ORAL CONTRACEPTIVE PILLS AND PARATHYROID FUNCTIONS

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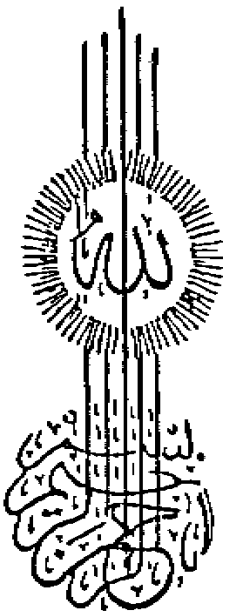
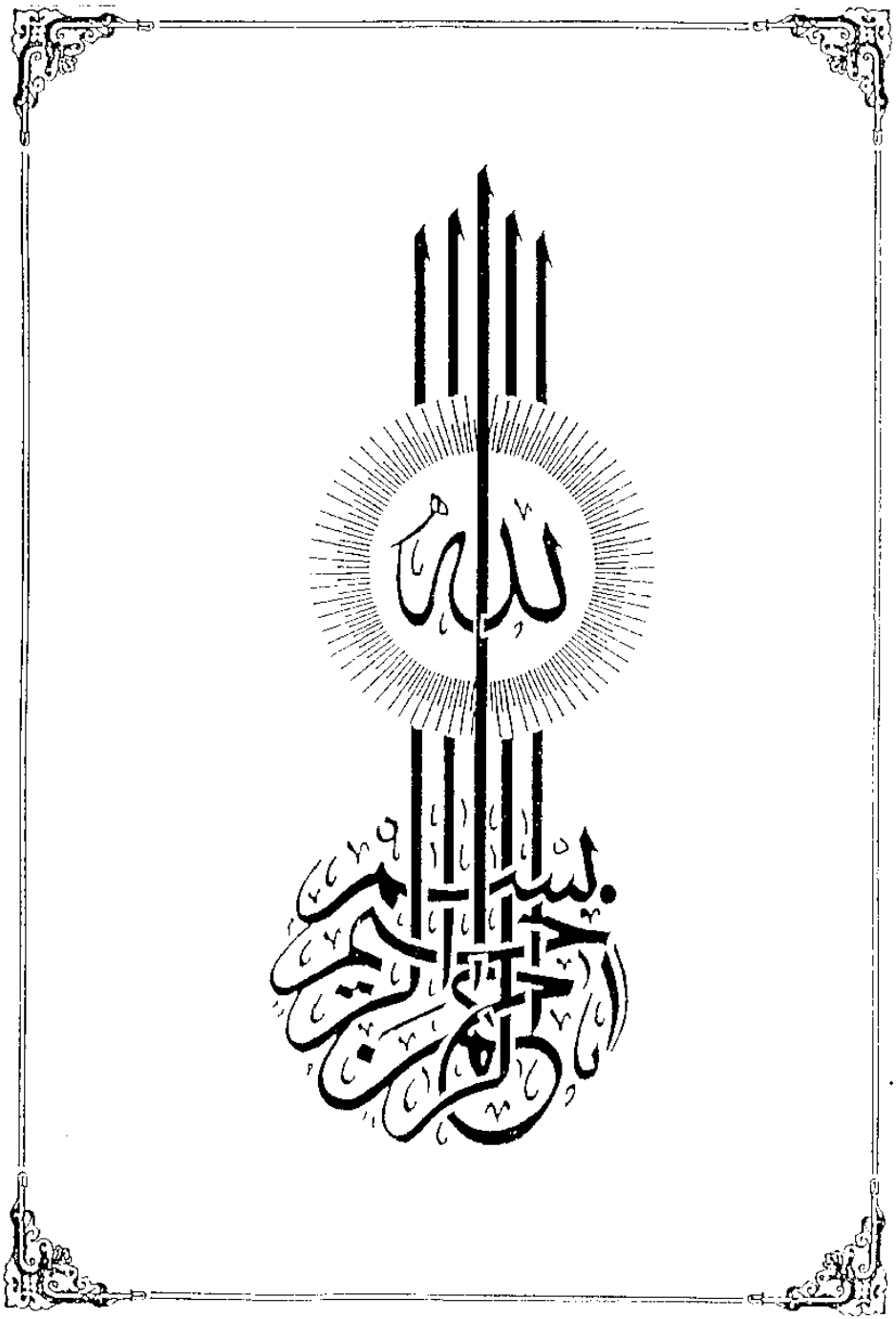


قالوا

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة (الآية ٣٢)



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Content

INTRODUCTION

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Oral contraceptive pills as a popular method of contraception in Egypt has been a matter of medical and public concern since their introduction.

Despite overall safety of O.C.P, several side effects has been raised such as deep vein thrombosis, thromboembolic stroke, haemorrhagic stroke, myocardial infarction, hypertension impairement of glucose tolerance, rarely hepatoma, cholestatic jaundice and breast cancer.

Minor side effects include gastrointestinal disorders, breast discomfort, weight gain and headache.

Two important trends have occured over the past ten years to avoid these risks, a shift towards pills containing 50µg or less estrogen and introduction of multiphasic pills.

Moses et al., 1982 reported a case of secondary hyperparathyroidism in women 41 years who had O.C.P for 9 years.

The aim of this work is to study some parathyroid functions associated with various periods of administration of O.C.P.

PARATHYROID HORMONE

Chemistry:

Parathyroid hormone is polypeptide made up of 84 amino acids with molecular weight of 9500. It is the principle regulator of the concentration of ionic calcium in extracellular fluid (Bringhurst et al., 1979).

The original gene product of parathyroid cell is 115 amino acid precursor termed pre-pro parathyroid hormone. It is synthesized on ribosomes bound to the memberane of endoplasmic reticulum and discharged into cisternal space. This process provides access of precursor to cistcrnal space of endoplasmic reticulum to the enzyme that remove the prescquence leaving 90 amino acid proparathyroid hormone in the Golgi apparatus. By removal of the remaining 6 amino terminal the amino acid sequence of 84 amino acid polypeptide is readied for secretion either in secretory granules package or in its free form (Habener Potts, 1981 and Gohn, 1981).

Control of secretion:

parathyroid hormone is rapidly released from parathroid gland in response to a fall in plasma ionic calcium and acts on kidney, intestine and bone to restore concentration of this cation to just above normal set point (Mayer 1979).

The concentration of extracellular ionic calcium is the major regulator of parathyroid hormone secretion.

Other factors such as plasma phosphate or blood pH influence secretion only indirectly by altering the degree to which calcium is complexed (phosphate) or bound to ablumin (pH). The effects of extracellular magnesium concentration on secretion are qualitatively similar to ionic calcium but physiologically are less importent.

Severe prolonged hypomagensemia markedly inhibit secretion of parathyroid hormone and may be associated with hypocalcaemia (Anast et al., 1972).

Direct parathyroid hormone secretagogues include B adrenergic agonists, prostaglandins and histamine (Gardner et al., 1978). These agents as well as decrease ionic calcium stimulate the production of cyclic 3,5 adenosine monophosphate in parathyroid cells and it is persumed that this compound mediate their action on hormones secretion.

A diurnal variation in plasma PTH has been described with maximal concentration in the early morning. It was found that changes in PTH were independent of plasma calcium changes and could not be abolished by calcium infusion on

the other hand it was considered that the main factor controlling the diurnal variation in PTH was the variation in plasma phosphate (Nordin 1976).

Mechanism of actionof PTH:

Parathyroid hormone binds to specific plasma membrane receptors of target cell (Nissenson, Arnaud 1979). These occupied receptors interact with guanyl nucleotide regulated membrane-bound adenylate cyclase to convert ATP to cyclic 3,5 AMP. Cyclic AMP is considered to be at least one intracellular second messenger responsible for mediating the final expression of action of the hormone (Strewler, Orloff 1977).

Biologic actions of PTH:

The principle function of PTH is regulation of the concentration of calcium in body fluid. This regulatory influence is accomplished by actions of the hormone on the kidney and bone to produce increase in the rate of transfer of calcium from glomerular filterate and skeletal tissue into the extracellular fluid. In addition, the hormone influences gastrointestinal absorption of calcium probably through indirect mechanism. Rapid regulation of serum calcium levels probably depends on simple buffering by large exchangeable calcium pool in bone. Intermediate regulation probably mediated by renal and intestinal mechanism (Hall et al., 1974).

I. Actions PTH on the kidney:

Parathyroid hormone acts most immediately on the kidney to increase renal tubular reabsorption of calcium and magensium thus conserving these two divalent cations and to increase phosphate and bicarbonate excretion by inhibiting their proximal tubular reabsorption (Strewler, Orloff 1977).

(a) Calcium reabsorption:

The increased rate of reabsorption of calcium by the renal tubule might be expected to decrease urinary calcium, however because of PTH-induced hypercalcemia, the calcium of tubular fluid may be increased more than the rate of reabsorption of calcium is increased, and the urinary calcium may be increased (hypercalciuria) (Robertl 1984).

The most recent studies had suggested that PTH enhanced calcium reabsorption takes place at some point distal to ascending thin limb of loop of Henle. The most recent studies indicate that thick ascending segment respond to PTH with increased calcium flukes and that cyclic AMP is intracellular mediator of this effects (Bourdea, Burg 1980).

Urinary excretion of cyclic AMP:

Approximately 40-50% of cyclic AMP excreted in the urine is derived from renal tub ular cells. Its production and cellular release into urine is almost under control of PTH (Kaminsky et al., 1970).

The component of urinary cyclic AMP can be accurately estimated and is termed nephrogenous cyclic AMP. It is increased above normal in about 80% of patients with primary hyperparathyroidism and large proportion of patients with malignancy (Stewart et al., 1980). It is thus not helpful in distinguishing between these two common disorders because low levels of nephrogenous cyclic AMP are present in patients with non parathyroid hypercalcemia (excluding malignancy), The test is however useful in those patients whose serum immuno PTH is equivocally increased, in such patients, low levelof nephrogenous cyclic AMP would suggest that serum iPTH value was artifactual and would be against primary hyperparathyroidism, where as a normal or increased value would confirm the validity of serum iPTH values and favors this condition (Fredric, 1985).

(b) Phosphate excretion:

PTH increases the rate of excretion of phosphate in the urine.It decreases the rate of reabsorption of phosphate in the proximal tubules. The net result is phospha-

turia or excessive loss of phosphate in the urine and an associated decrease of plasma phosphorus. This renal effect is appropriate because resportion of bone under the influence of PTH releases both calcium and phosphorus into plams and if phosphorus were not excreted the dissociation constant (Ca^{++}) x (HPO_4) = K might not be maintained (Robertal 1984).

The most important indirect effects of the phosphaturic action of the hormone either directly or by its hypophosphatemic action stimulate the activity of renal tubular 25-OH-1 alpha-hydroxylase to convert 25 hydroxycholecalciferol to its major biologically active metabolite 1 – 25 dihydroxycholecalciferol. This metabolite acts directly on intestinal mucosal cell to increase calcium absorption and on bone to increase resorption (Kumar, 1980).

PTH causes a net decrease in proximal reabsorption of phosphate, and this effect is mediated through CAMP generated in response to hormone. There is further evidence that in addition to proximal effect there is also distal tubular effect of PTH that similarly produce decrease reabsorption of phosphate. The existence of multiple sites of action of PTH along the course of the nephron is substantiated further by biochemical results on segregated areas of the nephron.

Since sodium reabsorption is inhibited by PTH in the proximal tubule it is possible that inhibition of phosphate reabsorption is secondary to effects on sodium (Bell et al., 1972). This possibility is made more tenable in that dibutyryl CAMP produces a similar influence on sodium and phosphate in the proximal tubule and CAMP is known to be capable of regulating sodium transport in number of tissue (Bell et al., 1972).

(c) Effects on bicarbonate:

PTH causes inhibtion of bicarbonate reabsorption in proximal renal tubule, hormone induced bicarbonaturia leads to produce acidosis which decrease the ability of ciruclating albumine to bind to calcium and thus increasing ionic calcium by physiochemical means (Fredric 1985).

(d) Effect on magnesium:

The action of PTH on magnesium reabsorption appears to be similar to that on calcium.Injection of highly purified PTH causes not only a decrease in calcium but also in magnesium excretion, by increasing the tubular reabsorption of magnesium. In most clinical conditions, it is difficult to separate the action of calcium from the action of PTH on magnesium reabsorption. In primary hyperparathyroidism and hypoparathyroid the blood magnesium is usually normal, but the highest plasma calcium are always associated with low magnsium and with decreased tubular reabsorption of magnesium (Nordin, 1976).

II. ACTIONOF PTH ON BONE

The effect of PTH on bone involves the control of plasma calcium concentration and regulationof bone remodeling and turn over (Wong 1982).

Bone remodeling is the resportion of older osteons and subsequent replacement with new bone formation and this involves the actions of osteoclasts responsible for degradation of bone and subsequent infiltration of osteoblasts to synthesize new collagen and allow mineralization of replacement osteons.

So it is now clear that PTH influences all three bone cell types osteoblast, osteoclasts and osteocytes it is clear from work with separated distinct cell types that PTH affects osteoblastic functions as well as osteoclastic function and that there are specific receptors for PTH on each.

To Summurise actions of PTH on bone we can say that PTH increase rate of bone resorption and increase rate of synthesis of bone collagen and stimulate bone formation, we **can explain the mechanism of each actions as following:**

Reduction in ionized calcium levels in plasma triggers an increase in PTH secretion which cause rapid release