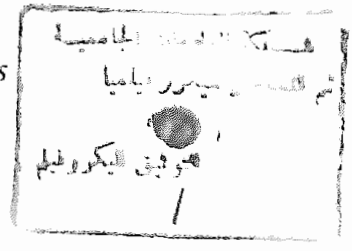
REVERSAL OF ENDOTHELIAL CELL DAMAGE AFTER DELIVERY IN CASES OF SEVERE PREGNANCY INDUCED HYPERTENSION AS INDICATED BY PLASMA FIBRONECTIN FIBRINOGEN AND PLATELET COUNT

Thesis Submitted for partial Fulfillment of Master Degree in Obstetrics and Gynaecology



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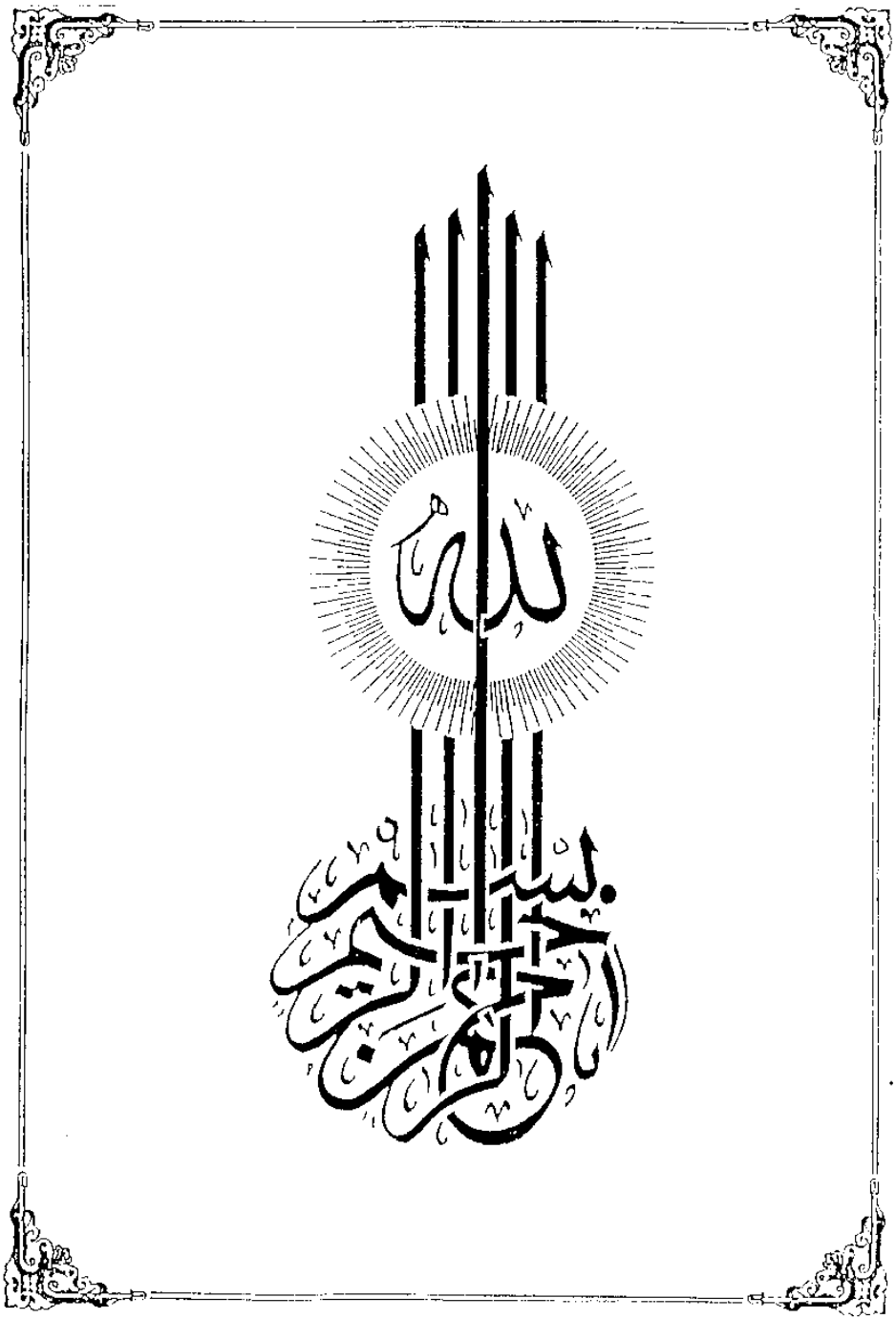
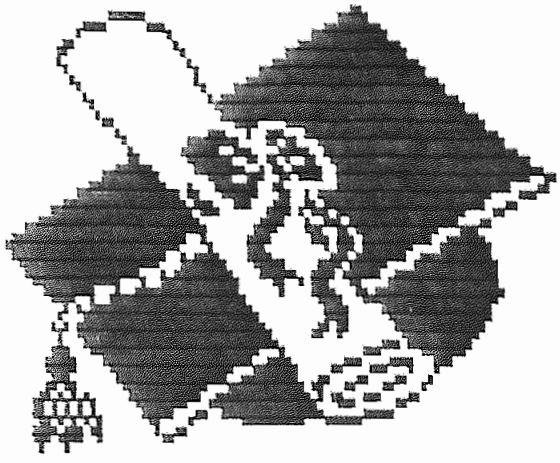


CONTENTS



INTRODUCTION AND AIM OF WORK

INTRODUCTION

Pregnancy induced hypertension is a specific condition which occurs only in human females during pregnancy. It is characterized by hypertension and proteinuria or edema, if untreated it may end in eclampsia which is characterized by convulsions. It is almost a disease of nulliparous women who are at the extremes of their reproductive age. The condition is characterized by increased maternal morbidity and perinatal mortality. Preeclampsia becomes evident clinically after the pathophysiologic process that may begin 3-4 months before hypertension appears (Pritchard, 1978).

The vascular endothelial damage plays an important role in pathophysiology of preeclampsia. It may cause platelet adherence to collagen exposed at sites of disrupted vascular endothelium and fibrinogen deposition subendothelially after passage from interendothelial leaks (Brunner and Gavras,1975). These cause thrombocytopenia and hypofibrinogenemia in cases of severe preeclampsia.

Fibronectin is a plasma glycoprotein which is involved in coagulation, platelet function tissue repair and the vascular endothelial basement membrane. Fibronectin has a soluble plasma form and insoluble tissue form. The insoluble form is called the cellular fibronectin which is produced by fibroblasts, endothelial cells, macrophages, blood platelets and is a wide spread component

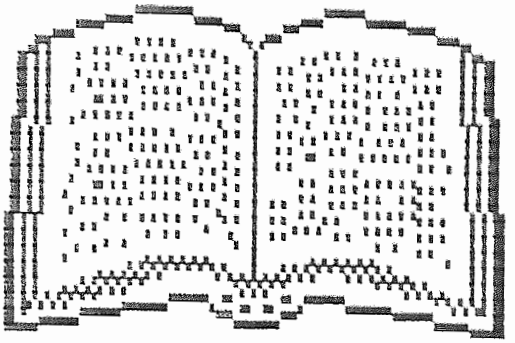
of conective tissue and basement membranes (Ballageer et al.,1989). Plasma fibronectin concentration was found to be abnormally elevated in preeclampsia and suggested that its measurment may serve as an early indicator of endothelial cell damage (Stubbs et al.,1984). The level of normally circulating fibronectin (200-400 μg/ml) is thought to result primarily from synthesis by vascular endothelium.

Fibronectin levels change in association with several disease states. Its level decreases in liver insufficiency, dissiminated intravascular coagulation (DIC), respiratory distress syndrome, sepsis, polytrauma and increases in patients with rheumatoid arthritis. It was found that its level is unchanged in normal pregnancy and in chronic hypertension with pregnancy (Ballageer et al.,1989).

AIM OF THE WORK

The aim of this study:

1. To detect plasma fibronectin, plasma fibrinogen and platelet count in cases with severe preeclampsia at the start of labour.
2. To detect changes that occur in these three parameters after delivery.
3. The correlation between fibronectin, fibrinogen levels and platelet count as all are indicators of endothelial cell damage.



REVIEW OF LITERATURE

REVIEW OF LITERATURE

Preeclampsia:

Pregnancy induced hypertension (PIH) is divided into three categories:-

1. Hypertension alone.
2. Preeclampsia.
3. Eclampsia.

Preeclampsia is the development of hypertension with proteinuria, edema or both, induced by pregnancy after the $20^{\underline{th}}$ week of gestation and sometimes earlier when there are extensive hydatidiform changes in the chorionic villi (Pritchard,1978).

Preeclampsia is almost a disease of nulliparous women (Pritchard,1978) . Although it most commonly affects the woman who is at the extremes of reproductive age, that is, teenagers or those older than 35 years; preeclampsia in the latter usually reflects pregnancy-aggravated hypertension. Pregnancy induced hypertension is occasionally seen in the multipara with multifetal pregnancy or fetal hydrops. Moreover, pregnancy-aggravated hypertension is common in multiparous with vascular diseases, including chronic essential hypertension and diabetes mellitus or those with coexisting renal disease (Pritchard 1978).

The diagnosis of preeclampsia has required the identification of blood pressure 140/90 or greater or an increase of 30 mm Hg systolic or 15 mm Hg diastolic over base line values, on at least two occasions six hoursor more apart plus proteinuria or generalised edema (Pritchard,1978). One third of women was found to develop generalised edema by the 38th week of pregnancy. The edema of preeclampsia involves the face and hands and is present in the morning after arising from bed.

Proteinuria is an important sign of preeclampsia. It is defined as presence of 300mg or more of protein in a 24 hr urine collection or a protein concentration of 1g/l or more in at least 2 random urine specimens collected 6 hours or more apart (Pritchard,1978).

The combination of proteinuria and hypertension during pregnancy markedly increase the risk of perinatal mortality. Mc-Cartney and co-workers (1971) in their extensive experience studing renal biopsy specimens of hypertensive pregnant women found that proteinuria was present when the glomerular lesion considered to be characteristic of preeclampsia was evident.

Pathophysiology of preeclampsia:-

Vasospasm:-

Vasospasm is basic to the disease process of preeclampsia-eclampsia. Several authers noted alternation in the size of arterioles in the nail bed, with evidence of segmental

spasm that produced alternate regions of contraction and dilatation (Pritchard,1978). marked arteriolar constriction was describedto the extent that capillary circulation was intermittently abolished. The vascular constriction imposes a resistance to blood flow and accounts for the development of arterial hypertension. Vasospasm exerts a noxious effect on the blood vessels themselves as well as the organs they supply. Circulation in the vasavasorum is impaired leading to damage of the vascular wall. Alternating segmental dilatation that accompanies the segmental arteriolar spasm contributes further to the development of vascular damage since endothelial integrity may be compromised by stretch in the dilated segments. Angiotensin II appears to have a direct action on endothelial cells causing them to contract. These events can create interendothelial leakes through which blood constituents including platelets and fibrinogen can pass and be deposited subendothelially (Brunner and Gavras,1975). The vascular changes together with local hypoxia of the surrounding tissues presumably lead to hemorrhage, necrosis and other disturbances that have been observed at times with severe PIH.

Increased pressor responces:-

Normally pregnant women develop refractoriness to the pressor effects of angiotensin II (Abdul Karim and Assuli,1961). Increased vascular reactivity to pressor hormones in women with early preeclampsia has been identified using angiotensin II or norepinephrine and vasopressin (Dieckman and Michel, 1937;

Browne,1946) . Subsequently, Gant and co-workers (1973) clearly demonstrated that increased vascular senstivity to angiotensin II occurs sometime before the onset of hypertension. Refractoriness to angiotensin II is not a generalised phenomenon, since aldosterone secretion is increased in pregnant women. That secretion is modulated by the action of angiotensin II on the cells of the zona glomerulosa of the adrenal cortex. Gant and co-workers (1974), Cunningham and associates (1975) and Everett and colleagues (1978a,1978b) concluded that in pregnant women the blunted pressor response to angiotensin II was brought about by a specific decrease in responsiveness of the vasculature. The refractoriness to angiotensin II appears to be mediated by the vascular tissue synthesis of a prostaglandin or prostaglandin like substance e.g. prostacyclin or PGE_2. The refractoriness to the pressor effect of angiotensin II in pregnant women can be abolished by administration of prostaglandin synthetase enzyme inhibitors,indomethacin and asprin (Everett and colleagues,1978a). It is interesting that pregnancy brings about an increased capacity for prostaglandin formation in vascular tissue, normally with relatively greater synthesis of prostaglandin that induce vasodilatation than of prostagtlandins that promote vasoconstriction e.g. prostaglandin $F_2\alpha$ (Pritchard, 1978).

The most obvious function of endothelium is the mechanical separation of blood products from collagen and smooth muscles of the vascular wall (Jaffe,1987). The interface between intra and extravascular compartments must allow transport of nutrients,

waste poducts, regulatory molecules and phagocytic cells across cellular basement membranes. Normally vascular endothelial surfaces resist platelet aggregation and coagullation. Platelet adherance to the endothelial cell surface is discouraged by other endothelial cell products including prostacyclin. Normal endothelial cells modify the contractile responses of subjacent vascular smooth muscles. The removal of vascular endothelium reversed the response of aortic strips to acetyl choline from relaxation to contraction (Roberts et al., 1989). Similar modification of vascular responses have been reported for numerous agonists in different vessels (Roberts et al.,1989).

Disruption of vascular endothelium eleminates the source of the potent vasodilator prostacyclin and other less well characterised agents that leads to relaxation of vascular smooth muscles, "endothelial derived relaxation factor" and another that enhances vasospasm "endothelial derived contracting factor" (Roberts et al., 1989). Another potent constrictor of vascular smooth muscle "endothelin" has been identified in media from cultures of vascular endothelium (Yanagisawa et al.,1988).

Activities of injured endothelial cells:-

With injury, the production of anticoagulants and vasopressor substances is reduced. Disturbances of endothelial tight junctional complexes and concomitant loss of regulated fluid and protein transport lead to extravasation of fluid and proteins from the intravascular space. In adition to the loss of protective

functions, injured endothelial cells also express new functions (Roberts et al.,1989). Procoagulant synthesis and activation of the clotting cascade occur at the sites of endothelial disruption and promote platelet aggeregation and clot formation. Injured endothelium produce mitogens at least one of which, platelet-derived growth factor, is also a potent vasoconstrictor. Increased membrane permeability, clot formation, vasospasm and blood vessel remodeling, while vital responses to disruption of vascular integrity can cause serious physiologic disturbances such as those implicated in the pathogenesis of atherosclerosis when inapproprately activated.

Endothelial cell injury in preeclampsia:-

There is a considerable evidence that endothelial cell injury is present in women with preeclampsia. The most consistent morphologic abnormality in preeclampstic women is the renal lesion termed "glomelular endotheliosis" (Roberts et al.,1989), in which glomelular capillary endothelial cells are engorged with intracellular inclusions. This finding is present in >70% of primiparous women with preeclampsia reverses completely after delivery. However, umblical cord arteries from infants of preeclamptic women have been reported to demonstrate endothelial cell disruption which were not present in similar vessels from infants of normal parturients (Roberts et al., 1989). However, it should be emphasized that functional abnormalities of endothelial cells can be present in vessels with grossly normal morphology. The prominent clinical features of preeclampsia (edema and