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An ongoing problem: Rhesus hemolytic disease of the newborn - A decade of experience in a single centre

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ABSTRACT

Background: The objectives were to evaluate the descriptive features of newborns with a diagnosis of Rhesus (Rh) hemolytic disease, to determine the morbidity and mortality rates, to evaluate the treatment methods and the factors affecting treatment requirements and clinical outcomes during a ten-year period at a tertiary center.

Methods: Newborn infants who had a positive direct Coombs test and/or had a history of intrauterine transfusion (IUT) due to Rh hemolytic disease were included. The data regarding the prenatal, natal and postnatal periods were collected from hospital records.

Results: A total of 260 neonates were included of which 51.2% were female. The mean ± standard deviation gestational age was 36.9 ± 2.7 weeks. The rate of preterm birth was 41.2%. Of 257 mothers whose obstetric medical history could be accessed, 87.2% were multigravida, whereas 76.3% were multiparous. Among mothers who had a reliable history of anti-D immunoglobulin prophylaxis (n=191), 51.3% had not received anti-D immunoglobulin prophylaxis in their previous pregnancies. The antenatal transfusion rate was 31.7% and the frequency of hydrops fetalis was 8.8%. While combined exchange transfusion (ET) and phototherapy (PT) was performed in 15.4% of the babies, the majority either needed phototherapy only (51.1%) or no treatment (33.5%). The mortality rate was 3.8 % (n = 10), and nine babies out of these 10 were those with severe hydrops fetalis.

Conclusion: This study showed that Rh hemolytic disease is still a major problem in developing countries. Multiple comorbidities may occur in addition to life threatening complications, including hydrops fetalis, anemia and severe hyperbilirubinemia. High rates of multiparity and low rates of anti-D immunoglobulin prophylaxis are potential barriers for the eradication of the disease. It should be remembered that Rh hemolytic disease is a preventable disease in the presence of appropriate antenatal follow-up and care facilities.

1. Introduction

After exposure of a Rhesus (Rh) (D)-negative mother to Rh (D) antigen, IgG-type anti-D antibodies are formed, which are able to cross the placenta and destroy fetal blood cells causing Rh hemolytic disease of the fetus or newborn [1,2]. Rh hemolytic disease has various clinical presentations. The most severe cases, which are untreated antenatally, may die *in utero* [3] or those who survive may be born with clinical features of hydrops fetalis, including hepatomegaly, splenomegaly, skin edema, ascites, pleural or pericardial effusion and anemia. However, some mildly or moderately affected newborns may either require phototherapy (PT) and/or exchange transfusion (ET) or do not require any treatment [3]. In some cases irreversible neurological damage may occur as a consequence of severe hyperbilirubinemia, which is not treated appropriately and promptly [3].

In a statistical study conducted in the USA in 2002, Rh (D) alloimmunization was detected in approximately 6.7 out of 1000 live births [4]. In a multicenter study in Turkey, which included 5620 newborns who were born over 35 weeks of gestational age and needed treatment due to hyperbilirubinemia, it was reported that hemolytic disease was found in 28.9% (n = 1624) but Rh hemolytic disease was found in 5.4% (n = 304) of the newborns [5].

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In the past, before anti-D immunoglobulin prophylaxis and intrauterine transfusion treatment (IUT), the perinatal mortality rate due to Rh hemolytic disease was around 50% and morbidity rates were high [6,7]. Perinatal mortality rate has decreased to 2–3% in experienced centers as a result of close follow-up of high-risk pregnant women, serial measurement of maternal anti-D levels, and serial antenatal ultrasound evaluation, in addition to performing amniocentesis, fetal blood sampling and intrauterine transfusions, if needed [2,7]. Mortality rates in Rh hemolytic disease decreased from 18.4 to 1.3 per 100,000 live births between 1977 and 1992 [8].

Rh hemolytic disease continues to be an important issue in low- and middle-income countries where fertility rates are high and there are difficulties in obtaining anti-D immunoglobulin prophylaxis. However, the disease has not been completely eradicated in developed countries either. In Turkey, there is little data regarding the frequency of Rh hemolytic disease, the spectrum of neonatal clinical findings, treatment strategies, and morbidity and mortality rates. For this reason, the aim was to evaluate the clinical findings, treatment methods, responses to treatment, morbidity and mortality rates of newborns with Rh hemolytic disease, who were followed and treated in a single Neonatal Unit during a 10 year-period.

2. Methods

Newborn infants who were born at Istanbul University, Istanbul Faculty of Medicine Hospital between 2007 and 2016, with a positive direct Coombs' test and/or a history of IUT due to Rh hemolytic disease were included in the study. Newborns with a history of IUT due to Rh hemolytic disease were included in the study regardless of the direct Coombs test result. Ethical approval was obtained from the Istanbul Medical Faculty Ethics Committee (No: 2016/812). The data regarding the prenatal, natal and postnatal periods were collected from the hospital database and patient files. Antenatal data of patients who received IUT were obtained from the records of the Division of Perinatology of the Department of Obstetrics and Gynecology.

Newborn infants whose antenatal follow-up was not performed at least once in our hospital, who were outborn and referred to our neonatal unit or who were inborn but transported to another hospital, and newborns with a positive direct Coombs test due to a reason other than Rh incompatibility, were not included in the study.

Demographic characteristics of the newborns and the mothers, obstetrical medical history, blood group and anti-D immunoglobulin prophylaxis status of the mothers were recorded. Family histories were evaluated. The gestational age, type of delivery, anthropometric measurements, physical examination findings, biochemical parameters, treatment methods and comorbidities of the babies were recorded.

The treatment criteria for hyperbilirubinemia reported in the guideline published by the American Academy of Pediatrics in 2004 were followed. For babies who were born below 35 weeks of age, the limits of ET and PT were based on the guideline updated by the Turkish Neonatology Society in 2014, according to birthweight [9–11]. Prophylactic intravenous immunoglobulin (IVIG) was given to neonates with a direct Coombs titer of 2+ and above according to our neonatal intensive care unit (NICU) protocol. IVIG was not given to patients with a direct Coombs titer of 1+ or if it could not be supplied.

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. In addition to descriptive statistical methods (mean, standard deviation, median, minimum, maximum, frequency, ratio), Student's *t*-Test was used for normally distributed quantitative data, and Mann Whitney *U* test was used for non-normally distributed quantitative data. One-way ANOVA Test was used in comparisons of normally distributed groups of three or more, and Bonferroni test in dual comparisons while Kruskal Wallis test was used for comparisons of groups of three or more that did not show normal distribution, and Mann Whitney *U* Test was used for dual comparisons. Pearson Chi-Square test, Fisher-Freeman-Halton test and Fisher's Exact test were used to compare qualitative data. The level of significance was accepted as $p < 0.05$ for all analyses.

3. Results

3.1. Demographic and descriptive data of the patient group

The records of 5985 babies born between 2007 and 2016 were reviewed, out of which 260 (4.3%) with the diagnosis of Rh hemolytic disease were included in the study. While 41.2% (n = 107) of the babies were born prematurely, 58.8% (n = 153) of them were term babies. The descriptive characteristics of the babies are shown in Table 1.

The ratio of the newborns who received IUT was 31.7% (n = 82). Hydrops fetalis was present in 8.8% (n = 23) of the babies. During postnatal follow-up, 5.4% (n = 14) of the patients died. The proportion of deaths which were directly related to Rh hemolytic disease was 3.8% (n = 10), whereas four babies died because of a reason other than Rh hemolytic disease (congenital heart disease n = 3, anhydramnios and severe pulmonary hypoplasia n = 1).

3.2. Data regarding maternal obstetric history and family history

Of 257 mothers with accessible obstetric medical history, 87.2% (n = 224) were multigravida and 76.3% (n = 196) were multiparous. The mean number of pregnancies was 3.8 ± 2.3 and the mean number of births was 2.6 ± 1.6. In 11.3% (n = 29) of the mothers there was a history of a previous child who died due to Rh hemolytic disease. Only 48.7% (n = 93) of the 191 mothers with a reliable medical history regarding anti-D prophylaxis had received anti-D prophylaxis in their previous pregnancies.

The rate of parental consanguinity was 20.5% (n = 53). The medical history of siblings could be accessed in 182 cases in which 65.9% (n = 120) had no history of hyperbilirubinemia, while 15.4% (n = 28) had siblings who received PT only and 18.6% (n = 34) had siblings who needed a combination of PT and ET. In 4.9% of the patients (n = 9), there was a history of a sibling with sequelae due to kernicterus.

3.3. Treatment requirements of the cases

While no ET or PT was needed in 33.5% (n = 87) of the babies, 51.1% (n = 133) received PT only and 15.4% (n = 40) needed both PT and ET. IVIG was given to 90.8% (n = 236) of the babies for prophylactic or therapeutic purpose. A small percentage of the babies (5.8%, n = 15) did not receive any treatment at all; no PT, ET, nor IVIG (Fig. 1).

The proportion of babies who received PT was 66.5% (n = 173). The mean duration of PT was 54.6 ± 41.7 (4–250) hours. Of the 173 babies who received PT, 23% (n = 40) also underwent ET, while 77% (n = 133) received PT only (Table 2).

Since IVIG therapy was used for prophylactic or therapeutic purposes, no comparison was made between babies who received or did not receive IVIG. The clinical features and comparison of the patients according to their treatment requirements are shown in Table 2.

Table 1
Descriptive characteristics of the newborns (n = 260).

Gender, n (%)	Female	133 (51.2)
	Male	127 (48.8)
Median (range) gestational age, weeks	37.5	(24.8–41.1)
Type of birth, n (%)	Vaginal	58 (22.3)
	C/S	202 (77.7)
Median (range) birth weight, g (n = 256)		2915 (800–4730)
Median (range) birth weight excluding cases with hydrops fetalis, g (n = 233)		2950 (800–4730)

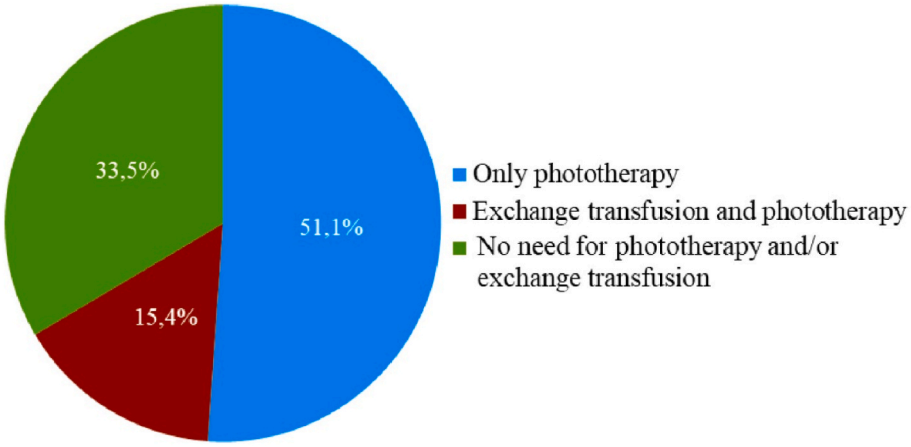


Fig. 1. Postnatal treatment requirements of the patients (n = 260).

Table 2
Treatment requirements according to clinical and laboratory findings.

		No PT/ET, (n = 87)	PT only, (n = 133)	PT + ET, (n = 40)	p
Antenatal transfusion	No	79 (90.8%)	86 (64.7%)	13 (32.5%)	**0.001**
	Yes	8 (9.2%)	47 (35.3%)	27 (67.5%)	
Hydrops fetalis	No	84 (96.6%)	124 (93.2%)	29 (72.5%)	**0.001**
	Yes	3 (3.4%)	9 (6.8%)	11 (27.5%)	
Median (range) cord bilirubin (mg/dL)		2.4 (1.2–5.8)	3.6 (1.2–10)	6.6 (3.4–11.5)	**0.001**
Mean±SD cord hematocrit (%)		49.4 ± 9.1	39.3 ± 10.5	29.6 ± 7.7	**0.001**
Median (range) serum albumin (g/dL)	Median (Min-max)	3.4 (1.9–4.3)	3.5 (1.4–4.4)	3.1 (1–4.1)	**0.003**
Direct Coombs' test	Negative	7 (8%)	31 (23.3%)	15 (37.5%)	**0.001**
	Positive	80 (92%)	102 (76.7%)	25 (62.5%)	
Median (range) direct Coombs' titer	Median (Min-max)	1 (1–4)	3 (1–4)	4 (1–4)	**0.029**
T Thrombocytopenia	No	86 (97.8%)	123 (92.4%)	20 (50%)	**0.001**
	Yes	2 (2.2%)	10 (7.5%)	20 (50%)	
Mean±SD maximum bilirubin (mg/dL)		7,9 ± 2,5	13,9 ± 4,3	17,1 ± 4,7	**0,001**
Postnatal red blood cell transfusion time	<7 days	2 (50%)	36 (60%)	20 (66.7%)	0.702
	≥7 days	2 (50%)	24 (40%)	10 (33.3%)	
Median (range) duration of hospitalization, days		3 (2–48)	7 (3–67)	11 (4–45)	**0.001**
Medical history of siblings	No hyperbilirubinemia	38 (82.6%)	61 (61.6%)	21 (56.8%)	**0.001**
	PT	7 (15.2%)	18 (18.2%)	3 (8.1%)	
	PT + ET	1 (2.2%)	16 (16.2%)	8 (21.6%)	
	Kernicterus	0 (0%)	4 (4%)	5 (13.5%)	

PT: Phototherapy, ET: Exchange Transfusion.

3.4. Comorbidities

Transient tachypnea of the newborn (TTN) was present in 17.7% (n = 46) and respiratory distress syndrome (RDS) was present in 4.2% (n = 11). The frequency of invasive ventilation requirement was 21.2% (n = 55). The mean duration of ventilation therapy was 138.2 ± 92.3 h. Early sepsis was diagnosed in 9.2% (n = 24) and late sepsis was diagnosed in 4.2% (n = 11) of the cases. Thrombocytopenia was present in 12.3% (n = 32) of babies while cholestasis was present in 5% (n = 13) of the babies.

3.5. Mortality

Fourteen of 260 (5.4%) newborns with Rh hemolytic disease died. The cause of mortality was Rh hemolytic disease in 3.8% (n = 10) of the patients. Other patients did not have significant signs of hemolysis. Three of them died due to congenital heart disease whereas one baby died due to anhydramnios and severe pulmonary hypoplasia.

The mean gestational age of the ten who died from Rh hemolytic disease was 34.4 ± 3.6 weeks, ranging from 27.6 to 40.0 weeks and the mean birth weight was 2439 ± 786 g (1400–3780); 80% (n = 8) were born preterm, 40% (n = 4) were small for gestational age, only one baby (10%) was born vaginally and 90% (n = 9) by Caesarean section. The proportion of cases with hydrops fetalis was 90% (n = 9) while 80% (n = 8) of them had a history of antenatal transfusion. Mechanical ventilator requirement occurred in 70% (n = 7). The comorbidities were early sepsis (80%, n = 8), late sepsis (50%, n = 5), RDS (80%, n = 8), TTN (10% n = 1), thrombocytopenia (40%,n = 4) and cholestasis (20%,n = 2). PT was required in 80% (n = 8) of the cases and ET was required in 50% (n = 5). The median (range) exitus time was 55.5 h (1 hour-70 days).

4. Discussion

The prevalence of Rh hemolytic disease has been reported as 276 per 100,000 live births worldwide, which has decreased to 2.5 per 100,000 live births in developed countries. However, it has still been reported to be as high as 529 per 100,000 live births in low and middle-income countries [12]. In the present study, 4.3% (n = 260) of 5985 newborns were hospitalized in our neonatal unit during a 10-year period because of Rh hemolytic disease. Since our hospital is a tertiary center for high-risk pregnancies, it is not possible to generalize this rate to our country. However, this study is the only study conducted in a tertiary center in Turkey, with the longest period and the highest number of patients.

It is known that in populations where the birth rates are high and anti-D prophylaxis is not widely available, the frequency of hemolytic disease increases and its severe forms occur more commonly [13]. In the

present study, the frequency of multigravid pregnancies and multiparities were high (87.3% and 76.3% respectively). It is reported that the average number of pregnancies per woman in Sub-Saharan Africa is between 4 and 7 and the incidence of Rh hemolytic disease is approximately August 3, 1000 live births. In our study, the average number of pregnancies was found to be 3.8 ± 2.3, which is of importance, since the risk of the disease and its severity increases as the number of pregnancies per individual increases [14]. In addition, in the present study, more than half of the 191 mothers (51.3 %) had not received anti-D immunoglobulin prophylaxis, which is proven to have a significant role in the prevention of Rh hemolytic disease. It has been reported that the rate of antenatal prophylaxis varies between 80 and 90% in developed countries, and the rate of postnatal prophylaxis is 95–100% [15]. In the present study, the anti-D immunoglobulin prophylaxis rate was much lower than it should have been, which was directly related to the presence of severe cases. Furthermore, administration of anti-D immunoglobulin prophylaxis in Turkey is probably lower than the rate found in this study because our center is a tertiary center and the socioeconomic status of the patients is relatively better than other regions of the country. The importance and efficacy of anti-D immunoglobulin prophylaxis should be highlighted and reinforced in antenatal care across the whole of Turkey.

The presence of a sibling with a history of requiring treatment for hyperbilirubinemia is also a risk factor for neonatal hyperbilirubinemia. There was a significant difference between the sibling medical histories of the group who underwent ET and PT, compared to the group who received only PT and the group who did not need either PT, ET or combined PT/ET. In the group who did not need any treatment, the rate of sibling history with no hyperbilirubinemia was significantly higher than the other two groups, and the need for ET and PT was less. Kernicterus was not reported in any of the siblings of the cases who did not require PT and/or ET. To the best of our knowledge, there is no other published study which has reported the relationship between disease severity and sibling medical history.

The need for ET varies between 20% and 70% in newborns with Rh hemolytic disease [16]. In a study conducted in India, it was reported that 30 of 51 neonates (57.7%) with Rh immunization required ET and 7 (13.7%) died [14]'. The reason for this wide range may be related to the use of different threshold values for ET. In a study by Smits-Wintjens et al., it was reported that the rate of ET decreased from 69% to less than 20% after the American Academy of Pediatrics (AAP) guideline was published in 2004 [9,16]. In the present study, only 15.4% of the newborns needed ET, 51% needed PT and/or ET treatment, and 33.5% did not need either of these treatments. The present study included a relatively heterogeneous group, since severe cases with a history of IUT and cases with no significant hemolysis were both included, which may explain these results. As the AAP guideline is used in our unit, it is not surprising that results are close those published previously. In addition, prophylactic IVIG treatment, which is frequently used in our unit, may have contributed to these results.

While the prevalence of deaths due to Rh hemolytic disease in countries from Eastern Europe/Central Asia, Latin America, Sub-Saharan Africa and South America is reported to be 119/100,000 live births, it was reported to be only 0.1% (1/100,000 live births) in high-income countries [12]. The mortality rate was 3.8% (n = 10) among patients with Rh hemolytic disease in our hospital, which is one of the biggest tertiary referral centers of Turkey. Ten out of 5985 babies (0.16%) who were hospitalized and followed up in our unit within ten years died due to Rh hemolytic disease, which is close to the death rate due to total Rh hemolytic disease in developed countries.

In a study conducted in the Netherlands, 103 newborns with gestational age over 35 weeks who were severely affected by Rh hemolytic disease were evaluated [17]. Of these, 63% were male, the mean birth weight was 3005 ± 420 g, and gestational age was 37 weeks. In contrast in the present study, only 48.8% of the cases were male, while the mean birth weight was 2883 ± 626 g and gestational age was 37 ± 2.7 weeks. Except for including patients with high antibody titer in the Dutch study, the study population is similar to the present study, with the exception of the sex mix. While 2% of the cases were hydropic at birth in the Dutch study, the rate of hydrops fetalis was more than four-fold higher at 8.8% (n = 23) in our study. This may be because of the referral of severe cases to our hospital, the non-compliance of the mothers with the recommended follow-up schedules, or the high multiparity rate in Turkey.

In the same Dutch study, the percentage of babies who underwent PT and ET was 98% and 44%, respectively, and the mean PT duration was 4.6 ± 1.8 days [17]. In the present study, these rates were 66.5% and 15.4%, respectively, and the mean PT duration was 2.3 ± 1.7 days. These different results are probably due to the inclusion of only severe cases in the Dutch study while our study population was heterogeneous. In addition, it can be speculated that prophylactic IVIG treatment in our unit may have reduced the need for ET. However, in the Dutch study by Rath et al., babies born between 2000 and 2011 were evaluated, and there was a lower threshold for ET and PT were used for babies born before 2005, prior to the publication of the AAP guidelines [17]. All these reasons may have led to the lower rate of ET and PT in our study. Of note, the rate of ET was 23.1% in the group receiving PT (n = 173) in our study, a result close to the study by Rath et al. [17].

While the prevalence of hydrops fetalis due to Rh hemolytic disease has decreased over the years due to preventive strategies and effective antenatal follow-up, cases of non-immune hydrops fetalis have predominated. In a study conducted in Turkey, the incidence of hydrops fetalis was 3.8/1000 and the incidence of immune hydrops fetalis was 1.8/1000 live births in a university hospital between 2002 and 2011 [18]. The rate of immune hydrops fetalis during the 10-year period in our study was 3.8/1000 live births. However, since immune hydrops fetalis cases due to blood group antigens other than Rh antigens and hydropic babies whose antenatal follow-up were not performed in our hospital were not included in our study, it is probable that the number of hydropic babies born in our hospital was higher. According to a study performed in Ankara, 16 (59.2%) of 27 cases of hydrops fetalis due to Rh hemolytic disease died [18]. In our study, 39% (n = 9) of newborns with hydrops fetalis died. While 90% (n = 9) of the deaths in the whole group (n = 10) were hydropic, all of the early neonatal deaths (n = 4) were hydropic, which indicates that hydrops is a significant risk factor for early neonatal death.

There is little published data regarding additional findings, such as cholestasis, thrombocytopenia and requirement for mechanical ventilation in newborns with Rh hemolytic disease. In a study evaluating 313 newborns with and without IUT diagnosed with hemolytic disease, the frequency of cholestasis was 13%, and it was concluded that a history of IUT and Rh (D) incompatibility were independent risk factors for cholestasis [19]. The frequency of IUT was 66% in this study [19]. For comparison, in the present study the frequency of cholestasis was 5% (n = 13) while the frequency of IUT was 31.5%. These differences may be related to the iron load due to IUT and tissue hypoxia caused by hydrops. There is a lack of published evidence concerning the frequency of cholestasis in Rh hemolytic disease and large-scale studies are needed.

Koenig et al. reported thrombocytopenia to be present in all hydropic newborns due to Rh hemolytic disease and in non-hydropic neonates who required ET, whereas thrombocytopenia was absent in all neonates who did not need ET [20]. In the present study, the incidence of thrombocytopenia was 12.3% (n = 32) in all cases, and 50% in cases who died. The incidence of thrombocytopenia was significantly different between groups in the present study, being 50% in the group who underwent ET, but dropped to 7.5% in the group who received PT only, while it was just 2.2% in the group who did not require PT and/or ET. This suggests that thrombocytopenia may be an accompanying finding and may be correlated with the severity of the disease. More research is needed on this subject.

In a randomized placebo-controlled study conducted by Smits-Wintjens et al., in 2011, 80 newborns with a history of IUT related to Rh hemolytic disease were included [21]. These authors reported that

there was no significant difference between the need for ET, the number of ETs, the duration of PT, maximum bilirubin levels, and need for transfusion due to late anemia between the groups who did or did not receive IVIG. In the present study, there was no need for blood transfusion in the postnatal period in the group who did not receive IVIG, but this is an expected result, since hemolysis was mild in these cases. Furthermore, we found that 24.5% of 236 cases who received IVIG needed red blood cell transfusion within the first seven days, 15.5% (n = 36) after seven days, and 60% (n = 142) did not need postnatal transfusion. In a randomized controlled study, Elalfy et al. reported that, when IVIG was given within the first 12 h after birth to babies with Rh hemolytic disease without IUT, a decrease in the duration of PT and a decrease in the requirement for ET were observed compared to the group that did not receive IVIG [22]. Conflicting results in the literature concerning the routine use of IVIG in newborns with Rh HD show the urgent need for a meta-analysis of randomized controlled studies. One of the limitations of our study is the lack of data regarding the evaluation of the efficacy of IVIG. The absence of a control group due to ethical issues and the retrospective design of the study limited the evaluation of the effectiveness of IVIG therapy.

In conclusion, the present study stands out from the other studies conducted in this field as it includes a large study population and wide spectrum of patients. In addition to severely affected babies who had undergone IUT due to Rh hemolytic disease, there were cases without significant hemolysis. Of note, the current study clearly shows that Rh hemolytic disease is still an ongoing problem in Turkey, as in other developing countries, because of high rates of multiparity and low rates of anti-D immunoglobulin prophylaxis. The presence of a sibling affected by Rh hemolytic disease, especially in severe cases, highlights the importance of Rh(D) prophylaxis and the importance of family planning in high-risk circumstances. Our study also shows that, in addition to life threatening complications including severe anemia, hyperbilirubinemia and hydrops fetalis, multiple comorbidities including cholestasis and thrombocytopenia may occur in Rh hemolytic disease. The death or sequelae of a baby due to Rh hemolytic disease, which is a preventable condition, should be a “never event” in the present day.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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