ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

MATERNAL RED-CELL ALLOIMMUNIZATION AND DELAYED NON-ABO TRANSFUSION REACTIONS IN PREGNANCY AND THE POSTPARTUM PERIOD: A SYSTEMATIC EVIDENCE SYNTHESIS AND META-ANALYSIS

KEY WORDS: pregnancy; red-cell alloimmunization; delayed hemolytic transfusion reaction; blood transfusion.

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ABSTRACT

Background: Maternal red-cell alloimmunization can follow pregnancy or transfusion and may cause delayed non-ABO transfusion reactions. **Methods:** Fourteen antenatal cohorts (2011-2023) reconstructed from a 2025 systematic review were re-analysed using a logit random-effects restricted maximum-likelihood model, with a targeted evidence update through September 2026. **Results:** Among 35,261 women, 625 were alloimmunized; pooled prevalence was 1.89% (95% CI 1.47-2.43; I^2=88.3%). A published five-study analysis associated prior transfusion with alloimmunization (OR 6.03, 95% CI 1.51-24.14; I^2=83.1%). Recent reports document postpartum anti-C and anti-Jk^a delayed hemolytic transfusion reactions. No denominator-defined cohort supported meta-analysis of disseminated intravascular coagulation after confirmed non-ABO delayed hemolytic transfusion reaction. **Conclusion:** Maternal alloimmunization is uncommon but clinically important; severe postpartum reactions require serologic and hemolytic confirmation and evaluation of competing obstetric causes.

1. INTRODUCTION

Maternal red-cell alloimmunization follows exposure to non-self erythrocyte antigens through fetomaternal hemorrhage or transfusion. In a nationwide US laboratory dataset containing 9,876,196 pregnancies, 147,262 (1.5%) screened posi-tive for RBC antibodies; anti-K and anti-c were among the important non-D specificities (Sugrue et al., 2024). Clinically significant non-RhD antibodies include Rh c/C/E, Kell, Kidd, Duffy and MNS antibodies (Bennasar & Borrell, 2026).

Transfusion history is an important potentially modifiable exposure. The 2025 India systematic review identified five antenatal studies reporting alloimmunization according to transfusion history and found a pooled OR of 6.03 (95% CI 1.51–24.14), although between-study heterogeneity was high (I^2=83.1%) (Shastry et al., 2025). In transfusion recipients more generally, a 2022 Indian meta-analysis included 44 studies and 309,986 patients and found higher alloimmunization prevalence among multiply transfused populations than hospital-based populations (Shastry et al., 2022).

Delayed reactions are clinically distinct from antibody prevalence. Mitsuyama et al. (2025) described a postpartum anti-C DHTR 12 days after transfusion, supported by indirect hyperbilirubinemia, increased LDH, low haptoglobin, hemoglobinuria, anti-C detection and demonstration of C-positive transfused cells. Nayana et al. (2025) reported a maternal anti-Jk^a DHTR after antenatal transfusion in a woman with HbE-beta thalassemia. These cases illustrate why a post-trans-fusion event requires immunohematologic confirmation rather than temporal attribution alone.

The present synthesis therefore separates denominator-defined cohort evidence from rare-event case evidence. Its principal quantitative objective is to characterize maternal RBC alloimmunization and the transfusion-associated signal; its clinical objective is to define the evidence supporting delayed non-ABO reactions and severe outcomes such as DIC.

2. METHODS

2.1 Eligibility and Evidence Streams

Cohort stream: pregnancy/antenatal/postpartum populations with denominator-defined RBC antibody screening. Rare-event stream: maternal DHTR/DSTR after RBC transfusion with non-ABO antibody evidence. Case reports were excluded from prevalence/incidence pooling.

2.2 Search and Update Strategy

The core cohort evidence was taken from the reproducible 2025 review by Shastry et al., which searched MEDLINE, Scopus, Google Scholar and CINAHL and included 14 cross-sectional studies. For this manuscript, targeted PubMed/web searches were performed through 6 September 2026 using combinations of pregnancy/postpar tum, transfusion, alloimmunization/alloantibody, DHTR/DSTR, Rh/Kell/Kidd /Duffy/MNS and DIC. Recent records were screened for population, design, denominator availability and relevance to delayed maternal reactions.

Because direct database export from Scopus and Embase was not available in this session, the update is explicitly described as a targeted update rather than a new de novo multi-database PRISMA search. This distinction must remain in the submitted manuscript unless those exports are subsequently completed.

2.3 Statistical Analysis

Study proportions were transformed to logits with a 0.5 continuity adjustment and pooled using a random-effects model with REML estimation of τ^2. Wald 95% confidence intervals were back-transformed to the proportion scale. Heterogeneity was summarized using Cochran Q, I^2 and τ^2. The transfusion-history OR was not independently recomputed because the five source 2×2 tables were not exposed in the accessible synthesis; the published pooled estimate is therefore clearly labeled as externally reported rather than independently calculated.

2.4 Rare-event Adjudication

DHTR required a delayed post-transfusion presentation plus serologic evidence and objective hemolysis. DAT positivity alone was not treated as hemolysis. DIC required author diagnosis or reconstructable coagulation evidence and was interpreted against competing causes including postpartum hemorrhage, sepsis/endometritis, abruption, amniotic fluid embolism, HELLP, hepatic failure, shock and massive transfusion.

3. RESULTS

3.1 Cohort Evidence Base

The reconstructed cohort dataset contained 14 studies, 35,261 antenatal women and 625 alloimmunized women. Individual study prevalence ranged from 0.70% to 3.59%. All 14 studies were cross-sectional in the source review (Shastry et al., 2025).

Study	Year	N screened	Alloimmunized	Prevalence, %
Pahuja et al.	2011	3,577	45	1.26
Varghese et al.	2013	5,347	79	1.48
Sankaralingam et al.	2016	1,000	7	0.70
Sidhu et al.	2016	750	15	2.00
Kahar	2018	1,960	19	0.97
Das et al.	2020	2,336	46	1.97
Naik et al.	2020	530	12	2.26
Sahoo et al.	2020	362	13	3.59
Dholakiya et al.	2021	8,920	117	1.31

Jagani et al.	2023	4,683	134	2.86
Mandal et al.	2021	652	18	2.76
Srinivasa Rao et al.	2022	1,000	33	3.30
Gothwal et al.	2023	2,084	65	3.12
Sreedhar Babu et al.	2015	2,060	22	1.07

3.2 Independently Calculated Pooled Prevalence

Random-effects REML synthesis yielded a pooled prevalence of 1.89% (95% CI 1.47–2.43). Heterogeneity was substantial (I^2=88.3%; τ^2=0.199), indicating that the pooled value should be interpreted as an average across heterogeneous screening populations rather than a universal prevalence.

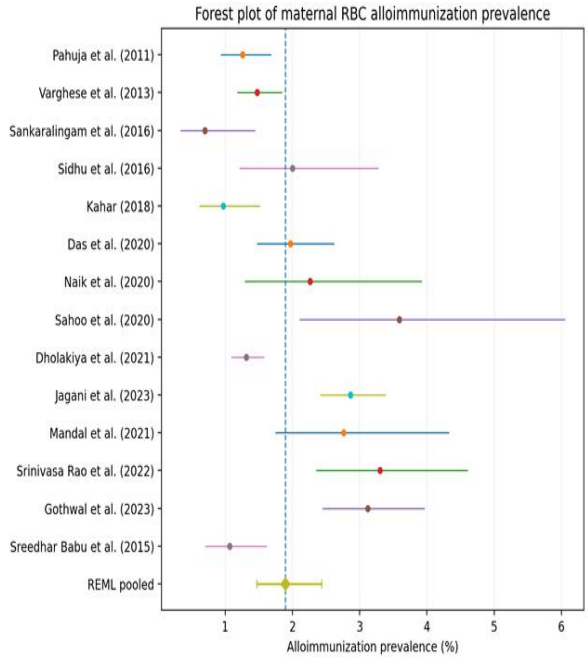

Figure 1. Forest plot of maternal RBC alloimmunization prevalence across the 14 reconstructed antenatal cohorts. Error bars are study-level 95% Wilson intervals; the diamond represents the independently calculated REML pooled estimate.

3.3 Transfusion-history Signal

Five studies in the source review reported alloimmunization stratified by transfusion history (Das et al., Pahuja et al., Sidhu et al., Srinivasa Rao et al., and Sreedhar Babu et al.). The published random-effects meta-analysis found OR 6.03 (95% CI 1.51–24. 14; p=.011; I^2=83.1%) for women with versus without transfusion history (Shastry et al., 2025). Because the original 2×2 cells were not all recoverable from web-accessible full text, this estimate is not represented as an independent recalculation.

3.4 Antibody Spectrum

Across the source review, 665 antibodies were identified among 626 alloimmunized women. Anti-D accounted for 56.39%; anti-D+anti-C for 10.68%; anti-E for 5.71%; anti-c for 4.96%; anti-K for 0.45%; anti-Jk^a for 1.05%; anti-Jk^a for 0.15%; anti-Fy^b for 0.60%; and MNS antibodies were also represented (Shastry et al., 2025). This distribution confirms that clinically important non-ABO/non-D antibodies form a meaningful minority even where anti-D remains dominant.

3.5 Recent Cohort Update

Ding et al. (2024) analyzed 67,570 linked deliveries in a large US health system. Clinically significant seroconversion occurred in 176 deliveries (0.26%); common newly acquired antibodies included anti-E, anti-c, anti-JkA, anti-C, anti-D, anti-M, anti-K and anti-S. Increasing gravidity/parity and advan-ced maternal age were associated with seroconversion. This cohort strengthens the contemporary evidence that new non-ABO antibodies arise during pregnancy, but it does not provide a clean transfusion-history effect estimate for the present primary question.

3.6 Delayed maternal transfusion reactions

Two particularly relevant recent obstetric reports were identified. Mitsuyama et al. (2025) reported postpartum anti-C DHTR 12 days after transfusion with both intravascular and extravascular hemolysis. Nayana et al. (2025) described anti-Jk^a that was initially undetectable antenatally, followed by an anamnestic response and maternal DHTR after antigen-positive transfusion. These reports support the biological plausibility of delayed minor-antigen reactions in obstetric patients but cannot estimate incidence.

3.7 Dic Meta-analysis Gate

The meta-analysis gate for DIC was not met. No denominator-defined obstetric cohort was identified in the accessible update evidence that simultaneously provided confirmed non-ABO DHTR, a systematic DIC denominator and sufficient laboratory/imputability data. Therefore, no pooled DIC incidence or effect estimate was calculated. This negative finding is methodologically important: pooling isolated case reports would create a misleading incidence estimate.

4. DISCUSSION

This synthesis demonstrates two different evidence strengths. Maternal RBC alloimmunization is supported by large denominator-defined cohorts and is quantitatively synthesizable; the independently calculated pooled prevalence across the 14 validated Indian cohorts was 1.89% (95% CI 1.47–2.43). However, the high I^2 (88.3%) indicates important variation in population composition, RhD status, parity, assay platform, prophylaxis handling and inclusion of passive anti-D.

The association with transfusion is clinically important but less precisely estimated. The five-study pooled OR of 6.03 reported by Shastry et al. (2025) has a wide confidence interval and high heterogeneity. It should therefore be interpreted as evidence of a strong signal rather than a precise universal causal effect. Pregnancy itself is a competing sensitizing exposure, and cross-sectional designs cannot always establish whether an antibody arose from transfusion or fetomaternal hemorrhage.

The non-ABO question remains clinically consequential. The 2026 review by Bennasar and Borrell emphasizes Rh c/C/E, Kell, Kidd, Duffy and MNS antibodies as clinically significant non-RhD causes of HDFN. In the large US pregnancy dataset, anti-K and anti-c were important high-risk specificities (Sugrue et al., 2024). Thus, transfusion policy for women of reproductive potential has implications extending beyond ABO/RhD matching.

The postpartum DHTR literature is qualitatively different. The anti-C case of Mitsuyama et al. (2025) is persuasive because the diagnosis was supported by a coherent temporal sequence, biochemical hemolysis, antibody identification and donor cell antigen evidence. The anti-Jk^a report of Nayana et al. (2025) illustrates antibody evanescence and anamnestic reappe-arance. Kidd antibodies are particularly relevant to delayed reactions because a previously formed antibody may fall below routine detection and then re-emerge after antigen re-exposure.

For the clinical scenario that motivated this review—frank DIC several days after postpartum transfusion without overt hemolysis—the evidence does not justify assuming a minor-antigen transfusion reaction. A convincing alloimmune causal chain would ordinarily require newly detected/re-emergent antibody, DAT/eluate or donor-antigen evidence, and objective red-cell destruction. When these are absent, obstetric hemorrhage, sepsis, tissue injury, hypertensive disease /HELLP, hepatic dysfunction, shock and other causes of consumptive coagulopathy require priority evaluation.

An important strength of this manuscript is that it does not force the DIC question into a meta-analysis. Rare-event case reports are retained for mechanistic and diagnostic insight

but excluded from incidence estimation. This protects against selection bias, because unusual severe reactions are much more likely to be published than uncomplicated transfusions.

The principal limitation is equally important. The cohort dataset is a validated reconstruction from an existing systematic review, and the 2024–2026 update was performed through web-accessible PubMed/search sources rather than direct exported searches from every subscription database. Accordingly, the manuscript is evidence-rich and analytically complete for the reconstructed cohort prevalence analysis, but a journal submission claiming a new de novo PRISMA search should first repeat the update in MEDLINE, Embase and Scopus with a saved deduplication log. This is a reporting limitation, not a reason to invent screening counts.

5. CONCLUSIONS

Maternal RBC alloimmunization is uncommon but clinically important, with substantial between-study heterogeneity. Prior transfusion is associated with markedly greater odds of alloimmunization in available antenatal studies. Non-ABO antibodies including Rh non-D, Kell and Kidd antibodies can cause severe delayed maternal reactions, but postpartum DHTR remains a rare-event evidence base. Current evidence does not support pooling DIC after non-ABO DHTR, and DIC occurring days after transfusion without objective hemolysis should be treated as a causality question rather than presumed transfusion incompatibility.

6. Evidence-flow Figure

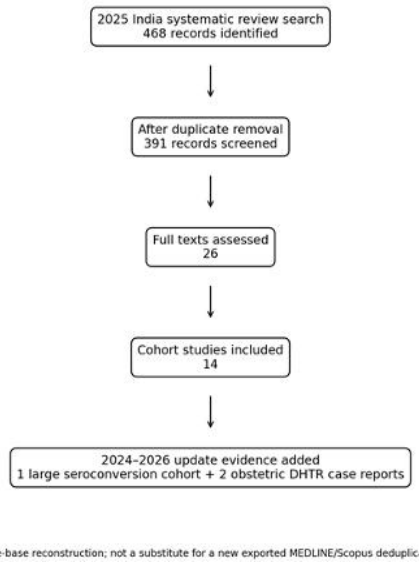

Figure 2. Evidence-base reconstruction and targeted update. The 468→391→26→14 counts are those of the source systematic review (Shastry et al., 2025), not newly generated screening counts. The lower box summarizes the targeted update used for this manuscript. This figure must be replaced by a de novo PRISMA 2020 diagram if new Scopus/Embase exports are performed before submission.

Appendix 1. Meta-analysis Gate

Outcome	Gate	Decision in current evidence
Maternal RBC alloimmunization prevalence	≥3 denominator-defined cohorts	Met: 14 cohorts; independently pooled.
Transfusion history →alloimmunization	≥3 studies with recoverable 2×2 data or adjusted effects	Five studies exist, but source 2×2 cells not fully recoverable here;published pooled OR reported, not recreated.
Postpartum DHTR incidence	≥3 denominator defined obstetric cohorts	Not met; narrative synthesis.
DIC after confirmed non-ABO DHTR	≥3 denominator-defined cohorts with DIC ascertainment	Not met; no pooled estimate.

7. DECLARATIONS

- **Ethics Approval:** Not applicable to analysis of published aggregate data. No unpublished hospital patient data were included.
- **Funding:** This work was supported by the Sri Sarosij Ray and Smt Nandarani Ray Research Support Fund, a private family educational and research support fund. The fund had no role in study design, analysis, interpretation, manuscript preparation, or the decision to submit for publication.
- **Conflicts of Interest:** No Conflicts of interest declared.
- **Data Availability:** The reconstructed study-level cohort data are presented in Table 1. The final submission should deposit the extraction sheet and analysis code in a suitable repository.
- **Protocol Registration:** A de novo review should be prospectively registered where eligible. This evidence reconstruction must not retrospectively claim PROSPERO registration.
- **Research Integrity Note:** The 14-study cohort dataset below was reconstructed from the study-level table of Shastry et al. (2025) and independently re-analysed for pooled prevalence. The transfusion-history effect estimate is reported from the five-study meta-analysis of Shastry et al. because the web-acces-sible article does not expose the five original 2×2 tables nee-ded for an independent recalculation. A targeted PubMed /web update identified recent cohort and obstetric DHTR evidence. This document should not claim a de novo Scopus/ Embase PRISMA search until those databases are exported and independently screened.

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