STUDIES ON CERTAIN MATERNAL INFECTIONS WHICH MAY PRODUCE CONGENITAL DEFECTS

Thesis Submitted For Partial Fulfilment
of Ph.D. Degree (Microbiology & Immunology).

Presented By

MONA OMAR ABBAS MOKHTAR
M.B., B.Ch.; M.Sc.(Microbiology & Immunology).

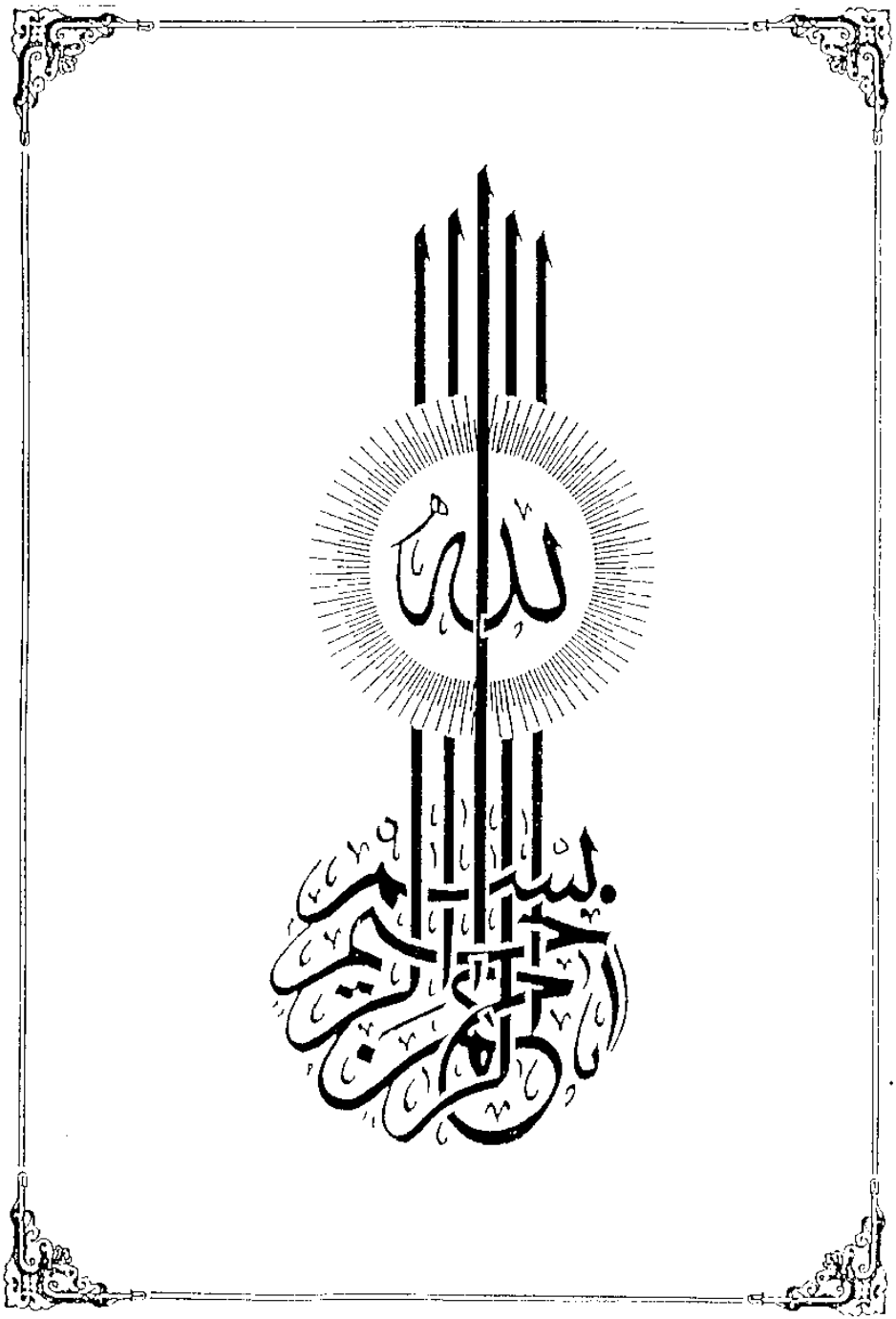
SUPERVISORS

Prof. Dr. MEDHAT DARWISH
Prof. and Chairman of Microbiology
and Immunology Department
Faculty of Medicine
Ain Shams University

Prof. Dr. RASHA KHALIL
Prof. of Microbiology and Immunology
Faculty of Medicine
Ain Shams University.

Prof. Dr. ALI ELYAN KHALAFALLAH
Prof. of Obstetrics and Gynaecology
Faculty of Medicine
Ain Shams University

198



ACKNOWLEDGMENT

I wish to express my thanks to Professor Dr. **MEDHAT DARWISH**, Head of the Microbiology and Immunology Department, for suggesting and planning this study and for his patince and experienced advices throghout the preparation of this thesis.

I wish to express my cordial appreciation and everlasting gratitude to Professor Dr. **ALI ELYAN**, Professor of Obstet. and Gynaecol, for his kind supervision.

I am deeply grateful to Professor Dr. **RASHA KHALIL**, Professor of Microbiology and Immunology , for her valuable advice and encouragement throughout this study.

Finally , I wish to thank all the staff members of Microbiology and Immunology Department for their kind co-operation.

C O N T E N T S

INTRODUCTION

I. INTRODUCTION

About 2 per cent of newborn infants have a major malformation. The incidence is as high as 5 per cent if one includes malformations detected later in childhood, such as abnormalities of the heart, kidneys, lungs and spine. About 9 percent of perinatal deaths are due to malformations. The cause of about 40 percent of congenital malformations is unknown, while only few teratogenic agents are known. One of these teratogenic agents is the intrauterine infections. Nelson (1987) has recorded that the most common intrauterine infections which may lead to congenital defects are:

A. Viral including Rubella virus, Cytomegalovirus and Herpes simplex virus infections.

B. Bacterial as Syphilis.

C. Parasitic as Toxoplasmosis.

Rubella virus is classified as a Togavirus; it is a single stranded RNA virus. Rubella is transmitted mainly via respiratory secretions. The incubation period is 14 to 21 days, after which the rash and lymphadenopathy may appear, the rash is macular or maculopapular. Fever is typically low grade or often absent (Jennifer et al., 1988). Rubella antibodies develop rapidly after the onset of rash. IgG antibodies persist for life while IgM antibodies usually appear 1-5 days after the onset of rash and persist for 6 to 12 weeks (Enders et al., 1985). Maternal viremia during

primary infection leads to placental infection and then disseminated infection of fetal tissues. If maternal infection occurs during the first 12 weeks of pregnancy, the rate of fetal infection and rubella-induced defects in live births is 90 to 100%. After 16 weeks the rate declines to 10 to 20% (Munro et al., 1987).

Cytomegalovirus (CMV) is a double-stranded DNA virus, belonging to the herpesvirus group (Andrews et al., 1972). Acquired infection with CMV is almost always asymptomatic. It establishes a "latent" or persistent infection of certain host cells and can reactivate, with renewed shedding of infectious virus years after the primary infection (Jordon, 1983).

Congenital CMV infections are also asyptomatic. However, a significant number of the inapparently infected will develop subtle disabilities later in life, rarely, a baby is born with the fulminant congenital cytomegalic inclusion disease (Ho, 1979). CMV can be transmitted in utero with both primary and reactivated maternal infections, a feature that accounts for the inordinately high incidence of congenital CMV infection in comparison with other intra-uterine viral infections (Ahlfors, 1982).

Herpes simplex virus (HSV) is another member of the herpesvirus group. It is one of the most common maladies affecting mankind. Transmission of Herpes simplex virus occurs mainly by direct contact with infected secretions. It can by differentiated into HSV-1 which is transmitted by contact with oral secretions and HSV-2 which is transmitted by contact with genital secretions (Duenas et al., 1972). HSV establishes latent states within certain types of cells they infect, genital recurrence is frequent but it is difficult to document since many cervical infections are asymptomatic (Chang et al., 1974). Congenital herpes is perceived to be a rare event. This rarity appears to be related to the likelihood that their presence early in gestation usually results in abortion (Gilles et al., 1985).

Syphilis is considered to be at the top of the list of diseases causing fetal abnormalities. Treponema pallidum is the spirochete that causes syphilis in human. It can be transmitted by sexual contact with infected persons and congenitaly by transplacental infection from infected mother to fetus (Larsen et al., 1988). The clinical manifestations of syphilis are classified by stage of infection as primary, secondary, latent, benign late and tertiary syphilis. Most fetal infections occur after the sixth month of pregnancy. This immunity of the fetus is caused in part, if not entirely by the layers of cylindrical langhan's cells of the early

placenta, which are intact until after the fourth month of gestation (Fiumara, 1970). Approximately 25% of infants infected in utero die before birth. Another 25% die shortly after birth if untreated. About 40% of infected untreated infants who survive develop late symptomatic syphilis (Fiumara, 1970).

Toxoplasmosis is the infection caused by the obligate intracellular protozoan Toxoplasma gondii. The two major routes of transmission of T. gondii are oral and congenital i.e. ingestion of raw or uncooked meat containing tissue cysts and transplacentaly from infected mother to the fetus through the trophozoites (Desmonts et al., 1974). A woman does not transmit the infection to her unborn child unless her primary infeciton occurs during that pregnancy, and it has not been proved that toxoplasmosis is a cause of spontaneous abortion. The clinical manifestations of congenital toxoplasmosis are related to many factors including age of the fetus at time of infection, dose and virulence of the infecting strain and the status of maternal and fetal defences (Krick, 1978).

Pregnancy has been known to be associated with depressed aspects of cell mediated immunity that permit fetal retention but that also may interfere with resistance to specific infections and neoplastic agents (Weinberg, 1984). Longitu-

dinal analysis of lymphocyte proliferative responses to soluble antigens reveals a marked diminution of immune response during the second and third trimester of pregnancy (Birkeland et al., 1980).

Circulating immune complexes (CICs) may form as a result of/or during pregnancy. Some authors as Messon et al. (1977) and Shena et al. (1979) found that there is high levels of CICs in cases of normal pregnancies. While others as knox et al. (1978) found no elevated values. Increased CIC levels have been found to be associated with several disorders e.g. viral and parasitic diseases (Marburg, 1986).

AIM OF WORK

II. Aim of the Work

The aim of this work is to find out the percentage of sera from pregnant women, reactive against certain intra-uterine infections which may produce congenital defects including Rubella virus, Cytomegalovirus, Herpes simplex virus, Treponema pallidum and Toxoplasma gondii.

The possible relationship between seropositivity to any of these agents and congenital abnormalities is explored. The immune function in the same group of pregnant women was also studied through detection of the level of circulating immune complexes.

REVIEW OF LETERATURE

A. CONGENITAL MALFORMATIONS

As previously mentioned, about 2 percent of newborn infants have a malformation. The incidence is as high as 5 percent if one includes malformations detected later in childhood, such as abnormalities of the heart, kidneys, lung and spine. Malformations are more common among spontaneous abortuses; many of these are severe and may be the cause of abortion. About 9 percent of perinatal deaths are due to malformations. A simple and arbitrary terminology has evolved for describing malformations. A major malformation has serious medical, surgical, or cosmotic consequences. A minor anomaly and a normal variation have no serious consequences and are differentiated on the bases that a minor anomaly occurs in 4 percent or less of children of the same race, whereas a normal variation is more common (Nelson, 1979).

Teratogenic environmental factors are mostly effective during the early phases of organ morphogenesis, when the process of cell proliferation and tissue differentiation is highly active. Later in development, after differentiation has taken place and the fetal membrane have formed, a noxious agent does the most damage to those cells which are growing fastest. Since morphogenesis of various organs occurs at different developmental times, it follows that different organs affected at different stages of development. The