Original Article

Proportion of Unsensitized Rh(D)-Negative Pregnant Women Delivered at Siriraj Hospital Who Received a Complete Course of Anti-D Immunoglobulin: An Awareness problem?

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Background: Rh(D) alloimmunization prophylaxis should be administered to unsensitized Rh(D)-negative pregnant women. A routine antenatal dose and a postpartum dose for women that delivered an Rh(D)-positive neonate are recommended. Due to a very low prevalence of Rh(D)-negative blood type in Thai population, awareness of this specific management may be lacking.

Objective: To determine the proportion of unsensitized Rh(D)-negative pregnant women that delivered at Siriraj Hospital who received a complete course of anti-D immunoglobulin and to determine the factors associated with the failure to achieve a complete administration as well as pregnancy and neonatal outcomes.

Materials and Methods: Medical records of 133 unsensitized Rh(D)-negative pregnant women were reviewed to determine the proportion of cases receiving a complete anti-D prophylaxis. Possible reasons for missing anti-D administration were postulated. Comparison between cases receiving and not receiving antenatal anti-D prophylaxis was performed in terms of associated factors. Pregnancy and neonatal outcomes were compared between women who received complete prophylaxis and those who did not.

Results: A complete anti-D prophylaxis was obtained in 71.4% of the women with antenatal dose given to 78.2%. Late antenatal care (OR 2.6, 95% CI 1.4 to 4.9) and late or no antenatal care at Siriraj Hospital (OR 7.1, 95% CI 2.8 to 17.9) were associated with missing antenatal anti-D administration. Desire for tubal sterilization and positive maternal Rh(D)-antibody in the third trimester appeared to be the causes of postpartum dose omission. Pregnancy and neonatal outcomes were comparable between women receiving and not receiving a complete anti-D prophylaxis.

Conclusion: The proportion of unsensitized Rh(D)-negative pregnant women delivering at Siriraj Hospital who received a complete anti-D prophylaxis was 71.4%. Late antenatal care, late or no antenatal care at Siriraj Hospital, desire for tubal sterilization, and positive maternal Rh(D)-antibody in the third trimester were associated with the incomplete Rh(D) alloimmunization prophylaxis.

Keywords: Rh(D)-negative, Alloimmunization, Anti-D immunoglobulin, Anti-D prophylaxis, Rh immunoglobulin

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Rhesus (Rh)(D)-negative blood type in pregnancy poses specific problems and needs extra attention. An Rh(D)-negative mother carrying an Rh(D)-positive fetus would possibly produce anti-D antibody following a sensitizing event such as feto-maternal hemorrhage, which can occur significantly at the time of delivery. In addition, feto-maternal hemorrhage can occur throughout even in an uneventful pregnancy with the amount of 0.07, 0.08, 0.13, and 0.19 mL of fetal blood entering maternal circulation during first, second, and third trimesters, and during delivery, respectively[1]. As small amount as 0.1 mL of fetal blood can effectively stimulate the production of anti-D antibody in maternal circulation[2-5], it can destroy the red blood cells of a Rh-positive fetus, leading to severe fetal anemia and immune hydrops fetalis or erythroblastosis fetalis in subsequent pregnancies. In addition, it can cause hemolytic disease of the newborn (HDNB), neonatal jaundice, and kernicterus. This phenomenon is recognized as Rh-alloimmunization. Anti-D immunoglobulin (anti-D IG) or RhIG administered to unsensitized Rh(D)-negative pregnant women can prevent the production of this antibody by neutralizing the

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fetal Rh(D)-antigen before it triggers maternal antibody response. RhIG administered within 72 hours postpartum can reduce the risk of sensitization between 13% to 16% and 0.5% to 1.8%[3,6-8]. The risk is reduced further to almost zero (0.14% to 0.2%) with an additional antenatal dose, given between 26 and 28 weeks' gestation[3,6-8] before the time when the volume of feto-maternal hemorrhage is large enough to stimulate the natural anti-D antibody production[1,9].

If a woman is found to be Rh(D)-negative, several next strategies are possible. With the first strategy, the baby's father is tested for Rh(D)-status[10]. If he is Rh(D)-negative, then the fetus would be Rh(D)-negative and no further specific management is needed. If the father is homozygous Rh(D)-positive, the fetus would be Rh(D) positive, the pregnancy would be managed as would be described below. If the father is heterozygous Rh(D)-positive, the fetal Rh(D)-status would be determined either by an invasive procedure, which needs RhIG administration before the procedure, or fetal Rh(D)-genotype assessment by maternal serum DNA screening, which is somewhat costly[11,12]. If the fetus is Rh(D)-positive, maternal anti-D antibody is determined to see if she has already been sensitized. If her anti-D antibody is negative, antenatal RhIG would be given at 26 to 28 weeks' gestation. If the woman is already sensitized or alloimmunized, the fetus would be monitored for signs of severe anemia and managed accordingly[13,14].

The alternative strategy is skipping the fetal Rh(D)-status determination procedure because approximately as high as 60% of the women would carry an Rh(D)-positive fetus and require prevention of alloimmunization anyway[2,3]. Rh(D)-negative women are tested for Rh(D)-antibody and routine antenatal RhIG administration is given to all those unsensitized[2,3,10]. This routine administration strategy has been shown to be more cost-effective than the targeted prophylaxis strategy[15,16].

Rh(D)-negative blood type among Thai population is relatively rare. The prevalence of Rh-negative in Thai pregnant women is about 0.31%[17], which is much lower than in European or North American population (about 15%)[8,18]. Due to this much lower prevalence, the proportion of Rh(D)-negative women carrying an Rh(D)-positive fetus is even higher than 60%. Routine antenatal RhIG administration at 26 to 28 weeks' gestation is employed for unsensitized Rh(D)-negative mothers. In addition, another dose is given within 72 hours after delivery if the neonate is Rh(D)-positive or if the result is not available.

The authors anticipated that due to the very low prevalence of this group of women, the awareness of this special management may be lower than expected. The primary objective of the present study was to determine the proportion of Rh(D)-negative pregnant women delivered at Siriraj Hospital, a university hospital, who received a complete course of RhIG. The secondary aims were to identify factors associated with the incomplete anti-D prophylaxis and to compare pregnancy and neonatal outcomes between women receiving and not receiving a complete RhIG course.

Materials and Methods

After approval from Siriraj Institutional Review Board (COA No. Si 273/2013), the medical records of unsensitized Rh(D)-negative pregnant women that delivered at Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University between January 2009 and April 2013 were reviewed. Women without antenatal care or with an incomplete medical record were excluded.

The sample size was calculated from data of a previous study[19], which documented 90% rate of complete course of RhIG administration. The current study used the level of confidence at 95%, the power at 90%, and the allowable error at 5%, resulting in 132 cases needed for analysis. Finally, the number needed for review including 10% attrition, thus was 146.

Patient data including age, parity, abortion history, place of antenatal care, gestational age of first prenatal care, gestational age of first visit at Siriraj Hospital, administration of RhIG, and pregnancy and neonatal outcomes were collected. Regarding places of antenatal care, women might have their entire antenatal care at various levels of medical facilities and then came to Siriraj Hospital for delivery only or might be referred for further antenatal care near term or for management of a particular condition. They might have had been previously cared for by a midwife, a general physician, or an obstetrician. Some women had their entire antenatal care at Siriraj Hospital since the first antenatal visit and had been cared for by obstetrician staff members or residents in training.

Cases receiving both RhIG at 26 to 28 weeks' gestation (antenatal dose) and within 72 hours after delivery (postpartum dose) were classified as complete group whereas cases missing one or both doses were classified as incomplete group. Women with the first antenatal care at later than 28 weeks' gestation were classified in "late antenatal care"

category. The proportion of Rh(D)-negative pregnant women who received a complete course of RhIG was determined. Possible reasons for missing antenatal or postnatal doses were obtained from the medical recorded. As routine antenatal RhIG administration was expected in all unsensitized Rh(D)-negative women and missing this dose would automatically render the women to achieve incomplete prophylaxis. Therefore, comparison between cases receiving and not receiving antenatal dose was considered more important. The authors primarily determined factors associated with omission of antenatal anti-D prophylaxis. Nevertheless, postpartum factors were also studied. Finally, pregnancy and neonatal outcomes were compared between groups. The data were analyzed using the PASW Statistics software, version 18.0 (SPSS Inc., Chicago, IL, USA). Mean, standard deviation, number, and percentage were used for descriptive data. For comparison between the two groups, chi-square or Fisher's exact test was used for categorical data and unpaired t-test was used for continuous data. A p-value of less than 0.05 was considered statistically significant. Odds ratios were used to express the risk magnitude.

Results

One hundred forty-six medical records of Rh(D)-negative pregnant women delivering at Siriraj Hospital were reviewed. Eight cases had incomplete data. Five cases were tested positive for Rh(D)-antibody since early pregnancy, therefore, already sensitized and were excluded. Altogether, 133 cases were available for analyses. Baseline population characteristics are shown in Table 1. Most cases (74.4%) were between 20 and 35 years old, 47.4% were nulliparous, about half had their first prenatal visit in the first trimester, approximately two third had their entire antenatal care at Siriraj Hospital, 91.7% of the cohort were delivered at term, and 51.9% of the cohort had a normal vaginal delivery.

Ninety-five women achieved both RhIG doses, accounting for 71.4%. Details of RhIG achievement of the cohort are shown in Table 2. Desire for tubal sterilization was noted in five women who did not receive any of the anti-D prophylaxis and in six women to whom the postpartum dose was not given. Supply shortage of RhIG was noted in three women who missed the antenatal dose. Another identifiable reason for not giving the postpartum dose to the women was positive anti-D antibody. Several women having antenatal RhIG administration before seeking antenatal care at Siriraj Hospital had not been tested for anti-D antibody. The test was performed on some of these women at Siriraj Hospital and nine of them had positive results. Three women with the positive result did not receive the postpartum RhIG dose. The last identifiable reason for withholding the postpartum RhIG dose was noted as "the mother had already missed the antenatal dose" in one case. The physician in charge probably had an idea that the postpartum dose would not be beneficial in this situation. No apparent reasons for incomplete anti-D prophylaxis were identified in several cases. Unawareness of the issue was most likely.

Table 3 compares possible associated factors with the missing of antenatal anti-D prophylaxis. The authors contemplated that, as RhIG was somewhat

Table 1. Baseline population characteristics (n=133)

Characteristics	n (%)
Maternal age (years)	
<20	13 (9.8)
≥20 to <35	99 (74.4)
≥35	21 (15.8)
Parity	
0	63 (47.4)
1	50 (37.6)
2	18 (13.5)
3	2 (1.5)
Abortion	
0	109 (82.0)
1	20 (15.0)
2	3 (2.3)
3	1 (0.7)
Trimester of first prenatal visit	
1st trimester	67 (50.4)
2nd trimester	49 (36.8)
3rd trimester	17 (12.8)
Antenatal care	
Siriraj Hospital only	90 (67.7)
Clinics and/or other hospitals only	18 (13.5)
Clinics and/or other hospitals then Siriraj Hospital	25 (18.8)
Gestational age at delivery, weeks	
≥28 to <34	3 (2.3)
≥34 to <37	8 (6.0)
≥37	122 (91.7)
Mode of delivery	
Normal vaginal delivery	69 (51.9)
Instrumental vaginal delivery	5 (3.7)
Cesarean delivery	59 (44.4)

Table 2. Details of RhIG (Rh immunoglobulin) achievement in the cohort

Antenatal dose	Postpartum dose	Number (n)	Note/reasons
✓	✓	95	- Complete (several cases with tubal sterilization) - May be more than needed
✓	×	9	- Tubal sterilization (n=6) - Positive anti-D antibody testing (n=3)
×	✓	19	- Supply shortage of RhIG (n=3) - Unknown reason (n=16) - Postpartum dose is still appropriate if not yet sensitized
×	×	10	- Tubal sterilization (n=5) - Unknown for antenatal dose missing (n=5) - Postpartum dose missing due to no antenatal dose (n=1) - Unknown reason for postpartum dose missing (n=4)

✓ Achievement of RhIG, × No achievement of RhIG

Table 3. Important factors reflecting the achievement of antenatal administration of anti-D prophylaxis

	With antenatal dose (n=104); n (%)	Without antenatal dose (n=29); n (%)	p-value
Maternal age (years)			0.87
Up to 25	34 (79.1)	9 (20.9)	
≥25	70 (77.8)	20 (22.2)	
Antenatal care			0.08
Siriraj Hospital	75 (83.3)	15 (16.7)	
Clinics and/or other hospitals	11 (61.1)	7 (38.9)	
Clinics and/or other hospitals then Siriraj Hospital	18 (72.0)	7 (28.0)	
Trimester of first prenatal visit			0.02*
1st trimester	54 (80.6)	13 (19.4)	
2nd trimester	41 (83.7)	8 (16.3)	
3rd trimester	9 (52.9)	8 (47.1)	
Trimester of first prenatal visit at Siriraj Hospital			<0.01**
1st trimester	36 (87.8)	5 (12.2)	
2nd trimester	40 (93.0)	3 (7.0)	
3rd trimester	17 (54.8)	14 (45.2)	
No	11 (61.1)	7 (38.9)	
Parity			0.06
Nulliparous	54 (85.7)	9 (14.3)	
Multiparous	50 (71.4)	20 (28.6)	
History of abortion			0.60
No	84 (77.1)	25 (22.9)	
Yes	20 (83.3)	4 (16.7)	

* First antenatal care at the 3rd trimester had an odds ratio of 2.6 (95% CI 1.4 to 4.9) compared to first antenatal care at the 1st/2nd trimesters for not achieving antenatal RhIG dose

** First antenatal care at Siriraj Hospital at the 3rd trimester or none at all had an odds ratio of 7.1 (95% CI 2.8 to 17.9) compared to first antenatal care at Siriraj Hospital at the 1st/2nd trimesters for not achieving antenatal RhIG dose

expensive, working-age women might be more able to afford it. However, there were no differences between women with the age up to 25 and older than 25 years old in achievement of antenatal RhIG. Neither did with the parity, history of abortion, and the venue of antenatal care. However, a slightly increasing trend was observed in venue of antenatal care. Approximately 60% of those who had the entire

Table 4. Pregnancy and neonatal outcomes between incomplete and complete groups

Pregnancy and neonatal outcomes	Anti-D Immunoglobulin administration; n (%)		p-value
	Complete group (n=95)	Incomplete group (n=38)	
Gestational age (weeks) at delivery; mean±SD	38.3±1.4	38.2±1.9	0.80
Route of delivery			0.35
Normal vaginal delivery	53 (76.8)	16 (23.2)	
Instrumental vaginal delivery	3 (60.0)	2 (40.0)	
Cesarean delivery	39 (66.1)	20 (33.9)	
Blood loss (mL); mean±SD	292±201	347±213	0.17
Postpartum hemorrhage			0.32
Yes	2 (50.0)	2 (50.0)	
No	93 (72.1)	36 (27.9)	
Blood replacement			0.49
Yes	1 (50.0)	1 (50.0)	
No	94 (71.8)	37 (28.2)	
Neonatal birth weight (g); mean±SD	3,036±398	2,941±481	0.25
5-minute Apgar score			-
Normal (≥7)	95 (71.4)	38 (28.6)	
Abnormal	0 (0.0)	0 (0.0)	
Neonatal jaundice			0.19
Hemolytic jaundice	2 (40.0)	3 (60.0)	
Physiological jaundice	50 (69.4)	22 (30.6)	
No	43 (76.8)	13 (23.2)	
Hydrops fetalis	0 (0.0)	0 (0.0)	-

SD=standard deviation

antenatal care at private clinics or other hospitals achieved the RhIG. Improvement in number (72%) had been observed in those who came to Siriraj Hospital after prior care at clinics or other hospitals. Lastly, more than 80% of women who had the entire antenatal care at Siriraj Hospital acquired the RhIG. Statistically significant factors associated with the achievement of antenatal RhIG were the trimester at the first prenatal visit and the trimester of the first visit to Siriraj Hospital. Because the antenatal RhIG dose is scheduled at 28 weeks' gestation, odds ratio (OR) of achieving this dose between the first antenatal visit at the first or second trimesters with the third trimester, and between the first visit at Siriraj Hospital at first or second trimesters with the third trimester or none. Late antenatal care had OR of 2.6 (95% CI 1.4 to 4.9) and late or no antenatal care at Siriraj Hospital had OR of 7.1 (95% CI 2.8 to 17.9) for not achieving the antenatal anti-D Ig administration.

Table 4 demonstrates the pregnancy outcomes between women in the incomplete and complete groups considering both antenatal and postpartum doses. The similarity of pregnancy outcomes between the two groups were not surprising as the effect of alloimmunization was not expected in the index pregnancy.

Discussion

Rh(D)-negative pregnant women are rarely found in our obstetric practice owing to the low incidence in Thailand[17]. Nevertheless, the antenatal and postpartum administrations of RhIG to all unsensitized Rh(D)-negative pregnant women with an Rh(D)-positive baby is still necessary to prevent maternal Rh alloimmunization and to decrease the risk of hemolytic disease of the fetus and newborn (HDFN) in subsequent pregnancies.

From the present study, the proportion of Rh(D)-negative pregnant women delivering at Siriraj Hospital who received a complete course of anti-D immunoglobulin was 71.4%. This number was lower than expected and might reflect certain misconceptions in management of this minor population. After scrutinizing the patients' details, the authors found

possible concepts for not giving the prophylaxis to these women as shown in Table 2. Desire for tubal sterilization was one of the known reasons for incomplete anti-D prophylaxis as mentioned in one study from Canada[20]. Some physicians believe that such cases would not be affected by any adverse event from Rh(D)-alloimmunization as there would be no subsequent pregnancies. The prophylaxis for women desiring tubal sterilization is not endorsed or refuted by the Royal College of Obstetricians and Gynaecologists guidelines[21]. The American College of Obstetricians and Gynecologists recommends Rh(D)-immunoprophylaxis regardless of the plan for sterilization because of the risk of failure rate of sterilization[3]. In addition, there could be a future situation where an Rh(D)-negative woman needs emergency blood transfusion while no Rh(D)-negative blood is available. If she is already sensitized, transfusion with Rh(D)-positive blood is contraindicated. On the other hand, some researchers comment about the low odds of these events and express some doubt about the cost-effectiveness in anti-D prophylaxis in women requiring tubal sterilization[22]. The authors suggest that in an area of low prevalence of Rh(D)-negative in general population, hence low availability of Rh(D)-negative blood donors, alloimmunization prevention for this group of women is a prudent practice.

A positive result of anti-D antibody testing is usually thought to be the result from the women being already sensitized and there is no benefit from anti-D prophylaxis. Instead, the surveillance for fetal anemia would be initiated. However, a thorough history taking about a prior administration of RhIG should be performed to distinguish between passive and active antibody[3]. If a passive immunity origin is likely, then the woman should be offered further anti-D prophylaxis according to the schedule.

In cases where the antenatal dose has been missed, the postpartum RhIG is still advisable. The majority of unsensitized Rh(D)-negative women without antenatal RhIG are still unsensitized during delivery and can achieve benefit from a postpartum RhIG dose. Indeed, the early stage of the study of alloimmunization prevention started with the postpartum RhIG administration[23,24].

RhIG accessibility complicates the issue of RhIG administration further. The cost of RhIG is rather high and some women cannot afford it. Occasional shortage of the RhIG is also another accessibility problem. Production of RhIG is currently from plasma of sensitized Rh(D)-negative people[2,25]. As the effectiveness of prevention of alloimmunization gets better, the source for RhIG dwindles. A synthetic RhIG could possibly solve the cost and availability problems. Several forms of human monoclonal anti-D-secreting cell lines are being developed[3,26].

Possible associated factors with incomplete prophylaxis were evaluated, emphasizing on the antenatal administration as it is the initial dose of the course and is recommended as routine for all unsensitized women. Table 3 shows that women who had their first prenatal visit at Siriraj Hospital in the first or second trimester were more likely to achieve the antenatal anti-D prophylaxis compared with those who had their first Siriraj Hospital visit in the third trimester or no visit. Although no significant association between the antenatal RhIG achievement and the place of antenatal care was found, an increasing trend was observed in the rates of this achievement from clinics or other hospitals, clinics or other hospitals then Siriraj Hospital, to Siriraj Hospital only at 61, 72, and 83%, respectively. The authors speculate that, due to the low incidence of Rh(D)-negative individuals, general awareness, and proper knowledge of how to take care of Rh-negative pregnant women are lacking. Even in Siriraj Hospital, a university hospital with a tertiary care facility and a referral center, which has more opportunities to see patients with rare conditions than other service health facilities, some physicians still had misconceptions in management of this group of patients as discussed earlier. Another important factor was the timing of the first antenatal care. Those who started their prenatal care at the third trimester tended to miss the antenatal anti-D administration. The authors also propose that the optimal timing of first antenatal visit should be emphasized. Additionally, the comprehensive understanding of health care providers including appropriate referral timing for optimal management might correct these problems.

Although the prevalence of cases receiving a complete course of anti-D prophylaxis in the present study was lower than expected, there were no significant differences in pregnancy and neonatal outcomes between the groups. Regarding neonatal jaundice, a previous study in Thai women revealed a correlation between anti-D prophylaxis and incidence of neonatal jaundice[17]. The number of women not receiving anti-D prophylaxis in the present study might be too small to reveal this difference.

The present study addresses the awareness of management of Thai Rh(D)-negative pregnant women. Problems of both public and health care providers'

awareness were raised. Various levels of health facilities were included. A number of study limitations are also appreciated. Firstly, the retrospective design prohibited the identification of reasons for missing anti-D doses in several cases. Health care providers' factors were not fully available. Secondly, neonatal Rh blood typing before consideration of maternal postpartum RhIG administration was not routinely performed. Neonatal Rh(D)-status determination could enhance the quality of management for Rh(D)-negative women as the RhIG could be more appropriately allocated to suitable women[2]. If neonatal blood type had been taken into account, the number of women receiving an "appropriate" RhIG administration might have been different. Finally, data were collected from 2009 to 2013. However, the unawareness problems are still evident in the current practice in the authors' point of view.

Conclusion

In summary, the prevalence of unsensitized Rh(D)-negative pregnant women that delivered at Siriraj Hospital who received a complete course of anti-D prophylaxis was 71.4%. Pregnancy and neonatal outcomes of the index pregnancy were not different between the groups. The unawareness of Rh(D)-negative issues of all healthcare provider levels and of the women appeared to be associated with unsuccessful Rh(D)-alloimmunization prophylaxis.

What is already known on this topic?

Unsensitized Rh(D)-negative pregnant women should obtain a special attention in alloimmunization prophylaxis. In area where the group of population are relatively prevalent, a complete prophylaxis course is established in 90% of women.

What this study adds?

Due to the very low prevalence of this group of population in Thailand, the awareness of the women and of the healthcare providers regarding this issue are lower than expected. Women should be informed of the importance of early antenatal care and alloimmunization prevention. In addition, even in a university hospital, several misconceptions exist among healthcare providers that need correction.

Conflicts of interest

The authors declare no conflicts of interest.

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