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Case Report

A case report of methemoglobinemia in pregnancy

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ABSTRACT

Methemoglobinemia is a rare form of functional anaemia which disrupts the ability to transport oxygen effectively by the haemoglobin leading to obstetrical as well as non-obstetrical complications. Our objective was to observe the antenatal, perinatal, and post-natal outcomes in women diagnosed with methemoglobinemia. A case report of two patients of methemoglobinemia admitted in a tertiary care centre of South Gujarat. The report displays a qualitative analysis of the diagnosis and management undertaken, providing a critical evaluation of their effectiveness and implications for future clinical practice. Methemoglobinemia, while uncommon, requires awareness for timely diagnosis and effective management. Congenital cases often go unnoticed until pregnancy, with methaemoglobin levels under 20% usually not necessitating treatment. Symptomatic individuals can benefit from methylene blue and hyperbaric oxygen therapies. Avoiding certain drugs and ensuring swift diagnosis, coupled with proper counselling, can lead to favourable pregnancy outcomes.

Keywords: Methemoglobinemia, Methaemoglobin, Pregnancy, Methylene blue

INTRODUCTION

Methemoglobinemia, a rare blood disorder characterized by the presence of elevated levels of methaemoglobin, poses unique challenges when encountered during pregnancy. Methaemoglobin, an altered form of haemoglobin, contains ferric iron (Fe^{3+}) instead of the normal ferrous iron (Fe^{2+}), impairing its ability to efficiently bind with oxygen and increased affinity to bound oxygen of methaemoglobin leading to disruption in the ability to transport oxygen efficiently resulting in the shift of oxygen disassociation curve towards the left.[1,2]

Although typically presenting at levels less than 1% in the blood under normal circumstances, elevated methaemoglobin levels can lead to tissue hypoxia, resulting in various clinical manifestations. Key symptoms of methemoglobinemia are related to the MetHb levels.

The sections ahead aim to provide a case comparison between two cases of methemoglobinemia in pregnancy with different methaemoglobin levels and their pregnancy outcomes including a comprehensive overview of the current understanding of methemoglobinemia in the context of pregnancy, incorporating insights from recent research.

CASE REPORTS

Case 1

A 30-year-old primigravida, an unbooked case presented to the labour room emergency department at 39-weeks period of gestation with labour pains. On examination, there was peripheral slate-grey cyanosis of her fingertips and toes. Her saturation was 86% on room air but she had no symptoms of breathlessness and no significant finding on respiratory and cardiovascular examination. Blood sample taken for further investigations was chocolate brown in colour. Her ABGA showed oxygen saturation of 81%. On further examination fetal distress was diagnosed and she was shifted for an emergency full-term LSCS under general anaesthesia under ASA class 3 with SOS ventilatory support for low saturation.

LSCS was uneventful although chocolaty brown blood was observed. She delivered an alive and healthy female child of 2.6 kg.

Post-LSCS she was shifted to OB ICU for further management and kept on 15 L O_2. Despite that, her saturation remained at 88% on room air. The disparity between her saturation and her clinical symptoms led us to perform further evaluation. A physician reference was given. On physician's advice ECG, 2D echo, D-dimer, repeat ABGA was done and an EDTA sample for methaemoglobin was sent in view of suspected hemoglobinopathy. The report of methaemoglobin showed a result of 31.5% and she was diagnosed with congenital methemoglobinemia as there was no history of any drugs/toxins causing acquired methemoglobinemia.

As the methaemoglobin percentage was high, a quantitative G6PD test was done before beginning the treatment as a G6PD deficiency prohibits treatment with methylene blue. The test outcome was indicative of normal levels of G6PD. So, methylene blue dye (1 mg/kg) was given in 5% dextrose over an hour after performing a patch test. A repeat methaemoglobin-level test was done the next day. The laboratory finding of methaemoglobin was 4.1%.

Following the administration of methylene blue, she was advised not to breastfeed the baby for the next 3 days considering that the half-life of IV methylene blue is 5-6.5 hours and there isn't sufficient evidence to eliminate the possibility of passage of methylene blue into breast milk when administered intravenously.[3]

She was discharged on the 8th post-operative day with no complications and a healthy baby. As this condition has genetic predisposition, the baby was subjected to evaluation.

Case 2

A 20-year-old primigravida, diagnosed case of congenital methemoglobinemia was referred to our hospital for pregnancy management. She had a family history of congenital methemoglobinemia diagnosed in her sibling. She did not have any genetic testing or estimation of cytochrome B5 reductase activity done. Her methaemoglobin levels at 8 RMOA were 13.3%. As she was asymptomatic, she was advised to take prophylactic ascorbic acid throughout her pregnancy.

She got admitted again with labour pain. During her active phase of labour foetal distress was detected and she was taken for an emergency full term LSCS under general anaesthesia. She delivered a healthy male child of 2.8 kg.

Post-LSCS she was shifted to OB ICU for further management. Her post-operative methaemoglobin levels were 17%. As she and the child were asymptomatic, they were discharged.

DISCUSSION

Methemoglobinemia can manifest as either congenital or acquired form. Inherited methemoglobinemia is due to a rare gene mutation of the CYB5R3 gene. They are of two types. Type-I is due to cytochrome B5 reductase (CYB5R) also known as NADH-dependent MetHb reductase or diaphorase-1 deficiency in erythrocytes only and type-II is due to deficiency of CYB5R in all cell types of the body. In cases of congenital methemoglobinemia, individuals might show no symptoms or might exhibit signs of cyanosis. Furthermore, a stable condition can deteriorate if the individual takes medications that trigger methemoglobinemia. While type I methemoglobinemia does not impact life expectancy, type II significantly shortens it and is associated with additional issues, including neurological and mental deficits, as well as abnormalities in growth.

Table 1: Levels of methemoglobinemia in blood and presenting symptoms.

Percentage of Methaemoglobin level	Symptoms
10	None (patients with underlying diseases may have more symptoms at lower level)
10-20	Slight discoloration (eg, pale, gray, blue) of the skin
20-30	Anxiety, headache, tachycardia, light headedness
30-50	Dyspnoea, weakness, confusion, chest pain
50-70	Arrhythmias; altered mental status, delirium, seizures, coma; profound acidosis
>70	Usually, death

Acquired methemoglobinemia is mostly caused by medications like amino salicylic acid, clofazimine, chloroquine, dapsone, local anaesthetics like topical sprays and creams including benzocaine, lidocaine, and prilocaine, menadione, metoclopramide, nitro-glycerine, phenacetin, phenazopyridine, primaquine, rasburicase, sulphonamides. Foods and beverages like frozen or dried foods that use nitrites or sodium nitrate as a preservative, mushrooms, root vegetables, leafy-green vegetables and well water (contains nitrates). Chemicals and environmental substances like acetanilide (used in varnishes, rubber, and dyes), anilines and aniline dyes (e.g. diaper and laundry marking inks, leather dyes, red wax crayons) and antifreeze.[4]

Symptoms are proportional to the methaemoglobin level as can be seen in Table 1.

Treatment

Mechanism of action

Methylene blue solution, used alongside supplemental oxygen, is a common treatment for methemoglobinemia.[5] This solution contains methylene blue trihydrate (3,7-bis (dimethylamino) phenazanthionium chloride trihydrate) as its active component. Methylene blue acts as a precursor that is transformed into colourless leucomethylene blue by erythrocyte flavin reductase, functioning as an electron donor. This conversion process necessitates NADPH, which acts as an electron acceptor. Leucomethylene blue facilitates the reduction of methaemoglobin (MetHb) to normal haemoglobin (Hb) and is simultaneously reverted to methylene blue, enabling its reuse in further MetHb reduction. Due to its ability to rapidly oxidize MetHb, methylene blue is effective for acute cases of methemoglobinemia. However, at high concentrations, its oxidizing property can exacerbate methemoglobinemia.

Individuals with G6PD deficiency are unable to use methylene blue for treatment because it can trigger haemolysis and further methemoglobinemia, owing to inadequate NADPH production necessary for converting methylene blue to its active form, as G6PD plays a crucial role in generating NADPH through the pentose phosphate pathway. Additionally, individuals lacking sufficient flavin reductase cannot benefit from methylene blue treatment due to the lack of necessary enzyme activity to activate the drug, rendering it ineffective.

Dosage

In cases of genetic methemoglobinemia, individuals are prescribed a daily oral dosage of methylene blue ranging from 50 to 250 mg indefinitely.[6] For those experiencing sudden (acute) exacerbated methemoglobinemia, a treatment of 1–2 mg/kg of a 1% methylene blue solution is given intravenously over more than 20 minutes, with a possible second dose if the initial treatment doesn't show adequate improvement within an hour. Before initiating methylene blue treatment for acquired methemoglobinemia, it's crucial to discontinue any medications that might be causing the increase in methaemoglobin levels, to halt further production of MetHb and to avoid potential adverse interactions with drugs such as aniline and dapsone. Patients without symptoms, as well as those with G6PD deficiency who develop methemoglobinemia, are typically treated only with supplemental oxygen rather than methylene blue.

For managing chronic methemoglobinemia, other options include administering ascorbic acid at a daily dose of 200-500 mg, which could lead to stone formation with prolonged use, or riboflavin, taken at 20 mg/day.*Side effects*

Methylene blue, when taken orally, can cause a range of side effects, particularly affecting the gastrointestinal tract. These may include symptoms such as nausea, vomiting, diarrhoea, stomach pain, an altered sense of taste, and discoloration of saliva and stools to blue. It is also associated with headaches, confusion, and shortness of breath. The drug can lead to increased sweating and the presence of blue urine. An overdose of methylene blue could lead to the skin turning blue, which might be wrongly identified as cyanosis or methemoglobinemia.

CONCLUSION

Though methemoglobinemia is a rare form of hemoglobinopathy but knowledge about this disease is essential for prompt diagnosis and better management. Most of the patients with congenital methemoglobinemia are relatively asymptomatic and are diagnosed during pregnancy. Levels of methaemoglobin less than 20% generally do not require additional treatment. For symptomatic patients, methylene blue and hyperbaric oxygen are available as better therapeutic options. Through proper counselling avoidance of drugs precipitating methemoglobinemia and prompt diagnosis good pregnancy outcomes can be achieved.

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REFERENCES

1. Turner MD, Karlis V, Glickman RS. The recognition, physiology, and treatment of medication induced methemoglobinemia: A case report. Anesth Prog. 2007;54:115 7.
2. Yang JJ, Lin N, Lv R, Sun J, Zhao F, Zhang J, et al. Methemoglobinemia misdiagnosed as ruptured ectopic pregnancy. Acta Anaesthesiol Scand. 2005;49(4):586-8.
3. David SR, Sawal NS, Bin Hamzah MN, Rajabalaya R. The blood blues: A review on methemoglobinemia - Treatment. J Pharmacol Pharmacother. 2018;9:1-5.
4. Cefalu JN, Joshi TV, Spalitta MJ, Kadi CJ, Diaz JH, Eskander JP, et al. Methemoglobinemia in the Operating Room and Intensive Care Unit: Early Recognition, Pathophysiology, and Management. Adv Ther. 2020;37(5):1714-23.
5. Denshaw Burke M, DelGiacco E, Curran AL, Savior DC, Kumar M. Methemoglobinemia Treatment & Management. Medscape. 2016. Available at: http://www.emedicine.medscape.com/ article/204178 treatment#showall. Accessed on 09 February 2024.
6. Schirmer RH, Adler H, Pickhardt M, Mandelkow E. “Lest we forget you – Methylene blue.”. Neurobiol Aging. 2011;32:2325.

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