CHAPTER

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Acute Infections in Pregnancy

Niteen D Karnik, Priya Bhate

INTRODUCTION

Pregnant women are a special high risk group since acute infections in them present the following challenges:

1. Maternal risk: The unique immunologically suppressed state of pregnancy makes infections like influenza, malaria, hepatitis E, and herpes simplex virus (HSV) infection severe. Evidence also exists for increased severity of measles, smallpox, malaria, HIV infection, and listeriosis.
2. Fetal risk: Congenital infections, intra-uterine growth retardation (IUGR), abortion or fetal death.
3. Diagnostic implications: Pregnant women may not mount an adequate febrile response masking the presence of infections. Acute febrile illnesses may mimic other conditions like acute fatty liver of pregnancy and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndromes. Certain diagnostic modalities (x-ray, CT scan) may not be appropriate in pregnancy.
4. Treatment implications: Prophylaxis (live vaccines) and certain drugs may not be safe in pregnancy.

CLASSIFICATION

Malaria

Pregnant women have a high risk of severe falciparum malaria presenting with severe anemia, hypoglycemia and acute pulmonary edema. Other complications include cerebral malaria, metabolic acidosis, acute kidney injury (AKI), convulsions, disseminated intravascular coagulation (DIC), shock and hyperpyrexia.

Based on Spectrum		
	System	**Syndrome**
1	Multisystem	acute febrile illnesses, tuberculosis
2	Neurological	meningitis, encephalitis
3	Cardiovascular	infective endocarditis
4	Gastro-intestinal	amoebic liver abscess, viral hepatitis, enteric fever
5	Respiratory	pneumonia
6	Renal	urinary tract infections
7	Others	chorioamnionitis, post operative sepsis, puerperal sepsis, retained products of conception, septic abortion

Fetal risks include abortion, stillbirth, IUGR, low birth weight (LBW) and rarely congenital malaria.

In areas with high transmission, malaria in the setting of high levels of acquired immunity contributes to anemia and IUGR especially in first pregnancy. In areas with low transmission, low levels of acquired immunity cause severe malaria.

Diagnosis: Peripheral smear or Rapid Diagnostic Tests

Treatment (WHO guidelines)

First trimester:

Quinine (10mg/kg q8h) plus Clindamycin (10mg/kg q12h) - 7 days

Second and third trimester:

Severe:

- Artesunate 2.4 mg/kg IV at 0, 12, 24 hr, then once daily plus Clindamycin (10mg/kg q12h)
- Start oral artemisinin-based combination therapy (ACT) once tolerated to complete 7 days

Uncomplicated:

- Oral ACT – 3 days

  Artemether + Lumefantrine, Artesunate + Amodiaquine/ Mefloquine, Dihydroartemisinin + Piperaquine
- In chloroquine-sensitive areas - Vivax malaria: Chloroquine 10 mg/kg - 3 days
- Other treatment - fluid therapy, 25% dextrose for hypoglycaemia, blood transfusion for severe anemia, sodium bicarbonate for metabolic acidosis, phenytoin or phenobarbital for seizures, renal replacement therapy for AKI, ventilator support

Based on Etiology	
Viral	Cytomegalovirus, Dengue, Hepatitis E, Herpes, HIV Influenza (H1N1), Measles, Mumps, Rubella, Varicella zoster, Zika virus
Bacterial	Chlamydia, Gonorrhea, Group B Streptococcus, Leptospira Listeria, Tuberculosis
Protozoal	Malaria, Toxoplasmosis
Fungal	Candida, Aspergillus

Table 1: Comparison of Dengue and HELLP syndrome

	Dengue	HELLP
Fever	Present	Absent
Bleeding	Can be present (mild to severe)	Absent, Present in DIC
Abdominal pain	Present/absent	Present/absent
Blood pressure	Low in dengue shock syndrome (with oliguria)	High (due to preeclampsia)
Ascites, pleural effusion	May be present due to plasma leakage	Absent
Leucocyte count	Decreased	No specific changes
Thrombocytopenia	Present	Present
Haematocrit	↑ In plasma leakage	Maybe normal / ↓
Haemolysis	Absent	Present
Liver enzymes	Mild to severe ↑	Mild to moderate ↑

for acute respiratory distress syndrome (ARDS), antibiotics for gram negative sepsis.

- Primaquine for radical treatment- contraindicated during pregnancy. Weekly chemoprophylaxis with chloroquine till completion of pregnancy; followed by primaquine as per G6PD status.
- In Africa, WHO recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), as part of antenatal care.

Leptospirosis

This zoonotic disease is known for its abortive effect in animals. In humans, it may be asymptomatic or may cause jaundice, AKI, ARDS, bleeding abnormalities, aseptic meningitis, myocarditis and multiorgan dysfunction. Leptospirosis in pregnancy can have vertical transmission and lead to fetal death, abortion, still birth and congenital leptospirosis. It is not known whether pregnant women are at a higher risk for complications from leptospirosis.

Diagnosis: IgM based immune-assay, microscopic agglutination test

Treatment:

Mild: Amoxicillin (500 mg PO q8h) or Ampicillin (500 mg PO q8h)

Moderate/severe leptospirosis:

Penicillin (1.5 million units IV or IM q6h) or Ceftriaxone (2 g/d IV) or Cefotaxime (1 g IV q6h) x 10-14 days

Chemoprophylaxis: Azithromycin (250 mg PO once or twice a week)

(Doxycycline- avoided in pregnancy)

Dengue

Dengue may cause undifferentiated fever, dengue hemorrhagic fever or dengue shock syndrome. Vertical transmission of dengue may occur in the perinatal period. Hyperemesis in early pregnancy may resemble a warning sign and delay recognition of severe dengue. The physiological low BP and tachycardia (due to increased blood volume and vasodilation) can mimic hypotensive shock. Bleeding due to thrombocytopenia or coagulopathy or vasculopathy may complicate delivery or surgical procedures. The gravid uterus decreases the tolerance to fluid accumulation due to plasma leakage (pleural effusion and ascites) and also makes these difficult to detect on clinical examination. Dengue with multiorgan failure can mimic HELLP syndrome as seen in Table 1.

Diagnosis: NS1Ag and Dengue PCR (in 1st week), Dengue IgM later

Treatment:

- Fluid therapy- goal should not be "normal BP and heart rate" as this may cause fluid overload in pregnancy. Urine output is a better indicator of adequate perfusion.
- Platelet transfusion – if active bleeding, platelet count <20,000/cc, during/at delivery
- Tocolytic agents /measures to postpone labour in the critical phase of dengue (no evidence, only case reports)
- Severe haemorrhage - transfusion of fresh whole blood/fresh packed red cells
- Oxytocin to prevent PPH

Hepatitis E Virus (HEV)

Hepatitis E is usually self-limiting with a case-fatality rate of <0.1%. India has reported a high incidence of HEV infection in pregnancy with a higher risk of acute liver failure (ALF) with a mortality upto 30–100%. However, in some countries (Egypt, USA and Europe), HEV infection in non pregnant and pregnant women does not differ. Genotype 1 is associated with high mortality in pregnant woman but not HEV genotypes 3 or 4. Pregnant women in the second or third trimester seem to be at an increased risk of ALF, fetal loss and mortality. The reason why HEV mortality is high in pregnancy and why there is a geographical difference in outcomes is still not clear.

Table 2: TORCH Infections in Pregnancy

Infection	Management
Toxoplasmosis: • Asymptomatic or flu like illness in mother • Fetal risk: chorioretinitis, hydrocephalus, microcephaly, intracranial calcification, hepatosplenomegaly, IUGR • Risk of vertical transmission increases with gestational age, (60% to 80% in 3rd trimester vs. 6% in 1st trimester)	• IgM positive- acute infection (may take weeks to appear and persist for years) • IgG positive- past infection; 4-fold rise suggests recent infection • Diagnosis of fetal infection: PCR of amniotic fluid • Spiramycin 3MU q8h throughout pregnancy to prevent fetal infection • If fetal infection present: daily pyrimethamine 1mg/kg (contraindicated in 1st trimester) and sulfadiazine (100mg/kg) with folinic acid • Consider MTP
Rubella: • Self limiting illness with rash in mother • Fetal risk: highest in 1st trimester • Congenital rubella syndrome can cause: • Sensorineural deafness (60–75%) • Cardiac defects(10–20%)- Pulmonary stenosis, Patent ductus arteriosus, Ventricular septal defect • Ophthalmic defects (10–25%)-Retinopathy, Cataracts, Microphthalmia • Neurological (10–25%)- Mental retardation, Microcephaly	Diagnosis by • 4 fold in rubella IgG Ab titre • Positive rubella-specific IgM Ab • Treatment is supportive • Consider MTP in early pregnancy • Live attenuated vaccine available; contraindicated during pregnancy
Cytomegalovirus: • Asymptomatic or flu like illness in the mother • Fetal risk: • 10-15% symptomatic at birth: IUGR, microcephaly, hepatosplenomegaly, jaundice, chorioretinitis, thrombocytopenia, DIC • 85–90% asymptomatic at birth, but may develop sensorineural deafness, delayed milestones, visual impairment	• Serology: if sonographic findings suggestive of CMV infection • IgG positive: denotes past infection • High IgG avidity: recurrent infection • Low IgG avidity: recent primary infection • IgM positive: acute infection • Consider MTP in early pregnancy
Herpes Simplex Virus: • Genital vesicles/ asymptomatic in mother • Fetus may get infected transplacentally (congenital) or during delivery (neonatal) • Congenital infection causes microcephaly, hepatosplenomegaly, IUGR and IUFD • Neonatal infection causes skin, eye, and mouth infection, encephalitis and disseminated disease (90% mortality)	• Caesarean section to reduce risk of neonatal infection • Antiviral therapy not recommended before 36 weeks • Suppressive antivirals after 36 weeks till delivery • Acyclovir: 400 mg q8h or 200 mg q6h • Valcyclovir: 500 mg q12h

Vertical transmission of HEV can cause severe hepatic dysfunction and mortality in fetus/neonates.

Diagnosis: Anti-HEV IgM antibodies

Treatment:

- Treatment of metabolic complications (hypoglycemia, hyponatremia, hypokalemia), cerebral edema (Mannitol, 3% NaCl) and supportive care
- Liver transplantation- the only validated treatment for ALF due to HEV

Expediting delivery may theoretically prevent ALF (no evidence).

H1N1 (Swine Flu)

Pregnant women have a 4- to 5-times higher rate of serious H1N1 illness. Mortality appears to be higher in the third trimester with fetal morbidity. Risk increases with coexisting organ disease, steroid therapy, diabetes

Table 3: Management of UTI in Pregnancy			
Asymptomatic bacteriuria	Positive urine culture (≥10 ^{5} cfu/mL of a single uropathogen in a single midstream clean catch urine sample) without symptoms of UTI.	oral antibiotics – 7 days	Ampicillin Cephalexin Nitrofurantoin
Acute cystitis	Urgency, frequency, dysuria, pyuria and haematuria without evidence of systemic illness.	oral antibiotics – 7 days	Ampicillin Cephalexin Nitrofurantoin
Acute pyelonephritis	Flank pain, nausea/ vomiting, fever (>38ºC), and/or renal angle tenderness with or without cystitis symptoms.	Start empirical IV antibiotics. Change as per culture & continue till patient is afebrile for 48 hours. Then, oral antibiotics to complete 10–14 days	Ampicillin + gentamicin Or cephalosporin

and HIV/AIDS. Pulmonary complications include ARDS and secondary bacterial pneumonia. Extrapulmonary complications are myositis, rhabdomyolysis, myopercarditis, encephalomyelitis and AKI

Diagnosis: throat/ respiratory secretion swab for RT-PCR. Specimens should be placed on ice (4°C) and transported immediately.

Treatment: Pregnant women with mild illness need oseltamivir 75 mg q12h for 5 days. Those with ARDS/ other complications may need 150 mg q12h. According to the CDC guidelines, chemoprophylaxis may be given for 7 days to women who are pregnant and upto 2 weeks postpartum who have had close contact with someone likely to have influenza.

TORCH Infections

Toxoplasmosis, rubella, cytomegalovirus and herpes, though mild in the mother, may cause very severe fetal infection. Routine TORCH screening in all pregnant women is expensive and not recommended. The SOGC guidelines for TORCH infections are summarized in Table 2.

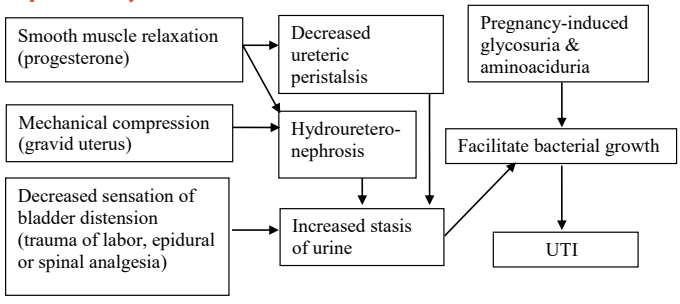
Zika Virus (ZV): Current global alert

- Neurotropic virus spread by Aedes mosquito
- Usually mild flu like illness in pregnancy
- Spatiotemporal association of cases of microcephaly with the ZV outbreak
- ZV has been isolated from the brains and CSF of neonates born with congenital microcephaly and identified in the placental tissue of infected mothers
- Other associations in neonates: craniofacial disproportion, spasticity, seizures, ocular abnormalities and ventriculomegaly
- No vaccines currently available

URINARY TRACT INFECTIONS (UTI)

Asymptomatic bacteriuria is usually benign in non pregnant women but may progress (upto 30%) to pyelonephritis in pregnancy. Bacteriuria is associated with preterm birth, LBW, and perinatal mortality. Pyelonephritis may lead to AKI, bacteraemia, ARDS, anaemia, hypertension, preterm labour and LBW. *Escherichia coli* is the most common cause of UTI in pregnancy.

Pathophysiology of increased risk of UTI in pregnancy is explained by



Most guidelines recommend a single urine culture at the first prenatal visit. In non-pregnant symptomatic patients with an identified uropathogen, a colony count of ≥ 10^2–10^3 cfu/mL may indicate infection. This cut-off though not evaluated in pregnancy, seems reasonable. Repeating urine cultures monthly until completion of pregnancy may be used to diagnose persistent or recurrent bacteriuria. Management of UTI in pregnancy is outlined in Table 3.

PUERPERAL SEPSIS (PS)

- Puerperal fever: Rise of temperature above 38°C maintained over 24 h from the end of the first to the end of the tenth day after delivery.
- The most common cause of puerperal fever is genital tract infection. Other causes include UTI, mastitis, wound infection and septic thrombophlebitis.

- PS is the third leading cause of death in pregnant women accounting for 15% of maternal mortality.
- Risk factors: caesarean section, unhygienic delivery practices, poor socioeconomic status, malnutrition, anemia, primiparity, prolonged labour, prolonged rupture of membranes, repeated vaginal examinations, obstetrical maneuovers, retained products of conception and postpartum hemorrhage.
- Maternal complications: peritonitis, pelvic abscess, septic shock, endotoxic shock
- May be endogenous (from patient's genital tract), exogenous (external contamination) or nosocomial
- Microbiology:
  - Aerobes: Streptococcus group A, B and D, Staphylococcus, Enterococcus, E.coli, Klelbsiella, Pseudomonas
  - Anaerobes: Anaerobic Streptococcus, Bacteroides, Clostridia
- Treatment: Antibiotics as per culture and sensitivity. Empirical antibiotics include Ampicillin + Gentamicin + Clindamycin

INFECTIVE ENDOCARDITIS (IE)

- Infective endocarditis in pregnancy has a low incidence (0.006%).
- The altered cardiovascular physiology of pregnancy and diminished febrile response can delay diagnosis. Any pregnant patient with unexplained fever and a cardiac murmur or pre existing heart disease should be carefully assessed for IE.
- Risk factors: Pre-existing cardiac lesion (rheumatic heart disease or congenital heart disease), IV drug abuse
- Complications: Heart failure and embolic events; maternal and fetal mortality is upto 33% and 29% respectively
- Treatment: Antibiotics as per culture and sensitivity. These include crystalline penicillin, ceftriaxone, gentamicin, vancomycin, ampicillin-sulbactum. Surgical treatment is delayed till infection has been eliminated with antibiotics. Cardiac surgery is not recommended during the first two trimesters. Elective delivery by caesarean section may be performed before cardiopulmonary bypass to minimize maternal and foetal risks.

ACUTE BACTERIAL MENINGITIS (ABM)

- Pregnancy does not have an increased predisposition for ABM
- Etiology: Streptococcus pneumonia, Neisseria meningitides, group B streptococci, Listeria monocytogenes, Haemophilus influenza type b
- Listeriosis has increased incidence and severity in pregnancy; and may cause intrauterine infection, abortion, chorioamnionitis, preterm delivery, and neonatal sepsis
- Empirical antibiotics for ABM: Ampicillin 12g/d, q4h + ceftriaxone 4g/d, q12h + vancomycin 45-60 mg/kg/d, q12h. Drug of choice for listeriosis is ampicillin 12g/d for 3 weeks.
- Adjunctive dexamethasone should be given

AMOEBIC LIVER ABSCESS

- Rare complication in pregnancy in developing countries
- Gravid uterus makes abdominal examination difficult and diagnosis may be delayed
- Presents with fever, right lower chest and abdominal pain
- Diagnosis: Abdominal ultrasound
- Treatment: Metronidazole 750 mg PO/IV – 5-10 days; Chloroquine may be given

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