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SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules

SFE-AFCE-SFMN 2022 Consensus on the management of thyroid nodules : Thyroid nodules and pregnancy

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ABSTRACT

The SFE-AFCE-SFMN 2022 consensus deals with the management of thyroid nodules, a condition that is a frequent reason for consultation in endocrinology. In more than 90% of cases, patients are euthyroid, with benign non-progressive nodules that do not warrant specific treatment. The clinician's objective is to detect malignant thyroid nodules at risk of recurrence and death, toxic nodules responsible for hyperthyroidism or compressive nodules warranting treatment.

The diagnosis and treatment of thyroid nodules requires close collaboration between endocrinologists, nuclear medicine physicians and surgeons, but also involves other specialists. Therefore, this consensus statement was established jointly by 3 societies: the French Society of Endocrinology (SFE), French Association of Endocrine Surgery (AFCE) and French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). The present section deals with the epidemiology and specificities of diagnosis and treatment of thyroid nodules in pregnant women.

1. Epidemiology

During pregnancy, several factors are thought to favor onset and growth of benign or malignant thyroid tumors: iodine deficiency, the stimulating effect of hCG on TSH receptors, and elevated TSH and estrogen.

Prevalence of thyroid nodules in pregnancy varies from 6% to 30% depending on the study population (including iodine status) and the definition of nodular pathology [1,2].

The influence of parity on onset and growth is controversial [3,4]. A Chinese study concluded that chronic estrogen exposure (in relation to the length of the reproductive period) promotes nodule growth [4]. An Italian study also showed that the increase in the rate of recurrence of thyroid nodules in the contralateral lobe after lobectomy correlated with the number of pregnancies [5]. On the other hand, a German cross-sectional study found no link between the presence of goiter or thyroid nodules and parity [3].

In addition to thyroid nodules, there is also the risk of thyroid cancer during pregnancy.

Estrogens can affect the tumoral microenvironment of thyroid cancer and favor progression [6]. Nevertheless, thyroid cancer has a low prevalence during pregnancy, at 14.4 per 100,000 births [7].

The impact of pregnancy on the prognosis of thyroid cancer is debated. There are few studies on the progression of thyroid cancer in relation to pregnancy, and all were cross-sectional or retrospective. They suggest that pregnancy, via the estrogen receptor Erα or not, may favoring benign and malignant thyroid tumor growth and worsen the prognosis for biological and structural remission of thyroid cancer occurring during or after pregnancy, without impacting survival [8–11].

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2. Diagnostic strategy

Pregnancy does not alter the initial assessment of a thyroid nodule (see Section 2).

2.1. Biochemistry

2.1.1. TSH

TSH assay is recommended and should be interpreted according to the term of pregnancy. Studies proposing TSH standards according to trimester are listed in the Appendix. TSH < 0.4 mIU/l is found in 15% of patients in the first trimester, in 10% in the second and in 4% in the third, due to the stimulating action of hCG, the concentration of which peaks between the 10th and 14th week of pregnancy [12,13]. In twin pregnancies, hCG level is higher and TSH level lower. Thus, in a series of 63 patients, TSH was < 0.2 mIU/l in 67% of cases where hCG level was > 200,000 IU/l and in 100% of those where hCG was > 400,000 IU/l [14].

In the first trimester, low TSH should first raise suspicion of transient gestational thyrotoxicosis secondary to elevated hCG that may be responsible for hyperemesis gravidarum [15]. A functional nodule can therefore be suggested only if the TSH is undetectable in the first trimester and remains so in the second trimester.

Toxic nodules are a rare cause of hyperthyroidism in pregnancy (< 10%) [15–18].

If there is any doubt about Graves' disease associated with a non-functioning nodule, the anti- TSHR antibody test will allow diagnosis

Recommendation 10.1

- Recommendation 10.1a – TSH testing is recommended for thyroid nodules found in pregnancy. Level of evidence, ++ Grade A.
- Recommendation 10.1b – A functional nodule should be considered during pregnancy if TSH is < 0.1 mIU/l, and remains so in the second trimester. Level of evidence ++ Grade A.

2.1.2. Calcitonin

Calcitonin testing is recommended if there is a familial or personal history of MEN2 or if surgery is intended. In other cases, calcitonin assay should be discussed again after delivery (see Calcitonin measurement outside pregnancy, Section 2). In the past, the literature reported elevated calcitonin [19,20]. This was not confirmed in a more recent study using current assay techniques [2].

Recommendation 10.2

Calcitonin testing in pregnancy is not recommended unless there is personal or familial history suggestive of MEN2 or surgery is intended. Level of evidence: expert opinion, Grade A

2.2. Imaging

2.2.1. Scintigraphy

Thyroid scintigraphy is contraindicated in pregnancy and it is important to ensure that there is no risk of pregnancy before performing it. If TSH is low, the scan should be postponed until after delivery or the end of breastfeeding [21–23].

Recommendation 10.3

Thyroid scintigraphy is contraindicated in pregnancy. Level of evidence +++, Grade A

2.2.2. Ultrasound/fine-needle biopsy

Known thyroid nodules prior to pregnancy should be differentiated from those discovered during pregnancy.

Ultrasound is recommended if a nodule is found during pregnancy [7,24].

The ultrasound criteria are identical to those used outside pregnancy, although the EU-TIRADS classification has not been specifically studied in this subpopulation [25], nor has elastography [26].

In the case of a known nodule explored before pregnancy with reassuring ultrasound exploration (EU-TIRADS 2-3, or 4 without criteria for fine-needle biopsy) or benign fine-needle biopsy, it is not necessary to check the ultrasound scan if it is less than 2 years old. The woman can be reassured that there is no progression during the pregnancy. However, cervical palpation is recommended at the end of the first trimester. If there is any doubt about subjective clinical progression (cervical discomfort, particularly when swallowing) and/or objective progression (increase in nodule volume or appearance of lymphadenopathy on cervical palpation), ultrasound should be carried out as soon as possible. If the exploration is older, it is advisable to repeat the ultrasound in the first trimester of pregnancy

Fine-needle biopsy should be performed in case of EU-TIRADS 5 nodule >1 cm or in case of suspicious lymphadenopathy. Timing is to be discussed according to the term of pregnancy. For EU-TIRADS 3, fine-needle biopsy is not recommended during pregnancy [24]. In case of EU-TIRADS 4 nodule, there is no consensus and fine-needle biopsy may be deferred until after delivery.

There are few studies evaluating the sensitivity and specificity of cytology in pregnancy. However, it seems that, while histology can demonstrate follicular hyperplasia during pregnancy, cytology is not modified [27]. Thus, in an early study of 40 pregnant patients, one-third of those with benign cytology were operated on, and all had benign histology. All cases of suspect cytology were operated on: 2 out of 4 suspicions were cancer, and three-quarters of follicular lesions were benign [28]. In another study, of 57 pregnant or immediate post-partum patients, out of 19 operated patients there were 7 benign cytologies and 3 histological suspicions of papillary cancer, all confirmed by histology, and 9 undetermined cytologies, 4 of which were cancers [8]. Fine-needle biopsy therefore seems to be interpretable whatever the trimester of the pregnancy, even though there are no specific prospective data [29].

An ultrasound check should be carried out at the beginning of the second trimester if any of the following criteria are observed: i) discomfort on swallowing, dysphonia, local discomfort, respiratory discomfort; ii) change in cervical palpation: increased thyroid nodule volume or appearance of cervical lymphadenopathies; iii) nodule initially classified as EU-TIRADS 4 or 5 [7,21].

Recommendation 10.4

- Recommendation 10.4a – Thyroid ultrasound should be performed as soon as a nodule is diagnosed during pregnancy. Level of evidence: expert opinion, Grade A.
- Recommendation 10.4a - The EU-TIRADS classification should be used in pregnancy. Level of evidence: expert opinion, Grade A.

Recommendation 10.5

- Recommendation 10.5a - If the thyroid nodule is known prior to pregnancy with EU-TIRADS classification 2-3 or 4 without fine-needle biopsy criteria in the 2 years prior to pregnancy, we do not recommend ultrasound monitoring during pregnancy, subject to reassuring cervical palpation at the end of the 1st trimester. Level of evidence: expert opinion, Grade B
- Recommendation 10.5b - If the thyroid nodule is known prior to pregnancy with an old ultrasound scan (>2 years), we recommend ultrasound monitoring during the 1st trimester of pregnancy. Level of evidence: expert opinion, Grade A

Recommendation 10.6

- Recommendation 10.6a - Fine-needle biopsy is recommended for EU-TIRADS 5 nodules >1 cm or suspicious lymphadenopathy in the first half of pregnancy. Level of evidence: expert opinion, Grade B
- Recommendation 10.6b - In other cases, fine-needle biopsy, if indicated, should be delayed until after delivery. Level of evidence: expert opinion, Grade A

Recommendation 10.7

Ultrasound should be checked at the beginning of the second trimester if there is clinical suspicion of progression or an EU-TIRADS 4 or 5 nodule. Level of evidence: expert opinion, Grade A

3. Management

3.1. Surveillance

Most nodules will only require monitoring during pregnancy.

Recommendation 10.8

In all cases, organization of post-pregnancy surveillance is necessary. The timing of the consultation should be decided jointly with the patient according to ultrasound and/or cytological criteria, ideally within 6 months of delivery if malignancy is suspected. Level of evidence: expert opinion, Grade A

3.2. Toxic nodule

In case of a known toxic nodule prior to pregnancy with TSH < 0.1 mIU/L, preconception treatment is preferred.

In the first trimester of pregnancy, in symptomatic forms, beta-blocker treatment can be initiated. Treatment with antithyroid drugs (ATD) is very rarely necessary. The decision should be made after discussion of the risk-benefit ratio: i.e., complications of hyperthyroidism during pregnancy [30,31] versus complications of ATDs [32,33], which are less frequent with propylthiouracil (PTU) than with other ATDs.

Since ATDs cross the placental barrier, if ATD treatment is continued into the second trimester (functional fetal thyroid from 18 weeks of pregnancy), the therapeutic objective is a maternal T4l at the upper limit of normal (1.5 to 2 × ULN)

in order to avoid fetal hypothyroidism. In this case, fetal ultrasound monitoring should be performed from 22 weeks onwards, looking for signs of fetal hypothyroidism (goiter).

Iodine supplementation should be avoided in this context.

The use of radioactive iodine is contraindicated during pregnancy.

Recommendation 10.9

- Recommendation 10.9a–In the case of symptomatic hyperthyroidism, symptomatic treatment (beta blockers) should be prescribed in first line. Treatment with antithyroid drugs (ATD) at the minimum effective dose (target T4l at the upper limit of normal) is necessary in rare cases. Level of evidence: expert opinion, Grade B
- Recommendation 10.9b–RAI treatment of a toxic nodule is contraindicated during pregnancy and should be deferred until after delivery. Level of evidence +++ Grade A

3.3. Suppressive treatment

As in the general population (see dedicated paragraph, Section 6), and even more so during pregnancy because of the risk of obstetric and fetal repercussions of hyperthyroxinemia, treatment to reduce the size of a benign euthyroid nodule is not recommended.

Recommendation 10.10

In pregnancy, L-thyroxine treatment for thyroid nodule is contraindicated. Level of evidence: Expert opinion, Grade A

3.4. Thermal ablation

There are no data on complications of thyroid thermal ablation in pregnancy. European guidelines on thyroid thermal ablation state that radiofrequency treatment is contraindicated in pregnancy [34].

Recommendation 10.11

We do not presently recommend thermal ablation in pregnancy. Level of evidence: expert opinion, Grade A

3.5. Management of thyroid microcarcinoma

In case of sub-centimetric EU-TIRADS 5 nodule or Bethesda V or VI fine-needle biopsy suggestive of papillary microcarcinoma discovered before or during pregnancy, active surveillance may be considered in the absence of suspected lymph-node involvement, due to excellent prognosis and lack of reported progression during pregnancy. A 2016 Japanese study reported that, in 50 women with thyroid microcarcinoma discovered before pregnancy, 90% of those followed up showed no progression [39]. Follow-up ultrasound should be performed at the beginning of the second trimester [35].

Recommendation 10.12

- Recommendation 10.12a–In case of known non-progressive papillary microcarcinoma, we recommend that surgery should not be performed during pregnancy and that reassessment should be scheduled within 6 months of delivery. Level of evidence: ++ Grade A
- Recommendation 10.12b–In case of known progressive papillary microcarcinoma in pregnancy, we recommend that the indication for surgery or continued surveillance should be discussed in a multidisciplinary team meeting. Level of evidence: ++ Grade A

3.6. Surgery

While benign or stable nodules should only be monitored, some suspicious or compressive nodules may warrant surgical treatment after multidisciplinary discussion.

Studies of thyroid surgery in pregnancy have shown no maternal and/or fetal complications if performed in the second trimester by a trained team [7,35]. When surgery is performed in the first trimester, there is a risk of miscarriage, whereas in the third trimester it increases the risk of preterm delivery.

Thyroid surgery is therefore usually proposed in the second trimester [7,35–37]. However, it should not be contraindicated at any stage of pregnancy if the mother's prognosis is at risk [37].

The surgical indication must be discussed and carried out by a trained multidisciplinary team. It requires obstetric and anesthesiologic precautions and must be performed in a center with a neonatal unit, after informing the obstetric team in accordance with the recommendations of the American College of Gynecologists and Obstetricians on non-obstetric surgical management during pregnancy [37].

Suspicion or diagnosis of thyroid cancer in the absence of lymph-node metastasis or aggressive criteria should not systematically lead to surgery during pregnancy. Surgery is nevertheless possible after discussion with the patient, depending particularly on the feasibility of early post-partum surgical management. The factors to be taken into account are the maternal prognosis and the risks

of maternal, fetal and neonatal complications of surgery during pregnancy.

Surgical management should be proposed during pregnancy in case of suspected cancer with aggressive criteria: tumor progression (50% volume or 20% diameter, taking into account the initial size; cf. Section 6), onset of lymph-node invasion, negative criteria on initial ultrasound (tumor size >4 cm, local, regional and/or lymph-node invasion).

If a cancer is found that warrants surgical management at the end of the second or third trimester, postpartum surgery should be proposed [7]. In this case, it is necessary to agree with the patient on the date of the appointment with the endocrinologist and/or thyroid surgeon in the post-partum period, in order to avoid frequent post-partum loss to follow-up, with the risk of negative progression.

Recommendation 10.13

- Recommendation 10.13a–We do not recommend routine surgery for thyroid cancer diagnosed in pregnancy in the absence of aggressive criteria. Level of evidence: +++ Grade A.
- Recommendation 10.13b–Thyroid cancer surgery in the second trimester of pregnancy may nevertheless be considered if the patient prefers and gives informed consent. Level of evidence: expert opinion, Grade B.
- Recommendation 10.13c–We recommend thyroid cancer surgery in the second trimester of pregnancy in case of tumor progression or aggressive criteria. Level of evidence: +++ Grade A.

Recommendation 10.14

If thyroid surgery is considered in pregnancy, we recommend that it be performed in the second trimester by a trained team in a suitable obstetric and neonatal environment. Level of evidence: +++ Grade A

Recommendation 10.15

We recommend scheduling the post partum appointment be brought forward in case of any cancer with surgical indication but not operated on during pregnancy. Level of evidence: expert opinion, Grade A

Recommendation 10.16

Breastfeeding is not contraindicated; duration is conditional on histology and indications for radioiodine therapy. Level of evidence: expert opinion, Grade A.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix 1. TSH values between the 2.5 and 97.5 percentiles in anti-TPO-negative patients, by iodine status.

Study	Method	N	iodine status	TSH mIU/L 1st trimester	2nd trimester	3rd trimester
Mannisto, 2011 Thyroid	Architect i2000	5080	Sufficient	0.08-3.54	0.11-4.24	NA
La'ulu 2011 Clin Chem	Architect i2000	2172	Low	0.02-2.69	NA	NA
Raverot V. 2012. Thyroid	Architect i2000	228	Moderate-low	0.03–2.90	0.34–2.90	0.24–5.70
Shen FX, 2014 Clin Biochem	Architect i2000	1191		0.16-3.78	0.34-3.51	0.34-4.32
Suleyman Akarsu. 2016 Clin Chem Lab med	Architect i2000	2430		0.49-2.33	0.51-3.44	0.58-4.31
Ollero.2019 Thyroid [1]	Architect i2000	400	Sufficient	0.13-4.16	0.31-3.73	0.58-4.36
Yann 2011 Clin Endocrinol (Oxf)	Advia centaur	505	Sufficient	0·03-4·51	0·05-4·50	0·47-4·54
Bestwick 2014 Clin Chim Acta	Advia centaur	16,334	Moderate-low	0.06-3.5	NA	
Li 2014 JCEM	Cobas elesys	640	Sufficient	0.1-4.34		NA
Medici Clin Endocrinol Metabol 2011	Vitros	5186	Sufficient	0.03-4.04	NA	

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