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Case Report

A Case of Very Severe Anemia in Pregnancy Combined with Beta-Thalassemia Major and Pre-Eclampsia

Xuan Gong, Xiaomin Xiao*

First School of Clinical Medicine, Jinan University, Guangzhou, China

Email address:

xiaoxiaomin55@126.com (Xiaomin Xiao), 1154437305@qq.com (Xuan Gong)

*Corresponding author

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Abstract: OBJECTIVE: To investigate the clinical diagnosis, preventive antenatal screening and antenatal diagnosis, pregnancy management, timing and mode of delivery and postnatal management of β-thalassaemia in pregnancy combined. METHODS: Retrospective analysis of the medical history and treatment of a patient with β-thalassaemia in pregnancy combined with pregnancy outcome. RESULTS: The patient recovered well, had a normal temperature, the abdominal incision was removed at 7 d, the II/nail healed, the general obstetric condition was acceptable and she was discharged successfully. CONCLUSION: Anaemia is very common in pregnancy, but very severe anaemia in pregnancy is extremely rare and it is important to define the cause of anaemia. Thalassaemia is a group of inherited chronic haemolytic disorders caused by autosomal defects, which can be aggravated by pregnancy. Thalassaemia can be divided into α-, β-, γ-, δ-, δβ- and other categories, and for β-thalassaemia it can be divided into mild, moderate and severe, with both intermediate and severe patients presenting early with obvious anaemic symptoms and relying on long-term transfusion therapy. The majority of these patients die in childhood and are extremely rare in pregnancy. Thalassaemia in pregnancy can directly affect the outcome of pregnancy and cause many near and long-term complications in the newborn, and timely antenatal screening and prenatal diagnosis can detect the disease early. Active obstetric management and timing of pregnancy can also help to improve maternal and infant pregnancy outcomes.

Keywords: Pregnancy, Beta-Thalassemia, Very Severe Anaemia, Pre-eclampsia

1. Introduction

Thalassaemia, also known as thalassaemia or peptidogenic anaemia, is a hereditary haemolytic anaemia caused by a defect in the peptide chain synthesis of peptide caused by a defect in the peptide gene, and is one of the most common single-gene genetic diseases in clinical practice, with alpha- and beta-thalassaemia being the most common. Thalassaemia is most common along the Mediterranean coast, in Africa and Southeast Asia, with a high prevalence south of the Yangtze River in China, especially in the two regions of Guangdong and Guangxi. Thalassaemia in pregnancy not only increases the level of anaemia, but also leads to an increased risk of anaemia-related obstetric complications and complications. In this article, we present a case of β-thalassaemia in pregnancy in a clinical setting and review the literature to enhance the obstetricians' understanding of the disease.

2. Case Reports

The patient, a 44-year-old female from Guangdong, was admitted on December 16, 2020 with "31+6 weeks of menopause, 40 years of anemia, aggravated for 1 week". g5p4, with one normal delivery in 2001, 2003, 2009 and 2013. No obstetric examination was performed during the current pregnancy. She complained of previous anemia for 40 years and hepatosplenomegaly for more than 30 years. She was previously diagnosed with thalassemia (not reported), no medication was applied to improve the anemia, no standardized systemic treatment was performed, and blood transfusions for anemia were performed several times (details not available). Her hemoglobin fluctuated from 39-61g/L

during pregnancy.2020-10-08, she was admitted to the Internal Medicine Department of the County People's Hospital due to dizziness and weakness of the limbs at 22 weeks of pregnancy, and was discharged after transfusion of 2U of type A erythrocyte suspension and rechecking hemoglobin at 43g/L. After 2 months, she was checked for routine hemoglobin of 37g/L and was transferred to our hospital in an emergency due to lack of matching blood source.

On admission, he had a body temperature of 36.4°C, pulse rate of 100 beats/min, respiration of 20 breaths/min, blood pressure of 162/69 mmHg, height of 157 cm, weight of 51 kg, BMI of 20.6, moderate anemia, prominent cheekbones [1], widened eye spacing, low nasal bridge, elevated forehead, mild yellowing of the skin, pale lips and lid conjunctiva, mild yellowing of the sclera, and depressed edema below both knees. The rest of the examination did not show any special. The obstetric examination did not show any abnormalities, and the uterus was as large as the gestational week. Complete examination: fetal ultrasound showed no abnormality; ECG suggested sinus tachycardia; cardiac ultrasound showed enlarged left atrium, mild mitral valve, cardiac function LVEF: 66%, E/A132/106=1.25, excluding heart failure. Ultrasound of liver, gallbladder, pancreas and spleen showed enlarged liver and spleen with hypoechoic mass in the splenic portal area, considering parasplenic. Related tests: blood type: A positive, WBC 20.57x10^9/L, RBC 3.29x10^12/L, PLT 387x10^9/L, HGB 38g/L, HCT 14.3%, MCV 43.6fl, MCH 11.5Pg, MCHC 264g/L, erythropoietin >782mIU/ml, Fe 53.7umol/L, total iron-binding capacity (TIBC) 157.5umol/L, transferrin (Tf) 2.677 g/L, transferrin receptor (sTfR) 119.8 nmol/L, ferritin (SF) 448.59ng/ml. exclude iron deficiency anemia, further refine the gene of thalassemia: 41-42, βE double heterozygote detected, no The α-thalassemia genotype was not detected. The remaining liver and kidney functions, coagulation function, G-6-PD, urine routine and stool routine were generally normal.

Close monitoring of maternal and infant vital signs. the patient's blood pressure fluctuated in 131-164/55-78mmHg, methyldopa 2# qh was given to reduce blood pressure, and 24h urine protein was quantified at 0.35g, supplementary diagnosis: preeclampsia, magnesium sulfate antispasmodic treatment was given. Blood pressure control was possible with regular testing. The patient's pregnancy was combined with very severe anemia, and blood transfusion therapy was proposed. Invasive prenatal diagnosis was also recommended, but the patient and family refused. Cross-matching test showed a positive antibody screen and a positive plasma screen for irregular antibodies [2] and after discussion with the haematology department it was felt that transfusion should still be given. After admission, 2 U of blood type A red blood cell suspension (+) was transfused on 12-17, 12-18 and 12-19, respectively, and furosemide 20 mg diuretic and dexamethasone 1O mg intravenous push were given half an hour before transfusion to prevent allergic reaction to blood transfusion. After 3 transfusions, HGB 63g/L, 12-22 repeat HGB 48g/L, re-infuse type A concentrated red blood cells (+)1U, 12-23 repeat HGB 42g/L. After joint consultation with obstetrics, hematology, anesthesiology and other departments, it was believed that the patient's blood transfusion treatment to improve anemia was not good, and combined with multiple high-risk factors such as preeclampsia and advanced age, the risk of continuing to be in labor was higher, and it was recommended to correct anemia with blood transfusion and actively terminate the pregnancy as appropriate. Dexamethasone for fetal lung maturation was completed at 33+1 weeks of gestation.

Ultrasonography performed on 12-25 revealed a bipedal previa with a biparietal diameter of 81 mm, a head circumference of 285 mm, and an estimated fetal weight of 1854 g ± 271 g.

After feeding A(+) 2 U concentrated red blood cells and preparing blood for 6 U concentrated red blood cell suspension, a lower uterine segment cesarean section was performed under combined lumbar and rigid anesthesia on December 26, 2020, along with an intraoperative bilateral tubal ligation. Neonatal condition: neonatal sex female, Apgar score 8-10-10, weight 1550g, transferred to neonatology. The patient was given postoperative cephalosporin antibiotics to prevent infection and intravenous indocin to promote contraction. Considering the patient's advanced age >35 years, ≥3 deliveries, post-cesarean section, pre-eclampsia and preterm delivery in this pregnancy, the risk of thrombosis assessment was high, and low molecular heparin LMWH (Kesse) was given immediately after delivery to prevent thrombosis. The patient's blood pressure fluctuated from 126-156/66-83 mmHg 2 days after surgery, and he continued to take oral methyldopa for antihypertensive treatment. 8 days after surgery, the patient's vital signs were stable, body temperature was normal, and the routine blood test was repeated with HGB 56g/L, WBC 5.56x10^9/L, N%: 60.3%, calcitoninogen: 1.142ng/ml, and antibiotics and low molecular heparin were stopped. The patient's abdominal incision was removed and healed II/nail, the abdomen was soft, the uterus was well restored, the fundus of the uterus was flat 3 transverse fingers above the pubic area, the malignant discharge was low, and the spleen was significantly reduced. The patient was successfully discharged from the hospital. The patient's general condition was acceptable 42 days after delivery by telephone follow-up.

3. Discussion

Anemia is very common during pregnancy. According to the World Health Organization (WHO) criteria, most pregnant women have mild anemia (Hb100-109 g/L), but in developing countries, moderate and severe anemia is still more frequent (Hb 70-99 g/L and Hb 40-69 L), and even very severe anemia (Hb<40 g/L). Anemia during pregnancy is usually associated with adverse pregnancy outcomes [3, 4], with near and long-term effects on both the mother and her fetus. It can increase the risk of miscarriage, obstructed labor, hypertensive disorders of pregnancy, premature rupture of membranes, puerperal infection and postpartum hemorrhage in mothers, and even cause maternal death; in the fetus, it can

lead to fetal growth restriction, intrauterine distress, and stillbirth. Therefore, correcting maternal anemia is of great significance to improve maternal and infant outcomes.

1) Identify the cause of anemia

There are more than one clinical types of anemia, and the clinical diagnosis should be strictly differential, to clarify the cause of anemia as soon as possible, and to take different treatments for different types. The combined thalassemia in this patient [5]: namely, dyscrasias, also known as maritime anemia, is a group of hereditary chronic hemolytic diseases caused by autosomal defects. Alpha- and beta-thalassemia are common, among which beta-thalassemia is one of the most common and harmful genetic diseases in southern China.

The patient was severely anemic since childhood and had a history of anemia for more than 40 years. Pregnancy not only increases the level of anemia, but also leads to an increased risk of obstetric complications and complications associated with anemia.

Routine blood tests are the simplest and most basic tests for the detection of thalassemia, with normal or varyingly decreased Hb, MCV < 82 fl, and MCH < 27 pg indicating positive screening for thalassemia [6, 7]. The combination of routine blood tests and HbA2 levels can initially determine whether the patient is a carrier and the type of thalassemia [8]. For suspected carriers of thalassemia, the gene for thalassemia should be tested as soon as possible, and serum ferritin should be tested at the same time to exclude iron deficiency anemia. Mutation analysis of this patient's β-geodystrophy gene revealed 41-42, βE double heterozygote, confirming the diagnosis of severe β-geodystrophy [9; 10], which is extremely rare in pregnancy. In this case, the lower level hospital should identify the cause, standardize the treatment, provide genetic guidance and make necessary interventions during pregnancy at the first visit of the patient. In this case, the lower hospitals should define the etiology, standardize the treatment, provide genetic guidance and make the necessary interventions during pregnancy at the first visit of this patient.

2) Prenatal diagnosis

Thalassemia in pregnancy can lead to adverse pregnancy outcomes such as fetal growth restriction, preterm delivery, and even intrauterine death [7], and may cause serious complications such as thromboembolism, cardiac lesions, and endocrine abnormalities [11]. Timely prenatal screening, prenatal diagnosis and effective treatment of thalassemia in pregnancy are clinically important to improve the pregnancy outcome of mother and child. There is an expert consensus that prenatal diagnosis is the gold standard for confirming the diagnosis of fetal geodystrophy and its staging. Currently, fetal specimens can be obtained for prenatal genetic diagnosis through invasive operations such as chorionic villus biopsy sampling, amniocentesis, and cord blood aspiration [8].

This patient has β-thalassemia major, which does not exclude the offspring from being thalassemia major, and further prenatal diagnosis was performed while perfecting the husband's thalassemia genetic test [7, 9, 12]. Newborns with genetic defects of thalassemia have a low survival rate and poor physical fitness, which will not only bring a greater burden to the family and society, but also violate the eugenic policy in China. This case suggests that clinicians should pay attention to the need to strengthen health education on thalassemia, increase group screening, premarital and preconception screening, and strengthen prenatal diagnosis-related efforts when seeing patients, which can help promote eugenics, improve the quality of newborns, and improve population quality in our country..

3) Pregnancy management

The key points in the management of thalassemia pregnancy are modified transfusion therapy, monitoring of hemodynamics, cardiac function indicators to prevent heart failure, and prevention of thrombosis, depending on the specific situation [13]. Cardiac complications are a major risk factor for patients with thalassemia [11]. In addition, thalassemia often causes liver involvement. Expert consensus states that patients with severe anemia should be screened for end-organ damage and managed for complications, and echocardiography, electrocardiography, and hepatobiliary-pancreatic-splenic ultrasound should be improved before planning a pregnancy [8].

Severely anemic patients should have regular blood tests during pregnancy, and when Hb <60 g/L, small and multiple transfusions should be given under close supervision [8].

Heart failure should be prevented with cardiotonic and diuretic drugs before transfusion, and the number of fluid drops should be strictly controlled during transfusion. For the presence of autoantibodies in the blood and difficulties in blood allocation, washing red blood cells can be used [14], but red blood cell suspension can still be given for treatment, Dexamethasone was given before transfusion as an anti-allergic agent to prevent hemolysis and allergic reactions. Closely monitor the patient's vital signs after transfusion and pay attention to any fever and other hemolytic reactions.

Mother's chronic anemia predisposes the fetus to intrauterine hypoxia, placental thrombosis and depletion of nutrients leading to FGR. Therefore, pregnant women with thalassemia combination should be monitored monthly for fetal biology after 24 weeks of gestation [15] to observe fetal growth.

The patients are extremely anemic and have poor tolerance for bleeding. Before the end of labor, in addition to routine labor management, it is necessary to cross-match blood as early as possible and also to know the Hb level so that the hemoglobin level can be raised above 60 g/L if possible, and it is safer if it can reach above 80 g/L [8].

4) Anemia combined with pre-eclampsia

Patients with anemia are at relatively higher risk for hypertensive disorders in pregnancy. The complex and rapidly changing condition of hypertensive disorders in pregnancy requires clinicians to closely monitor the patient's condition, keep abreast of the severity and progression of the condition, intervene reasonably, prevent and treat early, and avoid the occurrence of adverse pregnancy outcomes.

The patient's blood pressure fluctuated between 131-164/55-78 mmHg, urinary protein was ≥0.3 g/24 h, and the diagnosis of severe preeclampsia was clear [16]. Patients

with systolic blood pressure ≥ 160 mmHg should be treated with antihypertensive therapy [17]. For those with uncomplicated organ function impairment, the target blood pressure is to control systolic blood pressure at 130-155 mmHg and diastolic blood pressure at 80-105 mmHg; however, blood pressure should not fall below 130/80 mmHg to ensure uteroplacental blood perfusion [16]. Pay attention to the individualized situation of blood pressure reduction. Control blood pressure not fluctuate too much, and strive to maintain a more stable target blood pressure. Antihypertensive means include life intervention and drug antihypertensive. Methyldopa, which excites alpha receptors in the vasomotor center and lowers blood pressure by inhibiting peripheral sympathetic nerves, is more effective when used in pregnancy. It is also given should magnesium sulfate antispasmodic therapy [18, 19]. Magnesium sulfate is the key drug for severe preeclampsia to prevent eclampsia seizures. The duration of medication was adjusted according to the needs of the disease, and the patient was monitored for the presence of knee tendon reflex, respiration ≥ 16 times/min, urine output ≥ 25 ml/h, while 10% calcium gluconate was available to prevent magnesium sulfate poisoning.

5) Timing of delivery and mode of delivery

Regarding the timing of delivery, the 2014 RCOG guidelines recommend that the timing of termination of pregnancy be determined by the obstetric status of the patient with thalassemia. And the China 2020 Expert Consensus on the management of thalassemia during pregnancy also states that the timing of delivery in patients with thalassemia is based on the degree of anemia and obstetric indications [8]. In addition to considering the type of thalassemia, the degree of anemia, and the effect of anemia treatment, a comprehensive assessment should be made based on the patient's reproductive history, gestational week, cervical condition, fetal previa, fetal position, and the presence of other obstetric high-risk factors.

This patient had poor results with transfusion therapy to improve anemia, in addition to the combination of preeclampsia and advanced age, and a postpartum hemorrhage score as high as 14. All things considered, the pregnancy could be terminated as soon as possible after completion of dexamethasone for fetal lung maturation.

Expert consensus: simple geodystrophy is not an indication for cesarean delivery [8], and patients with geodystrophy can have a vaginal trial of labor. When combined with a mixed breech presentation, cesarean section is performed to end the delivery.

The operation should be performed by a skilled and experienced surgeon to minimize the operation time and to reduce intraoperative bleeding by strictly suturing the incision and surrounding blood vessels. The patient has splenomegaly, so abdominal pressure during fetal delivery was strictly prohibited and uterine pressure must be careful and gentle to avoid rupture of the liver and spleen [20]. Pay attention to strengthening contractions after surgery and increase the use of contracting medications to help uterine recovery as appropriate.

6) Postpartum precautions

The period of 3 days after delivery, especially the 24 hours after delivery, is still a risk period for heart failure, and the mother should be well rested and closely monitored.

The risk of postpartum venous thrombosis remains high under the combined effects of pregnancy [21; 22] and geodystrophy. Some studies have recommended the use of low-molecular heparin [7; 21] for 6 weeks after delivery to prevent thrombosis.

Timely review the blood routine and coagulation function after delivery, give blood transfusion again if necessary, and strengthen the management of anemia. Closely monitor the amount of vaginal bleeding and uterine regeneration. If more bleeding or even DIC occurs, actively resuscitate the patient, and if necessary, remove the uterus. After discharge from the hospital, consult the hematology department and encourage breastfeeding.

4. Conclusion

The cause of anaemia should be identified as early as possible in patients with anaemia in pregnancy, especially in those with very severe anaemia. Thalassaemia major in pregnancy is extremely rare and may be clinically underdiagnosed or misdiagnosed as iron deficiency anaemia, but often thalassaemia is more dangerous as a genetic defective genetic disorder and therefore standardised management of patients with thalassaemia in pregnancy is particularly important. Prenatal genetic counselling and prenatal diagnosis should be carried out. Patients with thalassaemia major may suffer from skeletal deformities, organ damage, impaired reproductive development and immune deficiency due to anaemia and iron deposits, and in severe cases, heart failure, which can seriously affect pregnancy outcomes. In severe cases of thalassaemia, glucose metabolism, thyroid and cardiac function should be assessed during pregnancy and the risk of deep vein thrombosis should be assessed and prevented, and blood transfusions should be administered promptly in severe cases. For other complications of pregnancy, a combination of treatment measures should be taken. The patient's Hb level should be monitored dynamically and the timing and mode of delivery should be decided according to the degree of anaemia and obstetric indications. Active management during labour to prevent post-partum haemorrhage. Postnatal prevention of heart failure and thrombosis and management of anaemia.

In conclusion, thalassaemia major in pregnancy is very rare in clinical practice and requires multidisciplinary management, comprehensive assessment of the mother and child, intensive perinatal monitoring and a balanced management of all factors to achieve the best possible maternal and child outcome.

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