

## INVITED COMMENTARY

## Effects of smoking on thyroid function

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Cigarette smoking has multiple effects on thyroid function. These include both pro- (e.g. thyroid-stimulating) and anti-thyroid actions and also actions that increase susceptibility to or exacerbation of the manifestations of Graves' disease. In this issue of the *Journal*, Gasparoni *et al.* describe the effects of parental smoking on fetal thyroid secretion and also on thyroid function of some of the same infants at one year of age (1). Before considering the results of this new study, it seems appropriate to review briefly earlier work on the effects of smoking on the thyroid in adults.

In normal adults, smoking has either no effect on thyroid function and size or a weak pro-thyroid effect. The abnormalities described include small goiters and small, thyrotropin-independent increases in thyroid function, most often small increases in serum triiodothyronine and thyroglobulin concentrations (see references 2 and 3 for reviews). These findings suggest that smoking in some way directly stimulates thyroid growth and function, but how it might do so is not known. Nicotine causes sympathetic activation, which can increase thyroid secretion. Alternatively, nicotine or some other component of tobacco smoke might have direct thyroid-stimulating actions. Despite the association with goiter and small increases in thyroid secretion, in several case-control studies smoking was not a risk factor for either non-toxic or toxic multinodular goiter, indicating that its overall contribution to these disorders must be small (4, 5). Most, if not all, of the subjects in these studies and in those to be described were women. Nevertheless, the conclusions are probably applicable to men.

Among patients with subclinical hypothyroidism, those who smoke have higher serum thyrotropin concentrations, a higher serum ratio of triiodothyronine to free thyroxine, and higher serum cholesterol and low-density lipoprotein cholesterol concentrations than those who do not smoke (6). In contrast, among patients with overt hypothyroidism, smokers and non-smokers have similar serum thyrotropin and thyroid hormone concentrations, but more symptoms, signs and biochemical and physiological changes of hypothyroidism (6). Thus smoking reduces thyroid secretion in patients with subclinical hypothyroidism and exacerbates the peripheral effects of thyroid deficiency in those patients and in patients with overt hypothyroidism. Notwithstanding these results, in the same case-control

studies cited above smoking was not a risk factor for chronic autoimmune thyroiditis (4, 5), although it was associated with postpartum thyroiditis, a precursor of chronic autoimmune thyroiditis, in one study (7).

At the other end of the spectrum, there is substantial evidence that smoking is a risk factor for Graves' hyperthyroidism, and especially Graves' ophthalmopathy (4, 5, 8, 9). In a case-control study done in The Netherlands, for example, the odds ratio for smoking among patients with Graves' hyperthyroidism was 1.9. It was 7.7 among those with Graves' hyperthyroidism and ophthalmopathy, and the ophthalmopathy was more severe in those who smoked (5). How might smoking contribute to the pathogenesis of Graves' disease? It might alter the structure of the thyrotropin receptor, making it more immunogenic in a way that leads to the production of thyrotropin-receptor stimulating antibodies that react strongly with retro-orbital tissue. It might augment immunologic responsiveness to whatever factor initiates Graves' disease or, on the other hand, it might impair restoration of tolerance to thyroid auto-antigens. Lastly, it might in some way sensitize retro-orbital tissue to the antibodies or other substances that cause ophthalmopathy.

The results of the effects of parental smoking on thyroid function of fetuses or infants aged one year, as described by Gasparoni *et al.* (1), provide additional insight into the interrelationships between smoking and thyroid dysfunction. They found that infants whose mothers and fathers smoked had higher cord serum thyroglobulin and thiocyanate concentrations than infants whose parents did not smoke. The infants had no other evidence of thyrotropin-independent thyroid stimulation, such as increased serum thyroxine or triiodothyronine or decreased serum thyrotropin concentrations, as has been reported by others (10). Thyroid size was not determined, but in another study it was increased in infants born of mothers who smoked (11). Of note is their finding that cord serum thyroglobulin concentrations were increased in the infants whose fathers, but not mothers, smoked, indicating that the component(s) of tobacco smoke that stimulates thyroglobulin secretion can be transferred passively. Also of note is the finding that at age one year the infants whose fathers and mothers both smoked had higher serum thyroglobulin and thiocyanate concentrations than the infants whose parents did not smoke (the infants whose

fathers but not mothers smoked had lesser increases in both measurements). Unfortunately, serum thyrotropin, thyroxine and tri-iodothyronine were not measured at this time. Nevertheless, the effects of parental smoking on thyroid function in fetuses and very young infants in causing thyrotropin-independent thyroid stimulation are similar to its effects in normal adults.

The effects of smoking on the thyroid have been attributed to thiocyanate, because serum thiocyanate concentrations are high in smokers and infants of smokers. However, the known thyroidal actions of thiocyanate are to inhibit iodide uptake and thyroid hormone synthesis and increase the efflux of iodide from the gland (12). These actions would be expected to cause thyrotropin-dependent thyroid stimulation, and therefore they are incompatible with the effects of smoking, which causes thyrotropin-independent thyroid stimulation in fetuses, one-year-old infants and most adults.

It is possible that thiocyanate has both anti- and pro-thyroid actions, like iodine and lithium carbonate, but if it does the pattern of its actions is quite different from that of iodine and lithium. Iodine and lithium have anti-thyroid actions in normal subjects, patients with hyperthyroidism, and patients with damaged thyroid glands (13, 14). Iodine has pro-thyroid actions in patients with nodular goiter (13), and lithium may be a risk factor for Graves' hyperthyroidism (15). If thiocyanate has both types of actions, the pattern is unique – a pro-thyroid action in normal subjects, including fetuses and infants; an anti-thyroid action in patients with subclinical hypothyroidism; an apparent thyroid hormone-antagonist action in patients with subclinical and overt hypothyroidism; and actions to increase susceptibility to Graves' hyperthyroidism and ophthalmopathy and exacerbate the clinical manifestations of the latter.

It seems more likely that the pro- and anti-thyroid actions of tobacco smoke, not to mention its effects in patients with Graves' disease, are a result of the effects of multiple components of the smoke, not just thiocyanate. Possible mechanisms by which smoking could cause a minor degree of thyrotropin-independent thyroid stimulation and contribute to Graves' hyperthyroidism and ophthalmopathy were discussed above. To be sure, there is no evidence for any of these mechanisms. Tobacco smoke contains many chemicals, and its composition must vary substantially, depending on the source of the tobacco and the way it is smoked; and of course the amount smoked also varies substantially. Given these variations, and variations in host

susceptibility to thyroid disease and to autoimmune thyroid disease, it seems appropriate to look beyond thiocyanate to explain the multiple thyroidal effects of smoking.

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