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SERUM ESTRADIOL LEVELS IN NORMAL MEN AND MEN WITH IDIOPATHIC INFERTILITY

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Serum estradiol levels were measured in 360 men attending an infertility clinic and 68 proven fertile men to determine whether estradiol measurements are clinically useful. The normal range of estradiol levels found in fertile men was 10–82 pg/ml. Serum concentrations of estradiol in azoospermic or oligozoospermic patients were significantly lower than those in normozoospermic men ($p < 0.021$). Serum concentrations of testosterone were also significantly decreased in infertile patients ($p < 0.025$). This decrease in serum estradiol may be partly due to reduced testosterone levels in these men because estradiol is mainly formed by peripheral aromatization of testosterone in fatty and muscle tissues. However, the exact mechanism for the decrease in the serum estradiol levels remains undetermined. It is concluded that serum estradiol levels are significantly low in the men with various testicular disorders.

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Key words: estradiol, infertility, spermatogenesis

INTRODUCTION

A normal endocrinological state is required for good quality semen parameters. Serum estradiol levels have rarely been investigated in infertile males and the relationship between serum estradiol concentrations and spermatogenesis is not clear.[1–4] Wu et al. demonstrated that serum estradiol levels were increased in patients with oligozoospermia or azoospermia.[2] Forti et al. also showed that serum estradiol levels were significantly increased in azoospermic patients[3] while Hargreave et al. reported that serum estradiol levels in infertile male patients were significantly decreased and its measurement was not clinically useful.[4] Thus, the results of studies dealing with the measurement of serum estradiol are conflicting and, therefore, the exact association between estradiol levels and male infertility remains to be established.

The aim of this study was to determine the estradiol levels in fertile and infertile males to determine whether estradiol provides prognostic information for subsequent management. This is the first large scale study of the clinical significance of estradiol in male infertility.

PATIENTS AND METHODS

Patients

We studied 360, otherwise normal, sexually-mature men, aged 23–43 years, with infertility of at least a 2-year duration. All were fully virilized and sexually active and none had any clinical evidence of hypogonadism or varicocele. All patients were diagnosed as having idiopathic male infertility. These men were classified as follows: group 1 (n = 69) azoospermia with high follicle-stimulating hormone (FSH) and high luteinizing hormone (LH) levels; group 2 (n = 72) azoospermia with high FSH and normal LH levels; group 3 (n = 75) severe oligozoospermia (sperm count > 0 and $< 5 \times 10^6$/ml); group 4 (n = 82) mild oligozoospermia (sperm count ≥ 5 and $< 20 \times 10^6$/ml). Since the hormone levels in infertile men with oligozoospermia were distributed over a wide range, we classified the patients into four groups by their levels of LH or testosterone. Estradiol levels were compared among these groups.

We also studied, as controls, 68 normal men, aged 25–45 years who had proven fertility and normal serum FSH, LH, and testosterone (T) levels. Because Leydig cell function is stable in normal men between the ages of 20 and 50 years,[5–6] these men were not precisely age-matched with the infertile men.

Measurement of hormone levels

All studies were performed in an outpatient setting from 8:30 to 9:00 a.m. Blood specimens were obtained for the measurement of serum FSH, LH, T and estradiol concentrations. Serum estradiol levels were measured by radioimmunoassay employing estradiol-6-carboxymethyloxime^{125}-1-iodohistamine as the radiolabel and rabbit antiserum against estradiol-6-carboxymethyloxime-bovine serum albumin. Separation of free from antibody-bound label is achieved by means of a solid-phase second antibody. Serum FSH, LH and T were also determined by

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radioimmunoassay. Normal values for FSH, LH, T and estradiol were 2.9–8.2 IU/l, 1.8–5.2 IU/l, 2.70–10.7 ng/ml and 15–60 pg/ml, respectively.

Statistical methods

All results are expressed as the mean ± SD. Statistical comparisons between groups were made by analysis of variance followed by Tukey's multiple range test. A probability less than 0.05 was considered to be statistically significant.

RESULTS

The serum hormone levels of the infertile and normal men are shown in Fig. 1. Serum FSH concentrations were significantly increased in the azoospermic patients (group 1: 34 ± 12.4 IU/l; group 2: 12.4 ± 9.8 IU/l) ($p < 0.001$) and severe oligozoospermic patients (12.5 ± 7.2 IU/l) ($p < 0.001$). Serum LH concentrations were significantly increased in the azoospermic patients with high FSH and high LH (10.6 ± 6.8 IU/l) ($p < 0.001$). Serum T levels were significantly decreased in the azoospermic groups (group 1: 4.10 ± 2.1 ng/ml; group 2: 3.69 ± 0.6 ng/ml) ($p < 0.003$) and oligozoospermic groups (group 3: 4.21 ± 0.89 ng/ml; group 4: 4.37 ± 0.63 ng/ml) ($p < 0.025$), compared with controls (5.82 ± 1.2 ng/ml). Serum estradiol levels were significantly reduced in the azoospermic groups (group 1: 19 ± 1.2 pg/ml; group 2: 18 ± 1.9 pg/ml) ($p < 0.021$) and oligozoospermic groups (group 3: 25 ± 2.5 pg/ml; group 4: 26.1 ± 2.9 pg/ml) ($p < 0.034$), compared with controls (37.1 ± 2.7 pg/ml). Both serum T and estradiol levels were significantly decreased in the infertile patients.

Serum estradiol levels were significantly decreased in the patients with increased LH or decreased T levels when compared with control values ($p < 0.01$) (Table 1). There were no oligozoospermic or azoospermic patients with low estradiol and high testosterone levels.

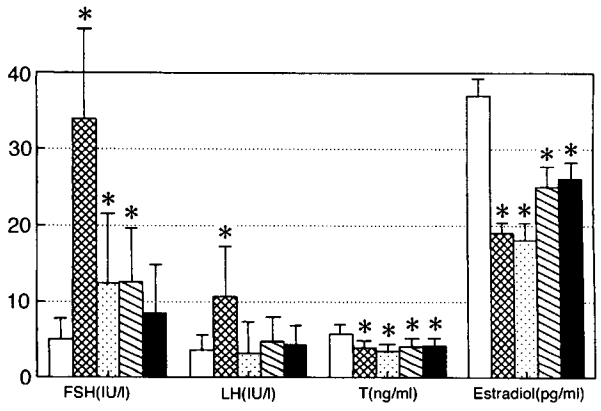

Fig. 1. *Serum FSH, LH, T, and estradiol levels in fertile and infertile males. ▨: group 1 (n = 69), azoospermia with high FSH and high LH; □: group 2 (n = 72), azoospermia with high FSH and normal LH; ▧: group 3 (n = 75), severe oligozoospermia (sperm count > 0 and < 5 × 10⁶/ml); ■: group 4 (n = 82), mild oligozoospermia (sperm count ≥ 5 and < 20 × 10⁶/ml); □: control. Asterisks indicate significant differences compared to the control value. See the text for the p value.*

DISCUSSION

Our results clearly indicate that serum concentrations of estradiol and testosterone in azoospermic or oligozoospermic patients were significantly lower than those in normozoospermic men. These results are partially consistent with our previous results which showed a significant decrease in serum testosterone and free testosterone levels in infertile patients.[7] However, the estradiol data differ from our previous results on serum levels of estradiol and sex hormone-binding globulin which showed no significant differences in these levels between normal and infertile patients.[7] The reason for this difference between the previous and present results might be explained by a difference in the nature of the research subjects in the two studies. The research subjects in the previous report consisted only of men with monotrophic elevation in serum FSH levels. In our present study the men with testicular disorders consisted of patients with increased levels of both FSH and LH, those with monotrophic elevation in FSH and those with monotrophic elevation in LH. It has been demonstrated that increased LH levels are related to decreased estradiol levels. Thus, the variability of the endocrine profile in the present study might account for the difference in the serum estradiol levels between the two studies. However, since it is considered that, in men, estradiol is mainly formed by peripheral aromatization of testosterone in fatty and muscle tissues,[8] our finding of a positive correlation between the two hormones is to be expected.

In animal experiments, Leydig cell aromatase activity is increased by administration of LH.[9] Sertoli

Table 1. *Comparison of serum estradiol levels in 4 groups classified by LH and T levels.*

	Control (n = 68)	Normal LH (n = 259)	Increased LH (n = 101)	Normal T (n = 169)	Decreased T (n = 191)
Value of estradiol (pg/ml)	37.1 ± 2.7	37.4 ± 3.8	20.1 ± 2.5*	48 ± 2.9	21 ± 3.3*

**Significant differences ($p < 0.01$) when compared with the control group. Figures in parentheses represent the number of patients.*

cell aromatase activity is increased by FSH[10] and inhibited by androgen alone[11] or by peritubular cell factors secreted under androgen stimulation.[12] Bujan et al. have reported that seminal estradiol is significantly increased in infertile men.[1] They interpreted this as due to testis dysfunction which could be the cause of an increase in seminal estradiol due to raised aromatase resulting from increased LH and FSH.[1] On the other hand, Santiemma et al. reported that the concentrations of seminal estrone and estrone sulfate as a major source of estradiol in oligozoospermic patients were significantly decreased compared with controls.[13] Therefore, there are conflicting results concerning seminal estradiol levels in infertile patients.

However, our present study showed that serum estradiol levels in patients with decreased testosterone and increased FSH or LH were significantly decreased. These results differ from the observations in previous animal experiments or the seminal estradiol levels of infertile men reported by Bujan et al.[2] Possibly this discrepancy is most likely explained by the fact that the estradiol measured in blood comes mainly from a non-testicular source.

Hargreave et al. demonstrated that infertile men had lower mean estradiol levels than fertile men, although estradiol levels in the infertile group gave no prognostic information about future fertility.[4] Our results are largely consistent with their findings except for the prognostic value of serum estradiol. The significance of the decrease in serum estradiol in the infertile patients is still unclear since it is not known whether it is the cause or the consequence of the alteration in the spermatogenesis of infertile men. We did not investigate the change in estradiol after testosterone replacement in the infertile patients in the present study. Thus, further studies are required to explore the role of estradiol in the treatment of infertile patients.

In conclusion, serum estradiol concentrations in infertile patients are significantly decreased. The reason for the decreased estradiol remains to be clarified. However, on the basis of our data, there is little benefit to be obtained from routine estradiol measurement as part of the investigation of men complaining of infertility.

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