Fetomaternal hemorrhage in normal vaginal delivery and in delivery by cesarean section

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BACKGROUND: The objective was to determine the incidence and volume of fetomaternal hemorrhage (FMH) in normal vaginal delivery and in delivery by cesarean section. Determination of these variables would enable optimalization of guidelines for D alloimmunization prophylaxis.

STUDY DESIGN AND METHODS: In a prospective cohort study, a total of 3457 examinations were performed, 2413 after normal vaginal delivery and 1044 after cesarean delivery. FMH was assessed by flow cytometry. (FMH is fetal red blood cell [RBC] volume; fetal blood volume is double [expected fetal hematocrit is 50%].)

RESULTS: The fetal RBC volume diagnosed in maternal circulation after delivery ranged from insignificant FMH of not more than 0.1 mL to excessive FMH of 65.9 mL (median, 0.7; mean, 0.78; SD, 1.48). FMH of more than 2.5 mL (immunoglobulin [Ig] G anti-D insufficient dose 50 μg) was observed in 1.4% (49/3457) and excessive volumes of FMH of more than 5 mL (insufficient dose, 100 μg) in 0.29% (10/3457). Delivery by cesarean section presented a higher risk of incidence of FMH of more than 2.5 mL (odds ratio, 2.2; $p = 0.004$) when compared with normal vaginal delivery. It did not, however, present a significant risk factor for the incidence of excessive volumes of FMH of more than 5 mL.

CONCLUSION: During normal vaginal delivery as well as during delivery by cesarean section, FMH of less than 5 mL occurs in the great majority of cases, and thus for the prevention of D alloimmunization, an IgG anti-D dose of 100 μg should be sufficient. Contrarily, only rarely does greater FMH occur and delivery by cesarean section does not present a risk factor.

When performing D alloimmunization prophylaxis in D– women after delivery of an D+ child, RhIG is often administered in a standard dose that is much higher than truly necessary. To precisely determine the dose of immunoglobulin (Ig) G anti-D needed to prevent D alloimmunization, it is necessary to determine the volume of incompatible fetal red blood cells (RBCs) that have entered the maternal circulation. If the volume of fetomaternal hemorrhage (FMH) is not assessed, usually an IgG anti-D dose of 100 to 300 μg is administered intramuscularly. The effectiveness of administering a standard dose of more than 100 μg to all women has not been demonstrated.[1-10] The goal of further studies should be establishing optimal doses of IgG anti-D. The effectiveness of immediate administration of lower doses of IgG anti-D in combination with screening of the volume of FMH and

ABBREVIATIONS: CA = carbonic anhydrase; FMH(s) = fetomaternal hemorrhage(s) (fetal red blood cell volume in maternal circulation); HbF = hemoglobin F.

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subsequent supplementation of IgG anti-D in case of necessity should be compared with the effectiveness of administering a single larger dose of IgG anti-D to everyone.[1,11]

Working hypothesis

IgG anti-D in a dose of 10 μg administered intramuscularly should cover 0.5 mL of fetal D+ RBCs or 1 mL of whole fetal blood.[1,11] FMH is the fetal RBC volume; fetal blood volume is double (expected fetal hematocrit [Hct] is 50%). In the great majority of deliveries, less than 2.5 mL of fetal RBCs (5 mL of whole fetal blood, sufficient dose of IgG anti-D 50 μg) enter the maternal circulation. Contrarily, only rarely does FMH exceeding 5 mL (10 mL of whole fetal blood, sufficient dose of IgG anti-D, 100 μg) occur during delivery. There is an increased risk of fetal RBCs entering the maternal circulation in deliveries by cesarean section.

The aim of this work was to determine the incidence and volume of FMH in normal vaginal delivery and in delivery by cesarean section. Determination of these variables would enable optimalization of guidelines for D alloimmunization prophylaxis.

MATERIALS AND METHODS

All assessments of FMH were performed at the University Hospitals in Olomouc and Ostrava in the years 2009 and 2010. The study included all pregnant women who did not have a clinically significant RBC alloantibody diagnosed during pregnancy. The tested women signed an informed consent form.

A total of 3457 examinations were performed in a prospective cohort study. The volume of FMH after normal vaginal delivery (control group, n = 2413) and after delivery by cesarean section (risk group, n = 1044) was assessed by flow cytometers (BD FACSCanto, Becton Dickinson International, Heidelberg, Germany; and CYTOMICS-FC500, Beckman Coulter, Prague, Czech Republic). All operative deliveries (cesarean section, vacuum extraction, forceps delivery), stillbirths, multiple pregnancies, and deliveries with manual placental evacuation and/or instrumental revision of the uterus were excluded from the control group (normal vaginal delivery).

The risk group (delivery by cesarean section) was further divided into subgroups: placental abruption (n = 12), singleton pregnancy (n = 911), and twin pregnancy (n = 121). All cesarean sections were performed using the same technique and instrumental revision of the uterine cavity was always performed after delivery of the placenta.

Sample collection

FMH assessment was performed from a venous blood sample from the mother collected into an ethylenediaminetetraacetate or heparin-treated test tube. A blood sample was taken from the mother 1 to 2 hours after delivery. A sample of 0.5 to 1.0 mL of venous blood was collected. Blood samples were stored at 2 to 8°C and processed within 24 hours of blood collection.

Laboratory processing

A fetal cell counting kit for the diagnosis of fetomaternal transfusion by flow cytometry (Fetal Cell Count, IQP-379, IQ Products, Groningen, the Netherlands) is designated to differentiate and quantitate human fetal RBCs in maternal blood. It is based on a sensitive o and precise flow cytometric technique that allows dual fluorescent detection of two intracellular antigens—hemoglobin F (HbF) and carbonic anhydrase (CA). The method is based on using a combination of two antibodies. The first is aimed against HbF, which is found in fetal RBCs, and in a small amount is also present in adult RBCs (F cells). The second antibody is aimed against CA, an enzyme present in adult RBCs and in very late stages of fetal cells. Fetal RBCs are detected by their bright HbF expression in combination with a complete lack of CA expression. In contrast, maternal RBCs have no HbF signal in combination with bright CA expression.

The procedure was performed according to the instructions given in the kit manual. A commercially supplied kit (FETALtrol, IQ Products) was used for quality control (QC) testing, which included three controls with defined ranges of measured values. All tested samples were measured against a negative control (nonlabeled sample). External QC was performed on a common sample to ensure standardization.

Calculation of the total volume of fetal RBCs entering maternal circulation

According to the Scientific Subcommittee of the Australian and New Zealand Society of Blood Transfusion,[12] FMH is calculated as

$$\text{FMH (mL)} = (1800 \times 1.22 \times E_F)/100.000,$$

where FMH is the fetal RBC volume in maternal circulation (mL; fetal blood volume is double [expected fetal Hct is 50%]); 1800 represents the maternal RBC volume, approximately 1800 mL; 1.22 indicates that the fetal RBCs are approximately 22% larger; and E_F is the fetal RBC number (HbF positive). A total number of 100,000 RBCs were evaluated. All formulae are based on approximations and estimates, even using the more accurate method of flow cytometry to enumerate cells.

Statistical analysis

The Shapiro-Wilk tests showed that the data do not have a normal distribution, which is why nonparametric methods were used for data processing. The differences

between control and experimental group in numeric variables (maternal age, gestational age, FMH) were compared using the Mann-Whitney U test. Mutual correlation of these variables was verified by calculation of the Spearman correlation coefficient. Comparison of control and experimental groups in the incidence of FMH (FMH of >1.8, >2.1, >2.5, and >5 mL) was performed using Fisher's exact test and odds ratio (OR) was calculated. All tests were performed at the 0.05 level of significance. Variable distribution was graphically represented by histograms and box graphs. Statistical software (SPSS, Version 15, SPSS, Inc., Chicago, IL) was used for statistical processing.

RESULTS

The comparison between maternal age and gestational age in control (normal vaginal delivery, n = 2413) and risk group (delivery by cesarean section, n = 1044) is presented in Table 1. Due to the large size of the patient set, even small differences seem significant, although they are not clinically significant.

The volume of fetal RBCs diagnosed in maternal circulation after delivery ranged from insignificant FMH of not more than 0.1 mL to excessive FMH of 65.9 mL (median, 0.7; mean, 0.78; SD, 1.48). Comparison of FMH values in control and risk groups is shown in Table 1.

In the control group (normal vaginal delivery) FMH of 1.8 mL (95.0 percentile) and FMH of 2.1 mL (97.5 percentile) were calculated. Subsequently, volumes of FMH of 2.5 mL (sufficient dose of IgG anti-D of 50 μg) and FMH of 5 mL (sufficient dose of IgG anti-D of 100 μg) were determined. The incidence of high volumes of FMH (>1.8, >2.1, and >2.5 mL) and excessive volumes (FMH > 5 mL, IgG anti-D insufficient dose of 100 μg) were then compared between the control and risk group (delivery by cesarean section; Fig. 1).

Our results show that delivery by cesarean section presents an increased risk for the incidence of high volumes of FMH of more than 1.8 mL (OR, 1.7; p = 0.001), FMH of more than 2.1 mL (OR, 1.8; p = 0.002), and FMH of more than 2.5 mL (OR, 2.2; p = 0.004). It does not, however, present a significant risk factor for the incidence of excessive volumes of FMH of more than 5 mL (Table 2).

FMH of 2.5 mL or less (sufficient dose of IgG anti-D, 50 μg) was present in 99.0% cases of normal vaginal deliveries (2388/2413). FMH of not more than 5 mL (sufficient dose of IgG anti-D, 100 μg) was present in 99.8% cases (2708/2413). In the remaining five cases, the FMHs were 5.1, 12.0, 12.4, 30.9, and 65.9 mL (11, 24, 25, 62, and 132 mL of whole fetal blood), and the sufficient doses of IgG anti-D were 110, 240, 250, 620, and 1320 μg (Fig. 1).

FMH of not more than 2.5 mL (sufficient dose of IgG anti-D, 50 μg) was present in 97.7% cases of deliveries by cesarean section (1021/1045). FMH of not more than 5 mL (sufficient dose of IgG anti-D, 100 μg) was present in 99.5% cases (1040/1045). In the remaining five cases, the FMHs were 5.1, 7.7, 15.4, 16.3, and 18.2 mL (11, 16, 31, 33, and 37 mL of whole fetal blood), and the sufficient doses of IgG anti-D were 110, 160, 310, 330, and 370 μg. All of these cases were deliveries by cesarean section in singleton pregnancies without placental abruption (Fig. 1).

TABLE 1. Comparison of control (normal vaginal delivery) and risk group (delivery by cesarean section) in numeric variables: maternal age, gestational age, and volume of FMH after delivery*

Characteristics	Control group, normal vaginal delivery (n = 2413)	Risk group, cesarean section (n = 1044)	p value
Maternal age (years)			
Minimum	15	17	0.001†
Maximum	47	44	
Median	30	30	
Mean	29.4	30.1	
SD	4.8	4.9	
Gestational age (days)			
Minimum	168	169	<0.0001†
Maximum	300	300	
Median	278	271	
Mean	275.3	265.9	
SD	12.9	21.0	
FMH (mL)			
Minimum	0	0	0.693†
Maximum	65.9	18.2	
Median	0.7	0.6	
Mean	0.77	0.80	
SD	1.61	1.12	

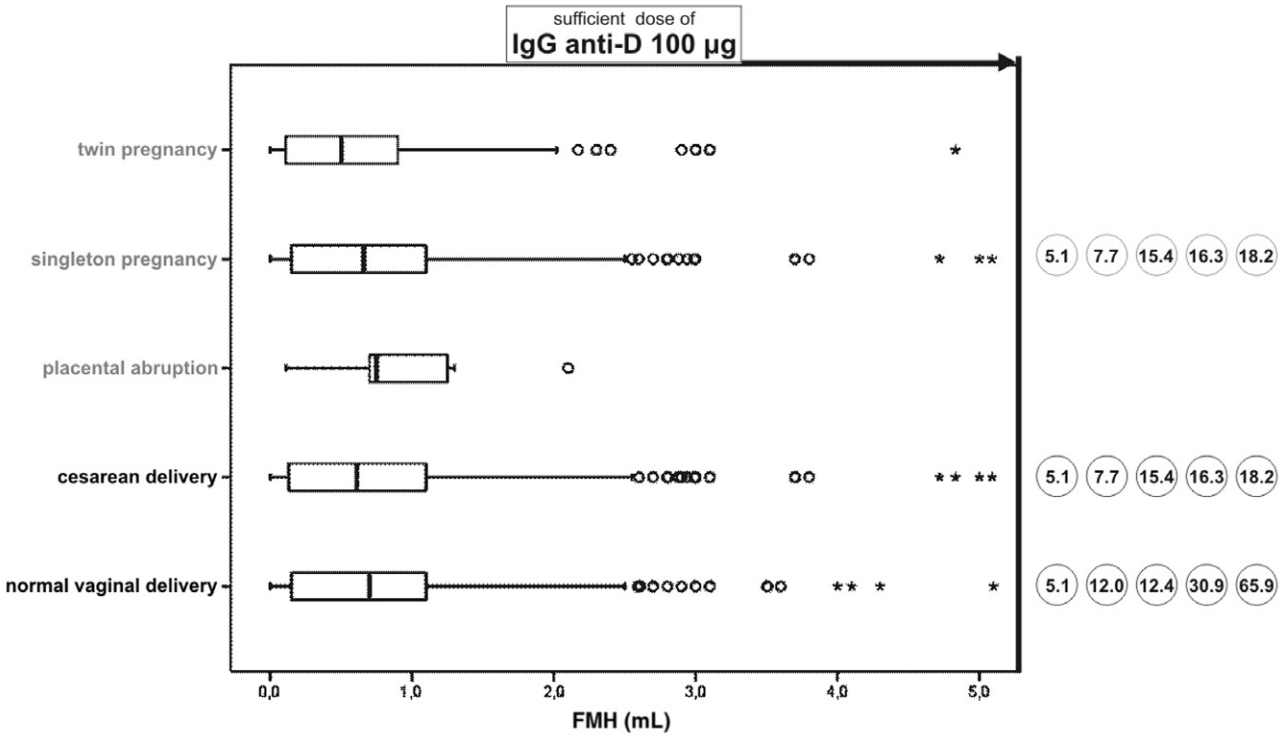
* FMH is fetal RBC volume; fetal blood volume is double (expected fetal Hct is 50%).
† Mann-Whitney U test.

DISCUSSION

It is generally accepted that IgG anti-D in a dose of 10 μg administered intramuscularly should cover 0.5 mL of fetal D+ RBCs or 1 mL of whole fetal blood.[1,11] This means that 50 μg (125 or 250 μg) of IgG anti-D should prevent alloimmunization after FMH of 5 mL (12.5 or 25 mL) of whole fetal blood.

In approximately 1.5% of deliveries, FMH exceeding 5 mL of whole fetal blood occurs, in only 1% of deliveries the fetal blood volume entering maternal circulation exceeds 12.5 mL, and in only 0.5% of deliveries it exceeds 25 mL.[13-16] However, in nearly 50% of all cases no risk factor is present.[15-17]

A number of countries therefore recommend assessing the volume of FMH after delivery to specify the dose of IgG anti-D necessary to prevent D alloimmunization of the mother



		FMH				
	Total n	≤ 1.8 ml n	> 1.8 ml n (%)	> 2.1 ml n (%)	> 2.5 ml n (%)	**> 5 ml** n (%)
normal vaginal delivery	2413	2309	104 (4.3)	55 (2.3)	25 (1)	5 (0.2)
cesarean delivery	1044	971	73 (7)	43 (4.1)	24 (2.3)	5 (0.5)
placental abruption	12	11	1 (8.3)	0	0	0
singleton pregnancy	911	847	64 (7)	36 (4)	20 (2.2)	5 (0.5)
twin pregnancy	121	111	10 (8.3)	7 (5.8)	4 (3.3)	0

Fig. 1. Distribution of the volume of FMH assessed after delivery in control (normal vaginal delivery) and risk group. Risk group (delivery by cesarean section) is further divided into subgroups: placental abruption, singleton, and twin pregnancies. If FMH is not more than 5 mL, a sufficient dose of IgG anti-D is 100 µg (thick line). Excessive volumes of FMH of more than 5 mL (IgG anti-D insufficient dose, 100 µg) are presented in absolute values (mL) in circles beside the graph.

(Australia, Canada, United States, Great Britain, France, Ireland, Czech Republic).[5-10] After delivery, the volume of FMH should be assessed.

Increased risk of fetal RBCs entering maternal circulation occurs during delivery by cesarean section,[18,19] stillbirth,[16] traumatic vaginal delivery, multiple birth delivery, delivery with signs of premature separation of the placenta, delivery with pathology in the third stage of labor, and so forth.

In our study, FMH exceeding 5 mL of whole fetal blood (sufficient dose of IgG anti-D, 50 µg) was diagnosed after delivery in 1.4% of cases (49/3457), after normal vaginal delivery in 1.0% (25/2413), and after delivery by cesarean section in 2.3% (24/1044), and delivery by cesarean section represented a significant risk factor. FMH exceeding 12.5 mL after delivery (sufficient dose of IgG anti-D, 125 µg) was present in only 0.23% cases (8/3457), after normal vaginal delivery in 0.17% (4/2413), and after delivery by cesarean section in 0.38% (4/1044), and delivery by cesarean section no longer presented a significant risk factor. FMH exceeding 25 mL after delivery (sufficient dose of IgG anti-D, 250 µg) was present in 0.17% cases (6/3457), after normal vaginal delivery in 0.12% (3/2423), and after delivery by cesarean section in 0.28% (3/1044), and delivery by cesarean section also no longer presented a significant risk factor. In our study, we noted a lower incidence of FMH exceeding 12.5 and 25 mL of whole fetal blood after delivery. In previous studies, however, the volume of FMH was assessed using the Kleihauer-Betke test, which compared to flow cytometry is less accurate and allows only semiquantitative determination of FMH volume.[20-22]

TABLE 2. Comparison of control (normal vaginal delivery) and risk group in incidence of elevated levels of FMH (>1.8, >2.1, >2.5, and >5 mL)*

FMH (mL)	Number (%)	Control group, n (%)	95% CI			p value
			OR	Lower	Upper	
CD						
>1.8	73/1044 (7)	104/2413 (4.3)	1.7	1.2	2.3	0.001
>2.1	43/1044 (4.1)	55/2413 (2.3)	1.8	1.2	2.8	0.003
>2.5	24/1044 (2.3)	25/2413 (1)	2.2	1.3	4	0.004
>5	5/1044 (0.5)	5/2413 (0.2)	2.3	0.7	8	0.172
CD—placental abruption						
>1.8	1/12 (8.3)	104/2413 (4.3)	2	0.2	15.8	0.413
>2.1	0					
>2.5						
>5						
CD—singleton pregnancy						
>1.8	64/911 (7)	104/2413 (4.3)	1.7	1.2	2.3	0.001
>2.1	36/911 (4)	55/2413 (2.3)	1.8	1.2	2.7	0.008
>2.5	20/911 (2.2)	25/2413 (1)	2.1	1.2	3.9	0.01
>5	5/911 (0.5)	5/2413 (0.2)	2.7	0.8	9.2	0.1
CD—twin pregnancy						
>1.8	10/121 (8.3)	104/2413 (4.3)	2	1	3.9	0.041
>2.1	7/121 (5.8)	55/2413 (2.3)	2.6	1.2	5.9	0.026
>2.5	4/121 (3.3)	25/2413 (1)	3.3	1.1	9.5	0.47
>5	0					

* Risk group (delivery by cesarean section) is further divided into subgroups: placental abruption, singleton, and twin pregnancies. If FMH is not more than 5 mL, a sufficient dose of IgG anti-D is 100 μg.
CD = cesarean delivery.

The recent prospective study of Uriel and colleagues[19,23] used flow cytometry to determine the volume of FMH during delivery; however, they describe only a small set of patients (n = 346) who were further divided into three groups: vaginal delivery (n = 196), vacuum extraction or forceps delivery (n = 59), and delivery by cesarean section (n = 55). The volume of FMH during delivery ranged from not more than 0.1 to 25.2 mL (mean, 0.25 mL; SD, 1.58 mL), vaginal delivery (mean, 0.12 mL; SD, 0.51 mL; median, 0.03 mL), delivery by cesarean section (mean, 0.67 mL; SD, 3.44 mL; median, 0.03 mL), the difference was statistically significant (p 0.001). A higher risk of incidence of FMH of more than 2.5 mL in deliveries by cesarean section was also not determined; however, the set of patients was small, and in this study, the volume of fetal RBCs assessed in maternal circulation immediately before delivery was subtracted from the FMH assessed after delivery. As such, this procedure has no clinical significance for D alloimmunization prophylaxis and for calculation of the sufficient dose of IgG anti-D.

RhIG, given within 72 hours after childbirth, reduces the risk of D alloimmunization in D– women who have given birth to a D+ infant and benefits were seen regardless of the ABO status of the mother and baby. IgG anti-D lowered the incidence of D alloimmunization 6 months after birth (relative risk, 0.04; 95% CI, 0.02-0.06) and in a subsequent pregnancy (relative risk, 0.12, 95% confidence interval, 0.07-0.23). However, the evidence on the optimal dose is limited. Higher doses (up to 200 μg) were more effective than lower doses (up to 50 μg) in preventing D alloimmunization in a subsequent pregnancy, but the effectiveness of administering a standard dose of over 100 μg to all women has not been demonstrated.[1]

In the vast majority of cases of normal vaginal deliveries as well as deliveries by cesarean section, FMH occurs in a fetal RBC volume of less than 5 mL (10-mL fetal blood volume) and therefore an IgG anti-D dose of 100 μg should be sufficient for the prevention of D alloimmunization. Contrarily, greater FMH only occurs rarely and delivery by cesarean section does not present a risk factor, but it is only possible to diagnose these few cases of excessive FMH by screening for the volume of FMH.

Sole administration of a standard dose of more than 100 μg to all seems to be ineffective. Immediate administration of a smaller dose of IgG anti-D (50 μg) in combination with screening for the volume of FMH and subsequent additional administration of IgG anti-D if necessary, rather than single administration of a standard higher dose (100 μg) to all, seems to be more effective. The optimal and economically most effective would be to apply a 250-μg dose of anti-D in the 28th week of gestation to all D– women with no anti-D alloantibodies, after the birth of an D+ child the fetal RBC volume that entered maternal circulation should be assessed, and only in indicated cases should a sufficient dose of IgG anti-D be administered postpartum.

Another possibility for improving effectiveness is an assessment of *RHD* genotype of the fetus from free fetal DNA circulating in maternal peripheral blood at the

beginning of pregnancy of a D– woman; if the fetus is *RHD*–, it is unnecessary to administer IgG anti-D at 28 weeks' gestation and to assess D fenotype of the baby after delivery; additionally it is not necessary to perform D alloimmunization prevention in other cases of potentially sensitizing events during pregnancy.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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