BIOCHEMICAL STUDIES OF CERTAIN ADRENO MEDULLARY FUNCTIONS IN NORMAL AND PRE-ECLAMPTIC PREGNANCIES

THESIS

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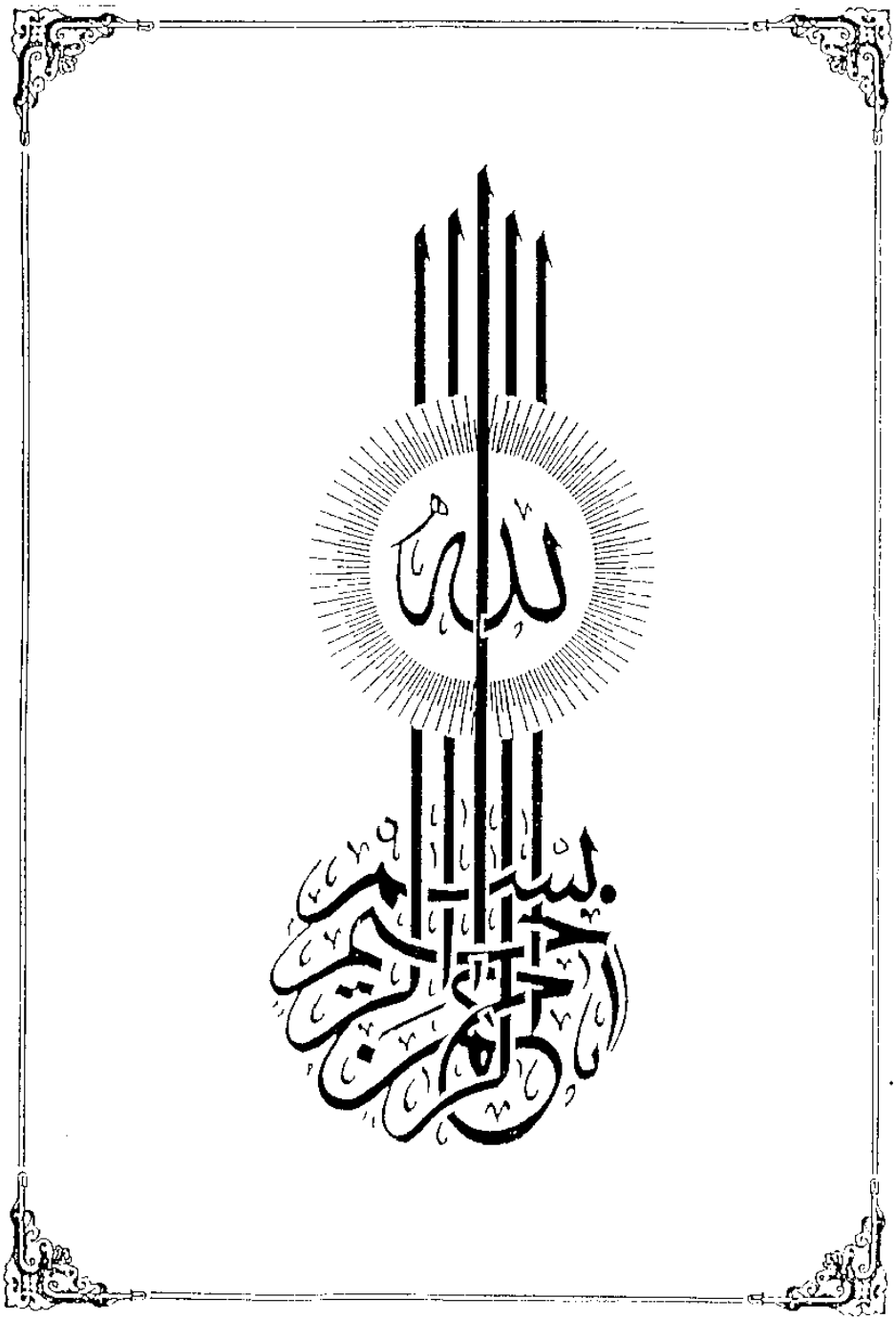
To the patients who cooperated to make this study possible, I offer the results of my work hoping to solve the problem of other patients suffering the same disease.



C O N T E N T S

I- INTRODUCTION

"Review of Literature"

Pre-eclamptic Toxaemia

Eclampsia is a graphic word that means sudden flash of light and it was given presumably because the condition occurred without warning like a flash of lightning. The use of the word eclampsia dates from the seventeenth century where it was recognized that generalized convulsions or fits prone to occur in pregnant or recently delivered women were of two main types:-

1) Those due to epilepsy, were not related to pregnancy and were rarely fatal.
2) Those associated only with pregnancy were frequently fatal and they were attributed to blood poisoning or toxaemia, caused by a poisonous substance derived from pregnancy.

Following the demonstration by Dr. Bright (1927), dropsy and albuminuria were basically related to renal disease. It was soon recognized that they were also features of the pregnancy toxaemia "Eclampsia".

Then as soon as the sphygmomanometer was invented in 1896 arterial hypertension came to be acknowledged as an important features of eclampsia and its appearance usually predated the actual occurrence of fits.

From the above background there gradually emerged the concept of pre-eclampsia as a less severe degree of the same pregnancy toxaemia in which hypertension, fluid retension and albuminuria appear in varying sequence and degree without convulsions on periods of loss of consciousness.

Many disorders associated with pregnancy are toxaemic in nature but the term specific toxaemia of pregnancy is only related to pre-eclampsia, imminant eclampsia and eclampsia.

Pre-eclampsia is now defined by the committee on terminology as"Development of gestational hypertension plus proteinuria or albuminuria or generalized oedema after 20 weeks of pregnancy."

Gestational hypertension is a sustained increase of 30 mmHg in systolic or of 15 mmHg or more in diastolic B.P. over the patient usual blood pressure. These are considered better criteria than the alternative standards of 140 mmHg systolic or 90 mmHg diastolic.

Nelson's definition (1955) of eclampsia is a sustained rise of diastolic pressure to 90 mmHg or higher. In the absence of proteinuria the diagnosis is mild pre-eclampsia while appearance of proteinuria makes it severe.

There had been various attempts to standardize the name of this well-known disease. It was called : Pre-eclamptic toxaemia, albuminuria of pregnancy, specific hypertensive disease of pregnancy, pre-eclampsia and lastly E.P.H gestosis i.e. Oedema, proteinuria and hypertension gestosis.

Clinically, it is defined by raised B.P. + albuminuria and oedema and hence the recent definition E.P.H. gestosis. The degree of each of the three cardinal signs vary in severity and there may be some additional symptoms such as: headache, epigastric pain, vomiting, reduced excretion of urine and dim vision. A minority of patients especially those who were not treated, occasionally pass into eclamptic convulsions and coma.

A typical case of toxaemia has no antecedent signs or symptoms with the possible exception of a sudden abnormal gain in weight due to water retention, which may not have been noticed either by the doctor or the patient herself.

Toxaemias of pregnancy are still the leading cause of maternal and perinatal mortality in Egypt and in other parts of the world. In unpublished reports into maternal and foetal mortalities in Egypt 20% of maternal deaths were caused by toxaemia of pregnancy and not less than 25% of the perinatal mortalities were due to the same cause.

Recently, it has been published (Lopez, Linores and Hernandez, Hemands 1976) that the maternal mortality rate in eclampsia varies from 0 - 20% in the contemporary medical literature, even though most authors pursue similar general therapeutic objectives. Furthermore many modern managements have not been able to improve significantly the results reported by Straganoff (1935) in the early part of this century.

This fact becomes a flugrant contradiction in view of the spectacular medical progress seen in the last fifty years.

Eden (1922), Straganoff (1935), and Peckham (1935) recognized important differences in the clinical picture of eclamptic women. Some cases would follow a rather benign uncomplicated course with prompt recovery, while others would frequently end in death. It becomes evident that any rational therapy could give optimal results in the first type of patients and be relatively unsuccessful with the second group. Thus without estimating the importance of a correct therapeutic approach that requires the expertly balanced individualization we consider that it is imperative to try to identify the dominant factors that may influence the course of the disease toward a lethal outcome independent of therapeutic consideration.

The death of the patient may be considered as the result of a variable association of factors within a limited clinico-pathological and therapeutic spectrum. The simultaneous or successive analysis of multiple factors has met with serious conceptual and programmatic difficulties. Its ability depends on the proper selection of variables on the possibility of quantitative estimation of corresponding parameters and on the existence of significant differences in the data under study.

Lopez (1976) said that the death of eclamptic patients resulted from a combination of several factors that showed a very wide individual variation. Since advancing age of the mother is associated with a very high incidence of coincidental renal and vascular diseases. This could be considered as the most important factor. Thus the age of the patient at the time of eclampsia is considered as the most clearly influential factor affecting the maternal mortality in eclampsia (Lopez 1976).

On the other hand relative aging and pregnancy may be associated with the emergence of previously non detectable underlying pathology. An increase in age within narrow range may be accompanied by general and regional changes that potentiate each other reciprocally and in the proper pathogenic setup render the patient more prone to fatal consequences.

But through study by (Lopez, Linares and Hernandez 1976)carried on postpartum findings of eclamptic patients, two important facts were detected:-

a) High incidence of chronic pyelonephritis,

b) High incidence of cardiac hypertrophy.

Whether the first finding was a mere coincidence and has no influence on the pathogenesis of eclampsia or not, this cannot be assessed up till now. Furthermore, according to Freedmant (1967) the incidence of non-obstructive chronic pyelonephritis found at autopsy varied from 0.6 - 2.4%. Sheehan, Lynch (1973) reported an incidence of large pyelonephritic scars in 5.7% of autopsied toxaemic women. The frequent occurrence of urinary infections among poor people, where pre-eclampsia is more common, can be taken as a reasonable association.

As far as cardiac hypertrophy is concerned, the paramount question is whether it resulted from the toxaemic episode alone or it existed prior to pregnancy. The fact that pre-eclampsia is seen more among women after 30 years of age would support the latter possibility.

Classification of Pre-eclampsia:-

The clinical diagnosis of pre-eclampsia is frequently a matter of conjecture, as the main features: Hypertension, oedema, proteinuria occur in a variety of pathological states. This basic difficulty in the precise diagnosis has resulted in confusion when aetiology and therapy are considered.

Hypertension in pregnancy may be a manifestation of essential hypertension (which can be unmasked for the first time in pregnancy), chronic renal disease or pre-eclampsia which may be mild or severe. Other medical conditions as the collagen vascular disease or pheochromocytoma though rare must be considered in the differential diagnosis.

During pregnancy, a blood pressure of 140/90 must be regarded as pathological; MacGillivary (1970) reported that most obstetricians consider the upper limit of blood pressure in normal pregnant women as 135/85 mmHg., and so a patient with pathological evidence of toxaemia has almost always a blood pressure above 135/85 mmHg., though hypertension by this standard does not indicate toxaemia. A precise diagnosis of hypertension can only be attempted if the patient's blood pressure is recorded early in the first trimester of pregnancy. Later, a physiological

mid-trimester fall in blood pressure may mask essential hypertension which only becomes evident later in pregnancy.

A classification advocated by the American Committee on Maternal Welfare (Eastman et al. 1952) which has the merit of simplicity is:-

1. Pre-eclampsia mild or severe.
2. Eclampsia.
3. Essential hypertension.
4. Chronic renal disease.
5. Unclassified group.

It is virtually impossible to exclude chronic renal disease on clinical grounds in cases diagnosed clinically as pre-eclampsia. In several series of renal biopsies, utilising both light microscopy and electron microscopy, although the clinical diagnosis of pre-eclampsia was established, yet chronic renal lesions was evident in nearly 20%.

Sheehan and Lunch (1973) considered that the classification of eclampsia is based primarily on the appearance or absence of the following:-

a) Clinical evidence of toxaemia during the course of pregnancy.

b) The final development of one or other kind of toxaemic crises.

c) Autopsy findings: In an investigation of the pathological changes in toxaemia, the presence or absence of the characteristic lesions must not be used for establishing the clinical diagnosis. Sheehan and Lunch (1973) have avoided allowing these pathological findings to influence the classification of their cases. Nevertheless, the autopsy findings are of importance in two ways.

Firstly, clinical features suggestive of an ordinary toxaemia may be discovered at autopsy to have been due to some medical complication whose existence was not recognized during life.

Secondly, what appeared clinically to be a toxaemic crises may be found at the autopsy to have been due to some other condition: for example the autopsy may reveal that coma was caused by uraemia or meningitis. For these reasons, the clinical diagnosis has always been reviewed in the light of the autopsy findings.

So considering the classification advocated by Sheehan and Lunch (1973) we have the following groups:-

1. Normal pregnancy. This means that toxaemia was absent, the patient blood pressure never exceeded 135 mmHg systolic and 85 mmHg diastolic. There was no

albuminuria, no oedema, no other symptoms that suggest pre-eclamptic complex.

2. No abnormality. The same as the normal group.

3. Minor toxaemia with systolic blood pressure 140 - 155 mmHg and diastolic 90 - 100 mmHg. Slight or moderate albuminuria, oedema of legs and no pre-eclamptic symptom complex.

4. Major toxaemia. This comprises more severe degree than the minor type, but with no toxaemic crises. This stage shows blood pressure over 155 mmHg systolic and 100 mmHg diastolic + gross albuminuria and oedema.

5. Toxaemic coma. Patient known to be toxaemic passes into sudden coma with no initial convulsions and no gross cerebral haemorrhage.

6. Primary cerebral haemorrhage which is the cause for coma.

7. Single fit only in a toxaemic patient.

8. Eclampsia. The diagnosis of eclampsia is put when there are two or more typical eclamptic convulsions followed by coma. Those cases are divided into four classes:-