EFFECT OF DEPOT MEDROXY PROGESTERONE ACETATE AS A LONG ACTING INJECTABLE CONTRACEPTIVE ON PROTEIN C ACTIVITY

Thesis

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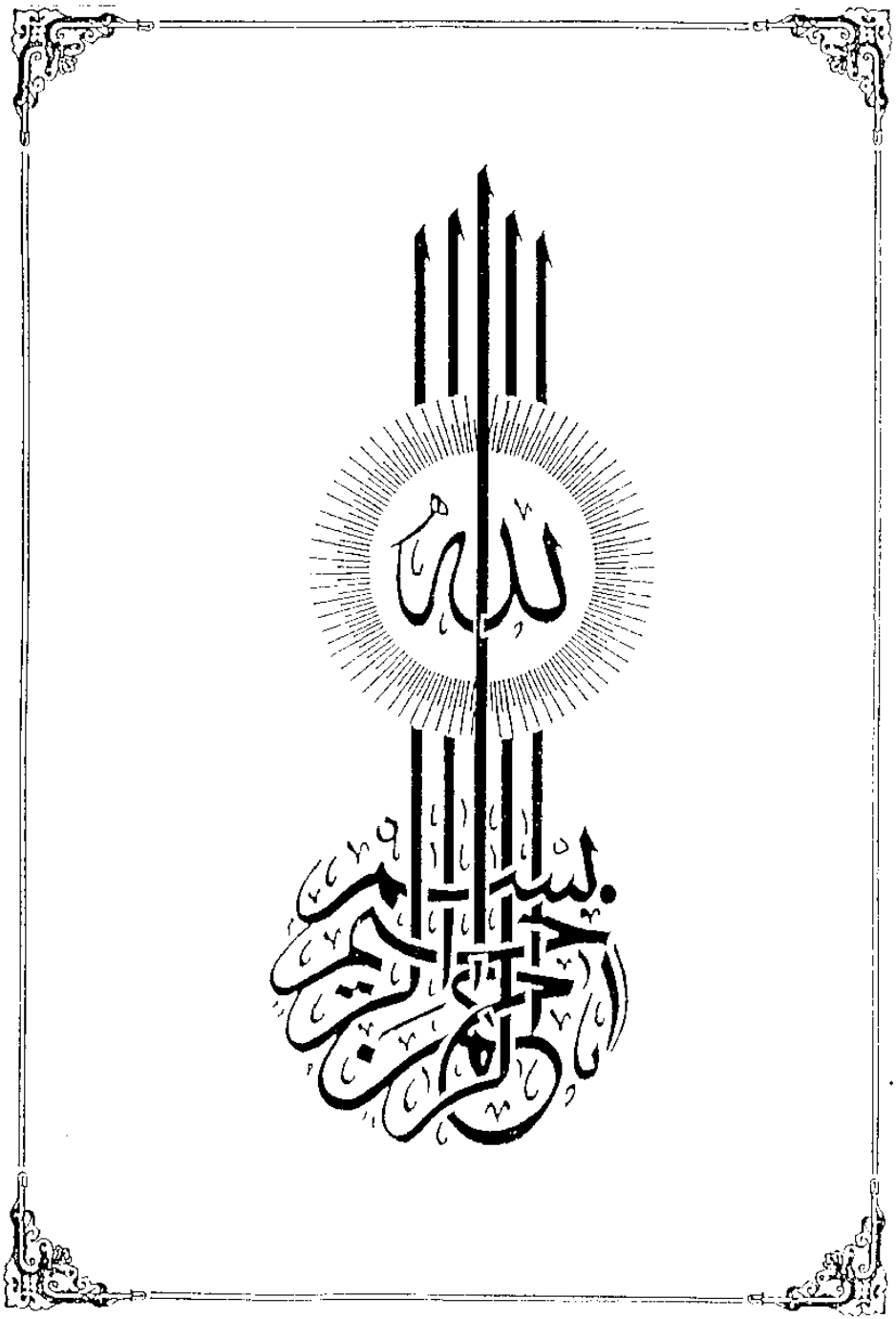

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INTRODUCTION

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One goal of contraceptive research is to develop effective, safe and reversible long-acting methods that do not require the user to take a daily action.

Progestins are among the most promising drugs for development of long-acting methods. At present they can be administered for this purpose in different forms including long-acting injectables which are now widely used in several countries. Furthermore, unlike most oral contraceptive, these agents do not contain estrogen and thus are free from adverse estrogenic effects.

Injectable contraceptives date back to 1957, when Junkmann and associates (Shering AG. Berlin), synthetized long-acting injectable ester of progestogen, norethisterone, including norethisterone oenanthate (NET-EN). it was the first injectable progestin used as a contraceptive and is marked under the trade name noristerat. (Liskin and Quillin, 1983).

In the same year, 1957, Medroxy progesterone acetate and its depot injectable form, (DMPA) (Depo-Provera) were developed in USA (Liskin & Quillin, 1983).

In 1960, the U.S. Food and Drug administration approved it for treatment of threatened or habitual abortion, premature labour and endometriosis (Fraser & Weisberg, 1981).

The first contraceptive trials began in 1963 and the first reports on contraceptive effect of DMPA were made in 1966 (Csapo et al., 1966). Since then, it is estimated that about 10 million women in more than 100 countries have used it for contraception.

The safety of progestins as a contraceptive agents was seriously challenged after the report of the Royal College of general practitioner which could link the incidence of total arterial diseases including astherosclerosis, myocardial infarction and thrombotic cerebral strokes to dose of progestin in oral contraceptive pills (Kay, 1980).

This association was, further, supported by other studies for examples (Mann and Vessey 1981, Slone et al., 1981).

The mechanisms of these unwanted effects of progestins have not been fully elcidated. Strong evidence that they may depend on the delicate interplay between coagulation mechanism and endothelial and intimal changes (Knopp et al., 1982).

Protein C is a vitamin K dependent plasma protein activated by thrombin in the presence of endothelial cell associated factor, thrombomodulin, which markedly increases the rate of activated protein C.

The activated protein C is a potent anticoagulant that inactivates activated coagulant factors, V and VIII.

Protein C. may also stimulate fibrinolysis and is one of the main parameters involved in the nontrombotic activity of endothelial cells.

Therefore, it is of potential importance to investigate the behaviour of protein C. in conditions associated with increased thrombogenic risk.

AIM OF THE WORK

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This study is an attempt to evaluate the changes in protein C. activity of the coagulation system during the use of Depot Medroxy Progesterone acetate as a long-acting injectable contraceptive in Egyptian females.

REVIEW OF LITERATURE

INJECTABLE CONTRACEPTIVE

History:

In 1957, Junkmann and his associates (Shering AG, Berlin), synthetized long acting injectable ester of the progestogen, norethisterone, i.e., norethisterone oenanthate (NET-EN). It was the first injectable progestin used as a contaceptive and is marked under the trade name noristerat.

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The first contraceptive trials began in 1963 and the first reports on contraceptive effect of DMPA were made in 1966 (Csapo et al., 1966).

In September 1974, the FDA announced its intent to approve DMPA for contraceptive use but only for women who were not able to use other methods or who had had contraceptive failures with other methods and who accepted a small possibility of permanent infertility (Liskin & Quillin 1983). But shortly afterwards the agency suspended its approval (Find, 1974).

On April, 11, 1984 the English Minister of health announced in the parliament the DMPA, under its trade name Depo-Provera will be licensed for long-term use in U.K. as a useful contraceptive method for women for whom other contraceptives are contraindicated, cause side effects or are otherwise unsuitable and who are seeking long-term contraception provided that they understand and accept the risk of side effects and uncertain delay in return of fertility (Wilson, 1985).

Pharmacology of Injectable Contraceptives:

Progestogens are either natural or synthetic:

1- Ester of 17 Hydroxy-Progesterone:

Addition of hydroxyl group to 17-alpha position of the progresterone will yield an inactive compound.

But if caproic acid is also attached to this hydroxyl group, an active compound, 17-alpha-hydroxy-progesterone caproate (Primolut Depot) is obtained (Fraser and Weisberg, 1981).

Methylation at C_6 of 17 alpha hydroxy progesterone acetate will produce medroxy progesterone acetate permitting both oral and parentral administration.

2- Derivatives of Testosterone:

If an ethinyl group is attached to 17-alpha position of testosterone, it will lead to the production of a compound with progestational activity called ethisterone (Clayton et al., 1980).

3- Derivatives of 19-Nortestosterone:

AN ethinyl group if added at C_{17} on the steroid ring and a methyl group at C_{19} result in norethisterone (Chad et al., 1982).

Then an acetate group added at C_{17} of norethisterone and esterification of the C_{17} hydroxyl group of norethisterone acetate will produce norethisterone oenanthate (NET-EN) (Fraser and Weisberg, 1981).

Depot Medroxy Progesterone Acetate (150 mg):

The three monthly injectable contraceptive used:

1- Chemical Structure:

DMPA is the depot injectable form of the progestin medroxy progesterone acetate (17-alpha acetoxy-6-alpha methyl, preg 4 ene, 3,20 dione), a progestin derived from natural hormone progesterone and is prepared in microcrystalline suspension that delays absorption of the hormone after injection (Elder, 1984).

DMPA has a molecular formula C_{24} H_{34} O_4 and a molecular weight of 386.51 (Duax et al., 1978). The unusual stereochemistry of the crystal structure of DMPA, involving an inverted A-ring conformation has been demonstrated by simple crystal x-ray analysis (Fraser and Weisberg, 1981).

2- Metabolism and Serum Blood Level:

Rapid absorption may be due to massaging the injection site at time of injection. The peak level of

DMPA is usually reached after ten days. That of 150 mg DMPA was 8.3 ± 3.16 mg/ml and remains detectable for 92 ± 44 days (Fotherby and Koetsawng, 1980).

The serum progesterone level does not increase until serum MPA had become undetectable denoting suppression of luteal function which persisted up to 100 days with doses of 100 & 150 mg DMPA (Perez-Palacios, 1981).

Little information is available about the metabolism and excretion of MPA despite the length of time this preparation has been available.

Identification of metabolites has proved to be extremely difficult, with a high proportion of urinary derivatives being highly polar or unconjugated neutral metabolites (Liskin and Quillin, 1983).

The extent of conjugation in the liver is not known while metabolic clearance studies indicate that MPA is rapidly removed from the blood stream. The metabolic clearance rate (MCR) of MPA has been measured at 1668 liters per 24/hours which is lower than that for progesterone but still indicative of rapid metabolism (Elder, 1984).

3- Mode of Action:

DMPA has a relatively high affinity for the human endometrial progesterone receptor than progesterone itself (Shapiro et al., 1978). It was suggested that this