SOME ASPECTS OF LIPID METABOLISM IN FIXED LOW DOSE AND TRIPHASIC ORAL CONTRACEPTIVE STEROIDS

Thesis

Submitted for the Partial Fulfilment of
Master Degree in Obstetric and Gynaecology

By

EZZ EL-DIN AHMED M. EL-ZAIDY
M.B.B.Ch.

Faculty of Medicine
Ain Shams University

Under Supervision of
Dr. ABBAS ABD EL SALAM GHAZY
Assist. prof. of Gynaecology and Obstetric

Dr. GAMAL ABD EL SALAM WAFA
Lecturer of Gynaecology & Obstetric
Ain Shams University.

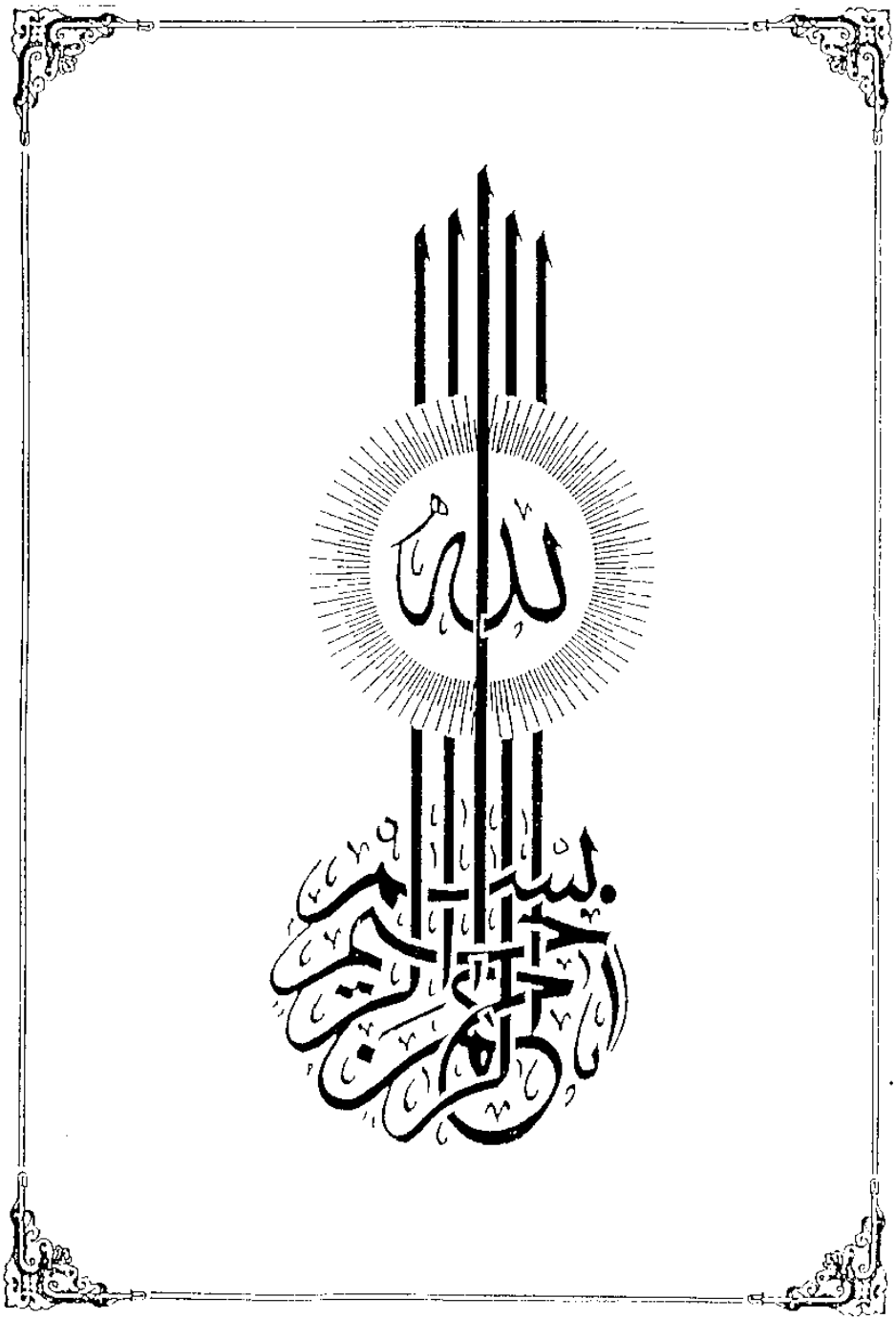
Dr. IMTIAZ ABD KAWY ISMAIL
Assist. prof. of Biochemistry
Ain Shams University

1987

ACKNOWLEDGEMENT

I would like to express my deep gratitude to Dr. Abbas Abd El Salam Ghazzy , Assist. Prof. of Gyn and Obs.,
Dr. Gamal Abd El Salam Wafa , Lecturer at Gyn. & Obs. and Dr. imtiaz Abd El Kawy Ismail Assist. Prof. of Biochemistry for thier close supervision, valuable advice, constant guidence and over whelming kindness throughout every stage of my study.

I am also deeply indebeted and grateful to Dr. Nahed Swelam Assist. prof. of Biochemistry for her valuable guidance, supervision and encouragement.



CONTENTS

ABREVIATIONS

E_2	estrogen
EE_2	ethinyl esradiol
LNG	levonorgestrel
D'SG	desogestrel
OC's	oral contraceptives.
HDL-c	High density lipoprotein-cholesterol
LDR-c	Low density liporptotein-cholesterol
VLDL	Very low density lipoprotein.
LH-RH	Lutinizing hormone-releasing hormone.
CVD	cardio-vascular disease.
CAD	coronary artery disease.
RCGP	Royal college general practioner.

INTRODUCTION

INTRODUCTION

Combined oral contraceptive pills are known to exert widespread metabolic effects. These metabolic changes have been reduced in magnitidue, but not completely elminated by use of the newer low dose oral contraceptive pill (Cullberg et al., 1982).

Cardiovascular disease is one of the more serious side effects of oral contraceptive use and these formulations have been considered a risk factor for CVD (Beck, 1981).

The evidence linking changes in lipid metabolism to CVD is very strong and oral contraception are known to affect lipid metabolism (Brooks 1984).

The oestrogen component was blamed for these effects to metabolic disturbance , and consequently the dose of oestrogen was reduced (Zador , and Nilsson 1977).

However, during the last few years, it has been evident that also the progestogen component may influence blood pressure and may be the cause of disturbance of lipid metabolism (Cullberg et al., 1979 and Larsson -Cohn et al., 1979).

As a result more attention was paid to the progestogenic part of the pill and a preparation with reduced progestogen dose associated with a minor increase of the oestrogen component was marketed (Lachnit-Fixon 1979) .

However not only dose but also the type of progestogen plays a role (cullberg et al., 1979).

The new triphasic pills are a response to the above evidence for the view that the safest combined oral contraceptive would use the lowest possible dose of both synthetic steroids, and progestogen intake is 39% less than that in the lowest fixed dose levonorgestrel product (Lachnit - Fixson 1980).

Although theoretically these agents should be even safer than the fixed dose formulations. It will be several years before sufficient epidemiological data become available to evaluate their safety (Mishell 1985).

AIM OF THE WORK

AIM OF THE WORK

The aim of this study was to compare the effect of two types of oral contraceptive pill regimes namely, triphasic and fixed low dose preparations on some lipid levels in serum.

ORAL CONTRACEPTIVES AN OVERVIEW

GENERAL DESCRIPTION OF THE TECHNOLOGY

All oral contraceptive pills presently in use are composed of steroidal compounds. Generally known as " the pill" , this method at this point in time is the only oral method available that can provide effective contraception.

The pill, although highly effective and acceptable to many, has some minor disadvbantages that lead frequently to discontinuation of use. It also carries the risk of rare but serious threats to health, including hep.atoma the capacity of causing blood clotting diseases, and possible implications for liver, gallbaldder, renal, and heart disease.

The development of the oral contraceptive pill has been described by two of those involved in the original clinical trials as one of the epochal events of the twentieth century(Goldzieher and Rudel, 1974).

They believe that this was a discovery that depended very greatly on a " coincidence of information, technological advances, intellectual and societal timeliness, and financial support". Although much work had gone before into the isolation and purification of ovarian hormones and in initial biological experiments with impure preparations, the first biological demonstration that the pure

bleeding (Pincus, et al., 1958).

Other successful clinical trials followed in different countries and as more trials were done, the dosages of the active steroids in the combination pills were progressively reduced to 5 mg and then to 2.5 mg of the progestin and to 100 ug and then to 75 ug of mestranol

Subsequently, it was shown that effective contraception can be achieved with as little as 0.5 mg of norethisterone and 35 ug of ethinyl estradiol.

Other more potent progestational agents have also been discovered and are used routinely in various oral combination pills now available (Viz. norethisterone acetate, ethynodiol diacetate , and levonorgestrel).

The main estrogens still used are mestranol, the 3-methyl ether of 17 -ethinyl estradiol, and ethinyl estradiol itself.
By 1973 it was estimated that 50 million women around the world were using oral contraceptives in both developed and less developed countries (Piotrow and Lee, 1974).

In developed countries, between 20 percent and 38 percent of couples using contrtaceptives were using oral contraceptive pills, so that this method of contraception had a tremendous impact in a very short time. Indeed, when they first became widely available,

these pill were considered to be the final answer to contraception, and it was believed that, apart from different variations on the same theme, few new types of conctraception would be needed. Different formulations of these same ingredients were indeed marketed f rom time to time but fell out of favor for a variety of reasons - increased side effects, lack of efficacy, presumed toxicity and other similar reasons.

One popular variant was the so-called sequential therapy that involved estrogen alone given for either 15 or 11 days during the follicular phase of the menstrual cycle, followed by a combination of estrogen and progestin for the remaining 5 or 10 days, respectively.

The consensus from all the various trials with this form of therapy was that there was an increased risk of an occasional breakthrough ovulation despite rgular tablet taking, the probability being inversely related to the dosage of estrogen (Gual et al., 1967).

The concept behidn the sequential therapy was that it more closely mimicked the normal menstrual cycle and theoretically should have caused a less frequent incidence of breakthrough bleeding. However, estrogen alone is not as effective in inhibiting pituitary gonadotropin release as the combinationof an estrogen and a progestin. Consequently, when owing to concerns about increased thromboembolic disease the dosage of estrogen in the contraceptive pills was

lowered to 30 ug or less, this amount was well below the amount required to inhibit ovulation when used by itself (about 80 ug), this tolled the death knell of the sequential preparations (Goldzieher and Rudel, 1974). Another option to the combination pill and one that eliminated the estrogenic component completely was the development of the so-called minipill. These pills were microdose formulations of progestins alone and were intially considered to be the logical successor to the combination pills. However , the minipill has not gained widespread acceptance by woman or family planning programs, and probably fewer than 500,000 women world wide use these preparations (Rinehart, 1975).

Usually the minipill consists of 0.35 mg or less of the progestational agent, the major ones being norethisterone and its acetate, levonorgestrel, lynestrenol, and quingestanol acetate.

Originally, the minipill formulations, contained 17 -acetoxyprogestins, but when these were withdrawn from the market becuase of presumed toxicity, only the 19-norsteroidal formulations were available.

Better packaging has prevented errors in dosing (failure to take tablets) that led to a number of method failures in early studies but even so-failure rates are still higher than with the combination pills. This difference is due to the different modes of action-ovulation inhibition versus changes in cervical mucus and sperm transport and

alterations of endometrial development so that implantation cannot occur.

Despite the original enthusiasm for this progestins alone and were intiailly considered to be the logical successor to the combination pills. However the minipill has not gained widespread acceptance by woman or family planning programs, and probably fewer than 500,000 women world wide use these preparations (Rinehart, 1975). Usually the minipill consists of 0.35 mg or less of the progestational agent. The major ones being norethisterone and its acetate , levonorgestrel, lynestrenal, and quingestanol acetate.

Originally , the minipill formulations contained 17 -acetoxy progestins, but when these were withdrawn from new method of contraception, the appearance of various adverse reactions has over the years tempered this enthusiasm and led to lowered continuation rats. Consequently, much of the present research in this field is directed toward assessing the safety and effectivenss of different preparations in healthy non-pregnant women, in lactating women, and in women with various disease and deficiency states and toward determining the risks of serious sequelae of pill use.

Last, efforts are under way to reduce the hormonal burden ingested by women. Researchers are developing sustained-release pills that would permit close to zero-order release on a daily-or perhaps even monthly-basis. The idea behind these efforts is that