Published in final edited form as:

J Perinatol. 2019 July ; 39(7): 920–926. doi:10.1038/s41372-019-0388-8.

Fetal thrombocytopenia in pregnancies complicated by fetal anemia due to red-cell alloimmunization: cohort study and metaanalysis

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Abstract

Objective: To estimate the prevalence and characteristics of fetal thrombocytopenia at the time of percutaneous umbilical cord sampling (PUBS) in pregnancies complicated by alloimmunization and to conduct a systematic review on fetal thrombocytopenia in these pregnancies.

Study Design: Retrospective cohort study of all patients undergoing PUBS at our institution from 2000–2017. Clinical data including fetal platelet counts were abstracted from the medical record and analyzed with routine statistical procedures. A systematic review and metaanalysis were also conducted according to standard procedures.

Result: At first procedure, prior to any transfusion, 13/36 fetuses (36%) had thrombocytopenia: 11/36 (31%) had moderate thrombocytopenia, and 2/36 (6%) had severe thrombocytopenia (14 patients had no platelet count at first procedure). The systematic review identified six studies, and the prevalence of fetal thrombocytopenia at the time of PUBS for alloimmunization was 18% (95% confidence interval 11%, 26%).

Conclusion: Thrombocytopenia is common and underappreciated in fetuses undergoing PUBS for alloimmunization.

Introduction

Maternal erythrocyte alloimmunization remains a continuing challenge, both from missed opportunities for Rh(D) immunoglobulin prophylaxis as well as alloimmunization with other

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Conflict of Interest: The authors have no conflicts of interest to declare.

"Supplementary information is available at JPER's website"

antibodies.[1] Surprisingly, despite the fact that the antigens involved are not expressed on platelets, fetal thrombocytopenia has been incidentally noted in cases of maternal red cell alloimmunization requiring percutaneous umbilical cord blood sampling (PUBS) and intrauterine transfusion (IUT).[2–5] Fetal thrombocytopenia can be defined as platelet count $<150 \times 10^9$/L and classified as moderate ($50 – 150 \times 10^9$/L) or severe ($<50 \times 10^9$/L).[2, 5] However to date, the frequency, clinical associations, and consequences of this thrombocytopenia are relatively poorly understood. Therefore, our objectives were to estimate the prevalence of fetal thrombocytopenia at the time of PUBS in pregnancies complicated by red cell alloimmunization and to investigate the associations between fetal thrombocytopenia and procedural factors and neonatal outcomes. To complement our study we also performed a systematic review and metaanalysis of the prevalence of fetal thrombocytopenia in cases of red cell alloimmunization.

Methods

Cohort Study

This is a retrospective cohort study of all patients undergoing PUBS for alloimmunization at Barnes-Jewish Hospital in St. Louis from 2000–2017. Patients undergoing PUBS for other indications, such as non-immune hydrops, were excluded. The decision to proceed with PUBS was based either on serial amniocentesis with delta OD 450 or, more recently, elevated middle cerebral artery Doppler velocity.[6] Demographic and clinical data were abstracted from the medical record. Patients were categorized by antibody status as anti-D alone, anti-D and other antibodies, or other antibodies only, based on their initial presentation. Fetal antigen status was not uniformly available. At our institution PUBS is performed using standard techniques. The umbilical vein at the cord insertion into the placenta is the usual target. One mL of fetal blood is taken in a heparinized syringe to the central laboratory for complete blood count, and an additional 1 mL sample is taken for immediate analysis of hemoglobin with a point-of-care device. In cases of fetal anemia, packed red blood cell transfusion is given to achieve a target hematocrit of 45%. Specifically, donor red blood cells are packed by the blood bank to achieve a donor hematocrit of approximately 85–90%. Blood used for transfusion is type O, Rh negative, negative for any antibody to which the patient is alloimmunized, leukocyte reduced, irradiated, washed, negative for cytomegalovirus, negative for hemoglobin S, and, in recent years, tested to ensure it is negative for the Zika virus. If the fetus is hydropic, then the transfusion is given as a split transfusion over two days. Fetal paralysis is used rarely.

Demographic, clinical, and outcome data were obtained from the medical record. Descriptive statistics were used to characterize the cohort. Fetal thrombocytopenia was defined as platelet count $<150 \times 10^9$/L and was classified as moderate ($50 – 150 \times 10^9$/L) or severe ($<50 \times 10^9$/L).[2, 5] Notably, platelet reference values do not vary across gestation.[4] We also extracted information on the mean platelet volume (MPV) and the maternal platelet count at first sampling. Chi-square or Fisher exact tests were used for categorical variables. Normality of continuous variables was checked with the Kolmogorov-Smirnov test and then parametric or nonparametric tests were used as appropriate. Correlations between opening and closing platelet counts were determined with Pearson’s correlation coefficient.

The study was approved by the Washington University in St. Louis Human Research Protection Office. A waiver of consent was granted due to the retrospective and noninterventional nature of the study. Given that we included all women who met inclusion criteria and the sample size was fixed, we did not perform an a priori sample size calculation. Study data were collected and managed using REDCap electronic data capture tools hosted at Washington University School of Medicine in St. Louis.[7] Analyses were performed in SAS software (version 9.2; SAS Institute, Inc, Cary, NC). A P-value <0.05 was considered statistically significant, and we did not adjust for multiple comparisons.

Systematic Review and Metaanalysis

A medical librarian (LES) searched published literature for records discussing fetal thrombocytopenia, fetal anemia, and fetal platelet count. The librarian created search strategies using a combination of keywords and controlled vocabulary in Ovid Medline 1946-, Embase.com 1947-, Scopus 1823-, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Protocols (Protocols), Cochrane Clinical Answers (ANSWERS), and Clinicaltrials.gov 1997-present. Search results were limited to humans by excluding animals using the OVID Medline human filter recommended in the *Cochrane Handbook for Systematic Reviews of Interventions.* All search strategies were completed in September 2018 and were re-run in January 2019. In the updated search, all records published before January 1, 2018 were deleted leaving only 2018 and 2019 citations, and then duplicates were removed to locate new unique references. The full search strategies are detailed in the Supplemental Appendix.

We included English language articles published prior to January 2019 that were observational studies reporting on fetal thrombocytopenia or platelet count in pregnancies complicated by fetal anemia due to maternal alloimmunization. We excluded case reports and review articles, as well as articles detailing fetal thrombocytopenia due to other etiologies such as neonatal alloimmune thrombocytopenia or infection. The primary outcome was fetal thrombocytopenia.

Titles and abstracts were screened by the first author (JIR) and full text articles were retrieved for all potentially relevant results. Full-text articles were reviewed against the inclusion criteria and then data from the eligible articles were extracted for presentation. We conducted a metaanalysis of proportion of thrombocytopenia at first PUBS procedure prior to any transfusion using the *metaprop* procedure in Stata IC/13.1, StataCorp, College Station, Texas.[8] The Freeman-Tukey Double arcsine transformation was performed and the random-effects model of DerSimonian and Laird was used.[8]

RESULTS

Cohort Study

There were 50 eligible patients (Table 1). The median gestational age at first procedure was 25 weeks (interquartile range 20, 28). A total of 158 PUBS procedures were performed with 143 in-utero transfusions. Opening platelet counts (range 8–485 × 10^9/L) were available for 120 PUBS. Of these procedures, 71 (59%) had no thrombocytopenia, 36 (30%) had

moderate thrombocytopenia, and 13 (11%) had severe thrombocytopenia. At first procedure, prior to any transfusion, 13/36 fetuses (36%) had thrombocytopenia, 11/36 (31%) had moderate thrombocytopenia, and 2/36 (6%) had severe thrombocytopenia (14 patients had no platelet count at first procedure). There were 7 patients with fetal platelet count <100 $\times 10^8$/L at first procedure. At subsequent procedures the prevalence of thrombocytopenia was 36/84 (43%). Overall, 25 (50%) patients had fetal thrombocytopenia in at least one procedure. There were 5 patients with no recorded fetal platelet count at any procedure. Platelet counts varied over time and there were only 3 patients with platelet counts consistently <150 $\times 10^9$/L at all procedures.

The MPV was normal (6.8–10.4 fl) in all 13 patients with fetal thrombocytopenia at first PUBS, with a median MPV of 7.8 fl (interquartile range 7.5, 7.9). There were five patients with maternal thrombocytopenia at time of first PUBS; of these 3 (60%) also had fetal thrombocytopenia, while the remaining 2 (40%) did not. Of the 13 cases of fetal thrombocytopenia, only 3/13 (23%) had concomitant maternal thrombocytopenia as well.

Procedural factors are noted in Table 2. The mean hemoglobin in the thrombocytopenic group was 6.8 g/dL (standard deviation 2.8 g/dL); while in the non-thrombocytopenic group it was 8.1 g/dL (standard deviation 3.1 g/dL), p=0.02. There were no associations between thrombocytopenia at the time of procedure and intraprocedural complications.

Thrombocytopenia was found during 16 (44%) of PUBS procedures (n=36) in patients with anti-D antibodies only, in 10 (28%) of PUBS in patients with anti-D and other antibodies (n=36), and in 23 (48%) of PUBS (n=48) in patients with only other kinds of antibodies (p=0.15). There was no association between antibody specificity and severe fetal thrombocytopenia (p=0.27).

Outcomes stratified by thrombocytopenia status are in Table 3. There was no association between antenatal thrombocytopenia and neonatal thrombocytopenia. However, it appeared that neonatal hemoglobin and gestational age at delivery were lower in the thrombocytopenic group, although this did not meet statistical significance. Finally, there were no adverse outcomes directly attributable to thrombocytopenia in the study population.

Systematic Review

The search resulted in 3,977 unique records which were included in the project library after excluding duplicates. In addition to these, 221 records were identified in ClinicalTrials.gov, resulting in a total of 4,198 unique records. The reference lists of the selected articles were hand searched for further references, which revealed 1 additional source, yielding a total of 4,199 citations.[9] The updated search performed in January 2019 identified 48 new unique records, for a final total of 4,246. Exact totals for each phase of the search process as well as fully reproducible search strategies for each database can be found in the Supplemental Appendix.

Figure 1 depicts the PRISMA Flow Diagram. After reviewing the titles and abstracts of each paper, 16 manuscripts (or abstracts if no full text papers were available) were screened against the inclusion and exclusion criteria. Of these 16 studies, 9 were excluded for failing

to meet inclusion criteria. Also the previously presented abstract of this article was excluded due to redundancy. In the end 6 studies were included in the systematic review.[2–5, 10, 11] Table 4 includes a summary of the included studies. Most, but not all studies, defined thrombocytopenia as a platelet count $<150 \times 10^9$/L on first blood sampling at the time of PUBS or fetoscopic procedure. The forest plot is in Figure 2. The overall estimated proportion of fetuses with thrombocytopenia at the time of PUBS for Rh alloimmunization was 18% (95% confidence interval 11%, 26%). Excluding a study that included only patients with anti-Kell antibodies did not substantially change this estimate (19%, 95% confidence interval 12%, 28%).[10] Similarly, excluding the two studies that only assessed thrombocytopenia in anemic fetuses did not materially change the results.[4, 11]

DISCUSSION

We found that fetal thrombocytopenia at the time of PUBS for suspected fetal anemia due to maternal alloimmunization was common, occurring in up to 40% of procedures and 50% of patients. Fetuses with more severe anemia were more likely to be thrombocytopenic. Platelet levels varied over time between procedures, with only a minority of patients having persistent thrombocytopenia. Finally, it appeared that neonatal hemoglobin and gestational age at delivery were lower in the thrombocytopenic group, although this did not meet statistical significance. The metaanalysis found that fetal thrombocytopenia complicates nearly 20% of initial PUBS in patients with maternal alloimmunization. However, the metaanalysis also noted significant heterogeneity in definitions of thrombocytopenia and associated outcomes.

To our knowledge there have not been any trials of platelet transfusion at the time of IUT in severely thrombocytopenic fetuses.[2] Our findings call into question whether treatment of fetal thrombocytopenia at the time of PUBS should be considered. However, such a policy would require platelets to be prepared for all fetuses, resulting in wasted platelets in 80% of cases. Furthermore, the balance between red blood cell transfusion and platelet transfusion is unclear, given that the addition of platelet transfusion would give extra volume to an already compromised fetus. It is also possible that correction of fetal thrombocytopenia would not affect outcomes in a meaningful way. Additionally, in a recent randomized trial, neonatal platelet transfusion resulted in adverse outcomes in preterm infants.[12] Further investigation is needed to answer these questions.

Our study has a number of strengths. It is a single-center study employing a uniform protocol for IUT. We were able to assess fetal platelet counts over time in fetuses with multiple PUBS procedures. Additionally, we were able to examine the associations between fetal thrombocytopenia and a number of procedural and outcomes factors. Finally, the systematic review and metaanalysis contextualize our findings.

On the other hand there are some limitations to consider. The study was retrospective and therefore data were not available on outcomes in all pregnancies. Additionally, hydrops was not uniformly recorded in the medical record and so we could not assess the relationship between thrombocytopenia and hydrops at the time of procedure. Furthermore, our samples are collected in heparinized syringes; these are heparinized by the physician at the time of

the procedure. The use of heparin may have altered platelet counts in the samples. Finally, our sample size was relatively small, which limited our statistical power.

To date the mechanism of fetal thrombocytopenia in alloimmunized pregnancies has not been elucidated. It is postulated that more anemic fetuses may have increased consumption or destruction of platelets.[2] Alternatively, hematopoiesis may be directed towards red cell production, thus decreasing production of platelets.[2] The fact that the MPV was normal in all patients with fetal thrombocytopenia at first PUBS may point to decreased production, rather than increased consumption, as the underlying etiology.[13] In fact, neonatal thrombocytopenia and neutropenia are seen in severely affected neonates with Rh hemolytic disease, and these neonates also have low or normal MPV, again suggesting decreased production as opposed to increased consumption of platelets.[14] On the other hand, of the 5 mothers with maternal thrombocytopenia, 3 had fetal thrombocytopenia and 2 did not, suggesting that maternal thrombocytopenia, possibly antibody mediated, may be a risk factor for fetal thrombocytopenia in alloimmunized patients, although the numbers are very small to make any definitive conclusions. Although IUT can suppress hematopoiesis, since the studies here are mostly limited to the first PUBS prior to IUT, this would not explain the thrombocytopenia seen at the first PUBS.[2] The co-existence of fetal thrombocytopenia and fetal anemia in alloimmunized pregnancies has been now observed for nearly 30 years.[5] It is time to move to the next step and further investigate the underlying mechanisms and potential consequences of this finding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (R01: HD 06161619-01A1, PI Cahill). Additionally supported by the National Institutes of Health [grant numbers UL1 TR000448 and P30 CA091842].

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Figure 1

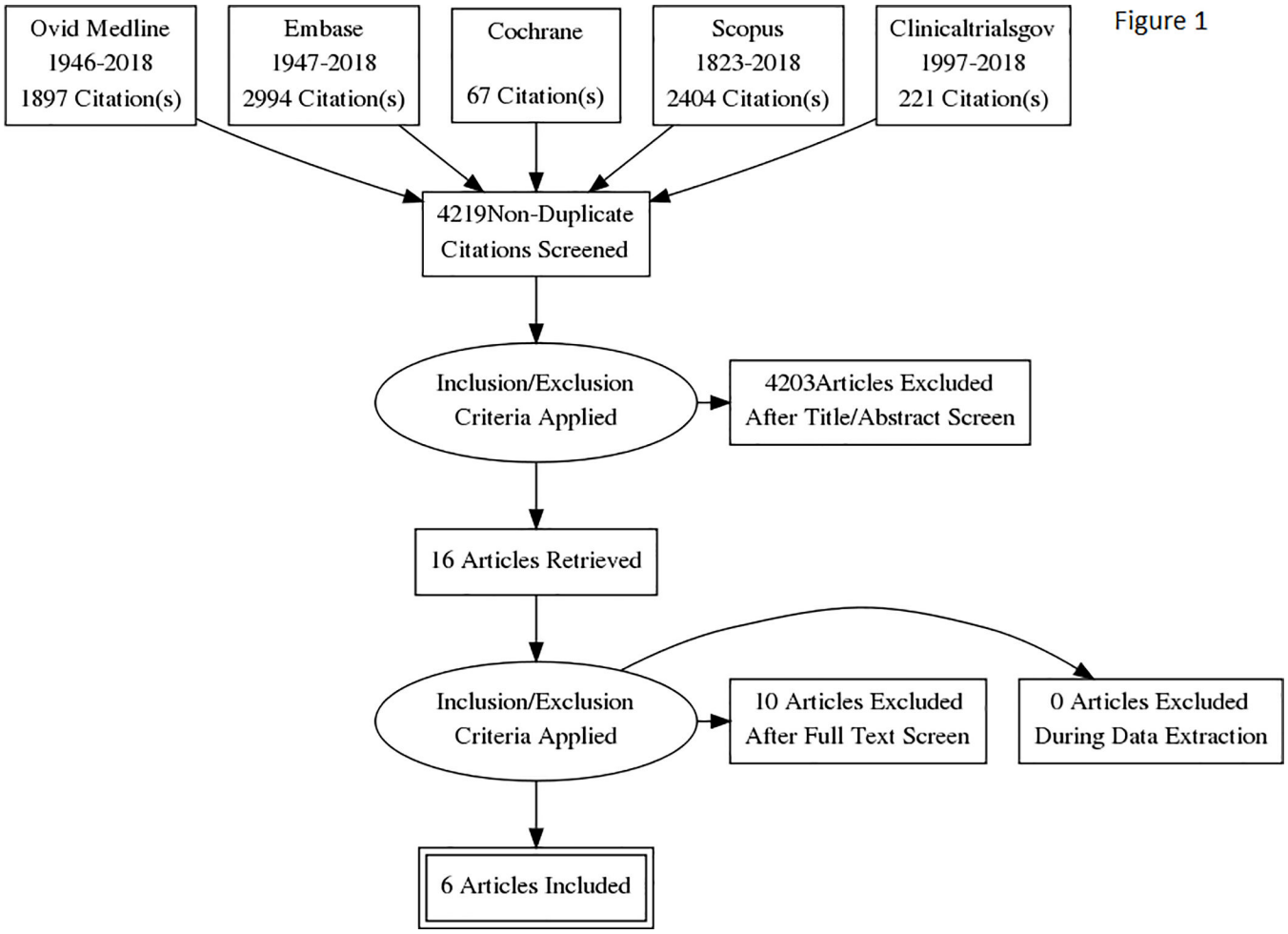

Figure 1:
PRISMA Flow Diagram

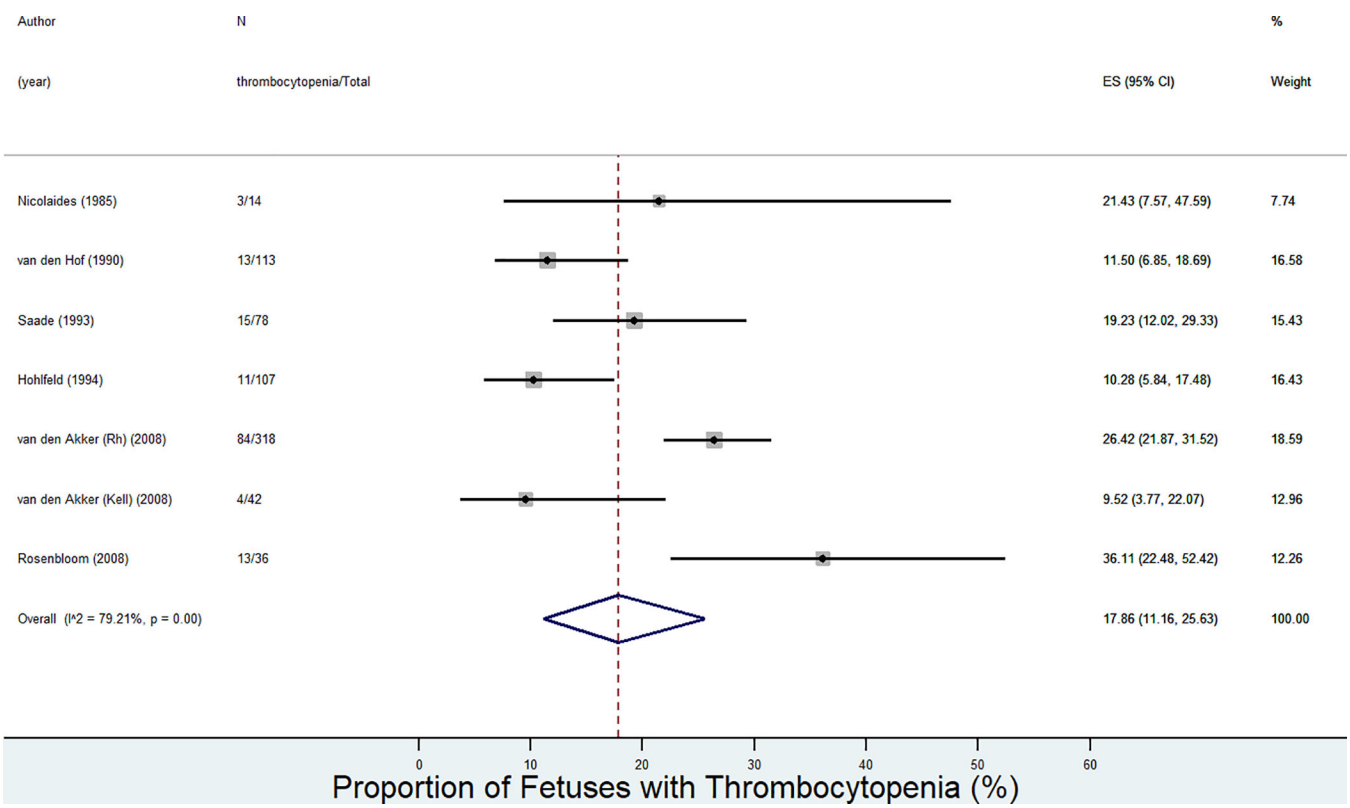

Figure 2:

Forest Plot of Prevalence of Fetal Thrombocytopenia at First Blood Sampling in Maternal Alloimmunization

Table 1:

Baseline Characteristics (N=50 Patients)

Characteristic	N (%) or median (IQR)
Maternal age, y	29 (26,33)
Body mass index, kg/m^2	28.4 (24.8, 33.1)
Parity	2 (1,3)
Prior affected pregnancy requiring in-utero transfusion	12 (24)
Gestational age at diagnosis, weeks	25 (20,28)
Antibodies	
Anti-D only	15 (30)
Other antibodies only	20 (40)
Anti-D and other antibodies	15 (30)
Fetal thrombocytopenia	
Ever severely thrombocytopenic	9 (18)
Ever moderately thrombocytopenic	16 (32)
Never thrombocytopenic	20 (40)
No platelet counts obtained	5 (10)
Neonatal platelet count * (× 10^9/L)	194 (145, 268)
PUBS per patient	3 (1,4)
Transfusions per patient	2 (1,4)
Intrauterine fetal demise	3 (6)
Gestational age at delivery, weeks	33 (29, 35)
Mode of delivery	
Vaginal	12 (24)
Cesarean	28 (56)
Unknown	10 (20)

PUBS: percutaneous umbilical cord sampling

* Available for 31 neonates

Table 2:

Procedural Factors (N=120 Procedures)

Characteristic	No thrombocytopenia N=71	Thrombocytopenia N=49	P*
Platelet count (× 10^9/L)	218 (197, 285)	86 (49, 118)	<0.001
Hemoglobin (g/dL)	8.1 ± 3.1	6.8 ± 2.8	0.02
Intraprocedural Complications*	9 (13)	4 (9)	0.56
Fetal Bradycardia	7 (10)	3 (6)	0.52
Emergent Delivery	3 (4)	2 (4)	1.0

* Each procedure counted only once, patient may have experienced both complications.

P from t-test, Mann-Whitney U, or Fisher-exact test

Table 3:

Outcomes by Antenatal Thrombocytopenia Status (N=45 Neonates)

Characteristic	No antenatal thrombocytopenia N=20	Moderate antenatal thrombocytopenia N=16	Severe antenatal thrombocytopenia N=9	P
Number of PUBS procedures	2 (1,3)	3 (2,4)	5 (4,6)	0.003
Neonatal platelet count ($\times 10^9$/L)	191 (129, 259) (N=12)	183 (117, 208) (N=13)	249 (195, 288) (N=4)	0.51
Neonatal hemoglobin (g/dL)	13.0 (11.8, 15.1) (N=12)	10.4 (7.9, 13.0) (N=13)	10.8 (8.6, 13.2) (N=4)	0.08
Thrombocytopenia at birth	5 (25) (N=12)	4 (25) (N=13)	1 (11) (N=4)	0.87
Intrauterine fetal demise	0 (0) (N=15)	0 (0) (N=14)	1 (11) (N=8)	0.22
Gestational age at delivery, weeks	35 (30,36) (N=15)	33 (31,36) (N=14)	29 (28,34) (N=8)	0.11

Numbers represent N (%) or median (interquartile range) (N= is number of available patients for that datapoint)

P from Kruskal–Wallis or Fisher exact test

Table 4:

Included Studies in Systematic Review

Author Year Location	Population	Control Group	Definition of Thrombocytopenia	Prevalence of Thrombocytopenia	Association between Anemia and Thrombocytopenia	Other Findings
Nicolaides[11] 1985 The United Kingdom	Patients with Rh(D) isoimmunization undergoing fetoscopic transfusion 14 fetuses with hemoglobin ≤ 4g/dL Only first blood sampling included	62 “normal controls”	Not defined	3/14 (21%)	Thrombocytopenia only assessed in anemic fetuses	None
van den Hof[5] 1990 The United Kingdom	Patients with red blood cell isoimmunization undergoing cordocentesis 113 fetuses with no prior transfusion	229 fetuses undergoing prenatal diagnosis	Platelet count <2 SD below the mean for gestational age. Normal range determined from fetuses undergoing prenatal diagnosis by cordocentesis	13/113 (12%)	Quadratic association between hemoglobin concentration and platelet count. Non-anemic fetuses with same platelet count as controls. Moderately anemic fetuses with higher platelet count than controls. Severely anemic fetuses with lower platelet count than controls.	Thrombocytopenia more common in hydropic fetuses
Saade[3] 1993 United States	Patients with red blood cell isoimmunization undergoing in utero transfusion 78 fetuses with no prior transfusion	64 fetuses undergoing funipuncture for other indications	Platelet count <150 × 10^9/L	15/78 (19%)	Thrombocytopenia linearly correlated with anemia	Thrombocytopenia more common in hydropic fetuses
Hohlfeld[4] 1994 France	Patients undergoing fetal blood sampling for various indications (n=5,194) 107 fetuses with Rh isoimmunization	Normal values determined from entire sampled population (n=5,194)	Platelet count <150 × 10^9/L	11/107 (10%)	All thrombocytopenic fetuses were anemic	Thrombocytopenia more common in hydropic fetuses
van den Akker[10] 2008 The Netherlands	Patients with “severe” anti-Kell isoimmunization 42 fetuses assessed before first transfusion	None	Platelet count <150 × 10^9/L Clinically significant thrombocytopenia defined as platelet count <50 × 10^9/L	4/42 (10%) 0 cases of clinically significant thrombocytopenia	Not reported	No clinically significant thrombocytopenia in hydropic fetuses

Author Year Location	Population	Control Group	Definition of Thrombocytopenia	Prevalence of Thrombocytopenia	Association between Anemia and Thrombocytopenia	Other Findings
van den Akker[2] 2008 The Netherlands	Patients undergoing fetal blood sampling and in utero transfusion for Rh(D) alloimmunization 318 fetuses assessed at first sampling 982 total samplings with 914 available platelet counts		Platelet count <150 × 10^9/L Severe thrombocytopenia defined as platelet count <50 × 10^9/L	84/318 fetuses (26%) 12/318 fetuses (4%) with severe thrombocytopenia 241/914 samplings (26%) 25/914 (3%) samplings severe thrombocytopenia	Week correlation between fetal hemoglobin and fetal platelet count.	Thrombocytopenia more common in hydropic fetuses