PROLACTIN AND DYSFUNCTIONAL UTERINE BLEEDING

Thesis Submitted

In Partial Fulfilment for Master Degree in Obstetrics And Gynaecology

By
Nehad Ismail Raafat

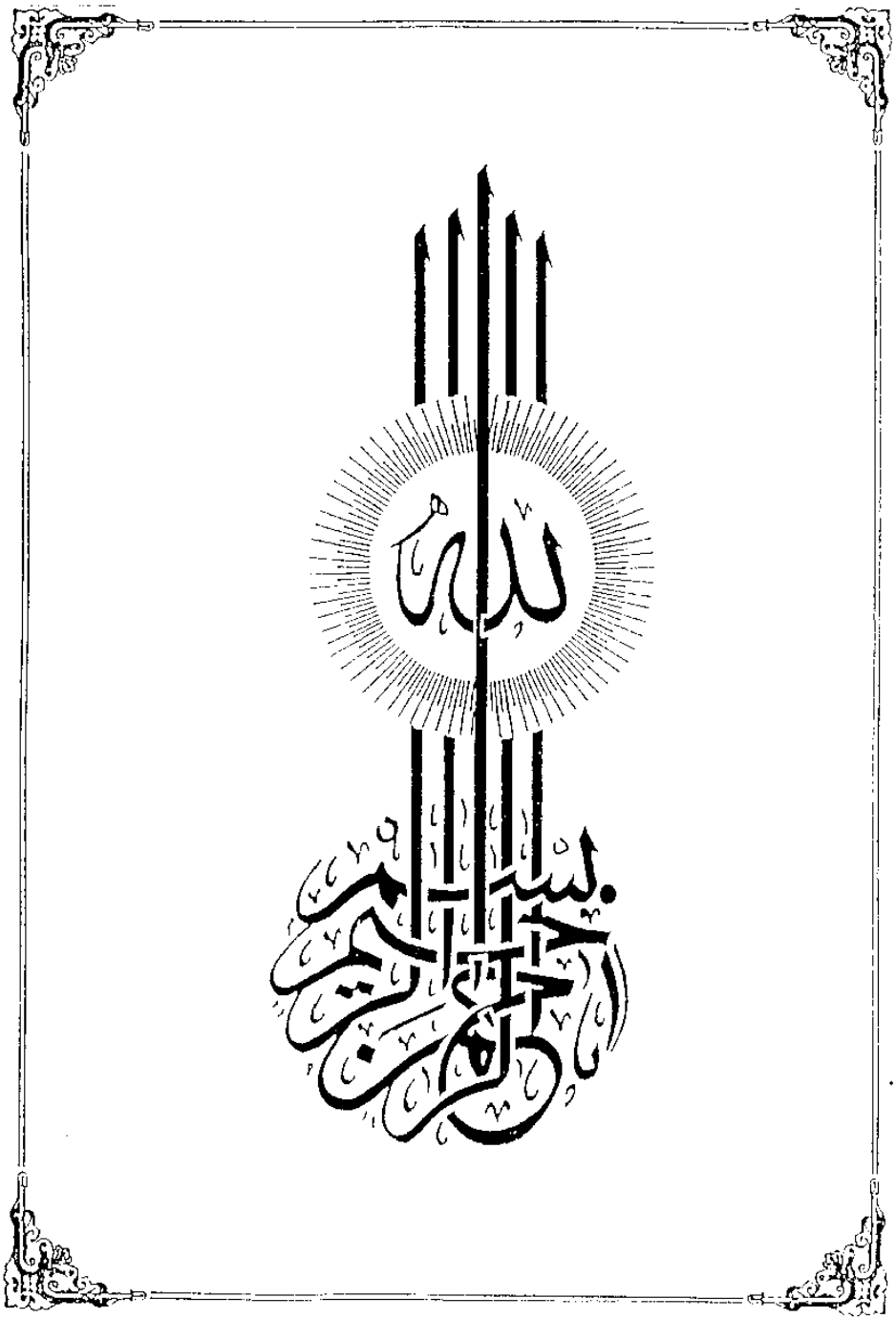
Under Supervision Of

Prof. Amin El-Zenini
Dr. Abbas Ghazi
Dr. Amal Edris
Dr. Ahmed El-Tawil

Ain Shams University
Cairo

1982

CONTENTS



xxxxxxxxxxxxxxxxx

ACNOWLEDGEMENT

I have the great pleasure to express my deepest thanks and gratitude to Professor Amin El Zenini for his kind supervision and great help in this work.

I can't find a suitable worde.to thank Dr.Abbas Ghazi for his faithfulness., patience and honsty and indeed without his great help this work would not come to light.

I am also highly indepted to Dr . Ahmed El.Tawil for facilitating to me the histopathological part of the thesis ,I thank also Dr.Amal Edris for the valuable help in the biochemical work.

I N T R O D U C T I O N

INTRODUCTION AND AIM OF PRESENT WORK

Dysfunctional uterine bleeding is excessive bleeding from the uterus in the reproductive age group in the absence of detectable organic lesions; by using such a definition fibroids, cancers, inflammations, endometriosis and pregnancy are excluded. It is obviously a diagnosis arrived at by elimination; whilst any abnormal bleeding in this age group might be dysfunctional in origin no bleeding should be so treated until the other causes have been checked and eliminated. The condition is found mostly at the two ends of reproductive life with 75 per cent of the cases occurring in the over 35-years age group.

The commonest guide to heavy menstruation is the patient's own history. Any woman who has menstruated for several years and then tells her doctor that the periods are getting heavier is usually correct. Commonly one inquires about alterations in the use of sanitary towels and internal tampons or the presence of clots in the menstruation. Any gross increase in the requirement of external or internal pads probably indicates increased menstrual loss. The addition of clots to menstruation implies an overcoming of the fibrinolytic system of the uterus. As elsewhere in medicine, diagnosis depend upon history examination and investigations. The history must be taken meticulously. It is probably best done by going over each of the last few menstrual periods in detail. If the patient has no clear recollection, a prospective history might be obtained by giving the patient a menstrual chart to fill in over the next few months. Further points to be elucidated in history-taking are those relating to a psychiatric upset. The loss of a husband or a job is very relevant. The investigator should remember that dysfunctional uterine haemorrhage may be a reflection of absence of other organs such as thyroid gland. It is wise to exclude symptoms of bladder or bowel which could be associated with a pelvic tumour.

Most women with dysfunctional uterine bleeding are not ovulating less than a quarter showing evidence of this at histological examination.

Commonly because of a reduction of progesterone metabolism following the absence of a corpus luteum after ovutation, unopposed oestrogen activity allows a greater development of the endometrium without the restrictive influence of progesterone. This results in an exaggerated proliferative phase depending on the degree of oestrogen stimulation. Then, when the constriction of spiral arteries occurs just before menstruation, degeneration, necrosis of the thicker endometrium causes more bleeding.

Hyperprolactinemia in association with the galactorrhea-amenorrhoea syndrome is a recognized cause of anovulatory infertility "Tyson, J.E., and Pinto , H. 1972" . Several recent reports have related infertility to hyperprolactinemia with lesser degrees of menstrual dysfunction. " Del Pozo , E., etal 1979". This prospective study is undertaken inorder to establish whether the measurement of serum prolactin would be of benefit in all women with dysfunctional uterine haemorrhage.

REVIEW OF LITERATURE

ENDOCRINE PHYSIOLOGY OF OVULATION

* Hypothalamic releasing hormone

The hypothalamic hormone responsible for the release of the gonadotrophins is thought to be the decapeptide LHRH , originally isolated from porcine and ovine hypothalami by schally et al (1971b) and Amoss et al (1971).Schally et al(1971 a) observed that the synthetic preparation of LHRH, although predominantly effecting LH release,was capable of stimulating the release of FSH in vivo and thus the presence of two separate releasing hormones was necessary to explain the physiological results.Similar results were obtained in vitro by Crighton and Foster (1972). Electrical impulses in the hypothalamic centres where LHRH is synthesised are thought to trigger the release of this hormone into the portal circulation.Probably these impulses are mediated via α adrenergic transmitters since α-adrenergic blockers effectively inhibit the release of LH , whilst β - bockers have no effect (Bhathacharya et al, 1972).

Since the release of LH and to some extent FSH occurs episodically it follows that the secretion of LHRH must also be pulsatile (Seyler and Reichin 1973),Both LH and FSH are secreted throughout the menstrual cycle and so it is expected that LHRH will follow this pattern probably with greater amounts being secreted just before and during the mid-cycle surge. Not much is known about the action of LHRH on the pituitary Level.

As is the case for most hormones,its action is probably mediated via cyclic AMP(cAMP).

* The Gonadotrophins

The gonadotrophins FSH and LH are glycoproteins with molecular weights of about 30.000.Chemically they consist of two non-identical subunits,the α and β chains which are approximately equal in size.The α

subunit is common to all the glycoprotein hormones (FSH LH,HCG and TSH) (Amir,1972) and if an antibody is produced against the subunit itself , it cross reacts with all other glycoprotein hormone molecules(Ross et al , 1972).Specific antibodies have however been produced against the individual β subunits(Vaitukaitis et al,1972)and no doubt these will lead to a better understanding of the mode of action of these hormones.

The gonadotrophins differ from most peptide hormones with respect to their carbohydrate content,which is particularly high(9to 30 per cent of the native molecule for FSH and 15 to 20 per cent for LH).One of the most important residues, in terms of biological potency,is the sialic or(neuraminic acid)content which varies from 1.4 per cent for LH to 5.2 per cent for FSH(Butt,1969).Removal of the sialic acid residues by treatment with the enzyme neuraminidase progressively reduces the biological activity (Braunstein et al,1971), a phenomenon thought to be due to an increased rate of clearance of the molecule from the circulation(Van Hall et al , 1971) rather than any interference with the hormone receptors (Tsuruhara et al,1972).

* Pituitary Production of FSH and LH.

The gonadotrophins are synthesised in the basophil cells of the anterior pituitary and probably both hormones are produced by same cell. Recent work using histological and immunological techniques with isotopically labelled antibodies,localised FSH and LH to within the same individual cell(Phifer,Midgley and Spicer,1973).

It seems likely that the two subunits of the gonadotrophins are synthesised and stored separately within the basophil cells,and it is not until the cell is stimulated that chemical coupling occur and the intact molecule is secreted into the general circulation.(Benveniste et al 1973).

* Half-Lives of FSH and LH in the General Circulation.

The half - lives of both FSH and LH have been determined in a number of ways,firstly by the fall in circulating hormone after hypophysectomy

(Yen et al , 1968) when LH was found to have an initial fast component of about 21 minutes and FSH of 3.9 hours (Yen et al 1970). The fall in blood levels of endogenous FSH and LH after administration of LHRH however gave much longer halflives of 90 minutes for LH and 426 minutes for FSH. These values agree well with those half-life values calculated from the endogenous peaks of LH seen in episodic secretion studies (Boyar et al, 1972 ; Nankin and Troen, 1972). These results suggest that the levels of LH and FSH normally found in the circulation are the product of two types of secretion , a basal continuous one and an episodic spurt release. In addition FSH and LH are probably to exert their differential actions by virtue of their different Half-lives.

* Site of action of the gonadotrophins

A prerequisite for a hormone to influence a specific target organ is a receptor site usually located on the cell membrane that is capable of taking up and binding the hormonal molecules. Once combined with their receptors most hormones including LH exert their effect through CAMP the hormonal messenger appears to influence the enzyme adenyl cyclase which in turn catalyses the conversion of ATP to cAMP via prostaglandin (Marsh, Mills and lemaire , 1972). FSH acts to develop the follicle to the pre-ovulatory stage but by itself it cannot stimulate steroid secretion . It is responsible for the increased O_2 uptake and protein synthesis in the ovarian cells and in particular the theca interna cells. On the other hand , LH appears to stimulate steroid secretion by all the cell types and probably a basal amount is necessary for steroid synthesis . One of its main sites of action seems to be the conversion of cholesterol to pregnenolone.

* The ovarian steroids

The major steroid-producing cells of the ovary are the theca interna cells and the granulosa cells of the follicle. Oestrogens are largely secreted by the theca cells which have good venous drainage thus facilitating the rapid release of steroid into the general circulation. In addition to oestradiol smaller amounts of oestrone, androstenedione, dehydroepiandro - sterone (DHEA) and 17 α OH progesterone are also secreted. The oestradiol secreted by the developing follicle under the influence of both FSH and LH, has a number of important functions amongst which is the stimulation

of the endometrium to a late proliferative stage and alteration of the characteristics of the cervical mucus(Davajan, Nakamura and Mishell, 1971) . It is also possible that rapidly increasing amounts of oestrogen produced by the major follicle have a suppressive action on the other follicles that started developing simultaneously at the beginning of the cycle (Monroe, jaffe and Midgley, 1972). Near ovulation the cells in the major follicle stop dividing , and merely increase in size by an increase in cell cytoplasm and also by the secretion of liquor into the follicle itself (Delforge et,al, 1972). The granulosa cells probably start secreting small amounts of progesterone into the centre of the follicle after the start of the LH surge but it is unlikely that much of it will get into the general cirulation due to the relatively impermeable basement membrane. The small rise in plasma progesterone along with a large rise in 17αOH progesterone frequently seen very shortly after the start of the LH surge but before actual ovulation (Kirton et al 1970) , probably represents partial luteinisation of the theca cells which continue to secrete oestrogen and some androgens throughout the luteal phase. Following ovulation the granulosa cells become vascularised and secrete large amounts of progesterone and oestrogen into the ovarian vein (Channing 1970; Ryan, Ryan, Petro and Kaiser 1968). The combined action of both oestrogen and progesterone converts the late proliferative endometrium to the secretory one necessary for implantation of the blastocyst.

THE NORMAL CYCLE

Since the introduction of radioimmunoassays a number of workers have performed longitudinal hormone profiles on groups of normal women (Yen , Vela , Rankin and Littell , 1970). The majority of these subjects were stated to be normal on the basis of regular menstrual cycles and sometimes a biphasic BBT, but since most of these normal volunteers are unmarried, their true fertility is unknown. Figures 1 to 4 represent the composite profiles derived from a large number of the published hormone patterns. This procedure effec-tively smooths out the interlaboratory between absolute concentrations due to differences in antisera, technique and so on.

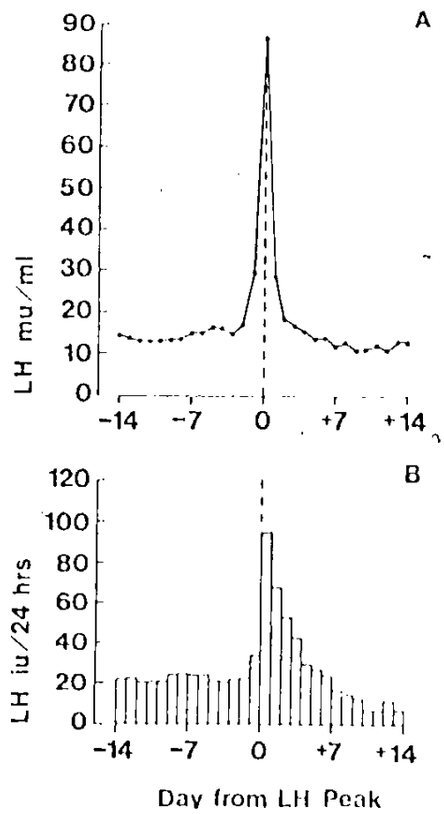


Figure 1. Mean daily luteinising hormone (LH) concentrations. Plasma levels in 126 normal cycles (A) and urine levels in 44 cycles (B).

Elizabeth Lenton I.D. Cooke, Clinics in Obstetric & Gynecology. I (2) : 313 - 330 August 1974.

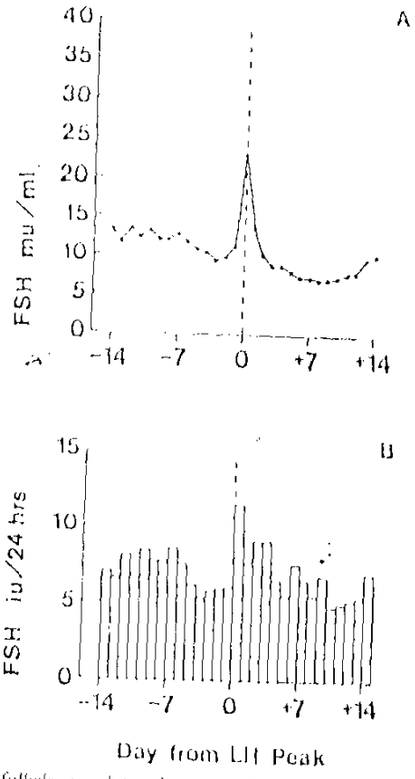


Figure 2. Mean daily follicle stimulating hormone (FSH) concentrations. Plasma levels in 116 normal cycles (A) and urine levels in 19 cycles (B).

Elizabeth Lenton I.D , Cooke Clinics in Obstetric & Gynecology.I (2) : 313 - 330 August 1974.