

Inhibition of Spermatogenesis by Progesterone and Androgen Combinations in C₃H Mice

Puspita Eka Wuyung, dr*; Dr. Oentoeng Soeradi, Drs**; Sudarto Pringgoutomo, dr*

Abstrak

Metoda kontrasepsi pria yang diharapkan akan dapat dikembangkan pada masa datang adalah kombinasi hormon progesteron dan androgen. Kombinasi progesteron, yakni norethisteron enantat yang seringkali digunakan sebagai kontrasepsi pada wanita, dan androgen, yakni testosteron enantat digunakan pada penelitian ini. Kombinasi ini diberikan dua kali pada mencit C₃H, dengan dosis ekuivalen pada manusia. Terdapat perbedaan bermakna, pada tingkat kepercayaan 5%, antara hitung pakhiten spermatosit primer antara kelompok yang diteliti dan kelompok kontrol. Namun tidak terdapat perbedaan yang bermakna antara berat testis serta garis tengah tubulus seminiferus kedua kelompok.

Abstract

A male contraceptive method hoped to be developed in the future is the hormonal combination of progesterone and androgen. A combination of progesterone, i.e. norethisteron enanthate, frequently used as a contraceptive in women, and androgen, i.e. testosterone enanthate, was used in this trial. It was administered twice to C₃H mice, with a dose equivalent to that of humans. At the 5% level, a significant difference was found in the total pachiten primary spermatocyte count between the study group and the control group. However, no significant difference was found between the weight of the testes or the diameter of the seminiferous tubule of both groups.

Keywords : Spermatogenesis, Inhibition, Progesterone, Androgen

INTRODUCTION

Knowledge of the male reproductive system has developed rapidly over the past 20 years. However, studies are still being undertaken to develop methods of fertility regulation in men using oral or parenteral hormonal contraceptives. Developing methods of fertility regulation in men are more complicated than in women, due to the complexity of the male reproductive system. It involves continuous control of daily sperm production without causing undesirable side effects such as impairment of sexual behavior and libido.¹

Steroid hormones, such as androgen and progesterone, suppress the secretion of pituitary gonado-

trophins through a negative feedback mechanism causing inhibition of testosterone secretion and spermatogenesis.^{2,3} The administration of androgen alone, however, is not sufficient to produce azoospermia, and furthermore, a long term administration of progesterone will lead to secondary sexual gland atrophy and decrease in libido.^{2,3,4} Therefore, the administration of these hormones separately can not be used for fertility regulation in men.

A study was done on the use of progesterone and androgen combinations in producing effective inhibition of spermatogenesis. The purpose of this study is to confirm whether the combination of norethisteron enanthate, a progestational agent, and testosterone

* Department of Pathological Anatomy, Faculty of Medicine, University of Indonesia, Jakarta

** Department of Medical Biology, Faculty of Medicine, University of Indonesia, Jakarta

enantate, an androgenic agent, will inhibit the development of spermatogenic cells and to observe the extent of the effect.

MATERIALS AND METHODS

Twenty seven C₃H male mice were divided into 3 equal groups. The first control group (Group I), received no intervention what so ever. The second control group (Group II), was given a combination of 0.1 cc norethisteron enanthate solvent and 0.1 cc testosterone enanthate solvent. The case group (Group III), received a combination of 0.1 cc norethisteron enanthate and 0.1 cc testosterone enanthate. These were injected intramuscularly into the left and right upper leg, on day 1 and day 18 of the seminiferous epithelial cycle. The 200 mg/cc norethisteron enanthate and 250 mg/cc testosterone enanthate given to a 50 kg human was equivalent to 0.08 mg/0.1 cc norethisteron enanthate and 0.1 mg/0.1 cc testosterone enanthate in mice with an average body weight of 20 g.

The mice were sacrificed 45 days after the first injection or 27 days after the second injection. The testes were weighed, fixed with Bouin solution, and prepared for histological examination. The diameter of the seminiferous tubule and the nuclei of both the spermatogonia and the pachiten primary spermatocytes were measured. Correction for the collected data was made using the Abercrombie formula.⁶ It was then tested using the Liliefors test. If found normal, it was analyzed further using One Way Anova, and tested for significance by the Least Significant Difference (LSD).

RESULTS

Significant differences were found in the total spermatogonium and pachiten primary spermatocyte counts between the case and control groups (table 1). No statistically significant difference was found between the weight of the testes or the diameter of the seminiferous tubule of the three groups.

Table 1. The average total of spermatogonia and pachiten primary spermatocytes in the control and case groups ($\bar{x} \pm SD$).

	G I	G II	G III
Spermatogonia	9.85 \pm 1.09*	9.72 \pm 0.99	8.65 \pm 1.07
Pachiten primary spermatocytes	11.81 \pm 1.52*	11.65 \pm 1.74	10.04 \pm 1.06

* significant at the 5% level

Table 2. The average weight of the testes and diameter of the seminiferous tubule in the control and case groups.

	G I	G II	G III
Weight of testes*	143.56 \pm 13.05	153.11 \pm 26.00	147.00 \pm 38.87
Diameter of seminiferous tubule**	82.04 \pm 5.16	82.08 \pm 4.46	81.85 \pm 3.89

* in milligrams

** in microns

DISCUSSION

Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) are essential to spermatogenesis. The secretion of these hormones is regulated by the hypothalamic Gonadotrophin Releasing Hormone (GnRH). Under the influence of LH, the Leydig cells will secrete testosterone which in turn acts on the epithelial cells of the seminiferous tubule causing a high local concentration of androgen essential to spermatogenesis.^{7,8} FSH and androgen or testosterone stimulate the Sertoli cells to secrete androgen-binding proteins.⁹

The administration of exogenous steroids interferes with spermatogenesis.^{10,11} Kar and Setty found that certain progesterone derivatives, such as norethisteron enanthate, inhibits the secretion of FSH and LH in male rats and interferes with spermatogenesis.¹² The inhibition of LH secretion suppresses the secretion of testosterone by the Leydig cells, which will inhibit the development of spermatogenic cells. The inhibition of FSH secretion lowers the sensitivity of the spermatogenic cells to testosterone which will reduce the production of androgen-binding proteins by the Sertoli cells and interferes with testosterone transportation to the spermatogenic cells. A similar condition is presumed to occur in the C₃H mice receiving a combination of norethisteron enanthate and testosterone enanthate, demonstrated by the decrease in the total spermatogonium and pachiten primary spermatocyte counts.

Terner and Laughlin have also found that the administration of progesterone and androgen combinations inhibits spermatogenesis.⁵ This inhibition is due to the antigonadotrophin effect of progesterone which suppresses the secretion of FSH and LH and causes a decrease in testosterone concentration. To preserve the function of the highly testosterone dependent reproductive organs without maintaining spermatogenesis, low dose testosterone can be administered. This is demonstrated by the decrease in the spermatogonium and pachiten primary spermatocyte

counts, without the reduction in the weight of the testes and the diameter of the seminiferous tubule.

CONCLUSIONS

The administration of norethisteron enanthate and testosterone enanthate combinations on day 1 and day 18 of the seminiferous epithelial cycle causes a decrease in the spermatogonia and the pachiten primary spermatocytes of C₃H mice without reducing the weight of the testes or the diameter of seminiferous tubule.

Further studies are needed to determine the effective dose resulting reversible azoospermia.

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