A REVIEW ON THE INTOXICATION
BY DRUGS INDUCING OVULATION

THESIS

Submitted in Partial Fulfilement of

The requirments For the Degree of

Master in General Medicine

BY

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Ain Shams University

1981

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عـرض للتسـمم بالعقاقـير المحفزة للتبويض

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Master Degree in General Medicine

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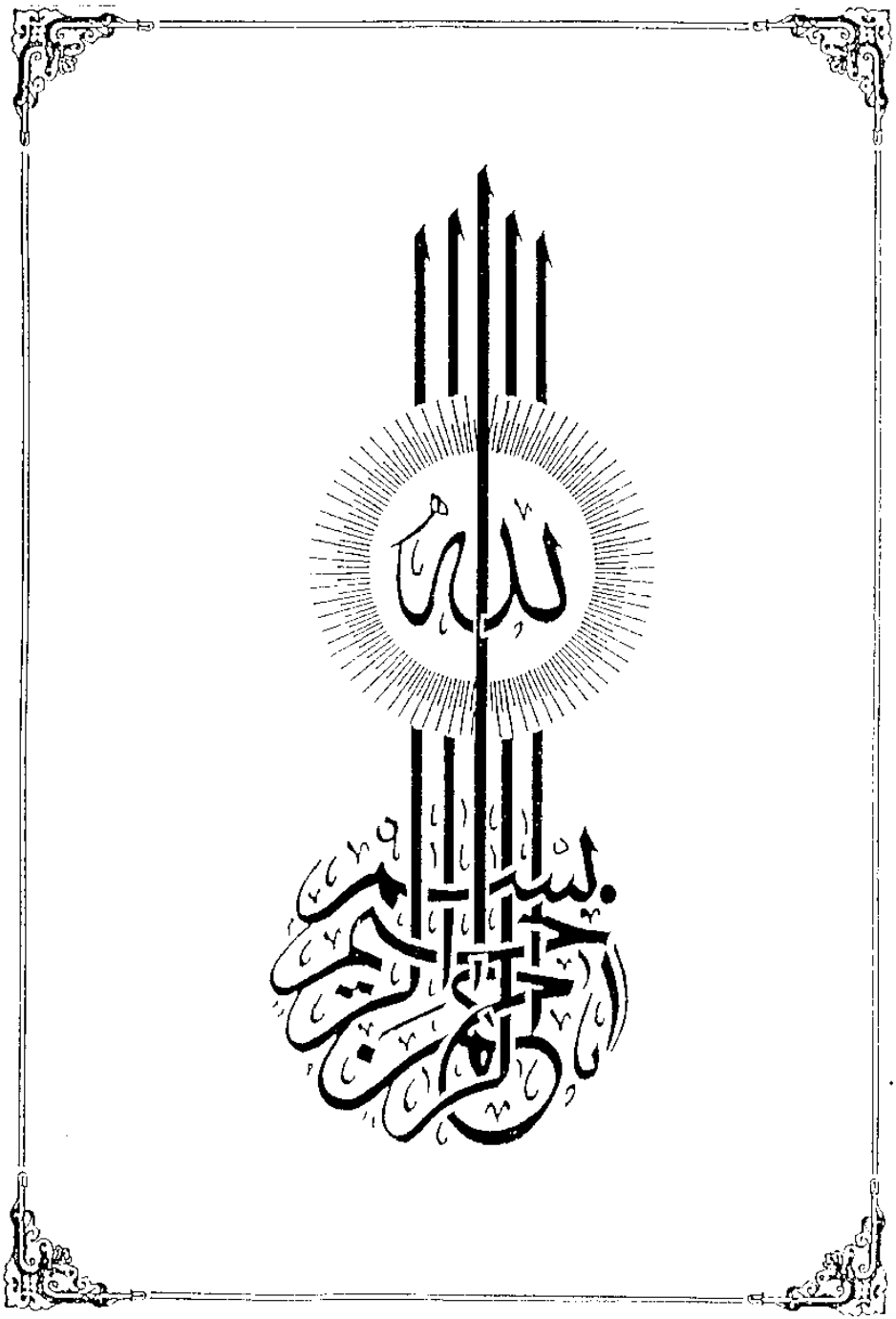


ACKNOWLEDGEMENT

In concluding this work, I wish to express my thanks to Professor Dr. MOHAMED MOUNIR EL-MEHAIRY Head of the General Medicine Department, Ain Shams University, For suggesting the idea of this study, his valuable help, encouragement and advice.

I also appreciate the help of Professor Dr. IBRAHIM NASSAR, Professor of the General Medicine, Ain Shams University, For his generous help in the study, his continuous guidance and Supervision.

To Professor Dr. LAILA EL-SEMARY, Assistant Professor of Forensic Medicine and Toxicology, Ain Shams University. I pay a special tribute for her valuable remarks , her Kind assistance and encouragement.

C O N T E N T S

AIM OF WORK

A wide variety of anovulatory and menstrual disorders have been the field of work of many investigators hoping for better management with different drugs inducing ovulation. Few problems in gynecologic practice are as challenging or taxing to the clinician as anovulatory infertility.

In the recent years a very good improvement is achieved in the methods of diagnosis and treatment of infertility. Anovulatory infertility is every day practice in any gynaecological unit and till now there are variable schemes and dosages used in different centres.

One cannot help but wonder, in this era of increasing awareness of the problems of population over-expansion, if the time, effort and money expended for these few pregnancies is justifiable. However, the desire of an individual couple to experience parenthood is one that no individual physician can deny.

The aim of this study is the revision of the pharmacotoxicological potential of three of the commonly used drugs inducing ovulation as well as effects of the therapeutic doses, protracted use and toxic hazards.

Such study will provide enlightment over the dangers that the patient may face. It is not intended as a medical restriction but as a toxicologically-oriented precaution.

HISTORICAL REVIEW

Although induction of ovulation in women has been of considerable research interest for several decades, for the clinician, however, the problem of ovulatory failure remains a frustrating dilemma.

Gluco corticoids have some merit in anovulatory women particulary in certain hirsute amenorrheic ones. Occasionally cyclic ostrogen and progesterone have been used successfully in functional amenorrhea to restore pituitary - ovarian balance. Striking results are frequently obtained with thyroid medication in subclinical hypothyroid patients with ovulatory failure. Wedge resection of the ovaries has proved a valuable procedure in the management of the stein-leventhal syndrome through the reduction of the ovarian mass. (Green blatt, 1961).

Clomiphene citrate, Human Menopausal Gonadotropins and Bromocriptine are the most widely used drugs in that field.

Clomiphene Citrate :

Clomiphene citrate was originally used experimentally as an oral contraceptive (Holtkamp, 1961). It has

been available for clinical investigation since 1960 (Daniel, 1967). Greenblatt, (1961) was the first to use it for induction of ovulation. The drug proved to be safer after at least monthly checkups and its use was extended to infertile patients with only minor problems of ovarian dysfunction (Payene, 1964 : Karow, 1968).

Clomiphene was first given to 4 females in the United States as a contraceptive agent, starting with 10 mg then the dose was increased up to 100 mg daily. It was observed that, the luteal phase was prolonged to 20-35 days. Clomiphene was also tried in amenorrheic patients and their endometrial biopsies revealed secretory endometrium, this directed the attention to give the drug to patients with ovulatory failure in order to induce ovulation. (Greenblatt, 1977).

Bromo-ergocriptine :

Ergot has a fascinating history. Over the centuries, its role and significance had undergone complete metamorphosis. Once a dreaded poisonous contaminant, it has changed to become a rich treasure house of valuable pharmaceuticals. Ergot was first mentioned by the German physician Adam lonitzer in 1582 as a remedy used by midwives for quickening childbirth. The

isolation of pharmacologically useful alkaloids started in 1906 with the discovery of ergotoxine. Stoll and Hofman in 1943, observed that ergotoxine is an extremely variable mixture of three alkaloids named ergocristine, ergocornine and ergokryptine. Later it was found that ergokryptine occurred in two isomeric forms, designated as ∝ and B-ergokryptine. (Hofmann, 1978).

Certain ergot alkaloids have been used since 1954 as investigational tools in the field of reproductie physiology. Shelesnyak (1956); observed that ergotoxine inhibits the formation of deciduomata in pseudogravid rats, and interferes with gestation in rats during the progravid phase.

Out of a great number of natural and synthetic ergot alkaloids 2-Br-∝-ergocryptine-methanesulfonate proved to be the most specific inhibitor of prolactin secretion with subsequent induction of ovulation in hyper prolactinaemic anovulatory females. (Fluckiger, 1976).

Human Menopausal Gonadotropins :

In the years following the delineation of the hypophyseal control of ovulation, numerous attempts were made to stimulated ovulation directly in the amenorrheic and anovulatory human female with exogenous gonadotropins.

The basic approach was to stimulate follicular growth with preparations rich in follicle-stimulating hormones, and then at the proper time of follicle ripening, to stimulate ovulation itself with extracts rich in luteinizing hormone.

Ry berg and Ostergaard, in 1939, described their results with gonadotropins derived from animal pituitary glands. The overall conception rate with animal gonadotropins as reviewed by Jones et al., 1960, proved to be quite low. Furthermore, repeated administration resulted in the development of antibodies against animal foreign proteins. Thus the successful induction of ovulation awaited the availability of relatively pure, or at least potent, preparations of human follicle stimulating hormone.

Gemzell et al., in 1958, reported the successful induction of ovulation and pregnancy in the human, utilizing FSH derived from human pituitary glands removed at autopsy.

This source of human pituitory FSH remained scarce, due to the limited supply of human pituitary glands.

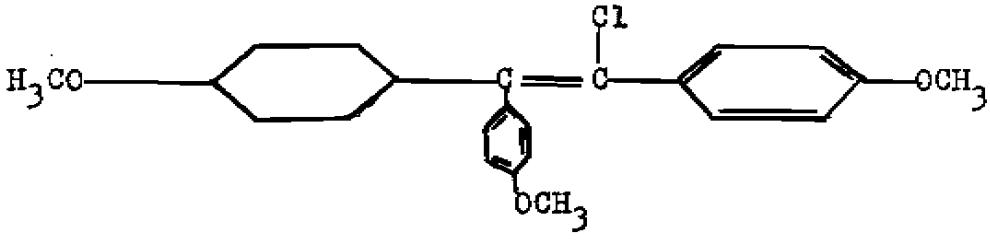
Successful induction of ovulation with gonadotropins derived from human postmenopausal urine, first described by lunenfeld, had ensured that a potentially unlimited supply of gonadotropins can ultimately be made available for clinical use. (Rosemberg et al., 1963; Vande and Turksoy, 1965; and Taymor et al., 1966).

CLOMIPHENE CITRATE

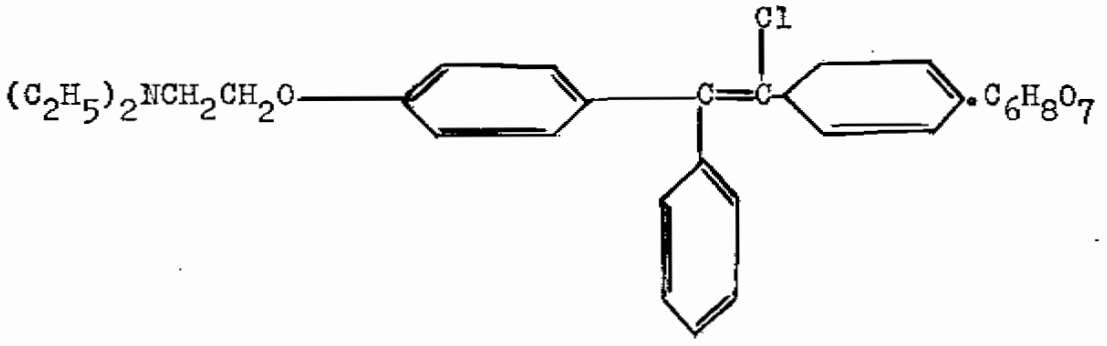
Chemistry :

Clomiphene citrate is an orally active synthetic nonsteroidal agent. It is an analogue of chloro trianisene and is structurally related to the potent synthetic estrogen diethyl stilbesterol, and was shown to have ovulation-inducing propensities in the human while possessing no progesterone-like, androgen-like or corticoid-like activity (Greenblatt, 1961). Its chemical name is (clomifene or clomiphene citrate) 2-[(P - B - chloro - phenul styryl) phenoxy] triethyl amine dihydrogen citrate (Todd, 1967).

The compound may appear either in cis or in trans-configuration; the cis-isomer being significantly more potent. The commercially available preparations are usually 1:1 mixtures of cisclomiphene and transclomiphene. (Greenblatt, 1967; Charles, et al., 1966; Macleod et al., 1970).



Chlorotrianisene(TACE)



Clomiphene citrate

(MRL-41)

Goodman, L.S., P_{1549}-P_{1550}, 1970

Dose, Administration and Pharmacokinetics:

The use of clomid was early limited to women with major endocrine defects and after failure of other treatments due to the frequent side effects reported by the early investigators. With more experience and smaller dosages (50-200mg) daily for a short period, 3 - 5 days of each cycle, the drug was effective and most of the side effects were eliminated. (Greenblatt, 1961).

The response to clomiphene is unpredictable; a dosage ineffective for some may be satisfactory for others. The usual initial dose is 50 - 100 mg. for

5 - 10 days; further dosage is adjusted according to the response, depending up on the type of the patient being treated and the sensitivity of the ovary. The first course of therapy may be started any time during an amenorrheic period or immediately after a progesterone - induced bleeding episode. (Greenblatt, et al., 1980).

The daily dose of 25 mg of cis-clomiphene was capable of negating the estrogenic effect of a daily dose of 1.25 mg of conjugated estrogens on the vaginal mucosa (Barnabas, 1970). In cases of anovulatory cycles; clomiphene is started usually on the 5th day of the menstrual cycle (the first day being the first day of menstrual bleeding); ovulation frequently occurs within 2-12 days after the cessation of therapy and at times during therapy.

As to the length of treatment, there are many instances in which medication was given for 6 - 36 courses, after which spontaneous ovulatory menses set in. In others, ovalution did not occur after conclusion of therapy. (Greenblott, et al., 1980).

In amenorrhoeic patients the course of treatment is guided by the temperature record. If the latter