Current clinical management of anti-Kell alloimmunization in pregnancy

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Abstract

Objectives: Few reports have been published of the current clinical management of anti-Kell alloimmunization in pregnancy; its low frequency of occurrence means that the few long series published have covered very ample time periods in which different kinds of clinical management have overlapped. The objective of the present paper is to present our experience in the current clinical management of pregnant women who are positive for the anti-Kell antibody.

Study design: A retrospective analysis was carried out of the case histories of pregnant women who were alloimmunized for the Kell antigen and who were studied and/or treated at the Department of Fetal Medicine in the Virgen de las Nieves University Hospital in Granada (Spain), between 2000 and 2004. The clinical management included the basal measurement of the titre of antibodies, the identification of the paternal phenotype (and that of the fetus, if necessary), the ultrasonographic monitoring of the fetus to detect signs of anaemia, sampling of fetal blood by cordocentesis when fetal anaemia was suspected, and fetal intravascular transfusion when necessary.

Results: Of the 10 pregnancies with anti-Kell antibodies, the Kell antigen was confirmed in the fetus in three cases, in all of which moderate to severe fetal anaemia developed, requiring fetal intravascular transfusions. Although one of the fetus developed antenatal hydrops, a good perinatal result was advised.

Conclusions: The current approach to anti-Kell alloimmunization enables pregnant women who have Kell-positive fetuses to be treated successfully.

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1. Introduction

Since prophylaxis by the administration of anti-D immunoglobulin to Rh-negative pregnant women became standard practice, the incidence of Rh alloimmunization among women of childbearing age has fallen, while alloimmunization against other erythrocyte antigens is becoming more common [1]. It has been calculated that alloimmunization of the Kell antigen occurs in approximately one of every 1000 pregnancies [2,3], equivalent to 29% of all alloimmunizations capable of producing neonatal haemolytic disease among women of childbearing age [1].

The alloimmunization of the Kell antigen may be caused by previous blood transfusions or be induced by fetal-maternal haemorrhage during pregnancy [3,4]. When a woman acquires alloimmunization by previous blood transfusion, there is only a small probability that the fetus will be a carrier of the antigen, because the low incidence of the Kell antigen among the general population (9% among whites and 2% among blacks) [5] means it is unlikely that the partner will have it. On the other hand, when alloimmunization is induced by a previous pregnancy, the probability of having a Kell-positive fetus in future pregnancies is around 50%, because almost all Kell-positive individuals are heterozygous for the Kell antigen [5]. Nevertheless, this low probability that an isoimmunized woman will have a Kell-positive fetus should not lead us to think that the risk of Kell alloimmunization is low, as there is a 44% probability of her being moderately to severely affected when the fetus has the Kell antigen [6].

It has been suggested that Kell alloimmunization is a different disease from Rh alloimmunization [6]. Unlike Rh alloimmunization, in which fetal anaemia results from a
haemolytic process, in anti-Kell alloimmunization the fetal anaemia is mainly caused by the suppression of erythropoiesis, which is directly induced by anti-Kell antibodies [7–9], because the antigen is expressed by the erythroid progenitor cells. This different physiopathological mechanism explains the clinical fact observed in Kell alloimmunization [2,10] that the determination of the concentration of bilirubin in amniotic liquid by means of ADO 450 is not useful for evaluating the severity of fetal anaemia, and also explains the fact that the phase of post-natal anaemia is more prolonged than with Rh alloimmunization. Additionally, the Kell antigen presents a much lower degree of immunogenicity than the one responsible for Rh alloimmunization, which would explain the fact that only 5% of Kell-negative individuals subjected to an incompatible transfusion develop an immune response with the formation of antibodies [11], and that the titres of maternal antibodies undergo few modifications during the pregnancy, such that their determination in series is of little utility [12].

The above-mentioned characteristics mean that a specific form of clinical management must be applied to this situation [5], including the basal measurement of the titre of antibodies, the identification of the paternal phenotype (and that of the fetus, if necessary), the ultrasonographic monitoring of the fetus to detect signs of anaemia, sampling of fetal blood by cordocentesis when fetal anaemia is suspected, and fetal intravascular transfusion when necessary, this being repeated periodically until delivery [6].

However, few reports have been published of the current clinical management of such a situation; its low frequency of occurrence means that the few long series published have covered very ample time periods in which different kinds of clinical management have overlapped.

The objective of the present paper is to present our experience in the current clinical management of pregnant women who are positive for the anti-Kell antibody.

2. Material and methods

A retrospective analysis was carried out of the case histories of pregnant women who were alloimmunized for the Kell antigen and who were studied and/or treated at the Department of Fetal Medicine in the Virgen de las Nieves University Hospital in Granada (Spain), between 2000 and 2004. During this period, 75 alloimmunized women were referred to our Department, of whom 10 (13.3%) presented anti-Kell antibodies.

Determinations in series of the antibody titre were carried out by doubling dilutions using the indirect antiglobulin technique. The determinations of the paternal phenotype and of that of the fetus were performed with specific antisera. In no case was amniocentesis used as a means of fetal evaluation.

Ultrasonographic monitoring of the fetus was mainly based on the ultrasonographic evaluation of signs of fetal wellbeing, the existence of fetal hydrops and the evaluation of the maximum velocity of the middle cerebral artery (MV-MCA), using the technique and the parameters described by Mari et al. [13]. All invasive procedures were carried out at 20–37 weeks of pregnancy.

Fetal blood samples were obtained by cordocentesis, by insertion of a 20 Gauge needle using continuous ultrasonic guidance. The puncture was preferentially made at the placental cord insertion. After confirming the intravascular situation of the needle, 1 ml of fetal blood was extracted for the immediate evaluation of the concentration of pre-transfusion haemoglobin, by means of a haemoglobinometer (B-Hemoglobin photometer, Hemocue AB, Ängelholm, Sweden). To minimise the effects of the increasing concentration of haemoglobin during the pregnancy, this concentration was expressed as multiples of the median (MoMs). These were obtained by dividing the concentration of haemoglobin observed by that expected for the corresponding gestational age, using the haemoglobin reference values according to the algorithm published by Mari et al. [13].

The necessity for intravascular fetal transfusion was determined after confirmation of anaemia, as determined from the sample of fetal blood. The degree of anaemia was considered severe when the concentration of Hb was less than 0.55 MoMs, moderate when it was between 0.55 and 0.64 MoMs, and mild when it was between 0.65 and 0.85 MoMs [13]. For this transfusion, we used Kell-negative blood, leukodepleted, irradiated and with a Hb concentration adjusted to 200 g/L. The quantity of blood to be transfused was determined using the algorithm published by Mandelbrot et al. [14], and we avoided an expansion of fetoplacental volaemia exceeding 50%. After the transfusion had ended, and after waiting for 2 min, another sample of fetal blood was extracted for evaluation of the post-transfusion Hb concentration. The successive transfusions were planned based on the initial gravity of each case (i.e.: the presence of bad obstetrical antecedents, the title of antibodies and the quantity of declining of the hemoglobina between transfusions), and the evaluation of MV-ACM.

3. Results

In our study, 7 (70%) of the 10 women with anti-Kell antibodies had a Kell-negative fetus, and 4 of these 7 (57.1%) had had a previous blood transfusion. In two cases we were unable to determine the cause of the alloimmunization, because of the absence of a prior blood transfusion and because of the Kell negativity of the fetus’ in what was a first pregnancy. Although the antibody titres were normally low, in one case a value of 1/512 was recorded. One of the fetuses was found to be suffering from Edwards’ syndrome, and the mother decided to interrupt the pregnancy after this diagnosis.

The remaining three mothers (30%) had Kell-positive fetuses, and all of them developed severe fetal anaemia, which in one case (Number 2) began with a situation of fetal hydrops in week 31 of the pregnancy. None of these women had any previous history of blood transfusions, and all had
had at least one previous pregnancy. Woman No. 2, in a previous pregnancy, had suffered the intrauterine death of the fetus at 33 weeks of pregnancy, which was not diagnosed as a case of anti-Kell alloimmunization. The other two pregnancies had no significant antecedents; in both cases, this was the mothers’ second pregnancy.

In these three cases, the basal antibody titre was 1/128. In two of the cases, the monitoring of the antibody titre revealed that it was not affected by successive cordocenteses and intrauterine transfusions. In all three cases, the antibody was present exclusively at the expense of the subclass IgG1.

Figs. 1–3 present, respectively, the individual development of the concentrations of the pre and post-transfusional haemoglobin among the cases affected by fetal anaemia, for each of the invasive procedures performed during the pregnancy. The mean of daily decrease of fetal hemoglobin between transfusions was 2.2 g/l (range = 0.2–7.8 g/l). In cases 1 and 2, the decrease in the concentration of haemoglobin after the first transfusion suggests a worsening of the alloimmunization after the first cordocentesis, although this phenomenon was not observed in case 3. In case 2, the most severe of the series, intrauterine exsanguinotransfusion was carried out, to reduce the risk of cardiac decompensation, in transfusions 2, 3 and 4, which achieved a lower rate of decline of the haemoglobin concentration between transfusions. In every case, despite the successive intrauterine transfusions, there was a fall in haemoglobin levels at weeks 30–31.

Fig. 1. Case 1: intrauterine transfusions and pre-transfusional evaluation of the maximum velocity of the middle cerebral artery.

Fig. 2. Case 2: intrauterine transfusions and pre-transfusional evaluation of the maximum velocity of the middle cerebral artery.

Fig. 3. Case 3: intrauterine transfusions and pre-transfusional evaluation of the maximum velocity of the middle cerebral artery.
Figs. 1–3 also show, respectively, for each of the cases affected, the MV-MCA immediately prior to the invasive procedure. For cases 1 and 2, this value was highly useful in determining the need to carry out an invasive procedure, but for case 3, the MV-MCA values were always at or below the normal range, and so were not useful, clinically.

In all three cases, the results of the pregnancy management applied were favourable. The three neonates received phototherapy as the sole post-natal treatment (none required exsanguinotransfusion). Their stay in hospital lasted 2–7 days, and only case 3 required the transfusion of erythrocytes at 10 days after delivery because of anaemia levels not less than 80 g/L. In none of the three cases was any other haemotherapeutic treatment required during post-natal control.

4. Discussion

In our series, 60% of the cases of anti-Kell alloimmunization did not have a post-transfusional origin that could be evidenced by anamnesis, which contradicts the idea that most such cases are of post-transfusional origin [2,15] and supports the notion that many cases of anti-Kell alloimmunization are induced by the pregnancy [4,11].

On the contrary to what is asserted in the literature, in the current approach to anti-Kell alloimmunization [16], our series makes it clear that this phenomenon may lead to a situation of severe fetal distress, as all three of the pregnant women who had a Kell-positive fetus at one stage or another developed moderate or severe anaemia, and in one case fetal hydrops occurred. The severity of anti-Kell alloimmunization is independent of the antibody titre, which is usually much lower than in the case of anti-D alloimmunization, and which requires an interventionist approach because of the poor prognosis and the tendency for hydrops fetalis to develop [11]. The intervention should be begun before week 28 of pregnancy, unless the existence of an unfavourable obstetric case history suggests an earlier action is advisable.

The rapid decline in haemoglobin concentration after the first cordocentesis, as observed in two of the cases in the present study, suggests that there may have occurred a worsening of the alloimmunization, perhaps as a consequence of the fetal-maternal haemorrhage related to cordocentesis [17,18], although there was no increase in the antibody titre to justify such a conclusion.

In this short series, the evaluation of the MV-MCA was significantly useful in two cases in determining the need to carry out the invasive technique, but was totally unhelpful in one case. This fact supports the idea that MV-MCA evaluation is very specific and that corresponding negative values cannot rule out the possibility of fetal anaemia [19].

On the contrary to what is asserted in the literature, in the cases examined in the present study it was not possible to determine a prolonged period of post-natal aplasia [20]. Only in one case were erythrocytes transfused, at 10 days after delivery, and in no cases was anaemia detected during the post-natal controls carried out.

The current approach to anti-Kell alloimmunization enables pregnant women who have Kell-positive fetuses to be treated successfully. Nevertheless, further studies are required in order to achieve a better definition of the peculiarities of Kell alloimmunization with respect to anti-D alloimmunization.

References