THE INFLUENCE OF MESTEROLONE ON SERUM GONADOTROPHINS

AZMY PESI BHARUCHA • R.K. BHATHENA

SUMMARY

The earlier view that mesterolone has little effect on the pituitary gonadal axis is now being questioned. Fifteen subjects with idiopathic oligozoospermia, were randomly treated with 100 mg per day of mesterolone (n=10), or placebo (n=5), for more than three months. Serum gonadotrophins and plasma testosterone were assayed before treatment, and after twelve weeks of treatment. There was a statistically significant suppression of serum FSH (p 0.01) and serum LH (p 0.05) with mesterolone. Plasma testosterone was not significantly altered by mesterolone therapy. The previous view that mesterolone has little influence on gonadotrophin secretion needs to be revised.

Hormonal treatment of male infertility has mainly involved the use of androgens and gonadotrophins for disturbances in spermatogenesis. Great interest was aroused by the synthesis of mestorolone in 1968 as a new androgen for the treatment of male infertility. Upto that time only C17 alkylated testosterone and androstenediol derivatives had been used for oral androgen therapy.

These steroids all have an inhibitory effect on gonadotrophin secretion by the hypophysis and on testicular function. Mestorolone proved to be a rather weak androgen but it was said to have the surprising and unique property that at a dosage sufficient to produce androgenic stimulation of the periopheral target tissues it had little or no effect on gonadotrophin secretion.

Accepted for Publication on 9/10/90

However, the past view that mestorolone has little effect on the pituitary gonadal axis is now being questioned. (Barnes et al 1973, Gordon et al 1975, Nikkanen 1979). This study was undertaken to observe the effects of mesterolone on serum gonadotrophine in subjects with idiopathic oligospermia.

Fifteen subfertile men, 22-46 years of age, with idiopathic oligospermia (with basal serum FSH, LH, testosterone and prolactin in the normal range for the adult male) were randomly treated (with their consent) with 50 mg twice daily of mesterolone (Pro-Viron, Schering Chemi-

cals Ltd., Sussex), or with placebo, 2 tablets twice daily for more than 3 months. Venous blood samples were collected at 9 a.m., before treatment, and during treatment after 12 weeks, to be assayed for serum FSH and LH. The blood samples were centrifuged, and the serum kept frozen around -20°C until assayed. Commercial kits of Serono Diagnostics were used. Intra-assay variability and inter-assay variability were less than 10 and 13%, respectively. For statistical analysis, data on hormones before treatment were compared with those obtained during treatment with the paired test.

The results demonstrated that in patients treated with mesterolone (n=10), there was a statistically significant decrease in serum FSH (p 0.01); the mean ± SEM before and after treatment were 7.3 ± 0.2 and 6.4 ± 0.2 (mIU/ml), respectively. There was a statistically significant decrease in serum (p 0.05); the mean ± SEM before and after treatment were 8.9 ± 0.3 and 8.1 ± 0.3 (mIU/ml), respectively. The values were not significantly influenced by treatment with placebo (n=5). The two treatment groups were found not to differ significantly (p 0.05) when the pre-treatment values of FSH and LH in the two groups were considered.

Plasma Testosterone was not significantly altered by mestorolone therapy as can be seen from Table II.

It is interesting to consider our results in the light of the reports by other workers. Franchimont (1983) and Wang et al (1974) have also reported suppression of gonadotrophins. These findings

TABLE 1
THE EFFECT OF MESTEROLONE (N=10) AND PLACEBO (N=5) ON SERUM GONADOTROPHIN LEVELS

	Before treatment	After 12 weeks of treatment	Difference	Statistical significance
F.S.H. (normal values 2-8mIU/ml)				
Mesterolone	7.3 ± 0.2	6.4 ± 0.2	0.9 ± 0.2	P 0.01
Placebo	6.7 ± 0.3	7.0 ± 0.5	0.3 ± 0.5	NS
L.H. (normal values 2-10mIU/ml)				
Mesterolone	8.9 ± 0.3	8.1 ± 0.3	0.8 ± 0.3	P 0.05
Placebo	8.0 ± 0.7	7.8 ± 0.5	0.2 ± 0.4	NS

TABLE II
THE EFFECTS OF MESTEROLONE (N=10) AND PLACEBO (N=5) ON PLASMA TESTOSTERONE LEVELS

	Before treatment	After 12 weeks of treatment	Difference	Statistical significance
Testosterone (normal values 4-9 mg/ml)				
Mesterolone	4.3 ± 0.2	4.9 ± 0.3	0.6 ± 0.3	NS
Placebo	4.5 ± 0.4	4.8± 0.4	0.3 ± 0.6	NS

suggest the involvement of the pituitary gonadal axis in the action of mesterolone. This is in contrast with some reports of other workers who have reported no significant suppression of gonadotrophins. (Barnes et al 1973, Gorden et al 1975, Nikkannen et al 1979).

The discrepancy observed with other results showing no significant variation of gonadotrophin levels could be related to the investigated subjects. Subjects with elevated FSH levels may differ radically from those with normal FSH levels, and the two groups cannot be considered comparable.

In this study of oligospermic subjects with normal gonadotrophin levels, a majority of subjects treated with mesterolone had high normal pretreatment levels of FSH and LH. In 9 of 10 subjects, the FSH levels were between 6.5 and 8.0 miU/ml, with the normal range being 2-8 mlU/ml. In 9 of the 10 subjects, the LH levels were between 8.0 and 10.0 miU/ml, with the normal range being 2-10 mlU/ml. In these 9 subjects, suppression of FSH occured in 7, and suppression of LF in 8 cases.

Gordon et al. administered mesterolone to 4 normal healthy male subjects but could establish significant gonadotrophin suppression in only 2 of them.

The controversial results may be due to several other factors. With different workers, there has been a widely variable dose of the drug, and the effect of mesterolone on hormones has been observed at variable periods of treatment. The results are also influenced by the varying sensitivity of the assay technique.

The precise mode and site of action of mesterolone require further investigation. Androgens and oestrogens suppress the secretion of FSH and LH.(Franchimont 1971, Swerdloff et al 1973, Franchimont 1983). Testosterone and androstenedione can be aromatized to oestrogens within the hypothalamus, and this conversion to oestrogen may be one mode of action by which there is a resultant suppression of gonadotrophins (Franchimont 1983). The suppression of gonadotrophins in subjects treated with mesterolone cannot result from such a mode of action, as the A ring is saturated, and it cannot be converted to oestrogens. Swerdloff et al (1973) and Franchimont have reported that the conversion of androgen to oestradiol is not a prerequisite for androgenic action at the hypothalemic level. Swerdloff et al have shown that testosterone and dihydroare equipotent in their effects on the secretion of LH. Mesterolone may perhaps therefore be suppressing pituitary gonadotrophins by a similar mechanism as the other reduced compounds dihydrotestosterone and 5a-androstane-3a,17B-diol.

It has been recently confirmed that Sertoli cells secrete inhibin which suppresses FSH secretion (Steinberger 1981 and Verhoeven 1983) Verhoeven and Franchimont have demonstrated that androgens promote the secretion of inhibin in a dose-dependent way, and reduce FSH secretion.

Our study demonstrates that with 100 mg of mesterolone per day, there is a modest, but statistically significant suppression of gonadotrophin secretion. The impression that mesterolone has little influence on gonadotrophin secretion needs to be revised.

References

1 *Barnes, E.W.; Irvine, W.J.; Ismail, A.A.: Brit med. J.1: 234. 1973.*

2 *Franchimont, P.:Secretion normale et patholo-*

gique de la somatotrophine et des gonadotrophines humanies, p.98 (Masson, 1971).

3 *Franchimont, P.: Hormone Res. 18:7-1983.*

4 *Gordon, R.D.; Thomas, M.J.; Poynting, J.M.; Stocks, A.E.: Andrologia 7:287-1975.*

5 *Nikkanen, V.: Andrologia 11:33-1979.*

6 *Steinberger, A.: In Franchimont, Channing, Intragonadal regulation of reproduction, 283-(Academic Press, London 1981).*

7 *Swerdloff, R.S.; Grover, P.K.; Jacobs, H.S.; Bain, J.: Steroids 21: 703-1983.*

8 *Verhoeven, G.; Franchimont, P.: Acta endocr. 102:136-1983.*

9 *Wang C.; Burger, H.G.; De Krester, D.M.; Dulmanis, A.; Hudson, B.; Keogh, E.J.; Suthers, M.B.: Andrologia 6:111-1974.*