Management of Pregnancies Complicated by Anti-Kell Isoimmunization

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Objective: To assess the efficacy of managing pregnancies complicated by anti-Kell isoimmunization using the methods developed for evaluating anti–Rh-D isoimmunization.

Methods: We reviewed 156 anti-Kell-positive pregnancies seen from 1959 to 1995, which were managed with serial maternal titers, amniotic fluid ΔOD450 determination, and funipuncture. Data on maternal titers, paternal phenotypes, invasive fetal testing and therapies, and neonatal outcomes were collected and analyzed to determine whether severely affected pregnancies were identified in time for successful fetal and neonatal therapy.

Results: Twenty-one fetuses were affected, eight with severe disease, and two fetuses in this group died. All of the severely affected fetuses were associated with maternal serum titers of at least 1:32. A critical titer of 1:32 was found to be 100% sensitive for identifying the affected pregnancies. The affected group had significantly higher amniotic fluid ΔOD450 values over the range of gestational ages than did the unaffected group (P < .001). The upper Liley curve was a specific discriminator for the diagnosis of affected fetuses, and the lower curve was specific for the diagnosis of unaffected or mild cases.

Conclusion: Fetal anemia due to anti-Kell isoimmunization might be due in part to erythropoietic suppression, but it is still largely a hemolytic process. The methods based on a hemolytic process, including use of a critical maternal serum titer of 1:32, serial amniotic fluid analyses when the titer was exceeded, and liberal use of funipuncture, were successful in identifying severely affected fetuses. (Obstet Gynecol 1999;93:667–73. © 1999 by The American College of Obstetricians and Gynecologists.)

Widespread use of anti–Rh-D immunoglobulin (Ig) in pregnant women who are D-antigen negative has led to an increasing proportion of isoimmunization due to atypical, non–Rh-D antibodies. Pregnancies complicated by isoimmunization due to atypical antibodies are generally managed in the same way as those with anti-D isoimmunization, which is largely a hemolytic process.1–3 Isoimmunization to the Kell antigen is a common cause of fetal and neonatal anemia due to one of these atypical antibodies.1

The Kell protein is a 93-kd transmembrane metallopeptidase important in the processing and metabolism of peptide hormones, and is believed to play a role in erythrocyte growth and differentiation.4,5 The antigenic nature of this protein can induce a pronounced isoimmune response in antigen-negative women exposed to Kell antigen-positive red blood cells (RBCs) through donor blood transfusions or transplacental passage of fetal RBCs during pregnancy. It has been proposed that the mechanism of fetal and neonatal anti-Kell isoimmune anemia is not solely hemolysis, as is the case with Rh disease, and that erythroid suppression is also important.6,7 The use of maternal history, critical serum titers, and spectrophotometric determination of amniotic fluid (AF) bilirubin in the monitoring of fetal anemia is predicated on a maternal alloimmune process that destroys fetal erythrocytes. Because this methodology relies on markers of maternal immune system activity and fetal hemolysis, it may not be adequate for pregnancies complicated by anti-Kell isoimmunization with possible hyporegenerative rather than hemolytic anemia.

We analyzed retrospectively the 37-year experience at the Ohio State University in the management of pregnancies complicated by anti-Kell isoimmunization. During this period, the management protocol developed for anti–Rh-D isoimmunization was used for anti-Kell, and we assessed its efficacy.
Materials and Methods

A computerized database containing the records of all women with isoimmunized pregnancies who received care at our medical center since 1959 was used to identify all pregnant women affected by anti-Kell. Obstetric care was provided by our staff physicians or by referring obstetricians from central and southeastern Ohio. Women were managed in consultation with the Ohio State University isoimmunization program, which provided all laboratory testing, interpretation, and suggested management. Data were obtained from the computerized database, patient charts, blood bank and physician records, and patient telephone interviews. Only laboratory data from our prenatal reference laboratory were included in the analyzed data set.

Data included maternal demographics and pregnancy history, paternal antigen testing, maternal indirect antiglobulin tests, results of optical density at 450 nm (OD450), fetal hematocrit, fetal total bilirubin, and percentages of nucleated fetal RBCs. Neonatal data included gestational age at delivery, birth weight, delivery hematocrit and total bilirubin, cord indirect antiglobulin test results and Kell antigen status, neonatal morbidity, and necessary treatment(s). To avoid potential confounding effects, we analyzed only data obtained before the initiation of therapy. Initial maternal titer and paternal antigen data were available for all pregnancies. Complete maternal and neonatal data were available for all patients who had invasive procedures (ie, amniocentesis, funipuncture, and transfusion). When patients had more than one anti-Kell isoimmunized pregnancy, only the initial pregnancy was included in the analyses. Patients with incomplete data were excluded.

Maternal titers were measured every 4–6 weeks when paternal antigen testing was Kell positive or unknown. Standard tube techniques for the indirect Coombs test, as endorsed by the American Association of Blood Banks, were used to determine antibody titers. Amniocentesis for spectrophotometric determination of AF bilirubin pigment was done when there was a history of an affected infant or when maternal antibody titers were greater than 1:16. The results were plotted on a modified version of the Liley graph that used the original zones defined by Liley but that also included lower gestational ages down to 20 weeks. The portion from 20 to 28 weeks was developed in the 1960s for the management of Rh disease and was validated with data obtained from patients at the Ohio State University (O’Shaughnessy, Amniotic fluid spectrophotometry is useful after 20 weeks’ gestation in the care of pregnancies complicated by red blood cell isoimmunization [abstract]. Am J Obstet Gynecol 1991;164:256).

Since 1986, funipuncture has been done when the change in OD450 was in the upper half of Liley zone II or in Liley zone III and the gestational age was remote from term.

Analyses of fetal blood included hemoglobin levels, total and direct bilirubin, and percentage of nucleated RBCs. For this analysis, we categorized the affected fetuses by the degree of neonatal anemia using thresholds similar to those defined by Liley: mild (neonatal hemoglobin at least 11 g/dL) or severe (neonatal hemoglobin 10.9 g/dL or less). Anemia was also defined as severe when hydrops fetalis was present or when fetal or neonatal blood transfusion was required. Delivery or fetal transfusion was done when severe fetal anemia (hemoglobin less than 10 g/dL) or hydrops fetalis was present. Umbilical cord blood specimens collected at delivery were tested for bound anti-Kell Ig by direct Coombs testing and for erythrocyte Kell antigen status.

Statistical and data analyses were done with JMP Statistical Discovery Software (SAS Institute Inc., Cary, NC) and Microsoft Excel (Microsoft Corporation, Redmond, WA). Alpha of .05 was considered significant. The Levene test was applied on continuous variables to test for equal variances. When variances were equal, Student t-test was used; otherwise Welch analysis of variance was performed. Fisher exact test was used for comparisons involving two groups of nominal or ordinal variables. Analysis of variance for repeated measures was used to compare the mean responses of groups when there were multiple observations of a continuous variable over time.

Results

There were 134 anti-Kell-positive women with 156 pregnancies at the Ohio State University from January 1959 to November 1995. When a woman had more than one anti-Kell-isoimmunized pregnancy, we analyzed only data from the initial pregnancy. Complete data for race and titer were available for 116 initial pregnancies. Eighty-three women (72%) were white and 33 (28%) were black. Nineteen affected infants were delivered by white women and no affected infants were delivered by black women (P = .002). The mean maternal age (+ standard deviation [SD]) at delivery was not significantly different (29.1 ± 3.9 years for affected infants versus 27.6 ± 5.8 years for those unaffected; P = .17). The mean gestational age at delivery was significantly less for affected pregnancies (35.8 ± 5.0 weeks for affected versus 38.0 ± 3.4 weeks for unaffected; P = .02).

Paternal serum testing for RBC Kell typing was done when paternity was certain. Paternal antigen status was considered unknown when paternity was not certain.
Table 1. Neonatal Outcomes in Eight Severely Affected Pregnancies

<table>
<thead>
<tr>
<th>No.</th>
<th>G-P</th>
<th>Blood trans</th>
<th>Past OB</th>
<th>High titer</th>
<th>Highest ΔOD_{450}</th>
<th>Low fetal Hgb</th>
<th>No. IUTs</th>
<th>EGA at delivery</th>
<th>Cord Hgb</th>
<th>Cord DAT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-1</td>
<td>Yes</td>
<td>Unaffected</td>
<td>1:256</td>
<td>0.22(III)</td>
<td>2.5</td>
<td>8</td>
<td>35</td>
<td>11.7</td>
<td>4+</td>
<td>HF, RDS, HB, XT1, ST1</td>
</tr>
<tr>
<td>2</td>
<td>5-1</td>
<td>No</td>
<td>Unaffected</td>
<td>1:256</td>
<td>0.16(II)</td>
<td>6.0</td>
<td>6</td>
<td>36</td>
<td>14.8</td>
<td>Neg</td>
<td>RDS, HB</td>
</tr>
<tr>
<td>3</td>
<td>1-0</td>
<td>Yes</td>
<td>N/A</td>
<td>1:32</td>
<td>0.13(II)</td>
<td>7.2</td>
<td>3</td>
<td>36</td>
<td>12.6</td>
<td>1+</td>
<td>HB, NEC</td>
</tr>
<tr>
<td>4</td>
<td>4-2</td>
<td>No</td>
<td>HB×2</td>
<td>1:64</td>
<td>0.18(III)</td>
<td>7.2</td>
<td>2</td>
<td>33</td>
<td>12.3</td>
<td>1+</td>
<td>RDS, IVH, HB, ST3</td>
</tr>
<tr>
<td>5</td>
<td>2-0</td>
<td>Yes</td>
<td>N/A</td>
<td>1:512</td>
<td>0.26(III)</td>
<td>6.1</td>
<td>3</td>
<td>23</td>
<td>ND</td>
<td>4+</td>
<td>IUFD</td>
</tr>
<tr>
<td>6</td>
<td>1-0</td>
<td>Yes</td>
<td>N/A</td>
<td>1:128</td>
<td>0.32(III)</td>
<td>ND</td>
<td>2 (IP)</td>
<td>31</td>
<td>10.6</td>
<td>Neg</td>
<td>HF, HB, RDS, XT1, ST2</td>
</tr>
<tr>
<td>7</td>
<td>3-1</td>
<td>Yes</td>
<td>Unaffected</td>
<td>1:32</td>
<td>0.14(II)</td>
<td>ND</td>
<td>0</td>
<td>25</td>
<td>ND</td>
<td>ND</td>
<td>IUFD, HF</td>
</tr>
<tr>
<td>8</td>
<td>5-1</td>
<td>No</td>
<td>Unaffected</td>
<td>1:128</td>
<td>0.15(II)</td>
<td>ND</td>
<td>0</td>
<td>36</td>
<td>11.0</td>
<td>4+</td>
<td>HB, ST1</td>
</tr>
</tbody>
</table>

G-P = gravida-para; blood trans = maternal history of blood transfusion; past OB = outcome in previous pregnancies; Hgb = hemoglobin; IUTs = fetal transfusions; EGA = estimated gestational age in weeks; Cord Hgb = umbilical cord hemoglobin (g/dL) at delivery; DAT = direct antiglobulin test; HF = hydrops fetalis; RDS = respiratory distress syndrome; HB = hyperbilirubinemia requiring phototherapy; XTn = number of exchange transfusions; STn = number of simple transfusions; N/A = not applicable; NEC = necrotizing enterocolitis; IVH = intraventricular hemorrhage; IUFD = fetal death; ND = not done; IP = intraperitoneal.

Of the 103 paternal serum samples analyzed for Kell antigen, 34 (33%) were Kell positive. The 53 pregnancies with unknown paternal antigen status were considered at risk, for a total of 87 at-risk pregnancies in 75 women. Forty-seven women (63%) at risk had a history of a blood transfusion, 12 (16%) had a known negative maternal history of receiving blood products, and 16 (21%) did not have documentation or could not recall.

One at-risk pregnancy that ended in fetal death (described later) was not included in the following analyses because of incomplete data. Twenty-one infants (24%), born to 20 at-risk women, were affected. Three of 52 pregnancies (5.8%) with unknown paternal Kell antigen status were affected, and 18 of 34 paternal Kell antigen–positive pregnancies (53%) were affected. No affected infants resulted from pregnancies with a negative paternal antigen status. Twenty infants from the at-risk pregnancies had umbilical cord blood that was Kell antigen positive. Eighteen umbilical cord blood specimens collected at delivery had positive direct antiglobulin tests. Two infants with severe anemia had negative cord blood direct antiglobulin tests at delivery, but both had received fetal transfusions, and one previously had a positive direct antiglobulin test from a funipuncture specimen. The other received two intraperitoneal transfusions in 1982, before the use of funipuncture at our institution, and fetal blood was not available for direct Coombs analysis in this case. Umbilical cord blood was not collected from one pregnancy that ended in fetal death at 25 weeks' gestation because of severe hydrops fetalis. This pregnancy was believed to be affected based on the clinical presentation of an elevated maternal serum anti-Kell titer of 1:32 and AF ΔOD_{450} in Liley zone II.

Eight infants (9.3%) among the at-risk pregnancies were severely affected. Table 1 presents the maternal data and neonatal outcomes of the eight severely affected infants. Two cases (2.3%) ended in fetal death, and among three cases (3.5%) of hydrops fetalis, one fetus died. In this case, from 1979 (Table 1, no. 7), the woman first presented for prenatal care at 25 weeks' gestation, and an anti-Kell titer of 1:32 was found on her serum screen. Amniocentesis and ultrasound were performed 2 days later and revealed hydrops fetalis; the fetus died on the same day. The second fetal death occurred after a transfusion and was procedure related. A third fetal death occurred in a woman with anti-Kell isoimmunization (titer 1:1024) at 39 weeks' gestation. This death occurred in 1966 and we were unable to confirm the clinical circumstances, so we did not include this pregnancy in our analyses. The neonate of subject no. 8 was delivered at 36 weeks and had umbilical cord hemoglobin of 11.0 g/dL at delivery, but the neonate's hemoglobin fell to 8.8 g/dL on the first day of life and a simple transfusion was given.

The severely affected group contained three nulliparas, four parous women with negative histories of affected infants, and one parous woman who may have had two previous mildly affected infants. This last woman was gravida 4, para 2, and her two children were delivered at term and needed phototherapy for hyperbilirubinemia, but did not require transfusions. The previous pregnancies were managed at another facility and are not included in this review. Two women in the severely affected group were followed at the Ohio State University in subsequent pregnancies; one had an unaffected infant and the other had a mildly affected infant.

Table 2 presents maternal and neonatal data from the 13 infants with mild anti-Kell isoimmunization. Five of the mildly affected fetuses had at least one funipuncture (range one to seven) for fetal blood analysis but did not require fetal therapy. One neonate required one simple transfusion on the fourth day of life, but the direct antiglobulin test on umbilical cord blood was positive for multiple maternal antibodies in addition to anti-
Table 2. Neonatal Outcomes in 13 Mildly Affected Pregnancies

<table>
<thead>
<tr>
<th>G-P</th>
<th>Blood trans</th>
<th>Past OB</th>
<th>High titer</th>
<th>Highest ΔOD450</th>
<th>Low fetal Hgb</th>
<th>EGA at delivery</th>
<th>Cord Hgb</th>
<th>Cord DAT</th>
<th>Complications</th>
</tr>
</thead>
</table>
| 4-3 | No          | Unaffected | 1:64   | 0.18(III) | 10.3 | 38 | 12.6 | 1+ | HB, 7 cordocenteses*
| 5-3 | Yes         | Unaffected | 1:128 | 0.13(II) | 10.3 | 37 | 12.7 | 4+ | HB, 4 cordocenteses
| 4-0 | Yes         | N/A       | 1:64   | 0.1(II)   | 10.7 | 39 | 11.2 | 1+ | HB, 5 cordocenteses
| 4-2 | Yes         | Unaffected | 1:32   | 0.055(I)  | 10.4 | 38 | 18.7 | 2+ | 1 funipuncture
| 5-4 | No          | Mild × 1  | ND     | 0.085(II) | 11.0 | 38 | ND | 1+ | 1 funipuncture†
| 3-2 | Unk         | HB × 2   | 1.8    | ND         | ND   | 37 | 12.2 | 1+ | None
| 5-3 | Unk         | Anemia    | 1.32   | 0.08(II)  | ND   | 40 | 20.2 | 2+ | HB
| 7-4 | Yes         | Unaffected | 1:4   | ND         | ND   | 40 | 15.8 | 3+ | None
| 3-1 | Yes         | Unaffected | 1:8   | ND         | ND   | 40 | ND | 1+ | None
| 5-3 | Yes         | Unaffected | 1:1   | ND         | ND   | 35 | 14.5 | 1+ | HB, ST1‡
| 4-3 | Yes         | Unaffected | 1:4   | ND         | ND   | 40 | 16.9 | 1+ | None
| 3-1 | Yes         | Unaffected | 1:8   | ND         | ND   | 40 | Unk | 1+ | None
| 3-1 | Yes         | Unaffected | Neg  | ND         | ND   | 39 | 16.3 | 1+ | None

Unk = unknown; other abbreviations as in Table 1.
* First affected pregnancy.
† Second affected pregnancy.
‡ Neonate also had indirect Coombs positive for A, B, and Rh-D.

Kell, and the anemia could not be considered solely due to anti-Kell. The mildly affected group included one nullipara, eight parous women with negative histories of affected infants, two women who might have had previous affected infants, and one woman with a confirmed affected infant in the past. The first two women had a history of two infants with hyperbilirubinemia requiring phototherapy and one infant with a history of “anemia,” respectively. These previous pregnancies were cared for at another facility and their data were not included in this analysis. The third woman previously had a mildly affected fetus (Table 2). In the second affected pregnancy, she had a funipuncture at 25 weeks’ gestation that did not demonstrate marked fetal anemia, and she was followed with serial amniocenteses that remained in the lower half of Liley zone II.

Three hundred forty-six maternal indirect Coombs titers were measured, 81 from pregnancies with confirmed Kell-negative fathers. There were 265 from at-risk women: 194 from the unaffected group, 43 from the mildly affected group, and 28 from the severely affected group. All titers were 1:32 or greater in the severely affected group, whereas 27 of 61 (44%) were 1:32 or higher in the other at-risk pregnancies (P = .005). A critical titer of 1:32 was 100% sensitive for identifying the severely affected pregnancies.

Amniocenteses for ΔOD450 was done in 36 women in their initial isoimmunized pregnancies. Twelve had affected pregnancies and 24 had pregnancies resulting in Kell-negative neonates. Sixty-four amniocenteses were done in the affected group and 46 in the unaffected group. The mean gestational age at amniocentesis was significantly less in the affected group than in the unaffected group (26.0 ± 4.5 weeks versus 29.9 ± 4.2 weeks; P < .001). To consider the effect of gestational age on ΔOD450, we stratified the data by gestational age at amniocentesis into three groups: less than 25 weeks, 25–32 weeks, and greater than 32 weeks. The gestational age groupings were chosen because the clinical significance of an affected pregnancy is substantially different for each of these ranges of gestational age. Analysis of variance with repeated measures was performed on the stratified data of logistic regression analysis of the ΔOD450 values to ascertain the difference between the affected and unaffected groups, taking into account the repeated measures and the fact that ΔOD450 varied over gestational age (R² = 0.92). The affected group had significantly higher ΔOD450 values than the unaffected group over the range of gestational ages (P < .001). The gestational age effect was also significant (P < .001).

Figure 1 contains the AF data obtained prior to the initiation of therapy with the affected group separated into severe and mild cases. The severely affected preg-
nancies are identified by numbers that correspond to the patient numbers in Table 1. Serial measurements for the severely affected pregnancies are connected with solid lines. Figure 1 also shows the modified Liley curves used at the Ohio State University for the management of Rh isoimmunization. Although the \( \Delta \text{OD}_{450} \) is an indirect measure of fetal anemia, the upper Liley curve proved to be a specific discriminator for diagnosing affected fetuses, and the lower curve was a specific discriminator for diagnosing unaffected or mild cases.

Fifty-two funipunctures were done in 17 pregnancies (ten affected and seven unaffected), and 24 fetal transfusions were done in six affected pregnancies. The initial fetal hemoglobin, total fetal bilirubin, and percentage of fetal nucleated RBCs were compared between the affected and unaffected groups. Only data from the initial funipuncture were used. In cases in which a woman had two affected pregnancies, only the values from the first affected pregnancy were used. The mean gestational age was not significantly different between the groups: 28.9 \( \pm \) 6.9 weeks in the affected group \((n = 9)\) versus 23.7 \( \pm \) 4.8 weeks in those unaffected \((n = 7)\) \((P = .12)\). The fetal hemoglobin was significantly lower in the affected group: 7.8 \( \pm \) 3.0 versus 11.0 \( \pm \) 0.7 g/dL \((P = .012)\). Total fetal bilirubin was not significantly different between the groups: 2.7 \( \pm \) 1.2 mg/dL in the affected group \((n = 4)\) versus 1.4 \( \pm \) 0.4 mg/dL in those unaffected \((n = 6)\) \((P = .12)\). The percentage of fetal nucleated RBCs also was not significantly different between the groups: 10.0 \( \pm \) 12.11 \((n = 8)\) versus 20.8 \( \pm \) 19.6 \((n = 6)\) \((P = .22)\).

Neonatal umbilical cord blood specimens were collected at delivery in 18 affected and 24 unaffected pregnancies. The mean gestational age at delivery did not differ between the groups: 37.4 \( \pm \) 2.9 weeks for the affected group \((n = 18)\) versus 36.0 \( \pm \) 3.2 weeks in the unaffected group \((n = 24)\) \((P = .16)\). The mean neonatal hemoglobin level was significantly lower in the affected group: 13.6 \( \pm \) 2.6 g/dL \((n = 18)\) versus 15.9 \( \pm \) 2.6 g/dL in the unaffected group \((n = 24)\) \((P = .007)\). The total bilirubin levels did not differ significantly between the groups: 3.1 \( \pm \) 1.4 mg/dL \((n = 15)\) versus 3.2 \( \pm \) 1.7 mg/dL \((n = 15)\), respectively \((P = .8)\).

**Discussion**

For more than 20 years, Kell antibodies have been known to cause hemolytic disease in newborns.\(^\text{12,13}\) As with Rh disease, paternal RBC typing is the first step in evaluating a gravida who has a positive indirect screen for anti-Kell. Approximately 90% of the population is Kell negative.\(^\text{14}\) Assuming that the positives are heterozygotes, a father with unknown antigen status would be expected to have an affected fetus about 5% of

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**Figure 1.** \( \Delta \text{OD}_{450} \) values for pregnancies severely affected (diamonds), mildly affected (triangles), and unaffected (circles) by anti-Kell isoimmunization at different gestational ages. Severely affected fetuses are identified by patient numbers, which correspond to numbers in Table 1. Serial values in individual severely affected fetuses are connected by solid lines. Dotted lines represent the upper and lower modified Liley curves used at the Ohio State University for the management of Rh isoimmunization. The portions of the curves from 16 to 20 weeks (dots and dashes) are straight-line extrapolations and are not based on data.
K1 antigen usually occurs in persons of European descent and is rare in blacks. In the 1980s, it was recognized that Kell isoimmunization was due to a process similar to that of Rh isoimmunization. Several other investigators reported large series (more than 100 pregnancies) of anti-Kell isoimmunization, and all but one study found that serum antibody titers were lower in Kell isoimmunization. Seventeen pregnancies were severely affected, and all but one had maternal serum titers of 1:32 or greater. In the single exception, the woman presented with a grossly hydropic fetus at 23 weeks’ gestation, had a titer of 1:8, and had no history of an affected infant. In our series, none of the severely affected pregnancies had a titer less than 1:32, which we found to be a sensitive discriminator for pregnancies that required amniocentesis.

The reliability of ΔOD450 values in Kell isoimmunization has been questioned because of reports of more serious fetal anemia presenting at lower values. Figure 1 depicts the trend of higher ΔOD450 values for affected fetuses, which is consistent with a hemolytic process. Caine and Mueller-Heubach and Bowman et al. found AF analysis to be reliable in most instances, but both groups had difficulty diagnosing the affected pregnancies when serial values of ΔOD450 dropped from the Liley zone II into zone I, particularly at gestational ages over 32 weeks. In our series, ΔOD450 was specific but not sensitive in distinguishing affected from unaffected fetuses. The values that fell in the middle zone (zone II) were not easily categorized, and those pregnancies required careful further analysis with serial amniocenteses and often funipuncture. In some affected pregnancies, ΔOD450 values dropped into a lower zone when serial values were collected, but no severely affected fetuses fell into and stayed within zone I. In unaffected pregnancies, serial ΔOD450 values decreased as gestational age increased. Funipuncture for fetal hemoglobin is recommended when the rate of decline of serial ΔOD450 measurements decreases or reaches a plateau. Caution should be exercised when using ΔOD450 values, especially when they fall in the middle zone. The limitations of AF analysis as an indirect indicator of fetal anemia should be recognized.

Our data from the funipuncture and umbilical cord specimens showed significantly lower hemoglobin levels in the affected fetuses and neonates. Total bilirubin levels did not differ significantly between affected and unaffected fetuses and neonates. The percentage of fetal nucleated RBCs also did not differ between the groups. These findings are consistent with a hyporegenerative pathophysiology. Vaughan et al. and Weiner and Widness reported decreased laboratory indices (fetal reticulocytes, bilirubin, and nucleated RBCs) of fetal erythropoiesis and hemolysis in pregnancies complicated by Kell isoimmunization, and Vaughan et al. recently demonstrated, in vitro, a dose-dependent suppression of hematopoietic progenitor cells by serum from women with circulating anti-Kell antibodies. Our experience suggests that although fetal anemia due to anti-Kell might be due in part to suppression of fetal erythropoiesis, the elevated ΔOD450 levels in the affected pregnancies indicate that the mechanism of anemia is also a hemolytic process.

Our management approach to pregnancies complicated by Rh isoimmunization has proved successful in managing more than 150 pregnancies with anti-Kell isoimmunization at the Ohio State University since 1959. Using our investigation guidelines, we did not have a single undiagnosed, severely affected fetus. There was one fetal death directly attributable to isoimmunization; however, the woman presented late for prenatal care with a hydropic fetus. This case (Table 1, no. 7) underscores the importance of early prenatal care in the diagnosis and management of isoimmunization. In addition, the fetus might have survived with modern sonography and fetal therapy. Maternal antibody titers with a threshold for amniocentesis of greater than 1:16 and ΔOD450 determinations are important in deciding which pregnancies need additional investigations such as fetal blood sampling. Fetal Kell antigen typing from amniocytes should decrease the number of blood samplings done on antigen-negative fetuses. A high index of suspicion should be maintained because the evaluations are not uniformly consistent with a purely hemolytic process. It is possible that erythroid suppression can mask the traditional indirect characteristics of fetal anemia. Bowman et al. suggested adopting a lower critical titer of 1:8 for anti-Kell isoimmunization.
data do not support this because all of our severely affected pregnancies had titers of at least 1:32.

References

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Reprints are not available.