CASE REPORT

Folic acid allergy in pregnancy: a case report

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Abstract

Folic acid intake prevents neural tube defects in the developing foetus. Folic acid allergy in pregnancy is very rare. Most physicians are unaware of this complication. Only 29 cases of folic acid allergy, mainly in non-pregnant women, have been reported in literature worldwide since 1949. In most reported cases, the involvement of folic acid was confirmed by the absence of symptoms after withdrawing folic acid. We present a case of folic acid allergy in a primigravida. The patient developed severe urticaria within hours of folic acid intake, followed by mild vaginal bleeding. Her symptoms improved within days of stopping folic acid. She delivered a healthy baby at term without anomalies or pregnancy complications. Allergy to folic acid was confirmed postnatally by oral intake of a lower dose of folic acid, where the patient again had urticaria that resolved when the medication was stopped.

Keywords: Pregnancy, Folic acid, Allergy.

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Introduction

Folic acid (FA) is an essential member of the vitamin B group. The terms folic acid and folate are used interchangeably. Folates are a family of essential nutrients related to FA that come from a natural source. In contrast, FA is the manufactured form used as a dietary supplement.[1] Since it is not synthesised in the human body, it is enlisted on the World Health Organisation's list of essential medicines.[2] This vitamin's role is crucial in synthesising DNA and RNA and is, therefore, important during periods of rapid cell division, such as pregnancy and foetal development.[2]

The intake of folic acid, or folate, prevents neural tube defects (NTDs) in the developing foetus. The daily recommended dose of FA to prevent NTDs is 400 micrograms. It should be started at least three months before conception and continued until the 12th week of gestation in all pregnancies.[3] A higher dose (up to 5mg per day) is indicated for some high-risk pregnancies, which should be continued throughout the pregnancy, e.g. if the mother is thalassemia major or has sickle cell disease.[3]

Many countries where food is fortified with FA have noticed a significant drop in the prevalence of NTDs.[4] Prolonged use of FA may improve male and female fertility while reducing the risk of certain cancers, stroke, and heart diseases.[4] Taking high doses of FA over a long time may reduce the risk of stroke. On the other hand, FA over-dosage may increase prostate cancer risk and mask the signs and symptoms of vitamin B12 deficiency.[4]

Folic acid allergy, which can be life-threatening, is extremely rare. Most physicians are unaware of this complication. Only 29 cases of FA allergy, mostly in non-pregnant women, have been reported in the literature worldwide since 1949.[5,6] Twelve of the 29 cases resulted from intravenous folinic acid in cancer patients. However, the remaining cases were reported after oral FA intake, and the clinical presentation ranged from mild skin rashes to anaphylactic shock.[6] A paper from Canada reviewed 15 local cases of FA allergy in 2014 and noted that most (93%) patients were non-pregnant women.[7] The dosage in these cases was 1mg/day or less. Clinical presentation varied in these patients. Two of the four pregnant women with FA allergy miscarried spontaneously without any other known risk factor. Laboratory tests to confirm FA allergy were not done for any of the 15 cases from Canada.[7] In the majority of cases reported in the literature, the involvement of FA was confirmed by the absence of symptoms after withdrawing FA.[6]

Case Report

A 26-year-old primigravida presented to the antenatal clinic at Community Medical Centre, Dubai, UAE, in June 2022, to confirm her pregnancy. There were no presenting complaints. The last menstrual period was five weeks before the presentation. It was a spontaneous conception with no previous history of medical comorbidities. Her sister was born with spina bifida. There was no preconception or current history of FA intake. She was not known to have drug allergies. The pregnancy was confirmed by testing serum beta hCG, and 5mg folic acid once daily was prescribed. A follow-up visit was planned to perform booking tests and a transvaginal ultrasound.

The patient presented the following day with a generalised

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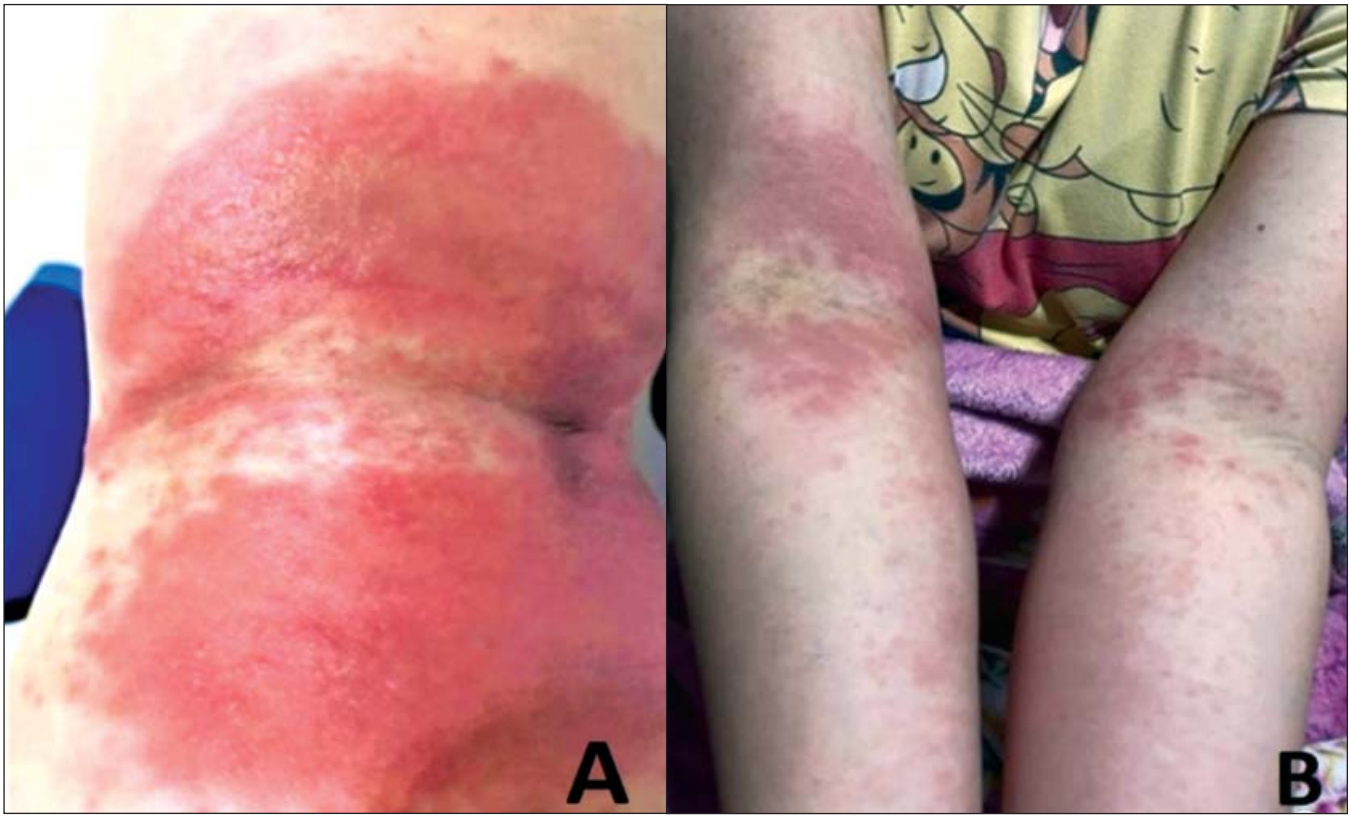

Figure: A) A generalised raised, itchy rash developed within hours of the intake of folic acid
B) Fading rash after stopping folic acid

raised and itchy rash (Figure 1A) and vaginal spotting. She did not have pain. The rash had appeared within a few hours of taking the first dose of FA. She was otherwise feeling well and did not have breathing difficulties. A transvaginal ultrasound was performed to confirm the location of the pregnancy. She was advised to discontinue taking FA, and oral Dydrogesterone 10mg twice daily was prescribed till 12 weeks gestation to support the pregnancy. She was referred to a dermatologist. Blood tests (complete blood count, liver function tests, and serum tryptase) showed normal results. The patient declined a skin prick test. Oral Loratadine (antihistamine) 10mg was prescribed once daily for seven days. She was advised to increase the intake of green leafy vegetables.

Her symptoms improved within days of containing the folic acid (Figure 1B). There was no further episode of vaginal bleeding. The patient was followed-up after two weeks, and the viability of the pregnancy was confirmed. She delivered a healthy baby at term without anomalies or pregnancy complications.

Allergy to folic acid was confirmed after the delivery of the baby by oral intake of low-dose (400 micrograms) folic acid, where the patient again had urticaria that resolved by stopping the medication.

Discussion

To our knowledge, this is the sixth reported case of FA allergy in pregnancy.[7,8] Hypersensitivity reactions to folic acid intake are probably secondary to an IgE-mediated mechanism.[6] IgE-mediated immediate hypersensitivity may result from conjugates formed between FA and self-proteins. However, hypersensitivity may also result from IgE-independent mechanisms, including activation of the complement system, direct activation of mast cells, and cytokine-mediated mechanisms.[6] The clinical presentation of this patient was unusual and most likely resulted from an IgE-independent mechanism. In contrast to an IgE-mediated reaction where patients may receive many doses of FA before the appearance of the first symptoms, giving the time for sensitisation,[5,6] symptoms usually appear after the first exposure to FA, in which case pre-existing IgE antibodies, e.g. acquired through tick bites, cause these reactions.[9] Symptoms such as urticaria, pruritus, hypotension, and tachycardia suggest IgE-mediated anaphylaxis, and skin tests are positive.[6] In reactions

unrelated to Ig-mediated reactions, most patients present with non-specific symptoms such as lower back pain and chills. Moreover, serum tryptase levels were not elevated as in the current patient, and the reaction can occur during the first exposure.[6] While most women with FA allergy miscarry, this patient reached term and had an uncomplicated pregnancy and delivery.

This patient had well-tolerated folate that had a natural source. There are three possible explanations. First, cooking may alter the naturally present folates non-allergenic. Second, antigens that provoke an immune response are absent or in minimal amounts in naturally occurring folate.[10] Third, it has been suggested that dietary folates are present as poly-glutamate, while pharmaceutical preparations contain their mono-glutamate form.[10] The human body has a limited ability for methylation and reduction of mono-glutamates to 5-methyltetrahydrofolate, and, therefore, an abnormally high concentration of mono glutamates in the blood facilitates an immediate hypersensitivity reaction.[10]

Conclusion

Folic acid allergy in pregnancy is rare, and the clinical picture may vary from patient to patient. It should be considered in the differential diagnosis of idiopathic anaphylaxis and suspected cereal allergy. A diet rich in natural folates may be an alternative for patients with folic acid hypersensitivity.

Disclaimer: The patient's consent was taken prior to the writing of the manuscript. The information in this article is designed to provide accurate information concerning the subject matter covered.

Conflicts of Interest: None to declare.

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AUTHORS' CONTRIBUTIONS:
BQ, MZ: Concept, design, provide materials, data collection, interpretation, analysis, processing, literature review and writing.
FS: Concept, design, supervision and revision.
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