

Thyroid function and intellectual development of infants nursed by mothers taking Methimazole

Azizi F, Khosniat M, Bahrainian M, Hedayati M. **A descriptive trial which examined the anti-thyroid effect of varying doses of maternal Methimazole therapy on breastfeeding infants.** J Clin Endocrinol Metab 2000;85:3233-8.

QUESTION

Can maternal Methimazole (MMI) therapy be given safely to thyrotoxic lactating mothers?

DESIGN

Descriptive trial for which the effect of increasing doses of maternal MMI were studied in breastfeeding infants after it was determined that the lower doses did not appear to affect infant thyroid functions.

SETTING

An Endocrine Research Center in Tehran, Iran

PATIENTS

139 thyrotoxic lactating mothers and infants were studied, 51 of whom had been treated with MMI during pregnancy, all who had overt signs and symptoms of thyrotoxicosis. Exclusions included women with mild symptoms and signs of thyrotoxicosis and those with T3/T4 ratio less than 20 ng/ug or an ESR of >30 mm/h. A group of 38 normal breast-fed infants, 2-8 months of age, whose mothers were euthyroid served as controls. A subgroup of 14 children of thyrotoxic lactating mothers and 17 controls between the ages of 48 and 74 months were evaluated for physical and neuropsychological development. The control group consisted of children with parenteral education and socioeconomic status levels close to the children of the thyrotoxic lactating mothers.

INTERVENTION

Doses of 5-20 mg MMI were studied. A total of 51 women who had been taking MMI during the pregnancy were maintained on a dose of 5 mg postpartum while lactating for a mean of 11 months. A second group of 46 women with postpartum thyrotoxicosis received 10 mg MMI for 2 months followed by 5-10 mg thereafter (months 3-12). A third group of 42 women with postpartum thyrotoxicosis took 20 mg of MMI for 2 months followed by 5-10 mg thereafter. In these patients, serum MMI was measured in the infants. The mean duration of therapy for these latter two groups was 13 months.

MAIN OUTCOME MEASURES

Serum total T4, T3, T3RU, and TSH (by IRMA) were measured before treatment and at 1,2,4,8, and 12 months in both lactating mothers and infants. Free T4 and free T3 indices were calculated. In 6 infants at 5-6 months of age, blood sample for MMI measurements were obtained 2 hours after breastfeeding in mothers who were on 10 mg MMI twice a day. In a subset of 14 infants of thyrotoxic lactating mothers and 17 controls, urinary iodine, thyroid antibodies, height, weight, and IQ (by Wechsler Preschool and Primary School of Intelligence and Goodenough tests) were measured at 48-74 months of age. Unpaired and paired Student's t tests and Z tests were used to compare continuous variables.

MAIN OUTCOME RESULTS

In all treated women, thyroid functions normalized by 3 months of MMI therapy. In all infants, the free T4 index, the free T3 index, and the TSH were normal before and up to 12 months. Serum MMI levels in all 6 infants whose mothers were given 10 mg of MMI 2 hours before nursing were <0.03 ug/ml. There was no difference in the weights, heights, thyroid functions, urinary iodine concentrations, thyroid antibodies, or IQ testing in the subgroup of 14 children of thyrotoxic lactating mothers compared to 14 controls. In 6 women who were rendered transiently hypothyroid (TSH concentration from 26-135 mU/L), all infants were euthyroid with TSH < 2.6 mU/L.

CONCLUSIONS

MMI can be safely administered during lactation in doses ranging from 5-20 mg per day.

COMMENTARY

Thyroid hormone is critical for normal brain development during intrauterine life and after birth. It plays an essential role in neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis, and regulation of certain neurotransmitters (1). There have been several recent publications suggesting that psychomotor and intellectual development might be impaired in infants born to mothers who were hypothyroid during pregnancy and that repletion of thyroid hormone within 2 months of birth in infants with congenital hypothyroidism may not be entirely successful in attaining maximal intellectual development (2,3). Therefore, it is imperative to ensure that the infant's thyroid function is not being adversely affected in mothers who are lactating while on antithyroid therapy.

Propylthiouricil is approved by the American Academy of Pediatricians for treatment in nursing mothers since a number of studies have demonstrated that it appears to cross minimally due to the fact that it is ionized at physiologic pH and 80% of the drug is protein bound (4). However, MMI has been shown to achieve a milk to plasma ratio of ~1 and a single dose of 40 mg of MMI could cause the infant to receive as much as 70 ug which could theoretically affect thyroid function. In this article, the investigators demonstrated that in 6 infants whose lactating mothers were given a dose of 20 mg MMI, the infant levels were <0.03ug/ml. In addition, doses ranging from 5-20 mg did not appear to affect thyroid function in the infant. This data is reassuring that low doses of MMI can be safely used in lactating mothers however the sample size for women taking 20 mg was relatively small and the duration this dose was given was short (<2 months). Propylthiouricil remains the preferred agent for lactating mothers, however MMI at doses of 5-20 mg appears to be an option for women who cannot take PTU. As is the case with all drugs given to lactating mothers, breastfeeding is safest if it is done immediately before a dose of medicine is given, and in the case of MMI, the half life in milk is 4.2 hours. Therefore it is unlikely that the infant will ingest a significant amount of drug if breastfeeding is timed immediately before the drug is taken and at least 4 hours after the drug is taken. However, the potential risk of thyroid dysfunction may exist (especially in preterm infants) and it is advisable to carefully monitor both mother and infant every 2 weeks with the use of either drug, at least initially.

Linda A. Barbour, MD, MSPH
Associate Professor of Medicine and Obstetrics and Gynecology
University of Colorado Health Sciences Center

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