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Maternal INFECTION
EXPOSURE to EXPRESSION

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Dr. S. Shantha Kumari
MD, DNB, FICOG FRCPI (Ireland), FRCOG

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- Chairperson ICOG 2018
- Consultant Yashoda hospitals
- ICOG secretary 2015-2017
- Member FIGO Working group on VaW
- Vice president FOGSI 2013
- ICOG governing Council Member
- IAGE Managing Committee Member
- National Corresponding editor for JOGI
- Organizing secretary AICOG 2011
- Chairperson MNNRRC 2008

Dear Friends,

Indian College of Obstetricians and Gynaecologists (ICOG), the academic wing of FOGSI is committed to provide clinical updates to all members. The objective is to develop standard practice protocols to help improve the skills of ObGy specialists all across the country. The theme "PPP – Principles, Protocols, and Practice" in each subspecialty is therefore adopted for the year 2018.

Infectious diseases during pregnancy should be treated as seriously as any other medical or surgical illness during pregnancy.Infections during pregnancy lead to nearly 15 million deaths worldwide. Immunological response during pregnancy induces a state of increased susceptibility to infections. The course of illness and severity of disease variesand is more severe as compared to the non pregnant state. Exposure to infections during the pre-conceptional and antenatal period can affect the maternal and fetal outcome adversely.

Maternal affection may vary from mild flu-like illness to a more severe form such as sepsis .The vertical transmission of the disease can lead to long-term sequels in the neonate and infant in form of cerebral palsy, sepsis, periventricular leukomalacia, hearing disability, cardiac anomalies, and so on. Infections during pregnancy increase the risk of miscarriage, preterm delivery, and stillbirth.Over the past few years with the emergence of new diseases such as influenza, Ebola virus, Zika virus, the treatment of pregnant women with these infectionshas become more challenging. However, the uses of novel antibiotics, anti-retroviral drugs, and vaccination havebeen found to be quite promising in improving the outcome of such pregnancies.Education, screening, and treatment are the essential components of preventing infections during pregnancy.

This issue brings the latest management on various infections during pregnancy. I hope that the readers will find this issue very informative and practically useful.

I wish happy reading to all of you.

Dr S. Shantha Kumari
Chairperson ICOG

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PRESIDENT'S MESSAGE

Dr. Jaideep Malhotra
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- Past Vice Chairperson, ICOG
- Member, FIGO Committee of Reproductive Medicine
- Member, FIGO Working Group on RDEH (reproductive & developmental environmental health)

Dear FOGSIANS,

Greetings,
"He who cures a disease may be the skillfullest, but he that prevents it is the safest physician."
Thomas Fuller

As we all know that pregnancy is a physiological process, evidence suggests a boosted maternal innate response which may represents a compensatory immune mechanism of the mother to protect the semiallogenic fetus. This makes the mother more susceptible to infections during pregnancy.

In the nineteenth and early twentieth century many pregnancies with infectious diseases were terminated as they were thought to worsen the course of pregnancy. However, with the advancing research in detection and treatment of infectious diseases during pregnancy the outcome has improved tremendously.

As FOGSI dedicates this year to "Adbhut Matrutva,"our present ICOG newsletter focuses on the current and up-to-date strategies in preventing, screening, diagnosing, and treating infectious diseases during pregnancy. This issue will also help the readers in navigating through complex issues related to vaccination during pregnancy, dealing with emerging diseases during pregnancy, and managing the newborns.

Hope you have an enriching experience while reading this issue.

Wishing all of you happy reading.

Dr Jaideep Malhotra
President FOGSI, 2018

PRESIDENT'S MESSAGE

Dr. Nandita Palshetkar
M.D, FCPS, FICOG

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- 1st Vice President FOGSI (2011)
- Organising Secretary AICOG 2013
- FNB Teacher in Reproductive Medicine

Dear FOGSIANS,

Warm Greetings !

Pregnancy is a physiological process unless complicated by some medical or surgical problem .Such high risk pregnancies need to be managed differently and will required a multidisciplinary management .These high risk pregnancies will affect the course of pregnancy and will alter the maternal and fetal outcome.

One such group of high risk pregnancies is the ones complicated by infectious diseases. Infections acquired before or during pregnancy may affect the mother and newborn to a variable extent depending upon the type and severity of the infection and the infecting agent.

This issue is dedicated to the various infections affecting pregnancy and provides evidences in treating and managing these cases. It also highlights the etiopathogenesis of fetal and maternal affection by the infectious agent which leads to the activation of Fetal Inflammatory Response Syndrome.

Hope you find this issue valuable and practically applicable in your day to day clinical practice.

Dr Nandita Palshetkar
President FOGSI (2019-20)

SECRETARY'S MESSAGE

Dr. Parag Biniwale
MD, FICOG

• Secretary, ICOG

Dear Friends,

An infection in pregnancy is a unique situation since the organism poses a threat to health of mother as well as the foetus. Perinatal counseling should address issue like possible risks of transmission, interventions to prevent transmission in-utero or postnatally, diagnosis of infection in the fetus or newborn and finally, postnatal management of the infant. Many congenital infections are asymptomatic at birth, but can have significant long term sequelae. Some congenital infections can be successfully prevented by timely intervention. Extensive counseling aims to assist parents with the process of disease and probable outcomes. The management depends on diagnostic and monitoring facilities, availability of neonatal care facility and parental wish.

Our team of experts has taken pains to give a detail account of these conditions. We have tried to simply the management aspects also so that clinicians will find this publication useful in tricky situations where evidence is limited. A special mention about Dr Ashok kumar, our editor who has chosen the right people to contribute and has compiled the articles to be user friendly! As always encouragement by ICOG Chairperson Dr S Shanthakumari & President FOGSI ICOG Dr Jaideep Malhotra makes us to do something different and useful for Obstetricians & Gynaecologists of our country.

Dr Parag Biniwale
Secretary, ICOG

FROM EDITOR'S PEN

Dr. Ashok Kumar
MD, PhD
FAMS, FICOG, FICMCH

- Director Professor:
  Department of Obstetrics and Gynecology
  Maulana azad Medical College &
  Lok Nayak hospital

Warm Greetings

Infection during pregnancy is a known cause leading to maternal and fetal morbidity and is responsible for nearly 16%of the maternal mortality. The various immunological changes during pregnancy pose a high risk foracquiring such infections. The focus is therefore on **"Infectious diseases during pregnancy – From exposure to expression."**

A pregnant lady can be exposed to various bacterial, viral, and protozoan infections which can be transmitted vertically to the fetus causing adverse fetal outcomes.This issue highlights the etiopathogenesis of fetal infection, fetal inflammatory response syndrome(FIRS),screening for various infections during pregnancy, and the effect of these on maternal and fetal outcome. There is emphasis on the current recommendations for managing pregnancies with exposure to infections such as: tuberculosis,HIV,hepatitis,malaria, syphilis, Group B streptococcus, and TORCH infections. A special section has been dedicated to the emerging infections during pregnancy which includes dengue fever, chikungunya, influenza (HINI), Zika, and Ebola virus.

These infections are known to cause miscarriages, preterm labor, and stillbirths. They can affect the fetus and the newborn by causing sequelae such as cerebral palsy periventricular, leukomalacia, cardiac abnormalities, etc. The only effective way to decrease the incidence of infectious diseases during pregnancy is by screening, vaccination, and educating about women heath. Last but not the least, vaccination during pregnancy has been highlighted also.

Hope our readers have an enriching experience while reading "Campus."

Dr Ashok Kumar
&
Editorial Team

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SECTION - I

Screening of Infections in Pregnancy

Introduction

In women, most infections are no more serious than in non-pregnant women of similar age. Infections in pregnancy may cause significant morbidity and mortality through various different mechanisms in pregnancy, when the immune system is weaker than usual which makes one more susceptible to contract infections, the body does not produce enough antibodies to fight the infection.

Some infections are more serious in pregnant than in non-pregnant women because of the potential for vertical transmission to the fetus or infant. Such congenital infections may lead to various forms of malformations, neurological developmental delay, and long-term consequences. Such infections include syphilis, varicella, rubella, cytomegalovirus (CMV), toxoplasmosis, parvovirus b-19, and human immunodeficiency virus (HIV).

Other maternal infections may adversely affect the course of pregnancy leading to increased risk for miscarriage or preterm delivery. Such infections include asymptomatic bacteriuria, vaginal bacteriosis [bacterial vaginosis, (BV)], chlamydia trachomatis, and listeriosis.

Some maternal infections are associated with possible severe neonatal sepsis, for example, Group B streptococcus infection or colonization and genital herpes. Pre-pregnancy or routine antenatal screening for presence of or susceptibility to these infections and their appropriate management can prevent adverse fetal or perinatal outcomes.

Uncommonly, serious infectious illness in the mother may lead to non-specific fetal or obstetric effects and lead to miscarriage, premature labor, or fetal death. Much more common and a source of anxiety is mild illness or suggestive laboratory findings in the absence of symptoms. Investigations and management are often difficult and are associated with potential ethical and medicolegal pitfalls.

This chapter discusses the most common infections in antenatal period and recommendations for their screening.

Screening for Infections in Pregnancy and Recommendations

Syphilis

It is a chronic systemic infectious process, secondary to infection with spirochete Treponemapallidum. Acquired and congenital syphilis infection is staged according to the time of acquisition of the primary infection. The risk of congenital transmission declines with increasing duration of maternal syphilis prior to pregnancy, that is, with the progress of maternal syphilis infection.

Screening for syphilis in pregnancy is to identify women with active syphilis to offer treatment of their own infection and to reduce the risks of baby developing congenital syphilis.

The objectives of the screening programme are to identify all women with positive/equivocal syphilis screening test results early in pregnancy and ensure their rapid assessment by an appropriate specialist, for example, genitourinary medicine within a multidisciplinary environment for antibiotics and discussion regarding the risks to the baby.

If the pregnant woman has an early untreated syphilis infection, 70%–100% infants will be infected and one-third will be still born.[1,2] Congenital syphilis is transmitted via the placenta. Screening tests have an accuracy of over 99%.The body's immune response to syphilis is the production of non-specific and specific treponemal antibodies. The first notable response to infection is the production of specific anti-treponemal immunoglobulin M (IgM) which is detectable towards the end of the second week of infection. By the time symptoms appear, most people infected with syphilis have detectable levels of IgG and IgM.3However, syphilis may also be asymptomatic and latent for many years.[4]

Serological tests of syphilis are the primary means of diagnosis, because most individuals infected are in the asymptomatic latent phase of the disease. They are classified into non-treponemal tests and treponemal tests. The non-treponemal tests include Venereal Disease Research Lab (VDRL) and Rapid Plasma

Reagin (RPR) tests. They detect non-specific treponemal antibodies. Treponemal tests detect specific treponemal antibodies and include a) FTA abs test – fluorescent treponemal antibody absorbed test, b) TPHA test – T pallidum hemagglutination assay, c) TPPA – T pallidum passive particle agglutination assay, d) EIAs – enzyme immunoassays detects IgG and IgM, and e) chemiluminescence immune assays. EIAs are over 98% sensitive and over 99% specific. These are rapidly replacing VDRL and TPHA colonization for syphilis screening in UK.

Non-treponemal tests give false positive reactions secondary to viral infections or auto-immune diseases. Conversely they give negative reactions especially in patients with very early primary or late syphilis, in patients with re-infection, or in those who are HIV positive (in them EIA are useful in detecting syphilis antibodies). The positive predictive value of non-treponemal tests is poor when used in low prevalence populations.

None of these serologic tests will detect syphilis in the incubation stage, which may last for an average of 25 days.[5] A reactive result on screening requires confirmatory testing with a different treponemal test of equal sensitivity, preferably with greater specificity. A discrepant result on confirmatory testing needs further testing.[6]

A quantitative non-treponemal test or a specific test for treponemal IgM is performed 1) to assess the stage of infection and2) to monitor the efficacy of treatment.

When To Screen?

- Screen all women in their first prenatal visit.
- Perform repeat screening in all pregnancies early in third trimester.
- Screen patients at delivery, if not screened previously or if at high risk.

How to Screen?

- Treponemal and Non-treponemal Test: Diagnostic Criteria–Positive treponemal and non-treponemal test.[4]

Recommendations

Screening for syphilis should be offered to all pregnant women at an early stage in antenatal care because treatment of syphilis is beneficial to the mother and the baby.[4]

Hepatitis B virus

It is a small enveloped double-standard DNA virus in the hepadnaviridae family. It is the etiologic agent in 40%–45% of hepatitis infections. Hepatitis B virus (HBV) infects the liver and many people infected with it have no symptoms. Post-exposure, it has an incubation period of 6 weeks to 6 months and this is inversely related to viral inoculum. It is excreted in various body fluids (blood, saliva, vaginal fluid, and breast milk) which may be highly infectious.

In India prevalence rate of HBsAg positivity in pregnant women varies from 1% to 9% (intermediate rate) accounting for one-fifth of the world HBV burden.[7] As per The World Health Organization (WHO)classification of HBV prevalence: High endemicity 8%, intermediate 2%–7%,andlow 2%. Being asymptomatic the disease burden is underappreciated. HBV is turning out into a global epidemic with a global estimate of 2 billion people being infected with HBV and 350 million people remaining infected chronically. About 1.5 million deaths occurring from HBV-related liver diseases, including end-stage cirrhosis and hepatocellular carcinoma each year.

There are up to10% of the 350 million Hepatitis B carriers in India. The carrier rate is 4.7%. Transmission of HBV from carrier mothers to babies can occur during perinatal period and is an important factor in determining the prevalence of infection in highly endemic areas.

Before HBV vaccine was integrated into the routine immunization programme about 10%–30% babies were becoming HBV carriers amongst mothers who were HbsAg positive but HbeAg negative. However, perinatal infection was higher (80%–90%) where mothers were also HBeAg positive.[8] In India, birth dose of Hepatitis B vaccine was introduced in the National Immunization Programme in 2008.[9]

Without intervention, infants born to HbsAg positive mother have a 90% risk of perinatal HBV infection. As many as 40% of males and 15% of females with perinatally acquired HBV will die of hepatocellular carcinoma or cirrhosis which highlights the need for effective prevention.[10] Prevention of perinatal transmission is possible with immunoprophylaxis of risk babies shortly after birth. Most newly infected adults (85%–90%) clear their infections, whereas the remaining 10%–15% becomes chronically infected.

Risk of chronic infection with HBV is inversely related to the age of onset of infection. The probability of developing the carrier state following HBV infection is greatest in early life and decreases with increasing age. Up to 90% babies born to carrier mothers become carriers and they are at very high risk of developing chronic liver disease at a younger age and represent the most important reservoir of infection in the community. Chronic carriers have 15%–30% risk of and they are 22 times more prone to die from hepatocellular carcinoma or cirrhosis than non-carriers.[11] Thus, prevention of transmission in this group by immunoprophylaxis at birth will decrease the overall carrier rate.

Perinatal mother-to-child transmission (MCT) of HBV is approximately 85%–95% and is preventable by active (vaccine) and passive (immunoglobulin) immunization to the baby at birth.

Screening consists of three stages:

- Screening for HbsAg
- Confirmatory testing with a new sample upon positive results

- Where infection is confirmed testing for Hepatitis B e-markers in order to determine whether the baby will need HBV immunoglobulin (HBIG) in addition to vaccine.[12]

Recommendation
Universal free serological testing for Hepatitis B virus should be offered to all pregnant women on an opt out basis so that effective postnatal intervention can be offered to infected women to decrease the risk of MCT.

Babies born to mother with HBV are at risk of acquiring infection and should be offered postnatal immunization (HBV vaccine series) within 24 h of delivery and at 1, 2, and 12 months to reduce the risk. A full course of vaccination in the first year of life is effective in reducing the risk of transmission to the baby.[13] In USA, all newborns are vaccinated against HBV as part of the Centers for Disease Control and Prevention(CDC's) recommendations to decrease HBV prevalence.[14]

In babies born to women with higher risk of transmission (those whose Hepatitis e-antigen, HBeAg is positive) the addition of HBIG within 12 h of birth can reduce the risk further.[15]

Hepatitis C Virus

Hepatitis C virus (HCV) is a major public health concern as it is one of the major causes of liver cirrhosis, hepatocellular carcinoma, and liver failure.[16] Virus is acquired through infected blood transfusions (pre HCV blood screening), injection of drugs, tattooing, body piercing, and MCT. HCV prevalence in pregnant population in UK ranges from 0.1% to 0.8%.[17]The risk of MCT lies between 3% to 5%.[18] No vaccine or treatment is available to prevent transmission. The risk of MCT of HCV increases with increasing maternal viral load.[19] Cesarean delivery is unlikely to reduce perinatal transmission as compared to vaginal delivery.

The clinical course of HCV in infants with vertical transmission is unclear, some children subsequently becomes HCV RNA negative and lose HCV antibodies by 6 months after birth.[20] Since HCV infection in adults is known to have a long latency period, the infected children may possibly develop long-term clinical outcomes.

Screening for HCV
1. Detection of anti-HCV antibodies in serum by EIAs.
2. Enzyme-linked immunosorbent assays (ELISAs).

Upon a positive result a second ELISA or a confirmatory recombinant immunoblot assay (RIBA) is performed on the same sample. If the second test is positive the women is informed and second sample is taken to confirm the diagnosis. Using the polymerase chain reaction (PCR) as the gold standard the sensitivity and specificity of third general assays is 100% and 66%, respectively. Upon confirmation of a positive screening test the woman is offered post-test counseling and referred to a hepatologist for the management and treatment of her infection.[21]

Recommendation
Pregnant woman should not be offered routine screening for Hepatitis C virus because there is insufficient evidence to support its effectiveness and cost effectiveness.

Rubella

It is a mild infection caused by Rubella virus. It is often (20%–50%) cases of asymptomatic, but may present with a febrile rash.[22] All infants infected during the first 11 weeks of pregnancy had rubella defects.[23]

If the women are infected in the first trimester, it can have serious consequences for the neonatal health. Congenital abnormalities such as heart defects, cataracts, fetal growth restriction (FGR), central nervous system (CNS) defects, and deafness follow.[24] Screening does not detect rubella infection in pregnancy and any woman presenting with a rash or who is exposed to others with a rash like illness should be investigated in accordance with the Health Protection Agency Guidelines for "Managing rash illness in pregnancy."[25]

The IgG and IgM titers should be measured even if she was previous positive for rubella IgG. Rarely women with apparently adequate immunity can be re-infected (although the risk of fetal abnormality is <5% even in the first trimester).

The aim of screening for rubella in early pregnancy is to identify susceptible women (IgG<10 IU/ml) so that postnatal vaccination may protect future pregnancies against rubella infections and its consequences in the fetus – congenital rubella syndrome.[26] The MMR administered prior to discharge from maternity services is to be followed. Women should be advised not to conceive within 1 month of vaccination.[27]

In the first 8–10 weeks of pregnancy symptomatic infection results in severe fatal damage in upto 90% of cases. After this period, the risk of damage is lower (50% in third trimester) and is likely to involve hearing impairment. Rubella defects are rare after 16 weeks gestation, that is, the risk of damage steeply falls after first trimester and is negligible after 16 weeks. Hence, rubella screening does not attempt to identify current affected pregnancies. There is also no treatment to prevent or reduce MCT of rubella for the current pregnancy.

Vaccination during pregnancy is contraindicated because of fears that vaccine could be teratogenic.[28] If the contact is in second or third trimester and rubella IgG was detected in the first trimester, further investigation is not necessary.

Recommendations
Rubella susceptibility screening should be offered early in ANC to identify women at risk of contracting

rubella infection and to enable vaccination in the postnatal period for the protection of future pregnancies.

Human Immunodeficiency Virus

HIV is a member of the retroviridae family, characterized by spherical, enveloped viruses. The virus envelope surrounds an icosahedral capsid that contains the viral genome and consists of two identical pieces of positive-sense, single-stranded RNA about 9.2 kb long. HIV has a total of nine genes that include three main genes – gag, pol, and env. Retroviruses are unique because the viral genome is transcribed into DNA via the viral enzyme reverse transcriptase, followed by integration into the host cell genome via the viral enzyme integrase. HIV also has the capacity to become latent within quiescent infected cells, which has made eradication of the virus thus far impossible.

The HIV envelope glycoprotein (gp 120) is a ligand for CD4 the cellular HIV receptor; thus HIV predominantly infects CD4+ cells, including T cells, monocytes, and macrophages.

Recommendations

Historically, HIV infection was diagnosed via virus-specific antibody detection; initial serologic screen was via ELISA and either the western blot (WB) or immunofluorescence antibody assay was performed for confirmation. The WB identifies antibodies and recognizes specific viral antigens, and it is considered positive when any two of the following three antigens are identified: p24 (capsid), gp41 (envelope), and gp 120/160 (envelope). Several salivary and/or rapid blood tests are available with efficacy comparable to ELISA. These tests have a limited ability to diagnose early HIV and HIV-2 infection because they detect HIV-specific immunoglobulin (Ig) G antibodies. Current recommendations are to screen with an HIV-1/2 antigen/antibody combination immunoassay, or "combo assay," with confirmation of infection with an HIV-1/HIV-2 antibody differentiation immunoassay and HIV-1 nucleic acid test (NAT) in a "opt out approach."[29] This strategy enables diagnosis of acute HIV-1 infection, detection of HIV-2 infection, and faster turnaround time. Enhancements of the combo assay include more accurate HIV-2 diagnosis, p24 antigen assessment (measurable 15 days post-infection), and detection of IgM antibodies (measurable 3–5 days after p24 antigen positivity), which enables confirmation of HIV infection days to weeks before the HIV WB becomes positive. Combined with an HIV-1 NAT, this narrows the window between the time of infection and immunoassay reactivity and enables the diagnosis of acute HIV-1 infection, which was not possible using ELISA/WB assessment.[30] Because the risk of HIV transmission from persons with acute and early infection is increased; this strategy may reduce perinatal HIV transmission.

Given the increasing prevalence of HIV infection and studies that demonstrate that identification of HIV-infected pregnant women and early antiretroviral therapy (ART) most effectively prevent perinatal HIV transmission, both the American College of Obstetricians and Gynaecologists (ACOG) and the CDC recommend an "opt out" approach to ensure routine HIV screening for all pregnant women, ideally performed at the first prenatal visit. The CDC also advocates for repeat testing in the third trimester, citing its cost effectiveness even in areas of low prevalence.[31] A second HIV test in the third trimester is recommended for women at an increased risk of HIV infection as well as who receive health care in facilities at which prenatal screening identifies at least one HIV-infected pregnant women per 1000 women screened.

Clinical Manifestations and Staging

The clinical presentation of HIV infection and/or acquired immunodeficiency syndrome (AIDS) depends on when infection occurred and whether immunodeficiency resulted. Following exposure and primary infection 50%–70% of individuals infected with HIV develop the acute retroviral syndrome following acute HIV infection, patient enter latent-phase infection, which can last approximately 5–10 years in untreated patients and comprises stage 1 and 2 of infection.

Stages of HIV Infection

CDC stage	CD4+ T-lymphocyte count and percentages
Stage 1 (HIV infection)	CD4+ T-lymphocyte count ≥500 cells/μl or >29%
Stage 2 (HIV infection)	CD4+ T-lymphocyte count 200–499 cells/μl or 14%–29%
Stage 3 (AIDS)	CD4+ T-lymphocyte count <200 cells/μl or <14%

During this asymptomatic phase of infection, in the absence of ART, chronic immune activation and progressive destruction of lymphatic tissue ensues.[32] If untreated, most patients will develop stage 3 infection, AIDS.

Asymptomatic Bacteriuria

The asymptomatic bacteriuria (ASB) is defined as persistent bacterial colonization of urinary tract without urinary symptoms. Local data on the incidence of ASB are not available, but it occurs in around 2%–5% of pregnant women in UK[33] and 2%–10% of women in USA.[34] Evidence of RCTs designed to show the benefits of treatment amongst women with ASB indicate an increased risk of preterm labor and pyelonephritis in women with untreated ASB compared with women without bacteriuria.[35] The reported increased incidence of pyelonephritis among pregnant women with ASB ranges from 1.8% to 28%. The reported increased incidence of preterm birth among pregnant women with ASB ranges from 2.1% to 12.8%.[36]

Investigations
Midstream urine culture is used as the reference standard for diagnosis of ASB. This is superior to rapid tests such as reagent strips for nitrite, protein, blood and leucocyte esterase, microscopic urine analysis, Gram staining with or without centrifugation, urinary interleukin or rapid enzymatic screening test (detection of catalase activity), or bioluminescence test. Positive culture is defined as >105 colonies/ml urine from a midstream clean catch specimen.

Recommendations
Pregnant women should be offered routine screening for ASB. A midstream urine culture at the first antenatal visit helps to detect for pre-existing ASB. The identification and treatment of the condition reduces the risk of preterm birth.

Asymptomatic BV (Vaginal Bacteriosis)

BV results from the relative deficiency of normal lactobacillus species in the vagina and relative overgrowth of anerobic bacteria. These may include Mobiluncus species, Gardnerella vaginalis, Prevotella species, and Mycoplasma hominis. This results in a reduction of the normal acidity of the vagina. It is the most common cause of vaginal discharge and malodour although 50% of women with BV infection during pregnancy will be asymptomatic.[37] Why these organisms, many of which are present in small numbers in the vagina normally, multiply is not well understood.

The condition is not sexually transmitted, although it is associated with sexual activity. The presence of BV during pregnancy varies according to the ethnicity and how often a population is screened. Local data are again lacking, but in general Asian populations have a lower incidence compared to the North American populations where it ranges from 8.8% in white women to 22.7% in black women.[38]BV is associated with preterm birth. Pregnant women with BV were found to be 1.85 times more likely to deliver preterm than women without BV.[39]This risk remains in women diagnosed with BV early in pregnancy even if the BV spontaneously recovers later in pregnancy. BV may be diagnosed either by Amsel's criteria (thin white gray homogenous discharge, pH>4.5, release of fishy odor on adding alkali, clue cells present in direct microscopy)or Nugent's criteria (Gram-stained vaginal smear to identify proportions of bacterial morphotypes using a scoring system– Score <4 normal, 4–6 intermediate, and >6 BA).[40]

Culture of G.vaginalis is not recommended as a diagnostic tool because it is not specific. Cervical Papanicolaou tests have limited clinical utility for the diagnosis of BV because of low sensitivity.

Recommendations
Pregnant women should not be offered routine screening for BV because the evidence suggest that identification and treatment of asymptomatic BV does not lower the risk for preterm birth and other adverse reproductive outcomes.

Cytomegalovirus

CMV is a member of the herpes virus family and the incidence in pregnant women is about 0.5%–1%. Herpes viruses have large complex genomes that replicate in the nucleus of infected cells and enable these viruses to establish acute, persistent, and latent infections. Recurrences occur from reactivation of latently infected cells. CMC is not highly contagious, transmission primarily occurs by contact with infected saliva or urine or it can also be transmitted via blood or sexual contact. The incubation period is about 40 days following exposure. In US, primary CMV infection in pregnant women ranges from 0.7% to 4% and recurrences can be upto 13.5%. Young infants and children with subclinical infections are major source of infectious CMV, approximately 50% of children who attend day care actively shed CMV virus in their saliva and/or urine and fomites within day care centers are potential sources of CMV infection. Thus, day care workers are at high risk for infections. Small children pose an infection risk to family members with annual sero-conversion rates of approximately 10% for parents and uninfected siblings.[41]CMV seroprevalence correlates with

- Low socioeconomic status
- Birth outside North America
- Increased parity and age
- Abnormal Pap smear
- Trichomonas infection
- The number of sexual partners

CMV infection is also increased in immunocompromised patients. Between 0.2%–2.2% of infants born in the US become infected with CMV in utero secondary to maternal infection. Another 6%–60% get infected within the first 6 months of life secondary to intrapartum transmission, environmental exposure, or breast feeding. However, infants infected peripartum rarely demonstrate serious sequelae of CMV infection.[42]

The primary infection is usually asymptomatic or produces only a mild non-specific glandular fever like illness. Following primary infection, the virus becomes latent and there is a periodic reactivation with viral shedding despite the presence of serum antibody. Relative depression of cell-mediated immunity is associated with pregnancy. This places the fetus at high risk for the sequelae of CMV infection which is transmitted transplacentally to the fetus.

Recommendations
Lab abnormalities at primary infection include atypical lymphocytosis, elevated hepatic transaminases, and a negative heterophile antibody response (which distinguishes CMV from the Epstein–Barr virus infection).

Active maternal infection is best diagnosed by culture, detection of CMV antigen, or DNA-PCR of blood, urine, saliva, amniotic fluid, or cervical secretions. Serologic tests are available but antibody levels may

not be detectable for upto 4 weeks after primary infection and titers can remain elevated, this makes the serologic diagnosis of reinfection difficult.

A four-fold increase in IgG titers within multiple specimens suggests active infection. IgM is used to diagnose recent or active infection, but both false positive and false negative results can occur. Routine CMV screening during pregnancy is not recommended secondary to high seroprevalence. Fetal infection is documented by amniotic fluid culture or PCR and PCR sensitivity approaches 100% in gestations >21 weeks.[43] Antenatal CMV detection does not predict the severity of congenital CMV infection and 80%–90% of children with congenital CMV infection have no neurological sequelae.

Toxoplasmosis

It is caused by an intracellular protozoan parasite Toxoplasma gondii. Like CMV infection primary toxoplasmosis is usually asymptomatic in healthy woman. Rarely fatigue, muscle pains, and sometimes lymphadenopathy appears. Once infected a lifelong antibody response provides immunity for further infection.

However, unlike CMV, toxoplasmosis during pregnancy can be treated potentially reducing the fetal effects. Average toxoplasmosis incidence among susceptible (i.e., antibody negative) women in Europe ranged from 2.4/1000 women in Finland and 16/1000 women in France. Approximately 75%–90% of pregnant women in UK are estimated to be susceptible to toxoplasmosis.[44]

Although asymptomatic women with perceived risk (example contact with cats) are often tested for toxoplasma IgG, pre-pregnancy, or antenatal screening is not recommended. Like CMV, toxoplasma infection remains latent for life, but clinical reactivation is confined to severely immunosuppressed individuals. Infants whose mother is seropositive before conception are not at risk, that is, maternal immunity protects against fetal infection.

For congenital toxoplasmosis to develop, the mother should have acquired the infection during current pregnancy. Toxoplasmosis infection is acquired via four routes in humans:

- Ingestion of viable tissue cysts in undercooked or uncooked meat or tachyzoites in the milk of intermediate hosts.
- Ingestion of oocytes excreted by cats and qcontaminated soil or water. So wash all fruits and vegetables well before use.
- Transplanted organs or blood products from other humans infected with toxoplasmosis.
- MCT when primary infection occurs during pregnancy.

The reported overall risk of congenital toxoplasmosis with primary infection with T. gondii increases from 6% to 26% from 7 to 15 weeks of gestation and rising to 32% to 93% at 29 to 34 weeks gestation.[45]

In contrast to the risk of transmission the risk of an infected infant developing clinical signs of the disease (the classic triad hydrocephalus, intracranial calcification, and retinochoroiditis which may lead to permanent neurological damage or visual impairment) is highest when infection occurs early in pregnancy declining from an estimated 61% at 13 weeks to 9% at 36 weeks.[46]

Available screening tests to determine seroconversion cannot distinguish between infection acquired during pregnancy or upto 12 months beforehand and women who have acquired infection before conception are not at risk of fetal infection.[47] Primary prevention of toxoplasmosis with the provision of information about how to avoid toxoplasma infection before or early in pregnancy, should be given.

Systematic review on the effects of antiparasitic treatment (spiramycin alone, pyrimethamine, sulphonamides, or their combination) on women who acquire primary toxoplasma infection during pregnancy showed inconsistent treatment effects. The drugs are well tolerated and non-teratogenic although sulpha drugs may carry a risk of kernicterus in infants and also of bone marrow suppression in mother and infants.[48]

Although universal screening with antenatal treatment reduced the number of cases of congenital toxoplasmosis, an additional 18.5 pregnancies were lost for each case avoided. Other costs include the unnecessary treatment and termination of uninfected and unaffected fetuses.

Neonatal screening aims to identify neonates with congenital toxoplasmosis in order to offer treatment and clinical followup. The vast majority of congenitally infected infants is asymptomatic in early infancy and would be missed by routine pediatric examinations. Neonatal screening is based on in the detection of toxoplasma specific IgM on Guthrie-card blood spots and has been found to detect 85% of infected infants.

Recommendations

Routine antenatal serological screening for toxoplasmosis should not be offered because the risks of screening may outweigh the potential benefits. Pregnant woman should be informed of the primary prevention measures to avoid toxoplasma infection such as:

- Washing hands before handling food.
- Thoroughly washing all fruits and vegetables including ready prepared salads.
- Thoroughly cooking raw meat and ready prepared chilled meals.
- Wearing gloves and thoroughly washing hands after handling soil and gardening.
- Avoiding cat feces in cat litter or in soil.

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SECTION - I

Understanding etiopathogenesis of infectious disease during pregnancy

Introduction

Infectious diseases during pregnancy can be caused by bacterial, viral, fungal, or parasitic invasion which can cause dreadful threat to women, claiming more than 15 million lives around the globe each year.[1] Usually, infectious diseases are self-limited in the healthy, immuno-competent individual. Pregnancy is a physiologically unique period where women are at risk of serious infection-related complications due to the obligatory immunologic changes to allow for a diminished inflammatory response and fetal tolerance.[2]

In addition to maternal risk, the potential for vertical or mother-to-child transmission is another attribute of infectious disease during pregnancy. Vertical transmission can occur through transplacental passage, often resulting in severe congenital malformations and long-term disability. Intrapartum infection occurs due to hematogenous spread or direct exposure to the maternal body fluids. Postnatal transmission can occur during breastfeeding period.[3]

Fetal Inflammatory Response Syndrome (FIRS)

Infection during pregnancy may cause fetal infection and inflammation which is defined by fetal inflammatory response syndrome (FIRS). The condition leads to polyorganic derangement, remote residual health disorders in an infant such as cerebral palsy and chronic lung disease, septic shock, and even death.[4–6] Cytokines released as a part of an inflammatory cascade are often selectively neurotoxin that causes damage to central nervous system. FIRS is characterized by the increase in the amount of interleukin 6 (IL-6) in fetal plasma by ≥11 pg/ml. Microorganisms and their toxins induce fetal mononuclear production of IL-6 and other inflammatory markers such as IL-1and tumor necrosis factor alpha (TNF-α). They increase the permeability of the hematoencephalic barrier, stimulate oligodendrocyte dysfunction, and reduce the myelin production. The manifestation of TNF-α, IL-1, and IL-6 in the brain of a newborn in 88% cases related to periventricular leukomalacia.[7]

Toxoplasmosis Infection

Toxoplasmosis is caused by an obligate intracellular protozoan, Toxoplasma gondii, and its infection is mainly acquired by the consumption of uncooked or raw meat. Water and food contaminated by oocytes excreted in the feces of infected cats represents another source of infection.[8] After ingestion, toxoplasma invades intestinal epithelial cells and spreads in circulation.[9] The incidence of primary toxoplasmosis in pregnant women ranges from 1 to [10] per 1000 pregnancies, depending on the part of the world, lifestyle, and socioeconomic status of the population.[10,11] The seroprevalence of antibodies in India has revealed wide variations from 4% to 57%.[12,13]

The parasites can cross placenta and cause congenital toxoplasmosis which usually does not appears at the time of birth. About 70%–90% of infants develop serious clinical illness in adulthood.[14] The severity of disease depends on the gestational age at transmission. The risk of transmission increases with advanced gestation age.

Maternal infection is usually asymptomatic and only a small percentage of patients develop low-grade fever,

malaise, and lymphadenopathy. Fetal infection leads to miscarriage, stillbirth, or severe neonatal diseases, like skull and encephalic anomalies, bulging fontanelle, abnormal muscle tone, seizures, nystagmus and delayed development of milestones. The classical triad having signs of hydrocephalus, chorioretinitis and intracranial calcifications reported rarely.[15] Fetus infected in the third trimester is often asymptomatic at birth.[16]

Screening for toxoplasmosis is not performed routinely unless mother is symptomatic or fetal structural abnormalities are detected at ultrasonography. For the diagnosis of toxoplasma infection, serological test done for the detection of IgM and IgG antibodies. If pregnant woman gets infected, as a result of immune response, IgM antibodies are produced followed by IgG antibodies. IgM antibodies last for 3 months, whereas IgG antibodies persist for life, providing immunity and preventing or reducing the severity of reinfection. The presence of positive IgM, negative IgG, or both positive usually reflects a recent infection. Isolation of toxoplasma in the amniotic fluid by polymerase chain reaction (PCR) represents the gold standard for the diagnosis of fetal infection.[17]

After detection, spiramycin should be considered in the first 18 weeks of gestation and started at the dose of 1g every 8h to prevent fetal infection. It reduces the rate of vertical transmission by 60%, especially if administered in the first trimester.[18,19] If fetal infection is confirmed by positive PCR on amniotic fluid or fetal abnormalities suggestive of fetal infection at the scan or mother acquiring infection after 18 weeks of gestation, a combination of pyrimethamine, sulfadiazine, and folinic acid is the another alternative. The rationale of this multidrug therapy is mainly to cure rather than prevent fetal infection.[9] After delivery, baby should be carefully examined by multidisciplinary team and a prolonged follow up is needed. Termination of pregnancy is indicated only if there is a strong evidence of fetal infection.

Hepatitis B Virus Infection

Hepatitis B virus (HBV) infection is caused by double-stranded DNA virus belongs to Hepadnaviridae family. More than 350 million people worldwide are infected with HBV; nearly 1 million people die annually.[20] Hepatitis B carrier rate in India is estimated to be 4.7%. However, a multicenter study detected Hepatitis B prevalence to be <1%.[21] Most infants are infected through contaminated blood or body fluids during delivery and breastfeeding. The rate of vertical transmission mostly depends on the gestational age with rates of 10%, 80%, and 90%, respectively, if infection occurs in the first, second, and third trimesters. If pregnant woman infected in advanced gestational age, the risk of chronic infection decreases.

Acute infection is manifested by flu-like symptoms in 25% cases. Most of the patients do not develop jaundice. Approximately 90% of individuals have spontaneous complete resolution; 5%–10% would become chronic carriers, and <1% manifests as lethal fulminant hepatitis.[22] The outcome of maternal infection is strictly dependent upon the stage of the disease. Patients with advanced cirrhosis may experience rupture of esophageal varices in upto 25% of cases.

Screening for Hepatitis B infection is routinely performed in every antenatal woman. HBV has three antigens: HBcAg (core antigen), HBsAg (surface antigen), and HBeAg. The surface antigen is the marker of ongoing HBV infection. The HBeAg is a marker of infectivity and viral replication.[23] An active disease is defined by presence of high viral load and elevated ALT.

If viral load is more than 106 copies/ml, antiviral prophylaxis should be started in third trimester.[22] Lamivudine is safe and effective in preventing perinatal transmission of the virus. Vaccination can be performed during pregnancy. Infants born with infected mothers need not be isolated. Infant should be given a combination of HBV vaccine and immunoglobulin within 12 h of delivery. The efficacy of combined active and passive immunization in preventing perinatal transmission is 85%–95%.[24]

If the partner is seronegative, vaccination and use of barrier contraceptives is a must. If health workers get contaminated, they should receive immunoglobulin as early as possible irrespective of vaccination status.

Syphilis Infection

Syphilis is a systemic disease caused by Gram-negative spirochete Treponemapallidum; always acquired by sexual contact. Congenital syphilis transmitted from mother-to-fetus by transplacental route. The World health organization (WHO) estimates that approximately 1.3 million pregnant woman have active syphilis infection annually.[25] This leads to a substantial burden of preventable morbidity and mortality including over 200,000 still births and fetal loses and >90,000 neonatal deaths.[26]

Syphilis is divided into the following stages:

a) Primary syphilis: Develops in 10–90 days following exposure. Usually heals spontaneously in 3–6 weeks. There is appearance of the syphilitic chancre involving the genital area, extra genital sites like lips, oropharynx, anus, breasts, and regional non-tender lymphadenopathy.
b) Secondary syphilis: Develops within 4–10 weeks of primary syphilis. Persistence of chancre seen in one-third of primary syphilis. This stage is again divided into – early and late syphilis. Early secondary syphilis usually resolves within 3–12 weeks and characterized by flu-like symptoms, low-grade fever, lymphadenopathy, and recurrent lesions. The late syphilis last for more than 1 year and not associated with clinical manifestations.
c) Tertiary stage: Extremely rare in woman of child-bearing age group, characterized by neurological, cardiovascular, and gummatus lesions.

The degree of fetal involvement is severe if infection is acquired during early stages of pregnancy. Congenital syphilis may cause still birth, preterm labor, growth restriction, fetal hydrops, and neonatal infection. Anemia, thrombocytopenia, hepatosplenomegaly, and skeletal involvement such as osteomyelitis, osteochondritis, or peritonitis is seen.[27]

The screening for syphilis is mandatory at first antenatal visit. A presumptive diagnosis is made using non-treponemal and treponemal test. Non-treponemal test includes the Venereal Disease Research Laboratory (VDRL) and rapid plasma regain (RPR), done as screening test and treponemal tests includes florescent treponemal antibody absorption (FTA-ABS) assay and the microheamaglutination assay for T. pallidum antibody (MHA-TP). Reactive screening tests should have confirmatory testing with non-treponemal tests with titer. Any woman who delivers a still born after 20 weeks gestation should be tested for syphilis.

The treatment for an early, secondary, or latent syphilis of >1 year duration is benzathine penicillin, 2.4 million units intramuscular (IM) in a single dose. In late latent syphilis for <1 year or unknown duration, administration of three doses of benzathine penicillin, 2.4 million units at 1 week interval is required. For neurosyphilis, procainepenicillin2.4 units IM daily with probenecid 500mg orally 4 qid, both for 10–14 days should be given.

Presence of anti-troponemal IgM antibodies in neonate is diagnostic of congenital syphilis. A VDRL titer four times greater than the maternal titer is also considered as congenital syphilis. Penicillin treatment should be started only after serological confirmation of the neonatal syphilis. Long-term follow up is needed in order to detect the late consequences of the infection.[27]

Rubella Infection

Rubella virus (RV) is a single-stranded RNA virus, member of Togaviridae family, infecting only humans. Transmission occurs by direct contact or airborne droplets. The incubation period is about 12–23 days. Individuals with Rubella are infectious from 1 week before the symptoms appear to 4 days after the onset of rashes. The maculopapular rash appears on the face and rapidly spread to the trunks and limbs, also associated with headache, sore throat, low-grade fever, and conjunctivitis. Serious complications such as encephalopathy and thrombocytopenia may occur.

The risk of transmission from the mother-to-fetus and rate of congenital defects have been reported to be 80%–85%, respectively, if infection occurs in the first 8 weeks of pregnancy.[28] The rate of pregnancy loss in first trimester is around 20%. If infection occurs within 11 weeks of gestation, possibility of fetal infection is 90%, 50% in 11–20 weeks, 37% in 20–35 weeks, and 100% in last month of pregnancy.[29]

RV induces multiorgan disease of the fetus known as congenital rubella syndrome, that is, heart disease, cataract, and deafness. Congenital heart disease, like ventricular septal defects, patent ductus arteiosus, pulmonary stenosis and coarctation of aorta along with deafness, and cataracts are found in nearly 50% of affected children. Other anomalies such as intra uterine growth retardation, encephalitis, microcephaly, mental retardation, thrombocytopenia, hepatosplenomegaly, obstructive jaundice, and changes of long bones are also seen.[30–34] Late complications are glaucoma, retinopathy, diabetes mellitus, thyroid dysfunction, panencephalitis, and a higher incidence of psychosis.[35]

Serological test is required, if mother is non-immune to RV and presents with rubella like symptoms or exposed to individuals with rubella infection in the first 16 weeks of gestation. Diagnosis of rubella infection in the fetus can be performed either by chorionic villous sampling, amniocentesis, or fetal blood sampling according to gestational age. PCR is the technique of choice in confirming fetal infection. A positive PCR with structural anomalies of fetus at scan indicates a poor outcome. A negative PCR indicates no infection, although false negatives are possible.[36]

After delivery, baby should be examined for the CNS, eyes, and cardiac anomalies. The overall risk to the fetus following reinfection in the first trimester has been reported as >10%.37Vaccination is the best way to prevent the infection in the women at least 28 days prior to conception.

Cytomegalovirus

The cytomegalovirus (CMV) is a double-stranded DNA virus, most common congenital infection in United State.[17]It remains latent within the host for many years and can reactivates. Reactivation is induced by immunological or hormonal changes in the host.[38] The CMV is transmitted to an infant during pregnancy, ingestion of infected human milk, and direct contact with urine and saliva.[16]

Most of the infected pregnant women are asymptomatic; occasionally causes malaise, lymphadenopathy, and hepatosplenomegaly. It is the most common cause of fetal infection, occurring in 0.5%–2% of live births.[39] Infant shows various complications such as optic atrophy, microcephaly, hypotonia, intracranial calcifications, decrease hearing, cardiomegaly, pericardial effusion, non-immunehydrops, pneumopathy, and thrombocytopenic purpura.[14] If the mother has a primary infection, fetal morbidity rate is very high.[40]

The diagnosis of the maternal CMV infection is made by culturing the virus from the urine or genital tract secretions and confirmed by serological test for detection of IgG and IgM antibodies. Detection of CMV in amniotic fluid and demonstration of fetal anomalies by ultrasonography actually correlate with severity of

fetal infection. It is very difficult to differentiate congenital and postnatal infection after 3 weeks of delivery.[40] The PCR technique is very frequently used for detection of this virus. Patients with symptomatic congenital CMV infection experience postnatal seizure in 10%–56% of children and 0.9% in asymptomatic patients.[41]

General hygiene should be emphasized as preventive measure. CMV should be screened before blood transfusion. There is no proven prenatal treatment for congenital CMV infection. The use of CMV hyperimmunoglobulin or antiviral drugs proposed to reduce the course of infection and the rate of vertical transmission.[42]Gencyclovir may be of value in treating chorio-retinitis caused by CMV.

In view of the fact that neurological impairment, hearing, and visual loss may not be evident immediately after birth, babies should be assessed sequentially during childhood by a multidisciplinary team.

HIV Infection

Human immunodeficiency virus (HIV) is the causative agent of acquired-immune deficiency syndrome (AIDS). The HIV can be transmitted through unprotected sex with an infected partner, transfusion of contaminated blood, infected needles, and from infected mother-to-child during pregnancy, delivery, or during breastfeeding.

Evidence suggests that antenatal, intra partum, and puerperal period are the times of increased risk for HIV acquisition.[43-45] In the initial stage HIV-infected patient remains asymptomatic. Infected individuals undergo a prolonged asymptomatic period thatkeep on shedding virus into most body fluids and are infective. At some point, the infected individuals develop symptoms and signs called AIDS-related complex (ARC). It is characterizes by generalized lymph node enlargement, fever, night sweats, weight loss, and unusual recurrent infection such as Herpes or Candidiasis.

Approximately 15%–25% of infants born to HIV-infected mothers will demonstrate the presence of the disease by 1 year of age. They may have growth retardation, microcephaly, and craniofacial abnormalities. In non-breastfeeding mothers, 60%–80% of the transmission occurs during labor and delivery, rest occurs in antepartum.[46] All infants of HIV-infected mothers have positive serology but levels of these antibodies decline gradually and by 6 months of age most non-infected infants will be seronegative.

HIV testing in every pregnant woman and partner is mandatory. The diagnosis is made by serological testing with the enzyme-linked immunosorbent assay (ELISA) which is extremely sensitive, specific, and easy to perform. After a sample has been found to be HIV positive, the sample should be retested before labeling as screening test positive. Other confirmatory tests are immunoflorescent assay and radio-immuno precipitation test.

The woman should have a CD4 cells count every trimester and serial ultrasonography to assess growth pattern of the fetus.[47] Standard treatment of HIV is HAART regimens using combination of nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. One of the principles governing treatment during pregnancy is to include zidovudine as a component of HAART.[48] Women with HIV infection should be delivered at 38 weeks of gestation to avoid rupture of membranes before delivery. During delivery health care personnel should take universal precaution. The new born treatment is oral zidovudine 2mg/kg every 6 h for the first 6 weeks of life.

HIV mother should either avoid complete breastfeeding or otherwise they must exclusively breastfeed upto 6 months of infant's life. To prevent the spread of HIV infection to their partner's one should use barrier contraceptives.

Chickenpox Infection

Chickenpox is caused by Varicella-zoster virus (VZV), is a DNA virus of the herpes family that is highly contagious. While chickenpox is the consequence of a primary infection with VZV, Herpes zoster is caused by reactivation of the virus due to immunosuppression, age, or hormonal changes. The incidence in pregnancy is 1–7 per 10,000 pregnancies.[49] H. zoster infection in pregnancy is less common(0.5 per 10,000 pregnancies).[50] The VZV is highly transmissible infective agent with <90% secondary attack rate. Incubation period is about 14–16 days.

The first sign of illness may be pruritus or the appearance of vesicles on the scalp or the trunk spreads to the face and extremities. The vesicles subsequently break open and crust over, rash usually lasts for 7–10 days. Maternal systemic complications may occur such as hepatitis, encephalitis, and pneumonia. One attack of chickenpox usually results in permanent immunity.

The rate of vertical transmission during first and second trimester is around 8%–9% and congenital varicella syndrome occurs in about 10% of cases, if maternal infection acquire before 20 weeks of gestation. Features of congenital varicella syndrome are ventriculomegaly, microcephaly, intracranial calcifications, hypoplasia, and ocular abnormalities like cataract, microphthalmia, intrauterine growth retardation (IUGR), limb dysplasia, skeletal abnormalities, placental anomalies, hydrops fetalis, and skin rashes. Varicella is particularly dangerous for the fetus if delivery occurs between 5 days before and

2 days after the onset of rash. Neonatal varicella is characterized by the presence of neurological, ocular, muscular, cutaneous, gastrointestinal, and genitourinary abnormalities which can lead to neonatal death in approximately 7% of cases.[51,52]

Diagnosis is usually based on clinical presentation. Detection of specific IgM or isolation of varicella virus by PCR in maternal blood confirms the diagnosis. Infected mother should receive oral acyclovir 15 mg/kg every 8 h within the onset of rash in order to treat the disease and to reduce the rate of complications. Women who are exposed to VZV should receive immunoglobulin within 72–96 h of exposure. If birth occurs 7 days prior or after the onset of rash, VZIG should be given. It is also recommended if neonates are exposed to chickenpox or shingles in the first 7 days of life. Neonatal infection should be treated with acyclovir.[53]

Malaria Infection

Malaria is a protozoal disease caused by plasmodium and is transmitted by the bite of Anopheline mosquitoes. About 109 countries in the world are endemic for malaria. In India, about 27% population lives in malaria high transmission areas and about 58% in low transmission areas.

Malaria in pregnancy can be considered as a "double trouble." Complications like anemia, fever, hypoglycemia, thrombocytopenia, cerebral malaria, pulmonary edema, puerperal sepsis, and even mortality can occur. Miscarriage, stillbirth, preterm labor, IUGR, intrauterine deaths are the most common clinical manifestations of fetus.

a) Examination of thick and thin smear of blood films stained with Giemsa stain along with quantification is the diagnostic tool. Chloroquine can be given at any time during pregnancy in a dose of 25mg/kg in divided doses for 3 days. Sulphadoxine and pyrimethamine combination is used in areas of chroquine resistance in a dose of 1500mg of sulphadoxine and 75mg of pyrimethamine for radical treatment. Quinine remains the drug of choice for the treatment of acute malaria, multidrug resistant malaria, and in travelers returning to the endemic areas. It is the most effective, well-tolerated, and safest drug during pregnancy, given in the dosage of 8–10mg/kg three times a day for 7 days. In areas with high malaria transmission, the Ministry of Health strives to implement the recommendations of WHO for pregnant women as: Intermittent preventive treatment (IPT) with atleast two doses of antimalarial drugs after quickening.
b) Use of insecticide-treated bed nets (ITN) throughout pregnancy and during the postpartum periods.
c) Prompt and effective case management of malaria illness.

Conclusion

Infection during pregnancy may cause severe morbidity and mortality to the fetus and newborn. Timely detection, counseling, and treatment will reduce the sequel of congenital infection in future. Infection control measure should be adopted during perinatal and postpartum period. Development of vaccines holds the most promising option to fight against infection.

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SECTION - I

Vaccinations during Pregnancy

Introduction

Pregnancyis a condition where we have to prevent disease to the mother as well as intrauterine fetus. Ideally woman should be vaccinated before she becomes pregnant.[1] Pregnancy should not deter a woman receiving vaccine which are safe during pregnancy. With rising incidence of communicable diseases and travel abroad by a pregnant woman it is important to give proper advice along with routine vaccination.

Extra Care of Vaccination for Pregnant Lady and Her Baby

The Centres for Disease Control suggests that vaccination is an integral part of pregnancy care as pregnant women and her baby are vulnerable populations.[2]

Pregnant women are at risk because:

1. Altered immune response
2. Increased risk of some infections
3. Increased risk of severe outcomes (maternal, fetal, or both) of some infections

Fetus, newborn are at risk because:

1. Immature immune response
2. Increased risk of some infections
3. Increased risk of severe outcomes of some infections
4. Infection sequelae can result in lifelong disability

Maternal and Fetal Outcome for Woman Contracting the Following Infection during Pregnancy

Measles: Increases chances of preterm birth and miscarriage

Mumps: In first trimester increases the risk of death of fetus

Chicken pox (Varicella): Mother may have fatal pneumonia. Baby will have congenital anomaly.

Rubella (German measles): Miscarriage and defect of the heart, eye, and brain

H1N1: The risk of morbidity from seasonal influenza is higher among pregnant women. This phenomenon was also observed during the recent outbreak, as pregnant women have had a higher rate of hospital admission than the general population. Pregnant women are at a higher risk of acute respiratory distress syndrome.

Vaccinations Issues During Pregnancy

1. Two doses of tetanus toxoid injection at least 28 days apart are to be given to all pregnant mothers commencing from second trimester. If the subsequent pregnancy occurs within 5 years only one booster is given.
2. Recent the Indian Academy of Pediatrics (IAP)guideline[3] advises that person who did not get vaccination between 11–18 years should receive a Tdap (tetanus, diphtheria, and acellular pertussis) vaccine and booster of Td every 10 years. IAP Advisory Committee on Immunization Practices (ACIP), therefore now suggests immunization of pregnant women with a single dose of Tdap during the third trimester (preferred during 27 through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination.[4] ACIP recommends that if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.[5]
3. The Federation of Obstetric and Gynecological Societies of India (FOGSI) recommends vaccination counseling as a part of pre-pregnancy

counseling. (Unvaccinated women) History of occurrence of vaccine preventable diseases, previous vaccinations administered, and allergic reactions to vaccinations must be recorded. Rubella, hepatitis B, and varicella vaccination should be given preferably during postmenstrual period. Pregnancy should be deferred for 3 months in case of rubella vaccine.[6]

4. H1N1 vaccination– Influenza vaccine: Influenza disease may cause hospitalization and medical complication. If vaccinated against influenza virus then antibody produced will protect the baby too. There is no vaccine available for influenza for baby of <6 months against influenza. No significant effect was found on major birth defects, preterm birth, or fetal growth restriction if vaccinated during pregnancy.[7]
5. Meningococcal vaccine – The global advisory committee of WHO did not recommend meningococcal vaccination during pregnancy because of chances of significant morbidity and mortality.[8]
6. Rabies vaccination – Purified vero cell rabies vaccine (PVRV) during pregnancyis found to be safe and effective without any adverse effect to the mother and baby.[9]
7. Hepatitis B: Hepatitis B vaccination with an ongoing pregnancy is safe and does not warrant a termination.

Vaccines to be Avoided in Pregnancy

1. Mumps-containing vaccine
2. Smallpox vaccine
3. Yellow fever vaccine
4. Typhoid vaccine
5. Oral polio vaccine
6. Influenza live vaccine (Nasal).

Postnatal Vaccination

Postnatal period is a good window period for vaccination. Vaccines such as rubella can be safely administered in concurrence with postnatal contraception.

Conclusion

Live vaccine should be avoided during pregnancy. Woman should be offered additional vaccination if not immunized earlier to prevent adverse fetal outcome if mother is having chance of contracting infection.

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SECTION - II
Infectious diseases during pregnancy

HIV in Pregnancy

Introduction

Human immunodeficiency virus (HIV) is a single-stranded RNA retrovirus belonging to genus of Lentivirus within the subfamily of Orthoretrovirinae. Worldwide [World Health Organization (WHO) 2010] there were 34 million HIV-infected people of which 16.8 million were women and 3.4 million were children. People living with HIV (PLHV) in India (2011) are 2.1 million. Of these, women constitute 39% of all PLHV and children <15 years constitute 7% of all infections. Mother-to-child transmission of HIV is a major route of HIV infection in children. Pregnancy has minimal, if any, effect on CD4+T cell counts, HIV-RNA levels, or disease progression. However, HIV infection in pregnancy has important implications on the fetus because of the risk of vertical transmission. Without any intervention, the risk of transmission of HIV from infected pregnant women to her child is estimated to be around 20%–45%. Use of antiretroviral therapy (ART) and syrup nevaripine (NVP) to mother–baby pairs has shown to be quite effective in reducing this transmission to as low as 10%.

The Goals of the Prevention of Parent-to-Child Transmission Programme[1]

In line with the WHO standards for a comprehensive strategy, the National Prevention of Parent-to-Child Transmission (PPTCT) programme recognizes the four elements integral to preventing HIV transmission among women and children. These are:

Prong 1: Primary prevention of HIV, especially among women of child-bearing age.
Prong 2: Preventing unintended pregnancies among women living with HIV.
Prong 3: Prevent HIV transmission from pregnant women infected with HIV to their child.
Prong 4: Provide care, support, and treatment to women living with HIV, her children, and fami-ly of women in child-bearing age.

Maternal Complications

- Incidence of fetal wastage exceeded 24%, higher rate of spontaneous abortion.
- Higher rates of ectopic pregnancy have been reported in HIV-positive women, which may be related to the effects of other concurrent sexually transmitted diseases.
- Genital tract infections such as Neisseria gonorrhoeae, Chlamydia trachomatis, Candida albicans, and Trichomonas vaginalis infection have been reported to be more common in women with HIV.
- Syphilis is more common in HIV-positive women.
- Bacterial pneumonia, urinary tract infections, and other infections are more common dur-ing pregnancy in HIV seropositive women.
- HIV-related opportunistic infections – Tuberculosis (TB) is the commonest opportunistic infection associated with HIV in the developing world.
- Herpes zoster is common in young HIV-positive women, although uncommon in this age group in the absence of HIV infection.
- Kaposi's sarcoma has been reported during pregnancy in HIV-positive women.
- Mean birth weights were about 120 g lower than in normal controls.
- Preterm birth–preterm labor may be more common in HIV-positive women, with rates as high as double those rates seen in uninfected women in some reports.
- Preterm rupture of membranes may also be increased (24.2%) in HIV-positive women and abruptio placentae have been described as more common in HIV-positive women.
- Increased stillbirth rates have been reported.
- Infectious complications are also more common during the postpartum period in HIV-positive women.
- Perinatal transmission of HIV – The rate of transmission is approximately 25%–30%. About 20% of perinatal HIV transmission occurs before 36 weeks, 50% near-term, and 30% intrapartum. Transmission rates for breastfeeding mothers may be as high as 30%–40%.

Diagnosis

The diagnosis of HIV infection is serologic, by virus culture or by detection of viral genetic ma-terial using the polymerase chain reaction (PCR). The screening test is the enzyme-linked im-munosorbent assay (ELISA). This test may produce false positive results and all positive tests should be followed by the Western blot analysis. The Western blot detects antibodies against p24, p31, gp41 and gp160, presence of these antibodies is a reliable indication of infection. The possibility of false positive diagnosis is almost nonexistent, if two ELISA and one Western blot is positive.

Current recommendations are to screen with an HIV-1/2 antigen/antibody combination immuno-assay, or "combo assay", with confirmation of infection with an HIV-1/HIV-2 antibody differen-tiation immunoassay and HIV-1 nucleic acid test (NAT). This strategy enables diagnosis of acute HIV-1 infection, detection of HIV-2 infection, and faster turnaround time.[1,2]

Enhancements of the combo assay include more accurate HIV-2 diagnosis, p24 antigen assess-ment (measurable 15 days post infection), and detection of IgM antibodies of HIV infection days to weeks before the HIV Western blot becomes positive.

Combined with an HIV-1 NAT, this narrows the window between the time of infection and im-munoassay reactivity and enables the diagnosis of acute HIV-1 infection, which was not possible using ELISA/Western blot assessment.

HIV-infected Pregnant Women Counseling and Testing Services

- Antenatal care (ensure at least four visits).
- Counseling on choices of continuation or medical termination of pregnancy (MTP) within the first 3 months of pregnancy only.
- Screening for TB.
- Screening and treatment for sexually transmitted infections (STIs).
- WHO clinical staging and CD4 testing.
- Counseling on positive living, safe delivery, birth planning, and infant feeding options.
- Safe sex counseling and HIV testing of spouse and other living children.
- Linkage to ART services.
- Provide ART regardless of WHO clinical stage and CD4 count.
- Nutrition counseling and linkages to government/ other nutrition programmes.
- Family-planning services.
- Exclusive breastfeeding (EBF) reinforcement/ infant feeding support through home visits.
- Psychosocial support through follow-up counseling, home visits, and support groups.

Management

The guidelines, regimens described here are in accordance with updated NACO guidelines for prevention of parent-to-child transmission using multidrug antiretroviral regimen.

Laboratory Monitoring of Pregnant Women Living with HIV

- Pregnant women who are newly diagnosed with HIV do not require any additional base-line investigations compared with non-pregnant women living with HIV other than those routinely performed in the general antenatal clinic.
- In women conceiving on combined ART (cART) there should be a minimum of one CD4 cell count at baseline and one at delivery.
- In women who commence cART in pregnancy, a CD4 cell count should be performed as per routine initiation of cART.
- In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after commencing cART, at least once every trimester, at 36 weeks, and at de-livery.
- In women commencing cART in pregnancy, liver function tests should be performed as per routine initiation of cART and then at each antenatal visit.
- In the event that a woman who has initiated cART during pregnancy has not suppressed plasma viral load <50 HIV RNA copies/ml at 36 weeks, the following interventions are recommended: review adherence and concomitant medication, perform resistance test if appropriate, consider therapeutic drug monitoring (TDM), and optimize to best regimen consider intensification.

Care During Antenatal Period

When to start?
According to the NACO guidelines 2013, ART should be started immediately after detection. ART should be started irrespective of the following:

- Gestational age
- CD4 count
- WHO clinical stage

Women conceiving on cART: Pregnant women who have been diagnosed with HIV before pregnancy should continue the same therapy during pregnancy also.

Women is not already on cART: Pregnant women detected with HIV first time during preg-nancy should be started on lifelong ART [tenofovir disoproxil fumarate + lamivudine + efavirenz (TDF + 3TC + EFV)] regardless of the gestational age, WHO stage, and CD4 count.

Late-presenting woman (in labor at term) not on treatment: Pregnant woman who present in labor and is found positive during screening test; initiate ART immediately. HIV test should be confirmed the next day by three rapid antibody tests and a CD4 count to be done [Table 1].

Table 1: Dosage Schedule and Common Side Effects with ART Drugs

Name of ARV	Dose	Major side effects
Tenofovir disoproxil fumarate (TDF)	300 mg/day	Nephrotoxicity, hypophos-phatemia
Lamivudine (3TC)	300 mg/day	Very few side effects: hypersen-sitivity, rarely pancreatitis
Efavirenz (EFV)	600 mg/day	Neuropsychiatric symptoms like hallucinations, suicidal ideations, nightmares, vivid dreams and so on
Lopinavir/ ritonavir (LPV/r)	400/100 mg BD	Gastrointestinal disturbances, glucose intolerance, lipodystro-phy, and hyperlipidemia

Monitoring Disease Status During Pregnancy

Plasma HIV RNA levels should be monitored at:

- The initial visit
- 2–4 weeks after initiating anti-retroviral regimen
- Monthly until RNA levels are undetectable
- Then atleast every 3 months during pregnancy
- HIV RNA levels should be assessed around 34–36 weeks gestation to decide about mode of delivery.

ART Regimen for HIV-infected Women

First-line Regimen

TDF (300 mg) + 3TC (300 mg) + EFV (600 mg)/day if there is no prior exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP)/EFV at any gestational age. Start as soon as possible, continue throughout pregnancy, delivery, breastfeeding, and there-after lifelong.

Special Scenarios[3,4]

1. ART Regimen for Pregnant Women Having Prior Exposure to NNRTIs for PPTCT

An NNRTI-based ART regimen such as TDF + 3TC + EFV may not be fully effective due to persistence of archived mutation to NNRTIs. Thus these women will require a protease inhibitor-based ART regimen, that is, TDF + 3TC (1 tablet daily) + LPV/r (lopinavir 200 mg/ritonavir 50 mg, 2 tablets BD).

2. Pregnant Women with Active TB

The risk of active TB is approximately 10 times higher in HIV-infected pregnant women com-pared to HIV-uninfected women. Active TB in HIV-infected pregnant women can contribute to increased risk of maternal mortality, low birth weight, and perinatal TB. A recent study in India found that maternal TB increases risk of HIV transmission from mother to child by 2.5 times. HIV-infected pregnant women with active TB should start ART irrespective of CD4 cell count. TB treatment should be started first and followed by ART as soon as feasible (usually after 2 weeks).

3. Pregnant Women with HIV-2 Infection

Although great majority of HIV infections in India are due to HIV-1, there are small foci of HIV-2 infection as well, primarily in western India. HIV-2 will also progress to AIDS, although progression is generally much slower. It has same modes of transmission as HIV-1, but mother-to-child transmission is less (0%–4%). NNRTI drugs, such as NVP and EFV are not effective against HIV-2 infection. Therefore, for the HIV-2 infection one should follow (1) standard adult guidelines for HIV-2 treatment which consists of 2 NRTIs + LPV/r and (2) prophylaxis NVP with AZT (instead of syp NVP) to be given to babies of mothers with HIV-2 infection.

If a pregnant woman has both HIV-1 and HIV-2 infections, she should receive standard first ART regimen (TDF + 3TC + EFV) recommended for women with HIV-1 infection.

4. For Women Co-infected with HIV and Hepatitis C Virus

No specific changes in treatment are recommended in the adult ART treatment guidelines. Co-infection with HIV and Hepatitis B (HBV)/Hepatitis C (HCV) is common among injecting drug users (IDUs). Hence, all women living with HIV who are recognized to be IDU's should routine-ly be offered testing for HBV and HCV infections and monitored.

5. Indications for Co-trimoxazole Prophylactic Therapy in Pregnancy

- Same as for other adults.
- Co-trimoxazole should be started if CD4 count is ≤250 cells/mm3 and continued through-out pregnancy, delivery, and breastfeeding as per National guidelines (dose: double strength tablet – 1 tablet daily). Co-trimoxazole prophylactic therapy (CPT) helps in de-creasing morbidity and mortality as it prevents opportunistic infections such as Pneumo-cystic pneumonia, Toxoplasmosis, diarrhea, as well as other bacterial infections.
- Ensure that pregnant women take their folate supplements regularly.

Obstetric Management

Antenatal Care

- Fetal ultrasound imaging should be performed as per National guidelines regardless of maternal HIV status.
- The combined screening test for trisomy 21 is recommended as this has the best sensitivi-ty and specificity and will minimize the number of women who may need invasive test-ing.
- Invasive prenatal diagnostic testing should not be performed until after the HIV status of the mother is known, and should ideally be deferred until HIV viral load has been ade-quately suppressed to <50 HIV RNA copies/ml.
- If not on cART and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence cART to in-clude raltegravir and be given a single dose of NVP 2–4 h prior to the procedure.
- External cephalic version (ECV) can be performed in women with HIV.

Mode of Delivery[5]

Women on lifelong ART or who have been started on ART during pregnancy should continue the same therapy during labor. Cesarean section is not recommended for prevention of mother-to-child transmission and should only be done for obstetric indication.

Safer Delivery Techniques

- Mother-to-child-transmission risk is increased by the prolonged rupture of membranes (PROM), repeated P/V examinations, instrumental delivery (vacuum or forceps), invasive fetal monitoring procedures, and episiotomy; so avoid all these.
- Follow all Universal Work Precautions (UWP).
- Suctioning of newborn with a nasogastric tube should be avoided unless there is meconium staining of liquor.
- Safer surgical techniques to be used during C-section, repairing wounds/lacerations, etc.
- Use "dry" hemostatic techniques to minimize bleeding; follow surgical fascial planes during dissection, judicious use of electrocautery.
- Use of round-tip blunt needles for C-section.
- Do not use fingers to hold the needle.
- Use forceps to receive and hold the needle.
- When transferring sharps to surgical assistant hold container for sharps.
- For disposal of tissues, placenta, and other medical/infectious waste material from the delivery of HIV patients standard waste disposal management guidelines to be followed.

Management of Spontaneous Rupture of Membranes[1,5]

- In all cases of term pre-labor spontaneous ROMs delivery should be expedited.
- If maternal HIV viral load is <50 HIV RNA copies/ml, immediate induction of labor is recommended, with a low threshold for treatment of intrapartum pyrexia. For women with a last measured plasma viral load of 50–999 HIV RNA copies/ml, immediate C-section should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors, and the woman's views.
- If maternal HIV viral load is ≥1000 RNA copies/ml plasma, immediate C-section is rec-ommended.
- The management of prolonged premature ROM (P-PROM) at ≥34 weeks is the same as term ROM except women who are 34–37 weeks' gestation will require group B Strepto-coccus prophylaxis in line with National guidelines.
- When P-PROM occurs at <34 weeks:
  1. Intramuscular steroids should be administered in accordance with National guidelines.
  2. Virological control should be optimized.
  3. There should be multidisciplinary discussion about the timing and mode of delivery.

Use of Intrapartum Intravenous Infusion of Zidovudine

Intrapartum intravenous zidovudine infusion is recommended in the following circumstances:

- For women with a viral load of >1000 HIV RNA copies/ml plasma who present in labor, or with ruptured membranes, or who are admitted for planned C-section.
- For untreated women presenting in labor or with ruptured membranes in whom the cur-rent viral load is not known.
- There are no data to support the use of intrapartum intravenous zidovudine infusion in women on cART with a plasma HIV viral load <1000 HIV RNA copies/ml.

Infusion is started with a loading dose of 2 mg/kg IV over 1 h followed by continuous infusion of 1 mg/kg/h until delivery. Those who are scheduled for elective C-section, the infusion should be started 3 h before the cesarean.

A single dose of NVP, regardless of CD4 cell count (even if available) or hepatitis status, should be given immediately as this rapidly crosses the placenta and within 2 h achieves, and then main-tains, effective concentrations in the neonate for up to 10 days, and cART should be commenced immediately.

NVP and raltegravir should be included in the regimen as they cross the placenta rapidly. In ad-dition, double-dose TDF (490 mg) has been shown to cross the

placenta rapidly to preload the infant and should be considered where the prematurity is such that the infant is likely to have difficulty taking post-exposure prophylaxis (PEP) in the first few days of life.

Fetal Complications

Fetal infections do not result in a specific pattern of fetal abnormalities, these include

- IUGR
- Microcephaly
- Cranio-facial anomalies (hypertelorism, prominent forehead, flat nasal bridge)

Infant PEP

- At birth, start syrup NVP prophylaxis immediately and give till 6 weeks.
- NVP prophylaxis extended up to 12 weeks if mother has not received adequate duration of ART to suppress viral replication [Tables 2 and 3].

Table 2: Dosage of NVP

Birth Weight	NVP daily dose (in mg)	NVP daily dose (in ml)
Infants with birth weight <2000 g	2 mg/kg OD	0.2 ml/kg OD
Birth weight 2000–2500 g	10 mg OD	1 ml OD
Birth weight > 2500 g	15 mg OD	1.5 ml OD

Prophylaxis with AZT Instead of Syrup NVP to Babies of Mothers with HIV-2

Table 3: Dosage of AZT

Birth Weight	AZT daily dose (in mg)	AZT daily dose (in ml)
Infants with birth weight <2000 g	5 mg/kg BD	0.5 ml/kg BD
Birth weight <2000 g	10 mg BD	1 ml BD
Birth weight ≥2500 g	15 mg BD	1.5 ml BD

- At 6 weeks start cotrimoxazole prophylaxis and continue until baby is 18 months old.
- Immunizations should be given as per National schedule.
- Start first dose of DPT/OPV/Hepatitis B vaccine (2nd dose).
- Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and severely immunosuppressed). If there is very low or low risk of HIV transmission, BCG at birth is indicated, this should not be delayed.
- Early infant diagnosis (EID): Do dried blood spot (DBS) at 6 weeks for all babies; if positive do WBS. If WBS is positive, start pediatric ART irrespective of CD4% for ba-bies >2 years.
- Repeat testing at 6 months, 12 months, and 6 weeks after cessation of breastfeeds.
- Confirmation of HIV status of all babies at 18 months using all three antibody rapid tests, irrespective of the earlier EID status or the fact that pediatric ART has already been initi-ated.
- No mixed feeding during first 6 months: Feeding a baby with both breasts and replace-ment feeds in the first 6 months is known as mixed feeding which leads to mucosal abra-sions in the gut of the baby facilitating HIV virus entry through these abrasions. Either give EBF or exclusive replacement feeds (ERF) for the first 6 months.

Recommendations for High Risk Infants[1,4]

- Infants born to mothers with HIV who are at high risk of acquiring HIV should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate quality evidence).
- Breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality ev-idence).
- Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong rec-ommendation, low-quality evidence for infants receiving only replacement feeding).

High-risk infants are defined as those: - born to women with established HIV infection who have received <4 weeks of ART at the time of delivery;

or born to women with established HIV infection with viral load >1000 copies/ml in the 4 weeks before delivery, if viral load measurement available;

or born to women with incident HIV infection during pregnancy or breastfeeding;

or identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Infant Feeding

In UK and other resource rich settings the safest way to feed infants born to mothers with HIV is with formula milk, as this eliminates ongoing risk of HIV exposure

after birth. Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT. Women who are virologically suppressed on cART with good adherence and who choose to breastfeed may be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation. Maternal cART (rather than neonatal PEP) is advised to minimize HIV transmission through breastfeeding.

Contraception

- Insertion of Cu-T (temporary contraceptive method) for HIV-infected mother at 6 weeks, if a postpartum IUD (PP-IUD) has already not been inserted within 48 h in addition to the use of condoms will prevent unwanted pregnancies (dual protection).
- Condoms should be consistently used by all HIV-infected males despite following any other family planning method (dual protection).
- Male sterilization in father to be encouraged (no scalpel vasectomy: NSV) between 18 months to 2 years when baby's survival has been ensured.

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SECTION - II
Infectious diseases during pregnancy

Hepatitis – Infectious Disease during Pregnancy

Introduction

The most common cause of jaundice in pregnancy is acute viral hepatitis (AVH).The course of hepatitis and pregnancy is generally unaffected except in hepatitis E and herpes simplex and its fulminant hepatitis can cause mortality in pregnant women. Similarly there is a risk of vertical transmission especially in hepatitis B. There could be an adverse outcome on the mother and fetus. The mode of delivery and breastfeeding are generally unaffected in viral hepatitis. Antiviral therapy in pregnancy can be initiated if required. Vaccination during pregnancy is not contraindicated and to be given if any pregnant woman is exposed to hepatitis B. Similarly, early recognition helps in taking appropriate steps in improving the outcome of pregnancy.

Maternal and Fetal Complications

Hepatitis A

Every year there are around 1.4 million cases have been reported.[1] Generally it does not progress to chronic hepatitis. The course of the disease is similar to non-pregnant woman. There is a slight increase in the risk of preterm labor, preterm premature separation of placenta (PROM), and premature separation of placenta but the risk of perinatal transmission is rare.[2]

Hepatitis B

Hepatitis B viral (HBV) infection is a global health problem. It is estimated to be around 240 million of chronic infection added every year.[3] Almost 90% of infected infants become chronic carriers in contrast to 5% in adults. Hence universal screening for pregnant women is mandatory. Sexual transmission is the most common mode of transmission in countries with low prevalence of hepatitis B, whereas perinatal transmission is the most common mode of transmission in high prevalent countries. Acute infection is usually benign, and neither there is increased risk of death nor teratogenicity. But the newborn could be either premature or growth restricted. The chronic infection neither affects the course of pregnancy nor does pregnancy affect its course. The risk of vertical transmission is as high as 90% without prophylaxis if the mother is positive with hepatitis Be-antigen and its only 10% if it is negative.[4]

The poor obstetric outcome happens only when there is cirrhosis with portal hypertension but because of anovulation and associated issues the chances of fertility decreases. If pregnancy occurs, there is an increased risk of decompensation and variceal bleeding and there could be maternal death and stillbirth.[5] Regular monitoring through endoscopy and beta blockers has improved the pregnancy rate to a greater extent.

There is a risk of vertical transmission during pregnancy but the risk is maximum in the intrapartum period. Without immunoprophylaxis the transmission rate goes upto 90% which can be reduced to 5%–10% with immunoprophylaxis. In those patients who have high viral load there is an increased risk of transmission during invasive fetal testing and if invasive fetal testing is required, amniocentesis is preferred instead of chorionic villous sampling (CVS). Non-invasive prenatal testing (NIPT) is an alternative option.

Hepatitis C

The risk of vertical transmission is approximately 5% if the mother is infected with hepatitis C and it is slightly more if the mother carries high viral RNA or co-infected with HIV.[6]

Hepatitis D

It requires co-infection with hepatitis B but the progression to cirrhosis is rapid. Prevention of hepatitis B is the cornerstone in the prevention of hepatitis D virus infection.

Hepatitis E

Infection with hepatitis E is also self-limiting, but it can be fatal and the case fatality rate can go upto 15%–20% and it is more in last trimester of pregnancy.[7] Poor antenatal care and malnutrition are the attributes responsible for severity of the disease and high mortality in pregnant women with Hepatitis E infection. Recent studies have evaluated the pathogenesis of hepatitis E in pregnancy. In a study by Kumar et al. from New Delhi, it was found that all nutritional parameters (anthropometric and biochemical parameters) were significantly lower in pregnant women with hepatitis E virus (HEV) infection as compared with healthy pregnant controls. Pregnant patient with acute liver failure had significantly low mid-upper arm circumference and lower levels of serum globulin, pre-albumin, and folate as compared to pregnant patients with non-HEV infection and AVH.[8]

The association of cytokines in hepatitis E with pregnancy outcome was studied by Kumar etal.[9] HEV viral load in AVH and fulminant hepatic failure of pregnant women were comparatively higher than non-pregnant women. Significantly higher levels of tumor necrosis factor alpha (TNF-α),interleukin-6 (IL-6), interferon-c (IFN-c), transforming growth factor beta 1 (TGF-β1) were present in HEV-infected pregnant women compared to non-pregnant women and controls. TNF-α, IL-6,IFN-c, and TGF-β1 had significant positive correlation with viral load, serum bilirubin, and prothrombin time in pregnant women. Higher levels of all four cytokines were found in pregnant women with HEV infection having adverse pregnancy outcome.[9]

Herpes Simplex Virus (HSV I and II)

Hepatitis due to HSV is rare but it can cause acute hepatic failure similar to hepatitis E infection. Both primary as well as latent infection can cause hepatitis and acute hepatic failure. Majority of the fetal infection (85%) occurs during perinatal period and only 10% occur in the postpartum; and the risk of vertical transmission is maximum (40%–44%) if the woman acquires primary infection at delivery.[10] Infected patients might require cesarean section if the predicted risk of transmission is high.

The maternal and fetal complications and its preventive measures have been summarized in Tables [Tables 4 and 5], respectively.

Table 4: Maternal and Fetal Complications in Viral Hepatitis

Type of viral infection	Risk to the mother	Risk to the fetus
Hepatitis A	PROM	Preterm labor, meconium peritonitis, fetal ascites
Hepatitis B	Flaring up of chronic hepatitis B	Risk of vertical transmission
Hepatitis C	None	Risk of vertical transmission(co-infected with HIV/high viral RNA)
Hepatitis E	Acute liver failure, abruption, eclampsia	Abruption, preterm labor
Herpes simplex virus	Acute liver failure	Neonatal HSV, disseminated HSV

Table 5: Mode of Transmission and Preventive Measures

Type of viral infection	Viral type	Mode of transmission	Preventive measure
Hepatitis A	Single-stranded RNA virus	Fecal oral route	Vaccination if travel to endemic areas/contact with hepatitis A
Hepatitis B	Double-stranded DNA virus	Sexual, needle stick, blood, perinatal	Active/passive immunization antiviral therapy for pregnant woman in selected cases
Hepatitis C	Single-stranded RNA virus	Perinatal	None
Hepatitis D	Incomplete RNA virus	Requires HBsAg coat for both transmission and replication	
Hepatitis E	Single-stranded RNA virus	Fecal oral	None
Herpes simplex virus	DNA virus	Sexual	Acyclovir for primary infection and recurrent infection; cesarean section if the risk of transmission is high

Diagnosis

Hepatitis A

Routine testing for hepatitis A is not required in pregnancy. In suspected cases presence of IgM anti-hepatitis A virus (HAV) antibody is diagnostic of acute viral infection. Presence of IgG anti-hepatitis A antibody confers lifelong immunity.

Hepatitis B

The American College of Obstetricians and Gynecologists (ACOG), the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the US Preventive Services Task Force recommend universal screening of all pregnantwomen.[11–13] Pregnancy provides an ideal opportunity for screening as well as to reduce the burden of chronic infection. In those who are HBsAg positive hepatitis B viral load and HBeAg to be done. Liver function test (LFT) is also required in pregnancy. Persistence of hepatitis BsAg for <6 months is a diagnostic criteria for chronic infection and presence of HBeAg indicates infectivity and ongoing viral replication [Table 6].

Hepatitis E

In any woman with suspected AVH, anti-hepatitis E antibody (IgG and IgM) testing to be done and those who have positive antibodies HEV RNA to be done for confirmation. The presence of IgG antibody does not give lifelong immunity against HEV.

Herpes Simplex Virus

The polymerase chain reaction (PCR) testing of HSV DNA will be helpful in the diagnosis of HSV infection.

Management

Hepatitis A

Treatment is mainly supportive in AVH. Hospitalization is required in selective patients like those with intractable vomiting and coagulopathy. Maintenance of appropriate nutrition is mandatory with limitation of physical activity. The close contacts should receive immunoprophylaxis.[12] There is no contraindication for vaginal delivery and breastfeeding. There are no risks of vertical transmission. In case mother is infected during labor appropriate precautions to be taken and notification to be sent to neonatologist.

Table 6: Serological Test Interpretation for Hepatitis B Virus

Serological markers					Interpretation
HBsAg	HBV DNA	Total Anti-HBc	Anti-HBc IgM	Anti-HBs	
-	-	-	-	-	Never infected
+	-	-	-	-	Early acute infection or first 18 days after vaccination
+	+	+	+	-	Acute infection
-	-	+	+	-	Acute infection but resolving
+	+ / -	+	-		Chronic infection
-	-	+	-	+	Immune from past infection
-	-	-	-	+	Post-HBV vaccination
-	-	+	-	-	False positive; low-level chronic infection; or passive transfer to infant born to HBsAg-positive mother

Hepatitis C

Universal screening is not required for hepatitis C in pregnancy. Selective screening in high risk individuals like HIV positive, those who are on long-term dialysis, and those with liver disease, etc. is recommended. Serological testing for the detection of anti-hepatitis C antibody is done in suspected cases. Seroconversion may take 6–10 weeks after infection. In case anti-HCV Ab is negative and if clinical suspicion remains high, HCV RNA can be done soon after infection.

Hepatitis B

All pregnant women who are HBSAg positive, should be tested for HBeAg, anti-HBe, and HBV DNA level. Universal maternal screening along with active and passive immunization of newborn have reduced the rate of transmission to 5%–10% from 90%. A high viral load of >200,000 IU/ml, equivalent to 6 log copies/ml reduces the effectiveness of immunoprophylaxis.[13] Another factor which affects the immunogenicity is the

presence of HBeAg. Assessment of underlying LFT is mandatory in all women.

Various studies have shown that antiviral therapy is needed in these women to minimize the failure rate of immunnoprophylaxis.[14] If antiviral agent is required for this purpose, it should be started between 28 to 32 weeks of pregnancy and it can be stopped after delivery. There is a small risk of hepatic flare once antiviral treatment is stopped and the mother should be closely monitored for a period of 6 months. HBV DNA and LFT have to be done periodically.

A meta-analysis has shown that antiviral therapy with lamivudine, telbivudine, or tenofovir have not shown any teratogenicity. There are no safety concerns for its use in pregnancy.[15] All three drugs have reduced the risk of transmission. Telbivudine was associated with high rate of normalization of liver enzyme, e-antigen seroconversion, and HBV suppression. Even though lamivudine is time tested, tenofovir (300mg/day) is the drug of choice. The concentration in breast milk is <5% of that of serum and there is limited data to suggest that breastfeeding is not contraindicated for those who are on antivirals. Lamivudine is specifically included in those who have co-infection with HIV. Some studies have shown tenofovir reduces the bone mineral density in the newborn and has the propensity for renal injury in mothers. The evidence is insufficient regarding long-term safety for newborns.

Hepatitis C

Ribavirin is the drug of choice for chronic hepatitis C virus (HCV) infection. In pregnancy the transmission rates are low (<5%) and ribavirin is teratogenic, hence its use in pregnancy is contraindicated. Even pegylated interferon can be used in non-pregnant women with chronic viral hepatitis. There is some adverse effect on fetal growth and it is also not preferred in pregnancy. Only supportive therapy is required.

Hepatitis E

There is no specific treatment during pregnancy in women with HEV infection. Both ribavirin and pegylated interferon which can be used in non-pregnant women should be avoided in pregnancy.[16] Prevention of acquiring HEV infection is better than treatment.

Herpes Simplex Virus

Acyclovir or valaciclovir are the drugs of choice. They are category B drug and can be safely used in pregnancy. The risks of liver transplantation or death rates were low for those who were treated than non-treated (55% and 88%).[10]

Management of Newborn

Hepatitis A

There is no risk of vertical transmission as well as neonatal hepatitis. Breastfeeding is also not contraindicated.

Hepatitis B

All infants born to HBV positive mothers should receive HBIG and HBV vaccine after birth. HBIG to be given within 24 h of birth and HBV to be given not later than 7 days of birth. The schedule has to be completed within 6 months of birth. A meta-analysis have shown that the relative risk of neonatal HBV infection in those who received HBV vaccine was 0.28 [95% confidence interval (CI) 0.2–0.4] compared to those who received placebo or no intervention.15 The incidence was further reduced to 0.08% (95% CI 0.03–0.17) when HBIG was given in addition to vaccine.[17] This complete course of HBIG and HBV vaccine results in >90% of seroconversion rates in neonates. Breastfeeding is not contraindicated.

Hepatitis C

Mode of delivery does not influence vertical transmission. But invasive procedures like fetal blood sampling should be avoided. Breastfeeding is not contraindicated unless there is sore or cracked nipple.

Hepatitis E

The risk of perinatal transmission reported in the literature is as high as 67% but unlike HBV and HCV, HEV infection is self-limited. The progression to chronic hepatitis or fulminant hepatitis is very rare. Breastfeeding is not contraindicated.

Herpes Simplex Virus

Risk of vertical transmission is high when there is primary infection (40%–44%) at birth compared to re-infection (<5%). Majority of the times (85%) infection occurs during perinatal period compared to postnatal period. Appropriate treatment with strict clinical vigilance reduces the morbidity and neonatal infections. There is no specific immunoprophylaxis available. Weekly acyclovir is needed from 36 weeks onwards if the women have recurrent infection. Invasive fetal monitoring should be avoided. Cesarean section is needed if primary infection or lesions occur during birth.

Management of Exposed Cases

Hepatitis A

HAV immunization is not indicated in all pregnant women as universal immunization. HAV vaccine is safe and is recommended based on certain risk factors

like those who travel to endemic areas and those on illegal drugs, etc. Prevention includes both active and passive immunization. But vaccine is the preferred prophylaxis. In addition to HAV vaccination, all patients who need post exposure prophylaxis should receive immunoglobulin (0.02ml/kg) within 2 weeks of exposure.[12] The primary vaccine is given in two doses at 6–12 months apart.

Hepatitis B

Hepatitis B vaccine is safe in pregnancy and lactation.[17] Routine vaccination is not needed in pregnancy but is recommended in high-risk populations. To complete the immunization schedule three doses are needed at the interval of 0, 1, and 6 months. For post exposure prophylaxis, anti-HBSIgG to be given as an adjunct to vaccine. Pregnant women who are exposed to HBV should receive immunoglobulin within 72h and HBV vaccine within 7 days of exposure.

High Risk Individuals

- Persons with multiple sex partners
- Homosexual men
- Intravenous drug users
- Healthcare workers
- Those co-infected with other sexually transmitted diseases
- Members of drug treatment centers
- Those in direct contact with an HBV-positive household members

Hepatitis C

There is no specific vaccine or immuoprophylaxis available for HCV infection. The main mode of transmission is through infected blood and body fluids. Less frequently it can get transmitted through sexual and perinatal transmission. Breastfeeding is not contraindicated in hepatitis C infection.

Hepatitis E

There is no specific immunoprophylaxis for hepatitis E infection. Prevention includes avoid travelling to endemic areas, safe water (boiling, chlorination, and bottled water), and avoidance of eating undercooked food.

Pregnant Women and Partner

If one partner is infected with HBV it is mandatory that the other partner has to be tested. If they are not immune or not infected they should complete all the doses of vaccine. Sexual contact is the least form of transmission for HCV, but there is no specific immunoprophylaxis for HCV. Prevention of HIV viral infection is important in such cases.

Conclusion

AVH is the most common cause of jaundice. The course of most viral hepatitis is usually unaffected in pregnancy. Hepatitis E is most commonly associated with acute hepatic encephalopathy and increased mortality in pregnancy. Hepatitis B can cause both acute and chronic hepatitis and pregnancy provides an excellent opportunity to reduce vertical transmission and reduce the global burden. Immunoprophylaxis is available for HAV and HBV and for others results are promising. Antiviral drugs are effective in reducing viral load in some viral hepatitis and presence of HIV can increase the transmission rates. Thorough understanding and cooperation with gastroenterologists will help in improving the maternal and fetal outcome in viral hepatitis.

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SECTION - II
Infectious diseases during pregnancy

TORCH Infections During Pregnancy

Introduction

TORCH is a non-exhaustive acronym used to refer to the main pathogens that may cause congenital infection in the fetus and newborn. This includes: Toxoplasmosis, Others (parvovirus B19, Varicella zoster, syphilis, hepatitis B), Rubella, Cytomegalovirus, and Herpes.

The unique maternal–fetal connection serves to protect the fetus from infectious agents whereas in some instances it provides a conduit for their transmission to the fetus, leading to serious fetal consequences. Gestational age of the fetus at the time of infection influences the degree of severity. All the infections have their own causative agent and generally spread through poor hygienic conditions, contaminated blood, water, soil, and airborne respiratory droplet.[1]

Pathology – The T2 bias: Pregnancy is associated with an increase in CD4-positive T cells secreting Th2-type cytokines like interleukins 4, 5, 10, and 13. Th1-type cytokine production, for example, interferon gamma and interleukin 2 – appears to be somewhat suppressed, leading to a Th2 bias in pregnancy. This bias affects the ability to rapidly eliminate certain intracellular pathogens during pregnancy.[2]

Toxoplasmosis

The infectious agent Toxoplasma gondii, is an obligate intracellular protozoan, has a life cycle with two distinct stages. The feline stage takes place in cat and unsporulated oocytes are secreted in the feces. The non-feline stage takes place within all warm-blooded animals, including humans. Globally, it is estimated that one-third of the population has been exposed to this parasite. The source of infection is ingestion of uncooked/raw meat containing toxoplasma cysts, water or food contaminated by oocyst excreted in the feces of infected cats. After ingestion, cyst acquires the active form, invades the intestinal cells, and spreads into circulation.[2]

Maternal symptoms include fatigue, fever, headache, muscle pain, rarely maculopapular rash, and posterior cervical lymphadenopathy. Maternal infection causes four-fold increase in pre-term delivery rates before 37 weeks.

Fetal Outcome

Though the frequency of vertical transmission increases with gestational age, from 5%–6% in first and second trimester to 70% in the third trimester, damage to the fetus occurs highest in earlier stages of pregnancy. Infection during first trimester leads to some sequelae at birth in 80% with about 5% perinatal deaths, whereas in the third trimester, only ten babies are born with some sequelae and there are no perinatal deaths.

The Classic Triad

Chorioretinitis, intracranial calcifications, and hydrocephalus are often accompanied by convulsions. Low birth weight, hepatosplenomegaly, jaundice, and anemia may be one of the manifestations of intrauterine infection.

Screening and Diagnosis

Ultrasound features of congenital toxoplasmosis are ventriculomegaly and calcifications, cataracts, hepatosplenomagaly, liver calcifications, and ascites. Screening for toxoplasmosis in antenatal period

should be performed in all immune compromised pregnant women. Enzyme-linked immunosorbent assay (ELISA) detection of specific anti-toxoplasma IgM and IgG in the maternal serum is used for detecting maternal infection. IgM antibodies appear by 10 days after infection and usually become negative within 3–4 months. Anti-toxoplasma IgG antibodies develop within 2–3 weeks peaks by 1–2 months usually persists for life. Thus IgM antibodies should not be alone used to diagnose acute toxoplasmosis.

Any positive test results should be confirmed by toxoplasma IgG avidity test. The term avidity refers to the strength with which an antibody binds with an antigen. Increasing avidity reflects progressive maturation of the human immune response. During early stage of disease, IgG antibodies show low avidity for the antigen that progressively increases and shows high avidity in 16–18 weeks. The presence of high avidity antibodies indicates the infection is acquired 16 weeks earlier, thus allowing an optimal estimation of the probability of vertical transmission. A high avidity in first trimester is reassuring and is unlikely to harm the fetus.

However, an IgG avidity positive result in second/third trimester of pregnancy cannot exclude the possibility of transmission. Amniocentesis and isolation of toxoplasma in amniotic fluid by the polymerase chain reaction (PCR) is the gold standard for diagnosis of fetal infection. Invasive test are performed after 18 weeks gestation when sensitivity and specificity for diagnosis of infection are significantly higher than in earlier gestations.

Management

Prenatal treatment is based on two regimens – spiramycin, used in women with acute infection early in pregnancy and pyrimethamine–sulfonamide combination with folic acid after 18 weeks or if fetal infection is suspected. Spiramycin reduces the rate of vertical transmission by 60%, especially when administered in first trimester of pregnancy. Spiramycin is started at the dose of 1 g (3 million units) every 8 h. It should be continued even in the presence of negative PCR or ultrasound findings.

In patients whom fetal infections are confirmed with PCR on amniotic fluid, a combination of pyrimethamine (50 mg every 12 h for 48 h followed by 50 mg daily), sulfadiazine (75 mg/kg followed by 50 mg/kg every 12 h), and folinic acid (10–20 mg daily). Pyrimethamine crosses the placenta, therefore should not be used in first trimester due to teratogenicity. Multidrug therapy is mainly used for cure rather than preventing the infection.

There is no vaccine for toxoplasmosis, so avoidance of infection is necessary to prevent congenital infection. Measures include: cooking meat at safe temperatures, peeling or thoroughly washing fruits and vegetables, wearing gloves when changing cat's litter, avoiding feeding cats raw or undercooked meat, and keeping cats indoor. Women at risk for congenital toxoplasmosis are those who acquire infection during the course of pregnancy, so that they convert from seronegative to seropositive status. If this occurs in first trimester of pregnancy, pregnancy termination is indicated and justified.

Postnatal Management

The majority of newborns with congenital toxoplasmosis do not show any signs of clinical disease at birth. When present, clinical features include epilepsy, psychomotor or mental retardation, blindness, strabismus, petechiae due to thrombocytopenia, and anemia. About 50% suffer from visual impairment. Treatment with pyrimethamine should continue up to 1 year of age. Toxoplasmosis is not a cause of recurrent abortions or repeated pregnancy loss. Hence screening for toxoplasmosis is not indicated in women with recurrent pregnancy loss.

Varicella Zoster

Varicella is a double-stranded DNA alpha herpes virus, acquired predominately in childhood, highly contagious and readily transmissible infective agent. Chickenpox is the consequence of primary infection with varicella zoster virus. Incidence of adult varicella is decreased after introduction of vaccination, may be due to herd immunity, thereby decreasing maternal–fetal infections.

Maternal Symptoms

Incubation period is 10–12 days, and infective period is a day before the onset of rash until the lesions are crusted. Primary infection is flu-like prodromal followed by pruritic vesicular rash, which crusts between 3–7 days. The disease is severe during adulthood with a mortality of 5% and pneumonia in 5%–10%.

Fetal Outcome

Fetus can be infected only during primary maternal infection. Ultrasound features of congenital varicella syndrome are ventriculomegaly, microcephaly, intracranial calcifications, cerebral hypoplasia, porencephaly, and ocular abnormalities like microphthalmia and cataract, growth restriction, lung hypoplasia, and hydrops fetalis are other features. Congenital varicella syndrome is diagnosed with the presence of chorioretinitis, microphthalmia, cerebral cortical atrophy, intrauterine growth restriction, hydronephrosis, limb hypoplasia, and cicatricial skin lesions. If the fetus is exposed to active infection just or during delivery, it could lead to neonatal varicella syndrome, a serious newborn infection, with upto 30% mortality.

Diagnosis

The characteristic rash provides an accurate diagnosis. Varicella can be recovered from vesicles by culture. The prenatal diagnosis of fetal varicella can be established with a combination of ultrasound, cordocentesis (IgM is present only after 20-week gestation), or chorionic villous sampling using PCR.

Treatment

Women with varicella infection should receive oral acyclovir 15 mg/kg every 8 h within 24 h of onset of rash. Varizig immunoglobulin can be used within 96 h of exposure to decrease the symptoms. Maternal infection before 20 weeks poses a risk of congenital varicella syndrome and serial antenatal scans and amniocentesis may be done for PCR. Varicella immunoglobulin should be given to fetus if maternal infection occurs in third trimester and delivery takes place 5 days before and 2 days after onset of rash.[2]

Cytomegalovirus

Cytomegalovirus (CMV) is the most common perinatal infection. Some evidence of fetal infection is found in almost 0.2%–2.5% of all neonates. It is a double-stranded DNA virus, member of herpes virus family. The virus has the capacity to establish a state of latent infection like any other virus of herpes family in the host after primary infection has occurred. Any immunological or hormonal changes can cause reactivation thus leading to reinfection.

CMV has an icosahedral protein capsid which contains the double-stranded DNA, while the capsid is surrounded by a proteinaceous tegument and an outer lipid envelope. CMV infection has two stages: lytic and latent phase. The lytic phase is characterized by induced viral DNA replication, whereas latent phase is characterized by reduction in viral gene expression, inhibition of the assembly, and egress of new viral progeny. Latent phase can reactivate into a lytic infection when immunity is low, thereby causing the disease and allowing viral spread. This occurs despite the high serum levels of anti-CMV IgG antibody. These antibodies neither prevent the maternal reactivation or reinfection nor do they prevent fetal vertical transmission.

Maternal Infection

Women who are seronegative before pregnancy but who develop CMV infection during pregnancy, are at greatest risk to have an infected fetus. Maternal infection is usually asymptomatic and the mother is generally unaware of being infected with the virus. But 10% of infected mothers have mononucleosis like syndrome characterized by fever, pharyngitis, lymphadenopathy, and polyarthritis. Immunocompromised women might develop myocarditis, pneumonitis, hepatitis, retinitis, gastroenteritis, and in some cases meningoencephalitis.

Fetal Outcome

Primary maternal CMV infection is transmitted to the fetus in 40% of cases, whereas in reactivated non-primary infection transmission rates are only 0.15%–1%. Transmission in first trimester is 36% and increases up to 40%–60% in second and third trimester. Some seropositive women can be reinfected with a different viral strain that can cause fetal infection and symptomatic congenital disease.

Infection occurs due to transplacental passage, by transmission at delivery due to contact of cervical secretions or blood after birth and via breast milk after birth. The outcome of the newborn is directly correlated to the most severe forms occurring with those contracting primary infection in the first 2 months of pregnancy.

Of those infected, 90% of the fetuses are usually asymptomatic at birth while 10% may manifest the symptoms of the disease. Of the latter, 30% experience neonatal demise. Among them 70% survived, 50% have major sequelae, and 10% are normal. Among the asymptomatic newborns, 10% may experience sensorineural hearing loss.[3]

CMV has particular tropism for neuronal cells of periventricular zone of the brain. In normal embryological development, these neuronal cells migrate from this zone toward the cortical plate between 12 to 24th weeks of gestation for the formation of brain fissure. The pathogenesis of brain damage is due to direct cytopathic effect of virus on neurons. Alternatively destruction of placenta might reduce the delivery of oxygen to the fetus thereby damaging the brain tissue.

Congenital infection syndrome includes growth restriction, microcephaly, intracranial calcifications, chorioretinitis, mental and motor retardation, sensorineural deafness, hepatosplenomagaly, jaundice, hemolytic anemia, and thrombocytopenic purpura. Neurological abnormalities include mental retardation, cerebral palsy, autism, epilepsy, blindness, and learning disabilities. CMV is also the main case of sensorineural hearing loss during childhood accounting for 10%–15% of all infected babies.

Prenatal Diagnosis

Routine prenatal CMV serological testing is not recommended during pregnancy. Testing is done only when mother has flu-like syndrome in early pregnancy or abnormal sonography findings are present.

Ultrasound feature of congenital CMV: CNS-ventriculomegaly (commonest), intraventricular hemorrhage, intraventricular adhesions, subependymal cysts, periventricular leukomalacia, microcephaly, lissencephaly, porencephaly, cerebellar agenesis, hypogenesis, hypoplasia, microphthalmia, hepatomegaly, splenomegaly, echogenic bowel, ascites, liver calcifications, cardiomegaly, pericardial effusions and calcifications, and non-immune hydrops. Intrauterine growth restriction and placental enlargement is also seen. As CMV infection is a progressive disease, serial ultrasound must be done. In later gestation magnetic resonance imaging (MRI) could be a better investigation.

The risk of transmission and bad neonatal infection is more with primary and early trimester infection. Since the detection of IgM does not necessarily imply the primary infection, other investigations like CMV avidity test must be carried out for timing the infection. CMV avidity test is currently the most reliable laboratory tool to identify primary infection. Women with positive anti-CMV IgM antibodies and low avidity are the ones who are at increased risk of transmitting the infection to fetus. If serology testing is positive, amniotic fluid PCR is offered. Invasive procedure should be done after 6 weeks of maternal infection or delayed until 20 weeks. This is because viral shedding by fetal kidneys is reduced in the first 20 weeks of pregnancy due to fetal diuresis. Increased IgG antibody titer without IgM antibody raised titer and high avidity usually denotes a non-primary infection. Abnormal sonography findings along with positive findings on amniotic fluid PCR have a positive predictive value of 75% risk of congenital infection. Fetal infection is unlikely if CMV is not detected in fetal sample obtained 6 weeks later than maternal infection or at 20 weeks of gestation. In some cases quantitative PCR is useful. A low viral load has favorable outcome.

Management

There is no proven prenatal treatment for congenital CMV infection. The use of hyperimmune globulin or the antiviral drugs given to mother has been proposed to reduce the course of infection and rate of vertical transmission. Antenatal valacyclovir is useful in reducing viral load. There is no vaccine available. Therefore targeted efforts toward good hygiene must be promoted.

Postnatal Management

Postnatal diagnosis depends on isolation of the virus in urine and saliva of the baby in first 2 weeks of life. Congenital CMV infection is a multi-organ disease and multidisciplinary teams are required in the follow-up care of such newborns. Ganiclovir administered for 6 weeks to neonates with symptomatic central nervous system disease prevents hearing deterioration.

Rubella

The rubella virus is a single-stranded RNA virus belonging to the Togavirus family. It spreads by inhalation of droplets from respiratory secretions or from direct contact.

Maternal Infection

Rubella enters the respiratory tract and disseminates to regional lymph nodes, where it replicates. Viremia occurs 7–9 days after exposure, when the placenta can become infected. Rubella causes a distinctive maculopapular rash. The rash is preceded by malaise, fever, headache, conjunctivitis, and post auricular and posterior cervical lymphadenopathy. The rash typically appears on the face and trunk and moves peripherally to the extremities within 1–2 days.

Fetal Outcome

The effects of rubella infection on the fetus vary with maternal age and parity as well as the gestational age at the time of infection. The risk of fetal seropositivity translating to a fetal defect in the first trimester is high; however, in the second and third trimesters although fetal seropositivity increases, the risk of fetal defects decreases. When maternal infection/exposure occurs in the first trimester, fetal infection rates are near 80%, dropping to 25% in the late second trimester and increasing again in the third trimester from 35% at 27–30 weeks gestation to nearly 100% beyond 36 weeks gestation. Therefore, the risk of congenital defects after maternal infection is essentially limited to the first 16 weeks of gestation.

Rubella infection during pregnancy poses significant risk to the fetus and neonate leading to the congenital rubella syndrome (CRS).

A wide range of abnormalities occurs with CRS, including (in increasing order of frequency) neurosensory deafness, mental retardation, cardiac anomalies (e.g., patent ductus arteriosus, pulmonary artery stenosis), ocular abnormalities (e.g., cataracts, retinopathy, microphthalmia, chorioretinitis), and intrauterine growth restriction. Hepatosplenomegaly and thrombocytopenic purpura also occur. Of adult survivors of CRS, 40% have insulin-dependent diabetes mellitus.

Diagnosis

The diagnosis of acute rubella is difficult, and a clinical diagnosis based on the rash is not reliable. Recent infection must be documented serologically. Acute infection can be documented by IgM specific to rubella or by a four-fold rise in IgG to rubella. The rubella IgM level rises early in the illness, peaks 7–10 days after the onset of symptoms, and persists for up to 4 weeks after

the rash. Congenital rubella infection has been documented by placental biopsy and by isolation of the virus from amniotic fluid. Rubella-specific IgM can be detected in fetal blood obtained by cordocentesis after 20 weeks gestation.[4]

Diagnosis of fetal infection is by chorionic villus sampling in early pregnancy and later by amniocentesis of amniotic fluid for rubella-specific PCR. Ultrasound diagnosis of CRS is extremely difficult other than the diagnosis of fetal growth restriction.

Management of Rubella Infection during Pregnancy

The management of the exposed pregnant woman depends on the gestation when exposure occurred and the type of immunity. In a pregnant woman who is exposed to rubella or who develops signs or symptoms of rubella, serological testing should be performed to determine immune status and risk of congenital rubella syndrome. Fetal risk for congenital infection after maternal reinfection during the first trimester is about 8% and appropriate counseling should be provided. Treatment of acute rubella infection is supportive. The prognosis is generally excellent for pregnant women with rubella infection. The best therapy for CRS is prevention. All girls should be vaccinated against rubella before entering the childbearing years. Rubella immunization should not be administered in pregnancy but may be safely given postpartum.

Genital Herpes

Herpes simplex virus (HSV) are DNA virus and belongs to alpha herpesviridae family. There are two antigenic types – HSV1 and HSV2. HSV 1 spreads by non-sexual contact causing oral herpes. HSV 2 is sexually transmitted causes genital herpes.

Maternal Infection

Genital HSV is characterized by the presence of ulcers in external genitalia, cervix, and perineum with pain, dysuria, vaginal discharge, and regional lymphadenopathy. Non-specific symptoms like fever, myalgia, and headache are usually present. Asymptomatic patients are infectious and reservoir for infection. The virus infects the epithelial mucosal cells and migrates along the nerves to reach the local ganglia. Here it persists throughout the life in a latent phase and can reactivate causing recurrent infection. Asymptomatic shedding occurs mainly after 1–3 weeks of acquiring the primary infection. The rate of asymptomatic shedding during pregnancy is between 0.2% to 7.4% and that during delivery ranges from 0.1% to 1.4%.

Fetal Outcome

HSV infection of the fetus can be acquired in utero, during labor or postpartum. Antepartum infection is uncommon accounting for 5%, mainly seen with disseminated disease before 20 weeks of gestation and usually leads to miscarriage, stillbirth, and congenital malformations involving the CNS, skin, and eyes. Preterm birth is seen after 20 weeks of gestation. Intrapartum infection during delivery is the most common route of transmission. During the second stage of labor, the virus from the maternal secretions enters the baby's eyes, upper respiratory tract, and the umbilical cord or through the scalp when internal fetal monitoring devices are used. With vaginal delivery, the risk of acquiring the infection is 60% with primary and 5% recurrent infection. The risk is markedly reduced with cesarean section.

Neonate herpes may present either with disseminated disease, CNS infection, or as a local infection involving the eyes, skin, or oral cavity. Infected babies present on day 10 of life with lethargy, irritability, and apnea followed by seizures, coagulopathy, liver involvement, cardiovascular complication, and sudden death. The organ primarily involved in disseminated disease is liver and the adrenal glands. Encephalitis may present with generalized intractable seizures and there could be neurological sequelae in the later childhood. Almost 50% of newborns have only localized disease in the skin, mouth, and eyes. Pneumonia is also a prominent complication, presenting from day 3 to 14 of life. Transplacental acquired antibodies are protective only against disseminated infection and not against localized disease.

Diagnosis

Viral isolation and culture, PCR and cytology are the definitive means of diagnosis in HSV infection. Cytology by scrapings from base of lesion from the cervix and vagina stained with Papanicolaou is simple and rapid means to identify the virus in 60%–80% of infection. The typical morphology shows intranuclear inclusions and multinucleated giant cells. Isolation by viral cultures results may not give positive results during the end of active infection. PCR assays will be positive only during viral shedding.[5]

After virus isolation, serology plays a main role in assessing the pregnant women with or at risk of genital infection and also differentiates between HSV 1 and 2 infections. Serology is more useful because antibodies develop weeks after primary infection and therefore a genital lesion with positive culture in the absence of antibody says primary infection whereas a similar lesion with positive antibody indicates reactivation.

Ultrasonography may show features of ventriculomegaly, hydrocephaly and microcephaly, non-immune fetal hydrops, liver calcifications, and growth restriction.

Management

Asymptomatic women along with their partners should be identified with serological testing by the end of second trimester. Nearly 22% of women might be negative for antibodies while their partners are positive, indicating that these women have 14% risk of developing primary genital infection and transmitting the virus to the fetus. Any women with HSV genital infection is considered at high risk and viral suppressive therapy in last 4 weeks of gestation is necessary.

Viral suppressive therapy is indicated after 36 weeks of gestation. Acyclovir, valacyclovir, and Famciclovir have similar efficacy and used for this purpose of reducing intrapartum neonatal transmission. Women presenting in labor with herpetic genital lesions or prodromal symptoms should be delivered by cesarean section. Cesarean is justified even after 4 h of ruptured membranes. Women treated with viral suppressive therapy or no active lesion can be allowed to deliver vaginally.[6]

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SECTION - II
Infectious diseases during pregnancy

Syphilis in Pregnancy

Introduction

Syphilis is a bacterial sexually transmitted infection caused by Treponema pallidum that results in substantial morbidity and mortality. If the disease remains untreated, it may last for many years; it is divided into early and late syphilis. Early syphilis consists of primary syphilis, secondary syphilis, and early latent syphilis, whereas late syphilis consists of late latent syphilis and tertiary syphilis. Mother-to-child transmission of syphilis (congenital syphilis) is usually devastating to the fetus in cases where maternal infection is not detected and treated sufficiently early in pregnancy. In 2012, an estimated 3,50,000 ad-verse pregnancy outcomes worldwide were attributed to syphilis including 1,43,000 early fetal deaths/stillbirths, 62,000 neonatal deaths, 44,000 preterm/low birth weight babies, and 1,02,000 infected infants.[1] Congenital syphilis can be prevented through implementa-tion of effective early screening and treatment strategies for syphilis in pregnant women.[2] CDC recommends that all persons who have syphilis should also be tested for human immunodeficiency virus (HIV) infection.[3] Genital sores caused by syphilis can bleed eas-ily and make it easier to transmit HIV infection with a two- to five-fold increased risk of acquiring HIV infection.[4] Clinical manifestations of acquired syphilis are not apparently altered by pregnancy. Syphilis is passed from person to person through direct contact with a syphilitic sore, called chancre. Transmission of the organism occurs during vaginal, anal, or oral sex. Sores of primary syphilis occur about 3 weeks after contact, mainly on the external genitals, vagina, cervix, anal canal or in the rectum. They are often unrec-ognized in women because they can be asymptomatic. Syphilitic sore is firm, round, small, and painless and lasts for 3–6 weeks.[5] Syphilitic sore is followed by widespread cutaneous, mucosal, and systemic dissemination of the spirochetes. This phase can last up to a year and is particularly contagious at this stage. Even without treatment both primary and secondary lesions resolve and the infection enters a latent stage. Despite the lack of clinical manifestations, the infection can still be transmitted to the fetus. Tertiary syphilis may occur in one-third of untreated people, approximately 3–15 years after the initial in-fection. It is characterized by infiltrative tumors of skin, bones, liver (gumma) (15%), central nervous system disorders (neurosyphilis) (6.5%), and cardiovascular problems (10%).[6]

Maternal and Fetal Complications

Maternal Complication

Syphilis during pregnancy can cause number of complications like abortion, hydraminos, preterm labor, and so on.[7]

Fetal Complications

T. pallidum can cross the placenta and can cause congenital fetal infection at any time during pregnancy. The degree of fetal involvement is more severe if the infection is ac-quired during the early stage of pregnancy. T. pallidum is responsible for a multi-organ disease in the fetus and the clinical scenario is highly dependent upon the gestational age at infection, degree of fetal involvement, and time of maternal treatment. The various fe-tal complications are:

- Hydrops
- Prematurity
- Fetal growth retardation
- Fetal distress
- Intrauterine death
- Early neonatal death

Survival with clinical manifestations of congenital syphilis which can be divided into early and late signs.

Early signs usually appear within 2 years of life and include respiratory symptoms, general lymphadenopathy, jaundice, hepatitis, ane-mia, thrombocytopenia, osteochondritis, periostitis, meningitis, and so on. Late signs include facial, bone deformities, teeth abnormalities, keratitis, and deafness.[7]

Diagnosis and Management

Clinical Diagnosis

Clinical findings depend upon the stage of the disease. Primary syphilis is characterized by firm, round, small, and painless ulcer mainly on vulva, cervix, and anal region with regional non-tender lymphadenopathy. The edge and base of the ulcer have a cartilagi-nous (button like) consistency on palpation. Secondary syphilis is characterized by local-ized or diffuse mucocutaneous rash with frequent involvement of the palms and soles with generalized non-tender lymphadenopathy. There can be large elevated plaques, that is, condylomata lata over anogenital region. Tertiary syphilis is characterized by impaired balance, paresthesia, sensorineural hearing and vision loss, dementia, incontinence, aortic aneurysms, bone pain, jaundice, and so on. Indurated, nodular, papulosquamous, or ul-cerative lesions can be seen over skin, known as cutaneous gummas.[8]

Serological Diagnosis

There are two types of serological tests for syphilis: non-treponemal and treponemal. Non-treponemal tests include the venereal disease research laboratory (VDRL) and rapid plas-ma reagin (RPR) tests. These are used for rapid screening; however, these are not highly specific and can give false positive results in acute febrile viral infections and some chronic autoimmune disorders. Non-treponemal tests may be false negative due to a prozone re-action (i.e., interference by high concentrations of antibodies in a specimen which can be uncovered by dilution and retesting).[9]

Non-treponemal tests may be qualitative or quantitative. Quantitative non-treponemal test titers can be used to monitor response to treatment. Titers are expected to decrease follow-ing effective treatment and increase in untreated active infection. A four-fold increase in titers is considered significant. Treponemal tests include the treponemal pallidum hemagglutination assay (TPHA), treponemal pallidum particle agglutination assay (TPPA), and the fluorescent treponemal antibody absorption (FTA-ABS) tests. These tests are highly specific and used as confirmatory test following a positive non-treponemal test. Trepo-nemal tests usually remain positive in 85% of the patients for the rest of their life, regard-less of treatment. Thus, a positive treponemal test does not distinguish between active in-fection and infection that has been previously treated.[9]

Sonographic Diagnosis

Prenatal ultrasound is used to diagnose congenital syphilis and features of congenital syphilis are:

- FGR
- Hydrops, ascites, pleural and pericardial effusion, general skin edema
- Placental thickening
- Hyperechogenic bowel, hepatic calcifications
- Hepatosplenomegaly
- Shortening of the long bone
- Bone deformity (bowing, curvature, and thickening)[7]

The WHO STI guideline recommends screening all pregnant women for syphilis during the first antenatal care visit.[9] The interpretation of serological tests must be made together with a good sexual history of the individual, a physical examination, confirma-tion about the stage of the disease, and about any other underlying diseases or infections.

Pregnant women with reactive treponemal screening tests should have additional quantitative non-treponemal testing because titers are essential for monitoring treatment response. For women with a history of adequate treatment of syphilis who do not have ongoing risk no further treatment is necessary. Women without a history of treatment should be staged and treated accordingly with a recommended penicillin regimen. When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis as sonographic signs of fetal or pla-cental syphilis indicate a greater risk for fetal treatment failure. Serologic titers should be repeated at 28–32 weeks gestation and at delivery, whereas serologic titers can be checked monthly in women at high risk of recurrence. Providers should ensure that the clinical and antibody responses are appropriate for the patient's stage of disease, although most women will deliver before their serologic response to treatment can be assessed de-finitively. Maternal treatment would be inadequate if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal antibody titer at delivery is four-fold higher than the pretreatment titer. Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch–Herxheimer reaction which is characterized by fever, headache, myalgia, and malaise, and it is caused by the release of treponemal endotoxin-like compounds during penicillin-mediated lysis. These women should be advised to seek obstetric attention after treatment, if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment, but concern for this compli-cation should not delay necessary treatment.[10]

Treatment of Newborn

The diagnosis of congenital syphilis can be difficult, as maternal non-treponemal and treponemal IgG

antibodies can be transferred through the placenta to the fetus, complicat-ing the interpretation of reactive serologic tests for syphilis in neonates. Therefore, treat-ment decisions frequently must be made on the basis of 1) identification of syphilis in the mother; 2) adequacy of maternal treatment; 3) presence of clinical, laboratory, or radio-graphic evidence of syphilis in the neonate; and 4) comparison of maternal (at delivery) and neonatal non-treponemal serologic titers using the same test, preferably conducted by the same laboratory. Any neonate at risk for congenital syphilis should receive a full eval-uation and testing for HIV infection.[10]

All neonates born to mothers who have reactive non-treponemal, treponemal test results should be evaluated with a quantitative non-treponemal serologic test (RPR or VDRL) performed on the neonate's serum, a four-fold higher titer than the mother's titer is con-sidered significant. Conducting a treponemal test on neonatal serum is not recommended because it is difficult to interpret. All neonates born to women who have reactive serologic tests for syphilis should be examined thoroughly for the evidence of congenital syphilis (e.g., non-immune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseu-doparalysis of an extremity). Pathologic examination of the placenta or umbilical cord us-ing specific staining (e.g., silver) or a T. pallidum polymerase chain reaction (PCR) test using a CLIA-validated test should be considered. Dark-field microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash and nasal discharge) al-so should be performed. In addition to these tests, cerebrospinal fluid (CSF) analysis for VDRL, cell count and protein, complete blood count, long-bone radiographs may be re-quired.[10]

Recommended Regimens for Treatment of Newborn

Aqueous crystalline penicillin G 1 lac–1.5 lac units/kg/day I/V for 10–15 days or procaine penicillin 50,000 units/kg/day I/M for 10–15 days.[9]

In infants who are clinically normal and serum quantitative non-treponemal serologic titer is less than or equal to four-fold the maternal titer but whose mothers had untreated syphi-lis, inadequately treated syphilis (including treatment within 30 days of delivery), or syph-ilis that was treated with non-penicillin regimens, the WHO STI guideline suggests aque-ous crystalline penicillin G or procaine penicillin.[9] Any neonate who has a normal physical examination and a serum quantitative non-treponemal serologic titer is less than or equal to four-fold the maternal titer and mother was treated during pregnancy, treatment was appropriate for the stage of infection, treatment was administered >4 weeks before de-livery, and the mother has no evidence of reinjection or relapse, treatment involves close monitoring of the infants with serologic follow-up every 2–3 months for 6 months. If fol-low up is not possible, then benzathine penicillin G 50,000 units/kg/dose I/M in a single dose is given.[10]

Treatment of Exposed Cases (Pregnant Women and Partners)

In Pregnant Women with Early Syphilis

The WHO STI guideline suggests using benzathine penicillin G 2.4 million units once I/M over procaine penicillin 1.2 million units I/M once daily for 10 days.[9] Penicillin G is the only known effective antimicrobial for preventing maternal transmission to the fetus and treating fetal infection.

The Jarisch–Herxheimer reaction can occur in some patients 2–12 h after receiving therapy for active syphilis. It is characterized by fever, headache, myalgia, and malaise, and it is caused by the release of treponemal endotoxin-like compounds during penicillin-mediated lysis. The Jarisch–Herxheimer reaction can increase the risk of premature labor and/or fetal distress during the second half of pregnancy.[10]

Some evidence suggests that additional therapy is beneficial for pregnant women. For women who have primary, secondary, or early latent syphilis a second dose of benzathine penicillin 2.4 million units I/M can be administered 1 week after the initial dose.[11]

The prevalence of reported penicillin allergy in developing countries is unknown; however, limited data suggest that penicillin is one of the most frequently reported allergies in some developing countries. Of persons reporting penicillin allergy, 10%–15% have a positive skin test suggestive of a penicillin allergy; these persons are at risk for an immunoglobulin E (IgE)-mediated allergic response to penicillin such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension). Re-administration of penicillin to patients with a history of IgE-mediated hypersensitivity re-actions can cause severe immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic persons, unless they undergo induction of drug tolerance (also referred to as "de-sensitization") to temporarily eliminate IgE-mediated hypersensitivity. Penicillin skin test-ing with the major and minor determinants of penicillin can reliably identify persons at high risk for IgE-mediated reactions to penicillin. Although the testing reagents are easily generated, only the major determinant [benzylpenicilloyl poly-L-lysine (Pre-Pen)] and penicillin G have been available commercially. Persons who have a positive skin test to one of the penicillin determinants can be desensitized. This is a straightforward, relatively safe procedure that can be performed orally or intravenously. Modified protocols might be considered based on an individual's symptoms, drug of choice, and route of administra-tion. Although the two approaches have not been compared, oral desensitization is regard-ed as safer and easier to perform. Desensitization should occur in a hospital setting because serious IgE-mediated allergic reactions can occur; the procedure

can usually be completed in approximately 4–12 h, after which time the first dose of penicillin is administered. After desensitization, penicillin should be maintained continuously for the duration of the course of therapy. Once the course is completed, if penicillin is required in the future, the desensitization procedure should be repeated. Persons with a history of severe non-IgE-mediated reactions (e.g., Stevens–Johnson syndrome, toxic epidermal necrolysis, intersti-tial nephritis, and hemolytic anemia) are not candidates for skin testing or challenge and should avoid penicillin indefinitely.[10]

In Case of Penicillin Allergy where Penicillin Desensitization is Not Possible

Erythromycin 500 mg orally 4 times daily for 14 days or azithromycin 2 g once orally or ceftriaxone 1 g I/M once daily for 10–14 days. Erythromycin and azithromycin do not cross the placental barrier completely and as a result the fetus is not treated. It is therefore necessary to treat the newborn infant soon after delivery.[9]

In Pregnant Women with Late Syphilis or Unknown Stage of Syphilis

WHO STI guideline suggests using benzathine penicillin G 2.4 million units I/M once weekly for 3 consecutive weeks over procaine penicillin 1.2 million units I/M once daily for 20 days. Missed doses are not acceptable for pregnant women receiving therapy for late latent syphilis. Pregnant women who miss any dose of therapy must repeat the full course of therapy.[9]

When benzathine penicillin or procaine penicillin cannot be used (in case of penicillin allergy where penicillin desensitization is not possible) erythromycin 500 mg orally 4 times daily for 30 days can be used.

Serologic follow-up is important to identify therapeutic success and detect reinjection. Most commonly, the FTA-ABS test will remain positive for the lifetime of the patient, while reaction to the VDRL test progressively declines and becomes negative. Serologic evidence of adequately treated syphilis in patients with early syphilis is demonstrated by at least a four-fold decrease in VDRL or RPR titers. If the disease has entered the latent phase before treatment, a large percent-age of patients may never attain a completely negative VDRL result. In these cases the evidence of adequate treatment will be a stable or declining RPR or VDRL titers of less than or equal to 1:4.[7]

Management of Sex Partners

Persons who have had sexual contact with a person who receives a diagnosis of primary, second-ary, or early latent syphilis within 90 days preceding the diagnosis should be treated presump-tively for early syphilis even if serologic tests are negative.[10]

Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis <90 days preceding the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and opportunity to follow-up is uncertain. If serologic test results are negative, no treatment is needed. If serologic test results are positive, treatment should be based on clinical and se-rologic evaluation and stage of syphilis.[7]

In some areas or populations with high rates of syphilis, health departments rec-ommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high non-treponemal serologic test titers (i.e., >1:32), because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.[10]

Long-term sex partners of persons who have late latent syphilis should be evalu-ated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.[10]

The following sex partners of persons with syphilis are considered at risk for in-fection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 1) 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, 2) 6 months plus duration of symptoms for those with secondary syphilis, and 3) 1 year for persons with early latent syphilis.[10]

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Malaria in Pregnancy

Introduction

Malaria during pregnancy is a major public health concern and an important contributor to maternal and infant morbidity and mortality in malaria-endemic countries.[1] Pregnant women are particularly susceptible to malaria, and in low-transmission settings they have a greater risk of severe Plasmodium falciparummalaria. Over the past 10 years, knowledge of the burden, economic costs, and consequences of malaria in pregnancy has improved, and the prevalence of malaria caused by P. falciparumhas declined substantially in some geographical areas. Furthermore, studies have also shown an increase in Plasmodium vivaxin pregnancy. Health system and household costs still limit access to prevention and treatment services. This article reviews the epidemiology, pathology, clinical symptoms, diagnosis, and treatment of malaria in pregnant women.

Epidemiology and Burden of Malaria during Pregnancy

Malaria is a parasitic infection transmitted by the female anopheline mosquito and caused by the four species of Plasmodium that infect humans: vivax, ovale, malariae, and falciparum. Of these,Plasmodium falciparumis the most deadly species. Pregnant women are three times more susceptible to suffer from severe disease as a result of malarial infection compared with their non-pregnant counterparts, and have a mortality rate from severe disease that approaches 50%.[2,3] In areas endemic for malaria, it is estimated that at least 25% of pregnant women are infected with malaria, with the highest risk for infection and morbidity in primigravida, adolescents, and those co-infected with the human immunodeficiency virus(HIV).[4] The second trimester appears to bring the highest rate of infection, supporting the need for antepartum care as part of malarial prevention and treatment efforts.

Effect of Malaria on Pregnancy

The majority of sequelae in pregnancy results from two main factors: the immunocompromised state of pregnancy and additional placental sequestration of infected erythrocytes. Splenic and placental sequestration of malaria-infected erythrocytes leads to folic acid deficiency and disproportionate severe anemia. It is also hypothesized that infected erythrocytes collected in the placenta stimulate pancreatic β-cell production of insulin, leading to hyperinsulinemia and hypoglycemia. Other maternal effects of malarial infection result from the "stickiness" of the infected erythrocytes that become trapped in small vessels, resulting in cerebral malaria, renal failure, and thrombocytopenia. All these contribute to the severity of disease during pregnancy. Case reports

confusing malaria infection with HELLP syndrome demonstrate the overlap in clinical and laboratory findings between the two diseases and the importance of proper diagnosis.[5]

The symptoms and complications of malaria in pregnancy vary according to malaria transmission intensity in the given geographical area, and the individual's level of acquired immunity.[6]

High-transmission Settings

In high-transmission settings, where levels of acquired immunity tends to be high, P.falciparum infection is usually asymptomatic, yet parasites may be present in the placenta and contribute to maternal anemia even in the absence of documented peripheral parasitemia. The greatest degree of placental infestation is seen in women who have the highest level of immunity, leading to milder maternal symptoms, may not receive the treatment and results in disproportionate increase in fetal complications.[2] Fetal complications result from this placental inflammation as well as maternal anemia, and manifest as stillbirth, intrauterine growth restriction, and low-birth-weight neonate, and thus in turn, are at higher risk for neonatal and newborn death. Congenital malaria is a relatively rare complication in areas with endemic malaria; however, newborn parasitemia may present 2–3 months after delivery when maternal antibodies wear off. In high-transmission settings, the adverse effects of P. Falciparum infection in pregnancy are most pronounced for women in their first pregnancy.

Low-transmission settings

In low-transmission settings, where women of reproductive age have relatively little acquired immunity to malaria is associated with maternal anemia, an increased risk of severe malaria, and it may lead to spontaneous abortion, stillbirth, prematurity, and low birth weight. In such settings, all pregnant women, regardless of the number of times they have been pregnant, are highly vulnerable to malaria.

Clinical Manifestations

Uncomplicated malaria: A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or rapid diagnostic test (RDT)) but with no features of severe malaria is defined as having uncomplicated malaria. A case of uncomplicated malaria usually presents with fever, rigors, headache, bodyache, fatigue, anorexia, and nausea as in non-pregnant state.

Severe malaria (complicated malaria): The World Health Organization (WHO) defines severe P. falciparum malaria as a patient with P. falciparum asexual parasitemia with evidence of organ dysfunction (cerebral malaria with generalized convulsions, pulmonary edema, severe anemia, renal failure, hypoglycemia, metabolic acidosis, circulatory collapse/shock, spontaneous bleeding, and laboratory evidence of DIC, macroscopic hemoglobinuria, hyperthermia, hyperparasitemia) [Figure 1]. The WHO definition of severe malaria applies for all patients, including pregnant women. A case of uncomplicated malaria can rapidly progress to severe malaria due to either delayed treatment or treatment failure.[3]

Diagnosis of Malaria

The diagnostic methods remains the same as standard methods as in non-pregnant adults. Microscopy of stained thick and thin blood smears remains the gold standard for confirmation of diagnosis of malaria as well to quantify the parasite load and to distinguish different species of malaria parasites and their different stages. RDTs are based on the detection of circulating parasite antigens. Several types of RDTs are available. Some of them can only detect P. falciparum, while others can detect other parasite species also. Currently available RDTs have been poor at detecting malaria in pregnant women and placental infections. In placental specimens, histopathology can also be used to identify parasites and resultant inflammatory responses.

Management of Malaria

Prevention

Malaria remains one of the most preventable causes of adverse birth outcomes. Current prevention of malarial disease in pregnancy relies on two main strategies: providing pregnant women with insecticide-treated bed nets (ITN) and intermittent presumptive treatment (IPT) with antimalarial medications. The WHO advises administration of at least three doses of sulfadoxine-pyrimethamine (SP) for IPTp, ideally at each of three antenatal care visits in the second and third trimesters (these antenatal visits should occur at 24–26 weeks, 32 weeks, and 36–38 weeks of gestation). Although its benefit may be limited given the emergence of drug resistance; dihydroartemisinin-piperaquine is a promising alternative agent. In a Cochrane Review comparing malarial chemoprophylaxis with no prophylaxis during pregnancy, Garner and Gülmezoglu found a significant reduction in maternal anemia, parasitemia, perinatal death, and a higher mean birth weight in the groups given IPT.[7] More recent studies in Nigeria that examined specific IPT regimens found significant reductions in maternal anemia with the use of sulfadoxine-pyrimethamine as compared with chloroquine, pyrimethamine, or no prophylaxis.[8,9] Sulfadoxine-pyrimethamine has been found safe in pregnancy when used intermittently as part of IPT.[10]

Women Infected with HIV

HIV-infected pregnant women who are not taking cotrimoxazole prophylaxis for opportunistic infections require more intensive IPTp dosing that is monthly administration of SP-IPTp to reduce the risk of

placental malaria. Pregnant women taking cotrimoxazole do not warrant IPTp during pregnancy, since cotrimoxazole provides protection against HIV-related opportunistic infections as well as malaria.

Travelers

Pregnant woman should be advised to defer travel to areas where risk of acquiring malaria is high until after delivery if feasible, else she should take chemoprophylaxis. The agents of choice are chloroquine (for travel to areas with chloroquine-sensitive malaria) and mefloquine (for travel to areas with chloroquine-resistant malaria).

Vaccine

Erythrocytes infected with P falciparum that express the surface protein VAR2CSA accumulate in the placenta, and VAR2CSA is an important target of protective immunity. Clinical trials for a VAR2CSA vaccine are ongoing, but sequence variation needs to be carefully studied.

Treatment of Malaria during Pregnancy

Treatment of malaria in pregnancy is a balance between potential fetal adverse effects from drug toxicity and improved clinical status with clearance of the parasite. In 2006, the WHO recommended a combination of quinine and clindamycin for the treatment of uncomplicated malaria in pregnancy; however, there is a risk of hypoglycemia with quinine use, as well as increasingly drug-resistant P falciparum. More data currently support the use of artemisinin-based combination therapy (ACT), which appears safe and effective in pregnancy. Two studies the PREGACT Study Group[11] and Kakuru et a.[12] present new findings to support the use of ACT in both the prevention and the treatment of uncomplicated P. falciparum malaria in pregnancy.

The WHO now recommends that all women in the second or third trimester of pregnancy, who have uncomplicated P. falciparum malaria, should be treated with ACT.[13] The short-acting but potent artemisinin component (i.e., artemether, artesunate, or dihydroartemisinin) reduces the number of parasites substantially during the first 3 days of treatment. The longer-acting partner drug (i.e., lumefantrine, piperaquine, amodiaquine, or mefloquine) eliminates the remaining parasites, thereby preventing recrudescent malaria. The longer-acting partner drug is also responsible for the post-treatment prophylactic effect. The same mechanism of action is used in intermittent preventive treatment, in which repeated curative antimalarial treatments eliminate potential asymptomatic infections and also prevent new infections. However, ACT is not currently recommended for intermittent preventive treatment in pregnancy and also not to be given in the first trimester of pregnancy except in exceptional circumstances when other drugs are not tolerated and if the benefit is judged to outweigh the risks.

Tetracycline, doxycycline, primaquine, and halofantrine are contraindicated in pregnancy and lactation; however, available data do not show teratogenic effects from doxycycline. Pregnancy is a contraindication for primaquine therapy since it is not possible to assess G6PD status of a fetus in utero. Primaquine for radical cure could be started after infant has been checked for G6PD deficiency. There are no human data on halofantrine exposure in pregnancy. The treatment of uncomplicated malaria in pregnant women has been summarized in Table 7.[14,15]

Severe Malaria in Pregnancy

WHO currently recommends parenteral antimalarial drugs should be given to pregnant women with severe malaria [Figure 1] in full doses without delay. Parenteral artesunate is the treatment of choice in all trimesters.[13] Treatment must not be delayed. If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained [Table 2].Intravenous quinine is associated with recurrent hypoglycemia, and also evidence supports the superiority of artesunate over quinine in the non-pregnant patient. In epidemic situations, if IV or intramuscular medication is unavailable, patients should receive artesunate suppositories and be transferred to a higher level facility.[3] Following administration of parenteral therapy (for at least 24 h and until oral medication can be tolerated), an oral regimen should be administered.

The management of severe malaria is possible in health facilities which are equipped with the: parenteral antimalarials, antibiotics, anticonvulsants, antipyretics, intravenous infusion equipment and fluids, special nursing for patients in coma, facilities for blood transfusion, well-equipped laboratory, and oxygen respirator. Obstetric advice should be sought at an early stage, a pediatrician alerted and blood glucose checked frequently. Hypoglycemia should be expected and it is often recurrent if the patient is receiving quinine. Severe malaria may also present immediately after delivery. Postpartum bacterial infection is a common complication and should be managed appropriately.

Management of Newborn

Congenital malariais an extremely rare condition which occurs due to trans-placental transmission of maternal infection. Clinical features include fever, irritability, feeding problems, anemia, hepatosplenomegaly, andjaundice. Clinical features commence only after 3 weeks due to the protective effect of transplacentally transmittedantibodies. The infants are treated with ACTS in the doses based upon their weight. ACT-SP should be avoided in the first weeks of life because it could aggravate neonatal hyperbilirubinemia. Primaquine should be avoided in the first 6 months of life and tetracyclines should be avoided throughout infancy.

Figure1:Classification of severity of malaria[3]

WHO Definition of Severe Malaria
The WHO defines severe *P. falciparum* malaria as a patient with *P. falciparum* asexual parasitemia and one of the following clinical features: • Impaired consciousness or coma, prostration, failure to feed, mutiple convulsions, acidotic breathing, circulatory collapse, clinical jaundice with evidence of other vital organ dysfunction, hemoglobinuria, abnormal spontaneous bleeding, and/or pulmonary edema. Laboratory findings can include: • Hypoglycemia (blood glucose <2.2 mmol/l or <40 mg/dl), metabolic acidosis (plasma bicarbonate <15 mmol/l), severe normocytic anemia (HB <5 g/dl), hemoglobinuria, hyperparasitemia (>2%/100,000 per µl in areas of hight stable malaria transmission), and renal impairment (serum creatinine >265 µmol/l)

Table 7: Oral Regimens for Treatment of Uncomplicated Malaria in Pregnant Women[14,15]

S.N.	Type of infection	Pregnancy	Antimalarials with doses
1.	Chloroquine resistant *P.falciparum* infection	First trimester	Quinine PLUS clindamycin Quinine: 542 mg base (650 mg salt) orally three times daily for 7 days Clindamycin: 20 mg base/kg/day (up to 1.8 g) orally divided in three doses daily for 7 days OR Artemisinin combination therapy (ACT) can be used as an alternate only if quinine + clindamycin is unavailable or treatment failure
		Second or third trimeste	Artemisinin combination therapy: One of the following: a. ACT-AL-Artemether (20 mg) –lumefantrine (120mg): Dosing – weight 25–34 kg– 3 tablets twice daily; ≥35 kg– 4 tablets twice daily for 3 days b. Artesunate (100mg)– amodiaquine(270mg): Dosing – ≥36 kg – 2 tablets per day orally for 3 days c. Artesunate (100mg) – mefloquine (220mg): Dosing – ≥30 kg– 2 tablets per day orally for 3 days d. Dihydroartemisinin (40mg)– piperaquine (320mg): Dosing – weight 36 – <50 kg – 3tablets/day; weight <80 kg – 4 tablets/day
2.	Chloroquine sensitive *P.falciparum* infection	All trimester	Chloroquine (CDC) 600 mg base (1000 mg salt) orally immediately, followed by 300 mg base (500 mg salt) orally at 6, 24, and 48 h. Total dose: 1500 mg base (2500 mg salt). OR Hydroxychloroquine 620 mg base (800 mg salt) orally immediately, followed by 310 mg base (400 mg salt) orally at 6, 24, and 48 h. Total dose: 1550 mg base (2000 mg salt) Oral artesunate and clindamycin are also an alternate therapy in any trimester of pregnancy; however, combination tablets are not available
3.	Chloroquine sensitive *P.vivex* *P.vivax* chloroquine resistance *P.ovale, P. malariae, P. knowlesi*	All trimester	Chloroquine (WHO): Total dose: 25 mg base/kg, administered as 10 mg base/kg orally on day 1 followed by 10 mg/kg orally on day 2 and 5 mg/kg base on day 3 First trimester– Quinine salt 10mg/kg 3 times daily for 7 days Second and third trimester – any ACTS containing mefloquinepiperaquine or lumefantrine In India these species are very rarely found in few places. *P. ovale* should be treated as *P. vivax* and *P. malariae* should be treated as *P. falciparum*. They are rarely resistant to chloroquine
4.	Preventing relapses in *P. vivax* infection in pregnancy and lactating women		Chloroquine or ACT to be followed by chemoprophylaxis with weekly chloroquine until delivery and breast feeding is completed, then on the basis of G6PD status primaquine could be started for radical cure as primaquine is contraindicated in pregnancy and lactation

Table 8: Parenteral Regimens for Treatment of Severe Malaria[13]

S.N.	Type of infection	Antimalarials with doses
1.	Artesunate (preferred)	2.4 mg/kg intravenously (first dose), followed by 2.4 mg/kg at 12 and 24 h, followed by 2.4 mg/kg once daily
2.	Artemether	3.2 mg/kg intramuscularly to the anterior thigh (first dose), followed by 1.6 mg/kg intramuscularly once daily
3.	Quinine dihydrochlorideplusclindamycin	16.7 mg base/kg (20 mg salt/kg) up to a maximum of 1150 mg base (1400 mg salt) in 5% dextrose loading dose over 4 h, followed by 8.35 mg base/kg (10 mg salt/kg) over 4 h at 8- or 12-h interval (maximum 1530 mg base/day (2100 mg salt/day)), starting 8 h after the beginning of the loading dose Clindamycin– 10 mg base/kg once (maximum 900 mg) followed by 15 mg base/kg per day (maximum 1350 mg) divided into three equal doses. Clindamycin may be administered intravenously initially; switch to oral dosing once patient is able to swallow: 20 mg base/kg/day orally (maximum 1800 mg) divided into three equal doses. Treatment course is 7 days
4.	Quinidine gluconate plus clindamycin	6.25 mg base/kg (10 mg salt/kg) loading dose intravenously (maximum 600 mg salt) in normal saline over 1–2 h, followed by 0.0125 mg base/kg/min (0.02 mg salt/kg/min) continuous infusion for at least 24 h Alternative: 15 mg base/kg (24 mg salt/kg) loading dose intravenously in normal saline over 4 h, followed by 7.5 mg base/kg (12 mg salt/kg) infused over 4 h every 8 h, starting 8 h after the beginning of the loading dose clindamycin as above doses

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SECTION - II
Infectious diseases during pregnancy

"Dengue and Chikungunya" – Infectious Diseases during Pregnancy

DENGUE IN PREGNANCY

Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease according to the National Guidelines for Clinical Management of Dengue Fever (GOI, December, 2014).[1] Almost half the world's population lives in countries where dengue is endemic. The World Health Organization (WHO) estimates at least 50–100 million infections occurs annually including 500,000 dengue hemorrhagic fever (DHF) cases and nearly 22,000 deaths.[2] Dengue virus was isolated in India for the first time in 1945. The first evidence of occurrence of dengue fever in the country was reported in 1956 from Vellore district in Tamil Nadu. The first case of DHF outbreak had occurred in Calcutta (West Bengal) in 1963.

Virus and Vector

The agent of dengue is single-stranded RNA virus having four serotypes which are designated as DENV-1, DENV-2, DENV-3, and DENV-4. This is of Flavivirus genus. These dengue viruses are transmitted from an infected person to others by the bite of the female Aedes (Ae.) mosquito. In India, Ae. aegypti is the main vector prevalent in most urban areas. The population of virus fluctuates with rainfall and water storage. Its lifespan is influenced by temperature and humidity. It survives best between 16°C and 30°C temperature and a relative humidity of 60%–80%. The incubation period of this virus is 4–10 days. Primary infection is believed to induce lifelong protective immunity to the infecting serotype. It can provide cross-protective immunity for clinical illness produced by other serotype for 2–3 months, but not long term.

Host

Dengue infects not only humans but also many species of lower primates. No age or gender predominance. Travel to a dengue endemic area is an important high-risk factor. Other routes are through blood transfusion (BT), organ transplantation, and vertical transmission in pregnancy.

Clinical Manifestations

Dengue viral-infected person may be asymptomatic or symptomatic and clinical manifestations vary from undifferentiated fever to florid hemorrhage and shock.[3–6] Symptomatic dengue virus infections are grouped into two categories:

1. **Undifferentiated dengue fever (UDF):** Mild-to-moderate fever, often difficult to distinguish from other viral infections. The symptoms of dengue fever (DF) may not be very distinguished and signs of bleeding or capillary leakage may be absent.

2. **Severe DF and DHF:** DHF is further classified into four severity grades (I–1V), based on platelet count, hematocrit, capillary leakage, bleeding, and hypotension. Non-severe cases may be DF and DHF Grade I and II without significant bleeding. Severe dengue may be DHF III and IV being defined as dengue shock syndrome (DSS) presenting with shock and features of severe capillary leakage, hepatic/renal/cardiac/pulmonary or central nervous system (CNS) involvement.

The 2009 Dengue Case Classification by WHO

The 2009 WHO criteria [Figure 2] classify dengue according to levels of severity: dengue without warning signs; dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets); and severe dengue (dengue with severe plasma leakage, severe bleeding, or organ failure).[7] Patients who recover following defervescence are considered to have non-severe dengue, but those who deteriorate tend to manifest warning signs. These individuals are likely to recover with intravenous rehydration. However, further deterioration is classified as severe dengue, though recovery is possible if appropriate and timely treatment is given.[7]

Figure 2: Dengue Case Classification by Severity

Criteria for dengue ± warning signs

Probable dengue	Warning signs*	Criteria for severe 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)	• Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleed • Lethargy; restlessness • Liver enlargement >2 cm • Laboratory: Increase in HCT concurrent with rapid decrease in platelet count* Requiring strict* observation and medical intervention observation and medical intervention	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

Course of Illness

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations.[8] After the incubation period, the illness begins abruptly and, in patients with moderate to severe disease, is followed by three phases – febrile, critical, and recovery.

Febrile Phase

Patients typically develop a high-grade fever suddenly, may be biphasic, lasting for 2–7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia, headache,[8] retro-orbital eye pain, photophobia, sore throat, an injected pharynx. Conjunctival injection and maculopapular rash usually appear after 3–4 days of fever and commonly seen on neck, face, and other parts of body. Anorexia, nausea, and vomiting are common.

A positive tourniquet test in this phase indicates an increased probability of dengue.[9,10] If disease progress to the critical phase, there can be appearance of petechiae and mucosal membrane bleeding,[9,11] easy bruising and bleeding at venipuncture sites, massive vaginal bleeding and gastrointestinal bleeding.[5] The earliest abnormality in the full blood count is a progressive decrease in total white cell count.[3]

Critical Phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. Instead of improving with the subsidence of high fever; patients with increased capillary permeability may manifest with the warning signs, mostly as a result of plasma leakage. The temperature drops to 37.5°C–38°C or less and remains below this level, usually on days 3–8 of illness. Progressive leukopenia[10] is followed by a rapid decrease in platelet count usually precedes plasma leakage. An increasing hematocrit above the baseline may be one of the earliest additional signs.[12,13] The period of clinically significant plasma leakage usually lasts 24–48 h. The degree of plasma leakage varies. A rising hematocrit precedes changes in blood pressure (BP) and pulse volume. The degree of hemoconcentration above the baseline hematocrit reflects the severity of plasma leakage. Hence, frequent hematocrit determinations are essential because they signal the need for possible adjustments in intravenous fluid therapy. A right lateral decubitus chest radiograph, ultrasound detection of free fluid in the chest or abdomen, or gall bladder wall edema may precede clinical detection. In addition to the plasma leakage, hemorrhagic manifestations such as easy bruising and bleeding at venipuncture sites occur frequently. Abnormal hemostasis and leakage of plasma leads to shock, bleeding, accumulation of fluid in pleural, and abdominal cavity. High morbidity and mortality in DHF/DSS are commonly associated with various organ involvements and metabolic derangement. Some patients progress to the critical phase of plasma leakage and shock before defervescence. Cases of dengue with warning signs will usually recover with intravenous rehydration. Some cases will deteriorate to severe dengue.

Warning Signs of Dengue

The warning signs mark the beginning of the critical phase.

- Recurrent vomiting, dehydration, electrolyte imbalances
- Pleural effusion/ascites/gall bladder edema on imaging
- Minor bleeding from different sites, scanty hemoptysis, hematemesis, hematuria, increase menstrual flow, gum bleeding, and so on
- Abdominal pain or discomfort
- Palpitation, breathlessness
- Hepatic dysfunction or hepatomegaly
- Decrease urinary output
- High HCT (>45%)
- Rapid fall in platelet count(<100000 cells/mm3), Progressive leucopenia(≤5000cells/mm3).[10]
- Cold clammy extremities with narrow pulse pressure, rapid pulse, and hypotension.

In addition, severe organ involvement may develop such as severe hepatitis, encephalitis, myocarditis, and/or severe bleeding, without obvious plasma leakage or shock.

Recovery phase

As the patient survives the 24–48 h critical phase, a gradual reabsorption of extravascular compartment fluid into circulatory system takes place in the following 48–72 h. General wellbeing improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes, and diuresis ensues.

Maternal and Fetal Complications

Maternal Complications

i. Preterm births (13%–55%), low birth weight and cesarean deliveries.
ii. Severe bleeding may complicate delivery and/or surgical procedures performed on pregnant patients with dengue during the critical phase and may lead to maternal death.
iii. Pleural effusion, ascites, and hypotension are commonly associated with DF in pregnancy. Involvement of lungs and liver is also common in pregnancy. Patients may have respiratory symptom due to massive pleural effusion and high SGOT/SGPT due to liver involvement. Complications of DF depend on the different stages of pregnancy like early, late, peripartum, and postpartum period. Pregnancy-induced hypertension, placental abruption, and preterm labor are more common in pregnant woman with dengue than with chikungunya fever (CF).[14,15]

Fetal Complications

Dengue in early stages of pregnancy may lead to abortion. There is insufficient data of probable embryopathy to mothers who had DF in the first trimester. Fetal death may occur due to plasma leakage compromising placental circulation. DF does not warrant termination of pregnancy.

Risk of vertical transmission: The risk of vertical transmission is well established among women with dengue during the perinatal period (1.6%–64%). Peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn.

Differential Diagnosis

Malaria, influenza, enteric fever, pharyngitis/tonsilitis, leptospirosis, chikungunia, ebola hemorrhagic fever.

Diagnosis

Laboratory diagnosis is not essential for clinical management.

1. Rapid NS1 antigen detected on Day 1–5 of fever in acute viremic state.
2. Dengue IgM detectable by Day 5 of illness (range 2–8 days). Detectable IgM persists in circulation for upto 60 days on an average. Other confirmatory test like dengue virus isolation, PCR, IgG ELISA, HI test, or compliment fixation tests, etc. are not recommended for routine clinical practice these days.
3. Complete blood count (CBC/FBC) as a baseline, as well as to monitor progress of disease is most important tool.

Management of Dengue in Pregnancy

Challenges in Recognition of Dengue Disease and Plasma Leakage in Pregnancy

Symptoms of hyperemesis during the first trimester of pregnancy and increase in circulating blood volume with generalized vasodilatation, resulting in an increased baseline heart rate and lower baseline BP, as well as a lower baseline hematocrit in second trimester are normal physiological changes of pregnancy. These changes resemble the warning signs of severe dengue and this may delay the recognition of severe dengue.[16]

Challenges in Monitoring and Management

- Close observation and monitoring, prompt, adequate, and appropriate replacement therapy during the pre-, intra-, and post-delivery periods are essential.
- Failure to recognize plasma leakage and/or shock early will lead to prolonged shock and eventually massive bleeding and multiorgan failure.
- There is no difference in fluid therapy compared with the non-pregnant state. However it is important to note that the growing gravid uterus may result in

narrower tolerance of fluid accumulation in the peritoneal and pleural cavity from plasma leakage. Hence excessive fluid replacement should be avoided.

- The increased baseline heart rate and a lower baseline BP are normal physiological changes in late pregnancy. Targeting an inappropriate heart rate and "normal" levels of BP could result in fluid overload and respiratory distress.
- The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, coagulopathy, and vasculopathy creates a substantial risk of severe hemorrhage.
- If severe hemorrhage occurs, replacement with transfusion of fresh whole blood/fresh packed red cells should be promptly instituted.
- Prophylactic platelet transfusion is not recommended unless obstetrically indicated.
- Delivery should take place in a hospital where blood/blood components and a team of skilled obstetricians and a neonatologist are available.
- Tocolysis and measures to postpone labor to a suitable time may be considered during the critical phase of dengue illness. However there is currently a lack of evidence on this practice.

Inevitable Delivery during Critical Phase

- If delivery is inevitable, bleeding should be anticipated and closely monitored.
- Blood and blood products should be cross-matched and saved in preparation for delivery.
- Trauma or injury should be kept to the minimum if possible.
- It is essential to check for complete removal of the placenta after delivery.
- Transfusion of platelet concentrates should be initiated during or at delivery but not too far ahead of delivery, as the platelet count is sustained by platelet transfusion for only a few hours during the critical phase.
- Fresh whole blood/fresh packed red cells transfusion should be administered as soon as possible if significant bleeding occurs. If blood loss can be quantified, it should be replaced immediately. Do not wait for blood loss to exceed 500 ml before replacement, as in postpartum hemorrhage. Do not wait for the hematocrit to decrease to low levels.
- Oxytocin infusion as per standard obstetrical practice should be commenced to contract the uterus after delivery to prevent postpartum hemorrhage.

Post Delivery

Newborns with mothers who had dengue just before or at delivery, should be closely monitored in hospital after birth in view of the risk of vertical transmission.[17,18] At or near-term/delivery, severe fetal or neonatal dengue illness and death may occur when there is insufficient time for the production of protective maternal antibodies. Clinicians should be aware that presentation in either maternal or neonatal disease may be atypical and confound diagnosis.

Congenital infection could eventually be suspected on clinical grounds and then confirmed in the laboratory.

Stepwise Management

Suspect Dengue in Pregnant Patients Coming with Fever

Do baseline CBC on D1/D2 of fever.

If WBC count normal/lower side suspect DF and repeat CBC after 24 h and compare further fall in platelets/rise in PCV (10% rise is considered as significant).

Admission Criteria

All pregnant patients with suspected DF are advised admission for close monitoring. Approach to clinical management of DF may vary depending on severity of illness. Conservative medical and obstetrical management is the treatment of choice.[16]

DF Without Warning Signs

Monitoring

- Four hourly temperature charting, pulse, BP, and pulse pressure
- Urine output monitoring 4–6 hourly (minimum 120 cc every 4 h)
- Capillary refill time
- Intake output record
- Daily CBC, other investigations if necessary
- Monitor warning signs

Treatment

- Adequate bed rest
- Adequate fluid intake
- Paracetamol, 4 g max. per day. Not to take other non-steroidal anti-inflammatory drug (NSAID) like ibuprofen and diclofenac sodium
- Tepid sponging for fever
- Withhold aspirin if she is taking it

DF With Warning Signs

Monitoring

- 1 hourly temperature charting, pulse, BP, and pulse pressure
- Urine output monitoring 4–6 hourly (Aim 0.5 ml/kg/H)

- Capillary refill time
- Intake output record
- CBC, HCT (before and after fluid replacement, then 6–12 hourly)
- Blood glucose
- Other organ functions (renal profile, liver profile, coagulation profile, as indicated)

Treatment

Give isotonic solutions such as 0.9% saline, ringer lactate, start with 5–7 ml/kg/h for 1–2 h, reduce to 3–5 ml/kg/h for 2–4 h, and then reduce to 2–3 ml/kg/h or less according to clinical response. Reassess clinical status and repeat hematocrit (HCT). If HCT remains the same or rises only minimally then continue with 2–3 ml/kg/h for another 2–4 h. If worsening of vital signs and rapidly rising HCT then increase rate to 5–10 ml/kg/h for 1–2 h. Reassess clinical status, repeat HCT and review fluid infusion rates accordingly. Reduce intravenous fluids gradually when the rate of plasma leakage decreases toward the end of the critical phase. This is indicated by adequate urine output and/or fluid intake or HCT decreases below the baseline value in a stable patient.

DF With Shock

Patients presents with any of the following features:

- Severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- Severe bleeding
- Severe organ impairment

These patients need institutional management in ICCU set up. Timely fluid management with appearance of any warning symptom practically prevents further complication. The action plan for treating patients with compensated shock is as follows [see Algorithms in Figures 3 and 4]:

- Draw blood for CBC, to know HCT.
- Also for group cross match and other organ function tests etc.
- Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/h over 1 h.
- Reassess patient's condition, If patient improves IV fluids should be reduced gradually to 5–7 ml/kg/h for 1–2 h, then to 3–5 ml/kg/h for 2–4 h, then to 2–3 ml/kg/h for 2–4 h, and then reduced further depending on hemodynamic status.
- IV fluids can be maintained for up to 24–48 h.
- If patient still unstable: Check HCT after first bolus. If HCT increases/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 ml/kg/h for 1 h.
- If improvement occurs after second bolus, reduce rate to 7–10 ml/kg/h for 1–2 h, continue to reduce as above.
- If HCT decreases, this indicates bleeding and need to cross-match and transfuse blood as soon as possible.

Convalescent Phase

Rise of WBC count followed by rise of platelet count, stabilization of HCT marks convalescent phase. Now watch for signs of fluid overload – cough, wheeze, tachypnea, rise of both SBP and DBP.

Discharge from Hospital

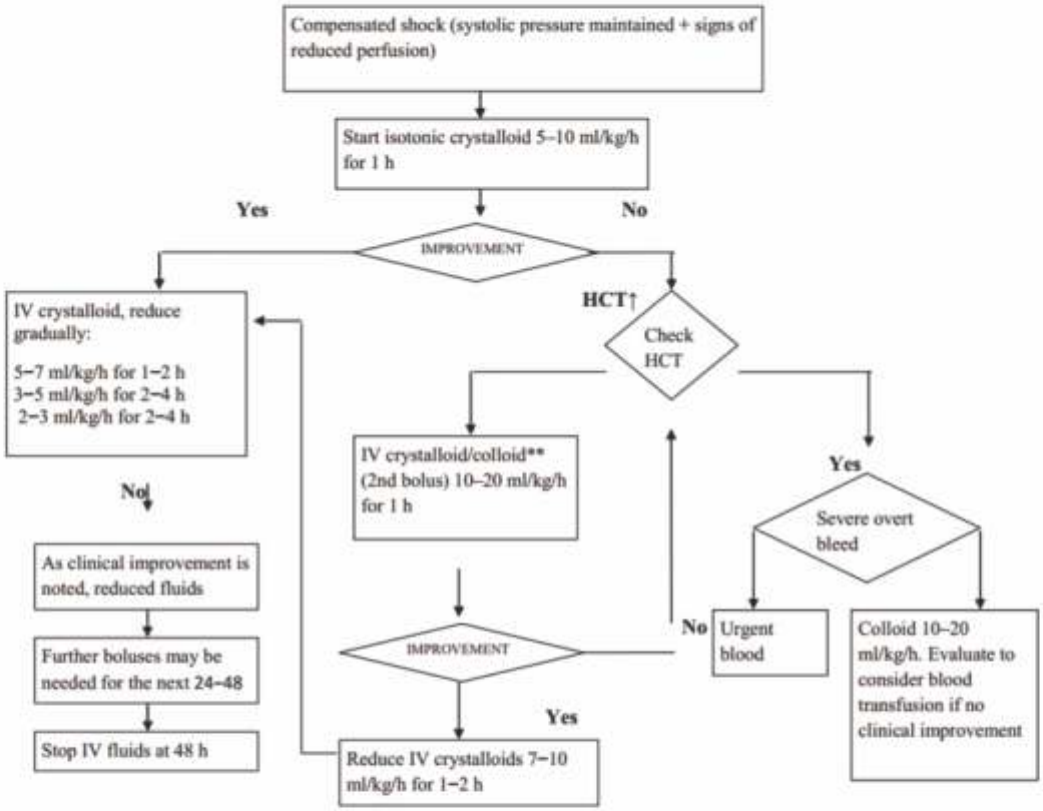
Afebrile for 24 h without antipyretics
Improved appetite
Normal HCT at baseline value
Rising trends of WBC and platelets

Precautions

1. No other NSAID (ibuprofen/diclofenac) for fever. Only paracetamol to be given. Daily dose should not exceed 4 g.
2. Normal saline (NS) 0.9% should be used for initial resuscitation. NS is preferred to ringer lactate and DNS. Plain dextrose solution NOT to be used. Colloids can be given only after 2 fluid boluses in patients of shock.
3. Indication of transfusion: Fresh BT if there is overt blood loss nearing 500 cc. No overt bleeding but drop in HCT without clinical improvement despite adequate fluid replacement.
4. Prophylactic platelet transfusion is NOT recommended unless delivery is inevitable (in coming 6 h) platelet count >50,000/cc and 75,000/cc for operative delivery. Clinically stable dengue with low or very low platelet count in critical/recovery phase – no platelet transfusion. Platelet transfusion may be given in presence of overt bleeding with low platelet counts.
5. There is NO role of steroid/IV immunoglobulin/ prophylactic antibiotics.
6. Operative delivery for obstetric indications only. AVOID Planned INDUCTION surgery. The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, and plasma leak creates a substantial risk of severe hemorrhage. Delivery should take place in a hospital where blood/blood components and a team of skilled obstetricians and a neonatologist are available.
7. Tocolytic agents and measures to postpone labor to a suitable time may be considered during the critical phase of dengue illness. However there is currently a lack of evidence on this practice.

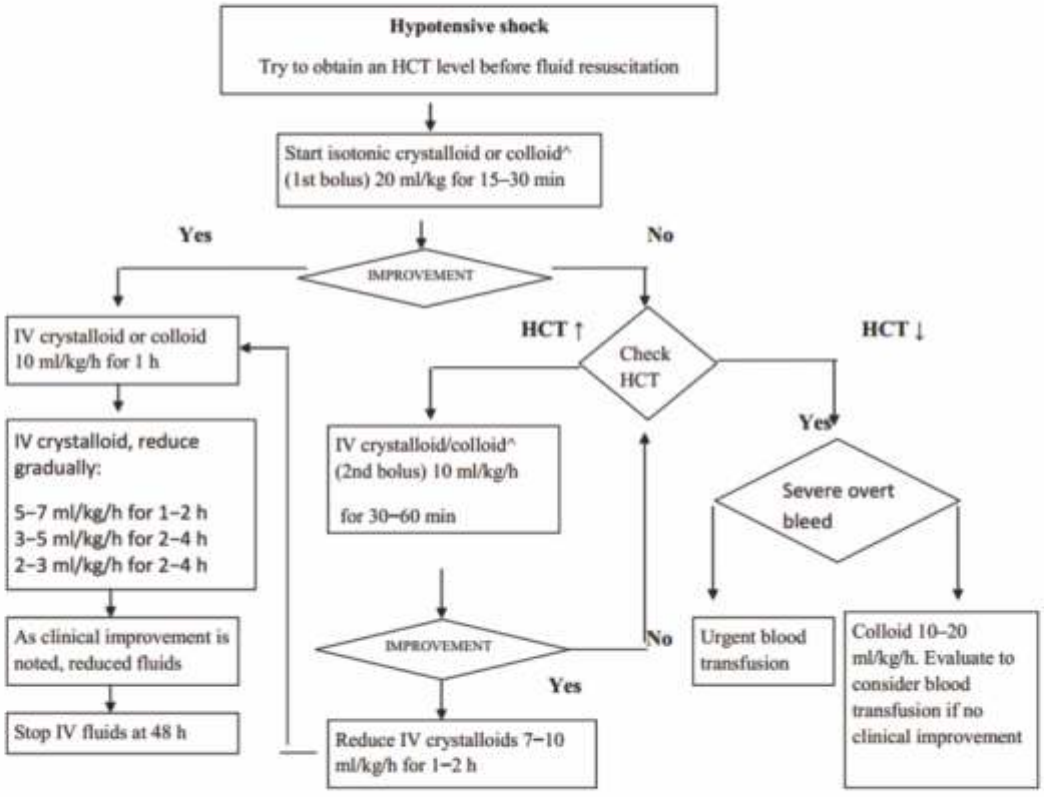
Timely intervention brings down fatality from 20% to 1%.

Figure 3: Algorithm for Fluid Management of Compensated Shock: In Adults



*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
**Colloid is preferable if the patient has already received previous boluses of crystalloid.
IV: intravenous, HCT: hematocrit, ↑: increased, ↓: decreased.

Figure 4: Algorithm for Fluid Management in Hypotensive Shock – Infants, Children, and Adults



^Colloid is preferable if the patient has already received previous boluses of crystalloid.
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
IV: intravenous, HCT: hematocrit, ↑: increased, ↓: decreased.

Management of Neonatal Dengue

When a pregnant or parturient woman develops signs consistent with dengue, the diagnosis of dengue should be considered in her neonate even if the neonate appears well in the first several days of life. Remember, that some neonates have become ill as long as 11 days after birth.[16] Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia, and hepatomegaly, to severe illness with pleural effusion, gastric bleeding, circulatory failure, massive intracerebral hemorrhage. Clinical presentation in the newborn infant does not appear to be associated with maternal disease severity or dengue immune status or mode of delivery. However, timing of maternal infection may be important; peripartum maternal infection may increase the likelihood of symptomatic disease in the newborn. The diagnosis of neonatal dengue could eventually be suspected on clinical grounds and then confirmed in the laboratory, but initial presentation may be confused with bacterial sepsis, birth trauma, and other causes of neonatal illness. Symptomatic and supportive treatment under close observation is the mainstay of treatment.[16,18,19]

Management of Exposed Cases (Pregnant Women and Partner)

It is vector-born viral disease. There is no direct increased risk to pregnant women's partner per se.

CHIKUNGUNYA IN PREGNANCY

Introduction

Chikungunya fever (CF) is an arthropod-borne viral disease caused by the chikungunya virus (CHIKV single-stranded RNA virus of genus Alphavirus).[20] First described during an outbreak of dengue-like illness in Tanzania in 1952–1953, the virus derives its name from the Makonde language and means "to become contorted" or "that which bends up."[21-23] These descriptors refer to the hallmark of the disease observed in adults, namely severe incapacitating arthralgia.

In its natural cycle, CHIKV is transmitted by the bite of female arboreal Aedes (Stegomyia) mosquitoes. The peridomestic Ae. Aegypti, was identified as the primary vector of CHIKV during its outbreaks, both in Africa and Asia.[24] It is only during the last decade that Ae. Albopticus (also known as the Asian tiger mosquito) has been recognized as a new propagating vector of CHIKV.[25]

Pathophysiology

The onset of CF coincides with viremia (incubation period 2–12 days with median duration 5 days).[26] CHIKV replicates in the liver, before reaching joint fibroblasts, muscle satellite, and skin epithelial cells, causing arthralgia, myalgia, and rash. Indeed, elective targeted sites where symptoms focus are typically infected, especially joint capsules, skeletal muscles, myotendinous insertions, and epidermis.[20]

Clinical Presentation

Acute phase illness – two stages are identified:
Viral stage – First 5–7 days in which viremia occurs.
Stage of convalescent – It follows viral stage for approximately next 10 days during which the symptoms improve and virus cannot detected in blood.

Signs and Symptoms

1. Sudden abrupt onset of high fever usually above 39°C (102°F) and sometime reaches upto 40°C (104°F).
2. Joint pain – Reported in 87%–98% patients. It occurs following fever, usually last for weeks or months, but may last for years, often results in stiffness and immobility of affected joints. Joints are affected in both hands and legs symmetrically.
3. Maculopapular rash – Occurs in 40%–50% cases occurring 2–5 days after onset of symptoms. Muscle pain, headache, and fatigue.
4. Abdominal pain, nausea, vomiting, diarrhea.
5. Eye inflammations – Iridocystitis, uveitis, retinal lesions.
6. Neurological disorders – Guillian–Barrè syndrome, palsies, flaccid paralysis, neuropathy, meningoencephalitis.

Chikungunya rarely causes hemorrhagic symptoms, if there, may be co-infection with dengue.

Chronic Phase

Most patient recover fully, but in some cases joint pain may persist for several months, or even years following acute infection.[27] This condition has been termed chronic Chikungunya virus-induced arthralgia.[28]

Maternal and Fetal Complications

To date, there is no reliable epidemiological data linking CHIKV exposure in the first trimester of gestation to an increased risk for miscarriage, nor to any type of congenital malformation.[29,30]

In the second and third trimester few case reports of antepartum fetal deaths reported. Developing the infection during pregnancy does not usually harm the mother or the fetus. The risk of vertical transmission is very rare. Importantly, CHIKV can be transmitted vertically with a probability of approximately 50%, when the parturient woman has a high viral load during the early stage of labor.[29,31,32] Fetal heart rate decelerations and meconium-stained amniotic fluid are common during labor.[32,33] Neither postponing delivery nor cesarean has been shown to be

protective. Contrary to dengue, there is also no increased risk for obstetric hemorrhage (placental abruption), preterm birth, or low birth weight.[29,30]

Diagnosis

Chikungunya infection can be confirmed by the detection of the virus, viral DNA, or specific antibodies in patient samples. Blood test is the only reliable way to identify Chikungunya.

Virological Method

RT-PCR: Viral RNA can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in specimen obtained from patient.

Serological Methods

CHIKV-specific IgM and IgG can be detected in serum by enzyme-like immunosorbent assay (ELISA) immunocapture. CHIKV-specific IgM are detectable from 3 to 8 days after the onset of infection (p.o.i.) and may persist for several months to up to 2 years. CHIKV-specific IgG are detectable from 4 to 10 days p.o.i. and may persist for years.

Diagnostic Testing Depends on Timing of Illness Onset

The molecular assays (TaqMan real-time PCR, RT-LAMP assay, and reverse transcription PCR) are more sensitive in the early stage of CF (2–5 days p.o.i.) when CHIKV-specific IgM are not yet detectable. In the later stages of CF (>5 days p.o.i.), CHIKV-specific IgM is more sensitive than PCR. Experts recommend that ELISA IgM be used as an initial screening test. Thirty current topics in Chikungunya followed by one of the molecular assays in samples negative for IgM in the early stage of CF.[34]

Management

Treatment

There is no specific antiviral treatment for CF. CF in pregnant women should be treated with antipyretics and non-aspirin analgesics to relieve the symptoms. Aspirin may increase the risk of bleeding. Despite anti-inflammatory effect, corticosteroids are not recommended in acute phase, as they may cause immunosuppression and worsen infection.

Vaccine

Currently no approved vaccine are available. Passive immunotherapy involving administration of anti-CHIKV hyperimmune human intravenous antibodies (immunoglobulin) may have potential benefits in treatment of Chikungunya. Studies are currently in progress.[35]

Prevention and Control

Preventive measures include community mobilization for eradication of breeding sites of Ae. mosquitoes, which primarily dwell in natural and artificial water-filled habitats. During epidemics, peri-domestic spraying of insecticides by residents and space spraying by vector controls teams are key for reducing adult mosquito populations.[36]

Appropriate clothing may minimize skin exposure. Insect repellents can be applied on exposed skin or clothing according to product label instructions. In addition, insecticide-treated nets are important for pregnant women who take day time naps.

Management of Newborn

Neonates who are prenatally infected with CHIKV are born with very low or even undetectable viremia. On an average, it takes 4–5 days (range: 3–7 days) for the viral load of CHIKV transmitted at birth to reach a level significant enough to cause clinical disease. Neonatal CHIKV infection almost invariably presents with fever, pain, and suckling difficulties often requiring enteral or parenteral nutrition.[32] Other common symptoms include limb edema, petechiae, and a skin rash such as maculopapular rash and intertriginous aphthous-like ulcers.[37] Thrombocytopenia, lymphopenia, and mild-to-moderate increases of serum aspartate aminotransferase (AST or SGOT) are frequent observations.

Life-threatening complications occur in half of the neonates and display two main clinical pictures: CHIKV-associated CNS disease (formerly reported as encephalopathy) that in fact consists of an encephalitis[38] and a multiple organ dysfunction (MOD) syndrome that combines a circulatory collapse (hypovolemic and hyperkinetic profile on echocardiography), lethargy, hemorrhages (disseminated intravascular coagulation), uremia, and cytolysis.[39] To date, only few CHIKV-associated deaths in neonates have been reported.[40–42]

For the neonates without neurological involvement, recovery was observed in 1–3 weeks without sequelae; however, future long-term studies will shed more light on the presence of subtle morbidities related to CF in these infants.[43] As in pregnant women, there is no specific treatment for CF. Management is symptomatic and focuses on adequate hydration, antipyretics, and analgesics (paracetamol/acetaminophen).[37] Experts recommend withholding salicylates, steroidal, and NSAIDs, as they may facilitate bleeding manifestations.[44] At pediatric ages, neonates and small infants below 6 months of age have the highest risk for case fatality and lifelong disabilities.

Management of Exposed Cases (Pregnant Women and Partner)

It is vector-born viral disease. There is no direct increased risk to pregnant women's partner.

Conclusion

Dengue and CF is a tropical arthropod-borne virus infection whose geographical distribution has grown steadily over the last decade as a result of global warming and globalization of transports. Dengue and CHIKV can also be transmitted vertically from mother-to-child during the perinatal period when the parturient woman is highly viremic during labor.

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SECTION - II
Infectious diseases during pregnancy

Group B Streptococcal Infection in Pregnancy

Introduction

The genera of Streptococcus consist of bacteria that are Gram-positive, spherical in shape, and are typically arranged in chains or pairs. They are non-spore forming and catalase negative facultative anaerobes. Streptococci are classified into major categories based on colony morphology, hemolysis on blood agar, Lancefield and capsule antigens, specific biochemical reactions, and resistance to physical and chemical factors. Group B streptococcus grows in pairs as diplococci and forms a typical appearance on sheep blood agar caused by destruction of erythrocytes. Depending on its surface antigen and expression of antigenic carbohydrates, the pathogenesis also differs.

From the perspective of an obstetrician, Group B streptococcus is of particular interest owing to the potential complications to both mothers and newborns. It is the leading cause of morbidity and mortality in neonates[1] in addition to causing various infections in the mothers including (but not restricted to) urinary tract infections (UTIs), vulvovaginitis, endometritis, intra-amniotic fluid infections, mastitis and wound infections. Group B streptococcus forms a part of the normal vaginal and lower gastrointestinal flora in 5%–30% of women.[1] The distribution of colonization differs among various ethnicities, geographic location, and age of the women but the incidence is similar among pregnant and non-pregnant women.[2] A major concern with Group B streptococcus is its non-classic colonization and its prevalence in about 25% of pregnant women with no specific risk factors,[3] making it very difficult to account for its role in the development of an asymptomatic or invasive infection.

Certain groups are more prone to infection by Group B Streptococcus, particularly among intra and postpartum women and neonates. Some of the identified risk factors include black race, massive maternal colonization, low levels of maternal antibodies, maternal age <20 years, maternal DM, bacteremia during pregnancy, premature rupture of membranes for <18 h, intrapartum fever, and with a history of a newborn with early onset neonatal SGB disease.[4,5]

Effect of Colonization by Group B Streptococcus during Pregnancy

Group B streptococcus is responsible for causing a lot of infections that threaten to disrupt maternal and fetal wellbeing.

Urinary Tract Infections

UTIs are the most common infections during pregnancy. The common causative organisms range from Escherichia coli to Klebsiella, but a small percentage is caused by Group B streptococcus. The symptoms are virtually indistinguishable to those caused by other bacteria, but it complicates up to seven percentage of pregnancies. Crucially, about 70% is asymptomatic,[6] making the diagnosis a tricky affair leading to complications such as premature rupture of membranes, preterm labor, and neonatal infections. In exceptional cases, it may even cause serious complications like acute pyelonephritis to the mother leading to adverse fetal outcomes.[1] Studies have failed to find a link between Group B streptococcus infections and adverse pregnancy outcomes, but the asymptomatic nature coupled with possible adverse outcomes warrant prompt treatment, whether symptomatic or not. A comprehensive study conducted by Nicolle et al.[7] concluded that it is necessary to treat even asymptomatic bacteriuria to prevent any unforeseen complications during pregnancy. They also suggested that the first line of treatment should be the oral administration of penicillin 250 mg PO 6 hourly for 4–7 days followed by a urine culture to spell out the next step of management.

Vaginitis

Group B streptococcus is also notorious for its association with vaginitis during pregnancy and is found more in women with excessive and/or purulent vaginal discharge. The literature regarding this is conflicting since Jensen and Andersen[8] found an association between colonization of Group B streptococcus and vaginitis, whereas Honig et al. and Shaw et al. found no association between the two, hinting to a casual association rather than a causal association[9,10] Till date, there are no studies to prove the importance of screening and treatment of vaginitis and symptomatic vaginitis needs to be treated based on the culture reports. Literature supports the fact that

even though treating asymptomatic vaginitis does not reduce the chance of preterm birth but does reduce the risk of premature rupture of membrane and low birth weight.

Preterm Premature Rupture of Membranes and Preterm Labor

A gynecological important complication of an infection with Group B streptococcus is preterm premature rupture of membranes (PROMs) at an early gestational period. This may be attributed to its ascending route of colonization. Studies regarding this are conflicting, with one train of thought proving only a casual association between Group B streptococcus infection and PROM/preterm delivery though convincing evidence has piled up showing a causal relationship between the same and neonatal Group B streptococcus infection.[11]

Effect of Colonization of Group B Streptococcus during Delivery

Intra-amniotic infection, a clinical diagnosis made based on symptoms including maternal body temperature >38°C, fetal tachycardia (>160 beats/min), uterine tenderness, and foul-smelling discharge is commonly caused by the commensals that colonize the vagina. One of the most common causative organisms is Group B streptococcus. The incidence of intra-amniotic infection (by virtue of a clinical diagnosis) is more during preterm delivery rather than term. Moreover, majority of cases in a setting of PROM do not produce classical clinical signs thereby increasing the associated risk. This may lead to sepsis, prolonged duration of labor, increased incidence of postpartum hemorrhage, and stillbirth.13 Intrapartum antibiotics are advised for patients with PROM to prevent the same.[14,15]

Effect of Colonization of Group B Streptococcus After Delivery

During postpartum period, Group B streptococcus is known to cause comparatively benign infections like mastitis,[16] wound infection to dreaded complications such as meningitis, endometritis, and bacterial sepsis.

Effect of Colonization of Group B Streptococcus on Neonates

SGB disease in neonates can occur as early onset disease which occurs up to 7th day of the life and accounts for 85% of the neonatal infections, late onset disease which occurs from 8th day until the 3rd month of life, and very late onset disease occurring after 1 month of life. The streptococcus B is known to cause vertical transmission in fetus due to its ascending route and with aspiration of the contaminated amniotic fluid where the whole scenario is accelerated with PROM and premature delivery of fetus.

To decrease the incidence of all the above presentations, Centre of Disease Control and Prevention recommends a few strategies to identify the colonization of Group B streptococcus in mothers during pregnancy and to identify the important maternal risk factors to curtail early onset infection. The routine screening at 35–37 weeks is strongly recommended by The American College of Obstetricians and Gynecologist (ACOG) followed by the appropriate management.[18,19]

Specimen Collection for Culture

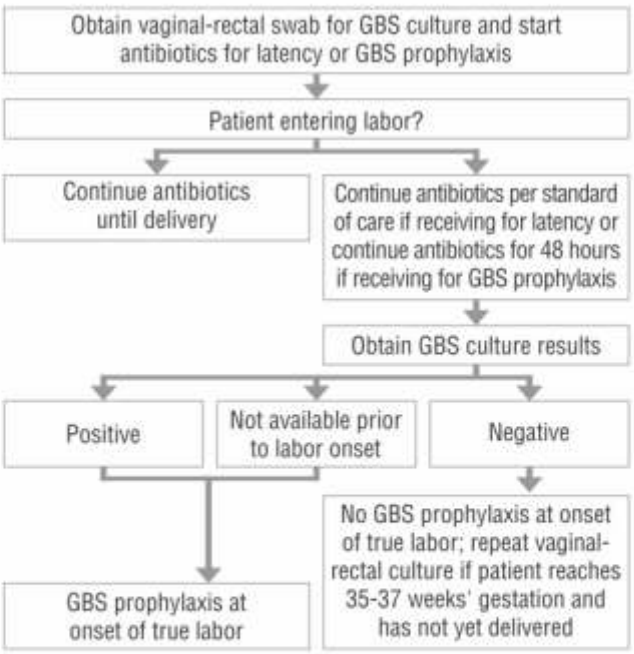
1. **Site:** Vaginal introitus, rectum (through the anal sphincter). This may be taken using the same swab or using two different swabs. It can be done either in an outpatient setting or by the patient herself.
2. **Transport medium:** Non-nutritive transport medium like Stuart's medium with or without charcoal. Even though Group B streptococcus can survive in the culture medium for several days at room temperature, it is recommended to refrigerate the sample immediately after collection.

Inclusion Criteria for Intrapartum Antibiotic Prophylaxis for Early Onset Group B Streptococcal Infection[19]

1. Any previous infant with invasive Group B streptococcal infection.
2. Group B streptococcal infection during any trimester in the present pregnancy.
3. A positive vaginal/rectal swab in late gestation in the present pregnancy.
4. Unknown status of Group B streptococcus at the onset of labor pains with delivery >37 weeks, rupture of amniotic membranes <18 h, and/or intrapartum temperature <100.4°F.

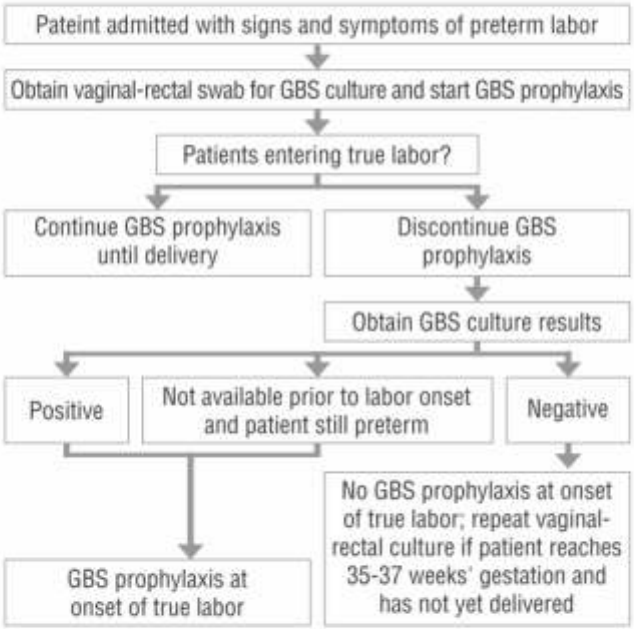
Various Algorithms as Identified for Screening for Group B Streptococcus and the Use of Intrapartum Antibiotic Prophylaxis have been Made by ACOG

Algorithm1: Screening of GBS with premature PROM[19]



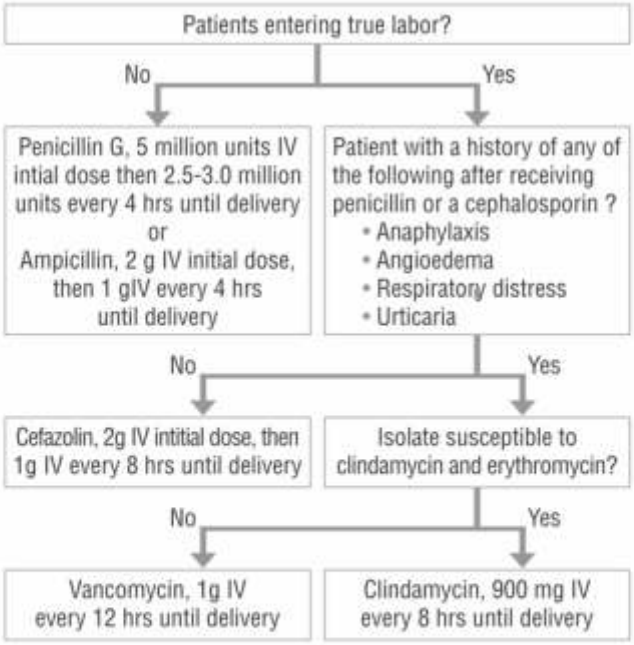
Antibiotics for latency in PPROM includes ampicillin 2 g intravenously once followed by 1 g every 6 hourly for at least 48 h. If other regimes are used, GBS prophylaxis should be initiated in addition. A negative culture is considered valid for 5 weeks, if any patient undergoes labor and is screened 5 weeks before she should undergo rescreening and should be managed again according to the algorithm.

Algorithm2: Screening of GBS colonization and use of intrapartum prophylaxis for women with preterm labor[19]



A negative culture is considered valid for 5 weeks, if any patient undergoes labor and is screened 5 weeks before she should undergo rescreening and should be managed again according to the algorithm.

Algorithm3: Screening of GBS colonization and use of intrapartum prophylaxis for prevention of early onset group B streptococcal infections[19]



These mentioned above are the standard protocols considered for the judicious use of intrapartum antibiotics for prevention of maternal and neonatal complications in a group B streptococcal infections.

Conclusion

On the basis of the review it becomes reflective to adopt rectovaginal culture for Group B streptococcus as part of our routine obstetric care, which would be proportional in detecting the early neonatal infection. It would further reduce the risk and rate of both maternal and neonatal morbidity. Further the judicious use of intrapartum antibiotic with a proper preventive strategy and surveillance would cut down on the rates and incidence of the same.

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SECTION - II
Infectious diseases during pregnancy

"Tuberculosis during Pregnancy"

Introduction

Tuberculosis (TB) was declared a public health emergency by the World Health Organization (WHO) in 2005, is among the three leading causes of death among women aged 15–45 years in high burden areas. Around 4,80,000 women died from TB in 2014, including 1,40,000 deaths among women who were human immunodeficiency virus (HIV)-positive. Out of 3,30,000 HIV-related TB deaths among adults (age ≥15) globally in 2014, more than 40% were among women, which accounted for almost one-third of all AIDS-related deaths among female adults.

Impact of TB on Maternal Health

As per a study, TB among mothers was found to be associated with a six-fold increase in perinatal deaths and a two-fold risk of premature birth and low birth weight.[1] Genital TB was significant cause of infertility in high TB-incidence settings.

A strong association has been demonstrated between TB and HIV. Pregnant women living with HIV increases risk of maternal and infant mortality by almost 300%.[2] In India, studies demonstrated that TB among mothers living with HIV is associated with more than double the risk of vertical transmission of HIV to the unborn child. Infants born to women with untreated TB may be of lower birth weight than those born to women without TB and in rare circumstances the infant may be born with TB. Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does its treatment.

Maternal Complications

The effects of TB on pregnancy depend upon the following factors:

- Type of TB
- Immune status of patient
- Site of the disease
- Extent of the disease
- Stage of pregnancy
- Mother's nutritional status
- Presence of concomitant disease
- Time of management
- Co-existence of HIV infection.

The pulmonary and extrapulmonary forms of TB affect pregnant women in the same way as the non-pregnant ones. A study of 27 pregnancies with culture positive MTB also detected abnormal radiographs among all the patients.[3] If anti-tuberculosis treatment (ATT) is initiated early in pregnancy, one can expect the same outcome as in non-pregnant females. Studies have also demonstrated that cases with late diagnosis were associated with four-fold increase in obstetric morbidity and a nine-fold increase in preterm labor.[4] Co-existing HIV infection is known to augment progression of TB and worsens the immunosuppression. The stage of pregnancy at which ATT is begun is the factor of paramount importance that chiefly determines the maternal outcomes in pregnancies associated with TB. Other causes which are associated with maternal morbidity and mortality are as follows:

- Anemia
- Poor nutritional states
- Hypoproteinaemia

Effect of Pregnancy on TB

Earlier it was believed that pulmonary cavities resulting from TB were believed to collapse as a result of the increased intra-abdominal pressure associated with pregnancy. This belief was widely held till the beginning of the fourteenth century. A German

physician recommended that young women with TB should get married and become pregnant to slow the progression of the disease. This was practiced in many areas till the nineteenth century.[5] While in the early twentieth century, induced abortion was recommended for these women.[6,7] Hedvall[8] has demonstrated no benefit/adverse effect of pregnancy on TB progression. Frequent, consecutive pregnancies may have a negative effect, as they may promote reactivation of latent TB.

Effects of Chemotherapy on Mother and Fetus

a) Maternal effects

Isoniazid (INH) may cause cutaneous hypersensitivity, hepatitis, peripheral neuropathy. INH-induced hepatitis risk may be 2.5 times higher in prenatal patients as compared to the general population.[1] Rifampicin may cause nausea, vomiting, and hepatitis. Retrobulbar neuritis due to ethambutol and ototoxicity and nephrotoxicity of streptomycin (or aminoglycosides) may get enhanced when used along with other ototoxic or nephrotoxic drugs.

b) Fetal effects

First-line drugs except streptomycin are safe. Congenital deafness has been reported in infants with the use of streptomycin and kanamycin during pregnancy and various birth defects with the use of Ethionamide and PAS.

Fetal Complication

Congenital TB is a rare complication of in utero TB infection while the risk of postnatal transmission is significantly higher.[9] It is a result of hematogenous spread through the umbilical vein to the fetal liver or by ingestion and aspiration of infected amniotic fluid. Primary focus develops in the liver, with involvement of the periportal lymph nodes. The tubercle bacilli infect the lungs secondarily, unlike in adults where over 80% of the primary infections occur in the lungs. Extrapulmonary, miliary, and meningeal TB in mother is high risk factors for congenital TB in neonates.

Diagnosis of congenital TB may be difficult due to similarity with other neonatal or congenital infections especially in the second to the third week of life. These symptoms include hepatosplenomegaly, respiratory distress, fever, and lymphadenopathy. Radiographic abnormalities may also be present but these generally appear later.[5]

Diagnosis

The diagnosis of neonatal TB[10] may, however, be facilitated by employing a set of diagnostic criteria developed by Cantwell et al.[11] including:

- Demonstration of primary hepatic complex/caseating granuloma on percutaneous liver biopsy at birth,
- TB infection of the placenta,
- Maternal genital tract TB,
- Demonstration of lesions during the first week of life.

Possibility of postnatal transmission must be excluded by a thorough investigation of all contacts, including hospital staffs and attendants. As per reports half of the neonates delivered with congenital TB may die, especially in the absence of treatment.[12]

Treatment/Management

- The management of TB in pregnancy is a multidisciplinary approach, with the team comprising the following staff persons

a. Obstetrician
b. Communicable disease specialty personnel
c. Neonatologist
d. Counseling unit
e. Public health officials

Treatment is achieved through the use of Directly Observed Therapy, Short Course (DOTS) which uses a combination therapy for 6 months. For patients with drug-susceptible TB and good drug adherence, these regimens will cure around 90% of TB cases. Treatment is done on outpatient basis, unless otherwise indicated. As per the The British Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the WHO[13,14] first-line anti-TB drugs in pregnancy are considered safe for the mother and the baby.

Prevention of Transmission

Maternal disease and therapy – Vertical transmission from mothers with tubercular pleural effusion or generalized adenopathy does not occur.[14] However, there is a lack of scientific literature regarding increased risk of congenital TB if mothers have resistant TB or concurrent HIV infection. Mothers who have completed ATT before delivery or have received ATT for at least 2 weeks duration before delivery are less likely to transmit the disease to the newborn as compared to untreated mothers.[15]

Prophylaxis[16]

Initiating INH prophylaxis for the neonate depends on factors like history of detection/duration of maternal disease (before, during, or after pregnancy), type of TB (pulmonary or extrapulmonary), and maternal compliance of treatment (regular or irregular). INH prophylaxis is recommended in the neonate if the mother has received treatment for <2 weeks, or those who are on therapy for >2 weeks but are sputum smear positive. The American Academy of Pediatrics (AAP) recommends INH prophylaxis to all neonates of mothers who are diagnosed with TB in the postpartum period and/or after the commencement of breastfeeding has started as these newborns are considered potentially infected. Dose recommended for prophylaxis is 10 mg/kg. The duration of prophylaxis is 6 months in India.

Nutrition and Breastfeeding[16]

Breastfeeding provides nutrition and has immunological benefits and all efforts to continue breastfeeding in newborns with mothers having TB should be made. As per the Malaysian Thoracic Society, in case of maternal sickness, if mother is smear positive at the time of delivery, mothers with multidrug-resistant TB (MDR TB), and when breastfeeding may not be possible, expressed breast milk feeding with personal hygiene should be adopted. As per the WHO, child to be fed under all circumstances, however, close contact with the baby should be reduced.. More research is required on the increased risk of neonatal transmission by breastfeeding in the presence of factors such as infection with resistant organisms (multiple or extensive drug resistance or co-infection with HIV). First-line ATT is secreted in milk in small quantity and causes no adverse effect on the child.

Isolation and Barrier Nursing[16]

Isolation is recommended when mother is sick, non-adherent to therapy, has resistant TB, or received ATT four less than 2 weeks or 3 weeks before starting ATT. Barrier nursing using face mask and appropriate cough hygiene should be adopted by breastfeeding mothers. Hand washing, disinfecting nasal secretions, and baby wipes are also recommended.

Bacille Calmette-Guérin Lymphadenitis

Bacille Calmette-Guérin (BCG) lymphadenitis is a complication of BCG vaccination. In the natural course of time two forms of lymphadenitis may be recognized:

a. Simple or non-suppurative lymphadenitis: It regresses spontaneously over a period of few weeks. Non-suppurative BCG lymphadenitis is best managed with expectant follow ups only, because medical treatment with erythromycin or anti-TB drugs do not hasten the regression or prevent development of suppuration.

b. Suppurative BCG lymphadenitis: Its features are the development of fluctuations in the swelling, with erythema/edema of overlying skin. Healing occurs through spontaneous perforation and sinus formation, followed by closure of the sinus by cicatrisation. Treatment is by needle aspiration to hasten resolution and prevent spontaneous perforation and sinus formation. Surgical excision is rarely needed and is meant for cases of failed needle aspiration or for draining BCG nodes.

Diagnosis of BCG Lymphadenitis

- Chest radiography, Mantoux reaction, and hematological analysis are not helpful.
- Isolated axillary (or supraclavicular/cervical) lymph node enlargement.
- History of BCG vaccination on the same side.
- Absence of tenderness and raised temperature over the swelling.
- Absence of fever and other constitutional symptoms.
- Fine needle aspiration cytology corroborates the clinical diagnosis in doubtful cases.

Management of Newborns

The following are the daily doses (mg per kg of body weight per day) rifampicin 10–12 mg/kg (max 600 mg/day), INH 10 mg/kg (max 300 mg/day), ethambutol 20–25 mg/kg (max 1500 mg/day), pyrazinamide 30–35 mg/kg (max 2000 mg/day), and streptomycin 15 mg/kg (max 1 g/day). There are six weight bands and three generic patient wise boxes are used in combination to treat patients in the six weight bands. In patients with TB meningitis on Category I treatment, the four drugs used during the intensive phase can either be HRZE or HRZS. The present evidence suggests that ethambutol can be used in children. Children who show poor or no response at 8 weeks of intensive phase may be given benefit of extension of IP for 1 more month. In patients with TB meningitis, spinal TB, miliary/disseminated TB, and osteoarticular TB, the continuation phase shall be extended by 3 months making the total duration of treatment to a total of 9 months. A further extension may be done for 3 more months in continuation phase (making the total duration of treatment to 12 months) on a case-to-case basis in case of delayed response and as per the discretion of the treating physician. Under the Revised National Tuberculosis Program (RNTCP), all patients shall be covered under directly observed daily therapy to ensure completion of treatment in every case put on treatment to prevent emergence of resistance, particularly to rifampicin.

Management of Exposed Cases

TB preventive therapy: The dose of INH for chemoprophylaxis is 10 mg/kg administered daily for 6 months. TB preventive therapy should be provided to:

a. All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG or nutritional status.
b. Chemoprophylaxis is also recommended for all HIV-infected children who either had a known exposure to an infectious TB case or are tuberculin skin test (TST) positive (≥5 mm in duration) but have no active TB disease.
c. All TST positive children who are receiving immunosuppressive therapy (e.g., children with nephrotic syndrome, acute leukemia, and so on).

d. A child born to mother who was diagnosed to have TB in pregnancy should receive prophylaxis for 6

months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH chemoprophylaxis is planned.[16]

Conclusion

TB is a leading cause of morbidity and mortality in women of reproductive age in India. The timely diagnosis of TB during pregnancy is of utmost importance to both the mother and the fetus. Strategic efforts to identify and document active TB disease in pregnant and post-partum cases are key steps to successful treatment and program execution. Infertility, poor reproductive performance, recurrent abortions, stillbirths, PROMS, and preterm labor are known effects of TB in pregnancy. The fetus may have intrauterine growth retardation, low birth weight, and increased risk of mortality. Diagnosis by ZN staining, fluorescence staining, and culture in solid as well as liquid automated media like BACTEC, MGIT 960 are microbiological methods. The Cartridge Based Nucleic Acid Amplification Test (CBNAAT) provides rapid diagnosis of infection as well as drug resistance patterns. DOTS under RNTCP is recommended by the Government of India.

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SECTION - III
Emerging Infections

H1N1 (Influenza), Zika, and Ebola Virus Diseases During Pregnancy

H1N1 (INFLUENZA) DURING PREGNANCY

Introduction

Seasonal influenza is caused by a number of circulating influenza viruses such as influenza A HINI, H3N2, H2N2, influenza B. Influenza viruses belong to Orthomyxoviridae family of viruses.

Pregnant women especially those with comorbidity are at increased risk for complications from all forms of influenza virus infections seasonal, zoonotic, and pandemic. Pregnant women appear to be approximately 4–5 times more likely to develop severe disease when compared to non-pregnant individual in general population and risk is highest in third trimester, infants, and young children <2 years with underlying chronic medical illness.[1] Transmission is airborne from person to person through large droplet infection, indirect contact by touching surface, or through direct close contact.

Signs and Symptoms

Spectrum of disease is caused by H1N1 broadly ranges from non-febrile to mild upper respiratory tract infection (URTI) and severe/fatal pneumonia. Symptoms commonly develop within 1 week of exposure and patients are contagious for approximately 8 days thereafter. Main route of transmission of influenza is via droplets that are expelled by speaking, sneezing, or coughing. Depending upon clinical presentation of H1N1 patients are divided into three categories:

Category A – mild symptoms: Fever, cough, sore throat with or without bodyache, headache, diarrhea, and vomiting. Non-pregnant patients no testing is recommended. The patients should be monitored for their progress and re-assessed at 24–48 h by the doctor. Patient should confine at home and should avoid visiting public places. Anti-viral therapy not recommended.

Category B – all categories A symptoms in high risk group: Pregnant women fall under this category. Age <5 and >65 years, comorbid conditions: lung disease, heart disease, liver disease, blood disorders, diabetes, neurological disorders, cancers, HIV/AIDS, and immunosuppressed on long-term steroid therapy. No testing is needed. One should start antiviral therapy. Home confinement and avoid visiting public places.

Category C – category A and B with any of the following: Chest pain, breathlessness, drowsiness, cyanosis, blood-stained sputum. Hypotension, testing is mandatory, admission to ICU, start antiviral therapy.

Complications

Pregnancy-related complications of novel H1N1 infection include: spontaneous abortions, preterm birth, non-reassuring fetal tracings (most commonly fetal tachycardia), and febrile morbidity. Hyperthermia in early pregnancy has been associated with neural tube defects and other congenital anomalies. Fever during labor is risk factor for neonatal seizures, newborn encephalopathy, cerebral palsy, and death.[2–4]

Management

A) Drug Treatment:

Oseltamivir is recommended and safe drug both for prophylaxis and treatment. Dose is 75 mg BD per oral for 5 days. It is safe in pregnancy in all trimesters.[5,6]

Supportive therapy is given as symptomatic treatment in the form of IV fluids, parenteral nutrition, oxygen therapy/ventilatory support. Paracetamol (Tab 500 mg PO 6 hourly) is prescribed for fever, myalgia, and

headache. Salicylates and aspirin are contraindicated. Antibiotics are to be given for treatment of any associated infection.

Chemoprophylaxis

It is recommended for contacts of suspected, probable, and confirmed cases. Contacts include household/social contacts, family members, workplace, school contacts, fellow travellers, and health-care personnel. It is given in dosage – Tab Oseltamivir 75 mg OD for 10 days.

B) Specific Treatment at Time of Presentation:

- Antenatal
  During pandemic of H1N1 influenza infection reduce antenatal visits to minimum. Triaging of influenza patients – having separate area for asymptomatic and severely ill patients. Mechanism should be in place for triaging – signage, posters, and banners should facilitate at arrival of health facility. Single patient room and use of face mask when outside room. Perform diagnostic testing and start empirical antiviral therapy immediately. Do not wait for the test results.
- Intrapartum
  On admission, check for signs and symptoms suggesting influenza infection. Mothers should use face mask throughout labor as tolerated. Protect the infant from exposure to respiratory secretions during or immediately after delivery. Immediately separate newborn to an open warmer by distance of >6 ft. Bathe infant as soon as the temperature is stable. Birth companion should be free of infection.

Postpartum

Temporary separation of the infected mother from the newborn within her room or in a separate room until the risk of transmission is reduced, that is, up to 24–48 h after delivery – in severely ill patient – thereafter mother can start breastfeeds. Patients with mild symptoms – practice rooming in, initiation of breastfeeding within 1 h and exclusive breastfeeding. Discharge criteria – 48 h – short hospital stay in stable patients.

ZIKA VIRUS DISEASE IN PREGNANCY

Introduction

Zika virus disease is an emerging viral disease transmitted through the bite of an infected Aedes mosquito. Zika virus was first identified in Uganda in 1947. Outbreaks of Zika virus disease have been recorded in Africa, America, Asia, and the Pacific.[7] Zika virus disease has the potential for further international spread given the wide geographical distribution of the mosquito vector, a lack of immunity among population in newly affected areas and the high volume of international travel. As of now, the disease has not been reported in India. However, the mosquito that transmits Zika virus, namely Aedes aegypti, also transmits dengue virus, is widely prevalent in India.[8]

Causative Agent

Zika virus disease is caused by Zika virus which belongs to the genre Flavivirus. The reservoir of infection is not known. Zika virus is transmitted to people through the bite of an infected mosquito from the Aedes genus, mainly Aedes aegypti, which usually bite during the morning and late afternoon hours. Transmission from an infected pregnant mother to her baby during pregnancy or around the time of birth is also now being seen as a distinct possibility.[9] The incubation period of Zika virus disease is 2–7 days.

Complications

There is scientific consensus that Zika virus is a cause of microcephaly (abnormally small head, which can be associated with mental and developmental abnormalities in children) and Guillan-Barré syndrome (a neurological disorder manifesting as paralysis).

Management

Diagnosis

Zika virus is diagnosed through polymerase chain reaction (PCR) and virus isolation from blood samples. Positive test result for Zika during pregnancy signals close monitoring and watch by health-care professional. Antenatal ultrasound for growth and development of fetus and look for signs of Zika virus infection during your pregnancy.

Treatment

Zika virus disease is usually relatively mild and requires no specific treatment. People sick with Zika virus should get plenty of rest, drink enough fluids, and treat pain and fever with paracetamol. If symptoms worsen, they should seek medical care and advice.

EBOLA VIRUS DISEASE IN PREGNANCY

Introduction

Ebola virus disease (EVD) (formerly known as Ebola hemorrhagic fever) is a severe, often fatal illness, with a death of up to 90%. The illness affects humans and non-human primates (monkeys, gorillas, and chimpanzees). EVD is a filovirus infection, transmitted to humans from an unknown animal reservoir. Human-to-human transmission efficiently propagates EVD through mucosal contact with infected body fluids. The incubation period is up to 21 days (median 5–9 days); however, transmission is only recognized from symptomatic patients.[10]

Complications

EVD in pregnancy is associated with a high rate of obstetric complications and poor maternal and

perinatal outcomes, including spontaneous abortion, pre-labor, rupture of membranes, preterm labor/preterm birth, antepartum and postpartum hemorrhage, intrauterine fetal death, stillbirth, and maternal death and neonatal death.

Diagnosis

Case Definition of Ebola

- **Suspected case** – Patient having history of travel or close contact with symptomatic persons travelling from Ebola virus disease affected areas in the past 21 days with high grade fever more than 101°F, along with one or more of following symptoms – headache, body ache, abdominal pain, diarrhea, and vomiting.
- **Confirmed case** – A case with above features and laboratory-confirmed evidence of Ebola virus infection at BSL-3 facility by any one of the following: IgM (ELISA), antigen detection, or RT-PCR.

Screening and Triaging of Pregnant Women

Careful clinical and epidemiologic history should be taken from all pregnant women to determine any EVD contact history or EVD signs and symptoms. A higher level of suspicion for Ebola infection should apply to women with the following EVD-associated pregnancy complications.

Treatment

Treatment for EVD-infected patients is supportive with particular focus given to the replacement of electrolytes and fluids and the management of distressing symptoms. Iron supplementation is recommended for all pregnant women in some guidelines.

Mortality rates from EVD in this epidemic are reported to be 50%–70%.[11] Survival is most likely dependent on the adequacy of immune response, as yet unrecognized host factors and the level of supportive care provided. Causes of death remain poorly understood but are likely to be due (in combination or alone) to a process of septic shock and multiorgan failure.[12]

The Ebola virus is able to cross the placenta and infect the amniotic fluid and fetus.[13] Ebola virus is able to survive for prolonged periods within decomposing human tissue, it remains prudent to treat the POC (including a full-term fetus) with full infection control precautions.[14]

Management

Current practice for Ebola confirmed pregnant women has been to manage the infection first, and the pregnancy after the woman has tested NAAT negative. It is considered safer to plan the delivery once viraemia has resolved to reduce the risk of EVD-associated disseminated intravascular coagulopathy (DIC), which may result in greater blood loss during and after delivery.

Safety of Health-care Workers – trained personnel entering high-risk area. Training should focus on the donning and doffing of full personnel protective equipment (PPE) and knowledge of the limits of PPE. The option of termination of pregnancy may also be discussed with the patient at an appropriate time.

Termination of Pregnancy

Use of mifepristone/misoprostol – oral drugs or manual vacuum. Aspiration in the first trimester. Minimal invasive procedure and exposure of health-care worker. All deliveries (at any gestation and whether during or after illness) should take place inside a high-risk area. Intravenous access should be gained at the earliest time, ideally prior to labor.

Fetal monitoring is not required during labor as obstetric interventions are not advised for suspected fetal distress. Surgical delivery for the sake of the fetus is likely to be futile, given the probability of neonatal death. Where surgery is considered for maternal reasons, a multi-disciplinary team should decide on the risks versus benefit ratio, ideally consulting with a medical ethical opinion. Vaginal examinations are not necessary and artificial rupture of membranes should be avoided to reduce the risk of body fluid exposure. Episiotomies and other surgical interventions should not be performed. Vaginal tears should have pressure applied to stop bleeding, but not be sutured. Active management of the third stage is recommended.

Postnatal

Any woman who has survived delivery following EVD infection must be carefully counseled. Lactation is suppressed with medication and is offered contraception at the time of discharge. Lactating EVD survivors whose breast milk is PCR positive or has not been tested should practice good hand and personal hygiene by immediately and thoroughly washing with soap and water after any contact with breast milk.

Management of Pregnant EVD Cases, Contacts, and Survivors

Pregnant women with EVD and pregnant women who survived EVD with ongoing pregnancies and contacts: Comprehensive Ebola IPC precautions must be used during childbirth and/or management of complications to prevent exposure to infectious intrauterine contents (i.e., amniotic fluid, placenta, and fetus). The neonates of such women should also be managed using Ebola IPC precautions for 21 days following birth.

EVD Survivors

There is no evidence that women who become pregnant after recovery from EVD are at risk of EVD transmission. Standard obstetric IPC precautions should be used when exposure to bodily fluids is possible during childbirth and/or management of complications.[15,16]

Prevention and Control

A) Risk of infection with virus and how to avoid it:

For H1N1 – Droplet infection
Pregnant women, new mothers, and newborn infants should avoid crowded public places. Follow respiratory etiquettes while sneezing, coughing, and talking. Hand hygiene, wash with soap and water, alcohol-based sanitizer. Restrict number of visitors. Improve airflow in living area by opening window.

For Zika virus – Vector-borne disease
Reducing mosquitoes through source reduction (removal and modification of breeding sites) and reducing contact between mosquitoes and people. For source reduction of mosquito breeding, it is important to empty, clean, or cover containers that can hold water such as buckets, flower pots, or tyres, so that places where mosquitoes can breed are removed. Personal protection using insect repellent; wearing clothes (preferably light-coloured) that covers as much of the body as possible; using physical barriers such as screens, closed doors and windows; and sleeping under mosquito nets. During outbreaks, spraying of insecticides should be carried out as per guidelines of National Vector Borne Disease Control Programme.[17]

For Ebola virus
Casual contact with asymptomatic patients – no risk. Symptomatic patients – avoid close contact with blood and body fluids.

B) In health-care settings:

Isolation of patient. Strict implementation and adherence to infection control practices. Standard operating procedures to be followed: Health-care workers apply standard precautions consistently with all patients – regardless of their diagnosis – in all work practices at all times. These include basic hand hygiene, respiratory hygiene, use of PPE (according to the risk of splashes or other contact with infected materials), safe injection practices, and safe handling after death of infected patient.

Proper handling and disposal/burial of bio-medical waste including organs and dead body. Comprehensive Ebola IPC precautions as recommended for care of EVD cases should be applied in the management of pregnant women and newborns at risk of EVD transmission which includes full PPE, including head cover, face mask, goggles or face shield, boots, coverall or gown, apron, double gloving with outer elbow length gloves, rigorous hand hygiene, appropriate waste, sharps, and laundry management environmental cleaning, and decontamination.[18,19]

C) In community setting:

Information and education – to spread awareness about H1N1, Zika, and Ebola disease. Dos and Don'ts to prevent spread in community. Avoid travel to affected country or geographic area.[20]

D) Vaccine:

FDA has approved the H1N1 monovalent vaccine as intramuscular injection (inactivated) is recommended and safe in all trimesters of pregnancy. Live intranasal vaccine should not be administered to pregnant women and children >2 years. Vaccination is also recommended for all health-care workers.[21]

Currently there is no vaccine available against Zika virus and Ebola virus disease.

Conclusion

H1N1 infections, Zika virus, and Ebola virus are emerging viral diseases which may alter course of pregnancy and result in poor perinatal outcome. Guiding principles of management are high degree of suspicion for diagnosis, early implementation of infection control, precautions to minimize nosocomial/household spread of disease, prompt treatment to prevent severe illness and death, early identification, and follow up of persons at risk.

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