CLONIDINE HCL : ADJUVANT THERAPY FOR INDUCTION OF OVULATION

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بسم الله الرحمن الرحيم

وقل رب زدنى علماً

صدق الله العظيم

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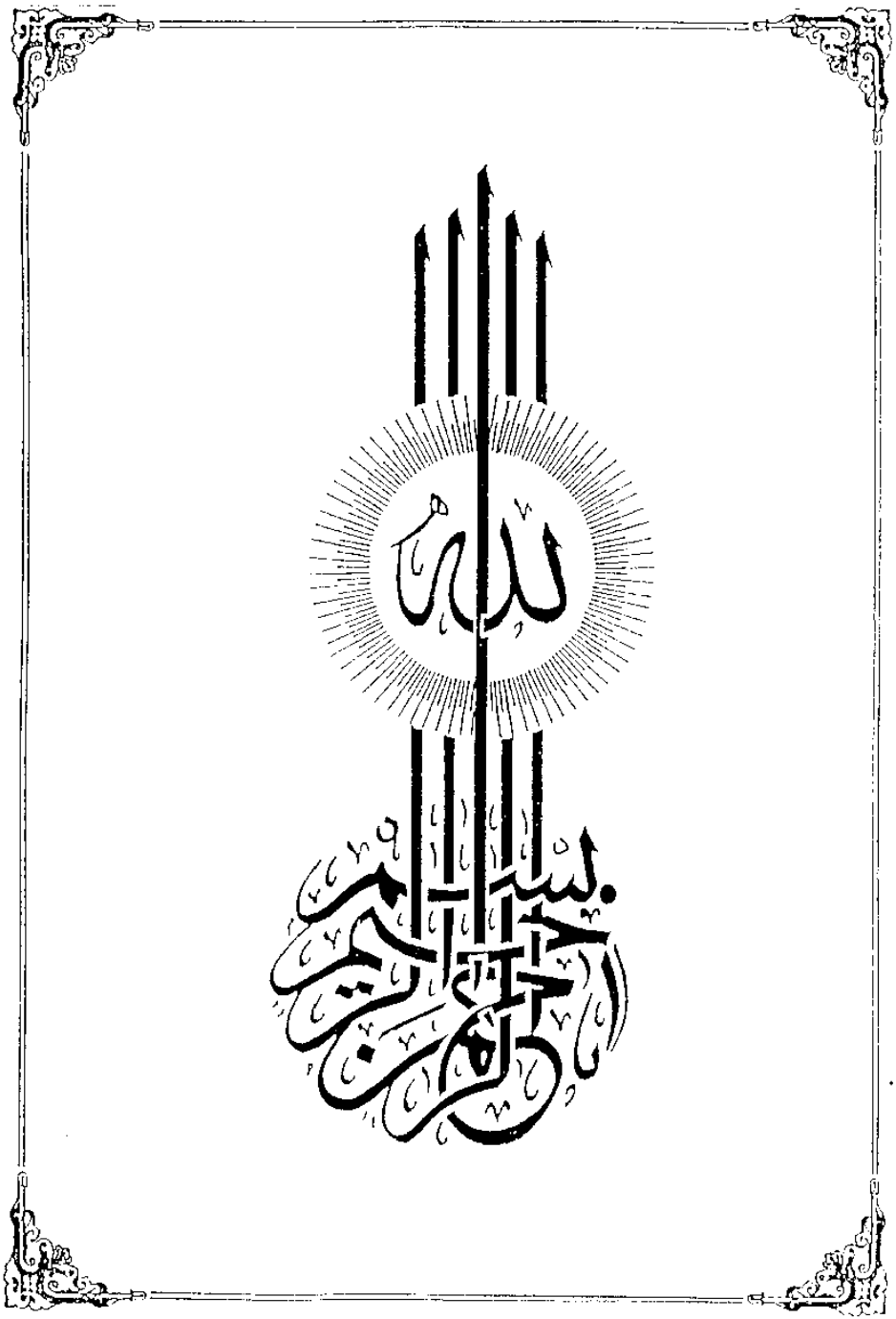

TO MY MOTHER

ACKNOWLEDGMENT

First of all I would like to thank ALLAH

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List of Abbreviation

BMI	Body mass index
C.C	Clomiphene Citrate
C.L	Corpus luteum
E_2	Oestradiol
ERT	Estrogen Replacement Therapy
ET	Embryo transfer
EGF	Epidermal growth factor
FSH	Follicular Stimulating hormone
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GnRh-a	Gonadotrophin Releasing hormone analogues
HCG	Human chorionic gonadotrophin
hGH	Human growth hormone
HMG	Human menopausal gonadotrophin
IGF-I	Insulin-like growth factor-I
IGF-II	Insulin-like growth factor-II
IVF	In Vitro Fertilization
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing hormone
MPA	Medroxy Progesterone Acetate
OHSS	Ovarian Hyperstimulation Syndrome
P	Progesterone
PCO	Polycystic ovaries
PCOD	Polycystic Ovarian Disease

CONTENTS

INTRODUCTION AND AIM OF THE WORK

Previous series of work have reported varied incidence of different causes of infertility . A lack or defective ovulation is one of the commonest causes of infertility in humans ; it has an incidence of 41% and 16 % in primary and secondary infertility respectively (***Hegab et al ., 1987***) .

In the past ; women with ovulatory dysfunction had little hope of achieving a pregnancy; today if lack of ovulation is the only problem causing infertility; a couple can expect their chances of conceiving to match the rate found in normal population (***Speroff et al., 1989***).

Clomiphene citrate , an orally active non steroidal agent distantly related to diethylstilbesterol was approved for clinical use in 1967 (***Ernest et al ., 1976***) . Other pharmacological preparations for induction of ovulation are available for general use , such as human menopausal gonadotrophin ; purified FSH ; and gonadotrophin releasing hormone and its analogous (***Speroff et al ., 1989***) .

Homburg et al ., 1988 demonstrated that treatment with hGH can augment the ovarian response to gonadotrophin stimulation in women with relatively resistant ovaries to human menopausal gonadotrophin therapy. These findings were confirmed by a case report by ***Blumenfeld and Lunenfeld 1989*** . Furthermore , ***Ovesen et al., 1992,*** demonstrated a relationship between anovulatory dysfunction and diminished growth hormone secretory capacity .

Clonidine HcL is an alpha adrenergic agonist that has been shown to be safe, reliable, sensitive agent for testing growth hormone reserve (*Lanes and Hurtado ., 1982*) . Clonidine is a potent growth hormone secretagogue in both animals and man and it acts via release of growth hormone releasing hormone (*Pintor et al ., 1987*) .

Ovulation by clomiphene citrate can be expected in only 80 % in properly selected patients (*Corlitsky et al ., 1978*) and drugs which are available for 10 - 20 % of women who fail to ovulate with clomiphene citrate are expensive .

In the presence of the evident relationship between growth hormone and ovarian functions , we will evaluate how clonidine (growth hormone secretagogue) can be an adjuvant to clomiphene as a cheap and suitable method for induction of ovulation and to reduce its failure rate .

The aim of this work is to assess the clinical value of the use of clonidine HcL (i.e. promotion of growth hormone release) as an adjuvant therapy to clomiphene citrate for induction of ovulation .

REVIEW OF LITERATURE

GROWTH HORMONE

Origin and control

Growth hormone (GH) constitutes the most abundant hormonal principle in the human pituitary gland ; Indeed ; it is estimated that as much as 5 to 10 mg of GH are present in adult pituitary somatotrophs . These cells , in turns , account for 35 % to 45 % of the total cellular mass of adult pituitary (***Daughaday WH .,1985***) .

Secretory control of GH by the pituitary somatotroph cells is affected in the hypothalamus by two specific neurohormones; one stimulating GH- releasing hormone (GH-RH) and the other inhibiting called somatostatin ; other neurotransmitters such as dopamine and opoids can affect the release of GH . Factors such as nutrition , exercise , stress ,insomnia ,age and hormonal status also influence the release of GH in humans (***De Leo et al ., 1993***) .

The rate of growth hormone in human increases and decreases within minutes, the normal concentration of growth hormone in the plasma of an adult is between 1.5 and 3 ng / ml (***Guyton ., 1991***) .

Chemistry and preparations

Growth hormone is a single - chain protein having 191 residues and a molecular weight (MW) of 22 Kd , the structure of human growth hormone is shown in figure 1 .

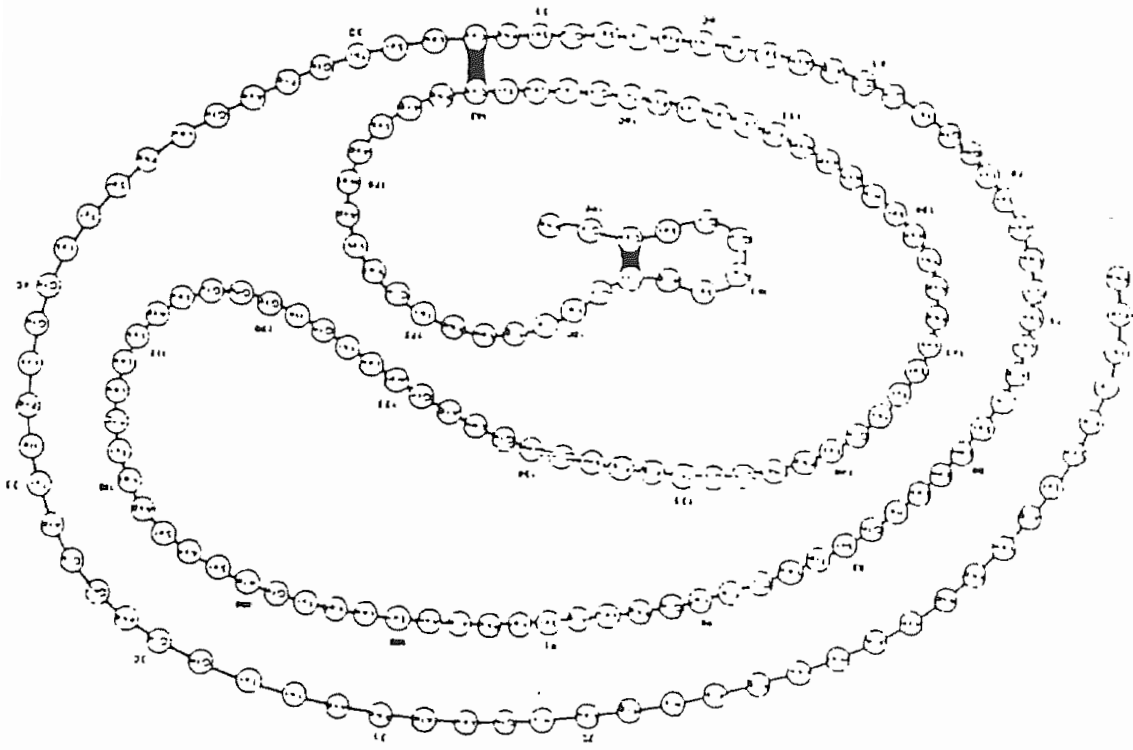

Fig. 1 Structure of growth hormone. The numbers identify the amino acid residue starting from the N-terminal (Guyton ., 1991)

Fractionation of serum by gel filtration consistently reveals three major isoforms of growth hormone approximately 20 to 22 Kd (monomeric GH) , 40 to 50 Kd (big GH) and ≥ 60 Kd (big, big GH) ; ***Ochoa et al ., 1993,*** demonstrated that in women with normal ovarian function and galactorrhea the monomeric (20 to 22 Kd) and dimeric (40 to 50 Kd) GH forms were elevated and comprised approximately 42 % of the total immunoreactivity ; in contrast , in normal women without galactorrhea the polymeric GH variants of ≥ 60 Kd constituted the major proportion of the total GH immunoreactivity , and the dimeric of 40 to 50 Kd was present in lesser amounts than in galactorrhaic women .

Now there are many forms of growth hormone for use such as : - Biosynthetic hGH (Norditropin ; Nordisk Gentofte A/S ; Denmark) , Biotropin (Israel) and human recombinant GH (Genotropin ; Kabi Pharmacia ; Uppsala , Sweden) .

Action

Growth hormone , in contrast to other hormones , does not function through a target gland but instead exerts its effects on all or almost all tissues of the body , Aside from its general effects in causing growth, growth hormone has many specific metabolic effects as well including specially :

(1) Increased rate of protein synthesis in all cells of the body.
(2) Increased mobilization of fatty acids from adipose tissue and increased use of fatty acids for energy .
(3) Decreased rate of glucose utilization throughout the body (***Guyton ., 1991***) .

Tests for GH reserve

Growth hormone releasing factor and clonidine HcL are deemed sensitive , reliable and safe for testing the pituitary reserve (***Slover et al., 1984***). Growth hormone releasing factor acts directly on the pituitary and is used to discriminate the hypothalamic versus pituitary origin of GH deficiency (***Laron et al., 1987***) .

The use of clonidine as a provocative agent for GH stimulation is based on large number of studies demonstrating an alpha adrenergic action on men .

In a study by ***Salat-Baroux et al., 1993,*** testing the GH secretory response to a single dose of clonidine administration as a provocative test and its benefit in co-stimulating of somatotropic axis during a treatment with gonadotropin in poor responders ; after an oral administration of 0.3 mg of clonidine , the first increase in GH levels is measured after 60 minutes while a peak value after 90 minutes , however in individual patients GH was still rising at time + 120 minutes .

Menashe et al ., 1990, proposed that clonidine test may serve as a preliminary differentiating indicator of the sensitivity of patients to gonadotropin stimulation , confirmatory study have been brought by ***Blumenfeld et al., 1991 .***

Rather than GH-RH and clonidine , arginine is speculated to stimulate GH secretion through cholinergic pathways and inhibition of hypothalamic somatostatin release (***Dieguez et al., 1988***) .

Finally , usage of L-dopa to test GH reserve in patients with polycystic ovarian disease was done by *Lee et al., 1993,* in patients with PCOD , L-dopa (500 mg/d) was given after overnight fast and on another day the same dose of L-dopa was administrated 60 minutes after pyridostigmine , GH samples were obtained at - 60 ,0 , 60 , 90 and 120 minutes ; they stated that GH responses to L-dopa were significantly lower in polycystic ovarian syndrome (PCOS) than those in controls , and pyridostigmine enhanced the GH response to L-dopa significantly in PCOS .

Acar and Kadanali., 1993, also tested the GH response to L-dopa , where serum GH measured - 30 minutes preceding administration of 500 mg L-dopa then at 0 , 30 , 60 , 90 , 120 and 180 minutes after L-dopa , this study demonstrated a reduced GH response to L-dopa among PCOS patients .

Relation of somatotrophic axis and reproduction

For many years , understanding of somatotrophic and reproductive axis have evolved essentially independently ; however it became apparent that in some circumstances , the reproductive and somatotrophic axis may be interdependent (*Adashi et al., 1994*) .

The mere fact that the ovary is targeted by GH and that it is a site of GH reception and action would warrant the characterization of GH as a gonadotrophin . Moreover , GH could be viewed as a co-gonadotropin capable of enhancing gonadotropin hormonal action but possibly incapable of acting by itself (*Katz et al., 1993*).

Growth hormone receptors and way of action on the ovary

Although the prospect of intraovarian GH generation is an attractive one , existing information tends to favor the notion that most of somatotrophic input to the ovary is derived from circulating GH pituitary gland origin (*Katz et al.,1993*)

Kaganowicz et al., 1992, demonstrated that immunoreactive GH has been found in 7 of 118 surgically removed human ovaries , the intra-ovarian concentration ranging from 50 to 51.000 ng /g tissue , more importantly all specimens were positive for GH by radioreceptor and radioimmune assays . This study provides evidence that human growth hormone or a molecule closely resembling it can be found in the human ovary.

Davies et al., 1980 and ***Lobie et al., 1992,*** by their studies on rat ovaries suggested wide spread distribution of GH receptor / binding protein in the rat ovaries .

Further confirmation was recently provided by ***Tiong and Herington., 1991***, their observations revealed transcripts corresponding to both GH receptors (4.5 Kb) and the GH binding protein (1.2 Kb) in the adult rat ovary .

Preliminary studies by Lazone et al ., 1990 documented the highly luteinized human granulosa cell as a site of GH reception , in contrast, no GH receptors were noted at the level of the theca-interstitial cell when assessed under comparable in vitro-circumstances.