

# LONG-TERM REGULATION OF MALE FERTILITY BY NORETHISTERONE ENANTHATE 'EPIDIDYMAL' IMPLANTS : EFFECT ON LIBIDO AND FERTILITY OF RABBITS

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**Summary:** Bilateral insertion of silastic capsules releasing 38-44  $\mu$ g norethisterone enanthate/24 h into the epididymal fat-pads was found to induce complete azoospermia leading to infertility in adult male rabbits 8 weeks after insertion of the progestin implants. The treatment did not exert any inhibitory effects on the libido and sexual behaviour of the animals as judged by objective parameters of mating. Further, the failure of the hormone-releasing implants was not found to exert any adverse effects on the embryos and pregnancy as indicated by the delivery of normal pups to females mated with implant-bearing males 3 weeks after the insertion of 'epididymal' implants.

**Key words :** 'Epididymal Implant'                      norethisterone enanthate                      libido  
sexual behaviour                                              pregnancy

## INTRODUCTION

Regulation of male fertility by systemic progestational steroids with or without the concurrent administration of testosterone preparations as suggested by Turner and McLaughlin (16), though found to be fairly effective in inducing azoospermia or oligospermia compatible with effective contraception, yet their use has been limited due to the relatively high incidence of drug-related side-effects, viz. adverse effects on the libido, sexual potentia and weight (5,6,8,12). Systemically administered long-acting progestins such as medroxyprogesterone acetate inhibit spermatogenesis via a negative feed-back mechanism operating through the hypothalamus-pituitary-testicular axis (5,8,12). This results in a suppression, either partial or complete, of the release of LH from the pituitary which in turn inhibits the steroid biosynthesis in the Leydig cells, in addition to arresting the post-spermatocyte stages of the spermatogenesis (9). There are evidence to suggest that systemic administration of massive dosages of progestins may also inhibit the androgen

contributions by the seminiferous tubules which may possibly be mediated via the progestin-induced decrease in the peripheral FSH (2,5,6). Cyproterone acetate, an antiandrogen, was initially reported to provide effective inhibition of male fertility without exerting any adverse effects on the accessory sexual functions including libido (10,11), however, the initial optimism about long-term regulation of male fertility by subdermal implants of Cyproterone acetate was not substantiated by subsequent studies of Schenck *et al.* (13) and Chatterjee *et al.* (1). Looking for a hormonal delivery system which would exert antifertility effects directly on and localized to the testis and/or epididymis, we have previously reported about the high antispermatogenic effects of norethisterone enanthate (N.E.) released in chronic micro-doses through silastic capsules implanted into the epididymal fat-pads of adult rats without an apparent effect on the leydig cells (14). The present study was designed to study the effect of N.E. 'epididymal' implants on the libido and fertility potential of male rabbits.

### MATERIALS AND METHODS

Mature male rabbits, body weight 2.2-2.8 kg, of the Institute colony were used in the study. The animals were caged individually and allowed food and water *ad libitum*. The assessment of the effect of progestin-implant treatment on the libido and fertility was investigated by mating the animals with adult does of proven fertility. Only such females as were 'receptive' to males were included in the study.

Polydimethylsiloxane (Silastic, Dow Corning Corporation, Midland, Michigan) capsules were prepared, processed and inserted into the epididymal fat-pads of the animals according to the method previously described (14). Briefly, however, the method involved the exposition of the two-epididymides along with the testes and epididymal fat-pad through a mid-ventral suprapubic incision followed by insertion of an implant into the fat-pad on either side with the help of a thin-walled 11 gauge trocar and canula and securing the implant in the fat with a short length silk/nylon monofilament. Post-operative antibiotic cover was provided to each animal for 3 days.

#### *Assessment of libido and accessory sexual function :*

Libido was observed in terms of relative latency in mounting and ejaculation after exposure of the treated males to a normal adult female as described by Stratton *et al.* (15).

#### *Assessment of antifertility effects :*

Following mating with implant-bearing or untreated control males, the females were laparotomized 9-10 days after mating under intravenous pentobarbitone sodium

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(50 mg/kg) anaesthesia and the number of corpora lutea and implantation sites recorded. The pregnancies, if any, were allowed to continue to term and at the time of delivery, number of pups born was also recorded.

## RESULTS

The results of the effect of bilaterally implanted 'epididymal' NE implants on the fertility of adult male rabbits are presented in Table I. The treatment with NE implants inserted into the epididymal fat-pads did not exert any significant contraceptive effect after 3 weeks as indicated by the average number of implantation sites in females mated with implant-bearing males. After 8 weeks, however, there were no pregnancies in animals mated with the same males. Further, with regard to the litter size in animals impregnated by males at 3 weeks of implant insertion, there was again no difference in the number of pups born as compared to the litter size in control animals. Also there were no apparent foetal abnormalities in these pups. The treatment was not found to exert any appreciable inhibitory effects on libido or sexual performance.

TABLE I : Incidence of pregnancy in rabbits mated with adult males bearing norethisterone enanthate epididymal implants.

Treatment group	No. of animals	Laparotomy on day 9-10 after mating	
		No. of corpora-lutea	Total No. of implantation sites
Control	5	6.3 ± 0.37† (4-8)	5.8 ± 0.47 (4-7)
Sham-operated control	5	6.8 ± 0.37 (4-8)	6.0 ± 0.42 (4-8)
NE implants	5	5.8 ± 0.37	—

†Values are Mean ± S.E

## DISCUSSION

Administration of microdose norethisterone enanthate locally through silastic capsules implanted into the epididymal fat-pads in close proximity of the ductuli efferentes and caput-epididymis was found to bring about effective inhibition of fertility in adult male rabbits without exerting any discernible inhibitory effects on the animals' libido. The

results also indicated that, even in the event of a 'method-failure', the treatment may not affect the pregnancy adversely as suggested by the normal gestation through delivery in animals mated with treated males 3 weeks after implant insertion by which time the method had not become fully effective. In a previous study we have also observed that epididymal implants releasing NE at the rate of approximately 22-44  $\mu\text{g}/24\text{ h}$  did not affect the leydig cells in rats and apparently also the libido in rats (14).

Selective inhibition of epididymal maturation of spermatozoa by hormonal interference has been attempted earlier by Prasad *et al.* (11) who demonstrated that cyproterone acetate administered through subdermal silastic implants inhibited maturation of the spermatozoa by selectively depriving the epididymis of its androgen requirement and thereby altering the epididymal metabolic activity (2, 10). These authors also maintained that cyproterone acetate, an anti-androgen, administered via subdermal implants did not exert any inhibitory effects on the libido, however, subsequent investigations (1,13) on the use of cyproterone acetate implants for long-term regulation of male fertility did not corroborate the observations of Prasad *et al.* Subdermal silastic implants of testosterone, and megestrol acetate supplemented with testosterone have, however, been reported to induce functional sterility without an adverse effect on the libido in rabbits (3) and human (4). In fact, there are limited observations on the effects of epididymal progestin implants, akin to the present study, in human males too (7).

In view of the above limitations of cyproterone acetate implants on the one hand and the results on the 'libido-sparing' effects of epididymal NE implants in the present study on the other, sustained local administration of norethisterone enanthate through 'epididymal' silastic capsules appears to be a potentially encouraging approach for long-term regulation of male fertility.

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