Successful Pregnancy Outcome in Malaysian Woman with Rare p Phenotype and Anti-PP1P^k Antibody

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Abstract We report the first case of young woman with the p phenotype and anti-PP1P^k antibody in the Malaysian population who was identified during a blood grouping and antibody screening procedure after her first miscarriage. Further family screening detected two other siblings who possessed the same rare phenotype and antibody. Because of difficulties in finding compatible units in the local population, the patient and her two siblings were advised to become regular blood donor. Their blood was frozen for future use. After she had two recurrent miscarriages, her third pregnancy was successfully managed using oral dydrogesterone, which was started from 10 weeks into the pregnancy. Her pregnancy was uneventful and she gave birth to a healthy term neonate.

Keywords p phenotype · Anti-PP1P^k · Dydrogesterone · Recurrent miscarriage

Introduction

The presence of the p phenotype is rare and associated with the presence of anti-PP1P^k antibody, a potent, naturally

occurring antibody, which forms because of a lack of P, P₁, and P^k antigens. Presence of anti-PP1P^k in the women of child bearing age group can lead to recurrent miscarriage in early pregnancy and haemolytic disease in newborns.

Many studies have suggested that regular plasmapheresis to lower the antibody level in women with the p phenotype and anti-PP1P^k could be helpful to prevent pregnancy loss [1–5]. However, in our district hospital, Sultan Abdul Halim Hospital, Sungai Petani of Kedah state, the plasmapheresis procedure is not readily available. To overcome this, we treating the patient with oral dydrogesterone to support her third pregnancy after two episodes of repeated miscarriage. To the best of our knowledge, this is the first case of a woman with the p phenotype and anti-PP1P^k antibody in the Malaysian population who was successfully managed using oral dydrogesterone, and gave birth to healthy term neonate. Dydrogesterone is a known treatment for luteal phase support in women with history of recurrent miscarriage [6, 7]. But use of dydrogesterone among pregnant women with anti-PP1P^k was never reported before. Thus by reporting this case, we hope to enlighten the benefits of oral dydrogesterone intake during the early stage of pregnancy among women with the p phenotype as an alternative when the plasmapheresis procedure is not readily available especially in resource-limited setting.

Case Presentation

A 27-year-old woman was referred from a local health clinic to our Antenatal Clinic for per vaginal bleeding at 12 weeks of gestation. An ultrasound scan was performed and diagnosis of missed miscarriage was confirmed. During routine antibody screening for blood reservation prior to surgical intervention following miscarriage, an unknown

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Fig. 1 Patient's family tree

antibody was detected. The blood sample was sent to the National Blood Centre (NBC) for further antibody identification. Her blood group and rhesus was O Positive and found to have rare p phenotype with IgM anti-PP1P^k antibody and was believed to be the first case detected in our Malaysian population. To exclude the endocrine and thrombophilia disorders, patients were tested also for full blood count and differential, thyroid function test, lupus anticoagulant testing, anticardiolipin antibody and anti double-stranded DNA, in which all the tests show negative result.

This patient was informed regarding the blood test result and its implications. She denied any previous history of blood transfusion. Both of her parents had a consanguineous marriage. When family screening was performed, we later found that her sister and brother also have this rare p phenotype and produced the same rare antibody (Fig. 1). Coincidentally, her sister also reported that she just had spontaneous miscarriage a few weeks before she came for family screening. Because of the rarity of their blood, the patient and her two siblings were advised to donate their

blood to be kept and stored at the NBC. The patient managed to donate her blood twice and the units were frozen for future use.

Approximately 1 year after the first identification of anti-PP1P^k antibody, our patient became pregnant again. Unfortunately, she did not aware about the pregnancy and only presented to the emergency unit after she passed out product of conception. She was then diagnosed with spontaneous miscarriage at about 8 weeks of gestation. She was advice to come early for subsequent pregnancy. Ten months later, she booked at our Antenatal Clinic for her third pregnancy. An ultrasound scan confirmed a viable foetus at 10 weeks of gestation. A discussion between obstetrician and transfusion medicine specialist was conducted to find the best solution to help and prolonged patient's pregnancy. Plasmapheresis is a recommended procedure in such cases of pregnant women with rare blood antibody. However, this modality is not available in our local setting. Being the first case that occurred in this country, we have no local guideline in managing such cases. Alternatively, based on the literature review, we

started this patient on oral dydrogesterone. She was placed on a regular follow-up with our resident obstetrician at our high-risk pregnancy clinic. This patient had ultrasound detail scanning twice; at first and second trimester to look for any congenital malformation. Fetal growth monitoring also has done every 2–3 weekly during her antenatal visit. However, no maternal antibody titre monitoring was done during pregnancy.

Because of the risk of bleeding during delivery and the possibility of requiring a blood transfusion, she was planned for delivery at other tertiary hospital near the NBC where her blood was kept. This is to make sure that her blood can be obtained in short period of time if any mishap happened during delivery. However, she went into spontaneous labour in our hospital at 37 weeks.

The patient's delivery was uncomplicated and no blood transfusion required. Baby's birth weight was 2.86 kg. No anemia or severe jaundice was observed during the neonatal period. Serum bilirubin level was not raised, thus no exchange transfusion required. Both mother and newborn were discharged in a good condition after delivery.

Discussion

Since its discovery in 1927 [8], many cases has been reported on women with p phenotypes. Unlike other patients in whom the p phenotype was identified after investigations done for recurrent miscarriage, our patient was diagnosed at her first miscarriage during a routine blood grouping and antibody screening. She was counselled regarding her rare condition and the risk of miscarriage in a subsequent pregnancy. Once diagnosed, family screening should be done as this rare condition shows recessive inheritance [9–12]. With regard to our patient, consanguineous marriage between her parents carried a higher rate of obtaining p inheritance among their children.

Because this is the first case of a p phenotype and anti-PP1P^k antibody detected among the Malaysian population, patient and her other two siblings were encouraged to become regular blood donor at National Blood Centre. This blood can be used for transfusion should a subsequent need arise. Red cell freezing method using glycerol was used to store the red blood cells at temperature of -80°C . Glycerol helps to prevent cellular dehydration and mechanical trauma of frozen red cells by crossing the cell membrane into the cytoplasm and create an osmotic force that stops the water from moving out of cells [13]. When the frozen red cells are needed for transfusion, it was thawed in a room temperature water bath and the glycerol must be removed (deglycerolization) gradually to avoid hemolysis. However, frozen red cells have several set-backs. Technically demanding method of glycerolization and

deglycerolization, costly procedure and limited 24 h post deglycerolization shelf life of red cells were limitation for frozen red cells use [14, 15]. Since the NBC located almost 400 km from our centre, we decided to transfer our patient to a tertiary hospital near the NBC as a precaution, and at the same time, try to avoid any wastage of precious blood resources. However, our patient went into spontaneous labour before we could transfer her to the hospital near NBC. In the future, this patient may need to be transferred earlier before she reaches the term period.

In this report, we highlight the use of dydrogesterone as an alternative in treating a woman with the rare p phenotype and anti-PP1P^k antibody, who had a good pregnancy outcome. Many published case reports have encouraged the use of the plasmapheresis procedure during pregnancy in women with the p phenotype with a history of recurrent miscarriage [1–5]. This procedure can reduce antibody titres, and begins between the 5th and 7th week of pregnancy. However, in our local setting, the plasmapheresis procedure is not readily available. Therefore, our patient was treated with oral dydrogesterone 10 mg twice daily as early at 10 weeks of pregnancy.

A successful pregnancy outcome among women with a history of recurrent miscarriage after being treated with dydrogesterone has been described in several reports [6, 7]. The mechanism of treatment with dydrogesterone is unclear, but it was postulated to be due to the production of 'asymmetric antibodies' by progesterone-induced blocking factor, which competes with precipitating antibodies [16]. This helps to reduce maternal anti-embryonic immune responses and decreases the risk of miscarriage. However, more reports are required to support the benefits of dydrogesterone intake in women with the p phenotype to sustain pregnancy.

Conclusion

Pregnant women with this rare antibody should be diagnosed as early as possible so that the appropriate treatment can be started early too. Apart from being the causes for recurrent miscarriage, the p phenotype and the presence of anti-PP1P^k antibody also lead to haemolytic disease of the newborn. There is a need to impose properly formulated protocols to manage such cases in future, particularly on maternal antibody level testing throughout pregnancy and fetal growth monitoring. There is also a need to make plasmapheresis procedure available in future as it shows a good pregnancy outcome in several reported cases. Although used of dydrogesterone can be an alternative to prolong the pregnancy like in this case, more reports are needed to support it benefits. Patients with this phenotype should be encouraged to donate their blood to be stored

frozen for future possible needs. Lastly, multidisciplinary collaboration is important for better management of this complex and rare case.

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