An Iron overload in anaemia with underlying haemoglobin constant spring in an antenatal mother in primary care

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TITLE OF CASE

An Iron overload in anaemia with underlying haemoglobin constant spring in an antenatal mother in primary care

SUMMARY

This is the case of a gravida 3 para 1 woman in her late 20s with underlying Hb Constant Spring who visited a healthcare clinic for an antenatal checkup. Towards the end of her second trimester, she experienced lethargy. During her antenatal booking, she was diagnosed with mild asymptomatic anaemia, high serum ferritin, T-Saturation of 88%, and abnormal liver function tests. She was referred to a hospital where an MRI scan revealed over 2 grams of iron deposits in her liver, leading to a revised diagnosis of iron overload. Treatment included desferoxamine and expectant management throughout her antenatal period, and her delivery was uncomplicated. While iron deficiency anaemia is common in pregnancy, it is crucial not to overlook iron deposition and the distinction from acute fatty liver of pregnancy to prevent treatment delays.

BACKGROUND

The case report serves as a stark reminder to healthcare providers that iron deficiency anaemia is a common concern during pregnancy, but atypical conditions such as iron overload must be noted. Differentiating between acute fatty liver of pregnancy and other underlying complications is crucial to avoiding delays in treatment.

Anaemia in pregnancy is defined as a haemoglobin level of <11 g/dl and is commonly related with iron deficiency. The global prevalence of anaemia in pregnancy has been reported as 29.9% (1). Due to the increased demand by the fetoplacental unit and the need to produce blood for compensation for blood loss during birth delivery, the need for iron increases significantly during pregnancy (1). Anaemia in pregnancy is correlated with a higher risk of postpartum hemorrhage, depression and reduced exercise tolerance. The study also found that low weight birth, stillbirth, preterm birth and impaired neurological development of infant/baby were substantially associated with anaemia during the first trimester and second trimester (2). However, the adverse pregnancy outcomes associated with high iron stores have been reported as well. Thus, our case report aimed to discuss the investigation and management of iron overload in pregnancy.

CASE PRESENTATION

A gravida 3 para 1 woman in her late 20s presented to a healthcare clinic for an antenatal checkup was found to be lethargic at the end of her second trimester. At the beginning of her antenatal care, she was asymptomatic although she had mild anaemia with her booking haemoglobin was 10.3g/dL. She also has underlying Hb Constant Spring and history of two pints of packed red cells transfused at age of eight-year-old after a car accident. However, she had no symptoms of anaemia, abdominal pain or distended, no yellowish skin discoloration, no bilateral legs swelling. Her oral intake is good, and she has not experienced any constitutional symptoms throughout her follow-up and she has been on an elemental iron dosage of 115mg ferrous fumarate tablets since her booking.

Iron study was performed for her anaemia investigation (Table 1). Subsequently, a baseline of kidney function test and liver function test were performed, and noted her alanine aminotransferase (ALT) was high at 70.6 IU/L. In view of her transaminitis, infectious screening for Hepatitis B and C were sent and

were non-reactive. Besides the follow-up by her family physician, she was referred to an outpatient medical clinic for shared care at 18 weeks of period of amenorrhea.

She was seen by the medical team at 20 weeks of period of amenorrhea. Serial serum ferritin and tests were sent for monitoring and showed an increase in trend to 3218ng/dL. An ultrasound hepatobiliary system was conducted. In the report, the liver was found to have hypoechoeic density, but normal liver size measurements without splenomegaly. As reported in the report, the results may indicate she has a fatty liver, so her medical team diagnosed her with Acute fatty liver of pregnancy and plans to monitor her serum ferritin and liver function tests in the third trimester. As a precaution, her ferrous ferritin tablets were withheld by medical team at 20 weeks period of amenorrhea.

However, she complained of lethargy at 22 weeks period of amenorrhea, and her haemoglobin level dropped from 10.3 g/dL to 8.8 g/dL after the ferrous fumarate was withheld for 5 weeks. She had no palpitations, syncope or dizziness. She did not suffer from liver or heart failure symptoms. Her fetal movement and oral intake were good. All physical examinations were unremarkable. At this point, her family physician reconsidered a differential diagnosis after looking at her clinical history, presentation, and after one month repeated laboratory investigations as shown in table 2. There were no elevated serum ammonia and urate. Swansea criteria for acute fatty liver of pregnancy (AFLP) were not met. She was also arranged for MRI of the T2 liver and cardiac to determine whether there was an iron overload. As a consequence of her symptomatic anaemia and her haemoglobin dropping to a moderate anaemia, her family physician restarted her on an elemental iron dosage of 115 mg ferrous fumarate tablets. The repeat haemoglobin level was 9.5g/dL two weeks later and was maintained throughout the pregnancy. Her MRI T2 report showed iron loading in her liver region of interest (ROI) 1,2 and 3 with values of 3.1±3.9ms, 3.0±3.7ms, 4.3±5.3ms (normal range: 14−37 ms) (Figure 1). MRI T2 scan also revealed iron loading in her heart region of interest (ROI) was at a value of 38.66±4.67ms (normal range: 24−45 ms) (Figure 2). In summary, there was no iron loading in her heart but moderate iron loading in her liver. Her diagnosis was revised to iron overload and updated to medical team.

INVESTIGATIONS *If relevant*

The initial result of iron study was presented in Table 1, demonstrating high levels of serum iron, transferrin and serum ferritin. During the subsequent follow-up, further investigation was performed (Table 2), and noted the Swansea criteria for AFLP were not met. She had high levels of total bilirubin, alanine transaminase and aspartate transaminase.

Table 1 Iron study

Investigation	Value	Normal range
Iron studies		
Iron	45	5.8-34.5 µmol/L
Transferrin	51.1	20-45 µmol/L
Transferrin saturation	88	20-50%
Ferritin	2819	15-150 µg/L

Table 2 Repeated laboratory investigation

Investigation	Value	Normal range

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Haematology		
Haemoglobin	10.5	12–16 g/dL
Total white cell count	17	4-11 x10^9/L
Platelet	371	150-400 x10^9/L
INR	1.1	0.9-1.2
PT	14.2	10- 15s
APTT	30.8	25- 40s
Creatinine	54.9	<80 µmol/L

Biochemistry		
ALT	58	<34 unit/L
AST	35	<33 unit/L
Total bilirubin	42	3-20 µmol/L

Other tests		
Serum uric acid	211	142.8-339.2 µmol/L
Fasting glucose	5.4	3.9-6.1 mmol/L

APTT, activated partial thromboplastin time; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalised ratio

DIFFERENTIAL DIAGNOSIS *If relevant*

- ***NIL***

TREATMENT *If relevant*

Continuation of iron tablets raised her haemoglobin level and maintained the haemoglobin level at 9.5g/dL until her third trimester. On her subsequent follow up at 30 weeks period of amenorrhea, desferoxamine injections were administered intramuscularly as part of chelation therapy for the patient.

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OUTCOME AND FOLLOW-UP

She underwent iron chelation in her third trimester and continues to be monitored and followed after delivery. The chelation therapy did not cause her any allergies or adverse effects and she successfully normalized her serum ferritin and transaminase levels. She had an uneventful spontaneous vaginal delivery with a healthy baby boy with birth weight of 3.5kg.

DISCUSSION *Include a very brief review of similar published cases*

Iron overload, also known as hemochromatosis, is a condition where there is too much iron stored in our body (3). Liver, heart and endocrine glands are the most common organs where the extra irons will deposit themselves at. Iron overload can be due to genetic inheritance, or their secondary causes including excessive parenteral and/or dietary consumption of iron, hemolysis or blood transfusion (3). There is no physiologic mechanism to eliminate extra irons in our body, therefore the regulation of iron absorption is essential to prevent accumulation of irons. Causes of iron overload include increased iron absorption, increased iron intake and repeated transfusion of red cells (4).

Ferritin is an intracellular protein that stores iron, which is helpful to reflect iron stores in the body. Due to increased absorption of iron, the level of serum ferritin will increase. Causes of hyperferritinemia include non-HIV infection, liver dysfunction, haematological malignancy, renal failure, solid tumour, iron overload and rheumatologic or inflammatory disease (5).

Iron overload during pregnancy can elevate the risk of adverse pregnancy outcome, causing deleterious effects on infant growth, cognition, and childhood Type 1 diabetes (6). Early detection of iron overload and its cause is essential to determine the treatment to prevent adverse effects towards both mother and child. For a more accurate evaluation of the body iron level, it is recommended to have serial serum ferritin and transferrin saturation levels (TRS) every three months (7). Total body iron storage can be portrayed by the serum ferritin levels, but TRS is a more sensitive tool to detect the iron overload disease (8). This is because the ferritin levels more than 200ng/ml in women and more than 300ng/ml in men is abnormal (9) and the serum ferritin in pregnant women is lower compared to normal women and usually remains low throughout the pregnancy despite prescribed iron supplementation. Also, ferritin levels can be increased during inflammation, liver disease as ferritin is an acute phase reactant protein (10). More than 98% of iron overload patients have a fasting TRS of more than 45% (8). The elevated TRS is also an indicator to start iron chelation therapy in hemochromatosis patients.

Due to costing and availability issues, serum ferritin is still used to monitor the iron storage in patients (11). As iron overload has been diagnosed, a further specific investigation is required to rule out organ involvement (3). A T2 Magnetic Resonance Image (T2 MRI), a highly reproductive tool that can help to understand the iron overload condition in the patient. It is able to measure the ventricular function of the heart and liver in the same scan, showing the relation between the intracellular iron stores and magnetic relaxation properties of tissues.

This case report highlights the importance of treatment for anaemia in pregnancy. According to the WHO, severe, moderate, and mild anaemia for pregnant women is defined as haemoglobin concentrations of less than 70 g/L, 70 to 99, and 100 to 109 g/L, respectively (12). Birthweight and preterm delivery were significantly affected by maternal anaemia in the general population. Based on international guidelines, pre-transfusional haemoglobin should be maintained at least 10 g/dL (13). A cohort study found that

placental abruption, severe postpartum haemorrhage and preterm birth were associated with anaemia during pregnancy, irrespective of its severity. For pregnant women with moderate or severe anaemia, increased risks of maternal mortality, shock, admission to the intensive care unit, foetal growth restriction, and stillbirth have been reported (12). According to the Australian Journal of General Practice, the first-line treatment for iron deficiency anaemia and iron deficiency is oral iron therapy. The response to the treatment should be monitored. If oral iron therapy is inadequate, intravenous iron can be given in the second and third trimesters (14).

The mainstay treatment of iron overload is iron chelation therapy. Considering its potential teratogenicity, the use of the iron chelator Desferrioxamine (DFO) in pregnant thalassemia women with iron excess has traditionally been discouraged. However, a study found that eliminating DFO during pregnancy may enhance tissue iron buildup and exacerbate organ damage brought on by iron (15). In fact, a study conducted among many pregnant thalassemia patients treated with DFO over several weeks or months of gestation failed to show evidence of a teratogenic effect. Furthermore, there is suspicion that DFO with large molecular size and charge cannot cross the placenta. In individuals with severe heart and liver iron overload, it may be reasonable to consider chelation therapy with DFO towards the end of the second trimester, as the potential benefits outweigh the potential risks to the foetus (13). In another study involving 32 pregnant women with beta-thalassemia major, participants received DFO in the second and third trimesters had favourable foetal outcomes (16). To eliminate excess iron in our patient with anaemia, we offered iron chelation therapy to her in her third trimester.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- To diagnose iron overload, both serum ferritin and T-Saturation should be done. An increase in serum ferritin is not specific to iron overload.
- In a patient with deranged liver function test with a high serum ferritin should raise the suspicion of iron overload and MRI of the liver should be considered.
- Anaemia in pregnancy should be treated promptly as it is associated with adverse pregnancy outcomes. In the case of iron overload, iron chelation therapy is safer to be started towards the end of the second trimester.
- The case illustrates the importance of clinicians navigating complex antenatal presentations with diligence and flexibility. Not all cases of transaminitis with hypoechoic density in the liver on ultrasound point to fatty liver or acute fatty liver of pregnancy. In this case, the iterative diagnostic process emphasizes the importance of taking into account evolving clinical features and seeking specialized investigations in order to solve the complex diagnostic puzzle of iron overload in a mild anaemia with underlying constant Hb.

REFERENCES

1. Abd Rahman R, Idris IB, Isa ZM, Rahman RA, Mahdy ZA. The Prevalence and Risk Factors of Iron Deficiency Anemia Among Pregnant Women in Malaysia: A Systematic Review. Front Nutr [Internet]. 2022 Apr 15 [cited 2022 Sep 26];9. Available from: /pmc/articles/PMC9051477/

2. Churchill D, Ali H, Moussa M, Donohue C, Pavord S, Robinson SE, et al. Maternal iron deficiency anaemia in pregnancy: Lessons from a national audit. Br J Haematol [Internet]. 2022 [cited 2022 Sep 26]; Available from: https://pubmed.ncbi.nlm.nih.gov/35922080/

3. McDowell LA, Kudaravalli P, Sticco KL. Iron Overload. Transfus Med Hemost Clin Lab Asp [Internet]. 2022 Apr 28 [cited 2022 Sep 17];359–60. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526131/

4. Hoffbrand's Essential Haematology - A. Victor Hoffbrand, David P. Steensma - Google Books [Internet]. [cited 2022 Sep 26]. Available from: https://books.google.com.my/books?hl=en&lr=&id=FsWxDwAAQBAJ&oi=fnd&pg=PA1&dq=Hoffbrand,+A.+V.,+%26+Steensma,+D.+P.+(2019).+Hoffbrand%27s+essential+haematology.+John+Wiley+%26+Sons.&ots=GDZhD1Ryjl&sig=a_p3YAfQ6VXlrJA5MuNZZAQioMQ#v=onepage&q&f=false

5. Senjo H, Higuchi T, Okada S, Takahashi O. Hyperferritinemia: causes and significance in a general hospital. Hematology [Internet]. 2018 Nov 26 [cited 2022 Sep 26];23(10):817–22. Available from: https://pubmed.ncbi.nlm.nih.gov/29914346/

6. Quezada-pinedo HG, Cassel F, Duijts L, Muckenthaler MU, Gassmann M, Jaddoe VWV, et al. Maternal Iron Status in Pregnancy and Child Health Outcomes after Birth: A Systematic Review and Meta-Analysis. Nutrients [Internet]. 2021 Jul 1 [cited 2022 Sep 26];13(7). Available from: https://pubmed.ncbi.nlm.nih.gov/34203528/

7. Rasel M, Mahboobi SK. Transfusion Iron Overload. StatPearls [Internet]. 2022 Jun 5 [cited 2022 Sep 26]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK562146/

8. Siah CW, Ombiga J, Adams LA, Trinder D, Olynyk JK. Normal Iron Metabolism and the Pathophysiology of Iron Overload Disorders. Clin Biochem Rev [Internet]. 2006 Feb [cited 2022 Sep 17];27(1):5. Available from: /pmc/articles/PMC1390789/

9. Adams P. Management of Elevated Serum Ferritin Levels. Gastroenterol Hepatol (N Y) [Internet]. 2008 May [cited 2022 Sep 17];4(5):333. Available from: /pmc/articles/PMC3093720/

10. Aloy-Amadi O, Akujobi AU, Nnodim J, Ndudim-Dike J, Edward A, Anokwute M. Serum Ferritin and Iron/TIBC of Pregnant Women Attending Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria: A Longitudinal Study. Clin Res Obstet Gynecol •. 2020;3.

11. Wood JC. Use of Magnetic Resonance Imaging to Monitor Iron Overload. Hematol Oncol Clin North Am [Internet]. 2014 [cited 2022 Sep 17];28(4):747. Available from: /pmc/articles/PMC4115249/

12. Shi H, Chen L, Wang Y, Sun M, Guo Y, Ma S, et al. Severity of Anemia During Pregnancy and Adverse Maternal and Fetal Outcomes. JAMA Netw open [Internet]. 2022 Feb 4 [cited 2022 Sep 26];5(2). Available from: https://pubmed.ncbi.nlm.nih.gov/35113162/

13. Origa R, Comitini F. Pregnancy in Thalassemia. Mediterr J Hematol Infect Dis [Internet]. 2019 [cited 2022 Sep 26];11(1):2019019. Available from: /pmc/articles/PMC6402552/

14. Frayne J, Pinchon D. Anaemia in pregnancy. Aust J Gen Pract. 2019 Mar 1;48(3).

15. Singer S, Vichinsky E. Deferoxamine treatment during pregnancy: Is it harmful? undefined. 1999;

16. Kumar RM, Rizk DEE, Khuranna A. Beta-thalassemia major and successful pregnancy. J Reprod Med [Internet]. 1997 May 1 [cited 2022 Sep 26];42(5):294–8. Available from: https://europepmc.org/article/med/9172120

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FIGURE/VIDEO CAPTIONS

From the MRI T2 scan of the liver, there was evidence of moderate iron overload (Figure 1).

MRI T2 of the heart showed normal result (Figure 2).

PATIENT'S PERSPECTIVE

I was worried that my condition might affect the well-being of my baby when doctor initially mentioned I had fatty liver. I was grateful that the condition of iron overload was picked up and treated accordingly.

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