Original Article

Methaemoglobinemia in Pregnancy: Case Series and Literature Review

Abstract

Background: Methaemoglobinemia is a rare disease complicating pregnancy and often diagnosed for the first time in perioperative or peripartum setting. **Aim:** To analyse the type of methaemoglobinemia, clinical presentation and pregnancy outcomes in our series of pregnant women with methaemoglobinemia. **Methods:** This is a single centre retrospective study of patients with methaemoglobinemia admitted between 2003 and 2015. **Results:** We had six pregnant women with methaemoglobinemia during the study period. Three women had congenital methaemoglobinemia and three of them had acquired methaemoglobinemia. Obstetric and foetal outcomes were good. **Conclusion:** Congenital methaemoglobinemia is reasonably well tolerated in pregnancy. With proper counselling, follow-up, avoidance of drugs associated with methaemoglobinemia and prompt diagnosis and management especially in cases of acquired methaemoglobinemia, we can achieve good pregnancy outcomes.

Keywords: *Acquired, case series, congenital, methaemoglobinemia, pregnancy*

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Introduction

The Fugates of troublesome Creek in Kentucky, many of whom had a blue-tinted complexion were found to have a rare medical condition called Methaemoglobinemia.[1] Not many physicians would have diagnosed this condition in their lifetime of clinical experience and would run the risk of missing the diagnosis when they come across a patient with this condition! Methaemoglobinemia has a varied aetiology and a wide clinical spectrum ranging from asymptomatic disease or mild bluish discoloration of skin to a life-threatening condition resulting in mortality. Ferrous ions (Fe^{2+}) of heme complexes bind to oxygen and are responsible for oxygen transfer to tissues. Ferrous ions get oxidized to ferric state (Fe^{3+}) by various physiological and pathological processes but we have natural reducing systems in place to convert ferric ions back to ferrous ions. Methaemoglobinemia occurs when enzyme activity capable of reducing ferric ions to ferrous ions is deficient. In methaemoglobin, ferric ions of heme complex are unable to bind oxygen and conversely cause allosteric change in the heme portion of partially oxidized haemoglobin resulting in increased affinity to bound oxygen.[2,3] This combination of inability to bind oxygen and increased affinity to bound oxygen of methaemoglobin results in reduction of oxygen transfer from blood to tissues, leading to tissue hypoxia. Methaemoglobinemia in pregnancy can have catastrophic effects due to tissue hypoxia affecting both mother and foetus and there are concerns of teratogenicity of methylene blue which is used for treatment.[4] There have been a few published case reports of methaemoglobinemia complicating pregnancy and literature in this regard is scant. To our knowledge, no case series or systematic reviews have been published so far. We present here a case series of six pregnant women affected with methaemoglobinemia.

Methods

This is a retrospective study done in a tertiary level, dedicated obstetric hospital in South India over a period of 15 years starting from 2003 to 2019. Data were collected from EMR (Electronic Medical Records) and verified with case sheets.

Results

We had six women with methaemoglobinemia during study period [Table 1]. Five women presented during their first pregnancy to our hospital and one woman presented to us in fifth pregnancy.

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Table 1: Type of methaemoglobinemia and pregnancy outcome

Pt No.	gravida	Meth (%)	C Or A	Cause	GA Delivery weeks	Mode delivery	PE	Foetal Outcome
1.	G1	16	C	HbM	38	LSCS	N	Good
2.	G5P3L3 A1	32	C	-	40	V	N	Pneumo-Thorax
3.	G1	14	C	HbM	32	LSCS	Y	Seizures, died on day 2
4	G1	5	A (AN)	Metoclop ramide	40	LSCS	Y	Good
5	G1	30	A (Postop)	-	38	LSCS	N	Good
6	G1	13	A (Postop)	-	37	LSCS	-	Good

Meth %-methaemoglobinemia (%), C-congenital, A-acquired, AN-antenatal period, Postop-post operative period, HbM-haemoglobin M, GA-gestational age, V-vaginal, PE- preeclampsia, Y- yes, N-no

Table 2: Summary of case of reports of methaemoglobinemia in pregnancy (literature review)

case	Author	gravida	Meth%	C or A	cause	GA @ delivery	Delivery mode	PE	FGR	Foetal OC
1	George Pepper[13]	G4P3L3, twins	21	C	Cyb5R	39	V	N	Y	1-Al 2-SB
2	Dudhe M[6]	G1	25	C	Cyb5R	38	LSCS	Y	N	Al
3	Adarsh Kulkarni[14]	G1	44	C	Cyb5R	36	LSCS	Y	N	Al
4	S Verma[15]	G2P1L1	-	C	-	38	LSCS	N	-	Al
5	Palaniap-pa S[5]	G1	32	C	HbM	-	-	-	-	Al
6	Neander[4]	G1	29	C	Cyb5R	-	-	-	-	-
7	Andrew C[9]	G2A1	34	A	LA	-	-	-	-	-
8	McDonnell[10]	-	12	A	LA	34	LSCS	-	-	-
9	Shivali[7]	G2P1L1	8	C	-	38	LSCS	-	N	Al
10	Sanjivini[16]	-	26	C	-	-	LSCS	-	-	Al
11	Yang[8]	G3P2L2	-	A	MM	37	v	N	N	Al
12	Jarupan M[17]	G1, twins	-	C	Cyb5R	38	LSCS	-	-	1-IUD 2-Al

Meth %-methaemoglobinemia (%), C-congenital, A-acquired, Cyb5R-Cyb5R deficiency, LA-local anaesthetic agent, MM-metobromuron/metolachlor, GA-gestational age, V-vaginal, PE- preeclampsia, FGR-foetal growth restriction, Y- yes, N-no, OC-outcome, Al-alive and well, SB-still born

Three women had been diagnosed to have congenital methaemoglobinemia previously and were referred to our hospital for pregnancy management. They were advised to take prophylactic ascorbic acid through-out pregnancy. Two women with congenital haemoglobinemia had lower segment caesarean section, indication being presumed foetal compromise and prolonged labour, respectively. Other three women had acquired methaemoglobinemia.

Of the three women referred with prior diagnosis of congenital methaemoglobinemia, one woman had strong family history of methaemoglobinemia. Two of her siblings (one brother and one sister) and maternal grandparents were known to have methaemoglobinemia. She did not have genetic testing or estimation of cytochrome B5 reductase activity (Cyb5R) done. Her first two pregnancies were uneventful and she had first-trimester miscarriage in third pregnancy. Her fourth pregnancy resulted in a baby born with hypotonia and seizures, which were controlled by day 6. Baby was 7 year old when she was referred to us in fifth pregnancy (in 2008) and had delayed milestones. She delivered a normal baby at 40 weeks of gestation. This baby developed spontaneous pneumothorax on day 2 of life. Baby was managed with an intercostal drain, was on mechanical ventilation for 3 days and required neonatal ICU care for 9 days, after which he was discharged in stable condition. One woman was diagnosed to have haemoglobin M at the age of 16 years when she was posted for appendectomy. She delivered at 32 weeks of gestation, delivered preterm baby who had refractory seizures and expired on day 2 of life. Third woman with congenital methaemoglobinemia also had haemoglobin M disease proven by haemoglobin electrophoresis. She delivered a healthy neonate at 38 weeks of gestation.

Three women had acquired methaemoglobinemia. All of them were asymptomatic and incidentally detected to have low SpO2 (oxygen saturation by pulse oximetry) and were documented to have elevated methaemoglobin level. Metoclopramide was considered possible etiologic agent in one woman who developed methaemoglobinemia in antenatal period. She had mild methaemoglobinemia (5%) and was

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only given oral Ascorbic acid. Etiologic agent in other two women could not be delineated. They developed methaemoglobinemia postoperatively. Second woman had methaemoglobin level of 30% and she was treated with intravenous Ascorbic acid. Third woman with acquired methaemoglobinemia was also asymptomatic and was not given any specific treatment. Their oxygen saturation improved spontaneously over 2–3 days.

Foetal outcomes: Out of 3 babies born to women with congenital methaemoglobinemia, one baby had refractory seizures and succumbed on day 2 of life. One baby had spontaneous pneumothorax, an unrelated complication and third baby was healthy. All three babies born to women with acquired methaemoglobinemia did not have cyanosis or congenital anomalies and neonatal arterial blood gas (ABG) s were normal.

Discussion

Methaemoglobinemia can be hereditary or acquired.

Hereditary methaemoglobinemia:

1. Cyb5R deficiency: Commonest type of hereditary or congenital disease is due to deficiency of Cyb5R. This is the key enzyme involved in reducing oxidized haemoglobin and preventing accumulation of methaemoglobin. This is an autosomal recessive disease, most affected people are either homozygous or compound heterozygous for a pathogenic variant of cytochrome b5 reductase 3 gene.[2,3] Cyb5R deficiency is further classified into 2 types. In type 1, there is deficiency of Cyb5R in red blood cells only and affected patients may have cyanosis, shortness of breath, fatigue etc. Life expectancy is usually normal and there is no increased risk in pregnancy.[2,3] Type 2 disease is rare and characterized by deficiency of cyb5R in all cells. Patients usually have severe neurological involvement and shortened life span.
2. Haemoglobin M disease: This is due to alteration in one of the globin chains of haemoglobin. Transmission is autosomal dominant, patients are often asymptomatic and may have cyanosis.[2,3]
3. Cytochrome b5 (which is the substrate for Cyb5R) deficiency: This is the rarest form of congenital methaemoglobinemia.

Acquired methaemoglobinemia:

Most cases of methaemoglobinemia are acquired. They have increased levels of methaemoglobin due to exposure to some exogenous drugs and toxins [Table 2]. Commonly implicated drugs are dapsone, topical aesthetic agents like benzocaine and prilocaine, chloroquine, and metoclopramide.[2] Chemicals and toxins like hydrogen peroxide, paraquat, benzene derivates, and nitrates have been implicated. Acquired methaemoglobinemia often occurs in susceptible individuals with less than 50% of Cyb5R as seen in premature infants and heterozygotes for Cyb5R deficiency. Cyanosis becomes apparent when methaemoglobin level is more than 1.5 gm/dL or 10%.[4,5] Severity of illness depends on the level of methaemoglobin, manifesting in mild-tomoderate symptoms if levels are between 20 and 50%, severe illness resulting in dyspnea, altered sensorium occur between 50% to 70% and methaemoglobin levels above 70% is fatal.[3]

We need to suspect methaemoglobinemia if there is discrepancy in Spo2 by pulse oximetry (low reading) and PaO2 on ABG (normal PaO2), SpO2 not improving with oxygen supplementation, unexplained cyanosis in the absence of cardiopulmonary disease, history of cyanosis in family members, development of symptoms like cyanosis, shortness of breath after exposure to drugs and toxins known to cause methaemoglobinemia.[6,7] Pulse oximetry does not detect methaemoglobin and Spo2 is low and does not improve with oxygen supplementation despite normal PaO2 on ABG. We need to have a high index suspicion to diagnose this condition. Once methaemoglobinemia is confirmed by testing the levels (above 5%), we need to distinguish whether it is congenital or acquired based on chronicity, family history, symptomatology and history of exposure to drugs and toxins. Haemoglobin M can be diagnosed by haemoglobin electrophoresis.[2,3] Estimation of Cy5bR enzymatic activity and genetic testing for pathogenic variant of CY5BR3 gene can confirm congenital methaemoglobinemia due to Cy5bR deficiency. Genetic testing can be offered prenatally in families with type 2 methaemoglobinemia.[3] Treatment depends on aetiology. In individuals with Cy5bR deficiency, cyanosis can be treated with oral Methylene blue (100–300 mg per day) or Ascorbic acid (1000 mg three times day).[3] Haemoglobin M disease is benign in nature and there is no effective therapy for cyanosis in these individuals.[3] Acquired methaemoglobinemia can be treated with discontinuing the offending drug, oxygen supplementation, supportive treatment and parenteral methylene blue. Methylene blue is indicated in severe disease and methaemoglobin levels above 30%.[3] Methylene blue is contraindicated in patients with G6PD deficiency. Methaemoglobin estimation should be carried out before administration of methylene blue as it interferes with estimation. Exchange transfusion and hyperbaric oxygen have been reported to be beneficial in severe cases.[3] Teratogenic potential of parenteral methylene blue is not clear. There have been a few case reports where parenteral methylene blue was given in antenatal period and there was no effect on the foetus.[4,8-10] Intraamniotic methylene blue is potentially teratogenic.[11,12]

We do not know with certainty whether Congenital methaemoglobinemia affects pregnancy outcomes as there are only a handful of case reports. Congenital methaemoglobinemia may not affect pregnancy

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outcomes but patients' symptomatology may worsen with advancing pregnancy due to increase in oxygen demands and physiological anaemia. Methaemoglobin levels may increase in women with congenital methaemoglobinemia (Cyb5R deficiency) with advancing gestational age as seen in case reports published by Palaniappan (2013) and Sljapic (1978).[5,18] Two out of six women in our series had preeclampsia. Acquired methaemoglobinemia can be life threatening if severe. Severe methaemoglobinemia can affect both the mother and the foetus. Patients with congenital methaemoglobinemia often have erythrocytosis and it is important to consider this and pre-pregnancy haemoglobin levels while interpreting patient's hemogram during pregnancy. Physiological shortness of breath in pregnancy is common but when these patients present with shortness of breath, it adds to the complexity of clinical dilemma in view of nonreliability of SpO2 measurement by conventional pulse oxymetry. Excess blood loss during delivery may decompensate previously asymptomatic patient. We need to have a lower threshold for packed red cell transfusion in postoperative period. Commonly used antiemetics like metoclopramide need to be avoided as they can worsen methaemoglobinemia. In perioperative period, it is essential to chart the list of drugs to be avoided (metoclopramide, aesthetic agents like prilocaine and benzocaine, nitrates, nitroglycerine, and sodium nitroprusside).[7] Meperidine, thiopental, propofol, succinylcholine, and inhalational anaesthetics are preferred agents for general anaesthesia in these patients.[7] As Spo2 is not reliable, it is difficult to monitor during operative delivery under general anaesthesia. Monitoring with co-oximetry is ideal in intraoperative period.[7,16,19,20] If co-oximetry is not available, we need to consider doing ABG in intraoperative period and consider giving 100% oxygen while the patient is under general anaesthesia. We need to prevent hypotension, hypothermia and blood loss which can affect tissue oxygenation and tackle conditions like pyrexia which can increase oxygen demands.[7,20]

Conclusion

Management of methaemoglobinemia in pregnancy depends on the etiology as prognosis and treatment vary. Congenital methaemoglobinemia is usually well tolerated in pregnancy but acquired methaemoglobinemia if severe and not treated promptly, can result in significant morbidity, rarely mortality and can affect the foetus too. Prenatal testing can be offered in families with type 2 congenital methaemoglobinemia. We need to be aware of the drugs which can worsen methaemoglobinemia, treatment options for both congenital and acquired methaemoglobinemia. Obstetricians, physicians and anaesthetists must be aware of this condition so as to make a prompt diagnosis and initiate treatment especially in cases of acquired methaemoglobinemia to prevent morbidity and mortality.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflicts of interest

There are no conflicts of interest.

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