Dengue in Pregnancy

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Outline

• Epidemiology
• Clinical manifestations
• Effect of pregnancy on dengue infection
• Effect of dengue infection on pregnancy
• Effect of dengue infection in fetus and neonate
• Management in pregnant women
Dengue virus (DENV)

- Single-stranded RNA virus
- Member of Flavivirus family

Selected Flaviruses

- Tick-borne encephalitis virus
  - West Nile virus
  - Murray Valley encephalitis virus
  - Japanese encephalitis virus
  - St. Louis encephalitis virus
  - DENV 1
  - DENV 3
  - DENV 2
  - DENV 4
  - Yellow Fever virus
DENGUE SEROTYPE
MALAYSIA
DENGUE DEATHS 1997 – 2015

Year

Number of Deaths


28 32 52 82 37 45 50 99 72 102 107 92 98 112 88 134 36 35 92 215 336

CFR 0.28
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<td>2017 (n=73)</td>
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<td>Obesity (Based on BMI (Adults) or NCHS chart (Children))</td>
<td>32%</td>
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<td>Renal Failure</td>
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<td>Pregnancy</td>
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<td>Immunocompromised (e.g. Leukimia/HIV positive/Patient on steroids/Chemotheraphy)</td>
<td>1%</td>
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Seroprevalence in Pregnant Women

**Table 1: Seroprevalence status.**

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<tr>
<th>Antibodies</th>
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<td>Past infection (IgG)</td>
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<td>Seronegative</td>
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<td><strong>Total</strong></td>
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NA Mohamad Ismail

The Scientific World Journal
Volume 2014, Article ID 436975,
“Dr Chow, this is nurse Aida, I am calling from ward dengue, the patient Mr Leong’s FBC is back, the platelet is now 7 only, how ah??......”
Clinical course of dengue

Dengue is a systemic and dynamic disease.

Dengue is NOT a platelet count disease

Acknowledgements

This curriculum was developed with technical assistance from the University of Malaya Medical Centre. Materials were contributed by the Ministry of Health, Singapore, the United States Centers for Disease Control and Prevention, and the University of Malaya Medical Centre.
Natural History of DENV Infections

Infection Incidence ~ 5% / year

- Asymptomatic 75%
- Symptomatic 25%
  - Dengue fever 95-99%
  - Severe dengue 1-5%
    - Survive 95-99.5%
    - Die 0.5 - 5%

Adapted from Vaccine 2004; 22: 1275-1280

Slide from WHO dengue training module
Case Definition

WHO 2009 classification

• *Probable dengue* - fever and 2 of the following criteria:
  • - nausea, vomiting
  • - aches and pains
  • - rash
  • - tourniquet test positive
  • - leucopenia
  • - any warning signs
What are the Warning Signs?

- Any abdominal pain/tenderness
- Persistent vomiting (≥3 times over 24 hours)
- Persistent diarrhoea (≥3 times over 24 hours)
- Third space fluid accumulation (such as ascites, pleural and pericardial effusion)
- Spontaneous bleeding tendency
- Lethargy/restlessness/confusion
- Tender liver
- Raised HCT with rapid drop in platelet:
  - HCT male <60 years - 46
  - HCT male >60 years - 42
  - HCT female (all age groups) - 40
  *median value of normal HCT in Malaysian population

33 level II-2.
BEWARE

• Vomiting
  – Hyperemesis gravidarum
• Headache
  – Pre eclampsia
• Abdominal pain
  – Threatened abortion
  – Preterm labour
Phases of dengue:

6 Key features:

1. Temperature
2. Oral intake
3. Urine output

Potential clinical issues

Laboratory changes

4. WBC
5. Platelet
6. HCT

Virology and Serology

Days of illness: 0 1 2 3 4 5 6 7 8 9 10

Febrile

Critical

Recovery

Dehydration

Shock

Bleeding

Reabsorption Fluid overload

Capillary permeability

Organ Impairment

Platelet

WBC

Haematocrit

IgM/IgG

Viraemia

Adapted from WCL Yip, 1980 by Hung NT, Lum LCS, Tan LH
Do all dengue patients enter critical phase?

NOT all patients will experience the critical phase

Clinical course of patient without significantly increased vascular permeability:

- Fever subsides → general condition improves and appetite recovers
- May have leukopenia
- Mild to moderate thrombocytopenia
Dengue case classification by severity 2009

**Dengue ± warning signs**

**Severe dengue**

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**Criteria for dengue ± warning signs**

**Probable dengue**
Live in/travel to dengue endemic area. Fever and 2 of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leucopenia
- Any warning sign

**Laboratory confirmed dengue** (important when no sign of plasma leakage)

**Warning signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- **Laboratory:** Increase in HCT concurrent with rapid decrease in platelet count

* Requiring strict observation and medical intervention

**Criteria for severe dengue**

1. **Severe plasma leakage** leading to:
   - Shock (DSS)
   - Fluid accumulation with respiratory distress

2. **Severe bleeding**
   as evaluated by clinician

3. **Severe organ involvement**
   - Liver: AST or ALT>=1000
   - CNS: Impaired consciousness
   - Heart and other organs
CLINICAL EXAMINATION: 5 in 1 touch

The “5-in-1 maneuver” magic touch – CCTV-R

Hold the patient’s hand to evaluate peripheral perfusion.

Save life in 30 seconds by recognizing shock

1. **Colour**
2. **Capillary refill**
3. **Temperature**
4. **Pulse Volume**
5. **Pulse Rate**
Diagnostic tests

• Dengue Combo test
  – NS1 Ag, Ig M and Ig G

• All suspected dengue cases should do dengue combo test
Non-Structural Protein-1 (NS1 Antigen)

- a highly conserved glycoprotein that seems to be essential for virus viability.
- Secretion of the NS1 protein can be found in dengue infection.
- This antigen is present in high concentrations in the sera of dengue infected patients during the **early phase of the disease**.
- The detection rate is better in acute sera of primary infection (75%-97.3%)
  - when compared to the acute sera of secondary infection (60-70%).
- NS1 Ag may be positive from Day 1-9 of illnesses.
Dengue infection: immune response

Primary Infection
Onset of symptoms

Antibody & Antigen level

Virus

NS1

IgM

Secondary Infection
Onset of symptoms

IgG

Time
RESULT:

NS1 positive
Ig M neg
Ig G neg

Early dengue

NS1 positive
Ig M positive
Ig G neg

Primary Dengue

NS1 positive
Ig M neg
Ig G neg

Secondary dengue

NS1 neg
Ig M neg
Ig G neg

NOT dengue
Effects of Pregnancy on Dengue

• Physiology of pregnancy
  – Cardiovascular – tachycardia, lower blood pressure
  – Hematological – lower HCT at 3rd trimester
  – HCO3 level lower

• Confuse with other pregnancy complications
  – Thrombocytopenia
  – HELLP syndrome
    • Thrombocytopenia
    • Raised liver enzymes
Effects on Mother

• Maternal death
  – Dengue shock with multiorgan failure
  – OR 3.38 to develop severe dengue

• Severe and prolonged bleeding
  – Intrapartum: LSCS, operative vaginal delivery
  – DSS

• Abortion
  – First trimester
  – 3.8% to 16%

Waduge R et al, J Clin Virol 2006
Effect of Dengue on Pregnancy

• Preterm birth (3%-17%)
  – Fever (high grade)
    • Stimulate uterine contractions
    • Heat shock protein causing damage to placenta and fetus
  – Immune response to dengue (eg. ILs, TNF )
    • Placental inflammation, trophoblast apoptosis

• Low birth weight (9-19%)

• Fetal death (4.7-13%)
  – Compromised feto-placental circulation

• Neural tube defect - fever

Tan PC et al, Obstet Gynecol 2008

Kariyawasm S et al, J Infect Dev Cries 2010
DENGE IN PREGNANCY

Nor Azlin Mohamed Ismail, Nirmala Kampan, Zaleha Abdullah Mahdy, Muhammad Abdul Jamil and Zainul Rashid Mohd Razi

Department of Obstetrics and Gynecology, Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Abstract. This was a retrospective study of patients with dengue infection in pregnancy from year 2000 till 2004. Data were analyzed by looking at the presentation, complications of patient and fetus, and pregnancy outcomes. There was a total of 16 cases with an increasing trend (0.12% in 2003 vs 0.25% in 2004). The mean age of patients was 30.19 ± 6.85 years. Fifty percent of patients were multiparae and in their third trimester. The average gestation was 24.44 weeks with 7.5 days being the average duration of ward admission. Tourniquet test was positive in 62.5% of patients. Dengue serology IgM was positive in 50% whereas dengue serology IgG were positive in 68.8% of patients. There were three cases of maternal death. One patient presented as missed abortion. Preterm deliveries happened in 50.0% of the women. There were 4 premature babies, one in-utero fetal death, and two fetuses which suffered acute fetal distress. Three babies required intensive care. One unrelated fetal anomaly resulted in early neonatal death.
Symptomatic Dengue Infection during Pregnancy and Infant Outcomes: A Retrospective Cohort Study

Eleanor E. Friedman¹*, Fadi Dallah², Emily W. Harville¹, Leann Myers³, Pierre Buekens¹, Gerard Breart⁴, Gabriel Carles²

¹ Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana, United States of America, ² Franck Joly Hospital, St. Laurent du Maroni, French Guiana, France, ³ Department of Biostatistics and Bioinformatics, Tulane School of Public Health and Tropical Medicine, New Orleans Louisiana, United States of America, ⁴ INSERM, U1153, Paris, France

Abstract

Background: Dengue is a mosquito-borne disease that is common in many tropical and subtropical areas. Dengue infections can occur at any age and time in the lifespan, including during pregnancy. Few large scale studies have been conducted to determine the risk of preterm birth (PTB) and low birthweight (LBW) for infants born to women who had symptomatic dengue infection during pregnancy.

Methodology/Principal Findings: This study is a retrospective cohort study using medical records from 1992–2010 from pregnant women who attended a public regional referral hospital in western French Guiana. Exposed pregnancies were those with laboratory confirmed cases of dengue fever during pregnancy. Each of the 86 exposed infants was matched to the three unexposed births that immediately followed them to form a stratum. Conditional logistic regression was used to analyze these matched strata. Three groups were examined: all infants regardless of gestational age, only infants ≥ 17 weeks of gestational age and their strata, and only infants ≥ 22 weeks of age and their strata. Odds ratios were adjusted (aOR) for maternal age, maternal ethnicity, maternal gravidity, interpregnancy interval and maternal anemia. There was an increased risk of PTB among women with symptomatic dengue; (aOR all infants: 3.34 (1.13, 9.89), aOR 17 weeks: 1.89 (0.61, 5.87), aOR 22 weeks: 1.41 (0.39, 5.20)) but this risk was only statistically significant when all infants were examined (p value = 0.03). Adjusted results for LBW were similar, with an increased risk in the exposed group (aOR All infants: 2.23 (1.01, 4.90), aOR 17 weeks: 1.67 (0.71, 3.93), aOR 22 weeks: 1.43 (0.56, 3.70)) which was only statistically significant when all infants were examined (p value = 0.05).

Conclusions/Significance: Symptomatic dengue infection during pregnancy may increase the risk of PTB and LBW for infants. More research is needed to confirm these results and to examine the role of dengue fever in miscarriage.
Objectives: To document clinical and laboratory findings in a cohort of hospitalised patients with dengue during pregnancy in Sri Lanka and compare their presentation and outcomes with previously published cases.

Study design: Clinical, laboratory, maternal and fetal outcomes and demographic information were collected from patients with confirmed dengue infections during pregnancy treated in a Maternity Hospital in Sri Lanka from 1 January 2000 to 30 June 2004. The Medline database was searched to identify reports relating to dengue infection during pregnancy since 1965.

Results: Twenty-six patients [mean (S.D.) age: 29 (4.2) years] were studied. One (3.8%), 2 (7.7%) and 20 (77%) presented in the first, second and third trimesters of pregnancy, and 3 (11.5%) in the immediate post-partum period. Seventeen (65.3%) had primary and nine (34.7%) secondary dengue infections. Ten (38.5%) had DF, 6 (23.1%): DHF grade I and 10 (38.5%): DHF grade II. Five (19.2%) and three (11.5%) patients who first presented with cough/breathlessness or vaginal bleeding, were initially managed as having a pulmonary embolism or a primary obstetric cause for their vaginal bleeding. Bradycardia was noted in three of the four patients who had a cardiac arrhythmia. Seven (26.9%) needed admission to an ICU. Raised AST and ALT levels were seen in 81.2% and 43.7% of 16 patients in whom liver function tests results were available. No fetal malformations were seen in any of the babies born. The single patient who developed DHF in the first trimester had an abortion while having acute symptoms of dengue.
77% in 3rd trimester
65.3% primary dengue
61.6% DHF Grade 1 and II
26.9% needed ICU admission (7 patients)
• Diagnosed in 3\textsuperscript{rd} trimester
  – None have acute symptoms at delivery
  – No prolonged bleeding
• One preterm delivery (36 weeks)
• 6 LSCS – obstetric indications
• 4 LBW
  – 2 due to PIH
  – 2 exact cause unknown
• 1 abortion (at 9 weeks)
Case Report

Dengue infections during pregnancy: case series from a tertiary care hospital in Sri Lanka

Sampath Kariyawasam and Hemantha Senanayake

Professorial Obstetrics Unit, De Soysa Maternity Hospital, Colombo 8, Sri Lanka

• Pregnant women serological diagnosed dengue from May 2009 to Dec 2009
• 15 pregnant women included
  – 3 in 2nd trimester, 12 in 3rd trimester
  – 6 primary dengue, 9 secondary dengue
  – 3 DF, 3 DHF I, 7 DHF II, 2 DSS
• 3 patients had CS
  – Acute genital herpes (plat 30,000)
  – Pre eclampsia (in recovery) at 33 weeks (114)
  – Refused trial VD post CS previously (178)
• 1 maternal death and fetal loss at 35 weeks (DSS – DHF IV)
• 1 fetal demise (24 weeks) but mother survived (DSS - DHF III)
• 8 needed ICU admissions (no beds)
• No spontaneous preterm delivery or LBW (except the PE patient)

• No postpartum hemorrhage
  – All had plat >100,000 during peripartum period (except one patient)
  – None developed spontaneous labour during acute illness or before recovery from thrombocytopenia
• Overall results not significant
  – Case series, sample size small
• Presence of clinical symptoms and severity of disease are related to the risk of adverse fetal outcome
  – LBW
  – Preterm birth
Vertical Transmission

• Disruption of placental barrier
  – Increased vascular permeability and endothelial damage
• Symptomatic dengue infection near time of delivery
• Severe dengue – prolonged viraemia
• Reported 1.6 % to 10.5%
Vertical Transmission

- Fever
- Hepatomegaly
- Thrombocytopenia
- Circulatory insufficiency
Management of Dengue in Pregnancy

• Multidisciplinary care
  – Obstetricians, Physicians, Anaesthesiologists, Primary care physicians

• Supportive care
  – Paracetamol
  – IV fluid

• No NSAIDS

• Low threshold for admission

• Avoid surgery during critical and recovery phase
Management of dengue

Step 1: History taking

Step 2: Clinical examination: 5-in-1 magic touch

Step 3: Investigations

Step 4: Diagnosis with dengue phase and severity

Step 5: Management decision

Group A
- Send home

Group B
- Refer for in-hospital management

Group C
- Require emergency treatment and urgent referral
Outpatient management: Group A

Patients who are able to “drink enough to pee enough”

Group A – Send home if patient meets all of the following:

Intake: Getting adequate volume of oral fluids
Output: Passing urine at least once every 4 to 6 hours
Does not have any warning signs
Has stable hematocrit and hemodynamic status
Does not have co-existing conditions

Provide Dengue Monitoring Card

1. Give anticipatory guidance before sending home (see patient handout)
2. Follow up daily
3. Do serial CBCs
4. Identify warning signs early
HOME CARE ADVICE FOR DENGUE PATIENTS

WHAT SHOULD BE DONE?

- Adequate bed rest
- Adequate fluid intake (more than 5 glasses for an average person)
  - Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley water.
  - Plain water alone is not sufficient and may cause electrolyte imbalance. (Nicaragua 2003, Level 8)
- Take paracetamol (not more than 4 gram per day)
- Tepid sponging
- If possible, use mosquito repellent or rest under a mosquito net even during daytime to prevent mosquito bites
- Look for mosquito breeding places in and around the home and eliminate them

WHAT SHOULD BE AVOIDED?

- Do not take non steroidal anti-inflammatory (NSAIDS) e.g. aspirin/mefenamic acid (ponstan) or steroids. If you are already taking these medications please consult your doctor.
- Antibiotics are not required

THE DANGER SIGNS OF DENGUE INFECTION
(IF ANY OF THESE ARE OBSERVED, PLEASE GO IMMEDIATELY TO THE NEAREST HOSPITAL)

1. Bleeding
   for example:
   - Red spots or patches on the skin
   - Bleeding from nose or gums
   - Vomiting blood
   - Black coloured stools
   - Heavy menstruation / vaginal bleeding

2. Frequent vomiting
3. Severe abdominal pain
4. Drowsiness or irritability
5. Pale, cold or clammy skin
6. Difficulty in breathing
# Dengue Monitoring Record

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<tr>
<th>Date</th>
<th>Temp (°C)</th>
<th>BP (mm Hg)</th>
<th>PR (min)</th>
<th>HCT (%)</th>
<th>WCC (x10^3/μl)</th>
<th>Platelet (x10^3/μl)</th>
<th>Attending Clinic/Tel No.</th>
<th>Next Appointment</th>
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Outpatient Management: Group B

Group B (any of following)

- Has warning signs
- Has co-existing condition: Diabetes mellitus
- Renal failure
- Pregnancy
- Infant
- Elderly
- Has social circumstances: Living alone
- Living far away without a reliable means of transport

1. Admit for inpatient care
2. Monitor hemodynamic status frequently
3. Use HCT to guide interventions
4. Use isotonic IV fluids judiciously
5. Correct metabolic acidosis, electrolytes as needed
Mode and Timing of Delivery

- Dengue infection not indication for elective delivery
- If premature labour
  - Advise to delay delivery till acute infection resolve
  - Tocolytic agents
  - Close fetal monitoring
- Avoid instrumental delivery if possible
  - Blood products ready
If delivery inevitable

- Anticipate bleeding with close monitoring
- GXM
- Avoid trauma or injury
- Transfuse platelets during or at delivery (6 hours)
  - Bleeding manifestation
  - CS and instrumental delivery: platelet > 50,000
- Active management of 3rd stage recommended
  - Prevent post partum hemorrhage
- Transfuse PC if significant bleeding occurs
- Newborns refer to paediatricians
Breast Feeding

• Transmission of dengue virus through breast feeding inconclusive
• One case report of significant dengue viral load detected in breast milk during acute viraemic phase
• Advisable to delay breast feeding during acute viraemic phase
Conclusion

• All pregnant mothers with dengue should be managed in hospitals by physician, anaesthetist and obstetric consultants
• Early diagnosis and prompt treatment to avoid adverse outcomes
• Blood and blood products should be transfused as indicated when operative delivery is decided
• Spontaneous vaginal delivery should be the preferred mode of delivery
Thank You