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Reply

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Thank you for offering us the opportunity to comment on the interesting letter from Dr. Singh. He has taken issue with the selection of a group of subjects and interpretation of the data presented [1]. In order to probe the suggested association between subclinical hypothyroidism and the genesis of polycystic ovary syndrome (PCOS) we had to include a group of subjects with subclinical hypothyroidism not associated with PCOS. These subjects were selected from over 200 women of reproductive age (including fellow scientists and staff members at our Institute) who were asked to volunteer for the study. Their thyroid gland activity was assessed. Only those who had marginal or moderate elevation of thyroid-stimulating hormone (TSH) with 3,5,3′-triiodothyronine (T_3) and thyroxine (T_4) within normal limits were selected for the study. The considered cut-off values for these hormone levels were: T_3 1.12 nmol/l (range, 1.12–3.15 nmol/l), T_4 58.8 nmol/l (range, 58.8–147.2 nmol/l), and TSH 4.0 μIU/ml (range, 0.2–4 μIU/ml). When the hormone levels of individual subjects were considered, all strictly satisfied the criteria proposed by Ingber [2]. The mean as well as the range for T_4 of this group were well within the euthyroid range. But, incidentally, statistical analysis did show a significant difference. This may be considered false reasoning.

Since luteinizing hormone (LH) levels usually remain elevated in PCOS, it seems reasonable to question whether elevated TSH levels in this group of patients was due to increased crossreactivity of the TSH antiserum with LH. We gratefully acknowledge Dr. Singh's comment in this respect, and we apologize for inadvertently omitting the data in the Materials and Methods section. However, contrary to his contention, this possibility can be discounted because the antiserum used for the assay had only 0.03% crossreactivity with LH.

Another point Dr. Singh seems to be making is that we extrapolated the proposition of Yen [3] to explain the differential effect of hypothyroidism on gonadotropin release. We believe our view was somewhat misinterpreted, because the view of Yen [3] was partly contradicted by us. Estrone (E_1) and estradiol (E_2) are metabolized by hydroxylation at the C16 and C2 positions. It is well documented that in hypothyroidism, 16α-hydroxylase activity predominates, favoring increased production of estriol (E_3). Yen [3] proposed that overproduction of E_3 led to inappropriate gonadal feedback, and was responsible for the development of PCOS. In contrast, we proposed that overproduction of E_3 (as it occurs in overt hypothyroidism and in some subclinical hypothyroid subjects who do not develop PCOS) actually renders the subject unsuitable for the development of PCOS. We emphasized that an increased E_2:E_3 ratio in association with elevated E_3 levels rather than elevated E_3 levels alone actually determine whether or not PCOS will develop [1].

Finally, since only few hypothyroid subjects develop PCOS, Dr. Singh is against the notion that hypothyroidism plays an etiological role in the development of PCOS. As mentioned in the article [1], we are in full agreement with his view that some subclinical hypothyroid subjects develop PCOS, while the others do not. But we are also convinced that hypothyroidism in these subjects was not a mere coincidence, because *L*-thyroxine alone could induce significant recovery in terms of regained ovulation and the disappearance of the polycystic nature of the ovary (as assessed by ultrasonography). On the basis of our observation, we hypothesize that a differential route of peripheral steroid hormone metabolism actually dictates whether a subject should or should not develop PCOS. But the question remains as yet unresolved as to why under the same state of hypothyroidism steroid hormone metabolism is channelled in a different direction. We believe further work on the coexistence of hypothyroidism and PCOS or 'PCO-like syndrome' could shed more light on this question, with clinical implications.

References

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