

Commentary

Hyperthyroidism in Pregnancy and Lactation: A Different Paradigm?

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Abbreviations: ATA, American Thyroid Association; GD, Graves disease; hCG, human chorionic gonadotropin; KI, potassium iodide; PTU, propylthiouracil; RAI, radioactive iodine; TRAb, thyrotropin receptor antibody.

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Graves disease (GD) and β -human chorionic gonadotropin (hCG)-mediated hyperthyroidism are the most common causes of hyperthyroidism in pregnancy. Whereas hCG-mediated hyperthyroidism is usually transient and benign, thyrotoxicosis due to GD warrants treatment. Fortunately, overt hyperthyroidism affects only 0.1% to 0.4% of pregnancies [1]; when it does occur, it is associated with an increased risk of adverse maternal and fetal outcomes.

Before the advent of thionamides, thyroidectomy was the only available treatment for thyrotoxic pregnant women and was accompanied by a high rate of fetal loss. Thionamides were developed between 1947 and 1953, thanks mainly to the pioneering work of Dr Edwin Bennet Astwood. In 1949, Chapman and Corner demonstrated that the fetal thyroid concentrated radioactive iodine (RAI), raising concerns about its use during pregnancy [2]. Since the discovery of thionamides, almost no new oral therapeutic options for GD have emerged. Although propylthiouracil (PTU) and methimazole are both known to have teratogenicity, particularly during the first trimester, these medications are considered safe for use during lactation and approved by the American Academy of Pediatrics. Additionally, thionamides and RAI have been shown to transfer to breast milk. In 1980, Kampmann et al showed that only 0.025% of the administered dose of PTU was

excreted in breast milk [3]. In a study of 139 thyrotoxic nursing mothers treated with up to 20 mg of methimazole daily, no deleterious effects on their infants' thyroid function or development were noted [4]. In a smaller study of 11 infants, there were no adverse effects on the thyroid function of breastfed infants whose mothers were treated with up to 750 mg of PTU daily [5].

According to the 2017 American Thyroid Association (ATA) guidelines, the lowest effective dose of both methimazole and PTU should be used in lactating women, since both medications are detectable in breastmilk. Whereas I^{131} is absolutely contraindicated in lactation, the ATA makes allowance for the use of I^{123} , if breastmilk is pumped and discarded for 3 to 4 days before breastfeeding is resumed. Iodine-induced hypothyroidism has been reported in infants exposed to high doses of inorganic iodine as reported previously by Hamada et al [6]. This is thought to be mediated by the homeostatic inhibition of thyroid hormone synthesis by decreased iodine uptake by the thyroid gland (Wolff-Chaikoff effect).

The present study by Hamada and colleagues [7] prospectively looked at the thyroid function of breastfed infants of women who opted for treatment of their mild GD with potassium iodide (KI). The authors built on their earlier study of 26 such infants in which only one infant

developed subclinical hypothyroidism that spontaneously resolved after stopping KI [6]. High iodine concentrations were demonstrated both in the breastmilk and infant urine. In the present study, the authors monitored the thyroid function of 100 breastfed infants (including the 26 from the previous study) with a median age of 5 months and a median maternal KI dose of 50 mg/day. They found that only 12 infants (~10%) developed subclinical hypothyroidism. Interestingly, the thyrotropin levels of 7 of these infants normalized despite continuation of KI and breastfeeding, likely because of escape from the Wolff-Chaikoff effect.

From our standpoint, this study highlights some interesting points. In Japan, KI has been studied extensively in the treatment of GD, often as an alternative option in thionamide intolerance or in preference to RAI. This underscores the international differences in the approach to GD management. In polls conducted in the 1990s, 69% of members of the ATA vs only 11% of members of the corresponding associations in Japan and Korea reported preferring RAI over antithyroid medications. Cultural and attitudinal barriers as well as safety restrictions applied to RAI pharmaceuticals are often cited as common reasons why RAI is not the treatment of choice outside the United States [8]. Secondly, Japan is an iodine-sufficient country where historically the daily iodine consumption has been reported to be greater than 500 mcg/day. Several epidemiological studies performed in areas with iodine deficiency have shown that a small increase in iodine supplementation increases the incidence of hyperthyroidism more than hypothyroidism, whereas the opposite is true in iodine-sufficient areas. After iodine fortification of salt was introduced in Denmark in 1998, the incidence of hypothyroidism increased, particularly in individuals with moderate iodine deficiency at baseline. The suppression of thyroid function with iodine administration is thought to be due to the autoregulatory mechanisms that protect against iodine-mediated thyroid hyperfunction, such as the Wolff-Chaikoff effect and thyroidal synthesis of iodinated arachidonic acid derivatives. It is likely that these mechanisms are less robust in children and the elderly. That could explain the low incidence of subclinical hypothyroidism noted by Hamada and colleagues in their infant patients. Another important consideration is that GD was mild in the pregnant women in this study. Generally, the severity of GD decreases during the third trimester because of a fall in the serum thyrotropin receptor antibody (TRAb) concentration or an increase in inhibitory TRAbs. However, GD tends to become exacerbated post partum and patients in remission are at increased risk of relapse. In these cases, KI may not be sufficient to treat thyrotoxicosis and switching to thionamides, thyroidectomy, or RAI may be necessary. Moreover, both stimulatory and inhibitory maternal TRAbs

cross the placenta and may affect fetal thyroid function for 2 to 3 months post partum. It would be interesting to know how these antibodies might affect the thyroid function of infants breastfed by mothers taking KI.

In conclusion, KI is emerging as a potentially safe and effective agent in the treatment of GD and the excellent study by Hamada et al is a welcome addition to the growing body of literature in this area. Similar investigations would need to be performed in iodine-deficient communities to test how KI interacts with the thyroid function of infants of iodine-deficient mothers with GD. Future studies should also focus on the cognitive and physical development of such infants to establish the long-term safety of KI in the treatment of GD in nursing women.

Additional Information

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