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Dengue fever during pregnancy

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ABSTRACT

Dengue fever during pregnancy is an expanding issue in Southeast Asia; however, the knowledge of adverse effects on mothers and neonates remains limited. Therefore, we aimed to determine the impact of dengue fever. The clinical information of 20 patients of dengue fever during pregnancy in Vietnam from January 1, 2015 to December 31, 2015 was collected and their outcomes were retrospectively investigated. A total of 18 patients (90%) presented with positivity of nonstructural protein 1, and a primary infection. Additionally, 4 patients (20%) had preterm deliveries and 1 (5%) had a stillborn child. All live-born neonates were discharged from the hospital uneventfully. Also, 6 patients (30%) required platelet transfusion and 3 of them received transfusion before delivery, but there were no maternal death. In addition, 3 cases of patients (15%) developed to postpartum hemorrhage (PPH), and their platelet concentrations were significantly lower than those of patients without PPH [90.0 (19.0 – 374.0) × 10^3 vs. 40.0 (12.0 – 57.0) × 10^3 cell/μl, p = 0.001]. In addition, patients with PPH also presented with elevated liver enzymes. Pregnant patients with low platelet counts should be recognized as being at high risk for PPH.

Keywords: dengue fever, thrombocytopenia, postpartum hemorrhage
Abbreviations: PPH, postpartum hemorrhage; NS, nonstructural protein; Ig, immunoglobulin

INTRODUCTION

Recently, it was reported that dengue is the most common cause of fever during pregnancy (46%) in Vientiane, Laos.[1)] In 2015, 82,000 patients in Vietnam had dengue infection with 25 deaths. The mortality rate for severe dengue fever is 0.8–2.5%, and pregnancy should be recognized as a coexisting risk factor for serious infection.[2)] However, the maternal and fetal

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outcomes remain not fully understood. The first systemic review could not determine whether maternal dengue infection is a risk for adverse effects, because there were few comparative studies.[3] Recently, the first systematic review on outcomes of neonates born to mother with dengue fever was reported, and it demonstrated that preterm birth and low birthweight were reported to be the most common adverse pregnancy outcomes; however, dengue fever was not significantly associated with these adverse outcomes, suggesting that symptomatic dengue fever may indicate risk.[4] Other adverse effects such as stillbirth or postpartum hemorrhage (PPH) remain unclear. This report describes the effect of maternal dengue infection on maternal and fetal outcomes and focuses on the clinical features of patients with PPH.

MATERIALS AND METHODS

The present study was approved by the ethics committee of the Nagoya University School of Medicine (approval number: 2015–0153) and Tu Du Hospital (approval number: HNVP2016). Patients were retrospectively enrolled, including those who initially presented with fever and were diagnosed with dengue fever by blood examination and were hospitalized in Tu Du Hospital, Vietnam, from January 1, 2015 to December 31, 2015. Tu Du Hospital is a tertiary level governmental hospital and the largest maternity hospital in South Vietnam. Critical cases were referred to this hospital in Ho Chi Minh City from the provinces of South Vietnam. Demographic data, clinical and laboratory findings, and maternal and fetal outcomes were collected. Dengue virus nonstructural protein (NS) 1 antigen and dengue immunoglobulin (Ig) M/IgG antibodies were detected by SD BIOLINE Dengue Duo (Standard diagnostics, Inc., Gyeonggi-do, Republic of Korea). Primary or secondary infections were determined by dengue IgG. PPH was clinically diagnosed by attending doctors, based on vital signs and total volume of bleeding at delivery. Platelet transfusion was also decided by each attending doctor, and their decisions were based on general conditions of patients. The patients were treated at clinical manifestation with the treatment mainly consisting of fluid replacement therapy or/and blood transfusion as reported previously.[2] Statistical analyses were performed using the SPSS 24.0 software package (IBM Corp., Armonk, NY). Differences between the groups were considered to be statistically significant at $p < 0.05$.

RESULTS

During the study period, there were 69,562 deliveries and 20 pregnant women were diagnosed as seropositive for dengue (0.0289%). The clinical characteristics and perinatal outcomes are depicted in Table 1. The transfusion of platelets was required in 6 cases. There was one case of stillbirth at 39 weeks, on the third day of disease (Supplementary Table). Patients were diagnosed after 4.6 ± 2.3 days after the onset of symptoms. Cesarean section was performed in 4 cases (20.0%). One of them was performed because of a category III fetal heart rate monitoring[5] with Apgar scores of 7 and 8 at 1 and 5 minute, and the other 3 Cesarean section were performed because of disproportion. Additionally, 2 cases (10.5%) had a low Apgar score (<7) at 1 minute. All live-born neonates were discharged from the hospital uneventfully. The factors related to PPH are depicted in Table 2. Total bleeding volume of case 1, 2 and 3 was approximately 1300, 1400, and 2000 ml, respectively (Supplementary Table). The concentrations of platelets in the maternal serum were significantly lower in these cases than those in cases without PPH ($p = 0.001$). All cases with PPH showed elevated liver enzymes, which were significantly higher than

Table 1 The clinical characteristics and perinatal outcomes of patients

Characteristics	n = 20
Age (years, mean ± SD)	24.8 ± 3.7
Primipara (n, %)	13 (65.0)
NS1 positive (n, %)	18 (90.0)
Secondary infection (n, %)	2 (10.0)
Bleeding manifestation * (n, %)	7 (35.0)
Hematocrit (%, median, min-max)	39 (29.5 – 42.5)
Platelet (× 10^3 cells/μl, median, min-max)	76 (12 – 374)
Thrombocytopenia (< 100,000 cells/μl, n, %)	12 (60.0)
Platelet transfusion (n, %)	6 (30.0)
Platelet transfusion before delivery (n, %)	3 (15.0)
Interval between onset of symptom and diagnosis (days, mean ± SD, n=19)	4.6 ± 2.3
Interval between onset of symptom and delivery (days, mean ± SD, n=19)	5.2 ± 2.5
Perinatal outcomes	n = 20
Gestational age at delivery (weeks, mean ± SD)	38.5 ± 1.5
Birth weight (g, mean ± SD)	3021.1 ± 415.8
Term but low birth weight (< 2500 g, n, %)	1 (5.0)
Preterm delivery (< 37 weeks, n, %)	4 (20.0)
Premature rupture of the membrane (n, %)	8 (40.0)
Stillbirth (n, %)	1 (5.0)
Category III fetal heart rate monitoring (n, %)	1/19 (5.3)
Cesarean section (n, %)	4 (20.0)
Postpartum hemorrhage (n, %)	3 (15.0)
< 7 of 1 minute Apgar score (n, %)	2/19 (10.5)
< 7 of 5 minute Apgar score (n, %)	0/19 (0.0)

*Petechia or bleeding in oral cavity.

those in patients without PPH (p = 0.004). There were 3 patients with thrombocytopenia (≤ 50 × 10^3 cells/μl) and without PPH, who underwent transfusion before delivery. No patient with PPH received platelet transfusion before delivery, but they required transfusion after delivery. Neither secondary infection (0/3 of PPH) nor bleeding manifestations (1/3 of PPH) were significantly associated with PPH.

All cases were diagnosed during the third trimester (Supplementary Table). There was no reported maternal death.

DISCUSSION

We demonstrated the perinatal outcomes of 20 pregnant women with dengue fever. The rates of preterm birth, low birth weight, and stillbirth were 20%, 5.0%, and 5.0%, respectively, which were similar to those in previous reports.[1,3,4] However, live-born neonates were discharged uneventfully. There were no miscarriages or congenital anomalies because all cases were diagnosed

Table 2 Comparison of clinical findings between no PPH and PPH patient with dengue

Number of Patients	No PPH (n=17)	PPH (n=3)	*P* value
Age (years, mean ± SD)*	25.0 ± 3.8	23.7 ± 3.5	0.58
Gestational age at delivery (weeks, mean ± SD)**	38.2 ± 1.8	38.6 ± 0.4	0.34
Birth weight (g, mean ± SD) *	2961.8 ± 423.0	3216.7 ± 354.7	0.34
Hematocrit (%, median, min-max)	39.0 (29.5 – 42.5)	39.0 (30.0 – 39.7)	0.364
Platelet ($\times 10^3$ cells/μl, median, min-max)**	90.0 (19.0 – 374.0)	40.0 (12.0 – 57.0)	0.001
Elevated liver enzyme (n, %)***	1 (5.9)	3 (100.0)	0.004
Interval from onset of symptom to diagnosis (days, mean ± SD)**	4.7 ± 2.4	4.3 ± 1.2	0.86
Interval from onset of symptom to delivery (days, mean ± SD)**	5.4 ± 2.7	4.3 ± 1.2	0.72
NS1 positive (n, %)***	16 (94.1)	2 (66.7)	0.28
Secondary infection (n, %)	2 (11.8)	0 (0.0)	0.72
Bleeding manifestation (n, %)	6 (35.2)	1 (5.9)	0.73
Platelet transfusion before delivery (n, %)	3 (17.6)	0 (0.0)	0.60
Platelet transfusion** (n, %)	3 (17.6)	3 (100.0)	0.018
Premature rupture of membranes (n, %)	7 (41.2)	1 (5.9)	0.67
Cesarean section (n, %)	3 (17.6)	1 (5.9)	0.51

Note: The differences were detected using *unpaired *t* - test, **Mann-Whitney *U* test, for continuous variables in accordance with normal or non-normal distribution. ***Fisher's exact test were used for categorical variables.

at the third trimester. The rate of PPH was 15.0% in this study, but others reported that it was approximately 10.0%,[6,7] and 19.0%.[8]

As reported previously,[1,4] most cases of dengue fever during pregnancy had favorable outcomes for the mothers and neonates; therefore, almost of them could continue their pregnancy until late term or full term period with adequate fluid replace therapy. However, 3 cases were complicated by PPH. PPH is a life-threatening complication,[8,9] but appropriate management including efficient transfusion would help maternal lives.[10-12] Thus, the risk factor of PPH among pregnant women complicated with dengue fever was also examined in the current study. Their platelet concentrations were significantly lower than those of patients without PPH. In addition, all cases presented with elevated liver enzymes. Low platelets and elevated liver enzymes were a part of the diagnostic criteria of HELLP syndrome, which is a severe obstetric disease.[13] Patients with similar clinical findings of HELLP syndrome maybe at risk of PPH although a large sample size is necessary to validate it. A previous report suggested that the presence of bleeding manifestations or clinical symptoms may be related to PPH[8] or adverse effects,[4] respectively, but this study could not confirm these findings. Secondary infections cause a severe infection,[2] but these were not significantly associated with PPH, which was similar to the previous report.[6] Low platelets and elevated liver enzymes might be predictive factors for PPH, and transfusion would be prepared for childbirth.

The limitation of this study is the small population. We could not exclude other risk factors of PPH in patients with dengue fever, although the relationship between low platelets and PPH seems reasonable.

From the findings in this study, all pregnant patients with denguefever should have their platelets evaluated. Although further investigation is required, patients with low platelets should be checked for elevated liver enzymes and managed to prevent PPH with platelets transfusion before delivery.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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Supplementary Table Clinical Profile of patients in this study

Patient No.	Age	Parity	GA	Int. 1	Int. 2	NS1	Infection	Platelet ($\times 10^3$ cells/μl)	Hct (%)	AST (IU/l)
1	24	1	38w4d	5	5	N	Primary	12	39	90
2	20	0	38w2d	5	5	P	Primary	40	39.7	1526
3	27	3	39w0d	3	3	P	Primary	57	30	53
4	24	0	36w6d	10	7	P	Primary	19	39	ND
5	31	1	33w6d	4	4	P	Primary	36	37.8	ND
6	28	0	39w5d	3	2	P	Primary	37	39	39
7	26	1	39w6d	6	6	P	Secondary	39	42	117
8	33	1	40w1d	5	3	P	Primary	52	41.1	ND
9	22	0	37w6d	7	6	P	Primary	68	41.7	ND
10	22	0	37w3d	7	7	P	Secondary	72	38.8	ND
11	25	0	39w1d	3	3	P	Primary	80	39.6	39
12	20	0	36w3d	10	9	P	Primary	90	40.1	ND
13	25	0	38w2d	9	9	N	Primary	100	41.3	ND
14	23	0	39w0d	5	3	P	Primary	114	36.2	33
15	22	0	39w4d	3	3	P	Primary	120	33.6	37
16	30	1	39w0d	2	2	P	Primary	140	29.5	19
17	22	0	39w4d	2	2	P	Primary	145	30.1	41
18	28	1	38w3d	6	6	P	Primary	145	41.6	ND
19	21	0	39w6d	4	3	P	Primary	184	42.5	47
20	23	0	34w6d	ND	ND	P	Primary	374	32.5	ND

Abbreviations: GA, gestational age at delivery; Int. 1, interval between onset of symptom and diagnosis; Int. 2, interval between onset of symptom and delivery; Hct, hematocrit; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BT, platelet transfusion; BT-pre, platelet transfusion before delivery; PROM, premature rupture of membrane; MOD, mode of delivery; Ap1/5, Apgar scores at 1/5minutes; PPH, postpartum hemorrhage; Pet, petechial; B, bleeding in oral cavity; N, negative; P, positive; VD, vaginal delivery; CS, Cesarean section; ND, not determined; IUFD, intrauterine fetal death
*category III for fetal heart monitoring.

Supplementary Table Continued

Patient No.	ALT (IU/l)	Bleeding	BT	BT-pre	PROM	MOD	Birth weight (g)	Ap1/5	PPH
1	34	Pet, B	Yes	No	Yes	VD	3150	8/9	Yes
2	934	N	Yes	No	No	CS	3600	6/8	Yes
3	11	N	Yes	No	No	VD	2900	8/9	Yes
4	ND	Pet	Yes	Yes	Yes	VD	3000	8/9	No
5	ND	Pet	Yes	Yes	No	VD	2250	7/8	No
6	40	Pet	Yes	Yes	Yes	VD	3000	8/9	No
7	49	Pet	No	No	No	VD	3300	8/9	No
8	ND	N	No	No	Yes	VD	3600	8/9	No
9	ND	N	No	No	No	VD	3100	8/9	No
10	ND	N	No	No	Yes	VD	2200	8/9	No
11	15	N	No	No	No	VD	3100	8/9	No
12	ND	Pet	No	No	Yes	CS	2400	6/7	No
13	ND	N	No	No	Yes	CS	3100	7/8	No
14	13	N	No	No	No	VD	3000	IUFD	No
15	9	N	No	No	No	VD	2600	8/9	No
16	9	N	No	No	No	VD	3600	8/9	No
17	16	N	No	No	No	VD	2950	7/8	No
18	ND	Pet	No	No	No	VD	3350	8/9	No
19	15	N	No	No	No	CS*	3200	7/8	No
20	ND	N	No	No	Yes	VD	2600	8/9	No