Although rubella was first recognized by German authors in the mid eighteenth century and called rotheln, the real credit goes to Sir Norman Gregg, an Australian ophthalmologist for his epoch-making paper in 1941. It described the association between congenital cataract and heart disease and maternal rubella occurring during the first trimester of pregnancy. This association gave the momentum to extensive research, both epidemiological and virological to find out the size of the problem and to isolate the virus. The latter achievement by Wheeler & Neva at Harvard, and Parkman et al. paved the way for vaccine production in 1969.

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The virus is a member of the togavirus group (toga means an outer garment or envelope). It is spherical in nature, measures about 50–70 nm in diameter. It consists of a nucleoid core, which is a single-strand RNA. An envelope of lipoprotein is acquired during the penetration of the virus into the cell. The lipid of the envelope is essential for the virus infectivity. On the envelope there are spiky surface projections with knobbed ends.

There are three types of structural proteins recognized in the virus. They are called E1, E2 and C. E1, with a molecular weight of 50 kDa is found in the surface projections whilst E2, with a molecular weight of 42–47 kDa is subdivided into E2a and E2b. Both E1 and E2 are glycoprotein in nature. Protein C with a molecular weight of 33 kDa is found within the nucleoid core.

Human beings are the only host for rubella virus and transmission is from person to person. The last pandemic of rubella was in 1964, during which in the USA only there were 12.5 million cases,
11,000 fetal deaths, 20,000 infants born with various defects and 2100 deaths in the neonatal period. This event cost the USA economy two billion dollars.\(^7\)

Pathology and Pathophysiology

Once the mother contracts rubella during pregnancy, viraemia occurs. Following that, seeding of the placenta takes place. This is followed by fetal infection. The virus may persist in the placenta for months but is infrequently recovered at birth; in contrast once the fetus is infected the virus persists throughout gestation and postnatally. Following fetal infection, the most important determining factor regarding the degree of damage is gestational age. If the exposure occurs before 8 weeks of pregnancy have been completed then the fetus will be severely affected, ranging from miscarriage or stillbirth to an infant with congenital rubella syndrome. If the infection occurs after 8 weeks and especially after 16 weeks, the outcome is more favourable and even an apparently normal infant may be produced.

Why is the timing of exposure so important? The short answer is that nobody knows but various theories have been put forward. Among these are:

1. Immature cells can easily become infected and support the growth of the virus especially when this occurs during the embryonal state when cell division is potentially active and disturbance of organogenesis may occur leading to malformations.

2. The placenta becomes increasingly resistant to infection with maturation.

3. The maturing fetal defences become capable of limiting and clearing the infection, especially after 18 weeks of gestation.

4. A combination of the above factors.

It was recognized very early following virus isolation, that it causes non-lytic infections in a variety of cells from different species especially in humans. This leads to its chronicity which is the hallmark of the intrauterine rubella infection. As a result of low grade chronic infection, large numbers of fetuses survive with varying degrees of damage. Pathological studies in therapeutically aborted fetuses have shown hypoplasia of the placenta with inflammatory foci in the chorionic villi, oedema, hyalination and necrosis. This is associated with damage to the endothelial cells of the blood vessels of the chorion. The latter finding led some authors to postulate that necrotic emboli may seed target organs in the fetus causing poor blood supply and subsequent organ failure.

Interference with cell mitosis, alteration of cell receptors to growth factors, chromosomal breaks, reduced cellular multiplication time and increased production of protein inhibitors that cause mitotic arrest have been reported recently followed rubella viral infection.\(^8\)–\(^11\)

The pathological changes in the fetus are seen in nearly every organ with hypoplasia being a common finding. The changes vary in degree and extent, and organ distribution depends on the gestational age at the time of infection, which could explain the wide spectrum of the clinical presentations.

Clinical Presentation

Before 1969 the incidence of congenital rubella syndrome (CRS) was 0.1% during the endemic years and rose to 2% during the 1964 pandemic in USA.\(^7\) Because of the persistence of the virus after birth, the disease is now considered as a chronic infection with a variable range of manifestations. Silent infection is more common than symptomatic in the neonatal period.

Schiff et al.,\(^12\) in his prospective study of 4005 serologically or virologically proven infections during the 1964 pandemic, found that 68% of infected newborns had subclinical infection during the neonatal period and up to 71% of those who were followed up developed signs and symptoms by their fifth birthday.

The clinical manifestations can be divided into three groups:

1. **Transient:** This includes hepatosplenomegaly, hepatitis, thrombocytopenia, purpura, myocarditis, haemolytic anaemia, adenopathy, bony translucency and encephalitis. These are due to either active infection or the presence of immune complexes or both. Although transient signs and symptoms resolve within days to weeks, they can be fulminating and lead to a mortality of up to 35% especially when associated with a major defect.\(^13\)

2. **Permanent manifestations:** These may appear at birth or during the first year of life and affect the heart (patent ductus arteriosus, pulmonary or aortic stenosis and Tetralogy of Fallot), central nervous system (CNS) with deafness of sensori-neural type, which can occur in up to 80% of babies and is usually bilateral and can be associated with language problems. The combination of the
two (deafness and language problem) could lead to the erroneous diagnosis of mental retardation in some of the affected children. The hearing loss can increase with time and sudden occurrence of total deafness has been reported in later years due to the persistence of the pathological process. Retinopathy of salt and pepper type has been reported usually unilaterally but when associated with cataract it can be bilateral. The permanent manifestations are due to structural defects or result from defective organogenesis and tissue destruction and scarring.

3. Developmental and late onset manifestations: These include various endocrinopathies, deafness, ocular changes and a progression of the CNS lesions. In one follow-up study, insulin-dependent diabetes mellitus was reported in up to 40% of adult survivors from the 1942 epidemic with a high frequency of HLA-D3. Thyroid dysfunction was found in 5% of children with the congenital rubella syndrome and was manifested as hyperthyroidism, hypothyroidism and thyroiditis. Growth hormone deficiency secondary to hypothalamic lesions, Addison’s disease and precocious puberty have been reported. Mental retardation, autism and other behavioural problems may be delayed in appearance and can be progressive. Progressive encephalopathy similar to subacute sclerosing panencephalitis (SSPE) has been described.

Diagnosis

Since the clinical diagnosis of maternal and congenital infection is unreliable, virological and/or serological confirmation has become imperative. Virus isolation from exposed pregnant women is impractical and difficult. In contrast to the congenitally infected fetus, virus isolation from nasopharyngeal washout, urine, faeces, blood and cerebrospinal fluid can be achieved in up to 84% of babies during the neonatal period. The virus is isolated in 33% at 6 months and about 3% at 1 year of age. Infants who have been infected are considered to become non-infectious by the age of 12–15 months.

Serological diagnosis depends either on a rising IgG antibody (AB) titre in paired sera during the acute and convalescent period in the exposed mother or detection of IgM antibody (AB) in a single sample from the mother or her baby. The failure of IgG AB transmitted through the placenta to disappear by 6 months of age indicates a fetal infection. Discussing the pros and cons of the various immunological tests are beyond the scope of this article. The topic is well reviewed by Craddock-Watson. An antibody index of above 1 (ratio of patient serum AB/control specimen) is indicative of recent rubella exposure. Initially the ratio is higher for IgM but later the IgG AB ratio becomes predominant.

Prenatal diagnosis is possible by virological and serological testing of the amniotic fluid, fetal blood IgM estimation and chorionic villus sampling for virus isolation, specific antigen or RNA detection. The latter method helps in early confirmation of prenatal infection. DNA hybridization of chorionic villus biopsies may yield a higher rate of virus detection.

Management

Every effort should be made to make a serological diagnosis in exposed mothers. This is because of the counselling implications. The risk of fetal infection is 100% when exposure occurs before 8 weeks of gestation have been completed. It reaches a nadir of 25% at 23–26 weeks to rise to 82% at 37 weeks. The overall risk for a defect in the offspring is 90% when maternal infection occurs at less than 8 weeks of gestation, 75% when it happens between 9 and 16 weeks and 14% at 17–18 weeks. No defect has been reported when exposure occurs after 17 weeks of gestation.

Once maternal exposure is confirmed before 12 weeks of gestation, termination of pregnancy as an option of treatment should be offered to the parents, although its implementation depends on the law of the land and the parents’ social and religious upbringing.

The management of individual cases requires frequent evaluation, because of the way the signs and symptoms evolve in this disease. A team approach with input from various subspecialities depends on the degree and type of the insult. Planning for hearing defects and the education of the infant is particularly important.

Prevention

In the developed world, with the introduction of the vaccine in 1969, and especially in countries where universal, childhood vaccination and selective high risk group vaccination programmes are employed, elimination of the disease is
possible. In the USA the incidence rate dropped from 62/100 000 live births in 1969 to 2/100 000 live births in 1987. Since 1969, three main types of vaccine have been developed, Cendehill, HPV-77 and RA 27/3; all are attenuated live vaccines. The RA 27/3 vaccine is the most widely used and can be given intranasally. The immune response induced by RA 27/3 vaccine is similar to that of the natural infection. The sero-conversion to all type of vaccines is 95% in those vaccinated at 12 months of age or more. The immunity induced is probably life-long.

Reinfecion following natural disease or vaccination, although very rare has been reported in pregnant women. There is a 1–2% chance of the offspring being infected but fetal defects following such exposures have not been confirmed. Accidental vaccination of women at childbearing age, 3 months before to 3 months after pregnancy by any of the three vaccines seems safe. In one series of 297 pregnant women followed by the Centre for Disease Control in the USA, none of them delivered a baby with CRS, even those who were exposed during the most susceptible period of 1–4 weeks’ gestation.

In a recent computer search at Riyadh Armed Forces Hospital 27 cases of CRS were found to have been diagnosed between 1980 and 1991. The majority were referred from other hospitals because of heart, eye and hearing defects. The diagnosis was confirmed serologically in a few patients only. This experience may represent only the tip of the iceberg if one considers the entire kingdom of Saudi Arabia.

A national CRS registry is necessary. This could be based either at the Ministry of Health or the newly formed Saudi Paediatric Association could set up a surveillance unit. All paediatricians and other health providers should report cases under their care following a proper work-up, in order to assess the size of the problem. A vaccination programme for women of childbearing age and other high risk groups may be necessary.

References