DOWN REGULATION OF PITUITARY GLAND AND ITS EFFECT ON PITUITARY GONADOTROPINS AND OVARIAN HORMONES

A Thesis

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By

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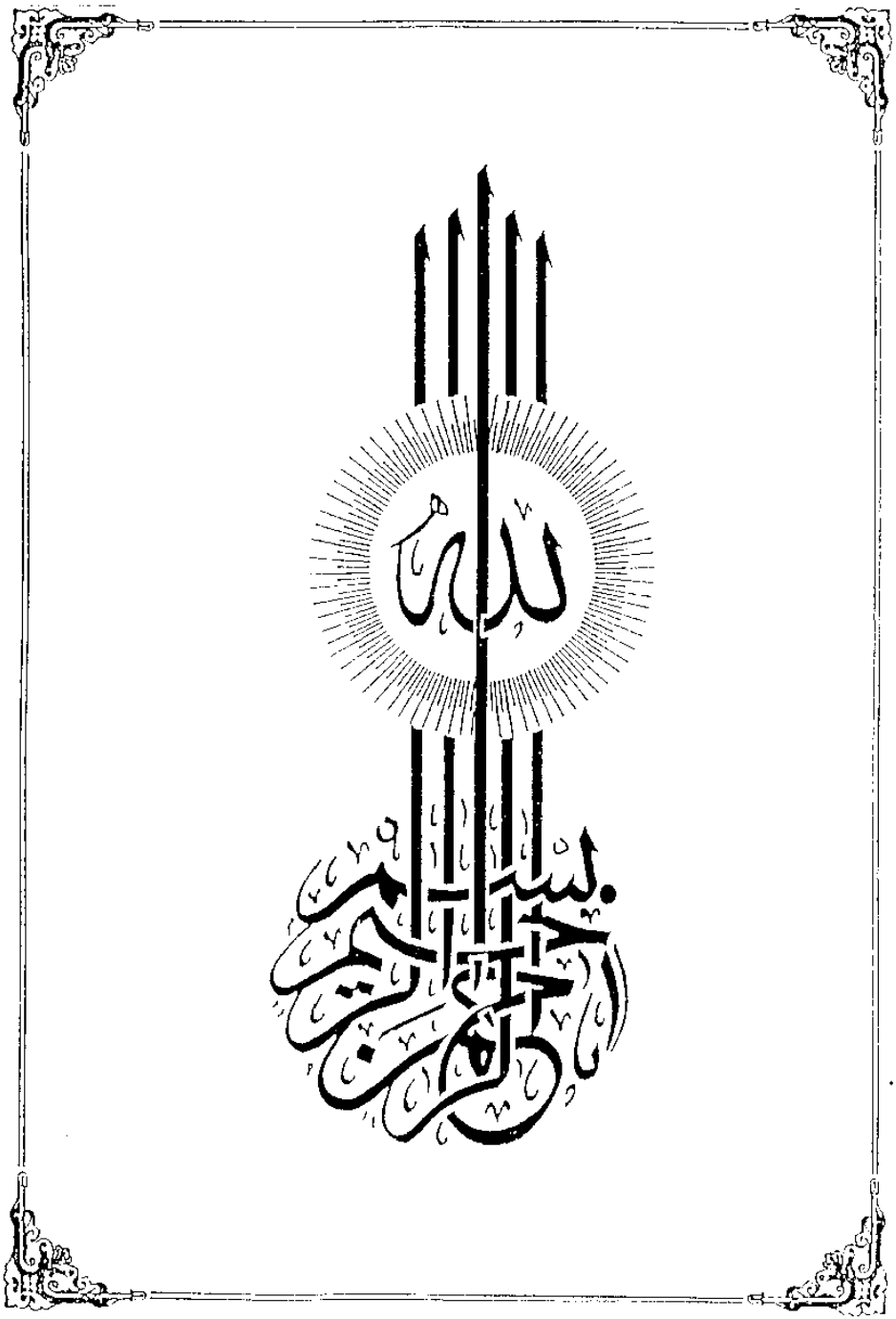
بسم الله الرحمن الرحيم

« وعلمك ما لم تكن تعلم

وكان فضل الله عليك عظيما »

صدق الله العظيم

(سورة النساء آية ١١٣)



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ABBREVIATIONS

LHRH	Luteinizing hormone releasing hormone
LHRHa	Luteinizing hormone releasing hormone analogue
GnRH	Gonadotropin releasing hormone
GnRHa	Gonadotropin releasing analogue
FSH	Follicular stimulating hormone
LH	Luteinizing hormone
HCG	Human chorionic gonadotropins
HMG	Human menopausal gonadotropins
GABA	Gamma amino buteric acid
VAID	Vasoactive intestinal peptide
GAD	Gonadotropin releasing hormone associated peptide
IP_3	Inositol 1,45, triphosphate
DAG	Diacyl glycerol
MAP	Medically assisted procreation
VIP	Vasoactive intestinal peptide
5-HT	5 hydroxy tryptamine

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Introduction

M. El Husseiny Soliman

INTRODUCTION

GnRH Analogue Therapy

GnRH secreted from the hypothalamus stimulation stimulates both the synthesis and release from the pituitary of the gonadotropins luteinizing hormone (LH) and of follicle stimulating hormone (FSH).

In males, LH and FSH stimulate the testes to produce testosterone, in females the gonadotropins stimulate the ovaries to produce oestrogens. The hypothalamus releases GnRH in a pulsatile manner, in males with a pulse interval of about 120 minutes, in females with a pulse interval of 90–200 minutes depending on the stage of the menstrual cycle. The pituitary responds by secreting FSH and LH in a similar pulsatile manner. The determination and synthesis of gonadotropin releasing hormone (GnRH or LHRH) by *Scally and Guillemin* (1971) represents a milestone in the recent history of fertility endocrinology. So the development of synthetic agonistic analogues become possible.

These analogues have a more long-acting effect and are considerably more patent than natural GnRH.

Agonistic analogues of GnRH (such as Decapeptyl-controlled release) were originally developed for the improvement of fertility. However, in long term treatment these analogues have a paradoxical effect. After a short period of increased FSH and LH secretion (Mostly in the first day of analogue injection) (*Zorn et al.*, 1988).

The pituitary becomes absolutely refractory to the analogue resulting in a sharp decrease in gonadotropins release, this in turn leads to an inhibition of synthesis and secretion of gonadal steroids (*Gouzinet et al.*, 1986). In females, estrogen reaches postmenopausal levels. This condition when achieved down regulation of the pituitary gland is reached which is now a well known practice prior to ovarian stimulation. Commonly, it is used in IVF-ET programs (*Howard et al.*, 1990), as there is a variable indication and advantage of this technique. It leads to initial creation of pharmacological hypophysectomy. Thereafter gradual stimulation is accomplished by parenteral pituitary gonadotropin therapy (*Meldrum et al.*, 1988 and *Droech et al.*, 1989).

This also minimizes the occurrence of adverse events as premature luteinization (*Cohen et al.*, 1985). Many authors as *Frydman et al.* (1988) and *Meveu et al.* (1987) believed that the routine use of GnRH for all patients undergoing IVF-ET trials may improve the results by decreasing cancellation due to premature LH surges.

Aim of the Work

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The aim of the present work is to study the effect of gonadotropin releasing hormone analogue (triptorelin intramuscular) on Egyptian women going to have IVF-ET trials as regards to: when pituitary blockade is complete and also the best time to start exogenous ovarian stimulation by human menopausal gonadotropins (HMG). This is achieved by studying the daily hormonal profile of pituitary gonadotropins (FSH, LH), gonadal steroids (estradiol and progesterone) and prolactin.

Review of Literature

HYPOTHALAMIC-PITUITARY INFLUENCE

A relationship between central nervous system activity and pituitary secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) was inferred from the classic studies of Smith and Greep (*Smith and Greep,* 1936) who demonstrated that gonadotropin concentrations fell when the pituitary gland was removed and transplanted elsewhere in the body, but rose again when the pituitary was retransplanted beneath the median eminence of the brain. Harris proposed the neurovascular hypothesis that the pituitary is regulated by hypothalamic factors secreted into the hypophysial portal vessels (*Harris et al.,* 1955). This neurovascular relationship between the hypothalamus and the pituitary was further defined in 1971 by researchers in the laboratories of Schally and Guillemin who isolated and characterized first thyrotropin releasing hormone (TRH) then gonadotropin releasing hormone (GnRH), also known as LH releasing hormone. GnRH is a decapeptide found in high concentration in the median eminence of the brain that simulates the release of LH and FSH from the pituitary gland. A cloned complementary DNA sequence encoding human GnRH has now been utilized by Nikolics and colleagues to detect a GnRH precursor protein (Nikolics et al., 1985). In mice a deletion in the GnRH gene has

been identified and believed to be responsible for the hypogonadal condition found in the hereditary hypogonadal mouse (*Mason et al.*, 1986). This condition mimics the human hypogonadal state known as Kallmann's syndrome (*Kallman et al.*, 1948) characterized by olfactory bulb agenesis, anosmia and hypogonadism. This clinical disorder is more frequently seen in men than women. Gonadal stimulation using exogenously administered GnRH in these patients has resulted in spermatogenesis or ovulation.

Following its discovery, initial attempts to induce ovulation with GnRH succeeded only when GnRH was given as a bolus after follicular development had been maximally stimulated with gonadotropin (*Kastin et al.*, 1971). Administration of GnRH as a daily injection failed to induce ovulation if prior gonadotropin stimulation of the ovary had not occurred. These initial attempts to induce ovulation with GnRH did not represent a failure to have identified the appropriate hormone responsible for pituitary LH and FSH secretion, but rather a failure in how to administer GnRH appropriately. Knobil and colleagues studied the regulation of gonadotropin secretion in adult female rhesus monkeys that had undergone bilateral radiofrequency lesions of the arcuate region of the medial basal hypothalamus. This procedure abolished secretion of endogenous GnRH and resulted in lowered LH and FSH levels and loss

of menstrual cycles in the monkeys (*Knobil et al.*, 1980; *Plant et al.*, 1978). On receiving unvarying intravenous pulses of synthetic GnRH at hourly intervals, normal gonadotropin levels and menstrual cycles were reestablished (*Naki et al.*, 1978).

This information from non-human primate studies provided the rationale for administering GnRH in pulsatile form to anovulatory human patients. When given in this manner, ovulation induction with GnRH has been quite successful (*Zacur*, 1985).

Knobil et al. (1980) initially argued that the release of pituitary LH resulted from an unvarying frequency and constant amplitude of release of hypothalamic GnRH and that GnRH was therefore permissive to pituitary LH secretion. That LH pulses during the human luteal phase exhibit greater amplitude and reduced frequency when compared with LH pulses during the follicular phase challenges this action (*Yen et al.*, 1974). This change in pulsatility may reflect progesterone modulation of hypothalamic GnRH release. As a consequence of these experimental findings, use of GnRH to induce ovulation and restore fertility may require modification during the luteal phase of the induced cycle, or supplementation with either human chorionic gonadotropin (hCG) or progesterone to maintain an adequate luteal phase (*Berger et al.*, 1985).