MEDICAL ADVERSE EFFECTS OF ORAL CONTRACEPTIVES AND ITS EFFECT ON BLOOD VISCOCITY

THESIS

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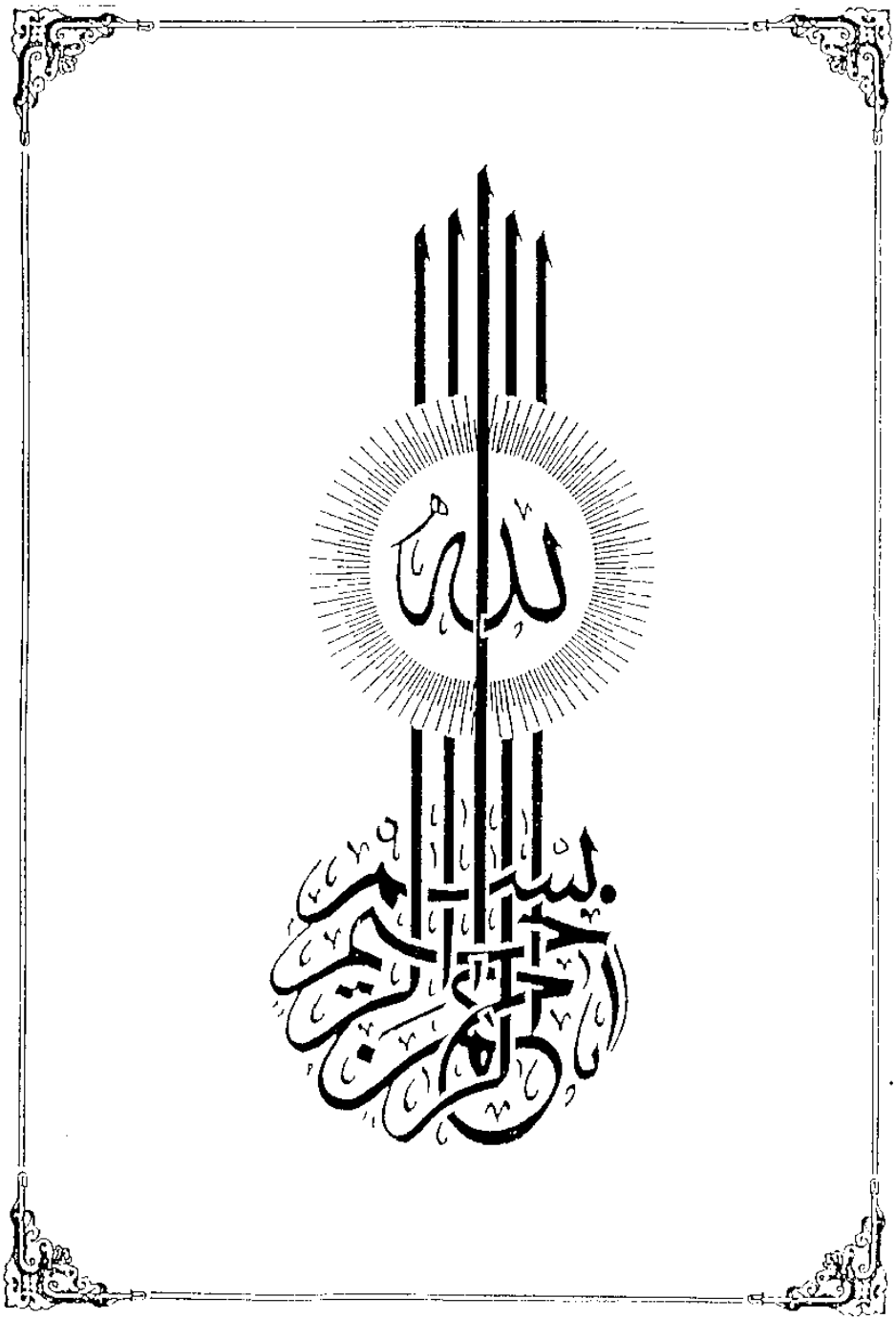

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INTRODUCTION

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The introduction of oral contraceptives in 1960 has had a profound social, economic, relegious, and political impact.

The efficancy and ease of use of oral contraceptives has led to their widspread use throughout most of the world, and their use increased rapidly. Worldwide it is estimated that 54 to 60 million women were current users of oral contraceptives in 1977 (Rinehart 1979).

The safety of oral contraceptives has been a matter of medical and public concern since their introduction . Evidence suggesting that oral contraceptives might have effects on health other than prevention of unwanted pregnancy began to appear shortly after the drugs were introduced .

Reports of potential compalications of oral contraceptives have appeared and provoked discussion concerning their effects on morbidity, mortality, and physiological indicators of health status . The complications of oral contraceptives have been assesed by means of case reports, case control studies, and numerous laboratory investigations have explored the effects of oral contraceptive on physiological processes that may important in determining how these drugs infleuence health and the occurrence of disease .

In this review many of the adverse effects and medical complications will be studied.In addition the relative and actual risk of each of these diseases is evaluated and the probable pathophysiology is delineated in order to determine which women are at increased risk of specific complications.

Also this work will deal with the effect of oral contraceptives on blood viscosity and its relation to many adverse effects of it .

HISTORY

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Toward the end of nineteenth century a number of investigators including Beard 1897 and Zochokke 1889 recognized that in various animal species ovulation did not occur in ovary which contained a well developed corpus luteum .

During the first three decades of twenteeth century evidence was accumulated indicating that extracts of corpus luteum were capable of inhibiting ovulation (Parkers1929).

In 1934 there was a major discovery in this field with the isolation of corpus luteum hormone, that was progestrone (Hartmann and Winsttstein 1934).

Following the isolation the physiological action of progestrone was studied and it rapidly become appeerent that the hormone was capable of inhibiting ovulation in a variety of animal species including rabbit and rat (Astwood 1939)

The trial of these anti-ovulatory in human subjects intiated by Pincus and his associates in New England,U.S. during 1958 and soon after more extensive trials were commenced in Puerto-Rico and Haiti (Pincus et al 1958)the effectivness of orally administrated progestional compounds as contraceptive

agents was rapidly established and over the past decades this form of fertility control has grown widely in popularity through the world .

PHARMACOLOGY

PHARMACOLOGY OF ORAL CONTRACEPTIVES

Among the first of the orally active steroids to be used in inhibiting ovulation,. Some had oestrogenic activity and some preparations of progestins .

⁎ Oestrogens :

In contraceptive preparations they are either ethinyl estradiol or mestranol. They are different from natural oestroidal and must be regarded as pharmacological drugs. Ethinyl oestradiol is a very potent oral oestrogen and is one of the two forms of oestrogen in every oral contraceptive (Goldzieher et al , 1975).

The most important difference between oestrogens used in combined contraceptive (ethinyl oestradiol, mestranol) and other oestrogenic drugs such as stillbestrol is that when traditional oestrogens are given to awomen the anterior pituitary escape the inhibitory effect after one or two cycles of therapy and ovulation may start again .

⁎ The Progestin Component :

The discovery of ethinyl substitution lead to the preparation of ethisterone, an orally active derivative of testosterone, in 1954 it was found that the removal of 19

carbon from ethisterone did not destory the oral activity. But most importantly, it changes the major hormonal effect from that of an androgen to that of progestational derivatives of testerone (19 nortesterone) the androgenic properties of these compounds were not totally eleminiated and minimal anabolic and androgenic potential remains within the structure. Clinical effects however are rare especially in new low dose pills . The impurity of 19 nortesterone i.e. androgenic as well as progestational effects is complicated further by the fact that they are metabolished within the body to oestrogenic compounds. This conversion to oestrogens varies in degree among the various steroids and probably between individuals .

The 19 nortesterone derivatives are norethisterone noreth indrone, norethisterone acetate, norethindrone acetate, ethynodiol diacetate, norgestrol and lynestranol.
Asecond group of progestines become available for use when it was discovered that acetylation of the 17-α hydroxy - progestrone in 17- α hydroxy group produced oral activity . Also hydroxylation at the 6th position is necessary to give sufficient progestational strength for human use , probably by inhibiting metabolism (Murad and Haynes , 1980).

The 17 -α hydroxy progestrone derivatives are medoxy progestrone acetate, megestral acetate,and chlormedinone acetate .

FIG. 1 : STRUCTURAL RELATIONSHIP OF VARIOUS PROGESTINS TO PROGESTERONE

✱ Mechanism Of Action :

The administration of estrogen and a progestin as contained in combined preparations could interfere with fertility in any of several ways. However, it is clear that, as currently used the mixture inhibit ovulation .

The question then that how is ovulation prevented and what other mechanisms might interfere with impregnation. The predominant effect of estrogen is to inhibit the secretion of F.S.H. while continued action of progestione serves to inhibit the release of L.H it is clear that ovulation can be prevented either by inhibiting the ovulatory stimulus or by preventing the growth of follicles, and this accords with the expermintal observations that follicular growth and ovulation can be prevented by either estrogen or progestrone given singly (Murad and Haynes,1980) . Measurment of circulating F.S.H and L.H. show that estrogen-progestion combinations supress both hormons. The plasma concentrations of F.S. H and L.H. are stable early follicular F.S.H. and midcycle F.S.H and L.H. peaks are not seen .

When oestrogen and progestrone are given sequentially oestrogen alone supresses F.S.H but causes irregular increase in L.H. when a progestin is then given, there is a brief rise in L.H. followed by a sustained decline.