

## Studies on Cervix in Albino Rat Treated With Norethisterone Heptanoate (Synthetic Progesterone)

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### Abstract

Noristerat or norethisterone or norethindrone heptanoate is a depot progestogen for hormonal contraception. Synthetic progestin (NET) exerted pharmacological effects at multiple levels of both the hypothalamic pituitary- Ovarian axis and the female genital tract. Norethisterone effect can be studied by cervix mucosa and myometrium histology.

**KEYWORDS:** NET, Noristerate, Norethisterone heptanoate,

### INTRODUCTION: NORETHISTERONE

Norethisterone was the first highly active oral progestational agent to be synthesized and to achieve wide spread use along with its acetate and enanthate esters.

### Chemistry

Norethisterone (norethindrone) C<sub>20</sub> H<sub>26</sub> O<sub>2</sub> : 17 $\beta$ - Ethinyl-19-nortestosterone, 17 $\beta$ -hydroxy-19-nor-17 $\beta$ -pregn-4-en-20-yn-3-one, 17 $\beta$ -ethinyl-17 $\beta$ -hydroxy-19-nor-androst-4-en-3-one.

### NORETHISTERONE HEPTANOATE

Noristerat or norethisterone or norethindrone or heptanoate is a depot progestogen for hormonal contraception. Engren, (1974) have defined norethisterone as an androgen with a typical progestational effect at sufficiently higher doses. Kobra et al. (1974) observed that fertility was not adversely affected even after long period of norethisterone treatment. Howard et al. (1975) suggested that norethisterone is supposed to exerted its antifertility effect. Erik Weiner et al. (1975) concluded that norethindrone enanthate inhibited ovulation. Howard et al.(1985) suggested that norethisterone heptanoate was the first synthetic progestational agent which was popularly used as a long acting injectable contraceptive. According to Chang et al. (1984) and Veldhuis et al; (1989) the synthetic progestins may have direct effect on ovary by influencing the LH and FSH ratio. Kim et al.(1991) reported suppression of ovarian activity and atrophy of endometrium in women treated with norethisterone. Corpus luteum, endometrium, fallopian tubes were reacted independently after norethisterone treatment.

Poindexter III et al. (1993) found that the synthetic progestin (NET) exerted pharmacological effects at multiple levels of both the hypothalamic pituitary- Ovarian axis and the female genital tract. Banerjee et al .(1986) studied the return of fertility following discontinuation of norethisterone oenanthate (NET-EN), in the same year Song Si (1993) reported that the main action of norethisterone visiting pill, when started during that early phase of the cycle is suppression of cervical mucus and endometrial function.

Song et al. (1993) studied the effects of different doses of norethisterone on ovarian function, hormone binding globulin and high density lipoprotein cholesterol.

The present study is designed to evaluate the possible direct influence of norethisterone as a synthetic progestins on the cervix : an histological aspect.

## **MATERIALS AND METHODS**

Young, healthy, sexually mature female albino rats of Wistar strain (120-150 gms body weight) with normal reproductive history were procured from Haffkine Biofarmaceuticals. The animals were kept under uncontrolled room ambient temperature and photoperiod . Food pellets marketed by Lipton India Limited and water provided **ad libitum**. The rats were acclimatized for a month to the laboratory conditions prior to the commencement of any experiment. Animals were divided into two sets control and for drug treatment, for each set of an experiment a population of female rats belonging closely to a certain weight group were selected, the reason for which all the groups of rats at the commencement of the treatment did not weigh the same .

The animals were divided into control and experimental groups. The treatment lasted for 24 weeks duration i.e 24 injection of i.m.injectable norethisterone heptanoate, est . The drug were of 100% purity which is available in the market with same trade name.

On the completion of the treatment period, the animals were weighed and sacrificed under light ether anaesthesia. The cervix was quickly excised cleared off the adhering fat blotted and weighed after which processed for the various light microscopic study studies .

## **OBSERVATIONS**

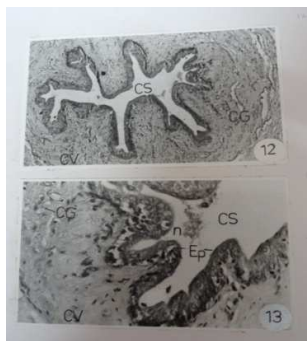
### **CERVIX :**

The cervix is composed of mucosa and myometrium. The mucosa lines the cervix ,the endocervix is continuous with that of the body of the uterus but differs from it , rather sharply in respect to the epithelium .

The epithelial cells in the cervix are very tall , rarely ciliated and secrete true mucus . Occasional clefts extend deep into the stroma and constitute the cervical gland (figs.1a,b). The cells lining these glands are extremely tall with abundant clear cytoplasm (fig.1a,b) .

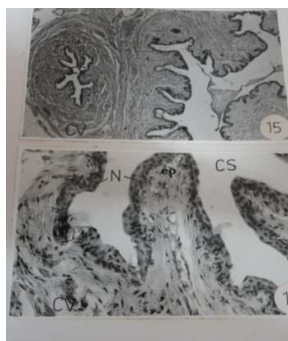
The cervical glands present at the mucosa differ from those of the uterine gland by their branched structure (fig.1a). They secrete mucus into the cervical canal . Unevenly stained nuclei are present at the centre of the epithelial cells. There is a normal nucleocytoplasmic distribution of the epithelial cells (fig.1b) .

## CONTROL CERVIX



**Fig. 1(a,b)** – X – 40 , X – 120  
section of control Cervix  
Showing cervical ossicle(CS),  
nucleated Stratified squamous  
epithelium (Ep) &cervical gland

## NOR-HN TREATED CERVIX



**Fig. 2(a,b)**- X – 40 , X - 120  
Norethisterone heptanoate treated Cervix  
Showing reduced cervical ossicle(CS),  
Columnar epithelial cells (Ep),  
Pyknotic nucei(N), dispersed stroma

## NOR-HN TREATED CERVIX

The incident of significant morphological features in the norethisterone treatment do not show any affect on the epithelial cell height but there is an onset of vacuolation in the epithelium. The nuclei are darkly stained and pyknotic, most of the nuclei are situated towards the basal region of epithelium ( fig.2a,b ).

Reduced cervical glands are a sign of glandular atrophy and is correlated with nonsecretory phase. The Change in nuclear density and appearance may cause the unequal nucleocytoplasmic distribution . Dispersed stroma and nuclear hypertrophy is evident in this specimen (fig.2a.b ).

Drug dosage used in this experiments conform to human dosage, the results are alarming. The cytoarchitecture of the epithelial cells of the cervix shows alterations at the cytological level.

Oestradiol hormone level of control and treated is shown in table no. 1.

**Table No. 1** + SEM Values

**HORMONAL VALUES**

SR.NO.	PARAMETER	CONTROL VALUE X1(6)	NOR-HNTREATED VALUE X2(6)
1	Oestradiol pg/ml	158.64 + 60.05	36.95 + 16.76

(\*P>0.05 Significantly different)

**DISCUSSION**

Norethisterone heptanoate treated cervix showed glandular atrophy correlated with the non secretory phase. Elestain (1976), Moghissi et al (1973), Larsson - Cohn et al. (1973) have shown that norethisterone minimizes general endocrine effect and the contraceptive action was targeted primarily on the cervical mucus . Our results are on similar lines.

Incidentally norethisterone enanthate another orally active progestational compound also has its peripheral mode of contraceptive action by making the cervical mucus hostile to sperm penetration (Zanartu et al. 1970) complementary findings have been recorded by Gallegoes et al. (1970).

Contraceptive action of progestogenic agents may exert in such a manner that changes in physical and chemical properties of cervical mucus may lead to inhibition of sperm transport. Similar observations have been reported by Kamran et al. (1971). Hormonal studies also supported that contraceptive efficacy may alter the cervical mucus since in NOR-HN treated rats decreased estradiol level was registered. In the present study of hormonal assay also reported the decreased value of oestradiol. Roland & Kesseru (1972) have further reported that progestational agents prevent mid cycle migration of sperm through the endocervical canal often at doses that have minimal effect on the condition of the sperm in the cervical mucus.

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