Thyroid nodule and differentiated thyroid cancer management in pregnancy. An Italian Association of Clinical Endocrinologists (AME) and Italian Thyroid Association (AIT) Joint Statement for Clinical Practice


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THYROID NODULES AND PREGNANCY

Adaptation of the thyroid gland during pregnancy

Many physiologic changes involving the thyroid gland occur during pregnancy. Iodine requirements increase due to the elevated renal iodine clearance, iodine transfer to the fetal compartment, augmented levels of serum T4-binding globulin, and inner-ring deiodination of T4 and T3 exerted by placenta (1). These changes are associated with an increase of thyroid hormones production by about 1.5-fold and an increase in iodine requirements by about 50% with a consequent augmented thyroid activity (1).

Thyroid function tests

Current clinical practice guidelines do not recommend a screening for thyroid function at the beginning of pregnancy, suggesting a thyroid hormone determination only for pregnant women who are at risk for thyroid dysfunction (2). However, when iodine supply is insufficient, pregnancy triggers a vicious circle that leads to excessive glandular stimulation (3). These modifications may induce enlargement of the thyroid gland, progressive increase of thyroid nodule volume, and appearance of new nodules during gestation (3-8).

In a pregnant woman, serum TSH values are influenced by the thyrotropic activity of hCG. During the 1st trimester, both the median and the 2.5 and 97.5 centiles of TSH levels are lower than in the non-pregnant population. As up to 20% of pregnancies are characterized by transiently low TSH values (9-15), the use of traditional reference ranges may be misleading. A subclinical hypothyroid patient with a slight TSH elevation before pregnancy may be at risk to be misdiagnosed as euthyroid during pregnancy; on the other hand, an euthyroid woman may be misclassified as affected by subclinical hyperthyroidism (10). Two studies in 1st-trimester pregnant women found a prevalence of blunted TSH values (TSH<0.03 mIU/l or <2.5 centile) of about 2% (16, 17). Hence, pregnant women with thyroid nodules may be at risk of an inappropriate diagnosis of autonomously functioning nodules if trimester-specific pregnancy reference ranges are not applied (2). As autoimmunity may coexist with a nodular gland, determination of anti-thyroid peroxidase (TPO) antibodies is useful to rule out the possibility of developing hypothyroidism during pregnancy (10). In case of low or undetectable serum TSH values, a determination of free T4 and free T3 should be performed to distinguish subclinical from overt hyperthyroidism. The former is not associated with adverse obstetrical complications, while the latter is a recognized risk factor (16, 21, 22).

Measurement of calcitonin in patients with a nodular thyroid gland is controversial (22-24), but a non-stimulated calcitonin measurement may be useful in the initial work-up of thyroid nodules. Calcitonin measurement is mandatory in pregnant women with a family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2), or with cytological findings suspicious for MTC.

Question 1. What is the clinical management of women who become pregnant in iodine-deficient areas?

Clinical Recommendation 1. Test serum TSH and TPOAb and advise an increase in iodine intake (250 μg/day) to avoid thyroid stimulation, with consequent volume enlargement, and the risk of an undetected subclinical hypothyroidism.
Prevalence of thyroid nodules in pregnancy

The incidence of thyroid nodules and the changes associated with pregnancy have been evaluated in areas with borderline or mild iodine deficiency. In a prospective study, thyroid nodules were diagnosed by ultrasound (US) during early gestation in 3% of a cohort of apparently normal pregnant women (24, 25). A follow-up thyroid US performed within a week after delivery revealed a 60% increase in the mean size of the nodules and the appearance of new nodules in 20% of these women. In a Northern Germany study, thyroid nodules were detected by US in 21% of 212 pregnant women. The prevalence was higher in women with prior pregnancies than in the nulliparous ones (25% vs 9%). Women with 3 or more pregnancies had a higher percentage of thyroid nodules, compared with women who had 1 or 2 prior pregnancies (34% vs 21%) (25, 26). In a study from Southern China, 221 women were studied prospectively since the 1st trimester of pregnancy. Thyroid US, as well as thyroid function tests and urinary iodine excretion were measured throughout pregnancy and in the post-partum period (26, 27). Thyroid nodules (>2 mm) were detected in 15% of women in the 1st trimester, with 5.4% of subjects having more than one nodule. A significant increase in the nodule volume was detected, and about 11% of patients developed new nodules during pregnancy. The overall prevalence of thyroid nodules 3 months post partum was 24.4% (with about 10% having a diameter >5 mm). Hence, in areas with mild iodine insufficiency, nodules are prone to increase in size during pregnancy and women with pre-existing thyroid lesions are at risk of developing new ones (1). Data on nodule growth and formation in iodine-sufficient areas are currently not available.

Question 2. Is measurement of serum calcitonin useful in pregnant women with thyroid nodules?

Clinical Recommendation 2. A single measurement of non-stimulated serum calcitonin may be useful in the initial evaluation of a thyroid nodule in pregnant women. Measurement is strongly recommended in pregnant women with a family history, a clinical or a fine-needle aspiration biopsy (FNAb) suspicion of MTC or MEN2.

Question 3. Can thyroid US be advised as a screening test in all pregnant women?

Clinical Recommendation 3. A careful physical examination of the thyroid gland is strongly suggested in pregnant women. Screening of thyroid disease by US is not recommended.

Diagnostic evaluation of a thyroid nodule in pregnancy

A family history of benign or malignant thyroid diseases should be searched for (27-29), as well as history of previous head and neck irradiation. Data on the rate of nodule growth should be recorded (29, 30). A careful physical examination should always be performed (30, 31). Pregnant women <20 yr old deserve special attention due to a malignancy rate 2-fold greater than in general population (31, 32).

Small thyroid nodules (<1 cm), incidentally discovered by US, do not need cytological examination unless suspicious for malignancy on US or clinical grounds (32, 33). Hence, only part of the nodules diagnosed during pregnancy need a FNAb, which should be performed on the basis of the patient’s history, clinical examination, and US features.

FNAb is a safe diagnostic tool in pregnancy (34-40). In pregnant women, due to the previously described thyroid stimulation, cytological modifications characterized by an hyperplastic picture with rare colloid may occur (40). This condition may lead to overestimate the cytological diagnosis of “follicular lesion”. In a small study on thyroid nodules in pregnancy, the patients underwent FNAb and all the cases with a cytological report of malignancy or suspicious for malignancy were submitted to thyroidectomy (40). One third of patients with benign cytology underwent surgery as well. At histological examination, all the cases classified as benign or malignant were confirmed; 2 of 4 suspicious nodules were diagnosed as papillary cancer; all the 3 follicular lesions were benign; and one of the 2 Hurthle cell lesions was malignant. A second study evaluated 57 cases of FNAb performed during pregnancy and the post-partum period (40, 41). The authors found a high percentage of cytological diagnosis of papillary cancer (21%) and suspicious for malignancy (5%). Nineteen of the 57 patients underwent thyroidectomy. Histological examination confirmed the diagnosis of benign cytology (7 patients) and of papillary cancer (3 patients); 2 cytologically suspicious lesions were benign; 3 of 5 cases of “follicular variant of papillary carcinoma” were malignant; and 2 follicular lesions were confirmed as benign. No controlled trial evaluated the reliability of FNAb in pregnancy, but these studies suggest a careful approach to nodules with cytological diagnosis of follicular lesion.

In pregnant patients with thyroid nodules associated with hyperthyroidism, the use of radionuclide scanning is contraindicated (41-44). In case of inadvertent radiiodine (RAI) administration, the fetus is exposed to radiation from the mother’s blood. However, since the fetal thyroid uptake of RAI begins only after 12 weeks of pregnancy, the exposure to maternal RAI prior to this time is not associated with fetal thyroid damage.

Question 4. How should a pregnant women found to have a thyroid nodule be managed?

Clinical Recommendation 4. A pregnant women found to have a thyroid nodule should be reassured and evaluated in the same way as if she were not pregnant. US and FNAb are as safe and reliable as in non-pregnant women. Only thyroid radionuclide scanning is contraindicated.

Question 5. When should the FNAb assessment of a thyroid nodule be performed in pregnancy?

Clinical Recommendation 5. A FNAb under US guidance should be performed on thyroid nodules with suspicious clinical or US findings.

Management of thyroid nodules benign at FNAb

The diagnosis of a thyroid nodule may be negatively experienced by the patient during pregnancy. It is important to reassure the pregnant women by stressing the concept that only a minority of nodules are malignant.