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Demographic and Behavioral Predictors of Severe Fetomaternal Hemorrhage: a Case-Control Study

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Abstract

Background—Fetomaternal hemorrhage (FMH) signifies failure of the placental barrier with whole blood transfer. Fetal anemia following FMH is associated with significant morbidity and mortality. If FMH is identified early, fetal anemia can be treated to minimize adverse outcomes. Risk factors for FMH are not known, limiting efforts to provide targeted screening for FMH.

Objective—To identify maternal and/or pregnancy characteristics associated with FMH that are recognizable prior to fetal morbidity.

Methods—This is the first published case-control study of FMH. Cases were identified from a prospectively maintained database of all hospital births between 1988 and 2010. Each case was matched to four controls by date and time of birth, allowing for assessment of a wide range of clinical and demographic data. Logistic regression modeling was used to assess the association between demographic and clinical characteristics and diagnosis of FMH.

Results—23 mother-baby pairs impacted by FMH and 92 matched controls were evaluated. Compared to controls, case mothers were more likely to have private insurance, work outside the home and at night during pregnancy. Cases were more likely to be delivered preterm, but preterm labor was not more common among cases. There was no difference in race/ethnicity of cases compared to controls.

Conclusions and Relevance—Severe FMH is associated with significant morbidity and mortality of the affected neonate. Women with FMH were more likely to work outside the home during pregnancy than women with normal pregnancies. This finding has implications for third-trimester screening of pregnant women who work in strenuous fields.

Keywords

fetomaternal hemorrhage; neonatal anemia; perinatal epidemiology; case-control

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BACKGROUND

Fetomaternal hemorrhage (FMH) is a poorly understood condition in which fetal whole blood crosses the placenta into the maternal circulation. This is most commonly a silent process in which a woman with a seemingly normal pregnancy does not experience symptoms related to the transfer of fetal blood.^[1] The fetus, however, can face significant harm if blood loss is substantial. Small volume fetal to maternal blood transfer can be detected following most births. Small volume blood transfer is problematic only if maternal alloimmunization results.^[2] Severe FMH, characterized by large volume fetal blood loss, is associated with high rates of neonatal morbidity and mortality.^[1, 3–5] The clinical impact of FMH depends on the amount of blood transferred and the timeframe over which the hemorrhage occurs.^[1, 6, 7] Although recent data indicate that placental inflammation due to infection may be implicated in FMH,^[8] the pathophysiology of the condition is poorly understood.

Fetomaternal hemorrhage is most commonly diagnosed via the Kleihauer-Betke acid elution test (KB) or flow cytometry.^[9] Both tests quantify fetal cells in a maternal blood sample. Retrospective studies in large populations document an incidence of FMH diagnosis of 1–2/10,000 live births.^[4, 5, 10] The true incidence of clinically significant FMH is likely much higher, however, as FMH testing is underutilized in clinical practice.^[4, 5, 11] Currently, testing for FMH after live birth occurs when significant fetal or neonatal anemia or is recognized.^[1, 2, 12, 13] Symptomatic fetal or neonatal anemia -- as evidenced by decreased fetal movement, sinusoidal fetal heart tracing, fetal or neonatal distress, or neonatal pallor -- are late consequences of severe FMH.

A number of risk factors have been suggested as predisposing factors for FMH (Table 1). Of these, placental abruption, abdominal trauma, and the presence of placental tumors carry the most support in retrospective studies and are physiologically plausible. FMH must follow a breach of the trophoblast, and it is not difficult to see how abruption, trauma, or tumor invasion could be associated with fetal blood transfer. These risk factors are not present in the majority of cases of severe FMH, however, and commonly occur without FMH as a notable sequellae.^[1, 5, 6, 10, 14–16] No prospective epidemiologic study of FMH has been completed in the general pregnant population, and predisposing factors for FMH are unknown in the vast majority of identified cases.^[1, 2, 15, 16]

Early recognition of large volume FMH can significantly reduce morbidity and mortality. Intrauterine transfusions, early operative delivery, and aggressive neonatal transfusion are viable options to prevent tissue hypoxia and end-organ damage due to anemia.^[1, 3, 17–19] Universal screening for FMH is not practical due to the cost of laboratory testing. As clinical and epidemiologic risk factors for FMH are unknown, targeted testing cannot be undertaken.

In this study, we investigated risk factors for FMH using a retrospective case-control approach. We hypothesize that distinct epidemiological and/or early clinical predictors of FMH can be identified. Our goal was to define a sub-population of pregnant women who

could benefit from targeted early screening for FMH and intervention prior to long-term adverse fetal/neonatal events related to severe anemia.

METHODS

This is a retrospective case-control study. Case participants were defined as live-birth mother-baby pairs where FMH was diagnosed by KB testing during the immediate postpartum period demonstrating 0.1mL or more of fetal blood in a maternal blood specimen. Cases were identified from a database of clinical information prospectively maintained for all patients admitted to the level I–IV newborn nurseries at our institution, as described previously.^[4] Neonates with hematocrit one standard deviation below the mean for gestational age within the first 4 hours of life were considered to have congenital anemia. The medical records for these patients were reviewed to identify those with associated FMH. Controls were selected from the general birth population at our institution. Controls were selected in a 4:1 ratio to cases by day and hour of birth; controls were the two births immediately prior to and immediately following the case subject. Cases and controls were born at our urban quaternary care medical center between January 1, 1988 and December 31, 2010. Medical records from the index pregnancy and perinatal admission were abstracted for a broad range of demographic and clinical information. All diagnoses included in the analyses were determined to be present if an attending physician note or problem list in the maternal obstetric or neonatal medical record noted the condition. Maternal diagnoses present during the index pregnancy, maternal procedures performed within 17 weeks of delivery (the lifespan of a fetal reticulocyte in the maternal circulation^[20]) and all neonatal diagnoses and procedures present during the birth hospitalization were included in analyses. Our hospital records included detailed demographic information on factors including age, race, insurance provider, and employment type and status.

Descriptive statistics included mean $\pm$ standard deviation for normally distributed data and median (interquartile range) for skewed data. Student's t-test, Pearson χ -square, Fisher's exact test, or Wilcoxon rank sum test were performed as appropriate. Correlations were assessed with Spearman's ρ . Bivariable logistic regression was used to obtain odds ratios and 95% confidence intervals for the association between individual case status and risk factor variables. Multivariable logistic regression was performed including potential causative factors significant in bivariable analyses. A 2-tailed α level of 0.05 was used for significance. For calculation of odds ratios involving cells with 0 observations, the 0.5 zero-cell correction was applied.^[21] Statistical analyses were conducted using SPSS software, version 22 (IBM, Armonk, NY, USA). This study was approved by the Mount Sinai Program for the Protection of Human Subjects.

RESULTS

Of 124,738 eligible mother-baby pairs, 23 (1.8 per 10,000) were diagnosed with FMH. Table 2 shows demographic and clinical information about the pregnancy that was known before the onset of labor or became apparent during labor and delivery. There were no differences in maternal race, age, or maternal hemoglobin or hematocrit prior to delivery between cases

and controls. There was not a significant difference in either the number of twin pregnancies or the incidence of invasive procedures during pregnancy (including amniocentesis and cephalic version) between cases and controls. Mothers of cases and controls were equally likely to have diabetes during pregnancy, experience physical trauma or vaginal bleeding during pregnancy, have pre-eclampsia, hypercoagulability, urinary tract infection, placental tumors or chorioamnionitis. There was no difference in the incidence of uterine anomaly, fibroids, or oligohydramnios between cases and controls. Use of drugs or tobacco reported during pregnancy was similar between the two groups. As reported in previous studies of FMH, abnormal fetal heart tracing, sinusoidal fetal heart tracing specifically, and placental abruption were more common in cases than controls ($p=0.005 - 0.043$). Female gender of the fetus was also weakly associated with FMH ($p=0.045$). Cases were more likely than controls to be born via emergent Cesarean delivery and to require resuscitation in the delivery room ($p<0.001$). They had lower Apgar scores at 1 or 5 minutes ($p<0.001$). Cases were delivered at an earlier median gestational age than controls (37.1 (35.0, 39.5) vs 39.3 (38.3, 40.3) weeks) and were more likely to be delivered preterm (less than 37 weeks gestational age) than controls ($p<0.001$). The median birth weight of cases was therefore lower than of controls (2.75 (2.35, 3.21) vs 3.42 (3.20, 3.67)), but small for gestational age birth was not more common among cases.

Mothers of cases were more likely to work during pregnancy ($p=0.036$) and to work at night ($p=0.035$). As some of the case mothers were night shift medical workers, work specifically in the medical field was evaluated, but was not a significant predictor of FMH. Private insurance was also associated with diagnosis of FMH ($p=0.012$). Maternal employment status during pregnancy was correlated with use of private insurance ($p=0.7$) and with Caucasian ethnicity ($p=0.4$). Multivariable models adjusting for non-correlated factors implicated in univariable analyses confirmed a significant association between maternal work during pregnancy and FMH (Table 3).

Table 4 shows clinical outcome information for cases and controls pertaining to the neonatal clinical course. As expected based on delivery room characteristics, cases were more likely than controls to be admitted to the neonatal intensive care unit (NICU) as opposed to the level I nursery ($p<0.001$). Mean hemoglobin at NICU admission was 7.2 ± 2.8 mg/dL for cases and 16.8 ± 2.4 mg/dL for controls ($p<0.001$). Case neonates were significantly more likely to undergo invasive procedures and had more frequent diagnosis of respiratory distress syndrome, hypotension, and persistence of the fetal circulation than controls ($p<0.001$ to 0.002). Cases were more likely to die in the neonatal period than controls ($p=0.03$).

DISCUSSION

Previous attempts to define the epidemiology of FMH have relied on large administrative databases without access to detailed case-level clinical and demographic data, have focused exclusively on Rh- women carrying Rh+ fetuses, and/or have focused on infant outcomes rather than prenatal risk-factor identification.[^{5, 6, 10, 14}] Additional reports of FMH are limited to case studies and small series, and have not broadened the understanding of predisposing clinical or demographic factors for the majority of cases of FMH.[^{7, 16, 22}] A recent study of placental pathology indicating that placental inflammation may play a role in

FMH^[8] provides a promising novel lead that deserves further evaluation for clinical significance.

We report a case-control study of FMH based on 23 years of experience with FMH at our institution. Our population demonstrated an incidence of FMH consistent with previous large population-based studies.^[5, 10] Although based on a modest number of cases of FMH, this study clarifies previously noted associations between FMH and race and socioeconomic status.^[5] Specifically, at our institution where a racially diverse patient population is cared for by a single neonatology group, we found no evidence of an association between race and FMH. We did, however find statistically significant associations between FMH and the correlated factors of maternal employment and private insurance. The effect size for this association was strongest in multivariable analysis adjusted for preterm delivery and gender of the fetus. Although the association between night shift work and FMH was not seen in multivariable analysis, this may be related to the small number of night shift workers seen in this study. In aggregate, our findings raise the possibility that strenuous work during pregnancy may be a risk factor for FMH. Previous studies of FMH have shown that abdominal trauma, a rare event during pregnancy, is associated with FMH. It is possible that, in some situations, women who undertake physically demanding work during pregnancy may be at risk for FMH by a similar mechanism.

Previous studies of FMH have not considered employment status or employment hours in analyses. Maternal employment status may have been an unmeasured confounder in previous studies of FMH. Although maternal work history is not often recorded in administrative databases, we had access to this information in our chart abstraction. In contrast, race and insurance payer, which are correlated with each other and with employment status, are often recorded in administrative databases such as those used in previous population-based studies of FMH. If private insurance status served as a marker of maternal employment rather than as a marker of socioeconomic status broadly, previously noted association between socioeconomic status and FMH seen in previous studies may represent misclassification of an actual association between maternal work history and FMH. In our study, we had access to specific information on maternal employment, and could separate women who worked during pregnancy from those who were homemakers, students, or unemployed but nonetheless covered by private insurance.

Our study also addressed the role of race and ethnicity in FMH. Our institution has a diverse patient mix; our study population was 40% Black or Hispanic. All patients admitted to our institution's NICU are cared for by the same physician group with uniform diagnostic and practice guidelines regardless of race or health insurance status. In this environment, the previously seen association between race and FMH was not significant. This supports our hypothesis that previously seen associations between race and FMH in population-based studies relying on administrative data were related to access to care and geographic practice patterns, rather than biology.^[5]

Our study also clarifies a previously documented association between preterm birth and FMH.^[5] As we found no association between preterm labor and FMH, we suggest preterm birth in our case population may have been a consequence of FMH in which fetal distress

prompted early delivery. This is in contrast to a possible association between spontaneous preterm birth and FMH.

As a single center retrospective study, our analyses have certain limitations. The absolute number of cases of FMH seen was small, so some analyses were underpowered. Although racially and socioeconomically diverse, our urban patient population may not be fully representative of other patient populations. As in most published studies of FMH, diagnosis of FMH in our study relied on a clinical diagnosis made in real time. As demonstrated in Table 3, our cases therefore represent the more severe, more clinically significant end of the FMH spectrum. Further prospective study is needed to evaluate the risk factors we propose in the broad population of pregnancies impacted by FMH.

CONCLUSION

We found a significant association between a mother's work history during pregnancy and diagnosis of clinically significant FMH in the perinatal period. If supported in larger studies, this finding would have important ramifications regarding both limitations of strenuous work during pregnancy and targeted screening for FMH among working women. Since the cost of life-long care for survivors of severe FMH is high, a laboratory screening strategy based on work history may be both feasible and cost-effective. As severe FMH is a rare condition, either a large multi-center prospective study or an international registry of cases may be needed to fully evaluate the associations proposed in the present study. Although there is no doubt that the majority of women can work safely during pregnancy, increased awareness of the possibility of FMH among women with demanding work schedules, particularly those involving night shifts, could aid early diagnosis by targeted prenatal FMH testing and early intervention to avoid significant fetal/neonatal morbidity and mortality in those cases where FMH occurs.

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Abbreviations

CI	confidence interval
FMH	fetomaternal hemorrhage
KB	Kleihauer-Betke acid elution test
NICU	neonatal intensive care unit
OR	odds ratio
SD	standard deviation

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Table 1

Previously Suggested Risk Factors Associated with Fetomaternal Hemorrhage

Maternal Characteristics	Fetal Characteristics	Placental/Uterine Characteristics	Interventions/Events
*Race/Ethnicity ^[5, 14]	Fetal anomalies ^[23]	Abruption ^[5, 24, 25]	*Amniocentesis/Invasive obstetric procedures ^[13, 23, 26]
Socioeconomic Status ^[5]	*Twin Gestation ^[14]	Umbilical vein anomalies ^[5, 22]	*External cephalic version ^[27]
Geographic region of delivery ^[5]		Chorioamnionitis ^[8]	Maternal abdominal trauma ^[28]
Pre-eclampsia		*Twin gestation ^[14]	
		Placental tumors ^[29]	

* Shown to be both associated with FMH and not associated with FMH in different studies

Table 2
Demographic and Clinical Factors Known Prior to or Immediately Following Birth

Factors Knowable During the Prenatal Period		Number (%) / Mean $\pm$ SD / Median (IQR) ¹		Univariable Logistic Regression	
		Cases (n = 23)	Controls (n = 92)	Odds Ratio	95% Confidence Interval
Maternal demographic factors	Maternal Caucasian race	16 (70)	53 (58.2)	1.9	0.7 – 5.3
	Maternal age	32.0 $\pm$ 6.6	30.5 $\pm$ 6.5	1.0	0.97 – 1.1
	Maternal private insurance	21 (91)	50 (60.2)	6.9	1.5 – 32 *
	Maternal physical trauma during pregnancy	0 (0)	3 (3.8)	0.53	0.02 – 13
	Maternal paid employment	18 (78)	43 (53)	3.2	1.1 – 9.4 *
	Maternal night work	3(13)	1 (1.2)	12	1.2 – 122 *
	Maternal work in the medical field	3 (13)	6 (7.5)	1.9	0.43 – 8.1
	Maternal UTI during pregnancy	0 (0)	6 (7.7)	0.26	0.01 – 5.4
	Maternal diabetes	1 (4)	4 (5.2)	0.83	0.09 – 7.8
	Maternal hypercoagulability	1 (4)	3 (3.9)	1.1	0.11 – 11
	Uterine anomaly	1 (4)	2 (2.6)	1.7	0.15 – 20
	Maternal chorioamnionitis	0 (0)	2 (2.4)	0.92	0.03 – 25
	Maternal pre-eclampsia	2 (8.7)	2 (2.4)	3.8	0.5 – 29
	Maternal tobacco use during pregnancy	1 (4.3)	4 (5.1)	0.85	0.09 – 8.0
	Maternal illicit drug use during pregnancy	0 (0)	2 (2.6)	0.83	0.03 – 23
Maternal obstetric factors	Vaginal bleeding during pregnancy	3 (14)	10 (12.8)	1.1	0.27 – 4.3
	Amniocentesis	5 (17)	16 (22)	1.3	0.43 – 4.1
	Cephalic version attempted	1 (4.3)	5 (6.1)	0.7	0.08 – 6.3
	Maternal hemoglobin prior to delivery (%)	11.9 (11.0, 12.8)	11.9 (11.1, 12.6)	0.89	0.62 – 1.3
	Female gender of fetus	16 (70)	42 (46)	2.7	1.0 – 7.2 *
	Fetus of appropriate size for gestational age	17 (74)	73 (79)	1.4	0.47 – 3.9
	Multiple gestation	0 (0)	4 (4.3)	0.47	0.21 – 10
	Fetal factors				
	Pregnancy factors				

		Number (%) / Mean $\pm$ SD / Median (IQR) ¹		Univariable Logistic Regression	
		Cases (n = 23)	Controls (n = 92)	Odds Ratio	95% Confidence Interval
Labor & Delivery	Placenta previa	1 (4)	1 (1.3)	3.5	0.21 – 59
	Vasa previa	0 (0)	0 (0)	--	--
	Velamentous insertion of the umbilical cord	0 (0)	0 (0)	--	--
	Subchorionic hematoma	0 (0)	1 (1.3)	1.9	0.05 – 81
	Placental tumor	0 (0)	0 (0)	--	--
	Placental abruption	3 (14)	0 (0)	37	1.2 – 1176*
	Preterm labor > 24hr	3 (13)	2 (2.4)	6.0	0.94 – 38
	Category II or III fetal heart tracing	12 (52)	17 (21)	4.0	1.5 – 11*
	Sinusoidal heart tracing	3 (13)	0 (0)	36	1.1 – 1137*
	Meconium passage prior to birth	7 (32)	16 (18)	2.2	0.8 – 6.2
	Emergent Cesarean birth	13 (57)	5 (6.1)	20	5.9 – 68*
	Gestational age at birth (weeks)	37.1 (35.0, 39.5)	39.3 (38.3, 40.3)	0.70	0.58 – 0.85*
	Preterm birth	11 (48)	6 (6.5)	13	4.1 – 42*
	Apgar score at 1 min	7 (5, 9)	9 (9, 9)	0.46	0.31 – 0.68*
	Apgar score at 5 min	8 (7, 9)	9 (9, 9)	0.12	0.04 – 0.38*

¹ SD = standard deviation; IQR = interquartile range

* Significant at p<0.05

Table 3

Multivariable Logistic Regression Modelling of Demographic and Clinical Factors Associated with FMH Known Prior to Birth

	Odds Ratio	95% Confidence Interval
Maternal private insurance ¹	15	2.0 – 106*
Maternal paid employment ¹	3.7	1.0 – 13*
Maternal night work ¹	12	0.8 – 184
Female gender of fetus ²	3.8	1.0 – 14*
Preterm birth ²	35	6.2 – 198*

¹ Adjusted for preterm delivery and female gender

² Adjusted for maternal private insurance and preterm birth

³ Adjusted for maternal private insurance and female gender

Table 4

Neonatal Characteristics of FMH-Impacted Pregnancies Compared to Controls

		Number (%) or Mean $\pm$ SD		p value
		Cases (n = 23)	Controls (n = 46)	
Neonatal course	NICU admission	23 (100)	11 (12)	<0.001 *
	First hemoglobin (mg/dL)	7.2 $\pm$ 2.8	16.8 $\pm$ 2.4	<0.001 *
	First reticulocyte count (%)	9.2 $\pm$ 5.6	7.4 $\pm$ 3.3	<0.001 *
	Highest total bilirubin (mg/dL)	10.6 $\pm$ 5.3	10.5 $\pm$ 2.5	0.913
	Intubation and mechanical ventilation	9 (39)	3 (3.3)	<0.001 *
	Central line placed	13 (57)	2 (2.2)	<0.001 *
	Blood (packed red cell) transfusion	17 (74)	2 (2.2)	<0.001 *
	Platelet transfusion	2 (8.7)	1 (1.1)	0.11
	Hypotension	8 (35)	4 (4.4)	<0.001 *
	Persistence of the fetal circulation	3 (13)	0 (0)	0.002 *
	Hypoxic-ischemic encephalopathy	2 (8.7)	0 (0)	<0.001 *
Post-NICU	Home	19 (83)	91 (99)	0.006 *
	Transitional or long-term care facility	1 (4.3)	0 (0)	0.12
	Deceased ^I	3 (13)	1 (1.1)	0.03 *

* Significant at p<0.05

^I Causes of death for cases were cerebral herniation, pulmonary hypertension, and cardiopulmonary arrest. Cause of death for the control was inborn error of metabolism.