



## Research Paper

## Pregnancy outcomes in papillary thyroid cancer survivors : A retrospective cohort study



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## ABSTRACT

**Objective:** The purpose of this study was to evaluate the pregnancy outcomes among papillary thyroid cancer survivors.**Methods:** 65 cases singleton gravidas of papillary thyroid cancer survivors treated in the Department of Obstetrics, Peking University People's Hospital between January 2011 and January 2020 were selected retrospectively as the study group, and 130 cases of singleton pregnancy during the same time were randomly selected as the control group. The differences in general conditions, maternal and fetal complications between the two groups were analyzed. Risk factors of maternal complications and fetal malformation in patients with papillary thyroid cancer survivors were analyzed. Data was analyzed with *t*-test,  $\chi^2$  test and logistic regression for statistical differences. **Results:** Totally 65 cases of papillary thyroid cancer with 70 pregnancies were analyzed, which including 65 cases achieved live birth, 5 cases underwent induced labor because of fetal malformation. The study group showed higher incidence in gestational diabetes(20% vs 10%), cesarean section(39.1% vs 24.6%), postpartum hemorrhage( $350 \pm 193$  ml vs  $290 \pm 181$  ml) and fetal malformation(5.7% vs 1.5%), and lower live birth rate(91.4% vs 99.2%) ( $P < 0.05$ ). Multivariate analysis by logistic regression found that the patient's age, thyroid function, operation mode and postoperative I-131 treatment were not the risk factors which may affect the pregnancy outcomes or fetal malformation.**Conclusion:** Elevated maternal and fetal complications were observed among pregnancies in papillary thyroid cancer survivors. Management of these survivors may require a careful gestation monitoring, and further investigation is needed.

## 1. Introduction

The incidence of thyroid cancer has been rising all over the world over the past decades.<sup>1</sup> The increase is affecting all age groups with an increased risk among women below 45 years old.<sup>2</sup> Papillary thyroid cancer is the most common type of differentiated thyroid cancer. Due to the progression of screening technology, the proportion of patients with early thyroid papillary cancer is increasing. For treatment, total or near total thyroidectomy is the standard treatment for patients diagnosed with thyroid cancer, followed by radioactive iodine administration as an adjunctive treatment in differentiated thyroid tumors with high risk

factors.<sup>3</sup> Several retrospective studies discussed the obstetric outcomes of thyroid cancer survivors reporting conflicting results regarding the risk factors of postpartum hemorrhage, gestational diabetes mellitus, cesarean section, pre-eclampsia, and preterm birth.<sup>4-6</sup> In this study, the clinical data of 65 pregnant women with history of papillary thyroid cancer were collected retrospectively to explore its influence on pregnancy outcomes and try to analyze the relative risk factors.

## 2. Materials and methods

Between January 2011 and January 2020, 65 patients with

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postoperative pregnancy of papillary thyroid cancer from January 2011 to January 2020 with complete clinical data were selected retrospectively as the study group. The patients with hypertension, diabetes, autoimmune diseases and hematological diseases before pregnancy were excluded. At the same time, according to the principle of 1:2, 130 cases of singleton pregnancy delivered in our hospital over the same period were randomly selected as the control group according to the patient's identification number. The control group had a previous history of thyroid disease and malignant tumor before pregnancy were excluded. General conditions (age and primiparas, neonatal weight, week of delivery and live birth), maternal complications (gestational diabetes mellitus, hypertensive disorder complicating pregnancy, oligohydramnios, premature delivery, premature rupture of membranes, cesarean section and postpartum hemorrhage) and fetal complications (fetal malformation, intrauterine growth restriction, neonatal asphyxia) were compared between the study group and control group.

Risk factors including thyroid function situation, operation mode, I-131 treatment and the interval after treatment were analyzed with regards to maternal complications and fetal malformation in patients with papillary thyroid cancer survivors were also analyzed. Thyroid function during pregnancy was retrospectively analyzed, which including normal, subclinical hyperthyroidism, and subclinical hypothyroidism. The inclusion criteria of subclinical hyperthyroidism group was: thyroid stimulating hormone (TSH) during pregnancy below 0.1 mU/L, with normal free triiodothyronine (FT3) and tetraiodothyronine (FT4). The inclusion criteria of subclinical hypothyroidism group was: TSH above 4.0 mU/L, with normal FT3 and FT4.<sup>3</sup>

### 2.1. Statistical analysis

SPSS 22.0 was used for statistical analysis. Quantitative data were showed as  $x \pm s$ , and *t*-test was used for comparison between the two groups. Categorical data were expressed by frequency and rate, and  $\chi^2$  test was used for inter group comparison. Logistic regression was used to analyze the risk factors of adverse maternal and fetal outcomes.  $P < 0.05$  was regarded as statistically significant.

## 3. Results

### 3.1. General information

In 65 cases of thyroid cancer, there were 26 patients with total thyroidectomy and 39 patients with partial thyroidectomy. Only 6 patients were treated with I131 after operation (according to high-risk factors). The median interval from the end of treatment (surgery or I131) to pregnancy was 2.5 years. All patients were treated with thyroxine tablets after operation according to the principles of thyroid cancer treatment. There were 17 patients with abnormal thyroid function during pregnancy, with 14 patients with subclinical hyperthyroidism and 3 patients with subclinical hypothyroidism. Totally 65 patients with thyroid cancer had 70 pregnancies, which including 65 cases achieved live birth, 5 cases underwent induced labor because of fetal malformation.

### 3.2. Comparison of maternal and fetal outcomes between study group and control group

Compared to the control group, the study group showed earlier gestational age of delivery; higher incidence of gestational diabetes (20% vs 10%), cesarean section (39.1% vs 24.6%), postpartum hemorrhage (350 ± 193 ml vs 290 ± 181 ml) and fetal malformation (5.7% vs 1.5%), and lower live birth rate (91.4% vs 99.2%) ( $P < 0.05$ ). There was no difference in the incidence of maternal and fetal outcomes such as age, proportion of primipara, neonatal weight, preterm birth, intrauterine fetal death, intrauterine growth restriction, neonatal asphyxia, gestational hypertension, oligohydramnios and premature rupture of membranes (see Table 1 for details).

**Table 1**

Maternal and fetal outcomes of postoperative patients with thyroid papillary carcinoma complicated with pregnancy [( $x \pm s$ ), cases].

	Thyroid cancer group N = 65 <sup>a</sup>	Control group N = 130	P value
<b>General conditions</b>			
Age [ $x \pm s$ ]	33.3 ± 4.2	32.3 ± 3.7	0.092
Primiparas [n (%)]	42(64.6%)	82(63.1%)	0.725
Week of delivery (w)	38.7 ± 1.4	39.1 ± 1.3	<b>0.013</b>
Neonatal weight (g) ( $x \pm s$ )	3288 ± 431	3378 ± 429	0.172
Live birth [n(%)]	64(91.4%)	129(99.2%)	<b>0.008</b>
<b>Maternal complications</b>			
Gestational diabetes mellitus [n(%)]	14(20%)	13(10%)	<b>0.041</b>
Hypertensive disorder complicating pregnancy [n(%)]	6(8.7%)	10(7.7%)	0.512
Oligohydramnios [n(%)]	4(5.7%)	3(2.3%)	0.196
Premature rupture of membranes [n(%)]	11(15.7%)	23(17.7%)	0.443
Premature delivery [n(%)]	3(4.3%)	1(0.7%)	0.124
Postpartum hemorrhage (ml) ( $x \pm s$ )	350 ± 193	290 ± 181	<b>0.046</b>
Cesarean section [n(%)]	25(39.1%)	32(24.6%)	<b>0.029</b>
<b>Fetal complications</b>			
Intrauterine growth restriction [n(%)]	1(1.4%)	2(1.5%)	0.719
Neonatal asphyxia [n(%)]	1(1.4%)	1(0.8%)	0.579
Fetal malformation [n(%)]	4(5.7%)	1(1.5%)	<b>0.033</b>

<sup>a</sup> 70 pregnancies in the 65 cases of thyroid cancer, and the proportion in this column except primipara was calculated according to the number of pregnancies.

### 3.3. Logistic regression analysis of risk factors for maternal and fetal adverse outcomes

The risk factors of maternal complications and fetal malformation were further analyzed, logistic regression analysis showed that thyroid function, operation mode, postoperative I-131 treatment and pregnancy interval were not the influencing factors of maternal complications and fetal malformation. ( $P > 0.05$ ) (Table 2).

## 4. Discussion

Thyroid cancer is a disease which arises mostly in women, with a considerable proportion in the reproductive age.<sup>7</sup> In this study we investigated the pregnancy outcomes and related risk factors in papillary thyroid cancer survivors. The major finding of this study is the higher proportion of maternal and fetal complications among pregnancies in papillary thyroid cancer survivors.

Previous studies rarely focused on the maternal and fetal outcomes of patients with thyroid cancer complicated with pregnancy, and the conclusions are not consistent. A retrospective study analyzing postoperative thyroid cancer survivors found no difference in pregnancy preeclampsia, gestational diabetes mellitus, cesarean section, postpartum hemorrhage, preterm delivery and low birth weight infants, but the incidence of implantation disease in the thyroid cancer group increased.<sup>4</sup> A retrospective cohort study on a U.S. inpatient sample database, including 581 pregnant women diagnosed with thyroid cancer, showed a higher incidence of preeclampsia, cesarean section, midwifery, blood transfusion, deep vein thrombosis and prolonged hospital stay in the thyroid cancer group.<sup>5</sup> Another study showed that maternal and fetal outcomes in 8 patients with thyroid papillary carcinoma complicated with pregnancy. Compared with the control group, the study group had no differences in abortion, live birth, cesarean section, and neonatal birth weight, but the incidence of neonatal low Apgar score increased.<sup>6</sup> Our preliminary study suggests that the incidence of complications during pregnancy, including gestational diabetes mellitus, cesarean section, postpartum hemorrhage and fetal malformation, is increased in patients with papillary thyroid carcinoma after treatment.

Thyroid hormone plays a key role in pregnancy maintenance and fetal development. The physiological requirement of thyroid hormone

**Table 2**

Logistic regression analysis of risk factors of maternal complications and fetal malformation in patients with papillary thyroid cancer survivors.

Risk factors	Maternal complications			Fetal malformation		
	OR	95%CI	P value	OR	95%CI	P value
Thyroid function	2.524	0.797–7.997	0.116	1.305	0.199–8.574	0.782
Operation mode	1.219	0.389–3.825	0.734	6.843	0.652–71.794	0.109
I-131 treatment	0.936	0.760–1.153	0.534	0.863	0.610–1.323	0.541
Pregnancy interval	0.686	0.182–2.581	0.577	0.707	0.188–2.664	0.608

increases about 30%–50% after pregnancy gradually.<sup>8,9</sup> A systematic review revealed that subclinical hypothyroidism in pregnancy is associated with multiple adverse maternal and neonatal outcomes, such as pregnancy loss, placental abruption, premature rupture of membranes and neonatal death.<sup>10</sup> Studies showed that hyperthyroidism in pregnancy was associated with abortion, pregnancy induced hypertension, premature birth, low birth weight infants, fetal growth restriction and stillbirth.<sup>11</sup> Another report confirmed that when TSH <1.2 mU/L, only 17.2% of women need to increase the dose of L-T4 during pregnancy.<sup>12</sup> Because of the postoperative suppressive therapy, the growth of L-T4 in these survivors was limited in our study, which 14 patients with subclinical hyperthyroidism and 3 patients with subclinical hypothyroidism.

This study also found that the incidence of fetal malformations in the study group increased significantly (5.7% VS 1.5%). Whether it was directly related to thyroid cancer or not, our study has not yet reached a clear conclusion. The observation of this phenomenon highlight the need for a larger sample size and the design of a prospective cohort study to reveal whether there is an internal correlation.

Total or near total thyroidectomy is the standard treatment for patients diagnosed with thyroid cancer, followed by radioactive iodine administration as an adjunctive treatment in differentiated thyroid tumors. I-131 treatment can reduce the long-term incidence rate of differentiated thyroid cancer and may improve survival rate. Among patients treated with I-131, 30% are expected to have transient amenorrhea or irregular menstruation, which usually disappears within one year. Male patients can show transient spermatogenesis disorder associated with elevated FSH, which can be reversed within 18 months after I-131 treatment. However, the risk of persistent male or female gonadal dysfunction may increase in some patients after repeated or highly accumulated radioactive iodine treatment. The effects of I-131 in either parent, on subsequent pregnancy outcomes and offspring have not been recorded.<sup>13,14</sup> Whether postoperative radiotherapy for thyroid papillary carcinoma can increase adverse outcomes in the mother and fetus and the occurrence of fetal malformation is still controversial.<sup>15,16</sup> I-131 treatment is generally safe, but most authorities recommend avoiding pregnancy up to one year after I-131 treatment, to have allow for complete replacement of irradiated sperm and reverse transient ovarian injury. The average pregnancy time of patients in this study group after radioactive I-131 treatment was 2.5 years. The risk factor analysis did not suggest that thyroid cancer treatment could increase the incidence of adverse maternal and fetal outcomes and fetal malformations.

As a retrospective study, comprehensive evaluation of the clinicopathological data of this article is limited and it is difficult that measurements of thyroid function could cover the entire pregnancy. Due to the limited clinical data of this research, the existing conclusions need to be further verified by expanding samples.

In conclusion, the incidence of maternal and fetal complications during pregnancy, including gestational diabetes mellitus, cesarean section, postpartum hemorrhage and fetal malformation, was increased in patients in papillary thyroid cancer survivors. Therefore, we suggest that monitoring of these survivors should be strengthened and further investigation is needed.

#### Ethical statement and patient's consent

Informed consent was waived because of the retrospective nature of

this study, which was approved by the Institutional Review Board of the Peking University People's Hospital.

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#### Declaration of competing interest

We have no conflict of interest to declare.

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