Original Article

Hemoconcentration in patients with HELLP syndrome -evaluation using urine-to-fluid ratio-

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ABSTRACT

Aim: The objective of this study was to determine whether the urine volume is disproportionately small relative to the amount of fluid replaced in postpartum patients with hematologically-detectable HELLP syndrome.

Methods: We conducted a retrospective observational study in 17 patients with HELLP syndrome and 23 control patients, all of whom underwent cesarean section. We confined the study population to women who showed laboratory data characteristic of HELLP syndrome and did not exhibit clinical manifestation of coagulopathy or multiorgan failure. We monitored the postpartum volumes of the urine and fluid replaced, and analyzed the ratio of urine volume/replaced fluid volume. The pre- and post-operative hemoglobin concentration (Hb) and hematocrit value (Ht) were also monitored.

Results; Compared to controls, patients with HELLP syndrome exhibited a significantly1) smaller urine-to fluid ratio on the day of delivery (0.21±0.13vs. 0.65±0.18) and on postoperative day1 (0.89±0.45vs.1.30±0.35), and also2) higher preoperative Hb (13.3±1.5g/dL vs.10.7±1.5g/dL) and Ht (39.1±4.4% vs. 32.1±3.9%). The high Hb and Ht observed in HELLP patients gradually decreased to8.5±1.6g/dL and26.4±5.8%, respectively, without bleeding by postoperative day3.

Conclusions; Compared to control women, patients with hematologically-detectable HELLP syndrome passed a smaller volume of urine that was disproportionate to the fluid replaced. This observation suggests that antenatal patients with hematologically-detectable HELLP syndrome suffer from severe hemoconcentration.

(key words : HELLP syndrome, hemoconcentration, fluid replacement, urine output)

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Introduction

It is widely known that in preeclampsia the circulating blood volume is reduced,[1,2] a phenomenon that is considered to be mainly due to reduced plasma volume: a decrease of 21% in the plasma volume was reported in patients with preeclampsia as compared with non-preeclamptic control women.[2]

The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) is closely associated with preeclampsia with regard to its pathogenesis/pathophysiology.[3,4] Although it has not yet been proven, some researchers consider that some, if not all, HELLP syndrome may be a very severe form of preeclampsia.[5] In fact, it was reported that acute renal failure requiring hemodialysis in pregnancy or postpartum was associated more often with HELLP syndrome than with "pure" preeclampsia without HELLP syndrome.[6] Reduced organ perfusion caused by a decrease in the plasma volume is the cause of organ dysfunction, including acute renal failure, in preeclampsia/HELLP syndrome.[5,7] The plasma volume is reduced in clinically-apparent HELLP syndrome, as it is in severe preeclampsia.

Although its clinical manifestation seems to occur abruptly, HELLP syndrome is not an "acute" disease. We have repeatedly demonstrated that a characteristic chronic process occurs before the clinical manifestation of HELLP syndrome: a gradual decline in the platelet count precedes the elevation of the serum level of aspartate aminotransferase (AST).[3,8,9] There is a hematologically- discernible stage of HELLP syndrome, in which various hematological changes occur without apparent manifestation of clinical signs, such as bleeding tendency, multiorgan failure, etc. Since clinically-apparent HELLP syndrome is characterized by severe reduction in plasma volume, and since hematologically-discernible HELLP syndrome precedes this stage, it is reasonable to assume that plasma volume reduction may also be present in the hematologically-detectable of HELLP syndrome. If so, patients with hematologically-detectable HELLP syndrome, in other words with presumed early-stage HELLP syndrome, would be expected to exhibit a high hemoglobin concentration (Hb) and hematocrit value (Ht) antenatally, and perhaps to pass a small urine volume that would be disproportionate to the amount of fluid replaced after delivery. Furthermore, a continued decline in Ht and Hb until the disappearance of hemoconcentration might be seen in the postpartum period. This study was an attempt to address this issue.

Subjects and Methods

We reviewed the medical records of 17 patients who showed hematological features as indicated below, characteristic of HELLP syndrome. Excluded were the cases with clinically-apparent HELLP syndrome; All 17 women showed no clinically-evident bleeding tendency and no physical signs of multiorgan failure, such as anuria requiring hemodialysis, respiratory dysfunction necessitating respiratory support, and liver dysfunction requiring hemoperfusion. Women abdominally gave birth to infants at Jichi Medical School Hospital between January 1996 and December 2000. HELLP syndrome was diagnosed if a patient exhibited a gradual antenatal decline in the platelet count to less than 120×10^9/L, a perinatal serum level of aspartate aminotransferase (AST) $>$ 50IU/L (normal reference value, $<$ 30IU/L), and a per-

inatal serum level of lactate dehydrogenase (LDH) >700IU/L (normal reference value, 215 to 410IU/L). Preeclampsia was defined as a systolic or diastolic blood pressure≧140mmHg or≧90mmHg, respectively, on 2 separate occasions 24hr apart, in association with the onset of proteinuria (≧300mg/24h) in a patient who had been normotensive during the first 20 weeks of pregnancy. As controls we selected 23 women without preeclampsia/HELLP who underwent elective cesarean section within several weeks prior to or after a patient with HELLP syndrome underwent cesarean section. Indications for cesarean section in controls were previous cesarean section, cephalo-pelvic-disproportion, or breech presentation.

All control patients and patients with HELLP syndrome were on nothing per os on the day of delivery (from 05 : 00h on the day of cesarean section to 05 : 00h the next morning) and postoperative day1 (the next 24 hours from 05 : 00h to 05 : 00h). Meals were served on and after postoperative day2. The volumes of urine and fluid replacement were monitored just after the patient entered the operating room for cesarean section. Via continuous venous route we replaced enough fluid so as to 1) maintain the systolic blood pressure of 80≦mmHg during operation and to 2) maintain the urine volume of 20≦cc/hr on postoperative dayland day2. The composition of fluid replaced was the same between the two groups. Urethral catheter was indwelled and urine volume was measured. Complete blood counts were performed preoperatively and on postoperative daylin all patients, and additional counts were done on postoperative days 2 to 4 in the 17 patients with HELLP syndrome. Results are presented as mean±SD. The paired t-test was used to compare the values for matched pairs, and the Mann-Whitney *U* test was used to compare the means of two independent groups. A level of $p<0.05$ was accepted as statistically significant.

Results

The laboratory data for the 17 patients with HELLP syndrome were as follows: the lowest platelet count of 73±37x10^9/L (range, 20x10^9/L to 118x 10^9/L) occurred on postoperative day 0.88±0.78, the highest AST level of 336±438IU/L (55IU/L to 1488IU/L) on postoperative day 0.88±1.22, and the highest LDH level of 1644±1597 (711IU/L to 7250IU/L) on postoperative day 0.79±0.78. Clinical signs of preeclampsia preceded the development of HELLP syndrome in 14 of 17 patients (Table 1). Neither body mass index nor estimated blood loss during parturition differed significantly between women with HELLP syndrome and control women.

Table 1. Demographics of study subjects

	HELLP syndrome	Control
No. of women	17	23
Age (years)	29.8±5.0	31.9±5.0
Nulliparous	10(59%)	10(43%)
Preeclampsia	14(82%)	0(0.0%)
Systolic BP (mmHg)	159±39	113±12 †
Diastolic BP (mmHg)	98±28	71±13 †
Gestational week at delivery	35.0±2.8	37.5±2.7 †
BMI at delivery	25.8±2.8	26.1±3.5
Blood loss at delivery (g) *	729±366	944±489

BP, blood pressure; BMI, body mass index.
* estimated blood loss including amniotic fluid.
† $p<0.01$vs women with HELLP syndrome.

Table 2. Relationship between urine volume and fluid volume replaced

	HELLP syndrome	Control	p-value
Day of delivery			
interval (hours) *	14.8±2.8	16.1±2.3	NS
urine (mL)	805±478	2191±747	$p<0.01$
fluid replacement (mL)	4139±1468	3368±550	NS
ratio †	0.21±0.13	0.65±0.18	$p<0.0001$
Postoperative day1§			
urine (mL)	2595±1202	2334±602	NS
fluid replacement (mL)	2997±752	1700±110	$p<0.01$
ratio †	0.89±0.45	1.30±0.35	$p<0.001$

* time interval from entering the operating room until 05 : 00h the next morning.
† volume ratio of urine-to- fluid replacement.
§ successive 24 hours from 05 : 00h to 05 : 00h.
NS, not significant.

None of the patients with HELLP syndrome required blood transfusion, or exhibited intraabdominal or abnormal vaginal bleeding postoperatively. Mild transient pulmonary edema not necessitating intratracheal intubation occurred during the first 24hr postpartum in 2 of the 17 patients with HELLP syndrome. All infants survived without discernible handicap/neurological sequelae.

The time interval from entering the operating room until 05 : 00h the next morning did not differ between the women with HELLP syndrome and control women (Table 2). During that period (on the day of delivery), patients with HELLP syndrome passed a significantly smaller urine volume than control women. Although women with HELLP syndrome tended to receive a larger amount of fluid replacement compared with control women, the difference did not reach a significant level. The ratio of urine volume/replaced fluid volume (urine-to-fluid ratio) was much lower in patients with HELLP syndrome than in control women. Although the volume of fluid replacement was significantly larger in patients with HELLP syndrome than in control women during the successive 24hr (postoperative day1), the urine volume of patients with HELLP syndrome was nearly equal to that of control women. The urine-to-fluid ratio exceeded1.0on postoperative day1in control women. However, this ratio was still below1.0in women with HELLP syndrome. Thus, the patients with HELLP syndrome passed a significantly smaller volume of urine(3400±1356mL vs. 4525±909mL, $p<0.05$), although they received a significantly larger volume of fluid replacement(7136±1885mL vs. 5068±550mL, $p<0.0001$) during the first 39hr postpartum compared to control women during the first40hr postpartum. On postoperative day2, patients with HELLP syndrome passed a urine volume of 3053±1333 mL, while they received fluid replacement of 2205±630mL, and thus appeared to have a urine-to-fluid ratio greater than 1.0. However, this figure was not completely accurate because oral feeding was initiated from postoperative day2.

Both the preoperative Ht and Hb were significantly higher in women with HELLP syndrome (39.1±4.4% and13.3±1.5g/dL, respectively) than in control women(32.1±3.9% and 10.7± 1.5g/dL, respectively) (Fig.1). In women with HELLP syndrome, the Ht gradually decreased to 26.4±5.8% by postoperative day 3, whereas it seemed not to change in control women. The drop in Ht was far out of proportion to the estimated blood loss in patients with HELLP syndrome. A similar change in Hb was observed in women with HELLP syndrome (Fig.1). All

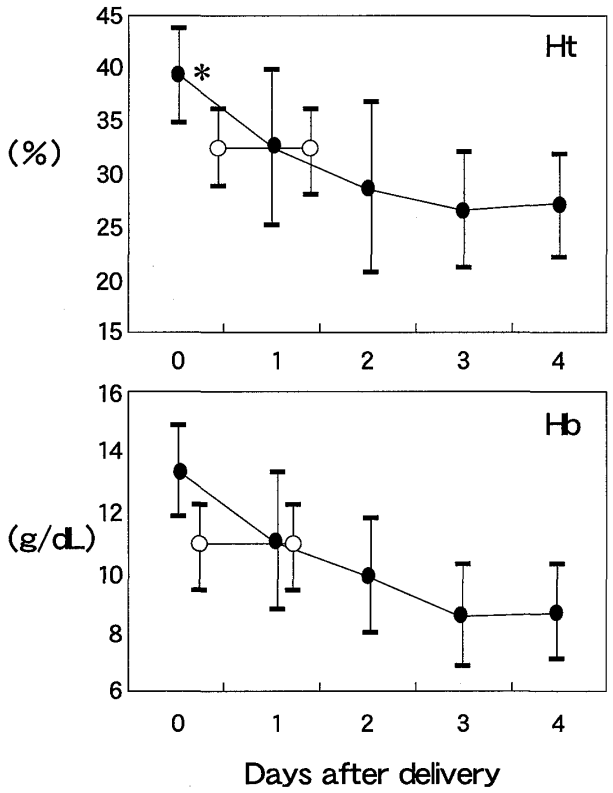

Fig. 1 : Changes in hematocrit value (Ht) and hemoglobin concentration (Hb)
Seventeen women with the HELLP syndrome(●)and23control women without preeclampsia/HELLP syndrome(○)were studied. *,p<0.001vs control women.

of the 17 women with HELLP syndrome and the 23 control women went home within 12 days postpartum without any complication.

Discussion

In this study we showed that women with hematologically-detectable HELLP syndrome had high antenatal Ht, passed a disproportionately small urine volume for the amount of fluid replaced during approximately the first 40hr postpartum compared with non-preeclamptic/non-HELLP control women. Women with HELLP syndrome also exhibited a postpartum drop in Ht far out of proportion to their estimated blood loss. All these findings are consistent with the hypothesis that a marked decrease of plasma volume occurs in women with hematologically-detectable HELLP syndrome.

We previously proposed that HELLP syndrome is not an acute and unpredictable illness, even though its clinical onset appears abruptly.[3,8] This proposal was based on our decade-long clinical experience and the results of our earlier studies, i.e., there is a gradual decline in the platelet count with or without a concomitant gradual decline in antithrombin III activity that continues until delivery, and this decline precedes the elevation of serum AST, while after parturition there is prompt normalization of the platelet count, antithrombin III activity, and serum level of AST.[3] Thus, the timing of delivery is likely to determine the absolute values of the postpartum platelet count and antithrombin III activity, suggesting that early detection of patients and early delivery may help to avoid a profound decrease in the platelet count/

antithrombin III activity[10,11] Our previous studies also suggested that a profound decrease in the circulating plasma volume led to perinatal oliguria/anuria in completed HELLP syndrome, and that this oliguria/anuria could be avoided by early delivery.[3,8] If untreated in this hematologically-detectable stage of HELLP syndrome, these hematological abnormalities may worsen to the extent that coagulopathy and multiorgan failure develop. We believe that there may be a stage (presumed early stage) of HELLP syndrome, in which hematologically-detectable changes occur without clinically-evident manifestation, although ethics did not permit us to confirm the presence of this presumed early-stage of HELLP syndrome. We conclude that hemoconcentration occurs even in women with hematologically-detectable HELLP syndrome.

Our finding of a markedly reduced postpartum urine-to-fluid ratio in patients with hematologically-detectable HELLP syndrome may be clinically important because it suggests that a large volume of fluid replacement may be needed to obtain an appropriate urine output in postpartum patients with HELLP syndrome. We were concerned about urine output, and our treatment protocol resulted in a significantly larger volume of fluid replacement in patients with HELLP syndrome than in control women. However, the actual urine volume was significantly smaller in patients with HELLP syndrome than in control women during approximately 1.5 days postpartum. Indeed, more severe oliguria, so-called "acute renal failure", may have developed in our patients with HELLP syndrome if the volume of fluid replacement had been more limited, although we can not verify it for the ethical reason.

Abnormal fluid retention as shown by symptoms such as pulmonary edema, ascites, pleural effusion, and skin edema is often seen in patients with preeclampsia and HELLP syndrome.[12,13,14] Mild postpartum pulmonary edema occurred transiently in 2 of 17 patients with HELLP syndrome in this study. Although a large volume of fluid replacement is often required to maintain renal blood flow and thereby to allow an appropriate urine output in patients with HELLP syndrome, a significant fraction of the infused fluid may escape from the intravascular space to the interstitial space, which may lead to pulmonary edema. Therefore, monitoring the oxygen saturation in the arterial blood is especially important for preventing hypoxemia due to pulmonary edema.

At present we do not know the mechanism of hemoconcentration observed in patients with HELLP syndrome, but it may be deduced from the mechanism of hemoconcentration in preeclampsia. In preeclampsia intervillous hypoxia is present, leading to the change in placental production of various substances including superoxide, lipid peroxide, endothelins, and various growth factors.[5] These changes may lead to systemic endothelial damage, resulting in the increased vascular permeability.[15,16,17] Fluid in the intravascular space leaks to the interstitial space, which causes hemoconcentration in patients with preeclampsia. Although the etiology and the mechanism of HELLP syndrome are still obscure, there are strong resemblances in the pathophysiology/pathogenesis between preeclampsia and HELLP syndrome.[3,4] Some researchers even consider that HELLP syndrome may be a very severe form of preeclampsia.[5] Vascular endothelial damage and increased vascular permeability may also account for the hemoconcentration observed in patients with HELLP syndrome. We must further study the

mechanism of hemoconcentration observed in this study.

There are some limitations in this study. First, we did not measure markers for the status of maternal hemoconcentration other than Hb/Ht/urine-to-fluid ration, ie, serum renin-angiotensin system and ADH system, urine specific gravity, electrolyte concentration and osmolality of the serum/urine etc. The analyse of these markers might have shed light on the mechanism of hemoconcentration in HELLP syndrome observed in this study. Second, the control patients were not matched for gestational age (HELLP vs control; 35±2.8 vs 37.5± 2.7 weeks of gestation). Reports indicated that there are no significant differences between 35 vs 37 weeks as far as maternal circulating blood volume and renal function are concerned.[18] Therefore, we believe that the difference in the gestational age between the two groups did not affect the present conclusion. Third, the definition of hematologically-detectable HELLP syndrome may be arbitrary. HELLP syndrome was originally defined as syndrome with "hematologically-detectable" trias, and therefore this word (hematologically-detectable HELLP syndrome) may be linguistically incorrect if strictly speaking. Furthermore, there may be a spectrum of HELLP-related conditions according to the disease severity. In this study, we defined hematologically-detectable HELLP syndrome as women in which laboratory findings for HELLP syndrome were observed without recognizable clinical manifestation (coagulopathy, multiple organ failure sign, etc). This definition may be quite practical and this notion of presumed early-stage HELLP syndrome may be clinically useful, although this definition has not yet been widely accepted among the perinatologists/obstetricians. In conclusion, women with hematologically-detectable HELLP syndrome were hemoconcentrated, as judged on the basis of urine output and the change in Hb/Ht. Clinicians must pay attention to the fact that women with HELLP syndrome, even in its "only-hematologically-discernible stage", passed a much smaller urine volume and exhibited a gradual decline in Hb/Ht in the postpartum period.

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HELLP症候群と血液濃縮—尿量／補液量比による評価—

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要　約

目的：帝王切開後のHELLP症候群褥婦では，HELLP症候群のない褥婦に比べて，分娩後尿量が少ない可能性がある。尿量／補液量比を用いて，これを評価することが本研究の目的である。

方法：帝王切開が行われた17名のHELLP症候群褥婦(分娩週数；35±2.8週，平均±標準偏差）と23名のHELLP症候群のないコントロール褥婦（37.5±2.7週）を研究対象とした。分娩周辺期に低血小板血症（12万／μl以下），高AST血症（50IU/L），高LDH血症（700IU/L）の3つを同時に示し，かつ出血傾向や他臓器不全などの臨床症候を示さない婦人を今回検討対象のHELLP症候群とした。手術室入室時から産褥まで尿量と補液量をモニターし，さらに血算を測定評価した。

成績：コントロールに比し，HELLP症候群婦人では　1)分娩当日および分娩翌日の尿量／補液量比は小さく（HELLP vs control: day0；0.21±0.13vs0.65±0.18，day1；0.89±0.45vs1.30±0.35），2）分娩前Hb（HELLP vs control:13.3±1.5vs10.7±1.5g/dL）およびHt（HELLP vs control:39.1±4.4vs32.1±3.9%）は高値であった。HELLP症候群婦人に認められたこの高Hb・高Htは産褥3日目には8.5±1.6mg/dLおよび26.4±5.8%にまで低下した。

結論：コントロール褥婦に比べHELLP症候群褥婦では，尿量は補液量に比し少量である（尿量／補液量比は小さい）。臨床症候を示さず血液データのみから診断されたHELLP症候群婦人では血液濃縮が存在する可能性がある。

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