Methaemoglobinaemia in pregnancy: Real world experience in a single centre in Malaysia

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Abstract
The literature on methaemoglobinaemia in pregnancy is scarce, imposing clinical challenges to both obstetricians and haematologists. We report a total of nine pregnancies with methaemoglobinaemia treated in our centre. Their methaemoglobin levels, mode of delivery, pregnancy management and outcome were summarized.

Keywords
Methaemoglobinaemia, pregnancy, congenital, acquired, outcome

Introduction
Methaemoglobinaemia, which is broadly divided into congenital or hereditary and acquired types, is rarely reported. It is a condition characterized by increased amount of haemoglobin in which the heme iron is oxidized to the ferric form.1 The literature on methaemoglobinaemia in pregnancy is scarce, imposing clinical challenges to both obstetricians and haematologists due to lack of awareness and limited diagnostic laboratory accessibility. Pregnancy morbidity such as foetal hypoxia, increased rates of threatened abortion, pre-eclampsia and hence higher caesarean rates were reported.2 We report a total of nine pregnancies with methaemoglobinaemia treated in our centre.

Case series
We collected clinical data from four patients, with a total of nine pregnancies. Their methaemoglobin levels, mode of delivery, pregnancy management and outcome were summarized in Table 1. Clinically, there were similar findings with presence of cyanosis and a saturation gap—the difference between oxygen saturation measured by pulse oximetry and arterial blood gas analysis. All had unremarkable echocardiography findings. The haemoglobin levels ranged from 11.2 g/L to 13.6 g/L with no laboratory evidence of haemolysis. There were no identifiable causes of methaemoglobinaemia in pregnancy for the first three patients (Madam A, B and C). All denied exposure to oxidant drugs or environmental toxins. Clinical findings of blue lips and fingers had been noticed since childhood. Genetic mutations for congenital methaemoglobinaemia were not performed due to limited resources at our setting.

Madam D, who was diagnosed with multi-bacillary leprosy during second trimester, had dapsone-induced methaemoglobinaemia 2 weeks after dapsone commencement. Dapsone was withheld and replaced by ofloxacin 200 mg twice daily throughout pregnancy. She delivered a healthy term baby via spontaneous vaginal delivery.

Discussion
Methaemoglobinaemia, an oxidised form of haemoglobin with left-shifted oxygen-haemoglobin dissociation curve, is often difficult to diagnose and poses a great clinical challenge.3 It is rarely reported in literature, possibly attributed to under-diagnosis and poor awareness among clinicians. It is a clinical syndrome with a wide spectrum of manifestations ranging from an asymptomatic disease course to fatality, with diversity in clinical presentations in between.3,4

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| Patient | Met-Hb levels during pregnancy (range, %) | Mode of delivery | Indication | Medication(s) | Pregnancy outcome | Baby outcome |
|---------|------------------------------------------|-----------------|------------|---------------|------------------|--------------|
| Madam A | 20.1–22.6 VAD | Prolonged second stage with acute fetal distress | Nil | Term, healthy baby | Healthy up to date |
| 1st (2011) | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| 2nd (2015) | 21.2–25.5 VAD | Prolonged second stage with acute fetal distress | Ascorbic acid 1g OD<sup>b</sup> | Term, healthy baby | Healthy up to date |
| 3rd (2020) | 22.3–24.4 SVD<sup>c</sup> (IOL<sup>d</sup>) at 38 weeks | Two previous pregnancies with prolonged second stage | Ascorbic acid 1g OD<sup>b</sup> | Term, healthy baby with birthweight 2.34 kg | Healthy up to date |
| Madam B | 40.2–41.6 Emergency LSCS<sup>e</sup> at 39 weeks | Acute fetal distress | Methylene blue 1 mg/kg single dose given intra-operatively with ascorbic acid 1g OD<sup>b</sup>; Met-Hb levels decreased to 3.2% and 3.6% 12h and 24 h post methylene blue, respectively | Term, healthy baby with birthweight 2.51 kg; A repeat Met-Hb 6 weeks postpartum was 25.1% | Healthy up to date |
| 1st (2015) | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| Madam C | 10.9–11.2 Emergency LSCS<sup>e</sup> at 39 weeks | Acute fetal distress and chorioamnionitis | Intravenous cefuroxime and metronidazole | Term, healthy baby | Healthy up to date |
| 1st (2016) | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| 2nd (2018) | N/A<sup>f</sup> | N/A<sup>f</sup> | N/A<sup>f</sup> | N/A<sup>f</sup> | Complete miscarriage at 8 weeks of gestational age | N/A<sup>f</sup> |
| 3rd (2019) | 11.0–13.1 Emergency LSCS<sup>e</sup> at 39 weeks | Acute fetal distress with prolonged second stage of labour | Ascorbic acid 1g OD<sup>b</sup> | Term, healthy baby with birthweight 2.59 kg; Healthy up to date | Healthy up to date |
| 4th (2021) | 12.5–19.3 Elective LSCS<sup>e</sup> at 38 weeks | 2 previous scars | Ascorbic acid 1g OD<sup>b</sup> | Term, healthy baby with birthweight 3.18 kg; Just delivered in March 2021 | |
| Madam D | N/A | SVD<sup>f</sup> at 39 weeks | N/A | Term, healthy baby with birthweight 2.36 kg | Healthy up to date |
| 1st (2019) | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; | &nbsp; |

<sup>a</sup>VAD: vacuum-assisted delivery.  
<sup>b</sup>OD: once daily.  
<sup>c</sup>SVD: spontaneous vaginal delivery.  
<sup>d</sup>IOL: induction of labor.  
<sup>e</sup>LSCS: lower segment caesarean section.  
<sup>f</sup>N/A: not applicable or not available.
Methaemoglobinaemia, which leads to fetal hypoxia, might have deleterious consequences on pregnancy outcome, with increased rates of threatened abortion and pre-eclampsia, particularly in presence of higher levels of methaemoglobin.

One study has found higher caesarean rates among cases with fetal hypoxia leading to acute fetal distress (AFD). Our case series reported three emergency lower segment caesarean section (LSCS) and two vacuum-assisted deliveries secondary to AFD, likely attributed to the hypoxic stress resulting from methaemoglobinaemia. One pregnancy (Madam C) resulted in maternal complications of acute respiratory distress syndrome and pulmonary oedema, which recovered well with supportive care. Whether there is any correlation between maternal and fetal outcomes and methaemoglobinaemia requires validation from future studies. More data is warranted to aid in the management plans for pregnancies with such disorder.

Supportive care and cessation of any offending triggers such as dapsone, as in the case of Madam D in our series, is often the mainstay treatment for mild methaemoglobinaemia. For moderate-to-severe forms, ascorbic acid, which prevents haemoglobin conversion to methaemoglobin due to its antioxidant effects, as well as methylene blue are recommended, particularly in symptomatic cases with methaemoglobin levels above 20%. In our series, methylene blue was administered in one pregnancy during emergency LSCS due to symptomatic presentation with methaemoglobin level above 40%. The teratogenic risk of methylene blue is negligible in this case as baby was delivered soon after its administration, consistent with a reported case. Clinicians should balance the risks and benefits of the use of methylene blue in pregnancy and a multidisciplinary team meeting involving obstetrician, haematologist and patient is highly advocated.

The limitations of our study include the unavailability of congenital methaemoglobinaemia genetic mutation workup due to limited local resources, taking pre-analytical and analytic confounders into consideration. This is an observational study of nine pregnancies managed in a single centre, lacking data standardization. We believe our report will add values to the future clinical practice guidelines on the management of methaemoglobinaemia in pregnancy, judging the real world data is lacking.

Conclusion

Our case highlighted the challenge posed in managing pregnant patients with methaemoglobinaemia. Clinical suspicion should be heightened in at risk patients who present with unexplained cyanosis and saturation gap, particularly when there are identifiable oxidizing events or similar family history. Clinical symptoms, methaemoglobin levels, maternal and fetal well-being and mode of delivery should be taken into account in the holistic management of such cases.

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Author contributions

ASOT and KCC were responsible for the study design, data collection, data analysis and manuscript writing. TSL and LPC were involved in the study design, data analysis and manuscript editing. All authors read and approved the final manuscript.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declaration of conflicting interests

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Ethical approval

This article does contain studies with human participants and was registered via National Medical Research Register Malaysia with a Research ID of NMRR-21-485-58671.

Informed consent

Written informed consent was obtained from the patient and her parents for the anonymised information to be published in this article.

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