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CHANGES IN LIPID METABOLISM UNDER THE INFLUENCE OF PROGESTAGEN IMPREGNATED I.U.D's

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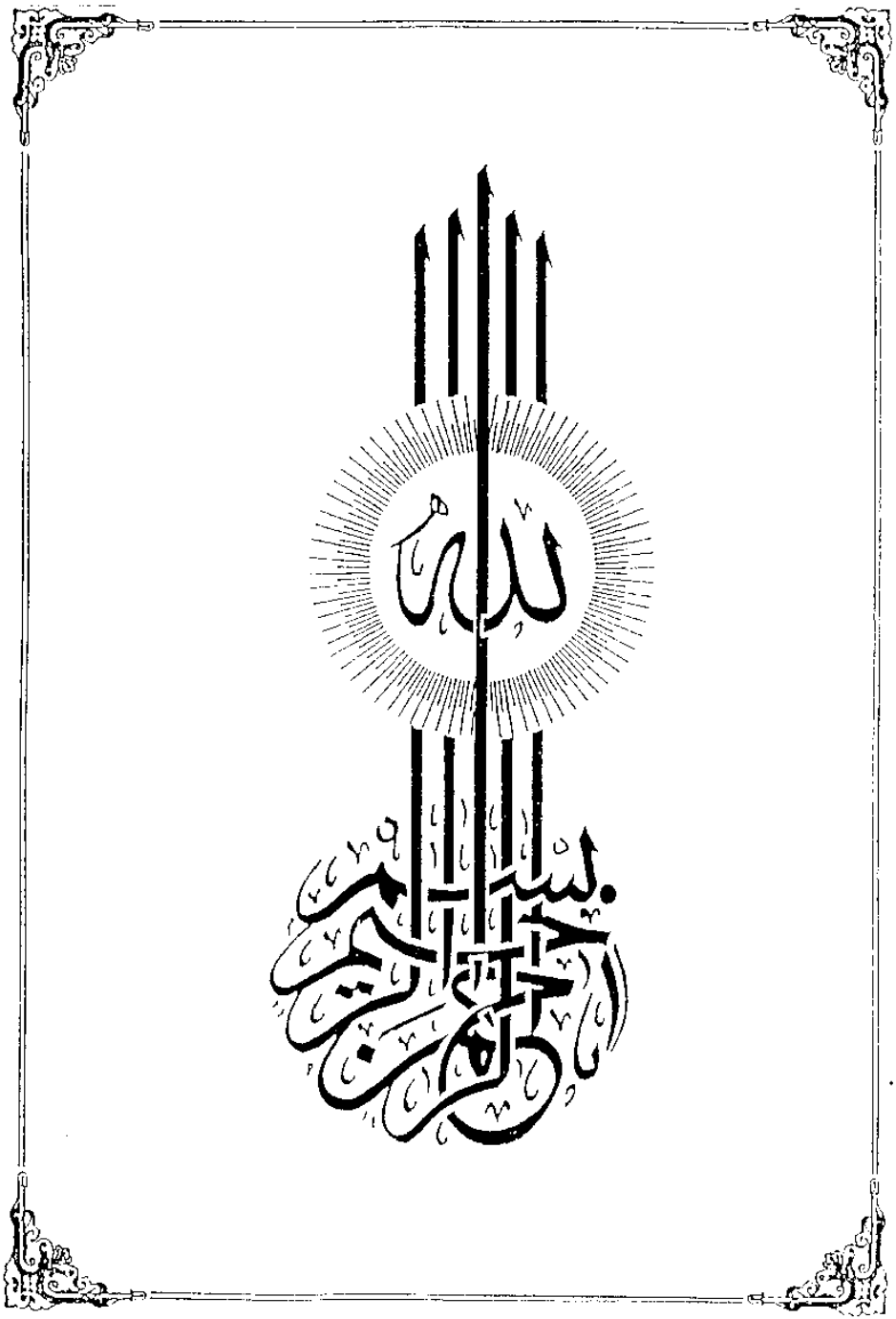

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INTRODUCTION AND AIM OF THE WORK

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Our human world suffers today from many complicated problems. One of the most important keystones of these problems is overpopulation. Control of overpopulation will definitely help to overcome such problems as economic retardation, famines, low socioeconomic standards, bad health and education services and many other problems. On the other hand, failure to control overpopulation only equals the greatest catastrophe that the human race has ever faced. Such control could be achieved by proper family planning programs. Adequate birth control methods are therefore extremely important.

Ideal contraceptive technique has not yet been discovered. The most popular two methods in use nowadays are the pills and the intrauterine contraceptive devices. For the developing world, the latter seems to be more adequate. Among its many advantages, it can be used for a long period with minimal medical care after a single act of motivation. Paramedical personnel can apply it after simple training programs. Ignorance of the patients is no obstacle for its use once simple explanation is given to them thus eliminating errors of use. It is cheap and requires no special surgical procedure for its application in most of the cases. Its effect, at least theoretically, is immediately reversible once the device is removed.

Inspite of all these advantages, the device is not a completely innocent tool. It may cause pain, uterine bleeding, vaginal discharge, increased risk of pelvic infection, perforation and above all unwanted pregnancy can still occur on top of it.

The new progesterone or progestogen impregnated IUDs seem to provide new hope for approaching as much as possible, the ideal contraceptive agent. They are associated with less blood loss, less pain, less expulsion and are very effective in preventing pregnancy (Zador et al., 1976; Nilsson et al., 1980 and El-Mahgoub, 1980).

But is it safe to use progestogens as contraceptive agents? This serious question was raised after the report of the Royal College of General Practitioners (RCGP) which could link the incidence of total arterial diseases including atherosclerosis, myocardial infarction, and thrombotic stroke to dose of progestogens in oral contraceptive pills (Kay, 1980). This association was further supported by other studies e.g. Mann and Vessey,, 1981; Slone et al., 1981.

While the mechanisms for these unwanted effects on cardiovascular system have not been fully elucidated, it is reasonable to suppose that changes in serum lipids might be implicated. Lipids are deeply involved in atherosclerosis and

the delicate interplay between coagulation mechanisms and endothelial and intimal changes should urge complete exploration of the area (Knopp et al., 1982).

The aim of this work is to study the effect of levonorgestrel, given in much smaller dose than oral contraceptive pills and by different route of administration i.e. intrauterine, on lipid metabolism. This would give a predictive value of the possible side effects of the new levonorgestrel impregnated IUDs on cardiovascular system. To achieve this, the following parameters will be measured before and after 6 and 12 months of application of levonorgestrel impregnated IUDs.

- Total serum lipids.
- Serum cholesterol, total, free, and esterified.
- Serum triglycerides.
- Lipoprotein electrophoresis.
- Serum SGOT as indicator of liver function.

REVIEW OF LITERATURE

HISTORY

The millions of intrauterine devices in use throughout the world today represent the modern application of an ancient concept. The first IUDs may have been pebbles inserted into the uteri of camels by Arabs and Turks who wanted to protect their saddle animals from pregnancy during long desert trips (Finch and Green, 1963).

Hippocrates is credited with using a hollow lead tube or sound to insert medication or pessaries into human uteri but translations differ as to whether the process was intended for contraception or other purposes (Davis, 1971; Southam, 1965).

In humans, the use of contraceptive pessaries was reported in the 11^{th} century by the Islamic Scientist Ibn Senna (Avicenna). During the late 19^{th} century, stem pessaries made from different materials were in use. These were technically not intrauterine devices since they did not rest entirely within the uterus, the bulk of the devices remained in the vagina while the stem extended through the cervical canal and protruded into the uterine cavity. They were inserted to correct uterine position, induce abortion as well as to prevent pregnancy (Finch and Green, 1963).

In 1902 wishbone-shaped pessary which extended into the uterus, was introduced by Dr. Carl Hollweg in Germany.

Although the original report mmade no mention of contraceptive effect, Hollweg stated somewhere else that the pessary had been inserted in 700 women for prevention of pregnancy (Tatum, 1972).

The first IUD designed solely for human contraception was developed in 1909 by a German physician, Richard Richter. The device was ring shaped and made of silkworm gut (Richter, 1909). Silkworm threads were also incorporated in a cervico-uterine device developed in 1923 by K. Pust, who combined the silkworm ring with the older stem pessary (Pust, 1923). Pust reported no pregnancies or serious complications among 453 women in whom he inserted the device. He distributed his IUD to other physicians but many refused to use it on the grounds that such a device would produce pelvic infection (Siddall, 1924).

A significant event in IUD history occured in the late 1920s when Ernst Graefenberg developed a silver ring to be placed entirely within the uterus (Graefenberg, 1930). Highly effective in preventing pregnancy, the Graefenberg's ring became popular first in Germany and then elsewhere. In 1934, Ota, working in Japan, introduced the ring that bears his name. Ota claimed that his gold or gold plated silver ring

yielded fewer failures (one pregnancy among 73 users) than Graefenberg's ring (five pregnancies among 51 users) (Ota, 1934).

Although enthusiasm greeted both devices initially, it was then replaced by skepticism and even condemnation and were considered ineffective and dangerous. In 1936, the Japanese government prohibited their use. Graefenberg was forced to abandon his ring because of opposition by European physicians. Before the development of antibiotics, physicians were reluctant to adopt any method that might increase the risk of pelvic infection (Davis, 1971). The conservative medical attitude towards IUDs lasted until the late 1950s, when technological progress promoted a reappraisal. Appreciation of the significance of the pioneering studies of Graefenberg and Ota came in 1959 with papers by Ishihawa in Japan and Oppenheimer in Israel. Both reported corresponding data on the longterm use of various intrauterine rings. These independent and impressive demonstrations of the effectiveness and safety of the intrauterine foreign body were major steps in opposition to the traditional objections against the use of IUD (Tatum, 1972).

In addition to advances in antibiotic therapy, which dispelled fears of uncontrollable infection, the technological factor that was crucial in the acceptance of IUDs was the development of polyethylene, a biologically inert plastic that

could be moulded into any desired configuration and would return to that configuration after being bent or straightened. So between 1959-1964, Margulies, Zipper, Sanhuerza, Lippes, Birnherg, Burnhill and Hall among many others designed and tested various forms of intrauterine contraceptive devices (Tatum, 1972).

Jack Lippes, of the USA added two important features to the device that bears his name, both of which have been incorporated in most of subsequently developed IUDs : a transcervical thread to assist in detecting and removing the device and a small amount of barium sulphate to render the device opaque to x rays (Lippes, 1962).

A new concept was put forward by Tatum, 1966, that an intrauterine contraceptive device should conform to the endometrial cavity rather than the cavity and myometrium being obliged to conform to the device. This new concept led to the development of Tatum T-loop and Davis sheild (Tatum, 1972). By 1970s, the focus of attention started to shift on to the so called second generation of IUDs. These were the bioactive or medicated devices in which the plastic IUD became the carrier of other substances such as metals, hormones and antibleeding agents. Zipper and his associates in Chile demonstrated that metallic copper in the rat uterus was an excellent contraceptive agent (Zipper et al., 1969A). Next, Zipper and

his associates added metallic zinc to metallic copper which increased the contraceptive efficiency (Zipper et al., 1969B).

The hormone releasing devices were first reported by Doyle and Clewe, in 1968 who used silicone elastomer rod IUD containing melengestrol acetate placed in 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 changes in the endometrium in oestrogen-primed castrated monkeys (Doyle and Clewe, 1968).

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. Silicon elastomer capsules containing progesterone were affixed to modified Lippes loops which were inserted into the uterine cavities of 34 women. Endometrial changes indicative of localized absorption of progesterone were demonstrated. These investigators concluded from their short experiments that histologic changes in the endometrium interfere with the normal reproductive process (Scommegna et al., 1970).

In a clinical trial, Pandya and Scommegna, (1972), inserted seven differently shaped progesterone-releasing IUDs in 109 women. The largest trials with progesterone-releasing IUDs have been performed using a modified T-shaped IUD,

originally described by Tatum (1972). The results of trials with this IUD, called the progestasert, have been presented by many authers e.g. Pharriss et al. (1974) and Martinez-Manautou et al., (1974).

Synthetic progestins have been used as an active compounds in steroid releasing IUDs. Horne et al., (1970), reported the effects of intrauterine administration of megestrol acetate in five women. Stryker et al., (1972), and Stryker, (1974), used medroxyprogesterone acetate in IUDs.

El-Mahgoub, (1975) attached sialastic tubing containing dnorgestrol to the vertical arm of a T-shaped IUD. Almost at the same time, Nilsson et al. used biodegradable polyacetate as steroid releasing polymer for intrauterine administration of d-norgestrel (Nilsson et al., 1975).

El- Mahgoub, (1982) reported his 3-year-experience with intracervical levonorgestrol-releasing mini T-system. Nowadays, hormone releasing devices are repeatedly and thoroughly investigated all over the world with the introduction of various modifications in both the type and dose of the hormone in the hope of reaching an ideal contraceptive technique.