Congenital Intrauterine Infections
Congenital Intrauterine Infections

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Preface

Congenital intrauterine infections did not receive much attention from Obstetricians, probably because they were not associated with serious maternal complications or immediate neonatal problems. However, since the observations made by Norman Gregg of the association between maternal rubella and congenital cataract in 1941, a spectrum of neonatal and infant problems and sometimes of sequelae developing much later have been traced back to intrauterine events especially during the period of fetal organogenesis.

The previous book by the author focused on the prominent features of four serious and baffling congenital TORCH group of infections. It reviewed basic microbiology and pathogenesis of TORCH syndrome, specific diagnostic approaches in mother and fetus/neonate, therapeutic options and strategies. This book includes most known Maternal Infections which may affect the unborn child, and the pregnancy outcome—the problem, incidence, diagnosis, management and prevention.

This book was conceived because a need was felt to upgrade knowledge, clarify doubts and proffer the advances in Perinatal Medicine on this subject. The main issues that confound the obstetrician and neonatologist are perinatal loss, infectious morbidity and congenital anomalies. Do infections cause recurrent abortions and stillbirths? Are IgG levels in mother a sign of acute maternal infection, and hence, are fetuses at risk? What are the risks to the fetus/neonate after maternal infection at different periods of gestation? How can the fetus be diagnosed as not infected in utero? Most confusing are the laboratory parameters. When in pregnancy should IgG/IgM or both be done? What is the interpretation of a positive or a negative test and how to manage a case with positive result? Is cesarean section required? What are the treatment options and prognosis and what to tell the couple?

At present, the interpretation of laboratory results are quite perplexing, different laboratories give contrasting reports, indicating need for referral laboratories. Of utmost concern for a developing country is whether universal screening should be performed or not. What if the baby is born with Congenital Infection? Medicolegal issues add to the stress. What is the magnitude of the problem in developing countries? These countries have difficulty in collecting reliable and accurate data of perinatal infection, and are more willing to allocate budget in prevention of diseases than for
Congenital Intrauterine Infections
treatment. Vaccines where available should be affordable and the Government should play an important role in enforcing immunization programs by intensive promotion or by legislation.

I hope the book will fill a long-standing void for information on Congenital and Perinatal Infections both for students and teachers of Perinatology.

Deepika Deka
Contents

Section 1: Maternal Fetal Sequelae

1. Clearing Misconceptions—Pregnancy Complications and Miscarriage Due to Maternal Infections 3
   Suneeta Mittal, Nupur Kothari

2. Outcome of Neonates Born with Congenital Infections 15
   Arti Maria, AK Deorari

3. Congenital Infections and Mental Retardation 30
   Madhulika Kabra

4. Intrauterine Infections: Ocular Manifestations 34
   P Vijayalakshmi

5. Congenital Infections and Hearing Loss 54
   Ramesh C Deka, Deepak Sarin, Venkatakarthikeyan C

6. Effects of Genital Tract Infections and Pregnancy Outcome 63
   Nandita Palshetkar, Parul Katiyar, Debchandan Roy

Section 2: Problem-based Approach to Maternal–Fetal Management

7. Avidity Testing to Pinpoint Timing of Maternal Infections during Pregnancy 81
   Sarman Singh

8. Prenatal Treatment of Toxoplasmosis 90
   Alka Kriplani, Biswa Bhusan Dash

9. Strategies for Management of Intrauterine Rubella Infection 102
   Deepika Deka

10. Decision Making in Intrauterine Cytomegalovirus Infection 110
    Anuradha Khar, Kamini A Rao

11. Streamlining Therapy of Pregnant Women with Genital Herpes 119
    Vatsla Dadhwal

12. Parvovirus B19—Fetal Implications and Therapy 128
    Sangeeta Gupta, Amar Bhide
Infections in the pregnant woman are an important cause of fetal and neonatal mortality and morbidity. Fetal and newborn injury causes lifelong morbidity for the survivors, with high emotional costs to the individual and the family plus a heavy economic burden for society. This is timely and relevant. Techniques are now available to prevent, detect, and treat those injuries that result from infection. If instituted, these would have beneficial results for both newborn survival and morbidity. “Congenital infection” commonly refers to transplacentally acquired infection from the infected mother, and can occur at any time during pregnancy. The effects of congenitally acquired infection may be quite different from and more severe than, the effects of the same infection acquired in infants or children (e.g. rubella in children usually results in a mild fever and itchy rash while congenital rubella can result in a baby being born with deafness, cataracts, heart defects or other problems). Most respiratory or gastrointestinal infections are localized, do not infect placenta nor cause significant damage. However, some organisms not only infect the placenta, but also the fetus (transplacental route). Some of these are infections with Toxoplasma gondii (T), Rubella (R), Cytomegalovirus (C) and Herpes Simplex Virus (H) and others (O – varicella zoster—VZV, human immunodeficiency virus—HIV, etc.). They have several clinical features in common and hence given the acronym “TORCH” group of infections. This term has served to increase awareness of a class of organisms that have a relatively benign or even symptomless course in the pregnant woman, but can cause havoc in the transplacentally infected fetus in the form of fetal loss, structural anomalies and developmental defects. Although this collective term suggests that some clinical features are not distinguishable by pathogen, the clinical syndrome
caused by one pathogen generally can be distinguished from infection caused by another pathogen on a clinical basis, authenticated by specific laboratory parameters. TORCH agents cause a varied spectrum of disease.

The World Health Organization is developing rubella and syphilis control strategies for the developing world. Cases of congenital infections are costly to health care systems but can be prevented through antenatal screening and treatment. The evolving European syphilis epidemic has resulted in an increased incidence of infection in reproductive age women and the emergence of cases of congenital syphilis. This reflects a failure of prenatal care delivery systems as well as syphilis control programs.

Placental infection has been implicated in the causation of abortion, preterm labour and still birth in index pregnancy and seroprevalence is higher in women with previous pregnancy loss. However, they do not generally cause recurrent fetal loss.5,6

Perinatal infections with organisms can also be contracted during vaginal delivery, via breast milk or by exposure in the neonatal period. During pregnancy and early labor, the infant is protected from the microbial flora of the mother’s genital tract, but after rupture of the maternal membranes the vaginal microflora can ascend. Colonization of the newborn and of the placenta may in some cases produce inflammation of fetal membranes, umbilical cord, and placenta. Aspiration of infected amniotic fluid or of some viruses present in the genital secretions (HSV, CMV, or HIV) or blood (Hepatitis B virus or HIV) may infect the infant during passage down the birth canal. Colonization of the skin especially abrasions or skin wounds, and mucosal surfaces (e.g. nasopharynx, oropharynx, conjunctiva, umbilical cord, external genitalia) occur. Invasion of the bloodstream may occur through the umbilical cord. Risk factors that predispose to infection are low birth weight, premature or prolonged rupture of maternal membranes, septic or traumatic delivery, fetal anoxia and maternal peripartum infection.

Developing countries have difficulty in collecting reliable and accurate data on perinatal infections, especially because serology is expensive. Magnitude of the problem needs to be studied, and India should prioritize perinatal problems, which may lead to avoiding focusing attention only on TORCH agents.7

**AGENTS CAUSING CONGENITAL INFECTIONS**

**VIRUSES**

CMV, HSV, Erythrovirus (Parvovirus) B19, Enteroviruses, Hepatitis B virus, VZV, HIV, Rubella.
Introduction: Congenital and Perinatal Infections

BACTERIA
Treponema pallidum, Mycobacterium tuberculosis, Salmonella typhi, Listeria monocytogenes, Campylobacter fetus, Borrelia burgdorferi.

FUNGI
Candida albicans.

PARASITES
Toxoplasma gondii, Plasmodium spp., Trypanosoma cruzi.

The more common organisms causing congenital infections include: CMV, HSV, Erythrovirus (Parvovirus) B19, Rubella, Hepatitis B virus, HIV, VZV, Treponema pallidum, Toxoplasma gondii.

AGENTS CAUSING PERINATAL INFECTIONS
The agents responsible for neonatal sepsis are usually found in the maternal birth canal and are the most common causes of neonatal sepsis.

BACTERIA
Common: Streptococcus pyogenes (Group A Streptococcus), Escherichia coli (sepsis, meningitis, pneumonia), Neisseria gonorrhoeae (Ophthalmia neonatorum, sepsis), Listeria monocytogenes, Chlamydia trachomatis (pneumonia and/or conjunctivitis).


VIRUSES
HSV (encephalitis, high mortality rate), Hepatitis B virus (usually asymptomatic, but can have symptoms similar to adults), HIV.

FUNGI
Candida albicans (mucocutaneous - thrush), lung (rare) infections.

PARASITES
Trichomonas vaginalis.
INCIDENCE

The incidence varies geographically and socially. Fetal infection has been reported to occur in up to 10% of pregnancies per year.\(^1\) Perinatal infections account for 2% and 3% of all congenital anomalies. The incidence of maternal infection by CMV and Toxoplasmosis is 2-10/1000 births,\(^8\) about 1% of all newborn infants excrete CMV. Up to 15% of infants are infected with *Chlamydia trachomatis*, of which about 33% develop conjunctivitis and one-sixth develop pneumonia. One to 8 infants per 1000 live births develop bacterial sepsis. Congenital or perinatal infections with HSV, *Toxoplasma gondii*, and VZV occurs in about 1 infant per 1000 live births. Unfortunately, the sequelae of infection with HSV, *T. gondii*, and VZV are usually severe.

In the United States, approximately 85% of women of child bearing age are susceptible to infection with *T. gondii*. An estimated 400-4000 cases of congenital toxoplasmosis occur in the US every year.\(^9\) The incidence is highest in France and Austria. In France, an estimated 44% of pregnant women are regularly checked for seroconversion, and between 5625 and 8850 women are treated during pregnancy every year to prevent congenital toxoplasmosis.\(^10\)

The incidence of congenital CMV infection varies between 0.15% and 2.0% and seems to correlate with the level of preexisting immunity in the population.\(^11\) In Japan, the annual incidence of symptomatic CMV disease is 1.6/100,000 live births.\(^12\) Prevalence of TORCH antibodies in pregnant Thai women was reported to be 15% for *Toxoplasma gondii*, 85-87% to rubella, 79-81% to herpes simplex, 100% to CMV.\(^13\) The risk for fetal CMV due to recurrent CMV was found to be the highest congenital infection. Of TORCH test for fetal medicine indications, only CMV is thought necessary in the United Kingdom.\(^4\)

Rubella and congenital rubella syndrome continue to be important health problems worldwide.\(^14\) The incidence of rubella decreased from 0.45/100,000 in 1990 to 0.1/100,000 in 1999 (ACOG, 2002). In 1989, the US established goal to eliminate indigenous rubella and congenital rubella syndrome (CRS) by 2000. Recently an infant with CRS was born to a mother who had immigrated to the UK, and targeted immunization has been recommended to new arrivals.\(^15\) Screening for primary rubella infection in pregnant women in China showed that it was much more than the sum of patients suffering from poliomyelitis and Japanese encephalitis.\(^16\) Epidemics of rubella still occur, as in Brazil in 1999-2000,\(^17\) Barbados in 1996.\(^18\)
The approximate rate of neonatal HSV infection is 0.1-0.3/1000 live births, of which 86% are natal, 10% postnatal and only 4% congenitally acquired.19

Worldwide, of the 12 million people infected with syphilis every year, two million are pregnant women.20 An estimated 50% of these pregnancies will end in fetal or perinatal death, low birth weight babies or babies born with congenital syphilis. The prevalence of N. gonorrhoeae in pregnancy ranges from 0.5 to 7%, risk factors being early onset of sexual activity, low socioeconomic status, unmarried status, urban dwelling, illicit drug use. C. trachomatis causing trachoma and blindness affects 40% of sexually active women in the developing world incidence in pregnancy has been quoted as varied as 2 to even 35%. Nonbacteriuric pyuria is a risk marker over and above the regular risk markers of STDs. The prevalence of T. vaginalis in pregnancy is 5-15%. Bacterial vaginosis, is a complex alteration of normal vaginal flora such that anaerobes predominate. Concentrations of Gardnerella vaginalis are noted to be 100 to 1000 times greater in women with bacterial vaginosis. Mycoplasma hominis, Bacteroides spp., Mobiluncus spp., Ureaplasma urealyticum, Fusobacterium sp., and peptostreptococci also overgrow in vaginosis.6 Risk factors include presence of T. vaginalis and sexual intercourse, frequent douching and spermicides. The prevalence of acute Hepatitis B disease is 1 to 2 per 1000 pregnancies, while that of chronic disease is 5 to 15 per 1000.

In India, data is scant. TORCH infections (mental retardation + multiple congenital anomalies) were one of the top reasons for referral to genetic clinic.21 Study of a rural population showed that IHA antibodies to toxoplasma was 18%, and 10% children before 9 years. were seropositive suggesting exposure or congenital infection.22 Seropositivity was found in 77% women and 37% men in North India.23 In a study at AIIMS, 12% of infants suspected to have congenital infection had CMV specific IgM antibodies; developmental delay, hepatosplenomegaly were prominent features.24 IgM was detected in 0.6% of all newborns screened at AIIMS.5 One hospital study from Madurai reported 46 CRS infants with sequelae seen between 1993-2001.25 Data from a tertiary referral center in India demonstrated high frequency of primary TORCH infection during pregnancy.26

A study recently carried out at AIIMS by the author found that 17.8% adolescent girls and 20% pregnant women were seronegative, identifying a group of women at risk for primary rubella infection during pregnancy.28
MATERNAL FETAL TRANSMISSION

Transmission varies depending on the organism and the trimester of pregnancy. In the acute (viremic or parasitemic) stage of maternal infection, placental infection is initiated and subsequently fetal infection occurs. Humoral immunity prevents or limits maternal and placental infection for some pathogens such as toxoplasma and rubella, but with CMV and HSV, recurrent episodes of viral shedding may occur. In the first half of pregnancy, the immune system of the fetus is immature, and the fetus also does not benefit from passive maternal immunity, as little or no IgG transfers across the placenta. Hence, immune response to early pregnancy infection is compromised at the critical period of ontogeny resulting in greater fetal injury, likelihood of fetal death or delivery of a symptomatic child.

Some organisms may reinfect a person with waning host immunity more than once—causing fetus to be infected, as in re-exposure of immune mothers to vaccinia, variola, and rubella viruses. Microbes may persist as a chronic asymptomatic infection, again causing fetal disease such as malaria, T. gondii (only when the mother is immunocompromised), syphilis, hepatitis, herpes zoster, and HSV. Congenital CMV and HIV infections have been observed in infants from consecutive pregnancies of the same mother. Acute infection immediately before conception may result in infection of the

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<th>Transplacental delivery</th>
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<td></td>
<td>1st Trim.</td>
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<tr>
<td><strong>Toxo</strong></td>
<td></td>
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<tr>
<td>Primary</td>
<td>10-15%</td>
</tr>
<tr>
<td></td>
<td>(severe)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>60% (4 wks)</td>
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<tr>
<td></td>
<td>25% (5-8 wks)</td>
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<tr>
<td></td>
<td>15% (9-12 wks)</td>
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<tr>
<td><strong>Rubella</strong></td>
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</tr>
<tr>
<td>Primary</td>
<td>30-40% (10% symptomatic, severe=1st and early 2nd trimester)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>0.2-2% (&lt;1% symptomatic)</td>
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<tr>
<td><strong>CMV</strong></td>
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<tr>
<td>Primary</td>
<td>Rare</td>
</tr>
<tr>
<td>Recurrent</td>
<td>40-60%</td>
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<td><strong>HSV</strong></td>
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<td>Primary</td>
<td>Rare</td>
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<td>Recurrent</td>
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- Pregnancy within 3 months of Rubella vaccine (rare - 3.5%)
fetus, and Congenital rubella has been reported where the mother was infected 3 weeks to 3 months before conception.

Untreated first-trimester hepatitis B infections result in 10% transmission to the fetus, whereas third trimester disease results in 80 to 90% neonatal infection. Transmission is usually a result of direct contact with body fluids at the time of delivery; transplacental transmission can possibly occur. The risk of Human papillomaviruses (HPV) transmission to the neonate is less than 1 in 10,000; manifestations may include laryngeal papillomatosis and genital tract or rectal disease. Vertical transmission rates of Chlamydia trachomatis are as high as 60–70%. Inclusion conjunctivitis develops during the first 2 weeks of life in 25–50% of these neonates, whereas another 10–20% develop chlamydial pneumonia within 4 months of birth.

**EFFECTS OF INFECTION OF THE EMBRYO AND FETUS, CONGENITAL TORCH COMPLEX**

Severity of fetal infection by infective organisms and their resultant consequences vary, depending on the virulence of the agent, the susceptibility and gestational age of the fetus, the route of infection, the immune status of the mother (immunocompromised state or immunized to the infection) and lastly, on timely diagnosis and appropriate institution of therapy where possible. The most critical factor in causing fetal infection resulting in fetal disease of varying gravity and prognosis is the time in embryogenesis and fetal development that the fetus is insulted.

Infection of the embryo or fetus can result in: death and resorption of the embryo, abortion and stillbirth of the fetus, and premature birth. Viruses and other difficult to culture organisms have been postulated as the aetiology of a number of obstetric and pediatric conditions of unknown cause, including stillbirth. It is clear that viral agents including rubella, human cytomegalovirus (CMV), parvovirus B19, herpes simplex virus (HSV), lymphocytic choriomeningitis virus (LCMV), and varicella zoster virus (VZV) may cause intrauterine deaths. Modern molecular techniques such as multiplex PCR, allow searches for multiple agents. It has been shown that toxoplasma does not cause recurrent abortions, may be responsible for sporadic abortion.

**Congenital TORCH complex** is described as clinically similar features of jaundice, petechiae, and hepatosplenomegaly - the classic “clinical triad” of TORCH baby. Cutaneous manifestations, including petechiae, purpura, jaundice, and dermal erythropoiesis, are commonly seen in toxoplasmosis, rubella, and cytomegalovirus infections. In herpes simplex virus infections,
Congenital Intrauterine Infections

80% of symptomatic infants show single or grouped cutaneous vesicles, oral ulcers, or conjunctivitis. Extracutaneous signs and symptoms are variable and can be severe. Intrauterine infections are important causes of childhood blindness in both developed and developing countries. Chorioretinal scars are the most characteristic eye manifestation of a congenital or prenatal infection.2

In mother infected with Human Immunodeficiency Virus (HIV), the fetus has a 25% chance of being infected, especially if she has a high viremia, AIDS, or a low CD4+ cell count. Up to 50% of infants get HIV from their mother late in pregnancy or during delivery. Maternal treatment during the last half of their pregnancy, during the birthing process, and treatment of the infant for 6 weeks following delivery can significantly lower transmission. Human immunodeficiency virus (HIV) infection is not associated with a greater risk for congenital malformations or stillbirth, though there appears to be an association, although not strong, between maternal HIV infection and an adverse perinatal outcome.

Parvovirus B19 is a recently recognized congenital infection, though a very common viral infection of children - Erythema infectiosum (Slapped cheek syndrome; fifth disease), infects and lyses human erythroblasts. Seronegative pregnant women can become infected which may be transmitted to the fetus in utero, resulting in fetal death (rare), nonimmune fetal hydrops (uncommon), birth defects (eyes, CNS), and prematurity. Perinatal and intrapartum infections are very rare.

Hepatitis B virus infection can be acquired in utero and perinatally. Though most infections are asymptomatic, they are much more likely to develop into chronic hepatitis and hepatocellular carcinoma. Varicella Zoster Virus rarely causes fetal infection; and fetal death happens if the infection occurs in the 1st or 2nd trimester, while congenital infections can result in eye abnormalities (chorioretinitis, cataracts) and skin scars.

In Varicella infection, risk of congenital varicella infection is greatest when maternal infection occurs in the first or second trimester. Infection in the peripartum period can result in neonatal varicella, and in pneumonitis in the pregnant women.

There is a significant association between maternal mumps in the first trimester and an increased risk of abortion. Measles but not mumps virus infections are linked to an increased premature birth rate.

Congenital syphilis may occur with maternal early infectious syphilis (usually primary and secondary stages) in pregnancy. Infants may be asymptomatic at birth, but by 10–14 days of life develop maculopapular rash and copious nasal discharge, “snuffles.” Other symptoms include
oropharyngeal mucous patches, lymphadenopathy, hepatosplenomegaly, jaundice, osteochondritis, iritis, and chorioretinitis. Prenancy complications are 15-34% incidence of stillbirth (rising to 75% if untreated), 85% pre-maturity, and 20-25% IUGR. It is associated with abortion, preterm delivery, stillbirth, congenital infection, and neonatal death. Syphilis may cause nonimmune hydrops.

Overall, 60-70% of liveborn infants have significant clinical disease.

There is growing evidence that Chlamydia trachomatis and Chlamydia-like organisms - Chlamydophila abortus, Chlamydophila psittaci and Chlamydophila pneumoniae infections may result in adverse pregnancy outcomes—abortion and fetal death.

Malaria can be a severe infection, resulting in spontaneous abortion, preterm delivery, low birth weight, stillbirth, congenital infection, and maternal death.

Perinatal infections can be very subtle and nonspecific such as respiratory distress, lethargy, poor feeding, jaundice, vomiting and diarrhea, hepatomegaly, pneumonitis, purpura, and meningoencephalitis.

Bacterial vaginosis in pregnancy has been associated with preterm birth, chorioamnionitis, premature rupture of the membranes, and postpartum or postabortion endometritis. C. trachomatis infection has been implicated in spontaneous abortion, fetal death, PROM, preterm delivery, and IUGR.

Obstetricians and neonatologists need to be aware of the prominent features of each congenital and perinatal infection rather than to consider them collectively.

**APPROACH TO CLINICAL MANAGEMENT**

The diagnosis of congenital intrauterine infections were earlier made only postnatally, of the symptomatic baby. Knowledge and understanding of the epidemiology, pathogenesis, transmission and sequelae, along with recent advances in ultrasonography, serology and molecular techniques have permitted state-of-the-art prenatal diagnosis and management *in utero* also.

**DIAGNOSIS OF MATERNAL INFECTION**

The most frustrating aspect of prevention of Congenital TORCH is the inability to diagnose maternal infection clinically, since in immunocompetent women it is usually mild or asymptomatic. Some clinical features are described below:
Congenital Intrauterine Infections

Toxo: Asymptomatic/mild malaise, lethargy, lymphadenopathy. Serious in immunocompromised—myocarditis, pneumonitis, chorioretinitis, encephalitis.

Rubella: “3 day facial rash”, post-auricular lymphadenopathy, arthralgia; asymptomatic/flulike symptoms.

CMV: Fatigue, infectious-mononucleosis like symptoms—malaise, lymphadenopathy, hepatosplenomegaly. Immunocompromised: retinitis, esophagitis, colitis.

HSV: Genital ulcers, leucorrhoea, pelvic pain, dysuria, hematuria.

For diagnosis of toxoplasmosis sometimes cytology from fine needle aspiration cytology (FNAC) showing reactive lymphoid hyperplasia, macrophages and epitheloid histiocytes, and Papanicolaou stained smear for toxoplasma cyst with bradyzoites can help. In HSV lesions, Papanicolaou’s, Wright’s or Giemsa’s stain of scrapings from base of the lesions show characteristic intranuclear inclusions and giant cells.

SCREENING AND DIAGNOSIS

Serologic tests are used to diagnose acute infection in pregnant woman and fetus, but false-positive tests occur frequently, therefore, serologic tests must be confirmed at a reference laboratory before abortion or treatment with potentially toxic drugs. In general, IgM production is the acute reaction, followed by IgG in 1-3 weeks. Diagnosis of acute maternal infection is made by seroconversion (IgG -ve mother, now IgG +ve), a fourfold increase in IgG serial titre over 2-3 weeks, or the demonstration of pathogen specific IgM; most labs use ELISA - IgG and IgM.1-3,34,35

In India, rarely is a woman’s serologic status known before pregnancy. Also, it is rare that serum levels can be kept, for paired two samples to be run. Obviously, most important is the ability to pinpoint accurate timing of maternal infection to the exact period of gestation. This is extremely perplexing and sometimes impossible. If accomplished, risk of fetal infection and disease can be approximated so that the couple can be counselled on the need for prenatal diagnosis. Use of less expensive and more accurate serologic tests, reliability and validity studies are lacking.

At present, in India, perhaps screening protocols for TORCH infections should not be done outside research trials, to study magnitude of the problem and cost effectiveness. Attention may be focussed on the high-risk group of women, those with clinical signs and symptoms of suspected TORCH infections, and complications in pregnancy (Table I.2) by specific laboratory
intro
a lot of work and anxiety, but yields little information. Many pregnancies with IUGR are screened for TORCH infections, the yield and cost of such a practice is not justified.

**PRENATAL DIAGNOSIS**

In the case of positive maternal serology, invasive testing for fetal infection and non-invasive ultrasonography are mandatory. It is extremely desirable that these tests are sensitive, specific and accurate, as, not only are the invasive tests of fetal diagnosis associated with slight procedural risks, false abnormal test may lead to abortion of a healthy fetus. An affected fetus may be sought to be treated, which again brings the question of how effective is fetal / neonatal therapy for congenital infections. An abnormal test result is best confirmed in a research, referral laboratory. Thus, interpretation of laboratory results is not just science, it is also an art.

Prenatal diagnosis is now possible with use of ultrasonography (U/S) and ultrasound guided procedures of amniocentesis, chorionic villus sampling and cord blood sampling for accurate diagnosis of fetal infection present or absent by sophisticated laboratory testing. Most affected fetuses appear sonographically normal, but serial scanning may reveal evolving findings. When abnormalities are detected on ultrasound, a thorough fetal evaluation

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**Table 1.3: Indications for maternal TORCH screen during pregnancy**

1. Clinical signs and symptoms of maternal TORCH infection—fever, fever with skin rash, exposure/contact (A significant “contact” is defined as being in the same room for over 15 minutes, or face-to-face contact).
2. Lymphadenopathy, unexplained hematological dyscrasias, other signs/symptoms.
3. Ultrasound evidence of markers for congenital TORCH.
4. ? IUGR, oligohydramnios, polyhydramnios.
5. Screening (routine/targeted in high-risk group), pre-conceptional, early first trimester booking HSV in third trimester/labor (? In India, data lacking. Not done in UK, USA).
6. Pregnant women at high risk for TORCH infections:
   - Toxoplasma—Exposure or consumption of raw meat, failure to wash home garden products, exposure to a recently weaned out-of-doors kitten or an ill cat, immunocompromised.
   - Rubella—Rubella nonimmune, R exposure
   - CMV—High-risk sexual behavior, STD, occupational exposure, blood transfusion
   - HSV—High-risk sexual behavior, history of STD, drug abuse, high-risk populations

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is recommended because of multiorgan involvement. However, by the time structural anomalies are visible on U/S, fetal organ damage is considerable and this is an important factor in decision making.

**FETAL THERAPY**

It depends on the infection. Strategy for specific management of each case needs to be planned, and parental counselling has to be done taking into consideration extent of fetal damage, options for therapy and anticipated prognosis. Rapid progress has recently been encountered in pharmaco-logically treating the unborn baby. Medical termination of pregnancy is still a very important management option in documented fetal infection especially with ultrasound evidence of organic disease. Prenatal antibiotic therapy significantly reduces the rate of sequelae among infected infants if started early.

Deciding the mode of delivery for pregnancy with active or suspected maternal HSV infection is crucial and cesarean section improves prognosis significantly. Suppressive acyclovir therapy reduces need for cesarean for recurrent herpes in women whose first episode genital herpes occurs during pregnancy (none of 21 treated versus 9/25 on placebo).

No specific therapy for congenital rubella or CMV infection has been established, so treatment is primarily supportive.

Congenital syphilis requires treatment with penicillin. Giving HIV positive pregnant women ART during pregnancy and delivery followed by treatment of the newborn significantly lowers the chances the newborn will be infected.

**NEONATAL MANAGEMENT**

Despite advances in prenatal diagnosis and therapy, a large number of congenitally infected babies are born worldwide. Prompt diagnosis and institution of therapy for herpes disease, toxoplasma and CMV disease is very crucial. However, neonatal morbidity and mortality is high and most symptomatic babies have grave consequences-neurological, organic and developmental problems, requiring rehabilitative measures. The eyes of newborns should be treated with erythromycin to prevent ophthalmia neonatorum. Meningitis due to various bacteria during delivery also can be treated with appropriate antibiotics. Some serious viral infections can be treated with antiviral agents (ganciclovir for CMV and HSV infections). Antifungal or parasitic agents may be required to treat infants infected by fungi or parasites.
Discouraging breastfeeding of the newborn in HIV (especially symptomatic mothers and mothers with low CD4 T cell counts) and Hepatitis B infected mothers will lower the child's chances of being infected following birth. Passive HB immunization is 85 to 95% effective in preventing perinatal transmission.

**PREVENTION**

Human immune serum globulin can be given to seronegative pregnant women exposed to rubella, varicella, measles, or hepatitis A virus. Proof of efficacy is undetermined and the immune serum globulin may not protect the fetus.

Health education and counseling may have profound impact as seen in France, where toxoplasmosis prevention strategies by application of simple hygienic measures during pregnancy have drastically reduced congenital toxoplasmosis by 60%.\textsuperscript{47,48} Vaccines need to be developed, the rubella vaccine has shown how CRS could be significantly controlled.\textsuperscript{37,49} Data indicate that preexisting immunity to CMV infection in the mother does not mitigate the outcome of congenital infection. Moreover, live vaccines may bear serious risk when transmittable to the fetus.\textsuperscript{11} Immunizations for Rubella, Hepatitis, and VZV should be given to women thinking of trying to become pregnant if they are seronegative. Live viral vaccines should be given 3-6 months before conception, appropriate preconception health care improves pregnancy outcomes. Women should be counseled on ways to prevent TORCH infections.\textsuperscript{50}

Lastly, knowledge, attitudes and practices of Obstetricians and Neonatologists on infections is important in reducing the burden of congenital infection.\textsuperscript{51} Survey of American College of Obstetricians and Gynaecologists (ACOG) (representative group known as the Collaborative Ambulatory Research Network (CARN) and randomly sampled fellows in the USA about toxoplasmosis showed that although the incidence of toxoplasmosis is low in US, up to 6000 congenital cases occur annually, 7% (CARN 10%, random 5%) had diagnosed one or more cases of acute toxoplasmosis in past year. Respondents were well informed about how to prevent toxoplasmosis. Most (CARN 70%, random 50%) were opposed to universal screening. However, only 12% (CARN 11%, random 12%) indicated that IgM test might be false-positive, and only 11% (CARN 14%, random 9%) were aware that FDA sent an advisory to all ACOG members that some Toxo IgM kits have high false-positive rates.\textsuperscript{52}
<table>
<thead>
<tr>
<th>Etiological agent</th>
<th>Diagnostic test</th>
<th>First visit</th>
<th>Third trimester</th>
<th>At delivery</th>
<th>Management</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>PPD</td>
<td>+</td>
<td></td>
<td></td>
<td>ATT</td>
<td></td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>Culture</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Serology</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Antigen</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Serology</td>
<td>+</td>
<td>+</td>
<td>+ (high prevalence areas)</td>
<td>Antibiotics</td>
<td>Avoid sexual intercourse with infected partner</td>
</tr>
<tr>
<td>Rubella</td>
<td>Serology</td>
<td>+</td>
<td></td>
<td></td>
<td>Prenatal diagnosis</td>
<td>Prepregnancy, Postpartum vaccine avoid exposure</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Examination culture</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cesarean section</td>
<td>Avoid contact</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acyclovir</td>
<td>Avoid sexual intercourse with infected partner</td>
</tr>
</tbody>
</table>

**Special care if exposed, in high risk group, or with clinical signs**

<table>
<thead>
<tr>
<th>Etiological agent</th>
<th>Diagnostic test</th>
<th>First visit</th>
<th>Management</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Serology</td>
<td>+</td>
<td>ART</td>
<td>Avoid sexual intercourse with infected partner</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Ultrasound, serology</td>
<td></td>
<td>Intrauterine transfusion</td>
<td>Avoid contact</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Serology, PCR culture (amniotic fluid, fetal blood)</td>
<td></td>
<td>Therapy prenatal diagnosis</td>
<td>Avoid eating raw or undercooked meat, contact with cat feces</td>
</tr>
<tr>
<td>VZV</td>
<td>Cytology</td>
<td></td>
<td>VZIG therapy</td>
<td>Avoid contact</td>
</tr>
</tbody>
</table>
Since 1984, the World Health Organization (WHO) European Region has had targets for reducing the burden of a number of communicable diseases. The cultural and economic diversity of the region, as in India, present a number of challenges that must be overcome before the regional targets are met. These include social factors, political will, economic costs associated with supplementary campaigns, and more effective communications with health professionals and the public, on the benefits and risks associated with immunizations. Vaccines where available, should be affordable and effective prevention guidelines should be workable in poorer nations. India needs to collect reliable and accurate data of perinatal infections, prioritise and tackle those that have serious public health problems and socioeconomic impact.

**IMPORTANT POINTS**

1. Management of mothers likely to have congenital infections is before pregnancy begins, because this is the best time for preventive measures.
2. Maternal infections may be symptomatic, mild or symptomless.
3. Maternal infection may not always result in fetal infection. The first trimester is usually the most dangerous time for the mother to acquire these infections, because there is a greater risk of the fetus being affected.
4. Congenital fetal infection may be of varying severity and extent of organs affected. Seriousness of fetal damage depends on: period of gestation at attack, more severe in early pregnancy (T,R,C), early pregnancy and labor (H), severity/load of maternal infection, immune status of mother and early institution of maternal/fetal/neonatal therapy.
5. TORCH panel should not be done to investigate recurrent fetal loss, or recurrent malformations. May be done to evaluate one fetal loss or malformations probably due to primary acute infection.
6. Screening for hepatitis B is recommended for all pregnant women at the initial antenatal visit.
7. For women at high-risk of syphilis and in populations with a high prevalence of syphilis, additional serologic testing at 28 weeks’ gestation and at delivery is recommended.
8. **TORCH serologic screen** should be done for targeted high-risk group only. Routine screening for TORCH infection in India not justified (data on prevalence of primary infection during pregnancy and cost effectiveness lacking). Not done in UK, USA.
i. Protocol in France/Austria for Toxo:
   • Pre-conception or early first trimester booking serology
   • If seronegative, repeat for seroconversion monthly or at end of every trimester.

ii. No use for first screen at late second/third trimester of pregnancy.

9. IgM antibody is a feature of acute infective reaction followed by IgG in 1-3 weeks. Acute maternal infection is present when there is seroconversion, fourfold rise of IgG over serial titres 2-4 weeks apart, presence of IgM antibody.

10. Serological methods should be confirmed at referral laboratory because IgM kits may be false-positive. Interpretation needs expertise to pinpoint time of maternal infection. IgG positive means woman has earlier had the infection or has been vaccinated. She is not at risk for toxo or rubella, but reactivation/recurrence of CMV and HSV may occur. Congenital infection after recurrent or reactivated maternal infection (CMV, HSV) is usually low and not severe or asymptomatic.

11. Counseling and prenatal diagnosis for in utero fetal infection can be done by ultrasonography for infection markers, chorionic villus sampling, cord blood sampling.

12. Severity of fetal infection is difficult to predict, but early pregnancy infection, heavy viral load and presence of ultrasound abnormality, augurs poor prognosis, and termination of pregnancy should be considered.

13. There is no therapy for fetal rubella and CMV. Early diagnosis and treatment of toxoplasmosis, and HSV (third trimester/labor) in mother and newborn improves prognosis.

14. Cesarean section is very effective in prevention of neonatal HSV in presence of active herpes simplex; it is not indicated for CMV.

15. Vaccination for rubella should be given to all females at 18 months and booster at 12 years. If non-immune, 3 months before planning conception, or if yet non-immune, postpartum. HBIG within the first 12 hours of birth, followed by active immunization with hepatitis B vaccinations is effective in preventing perinatal hepatitis B transmission.

16. Knowledge, awareness and practices of Perinatologists is very important in reducing burden of Congenital or perinatal infections. Political will and more effective communications with health professionals and the public on preventive and immunization programmes are needed in India. Data is needed on congenital infections during pregnancy / labor and in newborn / children (to prioritise and tackle those that have public health problems and cause socio-economic loss) and on cost effectiveness of screening, prenatal diagnosis and therapy.
REFERENCES

Introduction: Congenital and Perinatal Infections