Alloimmune Red Blood Cell Antibodies: Prevalence and Pathogenicity in a Canadian Prenatal Population

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Abstract

Objective: The goals of this study were to determine the prevalence and relative frequencies of red blood cell antibodies in a Canadian prenatal population, and to evaluate the fetal and neonatal outcomes of affected pregnancies.

Methods: We conducted a retrospective review of pregnancies that screened positive for red cell antibodies between 2006 and 2010. The following antibodies were included: anti-D, -C, -c, -E, -e, -Fya, -Fyb, -Jka, and–Jkb. Cases of anti-Kell as the sole antibody were excluded. Fetal and neonatal outcome data were then collected and analyzed.

Results: The population prevalence of a positive antibody screen was 0.36%. Anti-E was the most frequent antibody at 48.5%, followed by anti-c and anti-Jka. Anti-D made up 6.8% of cases, but had significantly higher titres and was responsible for the majority of severely affected fetuses. Sixteen cases in our series experienced severe adverse fetal or neonatal outcomes. All severe outcomes occurred in cases that had a maximum titre of ≥ 8.

Conclusion: Despite the decreasing incidence of anti-D alloimmunization, anti-D remains responsible for the majority of severe cases of hemolytic disease of the fetus and newborn.

Résumé

Objectif : Cette étude avait pour objectif de déterminer la prévalence et la fréquence relative des anticorps anti-érythrocytaires au sein d'une population prénatale canadienne, et d'évaluer les issues fœtales et néonatales des grossesses affectées.

Méthodes : Nous avons mené une analyse rétrospective portant sur les grossesses qui ont obtenu des résultats positifs au dépistage des anticorps anti-érythrocytaires entre 2006 et 2010. Les anticorps suivants ont été inclus : anti-D, -C, -c, -E, -e, -Fya, -Fyb, -Jka et -Jkb. Les cas où l'anti-Kell constituait le seul anticorps ont été exclus. Des données sur les issues fœtales et néonatales ont par la suite été recueillies et analysées.

Résultats : La prévalence populationnelle de l'obtention d'un résultat positif au dépistage des anticorps a été de 0,36 %. L'anti-E a été l'anticorps le plus fréquent à 48,5 %, suivi de l'anti-c et de l'anti-Jka. Bien que l'anti-D n'ait constitué que 6,8 % des cas, ses titres étaient considérablement accrus et il a été à l'origine de la majorité des cas de fœtus gravement affecté. Dans le cadre de notre série, seize cas ont connu des issues indésirables fœtales ou néonatales graves. Toutes les issues graves ont été constatées dans les cas qui présentaient un titre maximum de ≥ 8.

Conclusion : Malgré l'incidence décroissante de l'allo-immunisation anti-D, l'anti-D demeure à l'origine de la majorité des cas graves de maladie hémolytique du fœtus et du nouveau-né.

Key Words: Alloimmunization, isoimmunization, rhesus, fetal anemia

Competing Interests: None declared.

Received on November 7, 2014

Accepted on January 26, 2015

J Obstet Gynaecol Can 2015;37(9):784–790

INTRODUCTION

Hemolytic disease of the fetus and newborn occurs when maternal alloantibodies cross the placenta and hemolyse fetal red blood cells. This can result in fetal anemia, hydrops, or intrauterine death. It can also cause severe neonatal anemia and hyperbilirubinemia, necessitating exchange transfusion and other therapies. Historically HDFN has been caused by antibodies to rhesus D antigen in most cases, although a large number of RBC antibodies are known to be able to cause the disease.[1–3] Maternal antibody titres have been shown to correlate with disease severity in HDFN due to anti-D, and are a key determinant in the management of alloimmunized pregnancies.[4] Most centres use an anti-D titre of 8 to 32 as the "critical titre," i.e., the titre above which adverse effects are known to occur.[3,5,6] Referral to a maternal–fetal medicine specialist and increased fetal surveillance including MCA Doppler velocimetry are generally instituted once this critical titre is reached.[7] Following the introduction of routine antenatal antibody screening and subsequent D immunization prevention with anti-D immune globulin, the burden of disease attributable to anti-D declined.[2,3] As a result, there has been increasing interest in HDFN caused by other RBC antibodies.[8] Previous studies have reported the prevalence of non-D antibodies in pregnancy to be between 0.13% and 0.33%,[8–10] although these data are either old or from homogenous populations; such data have not been available for a Canadian population.[3] Furthermore, the critical titres of other RBC antibodies are not well established.

The objectives of this study were to determine the prevalence and relative frequencies of RBC antibodies in a Canadian prenatal population, to evaluate the fetal and neonatal outcomes of these pregnancies, and to examine the relationship between antibody titres and pregnancy outcomes.

METHODS

We conducted a retrospective review of pregnancies that screened positive for RBC antibodies between January 1, 2006, and December 31, 2010, inclusive. The following antibodies were included: anti-D, -E, -e, -C, -c, -Fya, -Fyb, -Jka, and -Jkb. Cases of anti-D served as the reference group. The Northern and Central Alberta Maternal Fetal Medicine Centre is located in Edmonton and serves an ethnically diverse population spread over central and northern Alberta, parts of northern British Columbia, the Northwest Territories, and Nunavut. Prenatal serological testing for the catchment area is centralized at the Canadian Blood Services Centre in Edmonton. Cases were therefore identified through the Canadian Blood Services database. Exclusion criteria included missing or duplicate data, residing outside the catchment area of the Northern and Central Alberta Maternal Fetal Medicine Centre, having passive or auto-antibodies, a non-prenatal sample, and exclusive presence of Kell antibody. Kell antibody was excluded because Kell titres are not routinely measured at our institution, given that Kell-mediated fetal anemia is known to correlate poorly with the titre.[11,12] Further, reporting of Kell antibody titres can be prone to misinterpretation, particularly interpretation of low titres as indicating a benign prognosis. Cases that were known to end in miscarriage or therapeutic abortion were excluded from the outcome data.

We recorded maternal ABO and Rh status, RBC antigen phenotype, antibody identity, and maximum titre reached during pregnancy, as determined by saline indirect antiglobulin technique. Paternal ABO and Rh status and antigen phenotype were also recorded when available. The data were then linked to the Alberta Perinatal database, and the following information was collected: maternal age, gravidity and parity, gestational age at delivery, type of labour, mode of delivery, birth weight, Apgar scores, and reason for induction of labour or operative delivery, if applicable. We searched perinatal ultrasound reports, and data on MCA Doppler velocimetry, spectral analysis of amniotic fluid (delta optical density 450, ΔOD450), and intrauterine transfusions were recorded.[7] Lastly, the laboratory information system database was used to extract data on neonatal blood group, direct antibody test result, maximum bilirubin level, minimum hemoglobin level and the use of blood products (ET, top-up transfusion, and IVIG administration).

We grouped outcome data into three composite primary outcomes:

1. severe adverse fetal outcome,
2. any adverse fetal outcome, and
3. severe adverse neonatal outcome.

The definitions of these composite outcomes are detailed in Table 1. For cases in which the reason for induction of labour or Caesarean section was missing or unclear, it was assumed not to be due to HDFN.

ABBREVIATIONS

ET	exchange transfusion
RBC	red blood cells
HDFN	hemolytic disease of the fetus and newborn
IUT	intrauterine transfusions
MCA	middle cerebral artery