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A review on TORCH: groups of congenital infection during pregnancy

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Abstract

TORCH, includes Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19, Hepatitis B), Rubella, Cytomegalovirus (CMV), and Herpes infections are some of the most common infections associated with congenital anomalies. Most of the TORCH infections have serious fetal consequences and there has no impact on fetal outcome. In the present article, we wanted to discuss about the causative agents/organism, mode of infection, symptoms, treatment, vaccination, available molecular biological techniques and public awareness regarding this infection.

Keywords: TORCH, Mode of infection, Diagnosis, Treatment.

Introduction

TORCH is an acronym which stands for Toxoplasmosis, Other (Parvovirus B19, Varicella-Zoster virus infection, Syphilis, Hepatitis B), Rubella virus, Cytomegalovirus infection and Herpes Simplex virus infection. These groups of infections are the main threats of serious congenital infection during pregnancy, which may ultimately cause fetal damage or other anomalies. In most cases, the infection can be severe enough to cause serious damage to a fetus than his/her mother. The gestational age of the fetus influenced the degree of severity.[1] The placenta forms a barrier between mother and fetus during the first trimester of pregnancy that protects the fetus from the humoral and cell mediated immunological response. Although, the fetus gets immunity from mother, they are seriously infected by these viruses due to lack of immunity after the first trimester of pregnancy. All the infections have their own causative agent and generally they spread through poor hygienic conditions, contaminated blood, water and soil and airborne respiratory droplet. Primary infection can damage more than the secondary or reactivated infection. Basically, each causative agent has distinct manifestation but some are common. It will be dangerous, if a fetus show microcephaly, intracranial calcifications, rash, intrauterine growth restriction, jaundice, hepatosplenomegaly, elevated transaminase concentrations and thrombocytopenia.[2] Some specific symptoms of these infections are tabulated in Table 1. Specific techniques have been discussed for detection of this disease in Table 2. The common cause of contamination of this disease has also been described in Figure 1. In the present article, we wanted to discuss about the causative agents/organism, mode of infection, symptoms, treatment, vaccination, available molecular biological techniques and public awareness regarding this infection.

Table 1: Specific symptoms of TORCH Disease

Symptoms	Organism
Intracranial Calcification	CMV, Toxoplasmosis
Cataracts	Rubella, HSV
Chorioretinitis	Toxoplasmosis, CMV
Bone lesions	Syphilis, Rubella
Blueberry muffin lesions	Rubella
Microcephaly	CMV
Hydrocephalus	Toxoplasmosis
Vesicles	HSV, VZV, Syphilis

Table 2: Specific techniques for detection of TORCH disease

Torch diseases	Serology	Culture	Histopathology	PCR technique
Toxoplasmosis	-	++++	+	+
Rubella virus infection	-	++++	+++	+++
Cytomegalo virus infection	++++	+	-	+
Herpes simplex virus infection	+/-	+++	-	+
Syphilis infection	+++	+	-	+

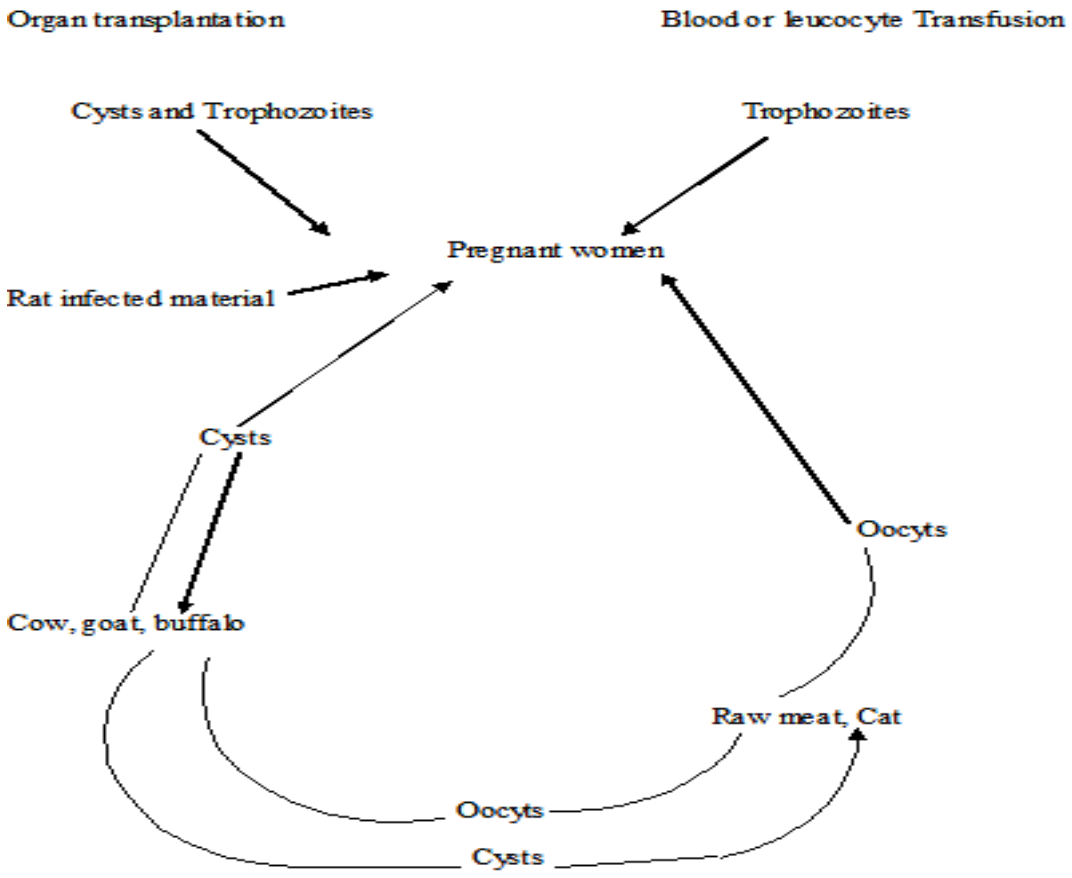

Figure 1: Cause and occurrence of TORCH disease

Toxoplasmosis Infection

Causative organism: Toxoplasmosis is usually a benign anthropozoonosis[3], caused by *Toxoplasma gondii* (*T. gondii*), an obligate intracellular protozoan.

Mode of infection: *T. gondii* is transmitted through the fecal matter of cat, eating raw meat, contaminated water and soil, and unpasteurized goat milk.[2] The parasites cross the placenta and infect infants. Congenital toxoplasmosis is usually not apparent at birth and about 70-90% of infants develop the serious clinical illness in adulthood.[1] Although, three different types of strain have been found in different species such as type I, type II, and type III, but in human, type I and type II are found in active form whereas type III is found in animals.[4]

Symptoms: Only 10-15% infant shows clear symptoms such as skull and encephalic anomalies, neurological afflictions, intracranial calcifications and eye anomalies. Moreover, only 5% infants have severe complications like thrombocytopenia, anemia, jaundice, hepatomegalia, maculopapular rash, CNS sequelae. The classic triad hydrocephalus, chorioretinitis, and intracranial calcifications reported very rare.[3] Fetuses infected in the third trimester are often asymptomatic at birth.[2]

Diagnosis: When a woman has infected with a pathogen during pregnancy, the normal immune response results in the production of IgM (Immunoglobulin M) antibodies followed by IgG antibodies. IgM antibodies against TORCH organisms usually persist for about 3 months, while IgG antibodies remain detectable for a lifetime, providing immunity and preventing or reducing the severity of reinfection. Thus, if IgM antibodies are present in a pregnant woman, a current or recent infection with the organism is predicted.[4] The causative organism can be isolated from placenta, serum, and cerebrospinal fluid.[2] Diagnostic testing for the causative organism in the fetus, whose mother has evidence of acute infection, can be performed more precisely as early as within 18 weeks of gestation using polymerase chain reaction (PCR) amplification of the B1 gene of *T. gondii*. Specific diagnostic tests like differential scanning calorimetric (DSC), IgM enzyme linked immunosorbent assay (ELISA), IgM immunosorbent agglutination assay (ISAGA), and anti P30 IgM were also performed to detect the causative organism.[3] Calcifications can be detected by the computed tomography scanning (CT scan) of the head. Elevation of protein level and pleocytosis can be seen in the cerebro-spinal fluid during toxoplasmosis.[2] Rising level of IgG and IgM antibodies in cord or neonatal sera also indicates the toxoplasmosis infection.

Treatment: After early detection, the mother can be treated with spiramycin (1500 mg every 12 hours) to prevent fetal infection. If the fetus is found to be infected, the treatment is changed to combination of pyrimethamine and sulfadiazine. This combination drugs may be recommended along with supplements of folinic acid to prevent the bone marrow suppression caused by pyrimethamine and sulfadiazine.[1]

Health education: Public awareness on proper maintaining of hygienic conditions is very important for the prevention of this infection. Women, who are planning to become pregnant, must be tested routinely. Other important parameters which will be considered for the prevention of this infection, such as eating properly cooked meat, wear gloves, wash hands with warm water along with soap after handling soil, and avoid handling cats or new kittens.[2]

Others Infections

Syphilis Infections

Causative organism: It is caused by gram negative spirochete *Treponema pallidum* (*T. pallidum*).[2] It has 100% vertical transmission ratings.[1]

Mode of infection: It is spread through direct contact with a spirochete containing lesion, sexually, or transplacentally.[2] Syphilis affects pregnant women in three stages:

(a) *Primary stage* – appearance of the syphilitic chancre and lymphadenitis.

(b) *Secondary stage*- rash on the hands and feet even after 2-10 weeks of chancre heals.

(c) *Tertiary stage*- neurological, cardiovascular, and gummatous lesions (granuloma of the skin and musculoskeletal system).

Congenital syphilis transmitted from mother to her children, those have primary and secondary stages of the disease rather than tertiary stage. Congenital syphilis can be divided into two phases: early disease (before two years) and late disease (after two years).[1]

Symptoms: Early manifestation could be hemorrhagic nasal discharge ("sniffles"), hepatosplenomegaly, jaundice, increased liver enzymes, lymphadenopathy, hemolytic

anemia, thrombocytopenia, osteochondritis and periostitis, mucocutanous rash, central nervous system abnormalities, failure to thrive, chorioretinitis, nephritis and nephrotic syndrome, parrot's pseudoparalysis.[6]

Late manifestations have signed such as Hutchinson teeth (small teeth with an abnormal central groove), mulberry molars (bulbous protrusions on the molar teeth resembling mulberries), hard palate perforation, eighth nerve deafness, interstitial keratitis, bony lesion, and saber shins (due to chronic periosteitis).[2]

Diagnosis: Diagnosis of syphilis can be performed using dark-field microscopy or detected using direct immune-fluorescence assay of the collected sample taken from lesions, placenta or umbilicus. A presumptive diagnosis is made using nontreponemal and treponemal tests. Non-treponemal tests included the venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests; and the treponemal tests, included the fluorescent treponemal antibody absorption (FTA-ABS) assay and the microhaemagglutination assay for *T. pallidum* antibody (MHA-TP).[7] Treponemal tests should not consider alone when false positive results have been shown by some other infections such as Lyme disease, yaws, pinta, and leptospirosis. Sometimes a false negative result may also be seen due to excessive antibodies known as "Prozone" effect.[2] New diagnostic methods such as enzyme immunoassay (EIA), polymerase chain reaction (PCR), and immunoblotting are used; they have greater sensitivity and specificity. EIA based on the antibody capture method utilizing (recombinant) treponemal antigen is commercially available. One such kit, the Captia Syph-G (Mercia Diagnostics, Guildford), which detects treponemal IgG, has sensitivity of 100% and a specificity of 99% when testing pregnant women.[7]

Treatment: In general, treatment of congenital syphilis requires a 10 days course of Penicillin (aqueous penicillin-G 100000 to 150000 units/kg/24 hours). Proper treatment of the mother leads to eliminate the risk of infection of infants. The infected infant should be followed up routinely until nontreponemal test reported negative.[3] In a study involving 204 pregnant women with primary, secondary, or early latent syphilis, a single intramuscular dose of benzathin penicillin, 2.4 million units prevented fetal infection in 98% of the cases. In this study the only treatment failure of maternal infection occurred in an HIV positive woman.[7]

Varicella-zoster virus Infection

Causative organism: It is a member of the herpes virus family.

Mode of infection: This virus transmitted through direct physical contact, airborne contact with droplets of respiratory secretions. A newly infected person is contagious from 1 to 2 days before the onset of rash. The average incubation period for varicella is 14 to 16 days (range 10–21 days). After the primary infection resolves, the virus enters the latent phase and remains dormant in the thoracic sensory ganglia. Reactivation may occur along the sensory dermatome to cause herpes zoster, or "shingles".[8]

Symptoms: Herpes zoster during pregnancy has been observed very rarely (one cases in 200000 pregnancies).[3] Only 2% of fetuses whose mother have infected with this virus in first 20 weeks of pregnancy will develop varicella zoster virus embryopathy.[1]

Various maternal symptoms such as chiken pox or "shingles" rash, haemorrhagic chickenpox, viral pneumonia, meningitis, encephalitis and various fetal symptom such as limb hypoplasia, paresis, microcephaly, hydrocephalus, microphthalmia, duodenal stenosis, jejuna dilatation, microcolon, atresia of the sigmoid colon, cicatricial lesions of skin/hypoplasia of tissues in a dermatomal distribution, cataracts, chorioretinitis, seizures, hypotonia, hypo-reflexia, encephalomyelitis, dorsal radiculitis, Homer's syndrome, bulbar dysphagia, nystagmus, anisocoria, corneal opacities, enophthalmia, hypoplasia of the optic discs, optic atrophy, squint, gastro-esophageal reflux, anal sphincter malfunction, neurogenic bladder, and micrognathia have been observed during infection .

Diagnosis: Polymerase chain reaction can be used to detect the viral DNA in tissue sample.[1] In cord blood sample of the infected infants, VZV specific IgM and IgG antibody can be easily detected.

Treatment: In case of severe maternal infection, antiviral agent acyclovir can be used for treatment. Varicella zoster virus immunoglobulins (VZIG 125 IU) used in combination therapy with acyclovir for the fetal infection.

Hepatitis B Infection

Causative organism: It is a DNA containing virus belonging to hepadnavirus family.[2]

Mode of infection: Most infants are infected through contaminated blood or body fluids during delivery. Intracellular HBV is not cytopathic. It replicates in

hepatocytes and interferes with hepatic functions. In order to counter attack the virus, the cytotoxic T cell is activated to fight against the HBV protein-producing cells. This results in inflammatory reaction and cellular damage.

Symptoms: Morbidity due to HBV is inversely proportional to the gestational age. If the gestational period at the time of acute infection increases, risk of chronic infection decreases. Chronic infection with HBV may lead to hepatocellular carcinoma or cirrhosis.[2]

Diagnosis: If a mother diagnosed with positive HBV surface antigen that show mother has an acute or chronic infection. Infant of an infected mother should be given combination of HBV vaccine and hepatitis B immunoglobulin within 12 hours of birth.[2]

Treatment: However, there was no specific treatment available for acute HBV, Lamivudine is recommended for chronic HBV in children above 2 years of age.

Parvovirus B19 Infection

Causative organism: It contains single stranded DNA as genetic material. It causes Erythema infectiosum (slapped cheek disease) in childhood.

Mode of infection: Infection is transmitted through air and contaminated blood. Infection of a negative mother occurs due to contact with children having Erythema infectiosum infection.

Symptoms: Maternal infection can lead to miscarriage and nonimmune hydrops fetalis development. Massive edema, pleural and pericardial effusions and peritoneal spaces characterize hydrops fetalis. In the fetus, virus interrupts the production of RBC thus leads to anemia, which causes cardiac arrest.[1]

Diagnosis: For routine diagnosis, the sociological investigations of amniotic fluid, fetal blood or tissue of the infant will be carried out using ELISA and RIA methods. If Mother is serologically positive for specific B19 antibodies are prone to infection. Ultrasound technique can also be performed to detect the development of fetal hydrops.[1]

Treatment: however, there is no specific treatment for B19 virus infection; intravenous immunoglobulin may be beneficial for the same.[1]

Rubella Infection

Causative organism: Rubella or German measles is a member of Togaviridae family. They are present with envelope and Icosahedral capsid, and have RNA as genetic material.[5]

Mode of infection: It is transmitted through direct contact or airborne droplets from the respiratory system. Its incubation period is about 2-3 weeks and is contagious.[1] Rubella virus enters into mother's body, spreads through blood, placenta, and infects the fetus (Webster 1998). Occurrence of infection in various stages of pregnancy is follows:

- 90% in first 11 weeks of pregnancy
- 50% in 11-20 weeks of pregnancy
- 37% in 20-35 weeks of pregnancy
- 100% in last month of pregnancy

Symptoms: During infection, mother feels various symptoms such as fever, malaise, urinary tract infection (URTI), lymphadenopathy (sub occipital), and conjunctivitis. Forchheimer's spots, maculopapular rash (rarely purpuric), Rubelliform rash (1-3 mm in diameter), arthralgia, arthritis, encephalitis, thrombocytopenia, haemorrhagic manifestations, neuritis, orchitis etc. Infant shows symptoms such as microcephaly, micrognathy, cleft lip/palate, encephalocele, anencephaly, hepatic calcifications, branch pulmonary artery stenosis, patent ductus arteriosus, ventricular septal defects, coarctation of the aorta, ocular cataracts, microphthalmia, glaucoma, pigmentary retinopathy, microphthalmos, hearing defects, purpuric skin lesions (blueberry muffin skin), anaemia, hepatitis etc.[6.]

Diagnosis: The diagnosis of infection can be carried out using a virus, isolated from nasopharyngeal secretion and detect the presence of specific IgM using HAI, Nt test. The IgM level can be estimated on the 23rd week of pregnancy. Some techniques such as the RNA probe and PCR are also used to detect the virus in amniotic fluid or chorionic villi.[3]

Health education: Vaccination is the best way of the prevention of infection in the women 28 days before conception. However, vaccine is not recommended for pregnant women, breastfeeding women may be vaccinated. Those women who are non-immune to rubella should avoid the infected person.[6]

Cytomegalovirus Infection

Causative organism: CMV is the member of herpes virus family, most common congenital infection in United State.[2]

Mode of infection: It is transmitted to an infant during pregnancy, ingestion of infected human milk, direct contact with urine and saliva.[2] It is easily spread in day care centers and family having many young children. Due to endogenous reactivation of virus, it can cause severe illness in the transplant recipient immunosuppressed patients.[2]

Symptoms: About 90% of primary infection are asymptomatic in mother and showed complications like fever, fatigue, myalgia, hepatitis, lymphadenopathy.[6] Infants showed various complications such as optic atropy, microcephaly, hypotonia, intracranial calcifications, and decrease hearing, pneumopathy, thrombocytopenic purpura.[1] If the mother has a primary infection during pregnancy, fetal morbidity rate is high.[6]

Diagnosis: Body fluids such as urine and pharyngeal secretions in the first three weeks after birth are very important for the detection of this virus. After 3 weeks of birth, it will be very difficult to differentiate between congenital and postnatal infection.[6] PCR technique is very frequently used for detection of this virus. Patients with congenital CMV infection are more likely to experience postnatal seizures. The reported frequency of postnatal seizure ranged from 10 to 56% in children with symptomatic congenital CMV infection whereas the rate was 0.9% in patients with asymptomatic congenital CMV infection.[7]

Treatment: However, various antiviral drugs are commonly used for treatment of non-specific infection, intravenous ganciclovir are used to treat congenital infection. New oral antiviral ganciclovir, valganciclovir, have promising effect to control the infection.

Herpes simplex virus Infection

Causative organism: They are member of herpesviridae family containing double stranded DNA. It is found in two forms HSV 1 and 2. HSV1 causes gingivostomatitis, pharyngitis, and not very often in genital infection but HSV2 mainly involve in the genital herpes.

Mode of infection: Infection with this virus occurs primarily through direct contact with infected lesions. Neonates acquire infection through an infected vaginal canal during birth. Postnatal infection can be spread through infected persons kissing or touching the infant.

Symptoms: About half of the women having primary infection are asymptomatic. About 20% mothers show symptoms like vulvovaginitis and cervicitis. About <30% of cases present with characteristic vesicular and ulcerated genital lesions. Infants show complications like-

(a) *Skin lesions:* vesicles, vesiculobullous, ulcer, pustular, erythematous, and scarring.

(b) *CNS lesions:* calcification, encephalomalacia, ventriculomegaly, microcephaly, hemorrhage, seizures, meningoencephalitis, and hypertonia/spasticity

(c) *Eye lesions:* keratoconjunctivitis, chorioretinitis, cataracts, retinal detachment.[6]

Diagnosis: Diagnosis can be carried out by taking the sample of urine, saliva, nasopharyngeal secretions. The person considers to be infected, if the result of serum HSV IgM, HSV PCR of the CSF or HSV culture of lesions comes positive. PCR of CSF may come negative in the first 5 days of infection. Skin, eye and mouth infection can be easily detected in 24-36 hours by viral culture.

Treatment: Intravenous acyclovir (20mg/kg) given for 14-21 days and blood cells count should be monitored during treatment schedule. Adequate hydration also requires minimizing kidney complications.

Advances in Diagnosis: Recently, new diagnosis method Protein microarray has been introduced. ELISA-based test and culture-based tests are time-consuming process and require large quantities of both samples and reagents, thus. After development of miniaturized, chip-based, microarray methods permit measurement of many analysts in the same small. This assay method permits many different analysts to be simultaneously determined, more sensitive and rapid than conventional system. Tissue microarray (TMA) technologies are particularly suited to diagnose due to it require small sample volumes. Microarray-based DNA analysis technologies used to track the activity of thousands of genes at once.[8-10]

Conclusion

On the basis of above review article TORCH disease is an intrauterine infection can cause congenital malformations like central nervous system, resulting in neurological abnormalities, visual impairment and deafness, in addition to other malformations, such as congenital heart disease.

Due to infection with many organism diagnoses and treatment is very difficult. Hydrocephalus, Intracranial calcification and Chorioretinitis are specific symptoms of the infection of Toxoplasmosis. The infection like toxoplasmosis can be treated with pyrimethamine but its use is limited due to teratogenic nature. In the rubella infection blueberry muffin lesions are specific symptoms, but it can be treated with vaccines. In the future there will be many more vaccines, treatment options and sophisticated diagnostic tools for TORCH disease. During the pregnancy all the drugs are not safe so in the time of treatment specific precaution should be taken. Avoid the drugs which have teratogenic activity. After advancement in the molecular technology, there will be more vaccine available. Generally vaccines are safe during pregnancy. Introduction of Genetics has been very useful tool in the TORCH disease. PCR techniques, DNA recombinant technology, Isolation of virus from the sample will be more useful in the future. Awareness about this disease in the people should be regularly done by health workers.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Boyer SG and Boyer KM. Update on TORCH Infections in the Newborn Infant, Newborn and Infant Nurs. Rev. 2004; 4: 70-80.

2. Pizzo JD. Focus on Diagnosis: Congenital Infection, Ped. in Review 2011; 32: 537-542.

3. Chiodo F, Verucchi G, Mori F, Attard L and Ricchi E. Infective diseases during pregnancy and their teratogenic effects, Ann. Ist. Super. Sanita 1993; 29: 57-67.

4. Sadik, M.S., H. Fatima, K. Jamil, C. Patil. Study of TORCH profile in patients with bad obstetric history, Biology and Medicine 2012; 4: 95-101

5. Mets MB and Chhabra MS. Eye Manifestations of intrauterine infections and their impact on childhood blindness, Surv. Ophthalmol. 2008; 53: 95-111.

6. Wilson-Davies, E.S.W., C. Aitken. When should the 'TORCH' study be requested, Paediatr. and Child health 2013; 23: 226-228.

7. William J L, Mehmet G. Syphilis in pregnancy. Sex Transm Infect 2000; 76:73-79.

8. Gardella, C, Brown, ZA. Managing varicella zoster infection in pregnancy, Cleveland clinical Journal of medicine 2007; 74:290-296.

9. Suzuki, Y., Y. Toribe, Y. Mogami, K. Yanagihara, M. Nishikawa. Epilepsy in patients with congenital cytomegalovirus infection, Brain Dev.2008; 30: 420-424.

10. Zhang CX, Mei Q, Zhu Y, Tang ZM, He NY, Lu ZH. Protein microarray-a new tool for detection of TORCH infections, Advanced Nanomaterials and Nanodevices, 8th International Conference on Electronic Materials (IUMRS-ICEM 2002, Xi'an, China) 2002, 396-407.