exposure: A case report

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Abstract

BACKGROUND

Vaginal stones are rare with current literature limited to case reports. Vaginal stones are classified as primary or secondary stones. Primary stones form in the vagina when there is urinary stasis. Secondary stones form in the presence of a vaginal foreign body that acts as a nidus for the deposition of urinary salts. Foreign bodies, such as surgical mesh, make vaginal stone formation more likely, particularly in patients with urinary incontinence and conditions that predispose them to urinary calculi formation.

CASE SUMMARY

A 71-year-old female with a history of sacrocolpopexy, hyperaldosteronism, and urgency urinary incontinence presented with vaginal stone accumulation overlying two areas of vaginal sacrocolpopexy mesh exposure. The vaginal stones were initially removed to permit examination, but the stones reaccumulated at the site of the exposed mesh, later requiring definitive surgical management.

CONCLUSION

Patients with vaginal mesh exposure and conditions that predispose them to kidney stones are not ideal candidates for expectant management of mesh exposure, particularly if they have coexisting urinary incontinence. These individuals should be counseled about possible vaginal stone accumulation, and surgical management should be considered.

Key Words: Vaginal stones; Urgency urinary incontinence; Sacrocolpopexy; Mesh complications; Mesh exposure; Case report

Core Tip: Patients with vaginal mesh exposure that have underlying conditions that predispose them to urinary calculi formation may be at increased risk of vaginal stone accumulation at the site of mesh exposure. Expectant management of the mesh exposure likely allows vaginal stones to accumulate as urine is persistently in contact with the foreign body. Definitive surgical management in the form of complete excision of the entire area of exposed mesh should be recommended to patients to avoid vaginal stone accumulation.

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INTRODUCTION

Vaginal foreign bodies, such as surgical mesh, are risk factors for the formation of secondary vaginal stones. When urine has prolonged contact with an exposed foreign body, secondary vaginal stones can form due to crystallization of stagnant urine. Urinary incontinence is therefore thought to contribute to vaginal stone formation[1]. We propose that individuals with exposed vaginal mesh and underlying medical conditions that place them at increased risk of kidney stones are prone to forming secondary vaginal stones. Following the CARE Checklist (2016) and with signed patient consent, we present the unique case of a patient with hyperaldosteronism and urgency urinary incontinence who had vaginal stone formation and later reaccumulation at the site of sacrocolpopexy mesh exposure.

CASE PRESENTATION

Chief complaints

A 71-year-old G4P4004 Caucasian female with known vaginal sacrocolpopexy mesh exposure that she previously opted to expectantly manage presented to urogynecology clinic with complaints of overactive bladder and urgency urinary incontinence.

History of present illness

The patient's symptoms of overactive bladder and urgency urinary incontinence had been worsening for about four years. Her urinary incontinence was nearly constant with dribbling throughout the day. Previous trials of oxybutynin, mirabegron, and solfenacin were ineffective.

History of past illness

In 2014, the patient underwent robotic-assisted supracervical hysterectomy, bilateral salpingo-oophrectomy, mesh sacrocolpopexy, posterior colporrhaphy, perineorrhaphy, retropubic midurethral sling insertion, and cystoscopy. One year after surgery, two areas of mesh exposure were identified at the anterior and posterior apices involving the sacrocolpopexy mesh. The patient was asymptomatic and opted to pursue expectant management. The patient was lost to follow-up until 2019 when she represented with the above chief complaint.

Personal and family history

Relevant personal history includes hyperaldosteronism, overactive bladder, urgency urinary incontinence, and tobacco use.

Physical examination

There was stone formation overlying the sacrocolpopexy mesh exposure sites at the anterior and posterior vaginal apices adjacent to the cervix. Given the degree of apical support maintained, office examination was difficult. Evaluation in the operating room was recommended.

In 2020, the patient underwent examination under anesthesia, cystourethroscopy, and vaginoscopy. On vaginoscopy, a midline anterior mesh exposure measuring approximately 3 cm (vertical) × 2 cm (transverse) × 3 mm (height) was identified with a 4 cm × 3 cm stone intermixed with the mesh fibers. A midline posterior mesh exposure measuring approximately 2.5 cm (vertical) × 0.5 cm (transverse) × 0.5 cm (height) was also identified with a 4 cm × 2 cm stone intermixed within the mesh fibers. Cystourethroscopy did not demonstrate any evidence of mesh exposure in the bladder or urethra, and vesicovaginal and urethrovaginal fistulae were specifically excluded. The majority of the calcifications were removed intraoperatively, which permitted improved visualization of the exposed mesh sites.

Laboratory examinations

Vaginal stone analysis was performed. The composition was noted to be 70% hydroxyapatite (calcium phosphate), 25% magnesium ammonium phosphate, and 5% ammonium acid urate.

Imaging examinations

None.

FINAL DIAGNOSIS

Following intraoperative evaluation, definitive surgical management with excision of the mesh exposure sites was planned. However, while awaiting surgery, the patient was in a motor vehicle accident requiring prolonged recovery. Additionally, factors related to coronavirus disease 2019 cases caused an approximately one-year delay in reevaluation. During this time, the vaginal stones reaccumulated at the exposed mesh sites. In 2021, mesh excision *via* a vaginal approach was performed. There was a 3 cm × 2 cm stone found anteriorly and a 2.5 cm × 0.5 cm stone found posteriorly. The stones were completely intermixed with the mesh strands (Figure 1). The patient was diagnosed with reaccumulation of vaginal stones at the site of exposed sacrocolpopexy mesh.

TREATMENT

The patient underwent excision of the entirety of the exposed mesh areas, concomitant removal of the stone material, and unremarkable cystourethroscopy. The stone analysis revealed a 100% hydroxyapatite composition.

OUTCOME AND FOLLOW-UP

The patient had no perioperative complications and did well postoperatively. On six-week follow-up examination, there was no evidence of continued mesh exposure or reaccumluation of vaginal stone material. The patient began intravesical onabotulinum toxin A injections for management of urgency urinary incontinence.

DISCUSSION

Sacrocolpopexy is a reconstructive surgical procedure that is performed to correct apical prolapse. A synthetic mesh is used to support the vagina, with or without the cervix, by affixing it to the anterior longitudinal ligament overlying the sacrum. The prevalence of mesh exposure following sacrocolpopexy is estimated to be as high as 10.5%[2]. While patients with mesh exposure may be asymptomatic, common presenting symptoms include pelvic pain, vaginal bleeding, and dyspareunia[3]. In this case, the patient was asymptomatic but was found to have vaginal stones on pelvic exam during follow-up examination. For a mesh exposure involving macroporous synthetic mesh, management strategies include expectant management, conservative management with the use of vaginal estrogen, or surgical management[3].

In general, data on vaginal stone formation are limited to case reports, and vaginal stones are therefore considered a rare phenomenon. Vaginal stones can be broadly categorized into primary or secondary stones. Primary stones typically result from urinary stasis within the vagina allowing for deposition of urinary salts. Some causes of primary stones include vaginal outlet obstruction, neurogenic bladder dysfunction, prolonged recumbent positioning such as in bedridden or paralyzed patients, and vesicovaginal, urethrovaginal, or ureterovaginal fistulae[4-7]. Secondary stones form in the vagina in the presence of a foreign body, such as contraceptive devices or exposed vaginal mesh, which acts as a nidus for urinary crystallization and subsequent stone formation[1].

Although limited data exist detailing the composition of vaginal stones, review of the current literature suggests that both primary and secondary vaginal stones are most commonly composed of struvite[1,4,5,8]. The proposed mechanism for struvite stone formation is that stasis of urine infected with urease-producing bacteria, such as *Klebsiella*, *Proteus mirabilis*, and *Escherichia coli*, causes the normally acidic environment of the vagina to become alkaline, which facilitates formation of struvite stones[9]. The first stone analysis for our patient revealed a predominantly hydroxyapatite composition (with a small struvite percentage), and the second stone analysis revealed 100% hydroxyapatite composition, which is a clear contrast to previously published cases of struvite vaginal stones. It is important to note that the composition of our patient's vaginal stones is more typical of kidney stones.

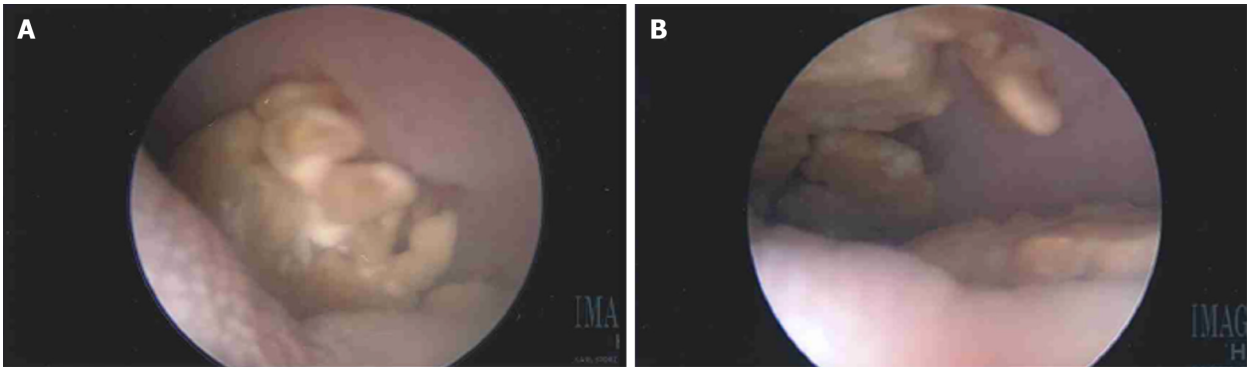

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Figure 1 Intraoperative image of vaginal stones. A and B: Vaginal stones overlying the site of sacrocolpopexy vaginal mesh exposure visualized during vaginoscopy.

The most common composition of kidney stones is calcium oxalate with a frequency of 67%, followed by hydroxyapatite stones with a frequency of 16%. Struvite kidney stones are relatively uncommon with a frequency of 3%[10].

The predominantly hydroxyapatite composition of our patient's vaginal stones is unusual since most published cases of vaginal stones report a struvite composition. Hydroxyapatite is more common for kidney stones. Our patient has no history of nephrolithiasis; but she does have hyperaldosteronism. We propose that this patient's history of hyperaldosteronism is responsible for the atypical composition of the secondary vaginal stones. Hyperaldosteronism causes hypercalciuria, phosphaturia, and hypocitraturia. These urinary changes are risk factors associated with kidney stone formation and recurrence [11]. In our patient's case, these urinary changes secondary to hyperaldosteronism likely contributed to the atypical composition of her vaginal stones, which more closely resemble that of the most common types of kidney stones rather than the typical struvite composition of vaginal stones. Therefore, it is prudent for clinicians to be aware of medical conditions that increase the risk of kidney stones because patients with such conditions may be at increased risk for forming vaginal stones.

In addition to the unusual hydroaxyapatite composition of this patient's vaginal stones, this patient's rapid reaccumulation of stone material overlying the mesh exposure after the initial stone removal is unique to this case. The reaccumulation suggests that patients with vaginal mesh exposure who are at increased risk of kidney stones may not be optimal candidates for expectant management, even if they have asymptomatic mesh exposure. This is particularly pertinent for individuals with risk factors for persistent contact of the mesh exposure to urine, such as significant urinary incontinence as with our patient. In addition, the short-interval reaccumulation of stones in this patient favors recommending excision of exposed mesh rather than temporizing measures, such as removal of the stone material only. Leaving exposed mesh is likely to result in reaccumulation of the vaginal stones.

Our patient's case highlights an example of vaginal stone formation overlying a vaginal mesh exposure in the setting of a medical condition that increases the risk of kidney stones. The stone analyses from this case suggest that individuals with underlying conditions that predispose them to kidney stones may be at increased risk of forming secondary vaginal stones with compositions that more closely resemble kidney stones rather than vaginal stones. This patient's case was also compounded by severe urgency urinary incontinence, which resulted in significant exposure of the mesh foreign body to urine. Individuals with a vaginal nidus, such as exposed mesh, that is in persistent contact with urine may be at higher risk of stone reaccumulation without definitive management. This case illustrates the importance of clinician awareness of conditions that increase the risk of kidney stones, as well as individualized patient counseling about the risk of developing stones overlying a mesh exposure. These patients are not optimal candidates for expectant management, and definitive surgical management with excision of the entire area of mesh exposure should be recommended.

CONCLUSION

Patients with vaginal mesh exposure and underlying conditions that predispose them to urinary calculi formation may not be ideal candidates for expectant management, especially if they have coexisting urinary incontinence. These individuals should be counseled about the possibility of stone accumulation, and surgical management should be considered. This unusual case adds to the current limited literature on vaginal stones. This case additionally helps to guide counseling of patients with vaginal mesh exposure that have concomitant risk factors for kidney stones and persistent contact of exposed mesh with urine.

FOOTNOTES

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EDITORIAL

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

Mike Etemady, Melika Hajizadeh, Beata Gidaszewski, Julie Ann Swain, Seng Chai Chua, Marjan Khajehei

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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

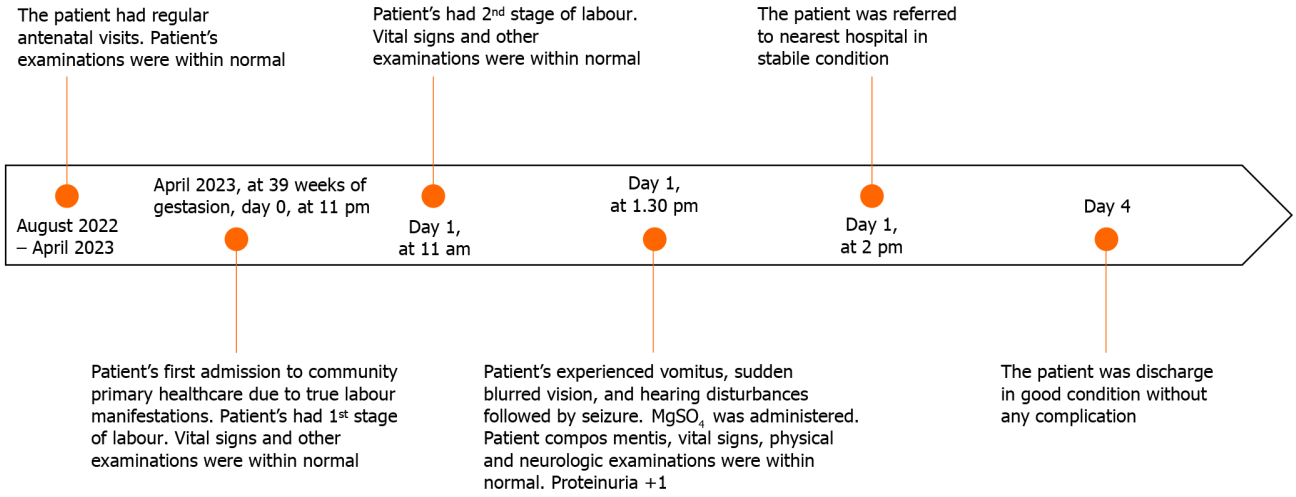

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Figure 1 Timeline of the case report.

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].

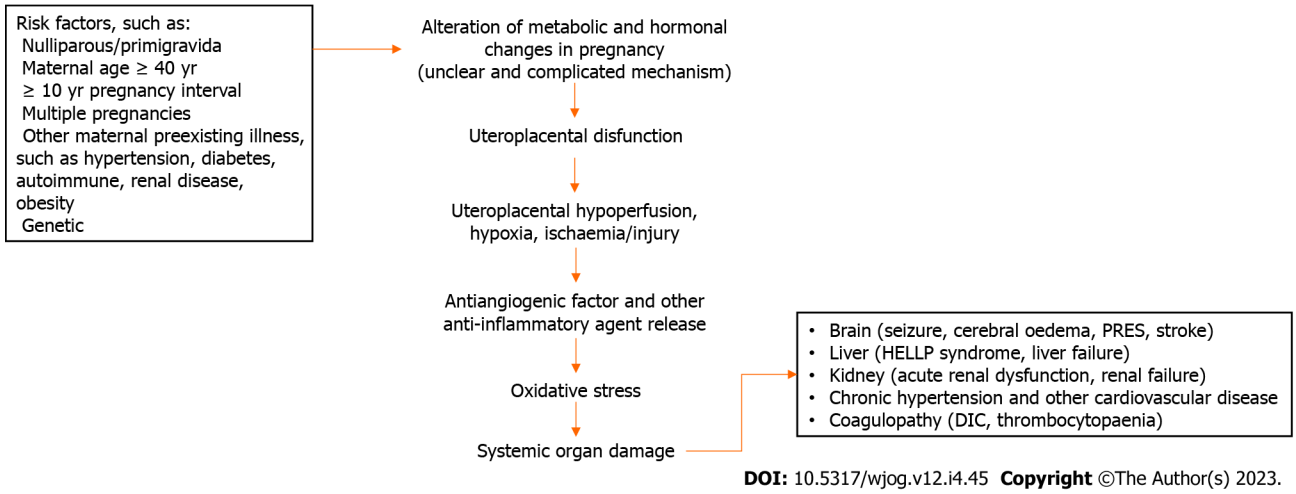

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Figure 2 Possible pathomechanisms of eclampsia.

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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