WITH INJECTABLE CONTRACEPTIVES

Thesis

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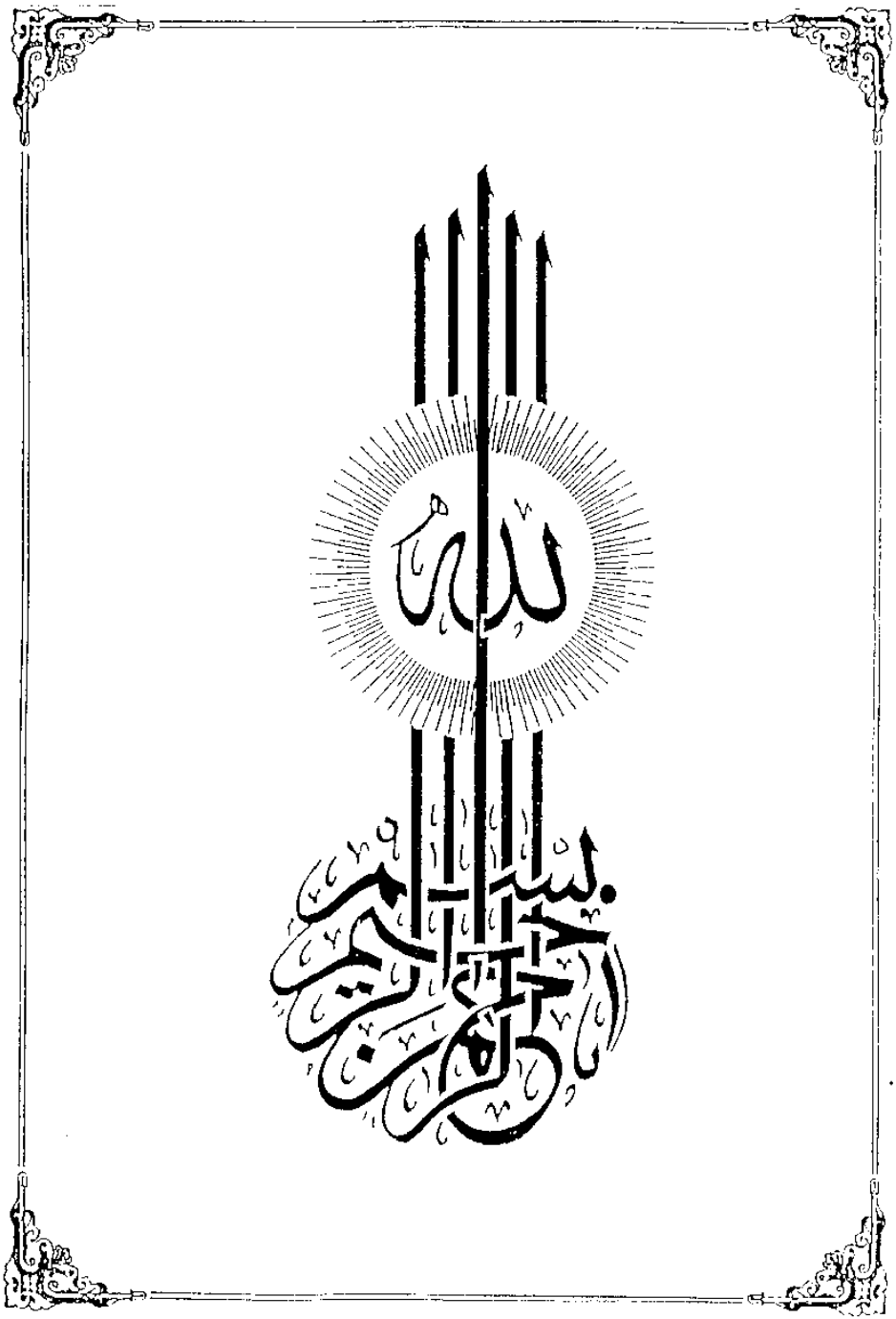

TO MY SON

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Aim of the work

The aim of this work is to make our knowledge up to date as regards the long acting injectable contraceptives.

It was mainly directed to evaluate the effect of injectable contraceptive (depot-medroxyprogesterone acetate (DMPA : Depot-provera) and nore-thisterone enanthate (NET-EN: Noriget) on the cervix and its mucus in parous ladies comparing them with different groups using other methods of contraception.

In this study, the changes in the cervical mucus include amount, viscosity, spinnbarkiet, crystallization phenomena and the changes in the external os of the cervix. This work also include the effect of these steroids hormonal contraception on the secretory immunoglobulin "A" (IgA) in the cervical mucus.

INTRODUCTION

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The presence of a wide variety of fertility control methods provides different alternatives to cope with the diversity in human customs and preferences.

The choice of a contraceptive is governed by many factors, such as specific family needs, availability of a method and its benefit/risk ratio, as well as cultural, socioeconomic, and psychological badkgrounds (Toppozada, Hafez, 1982).

In the continuing search for better methods of family plannings, long-acting progestins offer both promise and problems. Progestins, which are synthetic hormones that act like the natural female hormone progesterone, can be administered in at least five different ways to prevent pregnancy for extended periods of time. They make possible:

- Injectable contraceptives,
- Hormone-releasing IUDs,
- Implants placed under the skin,
- Vaginal rings, and
- Once-a-month oral Pills.

The effectiveness of some progestins can be prolonged by incorporating them in an injectable solution or a carrier

that gradually releases the hormone. Thus they can be effective for one month to five years or more (Liskin,et al 1983).

Injectable hormonal contraception with the two long-acting steroid preparations, depto-medroxy-progesterone acetate (DMPA: Depot-provora) and norethisterone enantate (NET-EN: Norigest) provides an effective means of fertility regulation and is becoming widely used in family planning programmes (WHO,1982).

Injectable hormonal contraceptives, when properly used, are among the most effective methods of contraception available today. (WHO, Geneva, 1982).

More research is needed on the effects and physiological consequences of the long-term use of these drugs on carbohydrate and lipid metabolism. In addition, well controlled studies are needed to examine the risk of neoplasia among women using the compounds and to asses the later development of infants who are exposed to DMPA or NET-EN in utero or through breast milk (Saxena, et al 1977).

Based on the extensive epidemiological biochemical, and clinical data available to date, DMPA and NET-EN appear to be acceptable methods of fertility regulation. Clinical evidence from more than 15 years of use shows no additional and possibily fewer adverse side-effects than are found with other hormonal methods of contraception (WHO, Geneva, 1982).

A number of advantages of the use of injectable contraception in different settings have been put forward and some of these are as follows:

(i) Highly effective contraceptives, equal to or better than combined oral contraceptives especially in terms of "use-effectiveness".

(ii) Long acting following a single injection.

(iii) Simple to administer.

(iv) Freedom from "fear of forgetting" which may occur with the Pill- and so acceptability has been high, especially in the rural areas. (Mahran 1982).

(v) Independent of coitus.

(vi) No estrogen side effects or complications.

(vii) Minimal gastrointestinal disturbance - and no real health hazards have been recorded.

(viii) In many counteries injections are equated with safe and "Powerful" medicine and are highly acceptable.

(ix) Continuation rates of use are high.

(x) The effect on milk production with injection administered post-natally was favorable in all but one study (Cairo University).

(xi) Regular 1 to 6 monthly contract with health personnel may allow detection and treatment of other problems. (Fraser et al, 1981, Mahran, 1982).

REVIEW OF LITERATURE

History of use

The first systemic contraceptives developed in the mid 1950s were short-acting progesterones administered orally. In 1953, it was discovered that esterifying a progestagon alcohol created a drug which had long-lasting effects when injected (Tyler et al, 1970). Junkmann and his associates later synthesized esters of the progesterone, norethisterone-including norethisterone enanthate. Medroxy progesterone acetate was developed by the Upjohn Company at about the same time (Babock et al, 1958). Schering AG began clinical trials on norethisterone enanthate"Norigest" in 1957).

The first clinical (trial) use of medroxy progesterone acetate was in clinical trials sponsored by the Upjohn Company as a treatment of threatened or habitual abortion and endometriosis. In 1960 the U.S. Food and Drug Administration approved it for these uses, on the basis of its safety - but without good data on its effectiveness (Fraser et al, 1981).

Medroxy progesterone acetate has been used since the 1950s for the treatment of a variety of conditions including endomteriosis,threatened abortion, precocious puberty, acromegaly, endometrial carcinoma, renal cancer, breast cancer, and premature labour; doses of up to several grams have been administered without apparent adverse effects.

In the early 1960s, it was noted that in women receiving DMPA for premature labour, the return of fertility following delivery was markedly delayed, and clinical trials of DMPA as a contraceptive agent were begun in 1963. Administered in a microcrystalline suspension by intramuscular injection DMPA exerts its contraceptive effect primarily by suppression of ovulation. However, it also has an indirect effect on the endometrium and direct action on the fallopian tubes and on the production of cervical mucus, all of which may play a role in reducing fertility (WHO, Geneva, 1982).

After initial clinical trials, a standard contraceptive regimen of 150 mg every 3 months was established, but since the late 1960, regimens of 300 mg to 500 mg every six months have also been studied.

Upjohn first applied to the FDA in 1967 for permission to market Depo-provera as a contraceptive in the U.S.A. At first questions about reversibility and relationship to breast cancer in beagle dogs, and more recently questions about cervical carcinoma-in-situ in humans and endometrial cancer in Rhesus monekys have delayed in a decision on marketing by the FDA. In 1978 the FDA finally decided to refuse marketing approval for DMPA as a contraceptive in the USA (U.S. FDA 1978), but the controversy and the expert hearings continue.

Northisterone enantate (NET-EN) has been in use as a contraceptive since 1966, although it has been used less extensively than DMPA, although the two drugs were synthesized at about the same time (Babock et al, 1958). (NET-EN) is administered as an oily preparation (of 200 mg of the long chain ester of norethisterone) by intramuscular injection, and has a mechanism of contraceptive action that appears to include inhibition of ovulation, premature luteolysis when ovulation occurs, and progestogenic effects on the cervical mucus. Effects on tubal function and the endometrium may also be involved in reducing fertility. (WHO, Geneva,1982).

Both steroids have a progestogenic effect on cervical mucus although the high efficacy of DMPA, given at 150 mg every 3 months, is almost certainly due entirely to suppression of ovulation for the treatment period (WHO, Geneva,1982).

Doubts that have been expressed regarding the safety and appropriateness of an injectable hormonal contraceptive for widespread use are related to their possible carcinogenicity, impairement of future reproductive function, adverse metabolic effects potential teratogenicity and other possible adverse effects on the progeny (as a result of exposure to the steroid hormones either in utero or via breast milk). At a special meeting convened in 1978, the Toxicology Review Panel of the WHO Special Programme, together with other expert scientists and representatives of six national