



Pregnancy with anti-PP1Pk antibody managed with prednisolone and low-molecular-weight heparin – A case report and literature review

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ABSTRACT

The anti-PP1Pk is a rare antibody associated with recurrent miscarriages, mainly in the first half of pregnancy. There seems to be a direct correlation between the antibody titer and risk of miscarriage. As this is a rare entity, few case reports have been published. The most frequently proposed therapeutic approaches are double-filtration plasmapheresis and plasma exchange therapy. The rationale behind them is to remove the cytotoxic antibodies from maternal circulation. Here, we present the case of a 30-year-old woman with a history of two spontaneous miscarriages and a pre-conception anti-PP1Pk antibody titer of 1:4. As soon as she became pregnant, she was placed on prednisolone and low-molecular-weight heparin (LMWH). Biweekly antibody titers were performed throughout the entire gestation and remained below 1:16. As the titers were considered to be low, plasmapheresis was not performed. The pregnancy was uneventful and she delivered a healthy newborn child at 37 weeks of gestation, with no signs of anaemia.

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1. Introduction

The anti-PP1Pk, previously known as anti-Tja, is a natural occurring antibody against P, P1 and Pk red cell antigens. Individuals in which these antigens are absent are known as having a p phenotype [1]. This phenotype is extremely rare, with an estimated worldwide prevalence of $5.8 \cdot 10^{-6}$ [2].

The anti-PP1Pk antibody has been associated with recurrent miscarriages, mainly in the first half of pregnancy [3,4]. The risk seems to be directly correlated with the anti-PP1Pk antibody titer and particularly with IgG type antibodies that cross the placenta [5].

There is no specific treatment or primary prevention strategy as this is a naturally occurring antibody [4].

After searching the MEDLINE (PubMed), Scopus, and Scielo databases, the authors found that most published case reports of successful pregnancies in p phenotype women describe the use of plasma exchange therapy or double-filtration plasmapheresis in their management [3,4,6–10]. The main purpose of these therapeutic approaches is to remove the cytotoxic antibodies from maternal circulation, as soon as the pregnancy is confirmed, in order to maintain antibody titers between 1:16 and 1:32 [4]. There are few case reports that describe the use of dydrogesterone or expectant management only [9,10].

In the last 25 years, from 1994 to 2019, only nine cases of pregnancies in women with anti-PP1Pk antibodies have been published in the aforementioned databases [3,4,6,8–12].

Here, we present a case of a successful pregnancy in a p phenotype woman, with a history of recurrent pregnancy loss, managed with close surveillance, biweekly antibody titers, without the need for plasma exchange therapy or double-filtration plasmapheresis.

2. Case

A 30-year-old healthy Caucasian woman was referred for a pre-conception appointment because she had previously had two spontaneous miscarriages. She had been evaluated at another institution during the former gestations and after both miscarriages. During that evaluation, chromosomal abnormalities, acquired thrombophilia, uterine malformations and endocrine pathology were excluded.

After the first miscarriage, she had been diagnosed with an MTHFR and PAI-1 heterozygosity. During the second pregnancy, she had been placed on low-molecular-weight heparin (LMWH), yet miscarried again. During the evaluation for recurrent pregnancy loss, three years before the present assessment, she was found to have antibodies against PP1Pk, with a titer of 1:128.

Following the first pre-conception appointment and after exclusion of other causes of recurrent miscarriages, an anti-PP1Pk titer was determined. The patient serum was evaluated through indirect antiglobulin test, against a panel of cells with a known phenotype, at 37 °C. The

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existence of anti-PP1Pk antibody was confirmed, with a titer of 1:4. The patient became pregnant one month after the test result.

As soon as the pregnancy was confirmed, at 5 weeks of gestation, she was put on prednisolone 10 mg/day and prophylactic LMWH 40 mg/day. Anti-PP1Pk antibody titer was promptly measured and repeated every two weeks throughout the entire pregnancy, with the intention to perform plasmapheresis if the titers were to increase.

In the biweekly measurements, the anti-PP1Pk antibody titer remained equal to or below 1:8. As the titers were so low, the multidisciplinary team, which included obstetrics, internal medicine and immunohematology specialists, decided not to perform plasmapheresis.

In the third trimester, she was found to have iron deficiency (ferritin 5 µg/L and transferrin saturation 6%) without anaemia (haemoglobin 12.1 mg/dL) and was given 1 g of intravenous ferric carboxymaltose at 33 and 34 weeks. No other problems were observed.

At 36 weeks of gestation, autologous blood withdrawal was performed and stored for potential future use.

The patient maintained the initial medication throughout the entire pregnancy, which was uneventful. She had an elective caesarean section at 37 weeks of gestation and delivered a healthy girl, with a birth weight of 2.445 g and an Apgar score 10–10 and no signs of anaemia.

3. Discussion

The P blood group was first described in 1927 and was believed to comprise three antigens: P1, Pk, and P. In the current classification, there are three different blood group systems, through which six antigens are distributed, based on the glycosyltransferase necessary for their synthesis. These blood group systems are: P1Pk, GLOB and FORS. P1Pk includes the Pk, P1, and NOR antigens; the GLOB system comprises the P and PX2 antigens; and the FORS system, the Forssman antigen. The P and Pk are high-frequency antigens and are present in more than 99.9% of people [1].

The different phenotypes are dependent on the type of glycosyltransferase that is mutated. The p phenotype, which is the null of this blood group system, is a recessive trait and results from inactivating mutations in the *A4GALT1* gene in chromosome 22q13.2, which is responsible for 4-α-galactosyltransferase synthesis. In the absence of this enzyme, Pk, P, and P1 antigens are not synthesized [1].

When the P, P1 and Pk antigens are absent, the anti-PP1Pk antibodies, which are composed of regular IgM type, regular or irregular IgG type antibodies, or a combination of both, naturally arise. The cytotoxic components seem primarily to belong to the IgG3 subclass. These antibodies cross the placental barrier, are efficient complement activators, and are responsible for antibody-mediated cytotoxicity, although not exclusively [13].

The presence of anti-PP1Pk antibody in women of reproductive age is associated with early recurrent miscarriage and, only to a minor degree, haemolytic disease in the newborn [3]. It is reported that 50–72% of miscarriages occur in the first 20 weeks of gestation [4]. It has been shown that the placenta contains a high density of Pk and P antigens, which appear on the trophoblast as early as the 3rd week of gestation. Antibodies against these antigens have been implicated in recurrent pregnancy loss [4]. The P1 antigen arises only in the 19th week of gestation and it has been proposed that it blocks the expression of other antigens, lowering the cytotoxic effect of anti-P and anti-Pk antibodies [4]. Even though the placenta seems to be the most important target of the anti-PP1Pk antibody complex, the precise mechanism of recurrent miscarriages is not completely understood [3,10].

Regarding management, there is no specific treatment for PP1Pk alloimmunization. Contrary to Rh and Kell alloimmunization, in which plasmapheresis is especially important in the last trimester, in anti-PP1Pk pregnancies, pre-conception surveillance and early treatment if necessary are essential [6].

Plasma exchange therapy and double-filtration plasmapheresis have been used as therapeutic approaches [3,4,6,8,11,12]. The main purpose

is to reduce antibody titers to 1:16 to 1:32, thereby preventing cytotoxicity and miscarriage. Treatment should begin as soon as the pregnancy is confirmed and should be maintained until at least the 18th week gestation. Its duration is controversial, however, especially beyond the 20th week of gestation [4,8].

In the present case, the patient had a high titer – 1:128 – after the second miscarriage, but the titer was spontaneously low – 1:4 – just before her first successful pregnancy, probably because anti-PP1Pk antibody occurs naturally. During the reported gestation, as the titer remained below 1:16, the multidisciplinary team decided not to perform plasmapheresis.

The patient was put on prednisolone and LMWH as soon as she became pregnant. Even though their use is currently controversial, corticosteroids were used for their known anti-inflammatory and immunosuppressive effects on T and NK cells, which seem to be altered in cases of recurrent miscarriages [14]. Although there is no consensus regarding the dosing and length of treatment, low-dose corticosteroids seem to increase pregnancy success without significantly increasing the risks [14,15]. The use of LMWH might also be arguable, on the one hand because MTHFR and PAI-1 mutations are presently of unknown clinical significance and on the other hand because there are studies in which prophylactic enoxaparin did not improve the chance of a live birth in women with a history of recurrent pregnancy loss [16]. Nevertheless, in other studies LMWH has shown to significantly lower the rate of miscarriage in women with a history of unexplained miscarriage negatively tested for antiphospholipid antibodies [17]. Besides inhibiting coagulation, heparin has anti-inflammatory effects, by blocking the activation of complement and preventing leukocyte adhesion to vascular endothelial cells and subsequent transmigration, with minimal adverse effects at prophylactic doses [18,19].

As described, in the third trimester the patient was found to have iron deficiency and was treated with ferric carboxymaltose at 33 and 34 weeks. Intravenous iron was chosen, as it increases haemoglobin and ferritin levels faster and more efficaciously, with fewer side-effects than oral iron, which was particularly important in this situation as there was a need to lessen the need for blood transfusion, since it would be very difficult to find compatible units for a patient with such a rare phenotype [20].

For the same reason, blood should be drawn before delivery, for possible future autologous transfusions [4]. These patients should be encouraged to become blood donors, for potential use by themselves or others with the same phenotype [10].

In conclusion, as the p phenotype is extremely rare, with few published case reports, little is known about the pregnancy management of women with this condition. In the presented case, antibody titers were assessed biweekly throughout the entire pregnancy and spontaneously remained below 1:16. We hypothesize that prednisolone might have had an effect on the persistently low antibody titers. For that reason, the multidisciplinary team decided not to perform plasmapheresis. Even though we do not know the extent of the impact that prednisolone and LMWH therapy had on the final result, we propose that p phenotype pregnancies can be safely managed without plasmapheresis or plasma exchange therapy, if the titers remain below 1:16, emphasizing the importance of repeat antibody titers, at least biweekly.

Contributors

All authors participated in the work, reviewed and edited the manuscript and approved its final version.

Declaration of Competing Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Ethical approval

Ethical approval to report this case was obtained from the ethics committee of the Hospital Prof. Doutor Fernando Fonseca (Approval ID: 14/2020).

Patient consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Provenance and peer review

This case report was peer reviewed.

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