European Review for Medical and Pharmacological Sciences 2020; 24: 10352-10358

Relation of meconium-stained amniotic fluid and postpartum hemorrhage: a retrospective cohort study

Z.-J. FANG, H.-F. LIU, Y.-L. ZHANG, L. YU, J.-Y. YAN

Department of Obstetrics and Gynecology, Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University, Fujian, China

Zhuanji Fang and Hongfei Liu contributed equally to the work

Abstract. – OBJECTIVE: Postpartum hemorrhage (PPH) is a major cause of maternal mortality and morbidity worldwide. The purpose of this study was to evaluate if meconium-stained amniotic fluid (MSAF) is a risk factor for PPH after vaginal delivery.

PATIENTS AND METHODS: We retrospectively analyzed medical records of all patients who had a vaginal delivery at Fujian Provincial Maternity and Children's Hospital, between 1st January 2013 to 31st December 2018. Women with cesarean deliveries, multiple pregnancies, abnormal coagulation profile, and those with concomitant liver or kidney disorders were excluded. Patients were classified into MSAF (n=13686) and clear amniotic fluid (AF) (n=41511) groups.

RESULTS: The incidence of PPH was significantly higher at 2.7% (370/13686) in the MSAF group as compared to 2.18% (904/41511) in the clear AF group (p=0.0004). There was no difference in the incidence of severe PPH between the two groups. Statistically significant difference in the incidence of PPH between MSAF and clear AF was seen in the maternal age groups of 30-34 and 35-39 years, gestational age>40weeks and >3 gravidity (p<0.05).

CONCLUSIONS: Our study demonstrates that MSAF is a significant risk factor for minor and moderate PPH. Presence of meconium could therefore alert clinicians to expect PPH and make arrangements for further patient management. Further basic research is required to evaluate the mechanism by which meconium influences the incidence of PPH.

Key Words:
Postpartum hemorrhage, Meconium, Bleeding, Risk factor.

Abbreviations

PPH: Postpartum haemorrhage; AF: Amniotic fluid; MSAF: Meconium-stained amniotic fluid; USG: ultrasonographic; OR: Odds ratio; CI: Confidence interval; SD: Standard Deviation.

Introduction

Postpartum hemorrhage (PPH) is a major cause of maternal mortality and morbidity worldwide. It is commonly defined as loss of more than 500 ml of blood following vaginal delivery and more than 1000 ml of bleeding following cesarean section in the first 24 hours[1]. PPH is a crippling problem affecting public healthcare systems worldwide contributing to increased healthcare costs[2]. The magnitude of the problem is not restricted to developing countries alone as data suggests even high-income countries have a significant incidence of PPH[3,4]. According to a study in China, approximately 7.45% of maternal deaths every year are because of PPH[5]. WHO research suggests 661,000 maternal deaths worldwide from 2003-2012 could be attributed to PPH[6]. Trends of PPH from different studies indicate that incidence of PPH has been increasing worldwide. Bateman et al[4] have reported a 27.5% increase of PPH rates from 1995 to 2004 in the USA. Ford et al[7] from Australia indicated a significant increase in PPH rates from 6.1% in 2003 to 8.3% in 2011.

The "Four T's"; tone, trauma, tissue, and thrombin, are used to describe the causes of PPH. According to literature, poor uterine tone (70%), trauma (20%), remnant placental tissue and coagulation disorders can all lead to PPH[8]. Studies have identified several risk factors for development of PPH including higher maternal age, prior history of PPH, multiple pregnancies, pre-eclampsia, cesarean delivery, amnionitis, uterine rupture, and placental rupture[9]. Bouchè et al[10] showed that meconium-stained amniotic fluid (MSAF) is also a risk factor for PPH after vaginal delivery. MSAF was shown to be significantly associated with higher risk of moderate and severe PPH than clear amniotic fluid (AF). In the absence of any other research on this subject, we therefore attempted to explore

Corresponding Author: Jianying Yan, MD; e-mail: yanjy2019@fjmu.edu.cn

the relationship of MSAF and incidence of PPH in our patient population by a retrospective study.

Patients and Methods

Patients

We retrospectively analyzed medical records of all patients who had a vaginal delivery at Fujian Provincial Maternity and Children's Hospital, between 1st January 2013 to 31st December 2018. Women with multiple pregnancies, abnormal coagulation profile, and those with concomitant liver or kidney disorders were excluded. Patients with cesarean sections were not included in the study to avoid possible bias in the results. The study was approved by the Institutional Ethics Committee. Informed written consent was obtained from all patients prior to deliveries. However, since records were retrospectively analyzed for this study with blinding of patient's identity, further consent for participation in the study was not necessary.

The following data was collected from the obstetric record of each patient: age, gestational age, gestational complications, gravidity, parity, mode of delivery, blood loss, neonatal birth weight, and placental weight. Based on the color of AF, patients were classified into two groups: MSAF and clear AF. We classified AF by its color and character. MSAF was defined as AF with any meconium i.e., fresh, old, thick, or thin; diagnosed during the first stage of labor. Gestational age was determined from patient provided details of last menstrual period and ultrasonographic (USG) examination.

Outcomes

Obstetric blood loss was measured using a calibrated patient drape for all women. Following delivery, the drape was placed under the patient for drainage of the AF. In all patients, blood loss was assessed for at least 60 mins or till active bleeding stopped. PPH was defined as a cumulative postpartum blood loss of ≥500 mL. We further classified PPH, according to the guidelines of the Royal College of Obstetricians and Gynecologists[1], as minor (blood loss of 500-1000 ml) or major (blood loss of >1000 ml). Major PPH was further sub-divided into moderate PPH (blood loss of 1000-2000 mL) and severe PPH (blood loss of >2000 mL). We classified maternal age (on 5-year intervals), gestational age and gravidity into different sub-groups to assess the influence of these variables on the incidence of PPH. The amount of bleeding in the two groups at different time points (30 mins, 45 mins, 60 mins, 90 mins, 120 mins) post-delivery was also compared.

Statistical Analysis

SPSS 19.0 (SPSS IBM, Armonk, NY, USA) was used to perform the statistical analysis. Continuous data are presented as means±standard deviation (SD) and were analyzed with the Student's *t*-test. Categorical data are presented as number (percentage, %), and were compared using χ^2-tests or Fisher exact test as appropriate. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Results were considered statistically significant for $p<0.05$.

Results

A total of 87,452 women delivered children at our institute during the study period. After excluding 29,987 caesarean deliveries and further 2268 patients based on the exclusion criteria, a total of 55,197 patients with vaginal deliveries were included in this study. 13,686 were classified in the MSAF group while 41511 in the clear AF group. The baseline characteristics of included patients are presented in Table I. There was no statistical difference in the maternal age of the two groups ($p=0.10$). The mean gestational age of MSAF group was significantly less as compared to the clear AF group ($p<0.0001$). The incidence of gestational hypertension and diabetes mellitus was higher in the MSAF group ($p<0.05$). Premature rupture of membrane was seen in 19.55% of women in MSAF group as compared to 32.6% of clear AF group ($p<0.0001$). There were statistically significant differences in gravidity and parity between the two groups ($p<0.0001$). Instrumental vaginal delivery, episiotomy and regional anesthesia were more frequently used in the MSAF group ($p<0.05$). The mean neonatal birth weight and placental weight was significantly higher in the clear AF group ($p<0.0001$).

The incidence of PPH was significantly higher at 2.7% (370/13686) in the MSAF group as compared to 2.18% (904/41511) in the clear AF group ($p=0.0004$). The odds of PPH were higher with the presence of meconium [OR: 1.25, 95% CI: 1.10, 1.41). Data on incidence of PPH in the two groups stratified on the basis of maternal age is presented in Table II. Statistically significant difference in the incidence of PPH between MSAF and clear AF was seen in the maternal age groups of 30-34 and 35-39 years ($p<0.05$). Similarly, data on the incidence of PPH stratified on the basis of gestational age is presented in Table III. Statistically significant

Table I. Baseline characteristics of study population.

Characteristics	MSAF (n=13686)	Clear AF (n=41511)	*p*-value
Maternal age (years)	29.35 ± 4.34	29.28±4.23	0.10
Gestational age (weeks)	38.24 ± 5.07	39.04±3.21	<0.0001
Gestational complications			
Hypertensive disorders of pregnancy	335 (2.45%)	880 (2.12%)	0.04
Preeclampsia	153 (1.12%)	327 (0.79%)	0.0003
Gestational diabetes mellitus	1822 (12.31%)	6890 (16.60%)	<0.0001
Premature rupture of membranes	2676 (19.55%)	13533 (32.60%)	<0.0001
Gravidity			<0.0001
=1	6077 (44.40%)	16685 (40.19%)	
=2	6894 (50.37%)	22422 (54.01%)	
>3	715 (5.23%)	2404 (5.8%)	
Parity			<0.0001
=0	537 (3.92%)	2405 (5.79%)	
=1	8281 (60.51%)	22837 (55.02%)	
>1	4868 (35.56%)	16269 (39.19%)	
Mode of delivery			
Instrumental vaginal	474 (3.46%)	724(1.74%)	<0.0001
Episiotomy	4050 (29.59%)	9446(22.76%)	0.005
Regional analgesia	148 (1.08%)	335(0.81%)	<0.0001
Birth weight (g)	3024±903.48	3196.19±539.93	<0.0001
<3000	3774 (27.58%)	10047 (24.20%)	<0.0001
3000-3499	5920 (43.25%)	18695 (47.81%)	
3500-3999	3585 (26.19%)	9195 (23.51%)	
≥4000	407 (2.97%)	3574 (9.14%)	
Placental weight (g)	570.40±146.74	598.21±120.86	<0.0001
Birth weight/Placental weight	5.4±7.07	5.55±6.56	=0.03

AF, amniotic fluid; MSAF, Meconium-stained AF. Data presented as mean ± standard deviation or number (percentage).

difference was seen in incidence of PPH between MSAF and clear AF groups only with gestational age of ≥40 weeks. The incidence of PPH based on gravidity is presented in Table IV. The risk of PPH was statistically significant in patients with prior history of pregnancies (>3 pregnancies).

The amount of bleeding at different time points from delivery in the two groups is presented in Table V. Total bleeding in MSAF was significantly greater as compared to clear AF group (p<0.0001). Bleeding during delivery and 30 minutes after delivery was significantly reduced in the clear AF group (p<0.0001), with no difference in the amount of hemorrhage after 45 mins. Data based on the classification of PPH is presented in Table VI. The incidence of minor and moderate PPH was significantly higher in MSAF group as compared to clear AF group (p<0.05). However, there were no differences in the incidence of severe PPH.

Table II. The incidence of PPH in different maternal age.

Maternal age (years)	No. (%) of PPH		*p*-value
	MSAF (n=13686)	Clear AF (n=41511)	
18-19	1/26 (3.84%)	5/190 (2.63%)	0.72
20-24	20/1097 (1.82%)	78/4363 (1.79%)	0.88
25-29	163/6818 (2.39%)	397/19764 (2.01%)	0.05
30-34	134/4529 (2.95%)	291/12447 (2.34%)	0.002
35-39	48/1126 (4.26%)	109/3999 (2.73%)	0.008
40-44	4/90 (4.44%)	24/748 (3.21%)	0.59
Total	370 /13686 (2.70%)	904/41511 (2.18%)	0.00038

AF, Amniotic fluid; MSAF; meconium-stained AF; PPH: Postpartum hemorrhage.

Table III. The incidence of PPH in different stage of gestational age.

Gestational age (weeks)	No. (%) of PPH		*p*-value
	MSAF (n=13686)	Clear AF (n=41511)	
34-35	3/157 (1.91%)	11/969 (1.14%)	0.4159
36-37	7/384 (1.82%)	76/3488 (2.18%)	0.6476
38-39	112/4805 (2.33%)	405/19644 (2.06%)	0.245
≥40	248/8340 (2.97%)	412/17410 (2.36%)	0.0039*
Total	370/13686 (2.70%)	904/41511 (2.18%)	0.00038*

AF, Amniotic fluid; MSAF; meconium-stained AF; PPH: Postpartum hemorrhage.

Table IV. The incidence of PPH in different Gravidity.

Gravidity	No. (%) of PPH		*p*-value
	MSAF (n=13686)	Clear amniotic fluid (n=41511)	
1	142/6077 (2.34%)	329/16685 (1.97%)	0.08
2	162/6894 (2.34%)	443/22422 (1.97%)	0.056
>3	66/715 (9.23%)	132/2404 (5.49%)	0.0003
Total	370 /13686 (2.70%)	904/41511 (2.18%)	0.0004*

Discussion

Our study demonstrates that the presence of MSAF significantly increases the risk of PPH after vaginal delivery. Risk is higher for minor (500-1000 ml) and moderate (1000-2000 ml) PPH but not for severe PPH (>2000 ml).

The exact etiology of MSAF is not clear. However, several risk factors of MSAF are reported in literature including obstetric factors like prolonged labor, post-term pregnancy, low-birth weight babies, oligohydramnios, intrauterine growth retardation, hypertensive disorders of pregnancy; medical factors like cholestasis

Table V. Blood bleeding of different stages in MSAF and clear amniotic fluid group.

Blood bleeding of different stages	MSAF (n = 13686)	Clear amniotic fluid (n = 41511)	*p*-value
During delivery	109.84 ± 77.57	103.40 ± 68.26	<0.0001*
30 min after delivery	43.29 ± 63.28	39.6 ± 47.74	<0.0001*
45 min after delivery	19.09 ± 24.28	19.07 ± 22.07	0.93
60 min after delivery	12.64 ± 21.99	12.64 ± 19.11	0.99
90 min after delivery	8.82 ± 28.13	8.77 ± 21.7	0.85
120 min after delivery	6.93 ± 21.34	6.61 ± 14.82	0.10
Total	200.62 ± 149.99	190.06 ± 118.91	<0.0001*

MSAF: Meconium-stained amniotic fluid.

Table VI. Classification of PPH in MSAF and clear amniotic fluid group.

PPH classification	Amount	MSAF (n=13686)	Clear amniotic fluid (n=41511)	OR (95% CI)
Minor	500-999 mL	290/13686 (2.18%)	747/41511 (1.92%)	1.18 (1.03-1.35)
Moderate	1000-2000 mL	71/13686 (0.51%)	138/41511(0.33%)	1.56 (1.17-2.08)
Severe	≥ 2000 mL	9/13686 (0.066%)	19/41511 (0.046%)	1.43 (0.65-3.17)
	Total	370/13686 (2.77%)	904/41511 (2.30%)	1.25 (1.10, 1.41)

AF, Amniotic fluid; MSAF; meconium-stained AF; PPH: Postpartum hemorrhage; OR, Odds ratio; CI, confidence interval.

of pregnancy, anemia; and socio-demographic risk factors like higher maternal age and maternal drug abuse[11]. While there was no difference in maternal age between the two groups in our study, the percentage of hypertensive disorders was higher (2.45% *vs.* 2.12%) in the MSAF group and the birth-weight in the MSAF group was significantly lower as compared to the clear AF group. There were other baseline differences in the two groups owing to the retrospective nature of the study.

MSAF is known to be an independent risk factor of perinatal complications[12]. Rodríguez Fernández et al[13] have demonstrated that MSAF is associated with pathological fetal heart rate patterns, intrapartum fevers, cesarean section deliveries, neonatal resuscitation, low Apgar scores and higher fetal-neonatal mortality. In another study by Hiersch et al[14], MSAF was reported to be an independent risk factor for operative delivery, respiratory morbidity and short-term neonatal morbidity. However, literature on the role of MSAF as a risk factor for PPH is limited. In our study, the odds of minor PPH and moderate PPH were significantly higher in the presence of MSAF. The findings of our study concur with the results of Bouchè et al[10] which also demonstrated higher odds of PPH in the presence of MSAF. However, in their study the difference was significant only for moderate [OR:1.3 (1.2-1.5)] and severe [OR:2.5(1.5-4.2)] PPH. The variation in the results may be explained by the overall lower incidence of severe PPH in our study population (0.08% *vs.* 0.05%) and the differences of definition of PPH between the two studies. Bouchè et al[10] did not analyze data of minor PPH but presented combined data of any blood loss <1000 ml. In another study, Mazor et al[12] have demonstrated no significant difference in PPH between MSAF and clear AF groups. Their non-significant result may be attributed to the small sample size of their study with an overall incidence of PPH only 0.5% as compared to 2.9% in our study population.

Like the previous study, lack of data on the effect of MSAF on the coagulation systems limits our ability to explain the role of MSAF in increasing PPH. Petroianu et al[15] in a study on pregnant mini-pigs have shown that infusion of native AF with meconium led to reduced platelet counts, prolonged PTT and reduced fibrinogen & protein C. Similar effects were seen after infusion of clear AF but the effects were much less pronounced. The authors concluded that unknown factors contained in meconium probably resulted in disorders of coagulation as meconium-free AF is not life-threatening despite infusion of very high volumes. With data reporting MSAF to be a risk factor for PPH, we believe our study will provide impetus to further basic research on the effect of meconium on coagulation profile.

On stratifying the incidence of PPH in the MSAF and clear AF groups based on maternal age, we found the significant difference between the incidence of PPH for the older age group 30-39 years but not for younger age groups (18-29 years). This was expected as increased maternal age is a known risk factor for PPH[16,17]. The lack of statistical difference for the age group >40 years may be due to insufficient sample size. Classifying our results based on gestational age and gravidity we found significant differences between the two groups for higher gestational age and previous history of pregnancies. The risk of PPH in the MSAF group was higher for gestational age of >40 weeks and gravidity of >3. A WHO multicounty survey on maternal and newborn health has reported higher gestational age and multiparity to be an independent risk factor for PPH[18].

Our study has some limitations. First, this is a single-center study retrospective study. Therefore, the influence of potential confounding factors on our results cannot be negated. Second, evaluation of AF and its characteristics was subjective across a long span of time which may have led to evaluation bias. Third, data on the amount of bleeding was assessed from the calibrated drapes by different nursing staff, which could have led to minor errors in reporting.

There are some novelties of our study. Our study is only the second one to assess the effects of MSAF on minor and moderate PPH. The large sample size of our study adds strength to our conclusions. Furthermore, we assessed the amount of bleeding at different time-points to provide clear evidence to clinicians.

Conclusions

Our study demonstrates that MSAF is a significant risk factor for minor and moderate PPH. Presence of meconium could therefore alert clinicians to expect PPH and make arrangements for further patient management. Further basic research is required to evaluate the mechanism by which meconium influences the incidence of PPH.

Acknowledgments

The authors thank the perinatal care providers at the department of obstetrics for their contribution to the data collection and the department of computer technology for their hard work on data management.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Fujian Provincial Maternity and Children Hospital, Number: 2018(1015) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All of the data were obtained from patient records. Formal consent was not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was supported by the Key Clinical Specialty Discipline Construction of Fujian, P.R.C ([2015] no. 593), the Fujian Provincial Health Technology Project (2017-CX-11), Fujian Science and Technology Project (2018Y0005) and the National Health and Family Planning Commission Science Foundation (2019-WJ-04).

Authors' contributions

ZF, HL and JY designed the project; YZ and LY were involved in data collection and data analysis; ZF and HL prepare the manuscript; JY edited the manuscript; all authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

References

1) Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalf of the Royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage [Internet]. Vol. 124, BJOG: An International Journal of Obstetrics & Gynaecology. 2017 [cited 2020 Mar 18]. p. e106-49. Available from: http://doi.wiley.com/10.1111/1471-0528.14178
2) Ngwenya S. Postpartum hemorrhage: incidence, risk factors, and outcomes in a low-resource setting. Int J Womens Health 2016; 8: 647-650.
3) H Habitamu D, Goshu YA, Zeleke LB. The magnitude and associated factors of postpartum hemorrhage among mothers who delivered at Debre Tabor general hospital 2018. BMC Res Notes 2019; 12: 618.
4) Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg 2010; 110: 1368-1373.
5) Li X, Zhu J, Dai L, Li M, Miao L, Liang J, Wang Y. Trends in maternal mortality due to obstetric hemorrhage in urban and rural China, 1996-2005. J Perinat Med 2011; 39: 35-41.
6) Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014; 2: e323-33.
7) Ford JB, Patterson JA, Seeho SK, Roberts CL. Trends and outcomes of postpartum haemorrhage, 2003-2011. BMC Pregnancy Childbirth 2015; 15: 334.
8) Sebghati M, Chandraharan E. An update on the risk factors for and management of obstetric haemorrhage. Womens Health (Lond) 2017; 13: 34-40.
9) Kramer MS, Berg C, Abenhaim H, Dahhou M, Rouleau J, Mehrabadi A, Joseph KS. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol 2013; 209: 449. e1-7.
10) Bouchè C, Wiesenfeld U, Ronfani L, Simeone R, Bogatti P, Skerk K, Ricci G. Meconium-stained amniotic fluid: a risk factor for postpartum hemorrhage. Ther Clin Risk Manag 2018; 14: 1671-1675.
11) ddisu D, Asres A, Gedefaw G, Asmer S. Prevalence of meconium stained amniotic fluid and its associated factors among women who gave birth at term in Felege Hiwot comprehensive specialized referral hospital, North West Ethiopia: a facility based cross-sectional study. BMC Pregnancy Childbirth 2018; 18: 429.
12) Mazor M, Hershkovitz R, Bashiri A, Maymon E, Schreiber R, Dukler D, Katz M, Shoham-Vardi I. Meconium stained amniotic fluid in preterm delivery is an independent risk factor for perinatal complications. Eur J Obstet Gynecol Reprod Biol 1998; 81: 9-13.
13) Rodríguez Fernández V, López Ramón Y Cajal CN, Marín Ortiz E, Couceiro Naveira E. Intrapartum and perinatal results associated with different degrees of staining of meconium stained amniotic fluid. Eur J Obstet Gynecol Reprod Biol 2018; 228: 65-70.
14) Hiersch L, Krispin E, Aviram A, Wiznitzer A, Yogev Y, Ashwal E. Hiersch L, Krispin E, Aviram A, Wiznitzer A, Yogev Y, Ashwal E. Effect of meconium-stained amniotic fluid on perinatal complications in low-risk pregnancies at term. Am J Perinatol 2016; 33: 378-384.
15) Petroianu GA, Altmannsberger SH, Maleck WH, Assmus HP, Friedberg C, Bergler WF, Rüfer R. Meconium and amniotic fluid embolism: effects on coagulation in pregnant mini-pigs. Crit Care Med 1999; 27: 348-355.

16) Ononge S, Mirembe F, Wandabwa J, Campbell OM. Incidence and risk factors for postpartum hemorrhage in Uganda. Reprod Health 2016; 13: 38.

17) Nyfløt LT, Sandven I, Stray-Pedersen B, Pettersen S, Al-Zirqi I, Rosenberg M, Jacobsen AF, Vangen S. Risk factors for severe postpartum hemorrhage: a case-control study. BMC Pregnancy Childbirth 2017; 17: 17.

18) Sheldon WR, Blum J, Vogel JP, Souza JP, Gülmezoglu AM, Winikoff B; WHO Multicountry Survey on Maternal and Newborn Health Research Network. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 Suppl 1: 5-13.