



Atypical preeclampsia-eclampsia syndrome at 18 weeks of gestation: A case report

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ABSTRACT

Background: Preeclampsia is currently defined as new-onset hypertension occurring with significant proteinuria, maternal organ dysfunction, and/or placental insufficiency at or after 20 weeks of gestation. In the majority of cases, it occurs before 48 h postpartum. Therefore, preeclampsia occurring before 20 weeks of gestation or after 48 h postpartum is atypical and may not be easily diagnosed.

Aim: A case of atypical preeclampsia is presented to highlight the need for increased vigilance by healthcare professionals to ensure timely diagnosis and treatment to prevent adverse outcomes.

Case Presentation: A 29-year-old woman, gravida 3, para 1, with one previous miscarriage, commenced antenatal care at 10 weeks of gestation. Based on history and physical examination, the only risk factor for preeclampsia identified was a primipaternity. The patient had a single mid-trimester scan but no robust multimodal screening for preeclampsia using ultrasound or biomarkers. At 18 weeks of gestation, she presented to a primary healthcare clinic with headache, epigastric pain, and a documented single blood pressure reading of 169/71 mmHg. She was placed on alpha-methyl dopa and managed as an outpatient. A day later, she had two episodes of seizures and was transferred to a tertiary hospital. She was diagnosed with atypical eclampsia and HELLP syndrome. Following MgSO₄ therapy and stabilization, an uneventful termination of pregnancy was performed, and she recovered fully.

Conclusion: Robust screening for preeclampsia using history and physical examination, ultrasonography, and biomarkers in the first trimester to identify women at high risk of the disease for prophylactic therapy with aspirin may prevent this disorder.

1. Introduction

Preeclampsia complicates 2–5% of pregnancies and is usually diagnosed at or after 20 weeks of gestation in women who develop new-onset hypertension and significant proteinuria, maternal organ dysfunction and/or placental insufficiency [1]. The burden of the disease is worse among women of African ancestry. For instance, preeclampsia-related maternal mortality is 3-fold higher in African Americans than in Caucasian women [2]. In South Africa, the burden is high, with an incidence of 9.3% [3,4], and the 2017–2019 triennial Saving Mother's Report showed that hypertensive disorders of pregnancy, particularly preeclampsia, is the leading direct cause of maternal mortality in South Africa, accounting for 17% of maternal deaths [5].

The pathogenesis of preeclampsia is not fully understood, but many

theories have been proposed [6]. In late-onset preeclampsia (defined as occurring at ≥ 34 weeks of gestation), the placenta overgrows its blood supply and/or becomes old, resulting in syncytiotrophoblastic stress. This usually occurs in mothers with a comorbidity such as obesity and diabetes. In early-onset preeclampsia (defined as occurring before 34 weeks of gestation), there is a lack of cytotrophoblastic invasion of spiral arteries at the placental bed, resulting in inadequate canalization of the vessels, abnormal blood flow, and syncytiotrophoblastic stress. Usually, the cytotrophoblastic invasion of spiral arteries occurs between 8 and 16 weeks of gestation (but is largely completed at 18 weeks) [7,8]. In both early- and late-onset preeclampsia, the syncytiotrophoblastic stress in a susceptible mother results in the release of mediators such as soluble fms-like tyrosine kinase-1 (sFlt-1) that damages vascular endothelium, which causes the clinical features of preeclampsia, which usually

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manifest at ≥ 20 weeks of gestation [6–8]. The threshold of 20 weeks of gestation used in the definition of preeclampsia is based on the pathogenesis of the disease and the distribution of gestational ages at which the clinical features manifest. Therefore, the occurrence of clinical features of preeclampsia at a gestational age of < 20 weeks is uncommon and atypical.

Atypical cases of preeclampsia are not easily diagnosed and may result in adverse outcomes. Previously, proteinuria and new-onset hypertension at ≥ 20 weeks were the only criteria required to make the diagnosis of preeclampsia, and this resulted in a high number of atypical cases [9]. The current diagnostic criteria for preeclampsia include maternal organ dysfunction and features of placental insufficiency and, as a result, the number of atypical preeclampsia has reduced [9]. Currently, atypical preeclampsia is defined as manifesting before 20 weeks of gestation or after 48 h postpartum [9,10]. In this article, we present a case of atypical preeclampsia manifesting as imminent eclampsia, haemolysis elevated liver enzymes and low platelets (HELLP) syndrome, and eclampsia at 18 weeks of gestation to show that despite the broadened definition of preeclampsia there are still atypical cases. It highlights the need for increased vigilance by healthcare professionals to ensure early recognition and appropriate management to prevent adverse outcomes.

2. Case Presentation

A 29-year-old woman, gravida 3, para 1, with one previous miscarriage and a caesarean section for cephalopelvic disproportion, booked for antenatal care at 10 weeks of gestation at a primary healthcare clinic with blood pressure (BP) 119/66 mmHg and a body mass index of 25 kg/m². She had been on treatment for human immunodeficiency virus (HIV) infection for 7 years with a viral load lower than detectable and CD4 of 434 cells/ μ l. The only known risk factor for hypertensive disorders of pregnancy based on history and physical examination was primipaternity. The patient was on a fixed-dose combination of tenofovir, efavirenz, and emtricitabine (TEE) for HIV treatment and had no complications. When she booked for antenatal care, full blood count (FBC) and liver function test (LFT) were not performed, in line with the national guideline [11]. She was not screened for preeclampsia using ultrasound or biomarkers because these modalities were unavailable. She had a single mid-trimester scan.

At 18 weeks of gestation she presented to the primary healthcare clinic with headache, epigastric pain, and a BP of 169/71 mmHg. Alpha-methyldopa was prescribed. Given her low-risk status for preeclampsia, she was discharged home. A day later, while at home, she had two witnessed episodes of generalised tonic-clonic seizures lasting approximately 2 min. She was transferred to the primary healthcare clinic and on arrival had BP 133/87 mmHg, 2+ proteinuria and a normal score on the Glasgow Coma Scale. She received a loading dose of MgSO₄ and was referred to a tertiary hospital.

At the tertiary hospital, she had a BP of 161/96 mmHg, but other vital parameters and clinical examination were normal, including a cardiovascular examination and a symphysis-fundal height of 18 weeks. She was admitted to an obstetric high-care unit, and received rapid-acting nifedipine, alpha-methyldopa, and a maintenance dose of MgSO₄. Blood tests showed a platelet count 35×10^9 /L, AST 130 U/L, ALT 66 U/L, and LDH 1638 U/L, which were in keeping with HELLP syndrome. Renal assessment was normal, with blood urea of 4.4 mmol/L and serum creatinine of 64 μ mol/L. She underwent medical termination of pregnancy because of the severity of her condition using a dual method – vaginal misoprostol 100 μ g 6 hourly for 4 doses and transcervical Foley catheter bulb – and delivered a 200 g fetus. A computerized tomography scan of the brain performed prior to the termination of pregnancy showed a posterior reversible encephalopathy syndrome. The patient recovered, was counselled, and discharged home on day 6 postpartum. She subsequently had a normal 12-week postnatal clinic visit with normal BP and a negative connective tissue screening.

3. Discussion

It would have been informative to know if low platelet count and abnormal liver enzymes were present at booking, especially given the history of HIV infection and anti-retroviral therapy (ART). However, in public healthcare facilities in South Africa, LFT and FBC are not routinely assessed in all pregnant women during the first antenatal clinic visit (booking visit). The mandatory blood tests performed at booking are haemoglobin concentration, rapid plasma regain, Rhesus D factor, and HIV counselling and testing [12]. For women living with HIV who are already on ART with no complications, viral load, CD4 count, and serum creatinine are also assessed at booking [11]. The serum creatinine helps with the assessment of the renal side-effects of tenofovir. This is because the first-line ART used by most people living with HIV who attend public healthcare facilities in South Africa is a fixed-dose combination of TEE. Not long ago, a fixed-dose combination of tenofovir, lamivudine, and dolutegravir (TLD) was introduced. The patients on these regimens (TEE or TLD) rarely develop liver toxicity. This is unlike those who were on a nevirapine-based regimen, particularly on a long-term basis early in the HIV epidemic. In women newly diagnosed with HIV infection, FBC and serum creatinine are performed and repeated at 3 months following the commencement of ART, and CD4 is assessed at the time of commencement of ART, while the viral load is checked 3 months afterward [11].

The diagnosis of preeclampsia before 20 weeks of gestation is often challenging. Recorded BP readings are questionable if the correct measurement techniques are not used [13]. During the measurement of BP, a validated device should be used to obtain serial measurements. The average of the last two readings should be recorded as the BP [14]. In pregnancy, a reading above or equal to a diastolic pressure of 110 mmHg and/or systolic pressure of 160 mmHg is severe hypertension [15], and a repeat BP measurement within 15 min is required [13,16,17]. If severe hypertension persists after 15 min, a rapid-acting antihypertensive drug should be administered, preferably within an hour [15,18]. This may prevent severe adverse maternal complications [14]. While alpha-methyldopa lowers BP in severe hypertension, an additional antihypertensive drug is often required [14]. Furthermore, preeclamptic patients presenting with severe hypertension and proteinuria, or hypertension with neurological clinical features, should also receive MgSO₄ therapy to prevent eclampsia [15]. These treatments are recommended in pregnancy hypertension guidelines [15,19], including the maternity care guidelines available in primary healthcare clinics in South Africa [12]. Patients presenting with atypical or severe features of preeclampsia should be referred to a specialist obstetric unit for further management to exclude differential diagnoses such as gestational trophoblastic diseases, antiphospholipid syndrome, lupus nephritis, thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and antiphospholipid syndrome [10,20,21]. This should be the standard of care regardless of the timing of the occurrence of the clinical features.

In cases of suspected preeclampsia, i.e., when there are incomplete diagnostic features, assessment of blood concentration of sFlt-1 and placental growth factor (PIGF) may be used to rule in or rule out the diagnosis if the gestational age is > 20 weeks [6,9,22]. The sFlt-1/PIGF ratio has been extensively studied after 20 weeks of gestation (and not earlier than 20 weeks) for its diagnostic and prognostic value. Therefore, the use of sFlt-1/PIGF ratio for diagnosing preeclampsia in the clinical setting during the first half of pregnancy is not supported by available evidence. Of note, in 2021, the International Society for Study of Hypertension in Pregnancy recommended a serum ratio > 38 as a marker of placental insufficiency [15]. The stated ratios are based on the laboratory analysis of sFlt-1 and PIGF using the Roche Elecsys platform. Nonetheless, the assessment of these angiogenic factors is not in routine clinical use in many countries, including South Africa, and there has been controversy about the ideal sFlt-1/PIGF diagnostic cut-off value for each racial group, with recent reports suggesting that black women may require a lower threshold than Caucasian women, and that black women

may be at a disadvantage with the threshold used currently [23,24]. This calls for additional studies in various settings to investigate the diagnostic thresholds. There is also a need to include cases of atypical preeclampsia in future studies.

Placental histology may help elucidate features of placental-mediated diseases such as fetal growth restriction and preeclampsia. Placental vascular malformations (including maldevelopment and malperfusion) are among the microscopic features that may support the diagnosis of preeclampsia [25]. In the index case, the placenta was not sent for histology due to logistic challenges.

The use of history and physical examination in addition to ultrasound and biomarkers as recommended by the Fetal Medicine Foundation [26] may help to identify women at high risk of developing preeclampsia. Those identified can be given preventive therapy using aspirin and calcium supplementation (where dietary intake is low, as is often the case in South Africa). The index patient did not have any robust multimodal/combined/multivariate screening for preeclampsia with ultrasonography and biomarkers such as pregnancy-associated plasma protein-A (PAPP-A) and angiogenic factors because of the unavailability of the tests. Due to limited resources, multimodal screening for preeclampsia is mostly available in the private healthcare sector in South Africa. The patient was on calcium supplementation as a general measure offered to all pregnant women receiving antenatal care in public healthcare facilities in South Africa. She was not on aspirin prophylaxis as she was regarded as being at low risk of developing preeclampsia based on history and physical examination. In the authors' opinion, the primipaternity was a major risk factor in the index case. Unfortunately, clinical history alone identifies only approximately 41% of women at risk of preeclampsia [27]. In a future pregnancy, the patient should receive both aspirin and calcium for the prevention of preeclampsia, and she was given this information.

The best multimodal screening for preeclampsia in early pregnancy includes maternal risk factors, uterine artery pulsatility index (UTPI), mean arterial pressure (MAP), and serum PIGF (or PAPP-A if PIGF is unavailable) [1,26]. The International Federation of Gynecology and Obstetrics (FIGO) recommends that where UTPI and/or PIGF are unavailable, maternal risk factors and MAP (and not maternal risk factors alone) should be used as the input parameters in the online calculator (<https://fetalmedicine.org/research/assess/preeclampsia/first-trimester>) to determine the risk [1]. When maternal risk factors, MAP, UTPI, and PIGF are used, a woman with a risk level of 1 in 100 or more is considered to be at high risk of preeclampsia [1]. Notably, universal aspirin prophylaxis has been advocated by some investigators, for a number of reasons, including support for the concept of libertarian paternalism [28] (which entails the provision of influenced options to assist an individual make a better choice while having the opportunity to opt-out), the favourable safety profile of aspirin, and its low economic cost in comparison with the healthcare cost of preeclampsia [29]. This may be of value in low- and middle-income countries where the burden of preeclampsia is high. However, concerns about and arguments against universal aspirin prophylaxis for preeclampsia include problems of pill burden, compliance with treatment, apprehension over foeto-maternal side-effects in low-risk pregnancy, and the long-term consequences of aspirin in the offspring. The side-effects include obstetric haemorrhages in the mother, and intra- and extra-cranial haemorrhage in the neonates [1,14,30,31]. Additionally, the number needed to treat to prevent one case of preeclampsia through universal aspirin prophylaxis is at least 500 [28], which is arguably high. Due to these concerns, universal aspirin prophylaxis for preeclampsia has not been approved. However, the US Preventive Services Task Force (USPSTF) recommends that aspirin prophylaxis may be considered if at least one moderate risk factor is present [32].

4. Conclusion

Robust screening for preeclampsia in the first trimester is

recommended to identify women at high risk of the disease and offer them preventive therapy such as aspirin. This is crucial given that atypical preeclampsia is often difficult to diagnose, and adverse outcomes may occur following a delay in the diagnosis and/or treatment. However, suspected cases of preeclampsia should be referred to a specialist-led obstetrical unit for further management and the exclusion of differential diagnoses.

Contributors

Ugonna Aja-Okorie was involved in patient care, participated in the conception of the case report, searched the literature, acquired and interpreted the data, and drafted the manuscript.

Nnabuike Chibuoke Ngene was involved in patient care, participated in the conception of the case report, searched the literature, contributed to data interpretation, supervised the work, and revised the article critically for important intellectual content.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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