Transfusion and Apheresis Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

# Three non-classical mechanisms for anemic disease of the fetus and newborn, based on maternal anti-Kell, anti-Ge3, anti-M, and anti-Jr[a] cases

Ohto Hitoshi[a,*], Gregory A. Denomme[b], Ito Shoichi[c], Ishida Atsushi[d], Kenneth E. Nollet[e], Yasuda Hiroyasu[f]

[a] Fukushima Medical University, Fukushima, 960-1295, Japan
[b] Blood Research Institute / Diagnostic Laboratories, Versiti, Milwaukee, WI, USA
[c] Japanese Red Cross Tohoku Block Blood Center, Sendai, Japan
[d] Department of Pediatrics, Gifu Prefectural Tajimi Hospital, Gifu, Japan
[e] Department of Blood Transfusion and Transplantation Immunology, Fukushima Medical University, Fukushima, Japan
[f] Fukushima Prefectural Hygiene Institute, Fukushima, Japan

ARTICLE INFO

*Keywords:*
Anemia
Fetus
Hemolysis
Icterus
Maternal antibody
Blood-type incompatible pregnancy

ABSTRACT

Maternal alloantibody-mediated hemolytic disease of the fetus and newborn (HDFN) ranges from no or mild symptoms to severe hydrops and intrauterine fetal demise. Hemolytic anti-D-mediated HDFN proceeds *via* a long-known mechanism, to which three other pathways to fetal/neonatal anemia may be added: (0) Fetal erythrocyte destruction can proceed by extravascular phagocytosis. (1) An apoptotic pathway has been described for anti-Kell, and anti-Ge3. (2) Erythropoietic suppression may arise from altered or deformed erythroblast architecture in anti-M-mediated disease. (3) Clonal escape from erythropoietic suppression is hypothesized to arise from maternal anti-Jr[a] immune pressure, albeit this requires further elucidation. Alloantibody-mediated anemic disease of the fetus and newborn (ADFN) is a designation we favor for cases when hemolysis or hyperbilirubinemia are not the dominant features, such as those provoked by anti-Kell, anti-Ge3, anti-M, and anti-Jr[a].

## 1. Introduction

Blood group incompatible hemolytic disease of the fetus and newborn (HDFN) is a condition in which maternal antibodies shortened the lifespan of red cells with cognate paternal alloantigens. During pregnancy, maternal IgG antibodies are actively transported across the placenta after binding to neonatal Fc receptors (FcRn) [1], with a tendency toward more IgG as gestation approaches term. This process correlates with maternal IgG concentration irrespective of potential harm to the fetus, as may arise when such antibodies encounter cognate alloantigens.

It has been long known that small numbers of fetal red cells commonly enter the maternal circulation; more recent investigations demonstrate that substantial concentrations of nucleic acids and microparticles from the fetus, and fetal (placental) tissue cross the placental barrier during normal pregnancy, more so during and just after delivery [2,3].

## 2. Classic pathway of fetal red cell destruction, mediated by maternal antibody: extravascular hemolysis

For typical RhD-HDFN, fetal red blood cells, sensitized by maternal anti-D and partially activated complement C3b, can be recognized, trapped, phagocytosed and destroyed by the mononuclear phagocytic system of the fetus/neonate itself, specifically by extravascular hemolytic processes of Fcγ receptor and complement C3b receptor-dependent pathways. Severely affected neonates show hemolysis, anemia, and icterus with elevated indirect bilirubin. Significant anemia induces compensatory fetal erythropoiesis characterized by increased reticulocytes and sometimes erythroblasts in the peripheral blood of the fetus/neonate [4]. Intrauterine transfusion diminishes the stimulus for the compensatory red cell production that is characterized by elevated fetal reticulocyte counts. Suppressed erythropoiesis may persist, prolonging postnatal anemia, which, in turn, may require additional red cell transfusion (Figure 1).

* Corresponding author.
*E-mail address:* hit-ohto@fmu.ac.jp (H. Ohto).

https://doi.org/10.1016/j.transci.2020.102949

Available online 16 September 2020

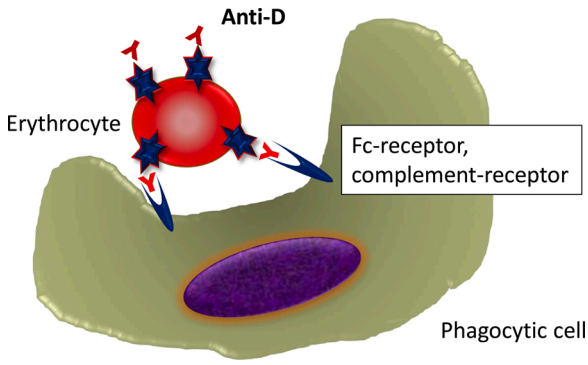


**Fig. 1.** Classic pathway of the pathogenesis of hemolytic disease of the fetus and newborn.
Extravascular destruction of maternal alloantibody-sensitized red cells of the fetus by phagocytic cells of the fetus and newborn *via* the mononuclear phagocytic system.

## 3. Alternative pathway of maternal alloantibody-mediated anemic disease of the fetus and newborn: suppression of erythropoiesis *via* apoptosis or other mechanisms

Different from the classic pathway associated with anti-D, herein we discuss mechanisms of developing fetal/neonatal anemia other than extravascular red cell destruction. Anti-Ge3, anti-Kell, and anti-M are associated with direct mechanisms involving apoptotic or erythropoietic suppression; for anti-Jr$^{a}$ we hypothesize a third mechanism with or without clonal escape.

### 3.1. *apoptotic pathway of erythroid progenitor cell death*

#### 3.1.1. *Anti-Kell-mediated anemic disease of the fetus and newborn (ADFN) (Fig. 2)*

The Kell glycoprotein (CD238) containing 732 amino-acids expresses at least 35 recognized blood group antigens. The single amino-acid of methionine replacing threonine at position 193 (Met193Thr) eliminates a N-glycosylation site of the Kell protein consisting the K (KEL1) and k (KEL2) epitope, respectively [5]. Expression of Kell glycoprotein on erythrocytes is not essential to their structure or function, however, Kx, which is covalently linked to Kell, is critical to normal morphology. Furthermore, Kell glycoprotein comprises part of a surface membrane complex with glycophorins C and D [6].

HDFN mortality dramatically declined during a 30-year-period in the Netherlands, as nationwide screening and intervention were systematically introduced. In a predominantly Caucasian population, incidence of maternal alloimmunization against D was followed by Kell, but hydrops from anti-Kell was still 3.5 times higher than from anti-D, and intrauterine transfusions begin about 3 weeks earlier in this well-organized Dutch health care system [7].

Early expression of Kell glycoprotein in committed progenitor cells (burst-forming unit erythroid and colony-forming unit erythroid) suggests its critical role in early stages of erythropoiesis [8]. Maternal anti-Kell often results in the suppression of fetal erythropoiesis at the progenitor level, as evidenced by *in vitro* inhibition of Kell + erythroid burst-forming units (BFU-E) and colony-forming units (CFU-E) [9]. Infants affected by maternal anti-Kell characteristically have lower reticulocyte counts corresponding to the severity of their anemia, along with lower bilirubin, but poor correlation between maternal antibody titer and the degree of anemia. Kell alloimmunization may lead to more severe fetal anemia and hydrops, rather than hyperbilirubinemia, when compared with D-alloimmunization due to early erythroid cell destruction before erythroid cells accumulate significant hemoglobin levels [10, 11]. Therefore, in anti-Kell-mediated incompatibility, ADFN might be a more appropriate designation than HDFN.

Since Kell glycoprotein is a metalloendopeptidase that cleaves endothelin-3 to produce bioactive endothelin-3, anti-Kell was once posited to modulate peptide growth factors on the cell surface [9]. However, this has been disputed, because KEL1(K) red cells have similar endothelin-3-converting enzymatic activity as those with the common KEL2 (k) phenotype [12].

The McLeod syndrome (MLS) is a progressive multisystem, neurodegerative disease affecting older individuals with X-chromosomal inherited neuroacanthocytosis. MLS patients have red blood cell abnormalities including immune-hematologic, morphological (acanthocytosis) functional impairments, as well as abnormal blood group in Kell and XK blood group antigen expression, and formation of anti-public red cell alloantibodies [13]. The XK protein with 444 amino-acids is forming

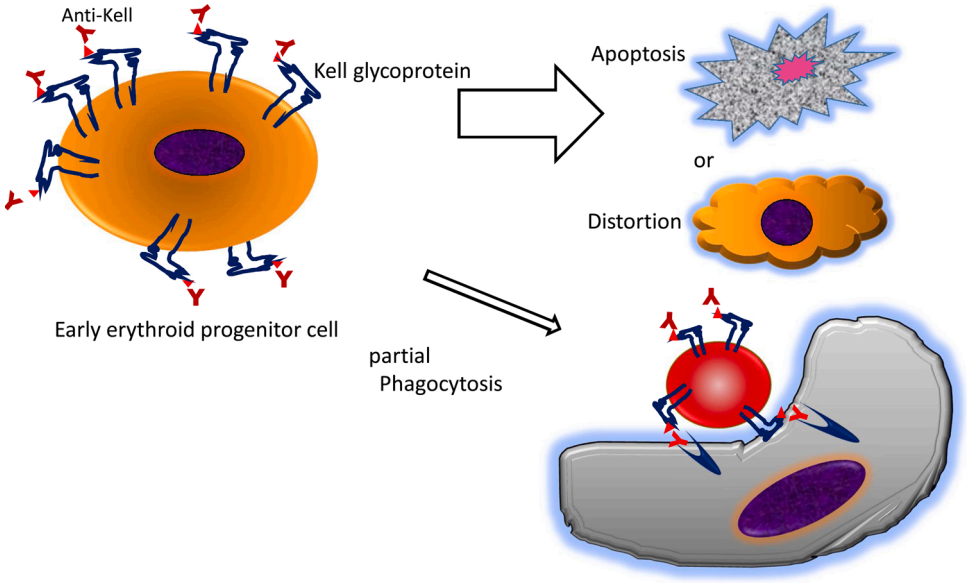


**Fig. 2.** Anti-Kell-mediated fetal erythroid suppression *via* progenitor cell apoptosis.
Maternal alloantibody against Kell antigen expressed on Kell glycophorin, which is critical to normal morphology in the early stage of erythropoiesis, suppresses fetal erythropoiesis at the progenitor level possibly *via* an apoptotic pathogenesis.

a heterodimer with Kell glycoprotein. Individuals with MLS lack the Kx antigen may raise anti-public red cell antibodies and need very rare Kx negative RBCs for transfusion. On the other hand, red cells of simple K null (Ko), usually not morbus itself, and therefore not develop anti-public antibodies against Kx blood group.

Although anti-Kell is involved in direct suppression *via* an apoptotic process or by inhibiting normal formation of the erythrocyte cytoskeleton, the classical pathway contributes to fetal anemia, as suggested by increased reticulocyte counts, 7.3 % or 133 $\times$ $10^9$/L before intrauterine transfusion [4]. Furthermore, among 93 anti-Kell affected infants, the titer 4 was the cut-off point for diagnostic accuracy, however, antibody-dependent cellular cytotoxicity bioassay was not helpful in identifying high risk pregnancies [14]. This study also supports that a non-classic pathogenesis is involved and may predominate in the progression of anti-Kell mediated ADFN.

#### 3.1.2. Anti-Gerbich (Ge)-mediated ADFN (Fig. 3)

The Ge blood group antigens are expressed on glycophorin C (GPC) and glycoprotein D (GPD); the former is expressed on very early erythroid progenitor cells, as shown in Table 1 [8,15]. GPC, in a ternary complex with protein 4 and p55, exists abundantly at 2.0 $\times$ $10^5$ copies per cell, 90 % of which are integrated in the cytoskeleton and deemed essential for maintaining red cell shape and membrane functions [16].

Maternal alloantibody against the high incidence Ge3 antigen causes late-onset or postnatal ADFN characterized by lower-than-expected reticulocyte counts unresponsive to erythropoietin treatment [17,18]. From monocyte monolayer assays with showing high values of 51%–98%, anti-Ge3 was once presumed to promote phagocytosis of Ge+ erythroid progenitors by phagocytic cells [19]. Anti-GPC profoundly inhibits growth in an erythroid cell line (K562) and increases exofacial phosphatidylserine expression [20]. Moreover, poly-caspase inhibitor (Z-VAD-FMK) of classical apoptosis failed to reverse the suppressive effect of anti-GPC. For these reasons anti-Ge3 is now thought to suppress erythroid proliferation *via* a non-classical apoptotic mechanism [21].

### 3.2. suppression of erythropoiesis via agglutination or altered/deformed erythrocyte progenitor cells

#### 3.2.1. anti-M-mediated ADFN (Fig. 4)

The MNS blood group system, with 49 antigens expressed on glycophorin A (GPA) and glycophorin B (GPB), are expressed later than GPC and Kell glycoprotein (Table 1). Importantly enough, GPA is the most abundant sialoglycoprotein of the erythrocyte membrane, with 1 $\times$ $10^6$ per cell [22]. Its O-glycan, carrying most of the sialic acid, contributes to the negative zeta potential of erythrocytes, which keeps erythrocytes from adhering to each other and to vascular endothelium [22].

**Table 1**
Order of cell-surface marker appearance on *in vitro* culture erythroid cord bloodCD34$^+$ cells.

| Target | Beginning | Interim | Reference |
|---|---|---|---|
| CD34 | day 0 (100 %) | day 7–9 (disappearance) | [8] |
| Glycophorin C (GPC) | day 0 (84 %) | all through (100 %) | [15] |
| Kell glycoprotein | day 0 (~20 %) (after GPC and before RhAG) | | [15] |
| Rh-associated glycoprotein (RhAG) | day 1–2 | day 7 (100 %) | [8] |
| | not noted | day 5–7 (50%) | [15] |
| | day 3–4 | day 9 (100 %) | [8] |
| Glycophorin A (GPA) | not noted | day 5–8 (50%) | [15] |
| | day 4–5 | day 9 (100 %) | [8] |
| Band 3 | not noted | day 6–11 (50%) | [15] |
| | day 7–9 | day 13–14 (100%) | [8] |
| RhD | not noted | day 7–14 (50%) | [15] |
| | day 10–12 | day 15 (100 %) | [8] |
| Rh CcEe | not noted | day 7–14 (50%) | [15] |
| Rh Ce | day 5–7 | day 13 (100 %) | [8] |

Anti-M is usually a naturally occurring IgM antibody, with low titer by indirect anti-globulin test (IAT) at 37 °C with higher titer at room temperature, and are clinically insignificant in blood transfusion. Anti-M is the second most detected alloantibody (excluding anti-Le$^a$ and anti-P1) among pregnant women, at 9.1 % in Japan, below anti-E (with or without anti-c) at 26.9 %, and 14 % in Stockholm [23,24].

The fetuses of women with anti-M range from asymptomatic to severely hydropic with intrauterine or neonatal demise [24]. In general, anti-M of the IgM class rarely switches to IgG to induce severe fetal disease among Caucasians [25]. Non-Caucasians may have a different risk profile. Among Japanese, maternal anti-M of predominantly IgM class, with low levels of IgG class, which can cause severe morbidity characterized by lower-than-expected reticulocyte counts and late-onset postpartum anemia for which transfusion support may be required for 30–60 days. However, hyperbilirubinemia is observed more frequently, compared to anti-Kell-mediated HDFN [26]. In a CFU-E assay, anti-M of 2% maternal serum directly suppressed M-positive erythroid precursor cell proliferation by 63 % suppression against MM cells and by 0% against NN cells [27].

These observations in anti-M-mediated HDFN/ADFN suggest that two mechanisms may be involved, principally by suppression of erythropoiesis, possibly agglutination of progenitor cells *via* decreased sialoglycoprotein on GPA and/or GPA deformed by maternal anti-M, and partly by immune destruction as with anti-D. However, the contribution of an apoptotic pathway has not been excluded.

## 4. Second alternative pathogenesis of maternal alloantibody-mediated ADFN: immune pressure with or without clonal escape

### 4.1. Anti-Jr$^a$-mediated ADFN with/without clonal escape of erythroid cell lineages (Fig. 5)

The JR blood group system has one antigen, Jr$^a$, with a high prevalence across different ethnic groups. Jr(a-) individuals are rare, but found largely in Asian populations [28]. Using a human monoclonal anti-Jr$^a$, 0.06 % (238 of 159,263 blood donors) were Jr(a-), with no significant difference between males and females. Among those identified as Jr(a-), anti-Jr$^a$ was detected in 33.7 % of women (35 of 104), but in none of 134 non-transfused men [29]. In fact, anti-Jr$^a$ is the fourth most frequently found clinically significant alloantibody after anti-E (with or without anti-c), anti-M, and anti-D among pregnant women in Japan [21], even though Jr$^a$ antigen sites are approximately 1/30 the number of Rh-E [30]. In antibody screen, anti-Jr$^a$ is detected more frequently among female than male patients, 1.2 % *vs* 0.2 %, $p < 0.01$ [23]. The Jr$^a$ antigen is carried by ABCG2 (ATP-binding cassette, family G, membrane 2), which is overexpressed on placental villi [31]. Jr$^a$ may be a sensitizing antigen during placental development early in pregnancy, and a relative lack of anti-Jr$^a$ in the fetal circulation suggests that anti-Jr$^a$ might be absorbed by placental antigens.

The severity of anti-Jr$^a$-disease ranges from no symptoms to severe anemia that needs intrauterine and exchange transfusion [32]. Of 39 reported newborns, only 10 developed anemia (hemoglobin level <10 g/dL). In contrast to anti-D-mediated HDFN, maternal anti-Jr$^a$ titer did not correlate with the severity of anemia, level of bilirubin, or any interventions required. The reticulocyte count did not increase, which suggest a lack of compensatory hematopoiesis. The total bilirubin levels were generally low. The direct antiglobulin test (DAT) was largely positive in mildly affected and conservatively treated neonates, whereas it was negative in half of anemic neonates. In the context of anti-Jr$^a$-mediated disease of the fetus and newborn that uniformly lacks evidence of hemolysis, we consider the term “HDFN” inaccurate, whereas alloantibody-mediated “ADFN” might be a more suitable designation. Because high titer anti-Jr$^a$ serum (1024) from a woman delivered ADFN failed to demonstrate suppression of BFU-E and CFU-E, direct

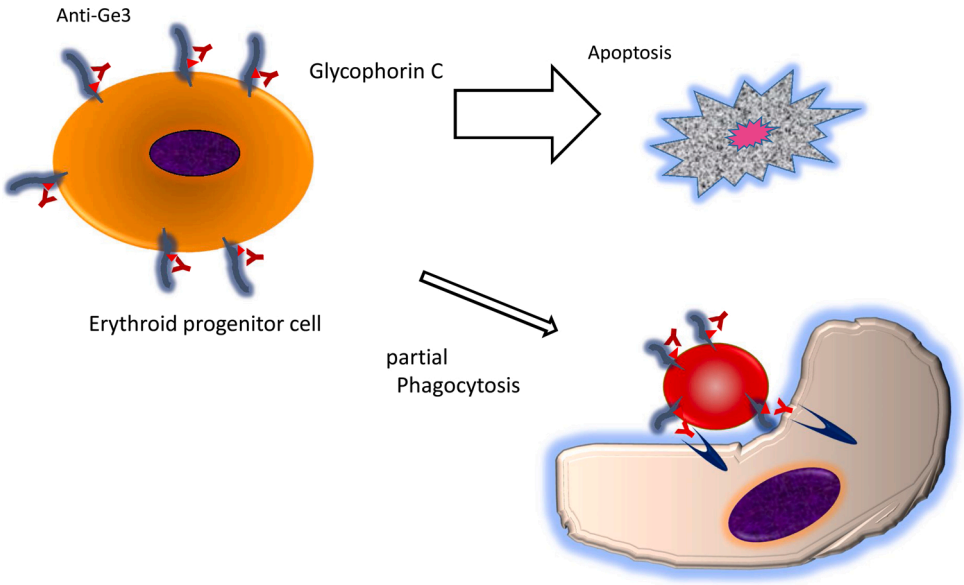


**Fig. 3.** Anti-Ge3-mediated fetal erythroid progenitor cell apoptosis.
Maternal alloantibody against Ge3 antigen of the Gerbich blood group system expressed on glycophorin C, which is tied to the cytoskeleton and is essential in maintaining red cell shape and membrane functions, is supposed to suppress erythroid proliferation *via* non-classical apoptosis.

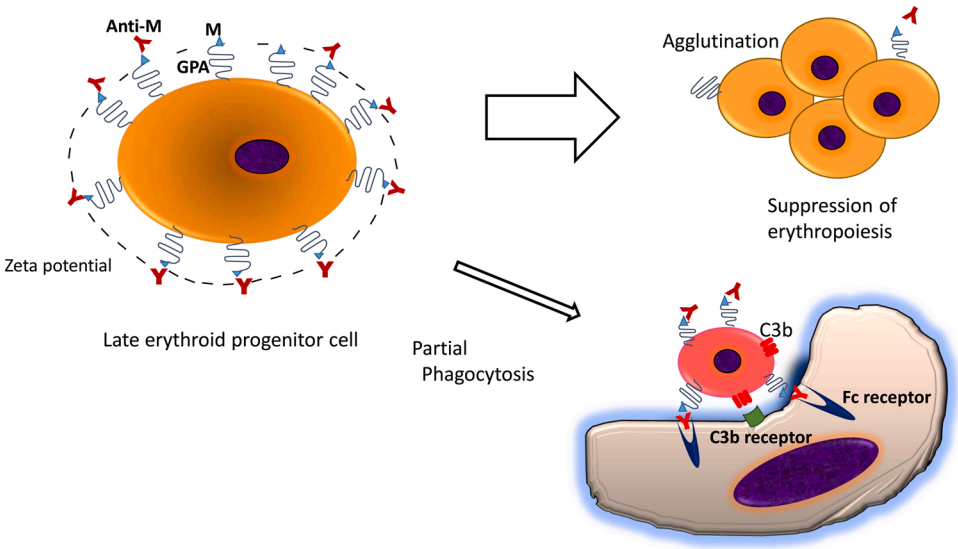


**Fig. 4.** Anti-M-mediated erythroid suppression *via* agglutination or altered/ deformed erythrocyte progenitor cells.
IgG class maternal alloantibody against M antigen expressed on glycophorin A, which contributes abundant sialoglycoprotein to erythrocyte membrane and keeps red cells from adhering to each other and to vascular endothelium, suppresses erythroid precursor cell proliferation possibly *via* agglutination or altered/deformed erythrocyte progenitor cells.

suppressive pathogenesis including apoptosis is unlikely [33].

In a case of anti-Jr$^a$-mediated ADFN, neonatal red cells were revealed to be Jr(a-), with only a fraction Jr(a+) after antibody-elution treatment at day 3 of life, becoming biphasic with Jr(a+) and Jr(a-) at 1 month, and totally Jr(a+) at 10 months [32]. This phenomenon, that recovery of Jr(a+) clones by 10 months of life, suggests that clonal escape from anti-Jr$^a$ immune pressure was brought by epigenetic modification of nucleic acids (DNA and RNA). If this phenomenon of suppressed Jr(a+) cells in neonates born to anti-Jr$^a$ mothers of high-titer is substantially universal, a plausible reason why many anti-Jr$^a$ ADFN cases are less severe may be proposed.

After allogeneic hematopoietic stem cell transplantation (allo-HST), relapse is still a major supervention. Current evidence shows that relapse is an adaptation of leukemic cell population to escape immune pressures such as altered expression of human leukocyte antigens (HLA), relevant metabolic changes, and production of anti-inflammatory cytokines [34, 35]. In lung cancer, loss of HLA heterogeneity occurs in 40 % and is associated with a subclonal neoantigen burden, and immune escape mechanisms [36]. If one non-targeted allele and one targeted alleles exist at a particular locus, as might be seen in cancer susceptibility phenomena, loss of the targeted allele may stimulate non-targeted antigen dominance. This immune-mediated pathophysiology is usually developed mainly by cytotoxic T cells and partly by antibodies.

Then, we hypothesize that maternal immune pressure, or antibody against Jr$^a$ antigen, can stimulate fetal clonal escape for the duration of maternal antibody presence, or temporal loss of heterogeneity in the Jr$^a$ locus.

## 5. Discussion

Herein, we discussed three different mechanisms in ADFN and one classic pathway of HDFN, however, multiple pathways may be actually involved in the morbidity of some cases. Certainly, maternal anti-Kell alloimmunization results in clinical and laboratory evidence of the

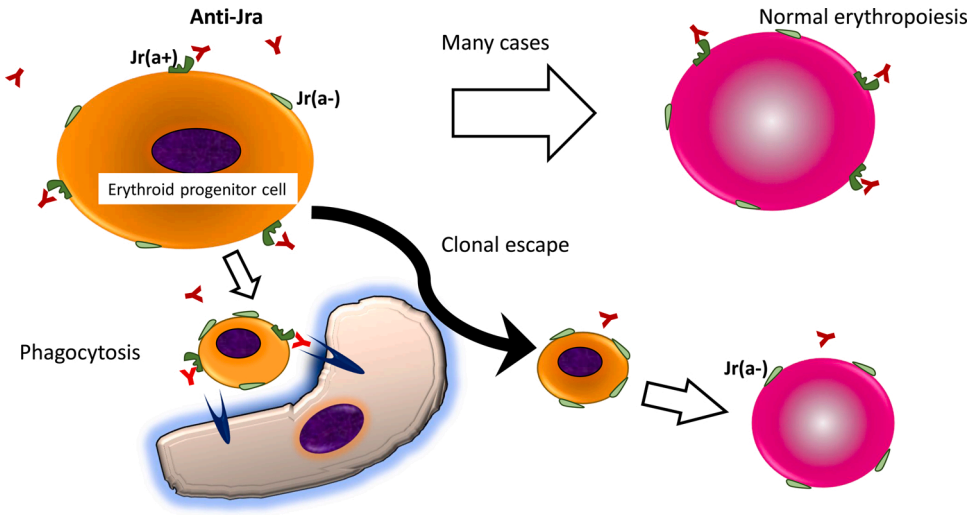


**Fig. 5.** Anti-Jr$^a$-mediated fetal red cell destruction with/without clonal escape from maternal immune pressure.
Maternal anti-Jr$^a$ causes no or little hemolysis in many fetuses, but may induce hemolysis in some, possibly *via* mechanism of extravascular cell destruction. A few affected cases provide almost normal erythropoiesis of Jr (a-), which is thought to be clonal evasion from anti-Jr$^a$ immune pressure.

classical pathway of hemolysis and antibody mediated erythroid cell suppression.

Further, the lowest level of IgG class anti-M as causative in very severe ADFN should be elucidated, including from the standpoint of allotypic variations, and Fc fucosylation and galactosylation in IgG, as suggested by allotypic variations of the IgG Fc region manifesting different abilities to induce phagocytosis [37,38].

Considering anti-A- and anti-B-mediated HDFN, these iso-antibodies rarely cause severe but usually no or mild diseases, because of the fewer number of A and B sites with less branches qualitatively on the fetal/neonatal erythrocytes with one-third of those of adult cells [39], possibly by epigenetic modification of nucleic acids. This change is in favor of having less damaged offspring which will tend to reproduce the peculiarities of their parents. Regarding anti-Jr$^a$-mediated ADFN, we speculate that intact neonates born to mothers with strong anti-Jr$^a$ may possibly have such a suppressed Jr$^a$ antigen site, which we should study further.

The additional mechanisms of fetal/neonatal anemia summarize herein outline important observations that require further elucidation. A better understanding of the effects of antibody binding on erythroid cell development and maturation may provide useful information applicable to the treatment of neonatal and adult acquired anemias.

## Funding

This research did not receive any grants from public funding agencies, or commercial sectors.

## Declaration of Competing Interest

These authors have no conflict of interest to declare, concerning with this manuscript.

## References

[1] Roopenian DC, Christianson GJ, Sproule TJ, Brown AC, Akilesh S, Jung N, et al. The MHC class-I like IgG receptor controls peripheral IgG transport, IgG homeostasis and fate of IgG-Fc-coupled drugs. J Immunol 2003;170:3528–33.
[2] Ariga H, Ohto H, Busch MP, Imamura R, Watson R, Reed W, et al. Kinetics of fetal cellular and cell-free DNA in the maternal circulation during and after pregnancy: implications for noninvasive prenatal diagnosis. Transfusion 2001;41:1524–30.
[3] Sato T, Fujimori K, Sato A, Ohto H. Microchimerism after induced or spontaneous abortion. Obstet Gynecol 2008;112:593–7.
[4] Ree IMC, Lopriore E, Zwier S, Bohringer S, Janssen MWM, Oepkes D, et al. Suppression of compensatory erythropoiesis in hemolytic disease of the fetus and newborn due to intrauterine transfusions. Am J Obstet Gynecol 2020;1:e1–10.
[5] Storry JR, Castilho L, Daniels G, Flegel WA, Garratty G, de Haas M, et al. International society of blood transfusion Cancun report (2012). Vox Sang 2014;107:90–6.
[6] Denomme GA. Kell and Kx blood group systems. Immunohematol 2015;31:14–9.
[7] Zwiers C, Oepkes D, Lopriore E, Klumper FJ, de Haas M, van Kamp IL. The near disappearance in relation to current state-of-art management of red cell alloimmunization. Prenat Diagn 2018;38:943–50.
[8] Southcott MJG, Tanner MJA, Anstee DJ. The expression of human blood group antigens during erythropoiesis in a cell culture system. Blood 1999;93:4425–35.
[9] Vaughan JT, Manning M, Warwick RM, Letsky EA, Murray NA, Roberts AG. Inhibition of erythroid progenitor cells by anti-Kell antibodies in fetal alloimmune anemia. N Engl J Med 1998;338:798–803.
[10] Kamphuis MM, Lindenburg I, van Kamp IL, Meerman RH, Kanhai HHH, Oepkes D. Implementation of routine screening for Kell antibodies: does it improve perinatal survival? Transfusion 2008;48:953–7.
[11] Daniels G, Hadley A, Green CA. Causes of fetal anemia in hemolytic disease due to anti-K. Transfusion 2003;43:115–6.
[12] Sha Q, Redman CM, Lee S. Endothelin-3-converting enzyme activity of the KEL1 and KEL6 phenotypes of the Kell blood group system. J Biol Chem 2006;281:7180–2.
[13] Frey BM, Gassner C, Jung HH. Neurodegeneration in the elderly – when the blood type matters: an overview of the McLeod syndrome with focus on hematological features. Transfus Apher Sci 2015;52:277–84.
[14] Slootweg YM, Lindenburg IT, Koelewijn JM, van Kamp IL, Oepkes D, de Haas M. Predicting anti-Kell-mediated hemolytic disease of the fetus and newborn: diagnostic accuracy of laboratory management. Am J Obstet Gynecol 2018;219(393):e1–8.
[15] Daniels G, Green C. Expression of red cell surface antigens during erythropoiesis. Vox Sang 2000;78(Suppl. 2):149–53.
[16] Jaskiewicz E, Peyrard T, Kaczmarek R, Zerka A, Jodlowska M, Czerwinski M, et al. The Gerbich blood group system: old knowledge, new importance. Transfus Med Rev 2018;32:111–6.
[17] Denomme GA, Shahcheraghi A, Blackall DP, Oza KK, Garratty G. Inhibition of erythroid progenitor cell growth by anti-Ge3. Br J Haematol 2006;133:443–50.
[18] Blackall DP, Pesek GD, Montgomery MM, Oza KK, Arndt PA, Garratty G, et al. Hemolytic disease of the fetus and newborn due to anti-Ge3: combined antibody-dependent hemolysis and erythroid precursor cell growth inhibition. Am J Perinatol 2008;25:541–5.
[19] Arndt PA, Garratty G, Daniels G, Green CA, Wilkes AM, Hunt P, et al. Late onset neonatal anaemia due to maternal anti-Ge: possible association with destruction of erythroid progenitors. Transfus Med 2005;15:125–32.
[20] Micieli JA, Wang D, Denomme GA. Anti-glycophorin C induces mitochondrial membrane depolarization and a loss of extracellular regulated kinase 1/2 protein kinase activity that is prevented by pretreatment with cytochalasin D: implications for hemolytic disease of the fetus and newborn caused by anti-Ge3. Transfusion 2010;50:1761–5.
[21] Wang D, Seto E, Shu J, Micieli JA, Fernandes BJ, Denomme GA. Antibody-mediated glycophorin C colligation on K562 cells induces phosphatidylserine exposure and cell death in an atypical apoptotic process. Transfusion 2013;53:2134–40.
[22] Palacajornsuk P. Review: molecular basis of MNS blood group variants. Immunohematol 2006;22:171–82.

[23] Takeshita A, Watanabe H, Fujihara H, Oshida M, Yurugi K, Tomoda Y, et al. Collaborative study of irregular erythrocyte antibodies in Japan: results from the Japanese study group of allo-immunity and antigen diversity in Asian populations. Transfus Apher Sci 2010;43:3–8.
[24] Wikman A, Edner A, Gryfelt G, Jonsson B, Henter J-I. Fetal hemolytic anemia and intrauterine death caused by anti-M immunization. Transfusion 2007;47:911–7.
[25] de Haas M, Thurik FF, Koelewijn JM, van der Schoot CE. Haemolytic disease of the fetus and newborn. Vox Sang 2015;109:99–113.
[26] Yasuda H, Ohto H, Nollet KE, Kawabata K, Saito S, Yagi Y, et al. Hemolytic disease of the fetus and newborn with late-onset anemia due to anti-M: a case report and review of the Japanese literature. Transfus Med Rev 2014;28:1–6.
[27] Ishida A, Ohto H, Yasuda H, Negishi T, Tsuiki H, Aeakawa T, et al. Anti-M antibody induced prolonged anemia following hemolytic disease of the newborn due to erythropoietic suppression in 2 siblings. J Pediatr Hematol Oncol 2015;37:e–375-e377.
[28] Castilho L, Reid ME. A review of the JR blood group system. Immunohematol 2013;29:63–8.
[29] Matsuda M, Okazaki K, Kanbe T, Sato H, Obara K, Igarashi H, et al. The frequency of Jr(a-) and anti-Jr$^{a}$ positive rates in blood donors from the North Kanto area. Jpn J Transfus Cell Therapy 2018;64:525–8.
[30] Miyazaki T, Kwon KW, Yamamoto K, Tone Y, Ihara H, Kato T, et al. A human monoclonal antibody to high-frequency red cell antigen Jra. Vox Sang 1994;66:51–4.
[31] Ganapathy V, Prasad PE, Ganapathy ME, Leibach FH. Placental transporters relevant to drug distribution across the maternal-fetal interface. J Pharmacol Exp Ther 2000;294:413–20.
[32] Ohto H, Katsuragi S, Yoshida A, Otake A, Tsuneyama H, Ogasawara K, et al. Anemic disease of the newborn with little increase in hemolysis and erythropoiesis due to maternal anti-Jr$^{a}$: a case study and review of the literature. Transfus Med Rev 2019;33:183–8.
[33] Sasamoto N, Tomimatsu T, Nagamine K, Oshida M, Kashiwagi H, Koyama S, et al. Fetal and neonatal anemia associated with anti-Jr$^{a}$: a case report showing a poorly hemolytic mechanism. J Obstet Gynaecol Res 2011;37:1132–6.
[34] Bernasconi P, Borsani O. Immune escape after hematopoietic stem cell transplantation (HSCT): from mechanisms to novel therapy. Cancers 2020;12:69.
[35] Kobayashi S, Kikuta A, Ito M, Sano H, Mochizuki K, Akaihata M, et al. Loss of mismatched HLA in myeloid/NK cell precursor acute leukemia relapse after T cell-replete haploidentical hematopoietic stem cell transplantation. Pediatr Blood Cancer 2014;61:1880–2.
[36] McGranahan N, Rosenthal R, Hiley CT, Rowan AJ, Watkins TBK, Wilson GA, et al. Allele-specific HLA loss and immune escape in lung cancer evolution. Cell 2017;171:1259–71.
[37] Kapur R, Della Valle L, Verhagen OJ, Hipgrave Ederveen A, Lighthrt P, de Haas M, et al. Prophylactic anti-D preparations display variable decreases in Fc-fucosylation of anti-D. Transfusion 2015;55:553–62.
[38] Cen SY, Holton M, Binnington B, Dennome GA, Howie HL, Lebedev JN, et al. IgG3 anti-Kell allotypic variation results in differential antigen binding and phagocytosis. Transfusion 2020;60:688–93.
[39] Economidou J, Hughes-Jones NC, Gardner B. Quantitative measurements concerning A and B antigen sites. Vox Sang 1967;12:321–8.