ENDOMETRIAL GLYCOGEN AND ITS RELATION TO INFERTILITY EFFECT OF INTRAUTERINE CONTRACEPTIVE DEVICE

by

KAMALA ACHARI,* M.B., M.S., F.I.C.S., F.A.C.S., F.R.C.O.G.

KRISHNI JE, M.B.B.S.

and

RAJ KUMARI NARONE,** M.B.B.S., M.S. (Path)

Although many investigations have been reported on the infertility effect of the intrauterine device, the mechanism of action of I.U.D. has not been elucidated yet. However, some evidences have been presented that I.U.D. might exert its main action at the uterus in inhibiting the implantation and the development of the blastocyst.

Hughes (1945) observed that in a normal individual glycogen seemed to be present in all tissues of the generative tract with which the ovum comes into contact. It is found in the cells of the cumulus oophorus while the egg is still in the Graafian follicle. It is present in the endometrium in increasing amounts after ovulation. He further noted that the distribution of glycogen in the endometrium seemed to follow a constant sequence of events according to the phase of the cycle.

Boutselis *et al* (1963) during their histochemical observations in normal human endometrium found that during early proliferative phase, glycogen was present in scant amounts, but becomes more noticeable before ovulation and remained confined to the basal portion of the glandular cells. Stromal deposition was scanty. Glycogen rapidly increased in the glandular cells following ovulation shifting from a subnuclear location through the cytoplasm. As the cycle progressed glycogen in large amount was secreted into the glandular lumen. Stromal cells also exhibited some amount of glycogen at this phase. This change in the glycogen accumulation has been suggested to play an important role in providing nutrition to the blastocyst before implantation.

In experimental animals accumulation of glycogen occurs in oestrogenic phase and in progestogenic phase glycogen granules disappear in normal condition. Parr (1966) working on rat's uterus, using histochemical procedures, has reported that accumulation of glycogen in the device containing horn as against no such accumulation in the control horn. He suggested the accumulation of glycogen to the defective secretory activity of epithelial cells in the presence of I.U.F.B. thereby causing not normally found glycogen to become evident in the epithelial and stromal cells close to the basement membrane.

Material and Methods

In this study the glycogen activity of endometrium of different groups of patients have been analysed to find out the

**Professor of Obstetrics and Gynaecology, P. W. Medical College, Patna. Bihar.*

***Registrar.*

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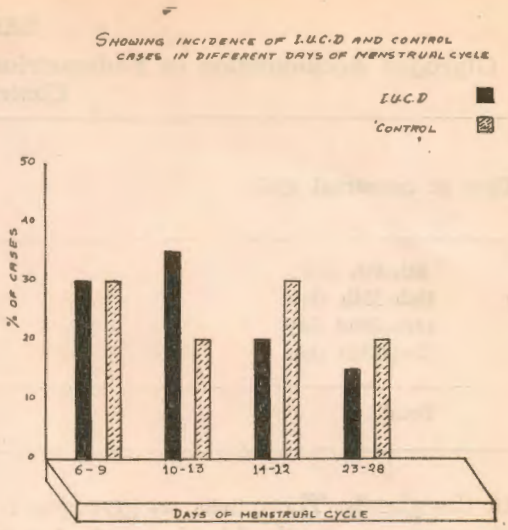
relationship of glycogen with infertility action of intrauterine device. The patients were divided into two groups:

Group I—consisted of 30 patients selected from the Out-patient's Clinic on the basis of the following criteria: (i) Regular menstrual cycle, (ii) parity one or above, (iii) no history of menstrual disorder within the last two years, and (iv) no evidence of inflammation of the genital tract. The age ranged from 21 to 38 years. After clinical evaluation of the patients, endometrial glycogen was estimated in various phases of menstrual cycle.

Group II—consisted of 60 patients who had insertions of I.U.C.D. 6 months to 3 years prior to investigation. Their age ranged from 21 to 38 years and they were selected on the basis of the following criteria: (1) Regular menstrual cycles i.e. menorrhagia cases were included, (ii) no history of menstrual disorder within the last two years. After clinical evaluation of the patients, endometrial glycogen was estimated in various phases of menstrual cycle. Histochemical study of endometrial glycogen was done by periodic Acid Schiff staining.

Graph I shows the number of cases studied in I.U.C.D. and control series on different days of menstrual cycle.

Table I shows the absence of glycogen



Graph i

in glands, stroma and blood vessels till the 13th day of menstrual cycle. It appeared in the glands from the 14th day of menstrual cycle and was present in small quantity in both, glands, stroma and blood vessels till the 24th day. It disappeared completely from all the endometrial structure after the 25th day.

Table II shows that the glycogen started appearing in the glands from the 9th day of menstrual cycle. In that phase no glycogen is seen either in the stroma or in the blood vessels. By 10th-13th day moderate amount of glycogen appeared

TABLE I

Glycogen Accumulation in Various Phases of Cycle in I.U.C.D. Series

Days of menstrual cycle	No. of cases	Glycogen accumulation		
		Glands	Stroma	Blood vessels
6th-13th day	39	—	—	—
14th-22nd day	12	++	++	+
23rd-24th day	3	+	+	—
25th-28th day	6	—	—	—
Total	60			

TABLE II

Glycogen Accumulation in Endometrium in Various Phases of Menstrual Cycle in Control Cases

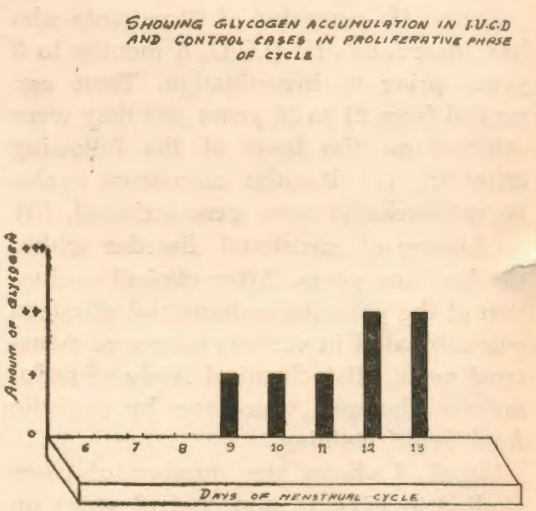
Days of menstrual cycle	No. of cases	Glycogen accumulation		
		Glands	Stroma	Blood vessels
6th-9th day	9	+	—	—
10th-13th day	6	++	—	—
14th-22nd day	9	+++	+	—
23rd-28th day	6	++	+	—
Total	30			

in the glands. There was no glycogen in the stroma or in the blood vessels. Large amount of glycogen appeared in the glands from the 14th day of cycle. Traces also started appearing in the stroma. From the 23rd day onwards there was gradual decrease of glandular glycogen. Glycogen content of the stroma showed a gradual decrease till it disappeared on the 27th day of the cycle.

Graph II shows the glycogen accumulation in I.U.C.D. and control series of cases in proliferative phase of the cycle. There was hardly any glycogen in the proliferative phase in I.U.C.D. series. Figs. I and II show the glycogen content in control and I.U.C.D. series.

Graph III shows the glycogen accumulation in I.U.C.D. and control series in cases in early secretory phase. The glycogen was in very small amount in I.U.C.D. series in all days of this phase. Microphotograph III and IV show the glycogen concentration in control and I.U.C.D. series.

Graph IV shows the glycogen accumulation in I.U.C.D. and control series in late secretory phase. There is very poor accumulation of glycogen in I.U.C.D. series. Figs. V and VI show presence of glycogen in control and I.U.C.D. series.

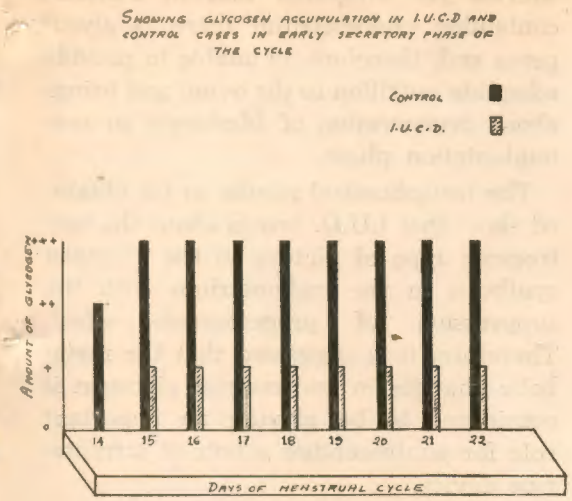


Graph ii

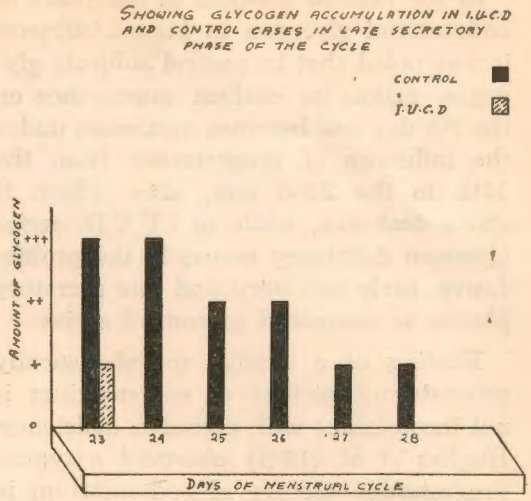
Discussion

Endometrial glycogen, the storage form of glucose, provided an essential nutriment for the developing and implanting blastocyst (Hughes, 1945) before it establishes firm contact with the mother by formation of the placenta. It is during these days of pre-and early nidation that many observers have stated that the trophoblast lived almost exclusively on glucose and oxygen (Hughes, 1945 and Boutselis *et al*, 1963).

Shahani *et al* (1959) emphasized that



Graph iii



Graph iv

an adequate carbohydrate metabolism must be considered as essential for pregnancy. Shetty (1959) while studying the biochemical variation of endometrium in subfertile women also emphasized carbohydrate metabolism to be intimately bound with the process of implantation.

Bo *et al* (1969) studied the level of glycogen in the uterus in presence of a foreign body. Glycogen is localised primarily in the myometrium of the rat uterus and its quantity is greatest at the pro-oestrous or following oestrogen stimulation. When oestrogen therapy was given to castrated rats having I.U.F.B., glycogen granules were prominant throughout the myometrium and stroma in all the three portions, (1) at the site of the foreign body, (2) superior to it, and (3) in the contralateral untraumatized horn. Following progesterone treatment, glycogen granules accumulated at the site of the foreign body, while sections superior to the foreign body and from the opposite control horn contained a few scattered granules. These observations indicate that the segment of the uterus containing I.U.F.B. does not respond to progesterone in a manner similar to portion of the uterus without the foreign body. Suppression of the progestational effect on the uterus at the site of foreign body has been noted by Joshi (1967) also, when he observed that I.U.F.B. prevented the uptake of 32P following progesterone stimulation. He suggested that the failure of uterus bearing the foreign body to respond to progesterone may play an important role in preventing implantation.

In rats I.U.F.B. causes accumulation of glycogen in the uterine horn which indicates progesterone deficiency, while in human being it causes depletion of endometrial glycogen which is suggestive of local suppression of progesterone activity. This difference is due to variation in normal physiological response of the uterus to progesterone stimulation in different species. In normal human endometrium oestrogen effect accounts for traces of glycogen in the endometrium, but accumulation of large quantity occurs in the secretory phase.

In the present analysis in the study of endometrial glycogen in human subjects it was noted that in control subjects glycogen makes its earliest appearance on the 9th day and becomes maximum under the influence of progesterone from the 14th to the 22nd day, after which it starts declining, while in I.U.C.D. series glycogen deficiency occurs in the proliferative, early secretory and late secretory phases as compared to control series.

Finding of a typical morphologically progesterone picture of endometrium is not inconsistant with glycogen deficiency. Hughes *et al* (1945) observed a typical progesterone picture of endometrium in association with glycopenia during their histochemical observations of endometrial glycogen in women with primary sterility. Zondek (1940) has also described "Glycopenic uteri" in infertility cases. Many other observers (Hughes *et al*, 1950, 1963 and Boutselis *et al*, 1963) have also reported a significant lowering in endometrial glycogen levels in cases of primary sterility and repeated abortions where no other abnormality was noted. Fredhandler's vitro studies (1968) have brought out the fact that glucose stimulated macromolecular biosynthesis and that its presence aided in the maintenance of gross morphological architecture of the blastocyst. Glucose has been observed to increase in amount in early fertilized avian egg and the eggs of lower mammals. There is evidence of necessity of glycogen for nutrition of the blastocyst in preimplantation phase in human subjects as well.

Greenwald (1965) demonstrated fragments of dead and degenerating blastocyst in cases with I.U.C.D. and pointed out that in uterus containing an I.U.C.D. the environment causes inability of blastocyst to get proper nutrition in the uterus. He suggested that in I U.C.D. containing endometrium there is glycopenia and, therefore, is unable to provide adequate nutrition to the ovum and brings about degeneration of blastocyst in preimplantation phase.

The histochemical results so far obtained show that I.U.D. brings about the oestrogenic type of picture in the glycogen synthesis in the endometrium with the suppression of progestogenic effect. Therefore, it is suggested that the metabolic changes in endometrial glycogen is considered to be playing an important role for contraceptive action of intrauterine device.

Summary

Glycogen evaluation in endometrium of 30 multiparous women in the age group of 21-38 years with normal menstrual cycles and 60 normal fertile women with I.U.C.D. in situ belonging to the same age and parity range have been carried on all phases of menstrual cycle. From a comparative study of the amount of endometrial glycogen estimated on various days of the menstrual cycle, both in control and I.U.C.D. cases, it has been found that there is glycogen depletion in I.U.C.D. cases.

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See Figs. on Art Paper II-III