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Histopathological effect of clomiphene citrate on epididymis Original study

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ABSTRACT

Clomiphene is a commonly used drug. It is used for Multiple Purposes and the role of clomiphene is under investigation in more diseases. Clomiphene citrate is used for medical induction of ovulation. It acts as a selective estrogen receptor modulator (SERM), having both estrogen agonist and antagonist properties. Clomiphene binds and blocks estrogen receptors in hypothalamus (i.e. antiestrogen. The effect of Clomiphene is not limited to the tissues only but serious side effects on long term use have been reported. The current study is aimed at determining the effects of Clomiphene on Testis.

KEY WORDS: Epididymis, gonadotrophin, Clomiphene, semineferous tubule, Hypothalamus, infertility

INTRODUCTION

Clomiphene citrate is a synthetic analogue of the non-steroidal estrogen chlorotrianisense, 1-(p-(diethylaminoethoxy)-pheny1)-1, 2 dipheny1-2-chloro-ethylene. Clomiphene citrate has a remarkable structural similarly to Estradiol which enables it to bind to estradiol receptors in various tissues such as the hypothalamus, hypothesis cerebri, ovaries, uterus and cervix. However unlike estradiol, Clomiphene citrate is unable to induce the synthesis of new estrabiol receptors, a process essential for the continuous blinding of estradiol to the target cells as well as the expression of estrogenic action. Clomiphene is most widely used drug in the treatment of anovulatory infertility. Ovulatory disturbances are present in 15-25% of couples with infertility. Clomiphene has also been used in conjunction with human gonadotropin and in vitro fertilization programs. Clomiphene has been used in treatment of male infertility due to oligospermia to stimulate gonadotropin release and enhance spermatogenesis. For male infertility 25 mg daily given for 24 days in a month with 6 days rest for upt produced estrogenic action. Clomiphene is commonly used by male anabolic steroid uses to bind the estrogen receptors in their bodies, thereby blocking the effects of estrogen i.e, gynecomastia. It also restores the body's natural production of testosterone. It is commonly uses as a "recovery drug" and taken toward the end of a steroid cycle. The most commonly accepted simplistic view of Clomiphene citrate action in the induction of ovulation is that it binds to the estradiol receptors in the hypothalamus to create a state of

hypoestrogenicity, thereby causing an enhanced Gonadotropin- releasing hormone (GnRH) release followed by an increased secretion of gonadotropins which induces ovulation. The intrafollicular concentrations of Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol and Androgens contribute to follicular growth. It is given for Amenorrhea and Anovulation following the use of OCP's (Post pill amenorrhea). Clomiphene citrate is the ovulatory agent customarily used first to achieve ovulation .In vitro fertilization, GIFT technique and Assisted Reproduction Technique and PCOS (Stein Leventhal Syndrome)

MATERIAL AND METHODS

The present study was aimed to determine the effect of clomiphene citrate on reproductive organs of rats. In the present study the experimental animals used were albino rats weighting on an average 150 gms. 64 healthy rats were used for the experimental study. The animals were studied in four groups.

GROUP A

(Control group)-in this group 16 rats were used. These were fed with routine food and tap water daily. In addition to the routine food and tap water 48 another rats were administered clomiphene citrate orally mixed with flour and water as pellets. According to the dose the treated rats were classified into following groups-

GROUP B

It comprised of 16 rats and was administered .5 mg/ 100 gm daily.

GROUP C

It comprised of 16 rats and was administered 3.5 mg/ 100 mg daily.

GROUP D

It comprised of 16 rats and was administered 5 mg/ 100 gm daily. Dose of the drug was calculated from human therapeutic dose. The animals were kept in four different cages comprising of group A, B, C and D. Each day routine diet was prepared for animals in each group. The diet would comprise of different vegetables and gram. Each animal from the cage was taken out fed with its usual food. The group a animals had routine food whereas the group B, C and D animals in addition to routine food were fed with clomiphene citrate mixed with flour as pellets. The process of administration was continued up to twelve weeks regularly. Four rats from each group were killed at intervals of 2, 4, 8 & 12 weeks respectively. The tissues were processed manually for block making as follows:

S.NO	STEP	MEDIUM	TYPE
1	Fixation	10% Formaline	12 hrs
2	Dehydration	Acetone	12 hrs
3	Clearing	Benzene	6 hrs
			3 changes at intervals of 2 hrs
4	Wax embedding	Paraffin wax at 56 degrees	3 hrs
			3-4 changes

OBSERVATIONS

The present study is aimed to observe the effects of clomiphene citrate on reproductive organs or male albino rats. In all 64 animals were used. These animals were grouped in various groups. Group A comprised the control group. Groups B, C and D received drug. Groups were subdivided into subgroups on the basis of duration of treatment. Progressive decrease in rate of weight rain was observed in general (Chat No; 1). The organs namely, Testis, Epididymis, Seminal vesicles and Prostate of

male albino rats were studied both macroscopically and microscopically.

EPIDIDYMIS

MARCROSCOPIC

On gross examination, a slight to moderate decrease in weight of epididymis was noticed from 4^{th} to 12^{th} weeks of experiment.

Average weights {in mgs} of epididymis

GROUP	SUBGROUPS	TIME WEEKS	EPIDIDYMIS Mgs/100gm B.W
A	A1	2	10
	A2	4	13
	A3	8	13
	A4	12	13
B	B1	2	12
	B2	4	11
	B3	8	11
	B4	12	10
C	C1	2	10
	C2	4	9
	C3	8	6
	C4	12	5
D	D1	2	9
	D2	4	7
	D3	8	6
	D4	12	4

MICROSCOPIC

The alterations in the epididymis were found in those rats in whom testicular changes were present and in general the more severe testicular changes, the more pronounced the epididymal alterations.

GROUP B

In this group rats were administered the lowest dose of clomiphene, 2.5 mg/100/day. Microscopic changes in the epididymis appeared after eight weeks {B3} of treatment in this group.

B1

The lumen of epididymis contained abundant sperm. Epididymis was lined by a columnar in shape and retained prominent apical microvilli. Light cells. No obvious change seen.

B2

Findings same as B1. No change from control seen in this group.

B3

Epithelium appeared shorter than normal; the principal cells remained columnar in shape and retained prominent apical microvilli. Light cells were increased in number. The lumen was smaller than in the normal specimen. Sperms were scarce

B4; Changes were more pronounced. The epithelium appeared shorter than normal and lumen lacked sperm.

GROUP C

In this group rats were administered the intermediate dose of clomiphene, 3.5 mg/100/day. Microscopic changes were present in the majority of treated animals at eight week interval {C3} and in all of those treated for 12 weeks {C4}

C1

The lumen of epididymis contained abundant sperm. Epididymis was lined by a columnar epithelium composed mainly of principal cells and light cells. No obvious change seen.

C2

Epithelium appeared shorter than normal; the principal cells remained columnar in shape and retained prominent apical microvillus. The lumen was smaller than in the normal specimen.

C3

Epithelium appeared shorter than normal. The lumen was smaller than in the normal specimen and lacked sperm.

C4. , The changes were more pronounced. The lumen lacked sperm whorls and the epithelium was shorter than in the normal.

GROUP D

In this group rats were administered the highest does of clomiphene, 5 mg/ 100/ day. Microscopic changes were present in most of the treated rats.

D1

Epithelium appeared shorter than normal, the principal cells remained columnar in shape and retained prominent apical microvilli .The lumen was smaller than in the normal specimen.

D2

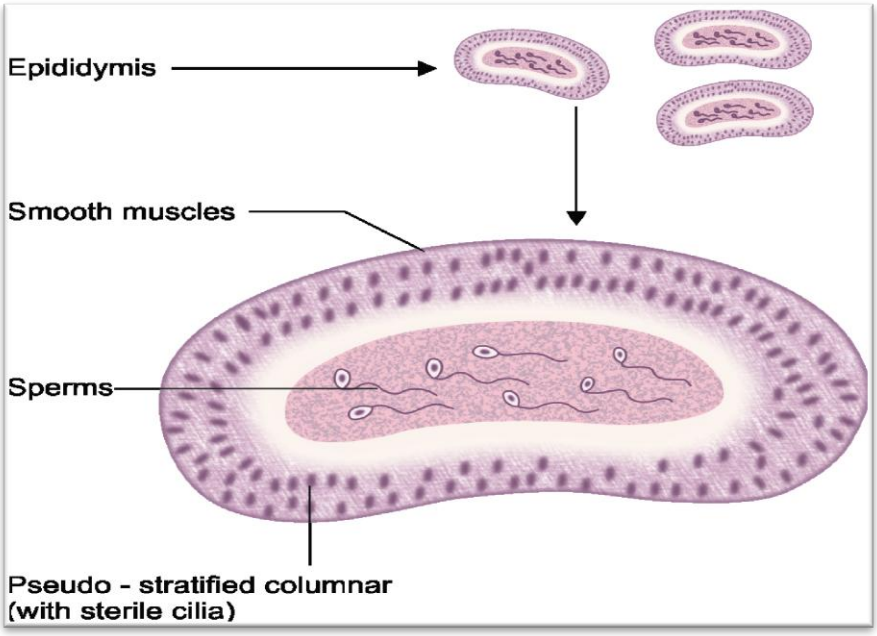
Epithelium appeared shorter than normal .The lumen was smaller than in the normal specimen.

D3

Epithelium appeared shorter than normal. The lumen was small, irregularly shaped, and lacking in sperm.

D4

More pronounced shortening of epithelium than normal and in some areas epithelium was completely atrophied.



Line Diagram showing Normal Epidymis

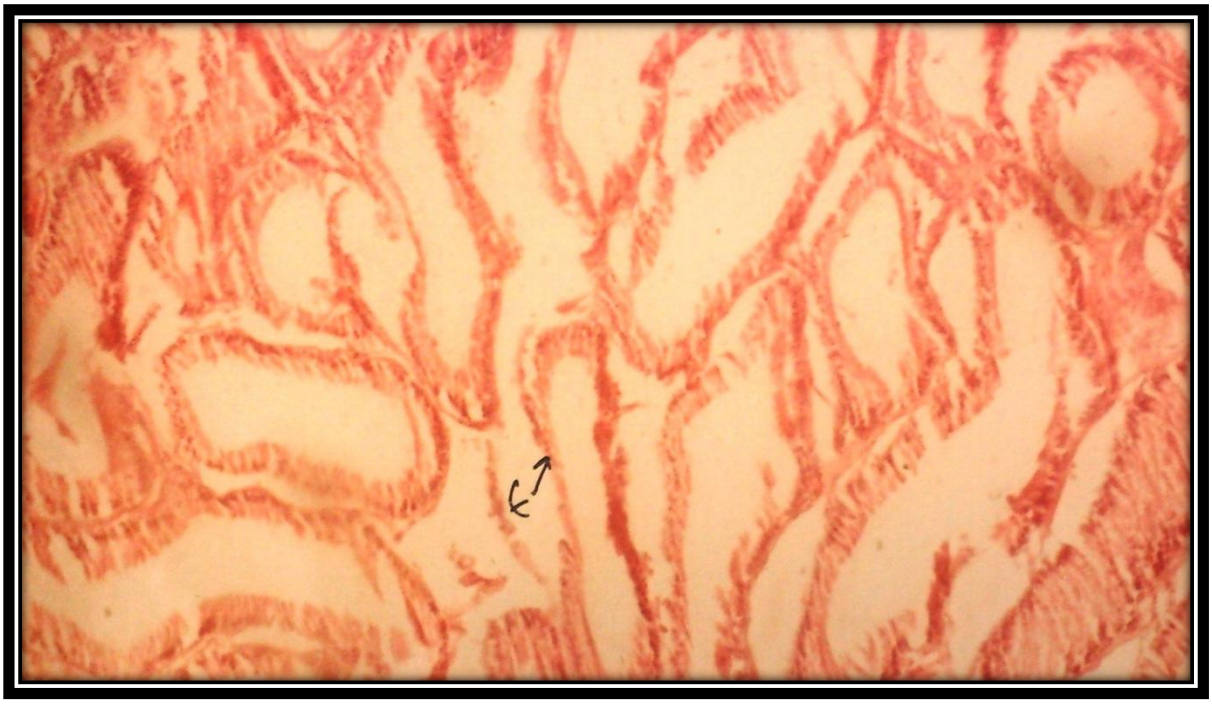


Fig. 1 : Micrograph of Epidymis of Rat in Group C3 showing shortening of epithelium. Magnification X 100

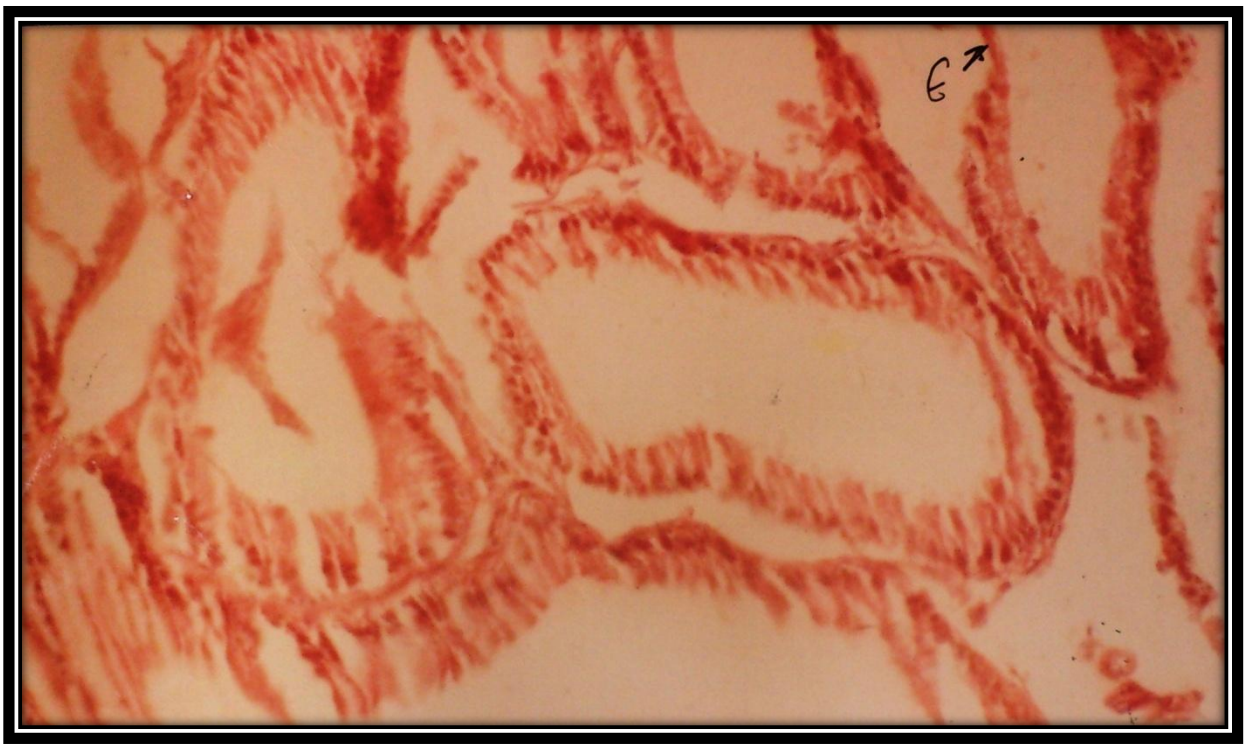


Fig. 2 : Micrograph of Epidymis of Rat in Group D3 showing shortening of epithelium. Lumen is narrowed and without spermatazoa

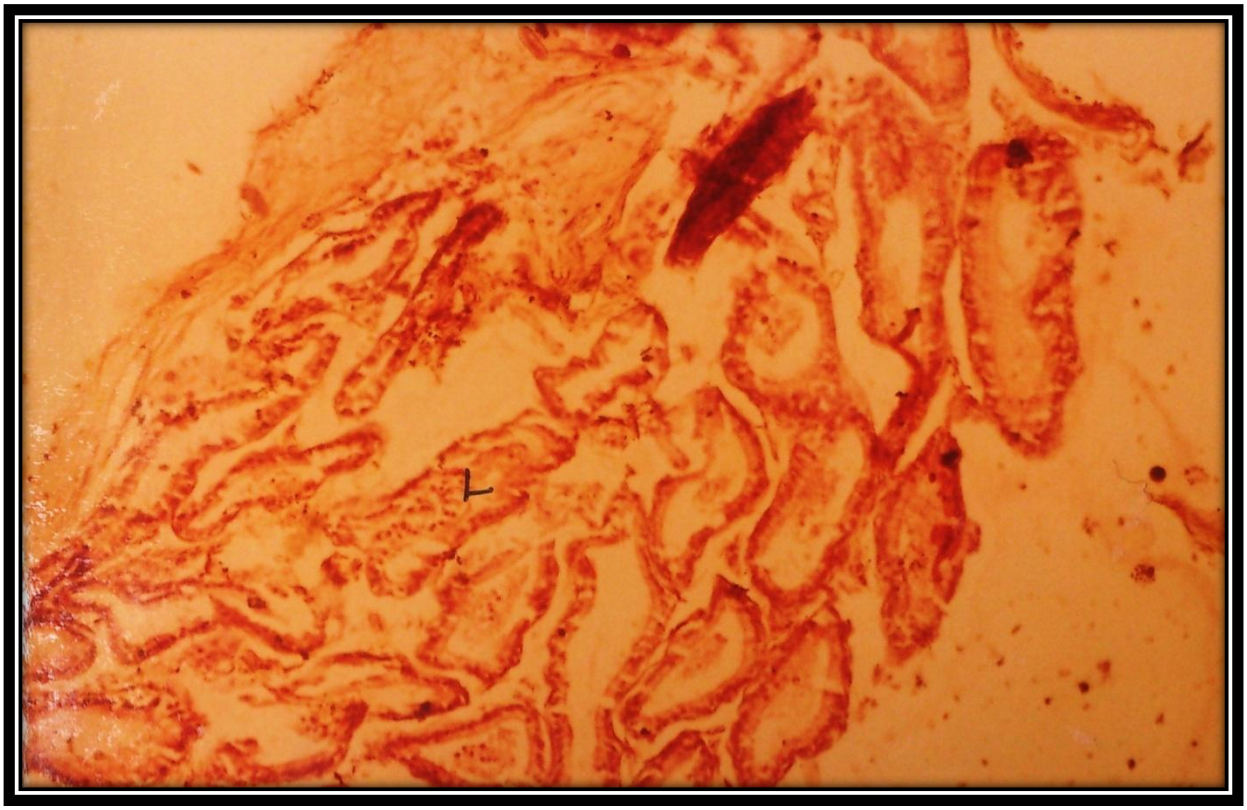


Fig. 3 : Micrograph of Epidymis of Rat Normal. Magnification X 40

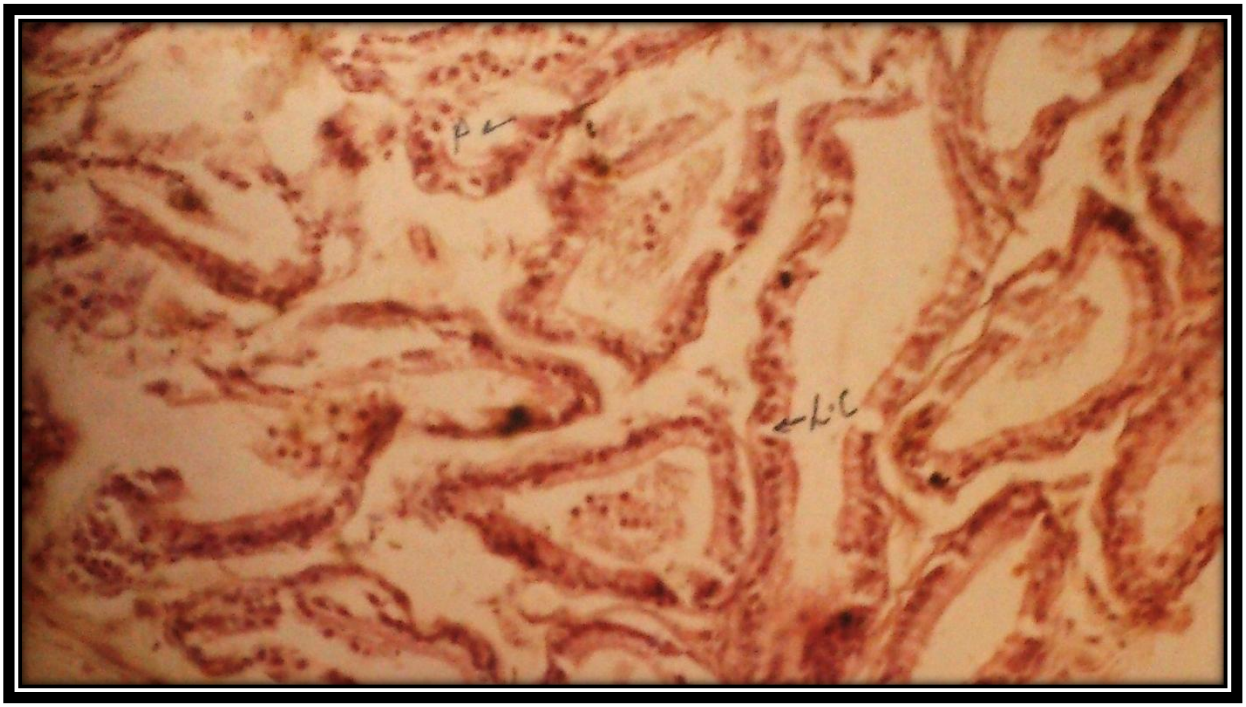


Fig. 4 : Micrograph of Epidymis of Rat in Group B3 showing shortening of epithelium. Microvilli can be seen. Magnification X 100

CONCLUSION

There was a general trend to reduction in the heights of the cells and to increased cytological alterations with increasing dose and length of treatment. Clomiphene treatment induced regressive histological changes in the epididymis as is true with the effects on other genital organs of males.

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