Fetal and Neonatal Alloimmune Thrombocytopenia: A Systematic Literature Review and Meta-analysis of Adverse Pregnancy-Related Outcomes to Support the Development of a Novel Prophylactic Therapeutic

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BACKGROUND

- Fetal/neonatal alloimmune thrombocytopenia (FNAIT) results from maternal alloimmunization against fetal human platelet antigens (HPA). It is a rare and potentially devastating condition that can cause intracranial hemorrhage in the fetus/neonate and subsequent death or lifelong disability. Prenatal screening does not usually include FNAIT; no therapy is available to prevent alloimmunization.
- Mother–fetus mismatch on antigen HPA-1a accounts for 75%-80% of FNAIT cases; alloimmunization is ~25-fold more frequent in women who are also positive for the major histocompatibility complex allele HLA-DRB3*01:01.
- RLYB212—a recombinant human immunoglobulin G1 monoclonal antibody—is in development to prevent HPA-1a maternal alloimmunization and, ultimately, prevent HPA-1a–related FNAIT and its consequences.
- Clinical development of RLYB212 requires real-world evidence on the size of the population at risk for alloimmunization and frequency of pregnancy/neonatal outcomes from FNAIT under standard care. This literature review was conducted to fill this knowledge gap.

OBJECTIVE

- To quantify the frequency of HPA-1a–negative, HLA-DRB3*01:01–positive pregnant women carrying an HPA-1a positive fetus and, among them, those who were newly alloimmunized (in the current pregnancy or parturition), and their associated pregnancy/neonatal outcomes.

METHODS

- PubMed and Embase were searched for articles published in 2008-2021; earlier studies were identified from existing reviews. The research question expressed in the PICOS framework is shown in Table 1. Two reviewers independently applied prespecified criteria to determine inclusion and assessed article quality. Results of meta-analysis using random-effects models are presented (PROSPERO registration: CRD42022309672).

Table 1. Research Question Expressed in the PICOS Framework

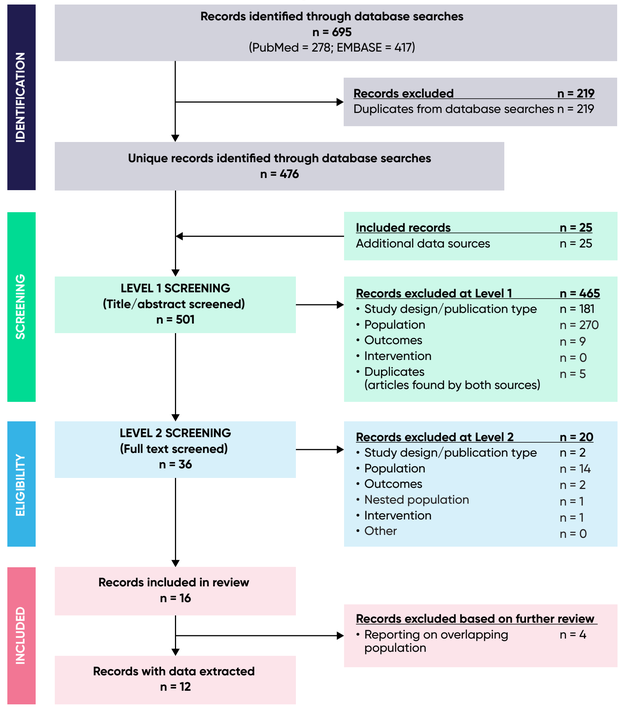
PICOS heading	Concept
Population	Women at higher risk for HPA-1a–related FNAIT
Intervention	Screening, prevalence, natural history, prenatal care
Comparison	Not applicable
Outcomes	Maternal alloimmunization to HPA-1a, pregnancy outcomes, selected neonatal outcomes Outcomes not included among the search terms to keep the search broad
Study design/ publication type	Original research, publication has abstract, conference abstracts not eligible, preprints not eligible
Time limit (not a PICOS heading)	Publication date since 1 January 2008

PICOS = population, intervention, comparison, outcomes, study design.

RESULTS

- Searches identified 501 unique records; 12 observational cohort studies (Figure 1) from Europe, Canada, and Egypt published from 1985 through 2018 were selected. Article quality was generally adequate.
- Of 198,062 screened pregnant women, 2.2% (95% confidence interval [CI], 2.0%-2.5%) were HPA-1a negative (Figure 2); 32.3% (28.6%-36.1%) of HPA-1a–negative women were HLA-DRB3*01:01 positive (at higher risk for alloimmunization; Figure 3). Articles did not report on the frequency of newly alloimmunized women who carried HPA-1a positive fetuses.
- Approximately 10% of HPA-1a–negative women were alloimmunized to HPA-1a (Figure 4). The prevalence of intracranial hemorrhage was 2.2% (0.7%-4.4%) among newborns of alloimmunized HPA-1a–negative women with unknown HLA-DRB3 status and an HPA-1a–positive/genotype unknown partner/fetus (Figure 5).

Figure 1. Records Included and Excluded During Title/Abstract and Full-Text Review



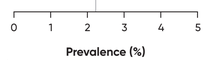
Adapted from Moher et al. (2009).

Note: Of the 36 articles selected for full-text screening (level 2 screening), 21 were identified only by the PubMed/Embase searches, 13 articles were identified only from studies previously identified by Rallybio and published reviews, and 2 articles were identified by both processes.

Figure 2. Prevalence of HPA-1a–Negative Women Among Screened Women

Study	Cases	Population	Prevalence (%) (95% CI)	Weight
Blanchette (1990)	81	5,000	1.6 (1.3-2.0)	8.6%
Davoren (2003)	54	4,090	1.3 (1.0-1.7)	8.2%
Debska (2018)	373	15,204	2.5 (2.2-2.7)	9.9%
Doughty (1995)	74	3,473	2.1 (1.7-2.7)	7.8%
Durand-Zaleski (1996)	52	2,066	2.5 (1.9-3.3)	6.6%
Husebekk (2012)	255	6,774	3.8 (3.3-4.2)	9.0%
Kjeldsen-Kragh (2007)	2,111	100,448	2.1 (2.0-2.2)	10.6%
Maslanka (2003)	144	8,013	1.8 (1.5-2.1)	9.3%
Mueller-Eckhardt (1985)	26	1,211	2.1 (1.4-3.1)	5.2%
Reznikoff-Etievant (1988)	27	860	3.1 (2.1-4.5)	4.3%
Turner (2005)	546	26,506	2.1 (1.9-2.2)	10.2%
Williamson (1998)	618	24,417	2.5 (2.3-2.7)	10.2%
Pooled, random effects		**198,062**	**2.2 (2.0-2.5)**	**100.0%**

Heterogeneity: I^2 = 91%

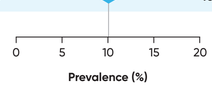


CI = confidence interval; HPA = human platelet antigen.

Figure 4. Prevalence of Alloimmunization to HPA-1a, Unknown Whether Preexisting or New, in HPA-1a–Negative Women

Study	Cases	Population	Prevalence (%) (95% CI)	Weight
Blanchette (1990)	3	50	6.0 (1.3-16.5)	1.5%
Debska (2018)	32	373	8.6 (5.9-11.9)	10.8%
Husebekk (2012)	23	224	10.3 (6.6-15.0)	6.5%
Kjeldsen-Kragh (2007)	210	1,990	10.6 (9.2-12.0)	57.4%
Maslanka (2003)	12	122	9.8 (5.2-16.6)	3.5%
Turner (2005)	25	318	7.9 (5.2-11.4)	9.2%
Williamson (1998)	46	387	11.9 (8.8-15.5)	11.2%
Pooled, random effects		**3,464**	**10.2 (9.2-11.2)**	**100.0%**

Heterogeneity: I^2 = 0%

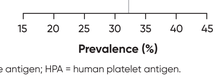


CI = confidence interval; HPA = human platelet antigen.

Figure 3. Prevalence of HLA-DRB3*01:01–Positive Women Among HPA-1a–Negative Women

Study	Cases	Population	Prevalence (%) (95% CI)	Weight
Doughty (1995)	22	71	31.0 (20.5-43.1)	11.9%
Husebekk (2012)	48	142	33.8 (26.1-42.2)	23.8%
Williamson (1998)	123	385	31.9 (27.3-36.9)	64.3%
Pooled, random effects		**598**	**32.3 (28.6-36.1)**	**100.0%**

Heterogeneity: I^2 = 0%

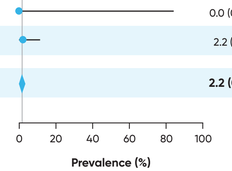


CI = confidence interval; HLA = human leukocyte antigen; HPA = human platelet antigen.

Figure 5. Prevalence of Neonatal Intracranial Hemorrhage Among Alloimmunized Women in the Post Hoc Population

Study	Cases	Population	Prevalence (%) (95% CI)	Weight
Blanchette (1990)	1	3	33.3 (0.8-90.6)	1.4%
Davoren (2003)	0	3	0.0 (0.0-70.8)	1.4%
Durand-Zaleski (1996)	0	4	0.0 (0.0-60.2)	1.7%
Husebekk (2012)	0	23	0.0 (0.0-14.8)	9.1%
Kjeldsen-Kragh (2007)	2	161	1.2 (0.2-4.4)	62.6%
Maslanka (2003)	1	12	8.3 (0.2-38.5)	4.8%
Mueller-Eckhardt (1985)	0	2	0.0 (0.0-84.2)	1.0%
Williamson (1998)	1	46	2.2 (0.1-11.5)	18.0%
Pooled, random effects		**254**	**2.2 (0.7-4.4)**	**100.0%**

Heterogeneity: I^2 = 0%



CI = confidence interval; HPA = human platelet antigen.

Note: The post hoc population consisted of women who were HPA 1a-negative, had unknown HLA-DRB3 status (or including all women who were tested regardless of the results), and had an HPA 1a–positive partner/fetus or for whom the HPA-1 genotypes of the partner and fetus were unknown.

CONCLUSIONS

Published research confirmed the frequency of FNAIT risk factors and outcomes but did not report on new alloimmunizations. A natural history study to fill this knowledge gap, along with the planned trial to assess RLYB212's efficacy in prevention of HPA-1a alloimmunization, is needed to characterize the potential value of RLYB212 in standard care.

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