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Intrauterine infections

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Infections of fetus and newborn are a significant cause of mortality and long term morbidity. Data on selected micro-organisms like rubella, cytomegalovirus, toxoplasma, herpes and syphilis, indicate that as many as 2 per cent of fetuses are infected *in utero* and up to 10 per cent of infants during delivery or in first few months. Intrauterine growth retardation is one of the common manifestations of intrauterine infections, hence a prospective study to determine the incidence of intrauterine infections in low birth weight babies was carried out. The data is discussed here and relevant literature is reviewed.

The study

Two hundred and thirty one new borns with birth weight of 2 kg or less were randomly chosen for this study, which extended over a period of one and half years. The data on socioeconomic and nutritional status, age, history of antenatal illness, medication or chronic systemic disorder, contact with pets and previous obstetric history, was recorded in detail. The newborns were examined in details and the anthropometrical parameters and gestational age were noted.

Cord blood samples of these 231 babies and blood samples of their 222 respective mothers, collected within 24 hours of delivery, were analysed for presence of antibodies against rubella, cytomegalovirus, toxoplasma, syphilis and hepatitis B surface antigen. Immunoglobulins, G, M and A were also estimated in cord blood. Tests were repeated after 4 and 8 weeks whenever initial antibody levels were high.

Tests employed for intrauterine infections were hemagglutination inhibition for rubella, complement fixation test for cytomegalovirus disease, indirect hemagglutination for toxoplasmosis and VDRL test for congenital syphilis. Australia antigen detection by counter immunoelectrophoresis was carried out for hepatitis B. Single radial immunodiffusion technique of Mancini *et al* was utilised for serum immunoglobulins.

Results

As the study was carried out in a general maternity hospital, 78·38 per cent of mothers belonged to low socio-economic group and 39·64 per cent were undernourished. 43·69 per cent of mothers had previous obstetric history of one or more of the following—previous low birth

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weight babies, abortions, preterm deliveries, still births. Antenatal history was noncontributory. In all 70·13 per cent of these newborns were small for gestational age i.e. less than 2 standard deviation of normal. Two of 231 newborns had splenomegaly. Bilirubin levels up to 7·5 mg/dl were observed in 34·2 per cent of newborns and 70·89 per cent of them had physiological jaundice.

The analysis of cord blood and maternal blood serological studies is presented in Table I. None of the samples had titres of 1 : 128 or more of antibodies against toxoplasma, rubella or cytomegalovirus disease. Some of the cord blood samples showed titres of more than 1 : 64. However, repeat analysis after 4 and 8 weeks failed to show consistent rise in titres. VDRL test was weakly positive in 0·90 per cent of cases but repeat studies after few weeks were negative. Also none of the samples had presence of Australia antigen. None of the cord blood samples had immunoglobulin M levels of more than or equal to 20 mg/dl.

Pathogenesis

Majority of infections in pregnant women involve gastrointestinal, respiratory and genitourinary tracts and either resolve spontaneously or are rapidly treated with antimicrobial agents. Such infections remain localised and usually have no effects on the developing fetus.[1] However, some of these infections can cause immediate as well as long term effects which are detrimental to health of fetus as well as infant later on. One of the common manifestations of intrauterine infections is intrauterine growth retardation. A variety of micro-organisms are known to infect the materno-placental-fetal Unit. For some, data is conclusive, in case of others it is highly suggestive (Table II).

Table I. Serum titres of antibodies against intrauterine infections

Sample	Test for	Negative	Positive titres*			
			Titres 1 : 16	1 : 32	1 : 64	>1:64
Mother's blood	Toxoplasmosis	86·49	11·26	0·45	1·35	0·45
	Rubella	72·97	22·97	0·45	2·70	0·90
	CMV	91·44	8·56	—	—	—
	VDRL	99·09	Weakly +ve in 0·90%			
	Au. Antigen	100	Nil	nil	nil	nil
Cord blood	Toxoplasmosis	87·39	12·16	—	0·45	—
	Rubella	75·23	19·37	2·70	2·25	0·45
	CMV disease	91·90	8·11	—	—	—
	VDRL (in relevant cases)	100	nil	nil	nil	nil

*% of all cases

Table II. Organisms known to cause intrauterine infections

Organisms with definite data
Viruses
Rubella, CMV, herpes simplex, varicella zoster, mumps, polio, rubeola, vaccinia, smallpox, echo, Coxsackie B, hepatitis B, influenza, Western equine encephalitis.
Bacteria
Treponema pallidum
Mycobacterium tuberculosis
L. monocytogenes
Vibrio fetus
Salmonell a typhosa
Borrelia leptospira
Staph. aureus
B. anthracis
Pasteurella tulerensis
Protozoa
Toxoplasma gondii
Plasmodia
Trypanosomes
Organisms with suggestive data
Viruses
Hepatitis A
LCM virus
Bacteria
Streptococcus pneumoniae
Protozoa
Leishmania donavani
Ascaris lumbricoides
Trichinella spiralis
Lymphogranuloma venerum

Infection of the fetus can occur transplacentally or as an extension of infection from adjacent areas e.g. peritoneum or genitalia, by transtubal or transmyometrial routes. Invasive monitoring and therapeutic procedures may be instrumental in some cases.

The micro-organisms invading the maternal blood stream may or may not involve the placenta and/or the fetus. Through the infected placenta, micro-organisms may disseminate to fetal blood stream via infected emboli of necrotic chorionic tissues or by direct extension of placental infection to fetal membranes with secondary amniotic fluid infection and aspiration by the fetus.[1] Maternal rubella, toxoplasma, cytomegalovirus disease and syphilis spread systemically, infect the placenta and may invade the fetal tissues. The disease in the fetus, if it occurs may result in resorption of the embryo, death of the fetus resulting in spontaneous abortion or still birth, clinical infection presenting in newborn period or at a later date or congenital malformations. The consequences of such fetal and/or placental infections are shown in Fig 1.

Variable effects of fetal infection are emphasized by reports of binovular twin pregnancies that produced one severely damaged infant and another with minimal or no detectable abnormalities.[2-5] A number of modifying factors probably determine the ultimate outcome of intrauterine infections, such as number and virulence of organisms, tissue tropism, stage of pregnancy, severity of maternal illness, associated placental damage and immunological status of the mother, placenta and fetus.[1]

Pathological features

Number of histopathological studies on placenta and/or fetus are available.[6-8] The pathological mechanisms may operate in different ways: (*a*) Angiopathy showing extensive damage to endothelium of the capillaries of the chorion. The infected

clumps of chorionic endothelial tissue may act as a seed source of micro-organism to fetus and cause vascular obstruction which ultimately results in fetal tissue damage.[6,7] This type of injury is seen in rubella; (*b*) Direct cytolysis with focal necrosis and resultant inflammatory response and subsequent healing may occur with fibrosis and occasionally calcification. Cytolysis at early periods of gestation also results in reduced absolute number of cells which cause intrauterine growth retardation. This is observed in infections like CMV or rubella;[8] (*c*) Immunological mechanisms and delayed hypersensitivity play major role in retinal and central nervous system pathology as in toxoplasmosis.

Clinical manifestations of neonatal infection acquired in utero or at delivery. Illnesses caused by some of these organisms may be typical or may run a sub-clinical course. Typical features of these infections are outlined in Table III. Majority of newborn infants infected ***in utero*** by rubella, ***Toxoplasma gandii*** or CMV have no congenital disease. Some have obvious multiorgan or single organ system involvement.[9,10] For instance intrauterine rubella infection may produce typical congenital rubella syndrome or may lead to hearing defect which may be the only manifestation.[11] Failure to thrive, psychomotor retardation and visual defects may follow toxoplasma, rubella and CMV infections.[12-16]

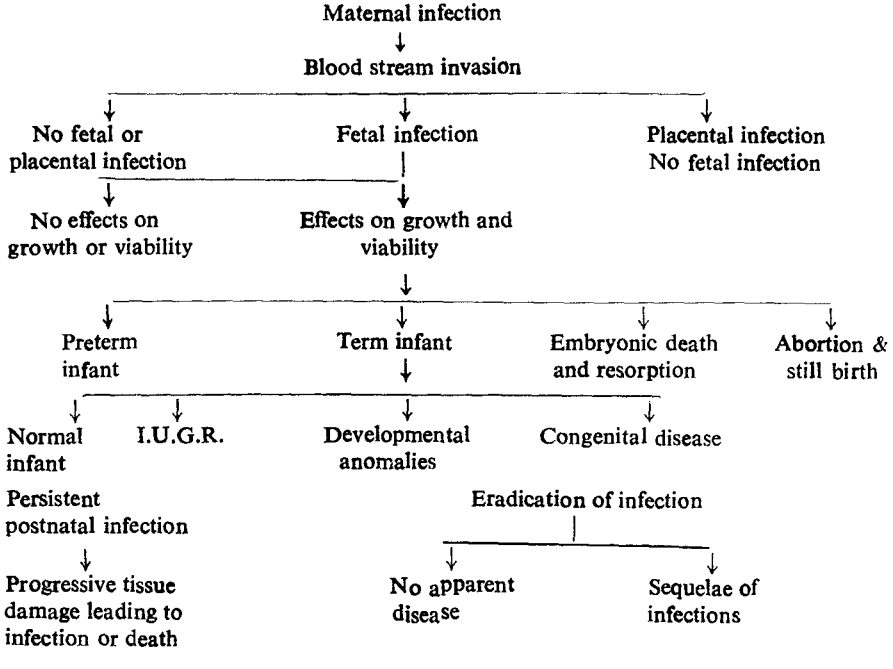

Fig. 1. Consequences of intrauterine infection.

Table III. Typical clinical manifestations of intrauterine infections

Hepto and/or splenomegaly
Jaundice
Adenopathy
Pneumonitis
Lesions of skins & mucous membrane
Petechiae or purpura
Vesicles
Maculopapular exanthems
Bone lesions
Lesions of CNS
Meningoencephalitis
Microcephaly, hydrocephaly
Intracranial calcifications
Hearing deficits
Lesions of CVS
Myocarditis
Congenital defects
Eye lesions
Glaucoma, cataracts
Chlorioretinitis or retinopathy
Optic atrophy, microphthalmia
Uveitis, conjunctivitis,
Keratoconjunctivitis

Persistence of infection postnatally has been the feature of certain intrauterine infections like rubella and CMV where organisms continue to survive and replicate in the tissues for months and years. In infected infants virus can be excreted from multiple sites like pharynx, urine, conjunctiva, feces etc. and is detectable in the CSF, bone marrow or circulating white blood cells.[22-24] In some intrauterine infections like rubella,[17] CMV,[16] toxoplasma,[13] herpes simplex, tuberculosis,[18] malaria and syphilis[2,19] progressive tissue destruction has been demonstrated e.g. progressive encephalitis in rubella.[20] Clinical manifestations of intrauterine infections may remain stable for many years followed by sudden deterioration of motor and mental functions.

Diagnosis and management

Serologic testing is the best means to establish or exclude a specific diagnosis of congenital infection in the newborn. If an infant is suspected of being infected because of physical findings or elevated IgM levels, the specific antibody titre of the mother and the infant against each agent should be determined at birth and again 2 to 6 months later. Infants born to a mother who has been infected prior to pregnancy will possess passively transferred antibodies approximately equal in titre to that of mother. However, 2 to 6 months later the mother will still have the same titre but the infant's titre will be much lower or undetectable. Infants who are congenitally infected also will have an antibody titre at birth that is similar to the material titre. At 6 months of age, however, the infant will still have a high titre because of active infection *in utero*. Once the baby has survived the neonatal period, serology becomes a very uncertain way of making the diagnosis of congenital infection.

The demonstration of fetal IgM antibody in cord sera signifies fetal infection and can be employed as an important confirmatory diagnostic tool for rubella or CMV disease. Isolation of virus from urine or throat or conjunctival or rectal swabs as well as from white blood cells, preferably in first few days of life is diagnostic of CMV infection. Diagnosis of symptomatic newborns suffering from toxoplasmosis can be done with histologic proof or isolation of parasite from placenta. Diagnosis of suspected cases, however, is done with serological techniques where elevated total immunoglobulins can be detected by Sabin Feldtman dye test or IgG can be detected by immuno

fluoroscence test. Diagnosis of congenital syphilis is done by demonstration of positive reagin tests e.g. VDRL on maternal and/or cord blood samples. Persistence of these tests and/or demonstration of specific IgM by immuno fluoroscence technique is necessary for definitive diagnosis. In addition to initial serologic approach, dark field microscopy, lumbar puncture, histopathology of placenta and radiological examination of bones may become necessary for diagnosis of congenital syphilis. Most children of asymptomatic chronic carrier mothers or mothers suffering from acute hepatitis B infection, who become HBsAg positive show no sign of clinical hepatitis but they may have persistently elevated serum transaminase levels and signs of chronic hepatitis may be seen on liver biopsy.

For prevention of rubella, live attenuated vaccine has been used with encouraging results. Routine childhood immunisation for achieving herd immunity in population has been advised. Also a direct approach of immunising women in childbearing age group is practised in some countries.[21] The prerequisite for this type of immunisation is absence of serum HI antibody. However, efficacy of this vaccine is still questionable. Unlike rubella, active prevention of CMV disease is not yet possible though initial steps towards use of live virus vaccine have already been taken. When primary infection is diagnosed early in gestation best approach will be termination of pregnancy. Certain drugs like ara-C, ara-A and IDU are currently under evaluation for treatment of infected infants. Decreasing risk of exposure to toxoplasma, among susceptible gravidas is a useful method of prevention of this disease.

Prevention of fetal involvement by treating the maternal infection with drug like Spiramycin has been advocated and practised by few European workers with moderate success. Postnatal treatment with sulfadiarine and pyrimethamine is recommended in all cases whether symptomatic or not.[25] In syphilis the mortality in untreated early infection is high ranging from 10 to 30 per cent. The corner stone of prevention and therapy of fetal syphilis is prompt recognition and treatment of maternal infection with longacting penicillin. The postnatal congenital syphilis should be treated with 10-14 days therapy with penicillin. Preventive measures in congenital hepatitis B infection are still controversial. It is advised that when mother has acute disease near the time of delivery, hyperimmune Hepatitis B immunoglobulin in doses of 0·16 ml/kg or standard immunoglobulin in the dose of 2 ml should be administered to the infant at birth and again a month later. And when mother is a chronic carrier, it is probably best to treat the infant with 0·04 ml/kg of hepatitis B immune globulin at birth and every 4 months for 3 doses.[26,27]

Discussion so far was concerning major organisms infecting the materno-placental-fetal unit. Few other micro-organisms affecting this unit, like herpes simplex, malaria and tuberculosis have not been discussed here. It is evident from clinical features of different intrauterine infections, that intrauterine growth retardation is one of the important manifestations of these diseases. Significant proportion of all low birth weight deliveries in India is due to intrauterine growth retardation. In a previous study by authors, no significant correlation could be demonstrated between maternal nutritional supplementation in pregnancy and

incidence of low birth weight deliveries. In the present study an attempt was made to find out whether intrauterine infections can be the cause of asymptomatic low birth weight babies in whom no other cause can be demonstrated. Majority of low birth weight babies from our series (70·13%) were small for gestational age. Most of the newborns did not reveal clinical signs which can point to any particular intrauterine infection. Except in few, antenatal history or examination findings were not able to explain low birth weight of newborns. Analysis of maternal blood samples though showed positive antibody titres in 13·51 per cent of cases for toxoplasmosis, 27·03 per cent for rubella and 8·56 per cent cases for CMV, titres were not more than or equal to 1 : 128 in any of the samples. Similarly none of the sample had presence of Australia antigen in it. The same was true for cord blood analysis. Though one case of toxoplasmosis and six cases for rubella had shown titres of 1 : 64 or above, follow up titres after 4 and 8 weeks were less than 1:8. VDRL test though was weakly positive in two of the maternal blood samples, it was negative for simultaneous cord blood samples. Thus it can be seen that in majority of asymptomatic low birth weight newborns, major intrauterine infections, known to cause growth retardation of fetus and subsequent hypoplastic growth of infant do not play a significant role in production of low birth weight. However, factors other than major intrauterine infections were found to be more important in etiology of low birth weight. It was observed that 82 per cent of undernourished mothers delivered babies with lower birth weights falling between 1 to 1·5 kg as compared to averagely nourished women who tend to deliver relatively higher weight babies i.e. between 1 to 1·7 to 2 kg (69%). Similarly babies born in lower socio-economic groups tend to have lower birth weights, more of small for gestational age and mothers from same group, tend to deliver at earlier gestational age. Similar phenomena is observed with undernourishment. Therefore, it is concluded that (*i*) factors like low socio-economic status, undernourishment of mothers are more important to consider in etiology of low birth weight newborns than major intrauterine infections; (*ii*) titres of antibodies against toxoplasmosis, rubella and cytomegalovirus disease up to 1:64 can be considered to be within normal limits and higher titres require follow up studies, (*iii*) considering the cost, it is not advisable to follow routine screening of low birth weight newborns for major intrauterine infection.

Conclusions

Intrauterine infections pose one of the major health hazards for developing fetus, which can have immediate or long term consequences. Clinical manifestations of intrauterine infections are varied and may be present at time of birth or may develop months or years after birth. These infections may cause single, multiple or no organ involvement. Many pathological and immunological mechanisms are important in production of the disease though in many cases they are yet unknown or poorly understood. Gestational age of conceptus and immunological status of materno-placental-fetal unit, are few of the important factors determining course and outcome of majority of intrauterine infections. Many microbiological and immunological

methods of diagnosis of intrauterine infections are available but high degree of clinical suspicion and meticulous follow up studies to detect long term consequences are important particularly in country like India where cost of these studies may outweigh to benefits of tests. One of the important clinical manifestations of intrauterine infection is intrauterine growth retardation but present study revealed no evidence of intrauterine infection in low birth weight babies. Considering the cost, it does not seem to be advisable to follow routine microbiological or immunological screening for major intrauterine infections, of low birth weight newborns who are otherwise asymptomatic.

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30 YEARS OF ERYTHROMYCIN USAGE

Erythromycin is a macrolide that acts by inhibiting the translocation reaction during protein synthesis. It is inactive against the enterobacteriaceae and *Pseudomonas aeruginosa* except under alkaline conditions. Erythromycin is active against most gram-positive bacteria; some gram-negative bacteria, including neisseria, bordetella, brucella, campylobacter and legionella; and treponema, chlamydia, and mycoplasma. The emergence of resistance to erythromycin is closely associated with its use and is often plasmid mediated. After its oral or parenteral administration, erythromycin diffuses readily into intracellular fluids and is actively concentrated intracellularly by polymorphonuclear leukocytes and alveolar macrophages.

Erythromycin, first introduced for clinical use 30 years ago, was found to be effective for the treatment of gram-positive bacterial infections. Emergence of resistance and the advent of penicillinase-resistant penicillins limited the use of erythromycin for serious staphylococcal infections; however, erythromycin remains among the drugs of choice for the treatment of acne, infections of the skin and soft tissues, streptococcal pharyngitis, bronchitis, pneumonitis, diphtheria, carriers of pertussis, and when administered with a sulfonamide, otitis media. Erythromycin is the drug of choice for the empiric treatment of outpatients with pneumonitis. Erythromycin is also the drug of choice for the treatment of legionella pneumonia and is effective therapy for chlamydia infections. Other uses of erythromycin include prophylaxis for elective colon operations and treatment of campylobacter enteritis, genitourinary infections, and some sexually transmitted diseases.

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