Clinical therapy and management of differentiated thyroid cancer in pregnant women.

Jiaqun Zou[1#], Lei Han[2#], Bo Gao[1], Chun Wang[1], Jie Yan[1], Xiaojuan Jiang[1*], Donglin Luo[1*]

[1]Department of Breast and Thyroid Surgery, Research Institute of Surgery, Daping Hospital, Third Military Medical University, Chongqing, China

[2]Department of Obstetrics and Gynecology, The 306th Hospital of the Chinese People's Liberation Army, Beijing, P. R. China

[#]These authors contribute equally.

Abstract

Differentiated thyroid cancer (DTC) is frequently found in mid-aged and young women. DTC has been the second common malignancy diagnosed during pregnancy. The clinical therapy of DTC has involvement of both mother's health and fetal safety and thus is usually difficult. Currently, there are still controversies in the therapy of DTC in pregnant women. Herein we summarize the advance in the surgical therapy, radioactive iodine therapy and thyroid hormone replacement therapy in pregnancy and after delivery and explore more effective strategies which are beneficial for the mother and fetus, which willprovide more evidence for the selection of strategies for the clinical management of DTC in pregnant women.

Keywords: Pregnancy, Differentiated thyroid cancer, Surgery, Radioactive iodine therapy, Thyroid hormone replacement therapy.

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Introduction

Differentiated thyroid cancer (DTC) is frequently found in mid-aged and young women, most of who are at the child-bearing age. With the development of diagnostic techniques and the delay at the child-bearing age of women worldwide, the incidence of DTC is increasing over year in the pregnant women, and DTC has become the second most common malignancy diagnosed during pregnancy (1.4/100000) [1]. DTC in pregnancy is divided into newly onset DTC in pregnancy and pre-existing DTC in pregnancy. The therapy of DTC in pregnancy may directly affect the mother's status and fetal development, and thus there are some controversies in this field. Herein, we summarize the advance in the surgical therapy of DTC in pregnancy.

Classification and Diagnosis of DTC in Pregnancy

DTC in pregnant women can be divided into three types: (1) there is no abnormality in the thyroid before pregnancy, but DTC is diagnosed after pregnancy; (2) DTC is diagnosed during pregnancy; (3) Women with uncontrollable DTC become pregnant. It is necessary to confirm the nature of thyroid nodules once they are found during pregnancy regardless the types, which, on one hand, is helpful to exclude the possibility of thyroid cancer and relieve the mental stress of patients and their relatives and on the other hand may guide the following therapies.

The history of present illness, past history and family history should be taken into account in the diagnosis of DTC during pregnancy, aiming to exclude risk factors (this is similar to the diagnosis in non-pregnant women). Once symptoms like persistent hoarseness, dysphonia, dyspnea and dysphagia and signs such as cervical lymphadenopathy are present, thyroid cancer is highly suspected. When the thyroid rapidly enlarges, becomes irregular or is adhesive to surrounding tissues, patients should be taken them seriously and targeted physical examination should be performed in these patients. Comprehensive analysis is required on the basis of findings from laboratory and imaging examinations. Several factors such as DTC, thyroiditis and estrogen fluctuation during pregnancy may increase the serum thyroglobulin (Tg), and thus the increased serum Tg cannot be used as a unique evidence for DTC [2]. Detection of Thyroid Stimulating Hormone (TSH) should be done in all the patients with thyroid nodules because studies have shown that the thyroid nodules in patients with low TSH are more likely malignant than in those with normal or high TSH [3]. Ultrasonography of the thyroid is still a preferred tool for the diagnosis and evaluation of DTC during pregnancy. Solid nodules with hypointense, nodules rich in blood, and nodules with irregular borderline, calcified foci or cervical lymph nodes are more likely malignant lesions [4]. Fine needle aspiration biopsy (FNAB) is the most accurate tool in the diagnosis of DTC during pregnancy and can be used in the diagnosis of solid thyroid nodules larger than 1 cm in diameter, with the sensitivity of 83%, specificity of 92%, and false positive rate of 5% and false negative rate of 5%. Ultrasound guided FNAB may increase the success rate of biopsy for micronodules and is applicable in patients with risk factors for thyroid cancer or thyroid nodules larger than 1 cm or suspected malignant, having a high sensitivity [5]. For thyroid

nodules highly suspected malignant, FNAB is not recommended [6], and radionuclide scanning is infeasible during pregnancy. To assure the reliability of FNAB, sample collection should be conducted at the suspected sites by ultrasonography, especially at the solid lesions. Repeated sample collected is accepted if necessary. However, FNAB usually fails to differentiate thyroid follicular carcinoma from follicular cell adenoma. Recent studies reveal that additional detection of several markers for thyroid cancer (such as Ras mutation, BRAF mutation and RET/PTC rearrangement) may increase the diagnostic accuracy [7].

Influence of Pregnancy on DTC

The incidence of DTC in pregnant women is 3 times that in common women, and thus pregnancy related estrogen and human chorionic gonadotropin (hCG) have been proposed important factors related to the pathogenesis of DTC in pregnancy [8]. In addition, clinical studies indicate that prior delivery, more than one pregnancy and use of drugs for ovulation induction (such as clomiphene) are risk factors for DTC [9], and oral contraceptives containing estrogen and hormone replacement therapy after menopause may also increase the risk for DTC [10]. However, several studies also report that exogenous estrogen is not related to DTC [11]. In studies on the evaluation of prognosis of DTC, results showed the prognosis of DTC in pregnant women was poorer than that in non-pregnant women [12], but no significant difference was observed in other studies [13]. There are still controversies in experiments. There is evidence showing that estrogen may promote the proliferation of DTC cells [10], but the stimulating effect of estrogen is only observed in normal thyroid cells in other studies [14]. Thus, pregnancy and relevant hormones may influence the pathogenesis and prognosis of DTC, but the extents and specific mechanisms are still unclear and required to be elucidated.

Surgical Therapy of DTC during Pregnancy

For DTC patients with indications for surgical intervention, it is a challenge that whether surgical dissection is performed during pregnancy. To date, no prospective studies have been conducted to compare the outcome of DTC in pregnant women who received surgical intervention during pregnancy and after delivery. Retrospective studies reveal that the hospital stay and medical cost in pregnant women who received thyroid and parathyroid surgery increased significantly as compared to non-pregnant women [15]. However, long term follow up shows the incidence of recurrent DTC was comparable between DTC women who received surgical intervention during pregnancy and after delivery [16]. Thus, the disadvantages of surgery during pregnancy should be balanced with the degree of anxiety and DTC growth during pregnancy.

The optimal time for surgical intervention is still indecisive for pregnant women, and individualized therapy is recommended in which the subjective views, risk factors and invasiveness of DTC should be taken into account. Once there are some risk factors or obstetric factors, or patients request surgical intervention, surgery should be performed in the second trimester (before 24 weeks gestational age) aiming to reduce the risk for spontaneous abortion [17]. The risk factors include cytological features showing malignant tendency, pathological and/or clinical characteristics showing invasiveness, rapid growth and presence of symptoms due to tumor-induced compression. Patients without risk factors may be further observed during pregnancy, ultrasonography of the thyroid should be performed once monthly, and surgery is considered after delivery.

DTC during Pregnancy and Radioactive Iodine Therapy

Generally, radioactive iodine (131I) therapy is not allowable for pregnant women with DTC because radiation at a high dose may cause thyroid dysfunction, attention deficit, memory loss, mental retardation, developmental abnormalities, cancers (such as leukemia) and other fetal consequences in the fetus [18]. Radioactive iodine therapy is performed only when the pregnancy is excluded. A large scale clinical study indicates that the risk for abortion increases for women who become pregnant within 6 months after radioactive iodine (131I) therapy [19], but the long term outcomes of mothers and their children are not directly associated with radioactive iodine therapy [20]. Thus, contraception is recommended for 6-12 months after radioactive iodine (131I) therapy due to DTC, aiming to reduce the risks for abortion and fetal malformations.

Radioactive iodine (131I) therapy is also not recommended for breast-feeding women because radioactive iodine may accumulate in the breast and be excreted via milk [16]. Considering that thyroid cancer has a slow growth, radioactive iodine (131I) therapy may be delayed in pregnant DTC patients after delivery, short term breast-feeding is recommended for 6-8 weeks under close monitoring, and then radioactive iodine therapy is performed [17]. Once radioactive iodine therapy is performed, breast-feeding should be stopped and is not allowable before the second delivery [16]. Dopaminergic drugs may be used to reduce the accumulation of 131I in the breast, but this treatment should be applied cautiously and physicians should communicate with patients.

Thyroid Hormone Replacement Therapy after Surgery for DTC

There are substantial changes in the thyroid and hormones secreted by the thyroid during the normal pregnancy. hCG which increases in the first trimester has similar structure to TSH and may promote the release of thyroxin, resulting in transient reduction in serum TSH[21]. In addition, elevated estrogen may increase the thyroid-binding globulin by 2-3 times, and the thyroid-binding globulin may change the serum contents of total thyroxin (T4), triiodothyronine (T3) and free thyroxin (FT) [22]. Moreover, the detection of thyroid hormones (especially the TSH) during pregnancy is susceptible to the interference by other hormones, gestational age and times of delivery [23]. The differences in the techniques and physiology, the measurement of thyroid hormones during pregnancy should be further modified, and the normal

references should be determined according to the gestational age.

The thyroid hormone replacement therapy is required in most pregnant women after total or subtotal thyroidectomy for DTC. Thyroid hormones of appropriate amount are important for both mother and fetus, and even mild thyroid dysfunction may cause adverse outcome to mother and/or fetus. Previous studies have shown that the intelligence quotient of children of untreated women with insidious hypothyroidism during pregnancy is lower than that of normal peers [24]. A one-time increment of TSH during pregnancy may increase the risks for abortion and fetal or neonatal death by 60% [25]. Moreover, the requirement for thyroid hormone replacement therapy in the first trimester is more urgent than in the second or third trimester [26]. On the contrary, subclinical hyperthyroidism with reduced TSH may not cause an adverse outcome of pregnancy [22].

Generally, blood TSH is an important indicator used to evaluate the efficacy of thyroid hormone replacement therapy after surgery for DTC in pregnancy. However, the defects in the detection of blood TSH and the complexity of physiology during pregnancy pose difficulties in the management of pregnant women. There is evidence showing that thyroid hormone at 100 μg/d is required to normalize the thyroid hormone during normal pregnancy for non-pregnant women after total thyroidectomy [22]. Thus, some physicians propose that DTC patients after surgery should consult physicians and receive relevant examinations to adjust the dose and usage of drugs to maintain TSH at 0.5-2.5 mIU/L. Once pregnancy is confirmed, additional thyroid hormone at 200 μg is required weekly when TSH is ≥ 1.5 mIU/L; additional thyroid hormone at 100 μg is required weekly when TSH is <1.5 mIU/L. Iron and calcium are commonly used before and after pregnancy and may reduce the absorbance of thyroid hormone. Thus, the iron/calcium and thyroid hormone should be administered separately [16]. The half-life of T4 is relatively long and thyroid hormone should be administered for at least 4-6 weeks before the plasma T4 becomes stable, and the interval between 2 detections of TSH is also 4-6 weeks, according to which the dose and usage of thyroid hormone are adjusted.

Management and Follow up of Pregnant Women with DTC

The management and follow up of pregnant women with DTC should be performed according to the types of risk factors. Periodic physical examination of the thyroid and monitoring of Tg and TSH thrice are required for a majority of pregnant DTC women with low risk (one lasting 1 month in first, second and third trimester), and other radioactive or stimulating examinations are not recommended. Although the serum Tg changes significantly in the pregnancy, the overall fluctuation is in the normal range in the absence of pregnancy [27]. For pregnant DTC women with high risk or women with recurrent DTC in the pregnancy, periodic examination of the thyroid should be strictly and carefully performed thrice as above mentioned, and additional neck ultrasound examination is also required. The progression of DTC is determined according to the Tg before and during pregnancy and results from neck ultrasound examination, and corresponding strategy is proposed for the therapy of DTC.

After reviewing the clinical management of DTC during pregnancy in previous studies, the therapy is usually intermittent, not integrated and not consistent among studies although multi-disciplinary proposals and therapies have been proposed by some experts [28]. In recent years, some physicians attempt to comprehensively and multi-disciplinarily treat DTC during pregnancy with the help of surgeons, radiologists, pathologists, experts in the obstetrics and gynecology, endocrinologist and nurse specialist, assuring that patients receive more rational strategies for the management and therapy of DTC and achieve better therapeutic efficacy [29]. This practice should be promoted and generalized [29].

Summary and Prospect

Pregnancy is related to the pathogenesis and prognosis of DTC. Surgical intervention and corresponding adjunctive therapy performed after delivery are relatively safe and predict a good prognosis for pregnant women with DTC. Surgery should be performed in the second trimester (before 24 weeks gestational age) once surgical intervention is necessary for DTC in pregnancy. Radioactive iodine therapy is not allowable during pregnancy and may be performed after breast-feeding for 6-8 weeks. Thyroid hormone replacement therapy may be conducted according to the post-operative thyroid hormone, and the use of thyroid hormone during pregnancy should be cautious. The accurate detection of thyroid hormone is dependent on the development of molecular technique. Periodic detection of Tg and TSH as well as physical examination of the thyroid thrice during pregnancy are required to determine the strategies for the therapy of DTC. Multi-disciplinary therapy of DTC in pregnancy is a future direction in the management of pregnant women with DTC.

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***Correspondence to:**

Xiaojuan Jiang

Department of Breast and Thyroid Surgery,

Research Institute of Surgery,

Daping Hospital, Third Military Medical University,

Chongqing, China.

Tel: 8602368757951

E-mail: ldl1967@sina.com; 1205786152@qq.com

Donglin Luo

Department of Breast and Thyroid Surgery,

Research Institute of Surgery,

Daping Hospital, Third Military Medical University,

Chongqing, China.

Tel: 8602368757951

E-mail: yanjie1986514@163.com