Review Article

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Fetal Infections Leading to Congenital Malformations

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Abstract

The objective of this review article is to appraise the different infectious causes leading to congenital malformations in a fetus. Apart from being traumatic to the parents, repeat pregnancy losses or having a congenitally malformed baby,it is a great challenge to diagnose and suspect this causes to the physician Literature search in pubmed and google scholar revealed various aspects of this infections. The mode of transfer to the fetus and the degree of the fetal affection depends on various factors like the gestational age of attack of organisms,the virulence of the organisms and the inocullum of the organism. Infection with Rubella,cytomegalovirus, toxoplasma gondi are the main organisms which are associated with congenital malformations in the fetus.this can lead to either a lethal effect or a defective organogenesis in the fetus. This article aims to throw a light on the various infections,their ill effects and mode of transfer to the fetus. Evidence also supports the routes of infection and the gestational age of contracting the infection by the fetus and the factors which determine the outcome of pregnancy after the fetal infections.

Keywords: Rubella; CMV; Toxoplasmosis; Congenital malformations.

Introduction

It is immensely traumatic for a pregnant woman to go through an unfavourable pregnancy outcome, maybe it is a missed abortion or a stillborn baby or an anomalous baby.

Congenital malformations a neonate can be due to infectious or non infectious causes. The non infectious causes are genetic, environmental and chromosomal abnormalities. The infectious causes mainly attribute to TORCH group of infections (Toxoplasma, others, Rubella, CMV, Herpes). The other group consists of coxsackie, parvovirus B19, echo, measles, mumps, hepatitis, encephalitis viruses.[1] Worldwide congenital HIV is a major cause of morbidity and mortality in infants. However, since it does not cause any malformations it is beyond the scope of this article.[2]

Routes of Infections

The vast majority of infections in pregnant woman involve the gastrointestinal tract and upper respiratory tract infections. Either they resolve spontaneously or are readily treated with antibiotics. Such infections remain localised and do not cause any effect on the developing foetus.

However, the transplacental spread after maternal infection and invasion of blood stream is the usual route by which the foetus gets infected.

Less frequently the source of infection can be a result of invasive procedures on the foetus for example cordocentesis , intrauterine transfusions.[3]

Many a times, before rupture of membranes organisms in the genital tract may invade the amniotic fluid and produce infection of the foetus. These gain entry in the uterus through

the microscopic defects in the membranes particularly in the devitalised area overlying the cervical os.

However, usually the foetal infections that occur are secondary to the transplacental route that is vertical transmission. These organisms are carried within the WBC or RBC in the blood stream.[4]

Factors Deciding the Fetal Effect

The very first factor which determines the effect on fetus is the gestational age. Earlier the insult more is the chance of congenital malformation, especially the period from 6 weeks to 12 weeks that is the period of organogenesis. It is very clear that any insult in this period will result in either a malformation or missed abortion or resorption of embryo. As the insult moves away from first trimester of pregnancy, although malformations may not be seen, still intrauterine growth retardation, preterm loss or chronic sequelae in post natal period is seen. Usually the insult in second trimester results in involvement of neural tissue and hence untoward chronic sequelae in childhood is seen.[5]

The inoculums of the virus is the next deciding factor. Obviously greater the inoculums more are the chances of foetal affection. Sometimes a very small load of organisms may not lead to any untoward effect on the fetus and a normal child may be born.

The virulence of the organism plays a pivotal role in the causation of malformation. A small inoculum of a highly potent organism can thus be fatal or can cause resorption of embryo.

The acute infections which are persistent in immediate preconception can affect the fetus. A prolonged viraemia or persistence of viruses in maternal tissue may be responsible for the early infection of the foetus.[6]

The stage of pregnancy associated placental damage and whether the infection is primary or recurrent decides the outcome of pregnancy.[6]

Result of the Organism Invading the Maternal Blood Stream

The microorganisms may invade inter villous spaces and remain localised causing placentites. The foetus may not be affected, the cause is unknown. However, the defence mechanism of foetus may operate, to take care of the foetal affection i.e. local production of immune factors and cytokines, placental macrophages and villous trophoblast action for example malaria, tuberculosis, syphilis, CMV, Rubella.

Secondly, the microorganisms may invade the placenta and go to foetal blood stream and spread the infection to foetus, e.g. toxoplasma gondii, CMV, rubella.

Invasion of the blood stream by microorganisms is very common in pregnant woman. However, the placenta and foetus both remain uninfected, e.g. pneumonia, pyelonephritis, abscesses, etc. Efficient clearance of microbes by reticuloendothelial system and circulating leucocytes may be responsible for minimal damage to placenta and foetus.

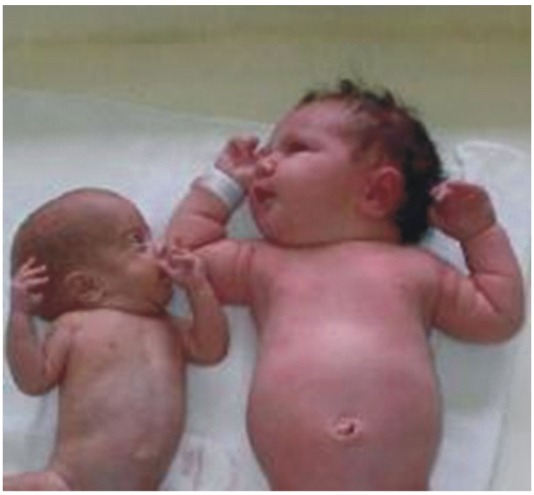
Fever, anorexia, circulating toxins may affect the pregnancy and result in preterm infants or still born baby.

The association of urinary tract infection in pregnancy results in low birth weight and preterm baby is a good example where foetus and placenta are not invaded by the organisms but result in abnormal development of the baby.[7]

Effect of the Infection on the Embryo and Fetus

Result of the infection can lead to missed abortion, congenital malformation or resorption of the embryo. Intrauterine growth retardation, preterm infants or developmental anomalies can be seen in live born babies. Sometimes the baby may be born normal but postnatal chronic sequelae may present e.g congenital cataract, hearing loss, neurological sequelae.

Fig 1: Intrauterine Growth Retardation



Infections which occur immediate preconceptionally can result in total resorption of the embryo in early pregnancy. However, this can go unnoticed and could be labelled as delayed menses.

Abortion and still born can occur when infection occurs from 6 wks to 8 wks. The organisms may interfere with the functions necessary for viability and hence causes missed abortion, e.g. toxoplasma. If the organism interferes with the development of the foetus it can lead to congenital malformation e.g. rubella and CMV.[8]

Intrauterine growth retardation can be seen if the organism interferes at the time of cell division. These babies have decreased number of morphologically normal cells and result in symmetrical IUGR eg toxoplasma, CMV, rubella, varicella zoster virus can cause congenital malformation in human foetuses. The exact pathogenesis remains obscure. This virus have viability to cause cell death (Amelia), altered cell growth (microcephaly, hydrocephalus, microphthalmia) as chromosomal damage. Inflammation and tissue destruction rather than teratogenesis is said to be the cause of malformations with this organisms.[9]

Clinical evidence of intraurterine infections may be present at birth or may be seen some years after birth. This results from tissue damage or secondary physiology change caused by invading organism. Congenital rubella, CMV, toxoplasma have signs of widely disseminated infections in neonatal period e.g. jaundice, thrombocytopenia, hepatosplenomegaly, pneumonia. This is secondary to invasion and proliferation of organism rather than defects in organogenesis. In some babies these signs are transient and disappear as neonatal defence mechanisms clear the organisms and control the tissue damage. However, if the damage is severe it leads to death of neonate.[10]

The majority of newborns infected in utero by rubella, toxoplasma, CMV or HIV gave no signs of congenital defects and are seen as normal babies. However as time elapses hearing loss, visual impairment, failure to thrive etc can be seen in these babies. Other babies may not manifest with any signs or symptoms and may be absolutely normal. The gestational age of insult, inoculums and virulence of organism decides the fate of baby.

Diagnosis of Infection in Pregnant Woman and Fetus

Symptomatic or clinical infection based on clinical signs and symptoms and careful physical examination gives a clue to the diagnosis.

Example rubella is mild respiratory infection with a typical rash characterised by sensory neural deafness, various ocular abnormalities, such as cataract, retinopathy, glaucoma, CVS defects e.g. PDA.

Majority of these viral infections can be asymptomatic or subclinical. There is no typical rash or any other symptoms e.g CMV, rubella, toxoplasma.

These are the cases where foetal loss or malformation is seen and later on the mothers are diagnosed with the infection11.

Recurrent or the chronic infection may invade the blood stream and remain dormant whenever the host immunity vanes off eg in pregnancy there is reinfection. The low levels of circulatory antibodies again rise and affect

Organisms Causing Congenital Malformations in Fetus and Syndromes[12]

Micro-organism	Signs
Toxoplasma gondii	Hydrocephalus, diffuse intracranial calcification, chorioretinitis
Rubella virus	Cardiac defects, sensorineural hearing loss, cataract
Cytomegalovirus	Microcephalus, periventricular calcification
Treponema pallidum	Bullous, macular, and eczematous skin lesions involving the palms and soles ; rhinorrhea ; dactylitis and other signs of osteochondritis and periostitis
Varicella-zoster virus	Limb abnormalities, cicatricial lesions
Parvovirus	Diffuse edema (in utero hydrops fetalis)
Human immunodeficiency virus(HIV)	Severe thrush, failure to thrive, recurrent bacterial infections, calcification of the basal ganglia

the foetus e.g toxoplasma, varicella, CMV.

Specific Diagnostic Tests

Isolation of microbial agent from body or tissue fluid can establish the diagnosis.

Serological diagnosis of infection in the pregnant woman requires the demonstration of significant rise of antibody titre against the suspected organism e.g toxoplasma, CMV, rubella.

Diagnosis in the foetus can be established by cordocentesis or amniocentesis and establish either the organism or antibody against the organism in foetal blood

Rubella

Gestational age at the time of maternal infections is the most important determinant for intrauterine transmissioin and fetal damage.The risk of fetal infections and congenital anomaliesdecreases with increasing gestational age. Fetal damage is rare beyond