Dengue Hemorrhagic Fever and its Effect on the Pregnancy Outcomes: A Case Series

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Abstract

Background: Dengue fever in pregnancy is associated with a more severe presentation and an increased risk of adverse obstetric and neonatal outcomes. We describe three cases of dengue fever in pregnancy with different fetal outcomes (intrauterine fetal death, fetal distress, and healthy neonate).

Case Illustration: The first case involves a 23-year-old G1P0A0 at 31-32 weeks of gestation complaining of reduced fetal movement. She presented with a high-grade fever, anaemic, and thrombocytopenic. Her liver function was increased with AST 447 U/L and ALT 403 U/L. The fetal heart rate could not be detected.

The second case involves a 26-year-old G3P2A0 at term pregnancy complaining of labor pain. She presented with vaginal bleeding, high-grade fever, and vomiting five days prior. Her liver function was also increased (AST 301 U/L and ALT 298 U/L). At presentation, fetal distress was detected. The third case involves a 19-year-old G2P1A0 presented with high-grade fever and nausea for five days. Her liver function was moderately increased (AST 68 U/L and ALT 76 U/L). She delivered a 3050-gram healthy neonate vaginally.

Discussion: Dengue fever causes adverse obstetric outcomes. Endothelial injury exacerbated by plasma loss leads to placental dysfunction and poor fetal conditions. Unfortunately, dengue fever in pregnancy is not yet specifically addressed in our national guidelines.

Conclusion: Increased severity of dengue fever in pregnancy may cause poor maternal and fetal outcomes.

Key words: Dengue fever, maternal, fetal, outcomes, pregnancy

Demam Berdarah *Dengue* dan Dampaknya terhadap Luaran Kehamilan: Sebuah Serial Kasus

Abstrak

Pendahuluan: Demam berdarah *dengue* pada kehamilan terkait dengan tingkat keparahan penyakit *dengue* yang lebih berat dan meningkatnya risiko komplikasi obstetrik dan neonatus. Serial kasus ini menyajikan tiga kasus demam berdarah pada kehamilan dengan luaran janin yang berbeda (kematian janin intrauterine, gawat janin, dan neonatus sehat).

Presentasi Kasus: Kasus pertama, G1P0A0 gravida 31 – 32 minggu, berusia 23 tahun, datang dengan keluhan utama berkurangnya gerakan janin. Keluhan demam, nyeri retro-orbital, mual, dan muntah dirasakan sejak 4 hari sebelumnya. Terdapat tanda konjungtiva anemis, trombositopenia, dan fungsi liver meningkat (AST 447 U/L dan ALT 403 U/L). Detak jantung janin tidak terdeteksi. Kasus kedua, G3P2A0 gravida aterm, 26 tahun, datang dengan keluhan mules-mules, perdarahan jalan lahir, demam, mual, dan muntah dirasakan sejak 5 hari sebelumnya. Pasien mengalami trombositopenia dan peningkatan fungsi liver (AST 301 U/L dan ALT 298 U/L). Pemeriksaan janin menunjukkan tanda gawat janin. Kasus ketiga, G2P1A0 gravida aterm, 19 tahun, datang dengan keluhan utama mules-mules. Keluhan demam dan mual dirasakan sejak 5 hari. Pemeriksaan menunjukkan trombositopenia dan fungsi liver sedikit meningkat (AST 68 U/L dan ALT 76 U/L). Pasien melahirkan neonatus sehat secara spontan dengan berat 3050 gram.

Diskusi: Kebocoran plasma merupakan pencetus dari kerusakan endotel sehingga dapat mengakibatkan disfungsi plasenta dan kondisi janin memburuk. Namun, belum ada panduan resmi tatalaksana demam berdarah pada kehamilan di Indonesia.

Kesimpulan: Meningkatnya tingkat keparahan demam berdarah pada kehamilan menyebabkan luaran maternal dan neonatus yang buruk.

Kata kunci: Demam *dengue*, maternal, fetus, luaran, kehamilan

Introduction

Dengue fever (DF) is a significant public health issue in regions characterized by tropical and subtropical climates. Approximately 50 million cases of dengue infection occur globally each year, and around 500,000 individuals with dengue hemorrhagic fever need to be hospitalized annually.[1] In Indonesia, the yearly occurrence was approximately 35 to 40 cases per 100,000 people, and the risk of death from the disease was 0.73%.[2] Dengue is characterized as a sudden onset of fever accompanied by one or more of the following indications: severe headache, pain behind the eyes, muscle and joint pain, skin rash, low white blood cell count, and hemorrhagic manifestations.[3] The incidence of dengue hemorrhagic fever (DHF) in Indonesia as of July 2020 was reported at 71,633 cases.[4]

There is a danger of transmission from mother to child before and during labor when DHF is present, and infections in pregnant women are more likely to be severe than in the general adult population. Multiple prior investigations by Tien et al.[5], Brar et al.[6], and Saroyo et al.[7], demonstrate that DHF during pregnancy is associated with an increased risk of infection and mother-to-child transmission before and after giving birth, compared to the general adult population.[2] A systematic literature review shows that dengue virus infection during pregnancy has been linked to an increased risk of having a baby born prematurely or with a low birth weight. Because much of the literature on the subject consists of only small studies, the review was unable to establish whether maternal dengue is a risk factor for unfavorable pregnancy outcomes.[6] According to these findings, pregnant women who contract dengue have a higher risk of infection than the general adult population, and there is a danger of mother-to-child transmission prior to and during delivery.[8]

Currently, there is no universally accepted consensus about the management of dengue illness in pregnant women.[9] An investigation of the consequences of dengue infection in pregnant women in a nation with a high prevalence of the disease, such as Indonesia, is crucial as the findings can serve as a foundation for making informed decisions and predicting the outlook for individuals affected by dengue infection. This study, consisting of 3 case studies, describes the severity of dengue infection in the mother and relate it to the condition of the fetus, which consists of healthy babies, fetal distress, and intrauterine fetal death (IUFD).

Case Illustration

Case 1: Intrauterine Fetal Death Outcome

A 23-year-old primigravida lady (G1P0A0) was referred from the peripheral hospital with a report of reduced fetal movement. The patient's mother had severe dengue illness. The patient initially exhibited symptoms, including a high-grade fever, pain behind the eyes, nausea, and vomiting for four days. The patient's gestational age was estimated to be between 31-32 weeks based on the last menstrual period (LMP). During the physical examination, the patient's blood pressure was measured at 110/70 mmHg, heart rate at 94 BPM, and temperature at 37.7°C. The blood examination showed a low level of hemoglobin (7.3 g/dL), a normal level of hematocrit (41.3%), a low platelet count (29,000/µL), and an increase in liver enzymes (AST 447 U/L and ALT 403 U/L). Additionally, the patient tested positive for Immunoglobulin M (IgM) and Immunoglobulin G (IgG) dengue serology, but there was no result for the NS1 antigen. (Table 1).

She was diagnosed with severe dengue due to severe bleeding. The patient was presented with high-grade fever, so the observation of fever condition was done. During her care in

Table 1 Daily Laboratory Trend of the Patient

Laboratory Parameters		Outside	Day 1	Day 2	Day 3
Blood Count	Hemoglobin (g/dL)	7.3	8.6	7.6	9.7
	Hematocrit (%)	37	36.4	23.7	20.8
	White blood cell (/mm^3)	6,500	17,100	31,400	35,100
	Platelet (/µL)	29,000	40,100	49,800	50,650
Liver function	AST (U/L)	447			386
	ALT (U/L)	401			367
Coagulation profile	Prothrombin time (PT)	15.5	16.2	18.1	14.5
	Activated partial thromboplastin time (aPTT)	36.2	35.1	34.1	33.1

the peripheral hospital, the patient was said to have a low platelet level (29,000 /µL). Due to severely decreased thrombocyte and the possibility of dengue fever, the patient was referred to a tertiary hospital. The patient was admitted to an Intensive Care Unit (ICU) due to severe bleeding, presenting as severe anemia. On obstetric examination, fundal height was measured at 29 cm, abdominal circumference at 98 cm, fetal lie head at 5/5, and back on right side. However, there was no sound of a fetal heart, and the contraction was not present. The estimated fetal weight was 1,900 grams. Due to the primiparity condition, pelvic assessment was conducted; and the pelvic was considered eligible for vaginal delivery. The patient was planned to termination with misoprostol 50mcg, on posterior fornix. Before the termination, the patient underwent improvement of general condition due to anemia condition. The hemoglobin deteriorated to 7.6 despite 3 packs of PRC transfusion. During the 3rd day of care, the hemoglobin level of the patient improved, and the vaginal delivery was done. There was no complication of bleeding during delivery. The baby was born spontaneously, without any sign of life. The fetus was diagnosed as stillbirth.

Case 2: Fetal Distress Outcome

A 26-year-old woman, G3P2A0, was referred from a primary healthcare (PHC) with complaint of labor pain in the last 5 hours before admission. The complaint was accompanied with vaginal bleeding and covered full of 3 pads, and this was the first vaginal bleeding that the patient experienced. The patient had no history of rupture of the membrane. The fetal movement was still felt by the mother. The patient initially exhibited symptoms including high-grade fever, retro-orbital discomfort, nausea, and vomiting for five days. She was a full-term pregnancy determined by the last menstrual period (LMP). The previous birth involved a cesarean section for the first kid because of a transverse lying position. The patient stated that she did not have a previous history of significant bleeding during a previous pregnancy. During the physical examination, the individual's blood pressure was measured at 100/70 mmHg, heart rate at 102 beats per minute, and temperature at 36.7°C. There was no apparent swelling. Assessing liver enlargement was challenging. The blood examination showed a low level of hemoglobin (9.4 g/dL), a low level of hematocrit (26.7%), a low platelet count (32,000/µL), and an increase in liver enzyme levels (AST 301 U/L and ALT 298 U/L). Additionally, she tested positive for Immunoglobulin M (IgM) and Immunoglobulin G (IgG) dengue serology, but there was no result for the NS1 antigen. (Table 2).

Table 2 Daily Laboratory Trend of The Patient

Laboratory Parameters		Outside	Day 1	Day 2	Day 3
Blood Count	Hemoglobin (g/dL)	9.4	**6.8**	8.1	9.6
	Hematocrit (%)	26.7	36.4	23.7	20.8
	White blood cell (/mm^3)	10,690	15,120	14,980	16,290
	Platelet (/µL)	32,000	36,890	49,800	53,760
Liver function	AST (U/L)	301			246
	ALT (U/L)	298			213
Coagulation profile	Prothrombin time (PT)	10.0	13.1	12.3	12.6
	Activated partial thromboplastin time (aPTT)	29.6	27.6	26.7	32.1

She was diagnosed with dengue with a warning sign. The patient was presented with high-grade fever for five days. Moreover, history of chronic disease was denied, and history of trauma during pregnancy was denied. Due to severely decreased thrombocyte (32,000/ µL) and the possibility of dengue fever, the patient was referred to a tertiary hospital. On obstetric examination, fundal height was measured at 32 cm, abdominal circumference at 95 cm, fetal lie head at 3/5, and back on left side. Meanwhile, fetal heart rate was measured at 100-90-144x/ minute, irregular.

A cardiotocography examination was performed on the patient; the results showed a baseline of 140150 bpm, variability >5 bpm, acceleration (+), and deceleration (+). The cardiotocography result showed category III, suggesting fetal distress. The patient was planned to hold intrauterine resuscitation and emergency cesarean section due to fetal distress. After 20 minutes of intrauterine resuscitation, cardiotocography still showed category III. The baby was delivered with APGAR 5/7, weight of 2,830 grams, and length of 47 cm. There was no complication of bleeding during delivery. The baby was tested for dengue transmission on day one, and the result was NS1, IgM, IgG, and dengue serology from vein blood was negative.

Case 3: Normal Outcome

A 19-year-old woman, G2P1A0, was referred from primary healthcare (PHC) with a complaint of labor pain in the last 6 hours before admission. The patient had no history of rupture of the membrane, while the fetal movement was still felt by the mother. She was presented initially with high-grade fever and nausea for five days. The patient experienced vomiting, but only once, and not persistent. The patient experienced aches and pains in the entire joint. Previous history of birth was spontaneous birth and preterm labor. The patient denied a history of profound bleeding in a prior pregnancy. History of chronic disease was denied. During the physical examination, the patient's blood pressure was measured at 110/70 mmHg, heart rate at 88 BPM, and temperature at 36.7°C. No swelling was apparent. Assessing liver enlargement was challenging. The blood examination showed a hemoglobin level within the normal range (14.2 g/dL), a low hematocrit level (29.8%), a low platelet count (61,000/ µL), and increased liver enzymes (AST 68 U/L and ALT 76 U/L). Additionally, the patient tested positive for Immunoglobulin M (IgM) and Immunoglobulin G (IgG) dengue serology, but there was no detection of NS1 antigen (Table 3).

She was diagnosed with dengue without

Table 3 Daily Laboratory Trend of The Patient

Laboratory Parameters		Outside	Day 1	Day 2	Day 3
Blood Count	Hemoglobin (g/dL)	14.2	13.1	13.6	13.8
	Hematocrit (%)	29.8	30.1	30.4	31.8
	White blood cell (/mm^3)	9,560	10,880	12,860	13,120
	Platelet (/µL)	61,000	71,800	86,000	100,200
Liver function	AST (U/L)	68			52
	ALT (U/L)	76			63
Coagulation profile	Prothrombin time (PT)	13.1	12.3	10.8	12.1
	Activated partial thromboplastin time (aPTT)	33.2	28.1	26.7	27.2

warning signs. Due to decreased thrombocyte (61,000 µL) and the possibility of dengue fever, the patient was referred to a tertiary hospital. On obstetric examination, fundal height was measured at 34 cm, abdominal circumference at 109 cm, fetal lie head at 2/5, and back on the left side. Meanwhile, fetal heart rate was measured at 140144x/minute, regular. The contraction was adequate, measured at 34x/10'/40". The estimated fetal weight was 3000 grams.

A cardiotocography examination was performed on the patient and showed a baseline of 144148 bpm, variability >5 bpm, acceleration (+), and deceleration (-). The cardiotocography result shows category I, suggesting a normal, healthy baby. The patient was planned to undergo spontaneous vaginal delivery. The baby was delivered with APGAR 7/9, weight of 3,050 grams, and length of 46 cm. There was no complication of bleeding during delivery. On the first day, the newborn underwent testing for dengue transmission. The NS1, IgM, IgG, and dengue serology tests conducted on the baby's blood from a vein were negative.

Discussion

The symptoms of dengue fever include a fever that lasts between two and seven days, followed by a defervescence phase that lasts between three and four days and causes shock due to extensive plasma leakage.[10] A clinical examination, diagnosis, treatment, and monitoring of dengue infection might be difficult during pregnancy. Prior research has demonstrated that dengue during pregnancy might heighten the likelihood of maternal hemorrhage, premature labor, insufficient amniotic fluid, fetal mortality, and vertical transmission resulting in newborn thrombocytopenia that needs a platelet transfusion. Serology is useful in differentiating between the clinical appearance of hemolysis, high liver enzyme, low platelet count (HELLP) syndrome, and other similar disorders that may cause confusion.[6]

During pregnancy, a woman's circulatory, pulmonary, and hematologic systems go through various physiologic shifts. After the third trimester, the plasma volume increases by roughly 40%, which results in dilutional anemia. This anemia covers the hemoconcentration that often happens during the defervescence phase of dengue with a warning sign, which is when the baby grows rapidly.[11] In this case series, the patient was referred to our hospital after four to five days of fever. Despite case number 1 having a normal hematocrit level, the patient endured significant bleeding, leading to severe anemia. The hemostatic abnormalities in both the mother and the infant result in an increased predisposition for bleeding, which

can lead to uncontrolled bleeding.[12]

The two most crucial components of management are the administration of fluids and the determination of which phase the patient is now in. The diagnosis of dengue fever during pregnancy undoubtedly has an impact on the management choices and decisions that must be made, given the paramount significance of the mode and timing of delivery.[13] In this case series, the first case was managed in ICU due to severe bleeding. The deterioration of the patient was severe dengue and must be carefully examined. However, the first case showed normal hemoconcentration. This situation aligns with the hypothesis of imitating the increase in blood concentration in severe cases of dengue fever. In a case report by Hariyanto H et al. in Indonesia[13], the patient was in a critical condition with a normal hematocrit level. The individual experienced a condition of shock characterized by changes in mental functioning and decreased blood flow. During this stage, it is crucial to conduct vigilant monitoring to prevent the mother from progressing to a state of shock.

Pregnant women have an increased susceptibility to more severe infections and a greater mortality rate resulting from dengue infection in comparison to the general population. The gestational age and phase of dengue infection have a crucial role in establishing the appropriate therapy and prognosis.[14] Moreover, this case series shows that severity was by fetal outcomes. The first case presented with severe dengue and severely increased liver enzymes, and the fetus had experienced intrauterine fetal death. In the second case, the patient experienced hemoglobin drops until 6.8, but the result of PRC infusion was good. Unfortunately, since admission, the patient had abnormal category III on cardiotocography and was diagnosed with fetal distress. The severity of dengue in the fetal distress cases was dengue with warning signs, with signs of bleeding. On the other hand, the third case had healthy babies, and the dengue was mild, without warning signs.

In the first case, the patient experienced fetal death. Fetal death was highly associated with maternal dengue. A systematic review and meta-analysis conducted by Rathore et al. found that DENV infection during pregnancy is linked to a higher risk of maternal mortality, stillbirth, and neonatal deaths. The pooled odds ratio (OR) for maternal mortality was 4.14 (95% CI, 1.17–14.73); for stillbirth was 2.71 (95% CI, 1.44–5.10); and for neonatal deaths was 3.03 (95% CI, 1.17–7.83), when compared to pregnancies without DENV infection.[15]

The severity of dengue fever symptoms is determined by several factors, including both the host and the virulence of the virus. Despite receiving preventative platelet transfusions, patients with dengue infection have been shown in some trials to experience clinical bleeding because of the illness's complex influence on the hemostatic system. In this case series, hemoglobin was deteriorating despite transfusion of PRCs. There is a possibility that the unfavorable outcome for the fetus was caused by placental circulation brought on by endothelial injury. This created increased vascular permeability, which in turn led to plasma loss. The risk of dengue fever in pregnancy is not addressed in national guidelines.

Conclusion

The fetal outcome of the pregnancy in this case series was determined in accordance with the severity of dengue in the mother. Due to the lack of a readily available national guideline, the management of dengue fever in pregnant patients in tertiary hospitals is still not as good as it may be, contributing to the delayed identification of dengue. A multidisciplinary team approach is required since there is an increased risk of morbidity

and mortality for both the mother and the fetus when the mother has dengue fever during the peripartum period.

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Author contributions

All authors contributed to the conceptualization of the presented case report. F.Y.A. wrote the initial draft of the case report with input from all authors. D.T. and S.A. made a substantial contribution to the design of the case report. All authors drafted or critically revised the case report for important content, approved the version to be published, and agreed to the integrity or accuracy of any part of the work. A.A.N.P. contributed significantly to resources for case report execution.

Patient Consent

Written informed consent was obtained from the patient for publication of the case report and accompanying images. The authors state that the patient gave his informed consent to have this case series published.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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