EFFECT OF COPPER AND STEROID RELEASE FROM INTRAUTERINE DEVICES (IUDs)

Thesis

Presented as a Partial Fulfilment

For the Degree of

M.Ch. Gyn. & Obst.

Faculty of Medicine, Ain Shams University

By

IBRAHIM YASSIN ABOU SENNA

M.B., B.Ch., D.G.O., D.S.

Clinical Demonstrator,

Department of Gynecology and Obstetrics

Ain Shams University

Cairo

(1974)

ACKNOWLEDGEMENT

This work has been done under the guidance and supervision of Professor Dr. M.I. Ragab, Professor of Obestetrics and Gynaecology who supplied the material for research*, and Professor Dr. A.M.Makhlouf, Professor of Obestetrics and Gynaecology, Ain Shams University.

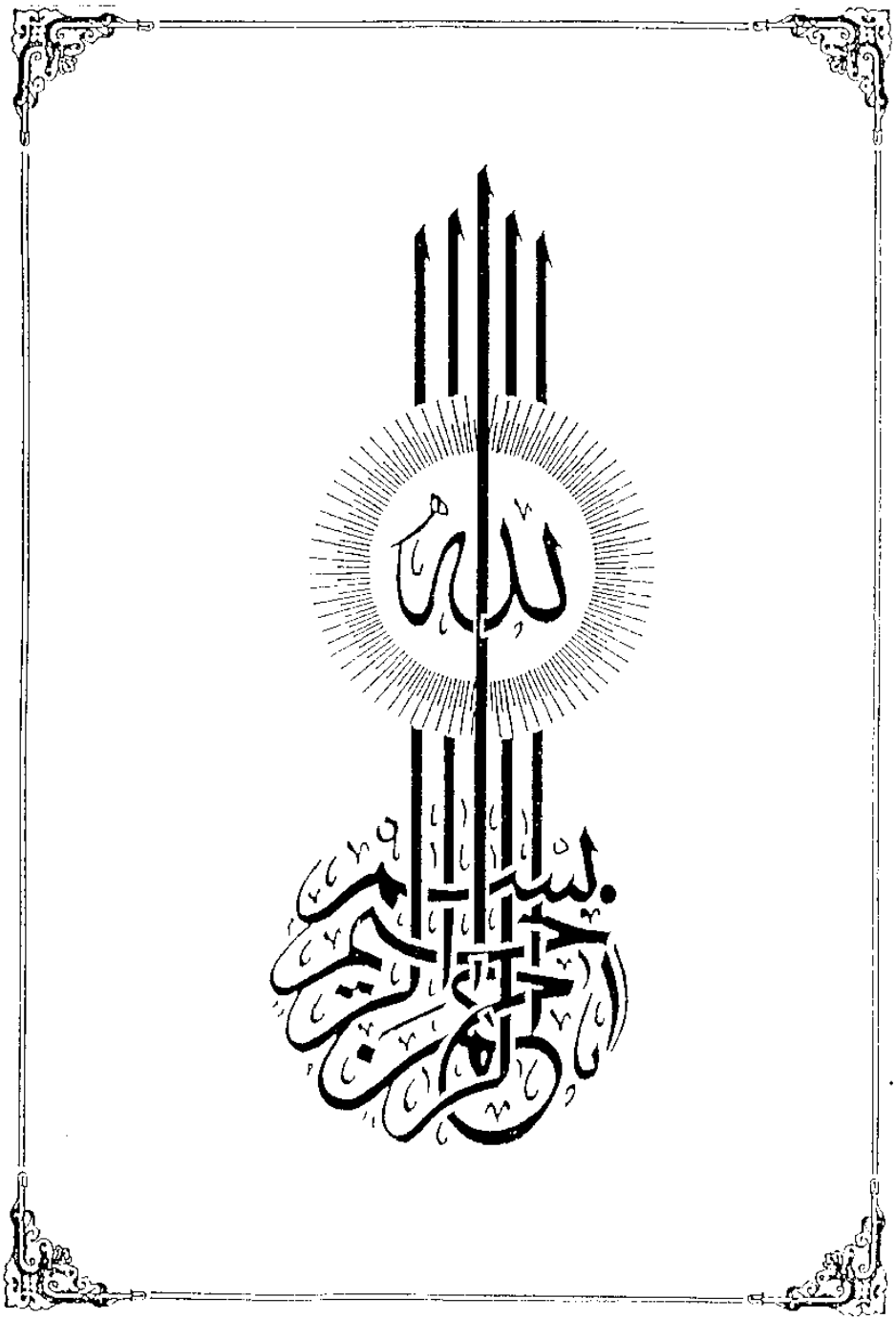
The candidate wishes to express his deep gratitude for their constant supervision, advice and valuable,help, orientation and encouragement throughout this work.

The candidate also would like to thank Professor Dr. M.B. Sammour, Professor of Obstetrics and Gynaecology and Dr. S. El-Mahgoub, Assistant Professor of Obestetrics and Gynaecology, Ain Shams University for their precious advice and guidance in preparing this work.

.. .. ..

* Materials supplied by Prof. M.I.Ragab:

100 plain spring coil
100 spring coil fitted é progesterone carrying silastic capsule.
100 spring coil fitted é mestranol carrying silastic capsule.
100 spring coil fitted é copper wire 500 mg.



C O N T E N T S

---o-o-o---

INTRODUCTION

For the last ten years, intrauterine devices have been used with varying success in clinical practice and in Family planning programs throughout the world. In theory, the IUD is close to an ideal contraceptive method. Although it requires a clinical procedure, the IUD is not related to coitus, usually requires only a single insertion, rarely causes systemic hazards, and provides long-term protection against pregnancy.

In practice, the first generation of IUDs posed problems of expulsion, accidental pregnancy, perforation, infection, pain and bleeding that made them less than ideal for many women.

A decade of international research has focused therefore on improving IUD performance by reducing the incidence of the three pertinent events in IUD failure. Buttressed by rigorus statistical analysis, IUD research has concentrated on three general areas: (1) Improved techniques and insertion; (2) optimal size and configuration of the device itself; and (3) Addition of bioactive substances to reinforce

the contraceptive effect or reducing bleeding and pain. Some progress has been made in the first area. Better insertion techniques plus improved training, more experience, and better patient selection have undoubtedly reduced the incidence of major complications as expulsion and perforation. In the second area - (IUD design) - little progress has been documented to date despite an amazing array of new IUD sizes, shapes, surface areas, and other physical dimensions. In the third area-bioactive devices - the addition of copper and hormones is one of the great achievements which proved to be of great value in reinforcement of the contraceptive effect of IUDs and in minimizing Bleeding, expulsion and pain.

The present study was undertaken to:

1. Evaluate a new insertion technique of the spring coil device in an attempt to reduce its expulsion.

2. Study the effect of addition of bioactive substances, namely copper, progesterone and mestranol to the plain (inert) spring coil device.

3. Study the release rates and pattern of progesterone and mestranol to determine optimum doses and silastic capsule lengths for further trials.

4. Study the effects of the active substances used on the endometrium.

5. Perform a comparative study to determine the ideal bioactive substance for long-term use.

.. .. ..

INTRAUTERINE CONTRACEPTION

HISTORICAL CONSIDERATIONS

The early history of IUDs is so poorly documented that the original concept has not been assigned to a person or infact to a specific century. Early mention has been made of the use of stones placed within the endometrial cavity of camels to prevent pregnancy during long trips across deserts. Undoubtedly a similar method had been applied to women at or about the same time.

These very early applications of the intrauterine foreign body as a means of regulating fertility may be considered as the EMBRYONAL stage of evolution of intrauterine contraception. This stage was relatively void of true scientific study and knowledge of the subject.

The INFANCY stage of IUD evolution began in 1920's with the ingenious and daring studies of Grafenberg, as reported in 1928[34]. His first device consisted of a six-pointed star made by tying three pieces of silk worm-gut together at the centre with silkwarm-gut also.

Grafenberg subsequently substituted a center tie made of thin silver wire for one of gut. The wire permitted detection with the uterine probe, and also rendered the star partially radio opaque. The star was so soft, however, that it was readily expelled from the uterus. In order to increase the retention rate, Grafenberg made the first intra-uterine ring. This device consisted of several turns of silk worm-gut making a ring approximately 2 cm. in diameter having a cross section of about 2 mm. The rings were then made more rigid as well as radio-paque by binding them with fine silver wire.

Although this silver bound gut ring was found by Gräfenberg to be highly effective, it was soon replaced by a ring made by joining the two ends of a tightly wound spiral of silver wire. The spirally wound ring possessed moderate spring properties, and hence could be compressed into a smaller and oblong configuration for insertion through the cer-vical canal. Its inherent resiliency then caused it to return to the original circular ring shape when it was released within the more spacious endometrial

cavity. This model of Gräfenberg ring was inserted by him into several thousand women and was the first intrauterine device commercially manufactured.

During the same decade that Grafenberg began his epoch-making studies, Ota (1934)[75] in Japan was working independently on intrauterine devices. Ota initially used silk worm-gut rings, and then developed small rings fabricated from flexible metals. Although the metal rings seemed to provide more effective contraception than did the gut rings, they were more difficult to insert. For this reason, ota and his disciples in Japan directed their development toward rings fabricated from various synthetic plastics. The 30 years infancy stage of IUD's as depicted by the works of Grafenberg and Ota anded when the significance of their pioneering studies was finally realized. Appreciation of their contributions came in 1959 with the papers by Ishihama (1959)[43] in Japan and Oppenheimer (1962)[73] (1969)[74] in Israel. Both Ishihama and Oppenheimer reported corroborating data on the long-term use of various intrauterine rings. with these independent and impressive demonstrations of effectiveness and safety of the intrauterine foreign body, the IUD entered its childhood stage.

The CHILDHOOD stage began between 1959-1964, when Margulies (1963)[59], Zipper and Sanhuerza(1963)[119], Lippes (1963)[56], Birnberg and Burnhill (1964)[5], Hall (1962)[37], (1963)[38], among many others in the United States and abroad, designed and tested various forms of intrauterine contraceptive devices.

In 1962, the population council launched an intensive research program which included relevant basic laboratory studies and clinical and field trials with promising IUD's. The data derived from these clinical studies were evaluated by the cooperative statistical program (C.S.P.) under the direction of Dr. Christopher Tietze (1962)[110], (1964)[111]. The most recent report on traditional IUD's by the C.S.P, as of 1968 covers approximately 547,000 women-months of use by almost 32,000 women. This extensive experience, particularly with the lippes loop bed the IUD into its adolescence. During the six years from 1962 to 1968, the loop was used more extensively than any other device. Because of the wide clinical experience with and the comprehensive evaluation of the loop, it became customary to use these data as points of reference

in evaluating the clinical effectiveness (also referred to as use effectiveness) of newly conceived shapes and sizes of intrauterine devices.

Although a wide variety of new devices were constructed from synthetic plastics, stainless steel, silicone rubber, and silkworm-gut, the associated side effects, such as bleeding, spotting, uterine cramps, lower abdominal pain, and noticed or unnoticed expulsion, resulted in growing dissatisfaction on the part of women and the medical profession. For the lippes loop size "D", these side effects may be translated to a discontinuation rate of 23 % at the end of the first year of use, and 35 % after 2 years of use. From a demographic view point, this level of use effectiveness is discouraging and pointed up the need to develop devices which could have more efficient performance. Thus the adolescent stage ended with a challenging mandate for improvement.

In (1968)[105], Tatum concluded that most if not all of the IUD's then in use shared one common deficiency. Each device by virtue of its shape and over-all dimensions forced the endometrial cavity to adjust to the

configuration of the device. As a result, the delicate endometrium is compressed and the myometrium is distended. This frequently results in bleeding from the endometrial surfaces as well as painful contractions as the myometrium reacts to oppose its distension and to expel the foreign body which has been placed within its cavity. A logical sequence to this hypothetical consideration was to determine the shape and size of a foreign body which would conform to the endometrial cavity and would thereby cause a minimum degree of distortion, even at the height of a uterine contraction. The concept that an IUD should conform to the endometrial cavity rather than the cavity and myometrium, being obliged to conform to the device, may be considered as the beginning of the <u>permissive stage</u> of IUD evolution.

Consideration of certain anatomic factors and functional characteristics of the human uterus are essential requisites for progression from a philosophical concept to practical application. When the endometrial cavity is empty, the mucosal surfaces are separated only by a small fil[illegible] of mucus and other

Preliminary experiences by Zipper and associates (1971)[124] showed that the combination of copper wire having a surface area of 30 mm^2 and a zinc wire having a surface area of 47 mm^2 resulted in a pregnancy rate of 0.0 per 100 women for 12 months, whereas the 30 mm^2 copper alone provided a pregnancy rate of 4.9. Thus, there appears to be some additive or synergistic action between copper and zinc in relation to their antifertility effect.

In this maturation stage of evolution must be included the hormone-releasing devices reported in (1968)[28] by Doyle and Clewe. Their preliminary studies applied the slow release principle of progestins from silicone rubber to silicone elastomer rods impregnated with melengestrol acetate placed within the uteri of rats, rabbits and monkeys. Their data demonstrated that steroids released from silicone elastomer rods within the uterine cavities increased the retention rate of the foreign body in rats and rabbits, and produced typical secretory type of endometrium in estrogen-primed castrated monkeys.

Croxatto, Vera and Parga in (1970)[19] were the first to show that a progestogen (megestrol acetage) within an intrauterine silicone elastomer capsule would prevent implantations in the experimental horn of a rabbit uterus, whereas normal implantations occurred in the contralateral control horn. Thus, these investigators demonstrated that a progestogen acting locally was a contraceptive. The IUD as a vehicle for steroids to be released within the endometrial cavity was carried one step further by the studies of Scommegna and associates in 1970[93]. Silicone elastomer capsules containing progesterone were affixed to modified lippes loops which were then inserted into the uterine cavities of human subjects. Endometrial changes indicative of localized absorption of progesterone were demonstrated. These investigators concluded from their short-term experiments that although the expulsion rate of the loop was not reduced by the presence of progesterone, there were histologic changes in the endometrium which presumably could interfere with the normal reproduction process.

.. .. ..