ELEVATED SECOND TRIMESTER HUMAN CHORIONIC GONADOTROPIN AND SUBSEQUENT PREGNANCY INDUCED HYPERTENSION

Thesis
Submitted For Partial Fulfillment of Master Degree In Obstetrics And Gynecology

by

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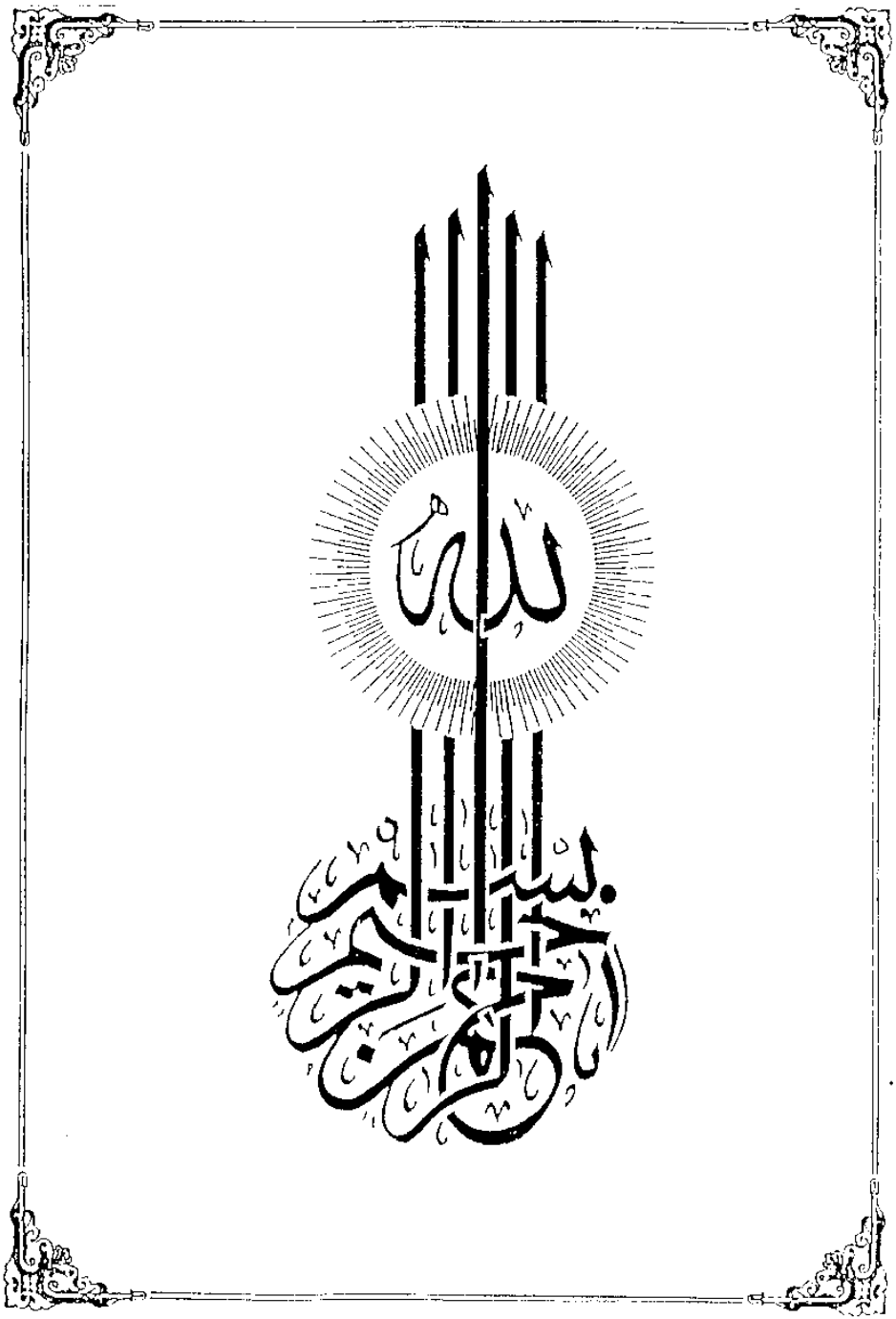

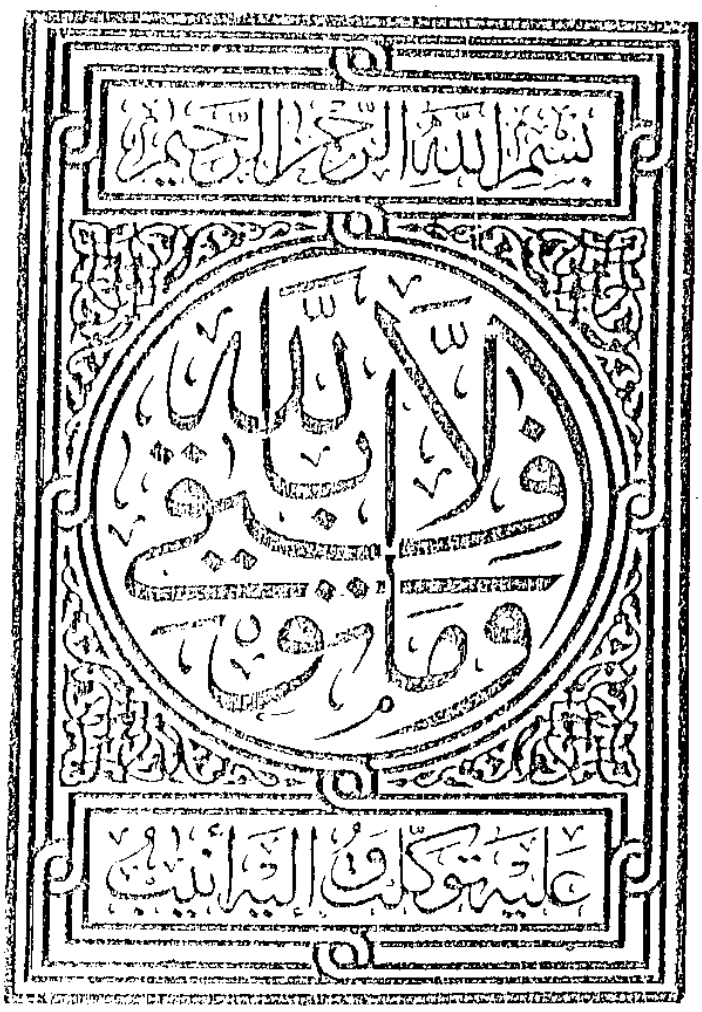

(بسم الله الرحمن الرحيم)

[الله يعلم ما تحمل كل أنثى وما تغيض الأرحام وما تزداد وكل شئ عنده بمقدار]

(الآية الثامنة من سورة الرعد) « صدق الله العظيم »

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Pregnancy induced hypertension is a multisystemic disease characterized by hypertension , oedema and or albuminuria . Although overt illness rarely appear untill the third trimester, there are multiple indications that the disease process begins early in pregnancy . Second trimester changes in several maternal serum factors and in maternal angiotensin sensitivity are among the frequent precursors of clinical symptoms ***(Soronsen et al., 1993).***

Placental abnormalities are a consistent finding in established pregnancy induced hypertension . As early as 1950 the placental hormone human chorionic gonadotropin (HCG) was reported to be elevated in toxaemia of pregnancy . Conditions such as twin and molar pregnancies , which are associated with elevated HCG levels , may show the potential role of HCG in pregnancy induced hypertension .So they hypothesized that elevated maternal serum HCG in the second trimester,would be associated with the later appearance of pregnancy induced hypertension ***(Sorensen et al., 1993)*** .

Said et al., (1984) reported that HCG is a gylcoprotein with closed structural similarities to pituitary luteinizing hormone (L.H) ; follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH) . Each of these molecules consist of two different peptide chains (subunits) called α and β. The α subunit is very similar in FSH , LH and HCG whereas the β subunit has a much less close resemblance in its amino acid sequence ***(Carlsen et al., 1973)*** . This has caused difficulties in producing specific antisera to HCG which do not cross react with other pituitary hormones .

The β subunit is the one which confers hormonal specificity and is , therefore, reffered to as the hormone specific subunit by ***Vaitukaitis et al ., (1972)*** who produced antisera specific to the β subunit of HCG for use in radioimmunoassay .

Beta HCG level were higher in high weight gain pregnancies that subsequently developed preeclampsia than in the high weight gain pregnancies that remained normotensive . In patients who went to develop preeclampsia , β HCG levels appear to rise even more towards the end of pregnancy when the clinical signs of preeclampsia appear . In patient who continued to be normotensive , β HCG levels tend to fall towards the end of gestation particularly after the 37th weeks ***(Said et al., 1984)*** .

AIM OF THE WORK : -

The aim of the work is to evaluate the efficiency of elevated 2nd trimester β HCG as a predictive test for pregnancy induced hypertension (P.I.H.).

REVIEW OF LITERATURE

HUMAN CHORIONIC GONADOTROPIN CHEMICAL STRUCTURE

Physiochemical properties :

Human chorionic gonadotropin (HCG) is a glycoprotein hormone produced by the placenta during pregnancy . Its molecular weight is 36.700 daltons and its isoelectric point is 4.5 ***(Birken and Canfield ,1978)*** .

It consists of a hormone nonspecific Subunit α with molecular weight of 14,500 daltons and a hormone specific β subunit with molecular weight of 22,200 daltons . The subuits are non covalently linked , and the primary aminoacid sequences of the subunits have been elucidated (Fig .1and 2). The α subunit contains 92 aminoacids , and the sequences nearly identical to those of subunits of the other glycoprotein hormones (viz ; human luteinizing hormone (hLH) , human follicle stimulating hormone (hFSH) , and human thyroid stimulating hormone (hTSH) ***(Saxena, 1983)*** .

The complementary HCG β subunit contains 145 aminoacids with several regions homologous to the other glycoprotein hormones β subunits such as FSH β and TSH β subunits and a striking homology of 80 aminoacids of the initial 115 with hLH β subunit (fig. 3), except that HCG β subunit contains an additional 30 aminoacids sequence at the C terminal which is rich in proline (fig.6) . The α subunit contains two while the β subunit five carbohydrate moieties attached to the protein chian . The monosaccharide sequences of the carbohydrate moities are shown in (fig. 4 and 5).In contrast to all other oligosaccharide side chains , the three oligosaccharide units of the carboxyl terminus of the HCG β subunit are O-glycosidically linked to serine instead of aspargine . ***(Saxena , 1983)*** .

1
Ala - Pro - Asp - Val - Glu - Asp - Cys - Pro - Glu - Cys - Thr- Leu - Glu - Asp - Pro-
10
Phe - Phe - Ser - Glu - Pro - Gly - Ala - Pro - Ile - Leu - Glx - Cys - Met - Gly - Cys - Cys -
30
Phe - Ser -Arg - Ala - Tyr -Pro - Thr - Pro - Leu - Arg - Ser - Lys - Lys - Thr - Met - Leu-
40
Val - Gln - Lys - Asn - Val - Thr - Ser - Glu - Ser - Thr - Cys - Cys - Val - Ala - Lys - Ser-
50 CHO 60
Tyr - Asn - Arg - Val - Thr - Val - Met - Gly - Gly - Phe - Lys - Val - Glu - Asn - His - Thr -
70
Ala - Gys - His - Gys - Ser - Thr - Cys - Tyr - Tyr - His - Lys - Ser
80
90

Fig 1 . Aminoacid sequenced of HCG-α . (Post et al ., 1980)

1
Ser - Lys - Glu - Pro - Leu - Arg - Pro - Arg - Cys - Arg - Pro - Ile - Asn - Ala- Thr - Leu -
10 CHO
Ala - Val - Glu - Lys - Glu - Gly - Cys - Pro- Val - Cys - Ile - Thr - Val - Asn - Thr - Thr -
20 CHO
Ile - Cys - Ala - Gly - Tyr - Cys - Pro - Thr - Met - Thr - Arg - Val - Leu - Gln - Gly -Val -
40
Leu - Pro - Ala - Leu - Pro - Gln - Val - Val - Cys - Asn - Tyr - Arg - Asp - Val - Arg - Phe-
50 60
Glu - Ser - Ile - Arg - Leu - Pro - Gly - Cys - Pro - Arg - Gly - Val - Asn - Pro - Val - Val -
70
Ser - Tyr -Ala - Val - Ala - Leu - Ser - Cys - Gln - Cys - Ala - Leu - Cys - Arg - Arg - Ser -
80
Thr - Thr - Asp - Cys - Gly- Gly - Pro - Lys - Asp - His - Pro - Leu - Thr - Cys - Asp - Asp -
90 100 110
Pro - Arg - Pro - Gln - Asp - Ser - Ser - Ser - Ser - Lys - Ala - Pro - Pro - Pro - Ser - Leu -
120 CHO
Pro - Ser - Pro - Ser - Arg - Leu - Pro - Gly - Pro - Ser - Asp - Thr - Pro - Ile - Leu - Pro -
130 CHO 140
Gln
145

FIG 2 . Amino acid sequence of HCG-β . (Saito et al ., 1977)

hCG-β : Ser - Lys- Glu - Pro - Leu - Arg - Pro - Arg - Gys - Arg - Pro - Ile-
hLH-β : - Arg- -Trp - -His

hCG β : Asn (CHO) -Ala - Thr - Leu - Ala - Val - Glu - Lys - Glu - Gly - Cys - pro -
hLH-β - Ile -

hCG-β : Val - Cys - Ile - Thr - Val - Asn (CHO) Thr - Thr - Ile - Cys - Ala - Gly-
hCH-β :

hCG-β : Tyr -Cys - Pro - Thr - Met - Thr - Arg - Val - Leu - Glu - Gly - Val -
hCG-β : - Arg - Met - Leu -

hCG-β : Leu - Pro -Ala - Leu - Pro - Gln - Val - Val - Cys - Asn - Tyr - Arg -
hLH-β : -Pro - Val - - Pro - - Thr -

hCG-β : Asp - Val - Arg - Phe - Glu - Ser - Ile - Arg - Leu - Pro - Gly - Cys -
hLH-β : Asx - - Glx -
hCG-β : Pro - Arg -Gln - Val - Asn - Pro - Val -Val - Ser - Tyr -Ala - Val -
hLH-β : - Asp - - Phe -Pro -
hCG-β : Ala - Leu - Ser -Cys - Gln - Cys - Ala - Leu - Cys - Arg - Arg - Ser -
hLH-β : - Arg - - Gly - Pro -
hCG-β : Thr - Thr - Asp - Cys - Gln - Gly - Pro - Lys - Asp - His - Pro - Leu-
hLH-β : - Ser - - Asx -

hCG-β : Thr - Cys - Asp - Asp -Pro - Arg - Phe - Gln - Asp -Ser- Ser- Ser-
hLH-β : - Asx - Glx -Asx - Ser - Lys - Gly -

hCG-β : Ser(CHO) - Lys - Ala -Pro -Pro - Pro - Ser(CHO) - Leu - Pro -Ser-

hCG-β : Pro - Ser -Arg - Leu - Pro - Gly - Pro - Ser (CHO) - Asp- Thr - Pro -

hCG-β : Ile - Leu - Pro - Gln

FIG.3 HCG-β and LH-β homology. (Saxena , (1983)

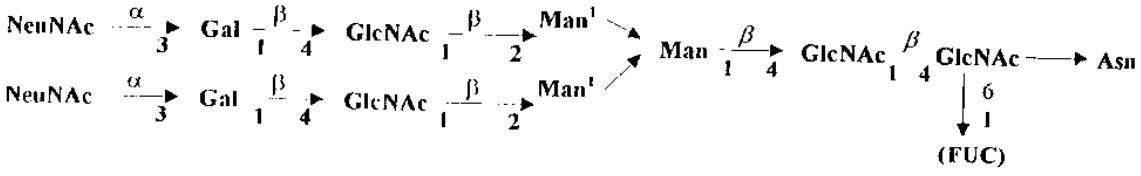

FIG. 4. Structure of N-glycosidic carbohydrate moieties of HCG(Saxena , 1983)

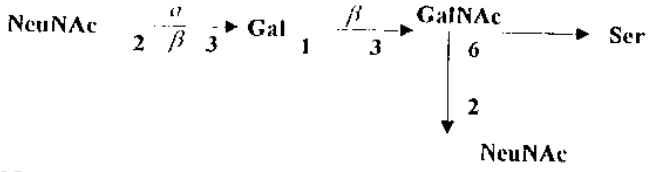

FIG.5.Structure of O-glycosidic carboydrate moieties of HCG- β(Saxena , 1983)

The carbohydrate component is composed of fructose , galactose , mannose , galactosamine , glucosamine and sailic acid . Alteration in the carbohydrate component (about one third of the molecular weight) especially the sailic acid residue change the biological properties , but not impairing receptor binding activity ***(Thotakura et al., 1990)*** .

The sialic acid residues of the HCG carbohydrate units influence biologic activity by promoting retention of HCG in the circulation .Removal of sialic acid by neuraminidase reduces the biologic activity of HCG measured in vivo due to increased metabolic clearance by the liver ***(Tsuruhara et al .,1972)***

Sialic acid residues are not necessary for receptor binding and asialo HCG exhibits only a partial loss of biologic activity in vitro (***Tsuruhara et al., 1972).*** However, partial reduction in biologic activity without a corresponding loss of receptor binding suggests a role for carbohydrate moieties in hormone action .If so , those moieties on the beta subunit must be most important.Selective removal of sialic acid from the alpha subunit does not deminish the in vitro biologic activity of HCG, but sialic acid removal from only the beta subunit reduces biological potency by more than 50 percent ***(Amir et al ., 1987).***

Wolf et al .,(1994) reported that the cellular localization and molecular control mechanisms of the production of HCG and free subunits in trophoblastic tissues remain uncertain .In situ hybridization studies have confirmed α HCG messenger RNA in cytotrophoblast, differentiating cytorophoblast, and in synctiotrophoblast , β HCG messenger RNA has been