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Changes in Maternal Serum Levels of C3 and C4 complement Components in Different Delivery Methods and Postpartum Hemorrhage

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ABSTRACT

Background: Activation of the complement system may play a role in the pathophysiology of human labor. Yet no unanimous conclusion has been drawn.

Objective: To compare the differences in maternal complement components C3 and C4 serum levels in cesarean section and the vaginal delivery at term and in the postpartum hemorrhage.

Methods: One hundred and sixty six women delivered at term were enrolled in this study. Maternal blood samples were obtained from 47 cases of elective cesarean section and 119 cases of the vaginal delivery. Serum complement levels were measured subsequently by immuno-scatter turbidimetry.

Results: The maternal complement levels declined significantly during delivery by both the cesarean section and the vaginal delivery ($P<0.01$) in comparison with the baseline. A much larger drop of C3 serum level was found in the postpartum hemorrhage and in the vaginal delivery, and the incidence of the postpartum hemorrhage has a positive correlation with the complement decline rate.

Conclusion: The complement system may be involved in the delivery process and represents a predictive value in postpartum hemorrhage.

Keywords: Cesarean Section, Complement 3, Complement 4, Postpartum Hemorrhage, Vaginal Delivery

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INTRODUCTION

The complement system constitutes one of the key effector mechanisms of antibody-dependent and antibody-independent immunity and is a major player in innate defense [1]. Activation of the complement system leads to the formation of bacterial, chemotactic, and opsonic factors as well as the formation of a membrane-attack complex, which may be pivotal in the pathophysiology of human labor suggested by recent evidence[2].

Current research suggested the involvement of complement in the pathogenesis of preterm birth [3]. There are relatively few studies on the complement system and the conclusions are contradictory. A small sample study by Michael D Benson et al. reported that

complement levels had a significant drop in percentage 11-15% immediately following childbirth [4], while another study reported no changes in maternal complement three(C3) and complement four (C4) concentrations through the last trimester of pregnancy and labor [5]. Different results were also obtained by Makoto Kato et al. stating that the C3 and C4 levels decreased significantly during delivery by the cesarean section, while C3 levels increased temporally during the vaginal delivery at term and decreased two hrs. later indicating a different complement response regarding different delivery methods [6]. More research is needed to study the differential activation of the complement system by various parturition methods.

The postpartum hemorrhage refers to at least 500 mL of total blood loss within 24 hrs. after delivery or intrapartum loss. 25% of maternal deaths in the world are caused by the postpartum hemorrhage [7]. The postpartum hemorrhage is attributed to several causes. Uterine atony accounts for approximately 80% of the cases and remains the main cause of the postpartum hemorrhage [8]. Yi Shen et al. reported that the postpartum acute myometritis, characterized by acute inflammatory changes with massive stromal edema, and increased numbers of C5a receptors in the myometrium, is the main cause of uterine atony [9]. Many studies have demonstrated that the administration of C1 esterase inhibitor (C1INH) could improve uterine contractions and decrease uterine bleeding rapidly [10, 11]. C1INH is an inhibitor against C1 esterase as well as the kallikrein-kinin system, and its physiological function is to split the C4-C2 complex. Thus, we speculate that the complement system may play a role in the postpartum hemorrhage caused by uterine atony. There is no available study on the changes in maternal complement levels in the postpartum hemorrhage currently.

In summary, our study aims to compare the differences in maternal complement levels between delivery by the cesarean section and the vaginal delivery and that in the postpartum hemorrhage caused by uterine atony.

MATERIALS AND METHODS

Patients

From February 2020 to April 2020, a total of 166 women delivered at the Beijing Shijitan Hospital, Beijing, China, were enrolled in this study. All the subjects had provided written informed consent before enrollment and the study was approved by the Ethics Committee and Institutional Review Board of The Beijing Shijitan Hospital, Capital Medical University.

Inclusion criteria:

(1) Term delivery

(2) Singleton pregnancy

(3) Volunteer to participate in the study and sign the consent form

Exclusion criteria

(1) Emergency cesarean section

(2) Combined with immune system diseases

(3) Already in labor when admitted

(4) Twin or multiple pregnancies

(5) Combined with chorionic amnionitis or infectious disease

Blood Collection

Maternal blood samples were obtained within 24 hrs. before the cesarean section and two hrs. after delivery in 47 elective cesarean section women. In 119 women with the vaginal delivery, maternal blood was sampled at the onset of labor and two hrs. after delivery. All the blood samples were obtained from the anterior cubital vein.

Measurement of C3 and C4

Blood samples were sent to the clinical laboratory of the Beijing Shijitan Hospital once obtained and serum C3 and C4 levels were measured subsequently by immuno-scatter turbidmetry with BNII Specific Protein Analyzer (Siemens, Germany).

Statistical Analysis

The data were analyzed using SPSS software (version 18.0; SPSS Inc., an IBM Company, Chicago, IL, USA) and expressed as mean±SD. A 95% confidence interval ($P<0.05$) was considered for statistically significant differences, which were assessed using the Student's *t*-test for the comparisons of the two study groups. Univariate analyses were performed to analyze the relationship between complement decline rate and the postpartum hemorrhage in the vaginal delivery, using the Chi-square tests.

RESULTS

The age and gestational age of the involved women are shown in Table 1.

The levels of maternal C3 and C4 two hrs. after delivery in the vaginal delivery group were 1.076±0.168g/L and 0.225±0.060g/L respectively, significantly lower than at the onset of labor, 1.202±0.162g/L and 0.240±0.065g/L (n=119, $P<0.01$ for each; Figures 1 A and B) .

The levels of maternal C3 and C4 two hrs. after delivery in the elective cesarean section group were 1.077±0.174g/L and 0.221±0.057 g/L respectively, significantly lower than at the onset of labor, 1.231±0.171g/L and 0.246±0.062g/L (n=47, $P<0.01$ for each; Figures 1 C and D).

The variation trend of C3 in the cesarean section and the vaginal delivery and C4 in the cesarean section is consistent with the results of Makoto Kato's study [6], while we also find a significant decline of C4 during the vaginal delivery. Michael D Benson et al. also reported a significant drop (11-15%) in the complement levels immediately following childbirth [4]. To sum up, the complement system is activated both in the cesarean section and the vaginal delivery at term.

We also analyzed the results according to the presence or absence of the postpartum hemorrhage in 166 cases. We found that the level of maternal C3 decreased significantly from 1.216±0.161g/L at the onset of labor or before the cesarean section to 1.096±0.159g/L two hrs. after delivery in the non-postpartum hemorrhage group, and the C4 level decreased from 0.242±0.067g/L to 0.225±0.061g/L (n=140, $P<0.01$decline rate: 9.9% and 7.0% for C3 and C4 respectively; Figures 2 A and B).

Similarly, the level of maternal C3 decreased from 1.178±0.181g/L at the onset of labor or before the cesarean section to 1.002±0.203g/L two hrs. after delivery significantly in the postpartum hemorrhage group, and the C4 level decreased from 0.242±0.051g/L to 0.216±0.042 g/L (n=26, $P<0.01$, decline rate: 14.9% and 10.7% for C3 and C4 respectively; Figures 2 C and D).

Table 1. Patients' demographic information

	Vaginal delivery (n=119)	Elective cesarean section (n=47)
Age (years) (mean±SD)	30.9±3.2	33.3±3.6
Gestational age (weeks) (mean±SD)	39.2±1.0	38.8±1.1
Parity(n)		
Parity 0	91	27
Parity 1	25	20
Parity 2	3	0
Newborn weight(g) (mean±SD)	3371.76±435.97	3388.30±493.07
Premature rupture of membrane(n)	27	3
Postpartum hemorrhage(n)	22	4
Previous cesarean section history（n）	0	14
Complications of pregnancy (n)		
DM or GDM	12	10
Hypertension in pregnancy	4	6

GDM: Gestational diabetes mellitus; GD: Gestational diabetes

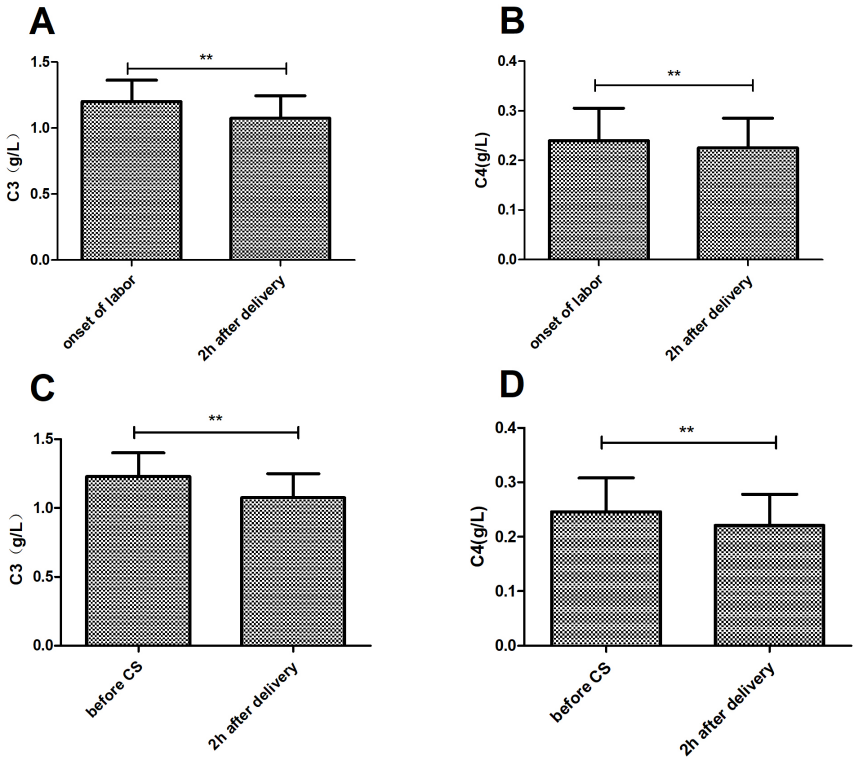

Figure 1. Maternal C3 and C4 levels at the onset of labor and two hrs. after delivery in the vaginal delivery group (A and B, n=119) and elective cesarean section group (C and D, n=47). CS: cesarean section. ** P<0.01.

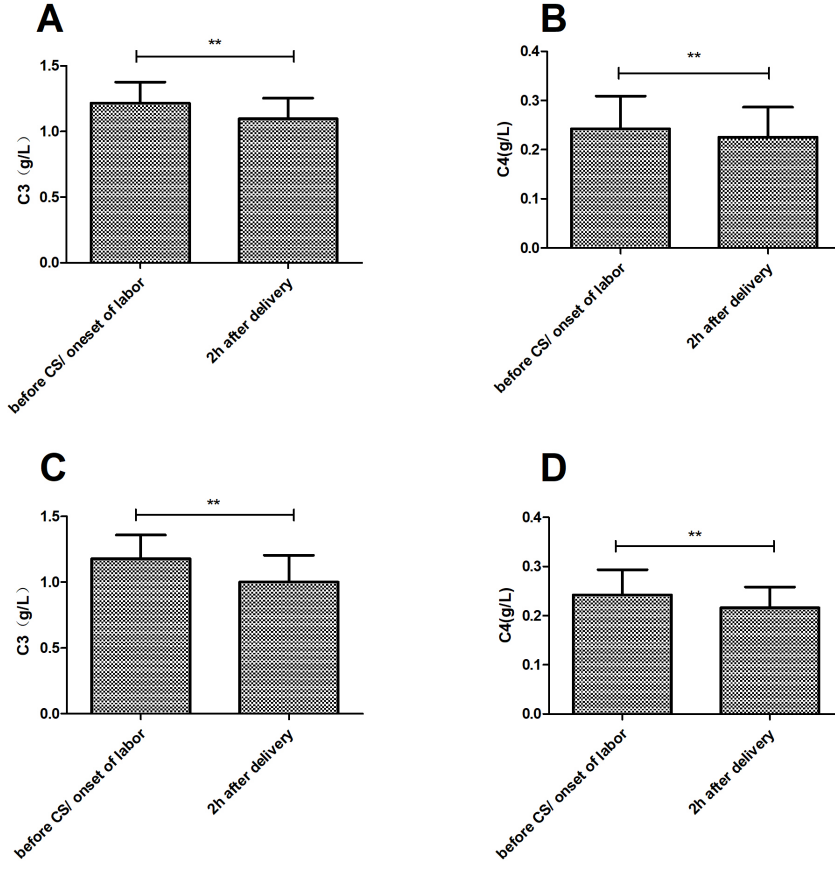

Figure 2. Maternal C3 and C4 levels at the onset of labor or before cesarean section and two hrs. after delivery in the non-postpartum hemorrhage group (A and B, n=140) and the postpartum hemorrhage group (C and D, n=26). CS: cesarean section. ** P<0.01.

The decline rate of maternal C3 and C4 levels in the postpartum hemorrhage group was much greater (14.9% vs 9.9% for C3 and 10.7% vs 7.0% for C4) than that in the non-postpartum hemorrhage group.

Taking the effect of delivery mode on complement into consideration, we separately studied 119 cases of the vaginal delivery. The changes in C3 and C4 levels in the postpartum hemorrhage are documented and the results are summarized in Table 2.

There were no differences in maternal C3 and C4 levels between the non-postpartum hemorrhage and the postpartum hemorrhage groups at the onset of labor. With or without the postpartum hemorrhage, the maternal C3 and C4 levels dropped significantly after delivery ($P<0.01$). Interestingly, the maternal C3 level was much lower in the postpartum hemorrhage group than that in the non-postpartum hemorrhage group 2 hrs. after delivery ($P<0.01$, decline rate: 15.8% vs 9.3%), while there were no significant differences at the onset of labor, indicating a remarkable reduction of C3 level in the postpartum hemorrhage.

Although there is no statistical significance, the maternal C4 level dropped 11.3% after delivery in the postpartum hemorrhage group while only 5.4% in the non-postpartum hemorrhage group.

Of the 166 included cases, the postpartum hemorrhage occurred in 22 cases in the vaginal delivery and 4 cases in elective cesarean section. The 26 cases of the postpartum hemorrhage were all caused by uterine atony. We analyzed the relationship between complement decline rate and the postpartum hemorrhage in 119 cases of the vaginal delivery.

When C3 declined greater than 10%, the incidence of the postpartum hemorrhage was 22.8%; while the decline rate exceeded 20%, the incidence of the postpartum hemorrhage significantly increased to 42.9% ($P<0.05$).

When C4 declined greater than 10% and 20%, the incidence of the postpartum hemorrhage significantly increased to 28.9% ($P<0.05$) and 71.4% ($P<0.01$).

The incidence of the postpartum hemorrhage significantly increased to 34.4% ($P<0.01$) when C3 and C4 both declined greater than 10%. The results are summarized in Table 3.

The outcomes suggested a positive relationship between the incidence of the postpartum hemorrhage and maternal C3 or C4 decline rate.

Table 2. The changes of maternal C3 and C4 levels during the vaginal delivery in the non-postpartum hemorrhage and the postpartum hemorrhage groups.

Complement level (mean±SD)	non-PPH group(n=99)		PPH group(n=22)	
	Onset of labor	2h after delivery	Onset of labor	2h after delivery
C3 (g/L)	1.207±0.157	1.095±0.156[a]	1.179±0.183	0.993±0.198[ab]
C4 (g/L)	0.241±0.068	0.228±0.063[a]	0.238±0.054	0.211±0.041[a]

PPH: the postpartum hemorrhage. When 2 hrs. after delivery compared with the onset of labor in both the non-PPH group and the PPH group , *a* mesas $P<0.01$; When 2 hrs. after delivery in the PPH group compared with that in the non-PPH group, *b* mesas $P<0.01$.

Table 3. The relationship between complement decline rate and the incidence of the postpartum hemorrhage in the vaginal delivery (n=119)

Complements decline rates	Proportion of cases	The incidence of PPH	P
C3 declined ＞10%	57/119	22.8%	0.345
C3 declined ＞20%	14/119	42.9%	0.023
C4 declined ＞10%	38/119	28.9%	0.044
C4 declined ＞20%	7/119	71.4%	0.002
C3 and C4 both declined ＞10%	32/119	34.4%	0.007

PPH: postpartum hemorrhage

DISCUSSION

The postpartum hemorrhage is one of the most common causes of maternal death around the world. Among several causes, uterine atony is the most common reason. Yi Shen et al. reported that postpartum acute myometritis is the main cause of uterine atony and the up-regulated expression of bradykinin receptor type 1 in the myometrium plays an important role in interstitial edema [9]. The increase of bradykinin caused by C1INH deficiency was key in the abrupt onset of interstitial edema in cases of hereditary angioedema [12]. Many studies have demonstrated that the administration of a C1 esterase inhibitor (C1INH), an inhibitor against C1 esterase, could improve uterine contractions and decrease uterine bleeding rapidly [10, 11]. Therefore, we speculate the complement system is involved in the postpartum hemorrhage caused by uterine atony.

In our study, we found that the maternal C3 and C4 levels fell significantly in delivery by both the cesarean section and the vaginal delivery, and a much more dramatic drop in C3 level in the postpartum hemorrhage group was found in the vaginal delivery. The possible reason may be the activation of the complement cascade, which leads to the formation of the membrane-attack complex and plays a role in the pathophysiology of the postpartum hemorrhage. Further research is needed to explore the specific mechanisms. Moreover, in the vaginal delivery, the incidence of the postpartum hemorrhage has a positive correlation with the maternal C3 or C4 decline rate, indicating a predictable complement level in the postpartum hemorrhage.

CONCLUSION

In summary, the complement system is involved in the delivery process and may intervene in the process of the postpartum hemorrhage. What is more, the decline rate of complement level might be predictable in the postpartum hemorrhage.

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DISCLOSURE

All authors of this paper have read and approved the final submitted version and are aware that they are listed as an author. There are no financial or other interests concerning the submitted manuscript that might be construed as a conflict of interest.

Conflict of Interest: None declared.

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