Antipaternal Lymphocytotoxic Antibodies In Pregnancy Induced Hypertension

THESIS

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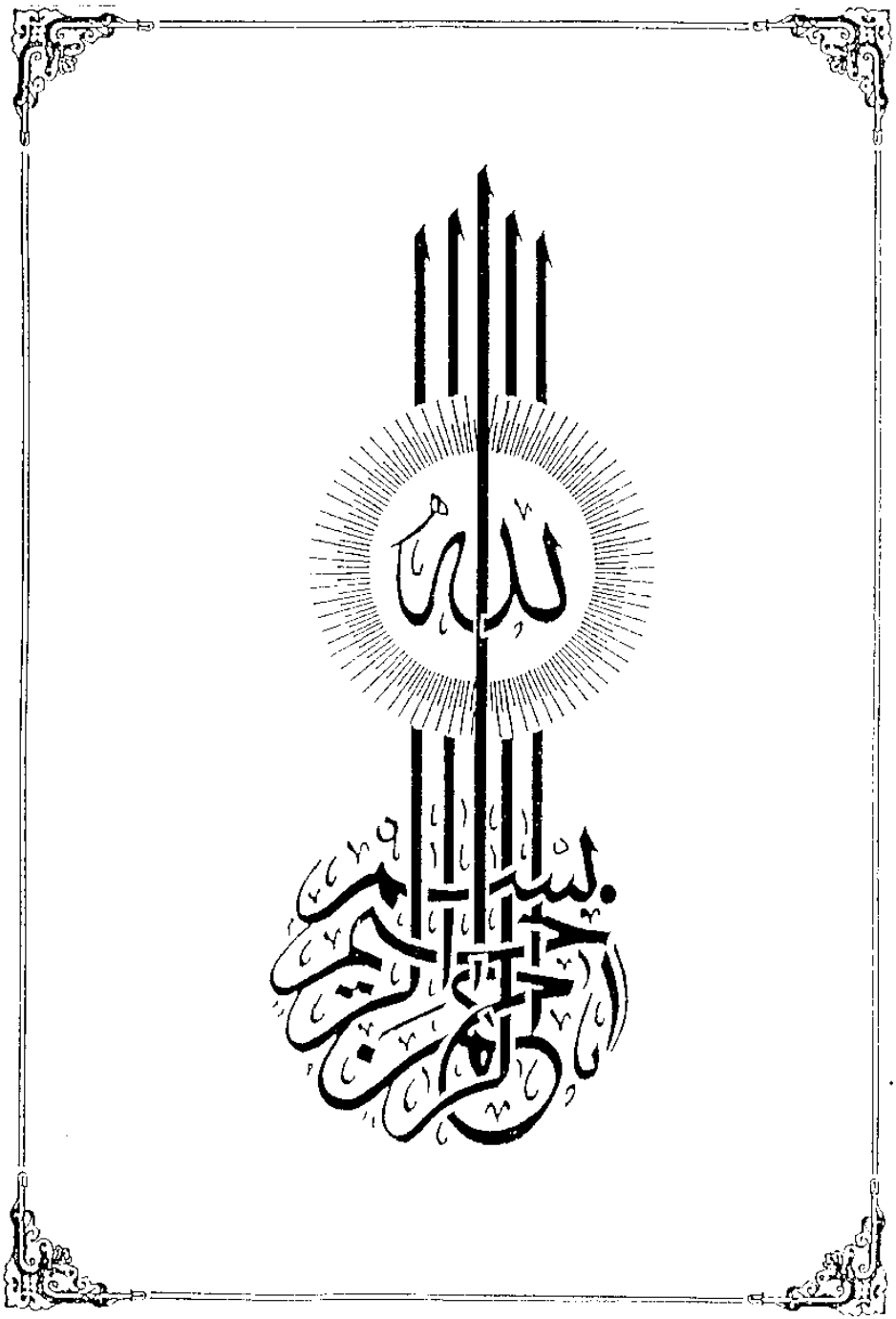

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INTRODUCTION

AND

AIM OF THE WORK

INTRODUCTION

Pregnancy induced hypertension (PIH) is one of the serious complications of pregnancy and is held responsible for a number of maternal and fetal morbidity and mortality (Chamberlain et al., 1975).

As our understanding of immunologic mechanisms has grown, many diseases of unknown aetiology have been shown to have an immunologic basis. So, recent awareness of the possible range of immunologic manifestations have stimulated reapprasial of certain ill-understood clinical problems in the field of reproduction for possible immune aetiological factors (Gill et al., 1982).

The last few decades have seen a rapid expansion in our knowledge of the immunology of the reproductive process. Advancing research has helped to outline the complex nature of the immunologic events that surround fertilization, implantation, and intrauterine tolerance, growth and development of the embryo. Over the years, investigations from around the world have begun to

unravel the mystery of the feto-maternal allograft. Although our understanding is far from complete, we have accumulated a tremendous amount of information about the immunologic events surrounding reproduction. Numerous alterations in the maternal immune response have been identified that evolve from the very beginning of gestation. A great deal has been uncovered regarding the success of the fetus as an allograft at both the maternal-fetal-placental interface and more distant sites of fetal-maternal cell contact (Landers et al, 1990).

The fetus, having inherited half of its transplantation antigen content from its father, may be considered a semi-allograft unit on its mother. Absence of evidence of fetal rejection has been considered an apparent paradox (Jenkins, 1988). The paradoxical survival of the fetal allograft has been described as "nature's transplantation success" (Anderson, 1971). The exact mechanism involved in the apparent success of the fetus as an allograft are only partially understood. Several hypotheses have been proposed, each of which is supported by substantial scientific investigation. The mechanism that link the various hypotheses and the many signals and unknown factors that initiate and regulate the system as a whole remain unclear (Landers et al., 1990).

By suggesting an immunological aetiology for pre-eclampsia, many details of this enigmatous disease can be better understood (Gill et al., 1982).

Kalmus (1946) considered that an offending fetal antigen might be responsible for pre-eclampsia, whilst Platt et al (1958) considered the opposite with fetal reaction to an offending maternal antigen leading to the condition.

Scott et al (1978) proposed that women with severe pre-eclampsia are hypoimmune with respect to non specific response as well as specific response to paternal antigens. This may or may not be associated with increased histocompatibility between the patient and her partner. It is further argued that this hypoimmune state is consistent with the first pregnancy preponderance of the syndrome, representing a primary immune response to pregnancy and/or paternal antigens and therefore of lower magnitude than to be expected with secondary responses after repeated exposure.

The commonly held concept now is that maternal recognition of the implanting embryo and the generation of a protective immune response is an absolute requirement for normal pregnancy. The break of such protective immune response may provide the conceptual

basis for the pathogenesis of certain pregnancy disorders among which PIH lies (Jenkins, 1988).

Caretti et al (1974) reported the presence of lymphocytotoxic antibodies more frequently in patients with pregnancy induced hypertension than in normal pregnant women. The rule of these antibodies in normal pregnancy is nuclear. It was suggested that these antibodies have a protective function in normal pregnancy by blocking a harmful maternal immune response, thereby protecting the fetus (Mendenhall, 1976). The stimulus responsible for these antibodies to develop and their exact role are still uncertain (Stirrate, 1985).

Immune (antigen-antibody) complexes are formed when antibodies combine with their corresponding tissue-fixed antigens or with antigens free in serum and other body fluids. It's assumed that pregnancy exposes the mother to an increasing influx of fetal antigens, which must be cleared by formation of complexes with maternal antibodies by removal via the reticuloendothelial system (Balasch et al., 1981b).

High serum levels of circulating immune complexes (CICs) were found in normal pregnancy by Masson et al (1977). Stirrate et al., 1978 confirmed this finding. Rote and Caudle (1983) found CICs valves not

significantly increased in pregnant women over control non pregnant women.

The study of possible levels and role of immune complexes in pre-eclampsia has resulted in controversial data. Evidence for CICs existence in patients with PIH has been demonstrated by Stirrate et al (1978) and Schena et al (1979) but others disputed these findings (Knox et al., 1978 and Balasch et al., 1981b). An important reason for disagreement may be the large number of methods designed to detect immune complexes in biologic fluids.

AIM OF THE WORK

In view of the conflicting data regarding the presence and role of lymphocytotoxic antibodies in the maternal serum during normal pregnancy, the first objective of the present work is a trial to elucidate this issue and to find out the occurrence of these antibodies in patients with pregnancy induced hypertension.

Several studies have focused on measuring circulating immune level during normal pregnancy and PIH, however controversial results were obtained. Our second objective is to measure the level of these immune complexes in the sera of normal pregnant women and women with PIH.

Lastly, this work is aiming to compare the results of the previous immunological parameters in the normotensive pregnancies and those complicated by PIH, which may contribute to a possible immunopathogenesis of this disease.

REVIEW OF LITERATURE

IMMUNOLOGY OF NORMAL PREGNANCY

* General consideration :

An organ grafted from one individual to another encounters a "histo-compatibility barrier". It is recognized as foreign, the host is sensitized ad graft is rejected. Recognition depends on cell surface histocompatibility antigens in the grafted tissues.

The host response to allogenic graft is dual and is composed of (1) synthesis of humoral antibodies which are capable of destroying components of lymphohemato-poietic system. These humoral antibodies produce effect on cellular immunity known as immunologic enhancement. (2) Production of blood-borne lymphocytes "effector cells" which infiltrate the parenchyma of the allograft and produces direct contact mediated cytopathogenic effect and indirect effect through lymphokines.

* **The Fetus As Allograft :**

The fetus, having inherited half of its transplantation antigen content from its father and the other half from its mother, may be considered a a semi-allograft on its mother. Absence of evidence of fetal rejection has been considered an apparent paradox and it is still a mystery how pregnant women tolerate the fetal allograft.

The immunological implications of pregnancy have only been perceived since Medawar (1953) made his observation in mice. He was led to ask "How does the pregnant mother continue to nourish within herself for many months a fetus which is antigenically foreign body ?!" Before answering this question, it is of great importance to determine the extent to which the pregnant female is immunologically aware of her genetically alien conceptus. Only then it is possible to assess fully relevance of any maternal immune responses to the establishment and maintenance of normal pregnancy.

It is stated or implied commonly that maternal immune recognition of the allogenic embryo is usually essential for the success of pregnancy. As transplanted allogenic tissues normally invoke an immunological rejection response in the host, it is necessary not only

to determine the reasons why this manifestly does not occur in the pregnant female but also to question how immune recognition of the embryo could conceivably beneficial (Billington, 1988).

According to Clark (1990), the conceptus in fact represents two grafts :

GRAFT ONE : Fetal tissue which is enclosed within a sac of membranous lined by fetal trophoblast cells that form the feto-maternal interface and placenta. Fetal tissue is immunogenic and susceptible to immunological recognition and rejection by the mother provided that contact between maternal lymphomyeloid cells and fetal cells occurs.

GRAFT TWO : Fetal trophoblast. It is a unique tissue. It has many special characters which will be discussed in details. The conceptus behave in a manner different from conventional allografts and this is due primarily to trophoblast (graft 2).

*** Fetomaternal Interface :**

At the tissue level, contact between mother and conceptus is through fetal trophoblast. It is the trophoblast that provides the fetal interface with the maternal decidua. It does so in a variety of biological