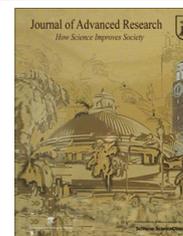




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**REVIEW**

A review on thyroid cancer during pregnancy: Multitasking is required



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ABSTRACT

Thyroid cancer is the second most common cancer diagnosed during pregnancy after breast cancer. The goal of management is to control malignancy and prevent maternal and fetal complications as a result of maternal hypothyroidism. The role of female sex hormones as an etiologic factor was investigated, with no clear association. Pregnancy can cause an increase in size of a previously existed thyroid nodule through the structural similarity between TSH and BHCG, and the normally expressed estrogen receptors on thyroid gland cells. Effect of pregnancy on development and prognosis of differentiated thyroid malignancies (papillary and follicular) has also been studied. The prognosis of thyroid cancer is not worse in patients diagnosed during pregnancy or those who got pregnant after curative treatment. Termination

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Pregnancy
Pregnancy related disorders
Tyrosine kinase inhibitors
Radioactive iodine

of pregnancy is not indicated at all, surgery can be delayed till after delivery except in rapidly growing aggressive tumors. While radioactive iodine ablation is absolutely contra-indicated, the new systemic therapies are not well studied during pregnancy. However, almost all these new agents are classified as FDA category C or D and are better to be avoided. The effect of pregnancy on other types of thyroid cancer (medullary and anaplastic thyroid tumors) is not well studied because of very low incidence with pregnancy. The endocrinological management of thyroid cancer during pregnancy is of utmost importance. The hypothyroidism after total thyroidectomy can cause fetal hypothyroidism. Therefore, the management of thyroid cancer related to pregnancy needs a multidisciplinary team.

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Introduction

Thyroid cancer is the second most common cancer diagnosed during pregnancy [1]. The management of thyroid cancer in

this situation has multiple goals: to control the malignancy, overcome the hormonal disturbances after thyroidectomy and to avoid drawbacks on fetus as a result of maternal hypothyroidism [2]. Total or near total thyroidectomy is the standard of care for patients diagnosed with thyroid cancer, followed by radioactive iodine administration as an adjunctive treatment in differentiated thyroid tumors.

Pregnancy is an absolute contraindication for radioactive iodine administration. The timing of surgery, the impact of pregnancy on prognosis of thyroid cancer and monitoring of pregnant women with thyroid cancer are important points to be discussed while treating a case presented with thyroid cancer related to pregnancy [3].

The aim of this article is to revise the medical literature for data related to this clinical situation, aiming to provide answers for questions regarding management of such patients.

Epidemiology and risk factors

The incidence of thyroid cancer is rising all over the world [4]. The increase is affecting all ethnic and age groups with an increased risk among women below 45 years old [5]. The increase may have some geographical variation with significant increase in Eastern Europe since the Chernobyl nuclear power plant accident and areas affected by radioactive fallout as Belarus and Ukraine [6]. The increase in incidence is not accompanied by an increase in mortality; this reflects the indolent nature of the disease, as the rise in cause specific mortality rates is expected many years later [4].

Whether this increase in incidence is a true increase or inflated by increase in diagnosis has been debated. Some authors attribute the increase in incidence to the increased utilization of sensitive radiological maneuvers i.e. ultrasound in health care, leading to diagnosis of lesions that otherwise was going to pass unnoticed. This premise can explain the increased incidence of small tumors. The increase in incidence of large tumors and the almost exclusive increase in papillary histopathology subtype can argue against the premise of false increase due to early detection and support the premise of a true increase in incidence worldwide [7].

Women are affected by thyroid cancer more than men as female to male ratio may reach to 3–1. Thyroid cancer is the second most common malignancy during pregnancy, preceded only by breast cancer with an incidence of 14 per 100,000 live births [1]. History of exposure to ionizing radiation, and iodine deficiency are well established risk factors for thyroid cancer. MEN2 is a genetic syndrome that affects 1–2% of all the

patients with thyroid cancer [4]. The female dominance and age specific increase in incidence in women during the child-bearing period suggested a possible role of sex hormones in developing thyroid cancer especially differentiated thyroid cancer (papillary and follicular thyroid cancers).

A pooled analysis of 14 case control studies included a total of 2247 female patients suggested a weak association of reproductive and menstrual factor as age at menarche, age at first pregnancy and menopause with the risk of thyroid cancer [8]. However, the hypothesis of this association has been also studied in large prospective cohorts with contradictory results. The California teachers cohort study investigated the effect of menstrual, reproductive and other hormonal factors including exogenous hormones intake on developing papillary thyroid cancer. This prospective cohort, which included 117,646 women has suggested an association between late age at menarche, longer menstrual cycle (more than 30 days) and the increased risk of papillary thyroid cancer [9]. On the other hand, the EPIC study, which is also a prospective cohort study with a large sample size (345,157 women), followed for a median of 11 years did not find strong association between reproductive factors and the risk of developing thyroid cancer [8]. Both studies, however, identified a positive association between recent pregnancy (within 5 years of cohort enrollment) and thyroid cancer risk [9,10].

A meta-analysis was conducted to solve this issue, with 21 studies including 406,329 cases. This meta-analysis suggested a strong association of parity (≥ 3 pregnancies) with the risk of thyroid cancer. It confirmed the previously noted observation of transient increased risk of thyroid cancer with recent pregnancy (≤ 5 years since the last pregnancy) [11].

Pregnancy and thyroid

Thyroid gland size normally increases by 30% during the first and third trimesters of pregnancy. TSH level fluctuates during pregnancy, as it decreases during the first trimester and then returns to normal. As the fetal thyroid cannot concentrate iodine till week 12 of gestation, maternal T4 is the only source of thyroid hormones for the fetus [12]. For monitoring of thyroid function during pregnancy, special reference ranges in relation to gestational age are used to avoid misinterpretation of thyroid function tests. This is of paramount importance in monitoring patients known to have thyroid cancer as TSH level guides suppressive treatment dose adjustment with levothyroxin [2,3,12].

The effect of pregnancy on thyroid gland could be explained by two main mechanisms, the increase in the level of HCG and the increase in circulating estrogen level. As both TSH and HCG are glycoprotein hormones with similar structure and encoded by the same gene [13], HCG stimulates TSH receptors and leads to increase in the activity of thyroid gland. TSH level subsequently decreases mainly during the first 12 weeks of gestation then back to normal [3,12,14]. HCG stimulating effect on thyroid gland can be noted in diseases causing very high levels of HCG as gestational trophoblastic diseases [15], with less than 10% of these patients presenting with manifest hyperthyroidism and thyrotoxicosis in rare cases [16].

Estrogen level exerts its effect through more complicated mechanisms; it has an indirect effect through increasing the

serum thyroxin binding globulin. The direct effect is through estrogen receptors presented on thyroid gland cells [17]. ER α and ER β are intracellular nuclear receptors that exist in normal and neoplastic thyroid cells. Estradiol binding to ER α enhances cell proliferation while ER β inhibits these effects and induces apoptosis [18,19]. Some recent studies showed different levels of expression of ER α and a decrease in increase in ER β in malignant thyroid cells in comparison with normal cells [20]. Estrogen DNA adducting with unbalanced estrogen metabolism in patients with thyroid cancer was also reported [21]. Another study suggested an association between ER expression and aggressiveness of disease at presentation and relapse [22].

Effect of pregnancy on thyroid cancer prognosis

A thyroid nodule is defined as a discrete lesion in the thyroid gland that is radiologically distinct from the surrounding parenchyma. Thyroid nodular diseases are common during pregnancy, with increase in newly developed nodules and also increase in size and number of previously existed nodules [23]. Thyroid cancer related to pregnancy is defined as differentiated thyroid cancer (DTC) diagnosed during pregnancy or within 12 months of childbirth [24].

The effect of pregnancy on prognosis of DTC has been studied to answer a pivotal question, if the pregnancy can worsen the prognosis of DTC or cause a relapse in a previously treated patient. There is an extensive amount of literature discussing the effect of pregnancy on thyroid cancer. To find a final conclusion, a systematic review published in 2011 revised 4 main studies to evaluate the effect of pregnancy on recurrence/persistence of disease as well as overall survival [24]. The primary outcome of these studies was different; in two studies the primary outcome was overall survival, in the third one, the primary outcomes were recurrent disease and death related to thyroid cancer, and in the fourth study the primary outcome was recurrent or persistent disease. Two of these 4 studies did not suggest a negative effect of pregnancy on overall survival [25,26]. The third study [27] showed also no increase in recurrence rates or disease related mortality, while the last one found an association between pregnancy and persistent or recurrent disease [22].

As the included studies were heterogeneous in methodology and with different primary outcome, so a meta-analysis could not be done, and the authors attributed this difference in outcomes to the difference in outcome measurement predictors, as this last trial used the level of Tg level, which is more sensitive and was not used by the other trials. While this is the case for DTC, the effect of pregnancy on micro papillary thyroid cancer carcinomas, which are defined as having a maximum diameter of ≤ 10 mm, was evaluated in a small retrospective study. This study indicated that its size may increase during pregnancy [28].

Pregnancy after treatment for DTC

Another question is the effect of pregnancy on previously treated patient with DTC; a retrospective study done on 72 patients previously treated with thyroidectomy and radioactive iodine ablation was done; 36 of the study population got pregnant after treatment and 36 were non-pregnant; and

the outcomes of treatment and the prognosis (in terms of scintigraphic relapse and metastasis, ultrasonographic relapse, lymphadenopathy and stage change at the beginning and at the end of follow-up) were not compromised with pregnancy [29]. This comes in partial agreement with previously published study by Hirsch et al. [30]. They concluded that pregnancy did not cause disease recurrence in papillary thyroid cancer survivors who had no structural or biochemical evidence of disease persistence at the time of conception, while in the presence of such evidence, disease progression might occur during pregnancy. Although the outcomes of treatment are not compromised by pregnancy, it is advised to avoid pregnancy for 12 months after radioactive iodine treatment to ensure remission [31].

Diagnostic approach and risk assessment of thyroid nodule during pregnancy

Till now, there is no consensus regarding screening for thyroid dysfunction neither during pregnancy nor for thyroid nodules [12,32]. If a thyroid nodule is found during physical examination or accidentally during an ultrasound examination, it should be assessed for suspicious of malignancy. The following criteria indicated the need for fine needle aspiration cytology: hypo-echogenic irregular nodule margins, absent peripheral halo of nodule, increased intra-nodular vascularization, presence of latero-cervical adenopathies, presence of microcalcifications, nodules taller than wider, and presence of microcalcifications [3,32].

Fine needle aspiration cytology is safe and convenient method for assessing a thyroid nodule; both ATA (American Thyroid Association) and ENDO (The Endocrine Society) recommend the performance of the procedure in this situation. Interpretation of its results should be done using Bethesda classification criteria for cytological assessment [3]. As previously mentioned, thyroid scan is contraindicated.

Timing of surgery

The standard primary treatment for patients with thyroid cancer remains total or near total thyroidectomy. In a pregnant woman, both maternal and fetal outcomes shall be considered before taking the decision of surgery. As previously mentioned, there is no evidence to support termination of pregnancy when the diagnosis of differentiated thyroid cancer is performed. The Endocrine Society for pregnancy-related differentiated thyroid cancer has recommended thyroidectomy after delivery for patients with no evidence of advanced disease or without rapid progression, and thyroidectomy in the second trimester of pregnancy for the others. Radioactive iodine should only be given after delivery and the ending of breast feeding [22]. Thus, and as it seems there is no negative impact for pregnancy on prognosis of differentiated thyroid cancer, the delay of surgery seems a reasonable approach to avoid postoperative complications. However, in some patients diagnosed during the first trimester of pregnancy, tumors may show aggressive behavior (aggressive or locally advanced histology, metastatic cervical lymph nodes diagnosed by cytology, severe compressive symptoms and the significant growth of a malignant nodule with > 50% in volume or > 20% in diameter in two dimensions). In such situations, surgery should be carried out during second

trimester and not be postponed till delivery [3,33]. Surgery during the second trimester is considered safe with no major morbidity either fetal or maternal. However, Kuy [34] and colleagues reported a higher incidence of postoperative complications in comparison with non-pregnant women submitted to thyroidectomy in terms of fetal, maternal, and surgical complications. This was clear in terms of in-hospital mortality, median length of stay, and hospital costs.

For patients diagnosed during the third trimester, surgery could be safely delayed after surgery to avoid the expected complications of surgery in this late period of pregnancy, as premature labor and hypotension during surgery caused by compression of gravid uterus on grand vessels [3,33,35].

Radioactive iodine (RAI) ablative therapy

Aiming to reduce recurrence and achieve long term control for distant metastatic disease, radioactive iodine ablation with I^{131} usually follows surgery in most patients with thyroid cancer. The patients planned to receive RAI should be tested for pregnancy before deciding treatment [36]. Exposure to radioactive iodine during pregnancy is contraindicated, and the hazards of this exposure include fetal hypothyroidism and cognitive disorders and mental retardation [35]. In patients requiring RAI therapy after delivery, breast feeding shall be stopped at least 6 weeks before ablative therapy and mothers should be advised against nursing [2]. There is no evidence that RAI can affect fertility or affect subsequent pregnancy [3], and a conservative approach is to avoid pregnancy for 12 months after RAI ablative therapy to ensure remission and attain adequate thyroid hormone replacement [31].

Therapy with levothyroxine (LT4)

A patient with thyroid cancer related to pregnancy needs LT4 treatment for different indications, as a suppressive treatment for those who were decided to postpone surgery till second trimester or after delivery, as a replacement therapy for a survivor of thyroid cancer after thyroidectomy, and as a suppressive therapy for patients with residual disease.

If cytopathology confirmed the diagnosis with DTC and the surgery was decided to be post-partum, it is advisable to start treatment with LT4. Suppressive treatment with LT4 aims to keep TSH level below 0.1–1 mU/l, with monthly monitoring of TSH and T4 levels [3,37].

As maternal hypothyroidism has serious drawbacks on the fetal development, so in a patient with history of thyroidectomy LT4 therapy is mandatory. Thyroxin hormone requirements increase by 20–30% during pregnancy, and the dose of levothyroxine should be adjusted within reference range specific for pregnancy. Other dietary supplements were used during pregnancy as iron and calcium can affect LT4 absorption, so close monitoring of thyroid function is mandatory [3,37]. If surgery was done during pregnancy, LT4 therapy should be started immediately after surgery [3]. In a patient under suppressive treatment with LT4 for a residual/persistent disease, the treatment in this case has a goal of keeping the TSH level below 0.1 mU/l indefinitely [33].

Systemic therapy for thyroid cancer during pregnancy

DTC refractory to RAI can be treated with tyrosine kinase inhibitors (TKIs). Motesanib diphosphate, axitinib, sorafenib, sunitinib and pazopanib are accepted treatment options. For medullary carcinoma of thyroid, vandetanib, cabozantinib, and lenvatinib are also treatment options [38].

The safety of these drugs during pregnancy and lactation was not studied in humans, with data available only from animal studies. FDA classifies sorafenib [39], sunitinib [40], axitinib [41] and pazopanib [42] as Category D. Safety concerns also imply the toxicities of these agents, vandetanib [43], lenvatinib [44] and cabozantinib [45] are also categorized as Category D, and vandetanib is known to induce cardiotoxicity that could be irreversible. Finally, chemotherapy either as a single agent or as a polychemotherapy has been abandoned due to poor results [37].

Conclusions

The management of thyroid cancer during pregnancy is a difficult clinical problem and must be managed through a multidisciplinary team using guidelines adopted by American Thyroid Association (ATA) and The Endocrine Society (ENDO). As radioactive iodine is contraindicated during pregnancy, ultrasound examination of thyroid gland is recommended in suspicious lesions with FNAC if needed for highly suspicious lesions. Termination of pregnancy is not indicated and surgical intervention can be delayed after delivery, while the role of TKIs in this population is poorly studied.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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