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Follow-up and evaluation of the pregnancy outcome in women of reproductive age with Graves' disease after ^{131}Iodine treatment

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ABSTRACT

The aims of the present study were to analyze the outcomes of pregnancy, after ^{131}I treatment, in patients of reproductive age with Graves' hyperthyroidism and to investigate the effects, if any, of the ^{131}I treatment on the mothers and newborns. From 2009 to 2014, 257 pregnant female patients with Graves' hyperthyroidism in the outpatients at the Department of Nuclear Medicine and 166 healthy pregnant women from the Department of Obstetrics at Sun Yat-Sen Memorial Hospital were included in our study. They were divided into a ^{131}I therapy group (n = 130) and an anti-thyroid drug (ATD) group (n = 127) according to their therapy before conception. The neonatal gender, rate of preterm birth, body weight ratio and occurrence of low birth weight [except for higher rates of abortion (odds ratio; OR = 2.023) and cesarean delivery (OR = 1.552) in patients with Graves' hyperthyroidism] showed no statistically significant differences from those of the healthy group ($P > 0.05$). The level of intrauterine growth restriction did not differ between the Graves' hyperthyroidism group and the healthy group (8 vs 2, 3.0% vs 1.2%). The outcomes of pregnancy among the ^{131}I therapy group, ATD group and healthy group also showed no significant differences. Of the patients treated with ^{131}I, no significant differences were observed in the outcomes of their pregnancies, whether they received propylthiouracil (PTU), levothyroxine or no additional drug treatment during pregnancy. Women with hyperthyroidism who were treated with ^{131}I therapy could have normal delivery if they ceased ^{131}I treatment for at least six months prior to conception and if their thyroid function was reasonably controlled and maintained using the medication: anti-thyroid drug and levothyroxine before and during pregnancy.

KEYWORDS: Graves' disease, Iodine radioisotopes, pregnancy outcome

INTRODUCTION

Currently, there are three major therapies for the treatment of hyperthyroidism—anti-thyroid drugs [mainly propylthiouracil (PTU) or methimazole (MMI)], radioactive iodine (^{131}I), and thyroidectomy. Over half a century, oral administration of ^{131}I has been proven to be an effective and widely used approach for the treatment of thyroid diseases. However, ^{131}I therapy in pregnant women is contraindicated because it may cause damage to the fetus. Therefore, the American Thyroid Association (ATA) suggests that a pregnancy test should be conducted for female patients of childbearing age 48 h before the ^{131}I therapy for exclusion of pregnancy [1]. However, ^{131}I therapy is still an option for female patients before pregnancy. Many patients, especially children, adolescents, and female patients of childbearing age, are not willing to undergo ^{131}I therapy because of the irradiation damage and hypothyroidism that occurs with an annual incidence of 2–3% after ^{131}I therapy [2].

Graves' disease, which is mainly identified in young women, is the most common cause of hyperthyroidism. Therefore, understanding the effects and safety of ^{131}I therapy in women of reproductive age is critically important. Many studies have evaluated the effects

of ^{131}I therapy on fetal growth and development, and pregnancy outcomes in pregnant patients with hyperthyroidism [3, 4], thyroid cancer patients [5, 6], and children and adolescents with hyperthyroidism [7–9]. The results from these studies suggest that ^{131}I therapy caused no significant radiation damage. However, the effects and pregnancy outcomes of ^{131}I therapy in female patients of childbearing age have not been fully understood. In the present study, we evaluated the pregnancy outcomes of female Graves' disease patients who received ^{131}I therapy at least six month prior to the pregnancy. Our results will provide evidence to guide the ^{131}I therapy for Graves' disease patients who are of childbearing age.

MATERIALS AND METHODS

This retrospective study was conducted in the Nuclear Medicine Department, Sun Yat-Sen Memorial Hospital, based on the medical records of female Graves' disease patients who became pregnant at least six months after ^{131}I therapy or antithyroid drug (ATD) treatment for hyperthyroidism. Healthy women who were pregnant at the same time (from 2009 to 2014) in the Obstetrics Department of the Sun Yat-Sen Memorial Hospital were included in the present study as controls. The study was approved by the Institutional Ethics Committee of the Sun Yat-Sen Memorial Hospital.

A total of 257 Graves' disease patients who became pregnant at least 6 months after ^{131}I therapy or ATD treatment were included in this retrospective study.

Patients for whom Graves' disease diagnosis was made during the pregnancy and abnormal thyroid function was not identified before pregnancy were excluded from this study. In addition, patients who had other thyroid diseases or other diseases, and Graves' disease patients who underwent thyroid surgery before pregnancy were also excluded from the present study. The average age of the 257 Graves' disease patients was 29 years (20–42 years) and the disease duration ranged from 8 to 35 months. A total of 166 healthy women with an average age of 28 years (20–41 years) were included in this study as controls. Of the 257 Graves' disease patients, 130 and 127 patients underwent ^{131}I therapy and ATD treatment, respectively. In both ^{131}I therapy and ATD treatment groups, the patients were divided into three subgroups according to the drugs used during pregnancy: the PTU group, the levothyroxine group and the 'no drug' group. Serum thyroid function test was conducted monthly to adjust the dose of ATDs to maintain a normal thyroid function. Antenatal care was also conducted monthly to record the pregnancy status and the health conditions of fetuses. Pregnancy outcomes were evaluated based on both the maternal bearing status and production mode, and the neonatal status, including premature birth (≥28 but <37 weeks) or full-term birth (≥37 but <42 weeks), neonatal gender, and birth weight (normal weight: ≥2.5 and ≤4.0 kg; abnormal weight: >2.5 or <4.0 kg).

Statistical analyses

Statistical analyses were conducted using SPSS 13.0 software. Measurement data were expressed as mean ± standard deviation. The Wilcoxon test or *t* test was used to compare the difference in measurement data between two groups. A one-way ANOVA or Kruskal–Wallis test was used to analyze the differences in measurement data between the three groups. Quantitative data was analyzed using the χ^2 test and the Fisher exact test. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Comparison of pregnancy outcomes between Graves' disease patients who have undergone ^{131}I therapy or ATD treatment and healthy women

Of the 257 Graves' disease patients who had undergone ^{131}I therapy or ATD treatment, 222 patients gave birth to 234 neonates and 35 patients (13%) had an abortion. Of the 166 healthy women, 154 women gave birth to 154 neonates and 12 women (7%) had abortion due to spontaneous abortion (n = 4), missed abortion (n = 2), congenital heart disease (n = 2), anencephaly (n = 1), intrauterine growth restriction (IUGR) (n = 1) or low progesterone of mother (n = 2). The pregnancy outcomes of the Graves' disease patients who had undergone ^{131}I therapy or ATD treatment and of the healthy women are shown in Table 1.

No significant differences in the intrauterine growth restriction, premature birth, neonatal gender, or birth weight were identified between the 257 Graves' disease patients who had undergone ^{131}I therapy or ATD treatment and the 166 healthy women. However, the Graves' disease patients who had undergone ^{131}I therapy or ATD treatment had significantly higher rates of abortion (χ^2 = 4.169, P = 0.041, OR = 2.036, 95% CI: 1.024–4.048) and cesarean delivery (χ^2 = 4.129, P = 0.042, OR = 1.552, 95% CI: 1.015–2.375) than the healthy women.

Comparison of pregnancy outcomes between Graves' disease patients who had undergone ^{131}I therapy, Graves' disease patients who had undergone ATD treatment, and healthy women

One hundred and twenty-five, three and two patients received one, two and three oral administrations of ^{131}I therapy, respectively (111–740 MBq). Of the 130 Graves' disease patients who had undergone ^{131}I therapy, 114 women had normal delivery and 16 women had no delivery: spontaneous abortion (n = 3), missed abortion (n = 1), IUGR (n = 6), harelip plus heart dysplasia (n = 1), induced abortion due to excessive thyroid stimulating hormone (TSH) level (n = 3), unwilling to reveal relevant details that had nothing to do with the treatment (n = 2). Four patients gave birth to two babies and one patients gave birth to three babies, separately. In addition, three patients gave birth to twins (Table 2). Of the 127 Graves' disease patients who had undergone ATD treatment, (age: mean 29.21, range 22–40), 108 patients gave birth to 111 neonates and 19 patients had no delivery: spontaneous abortion (n = 7), missed abortion (n = 1), IUGR (n = 2), induced abortion due to fetal congenital heart disease (n = 1) and fetal deformities (n = 1), unwilling to reveal relevant details that had nothing to do with the treatment (n = 7), fetal congenital heart disease and one had fetal deformities with B ultrasound. Two patients gave birth to two babies, and one patient gave birth to twins (Table 2).

In the ^{131}I therapy and ATD treatment groups, patients were treated with drugs (PTU or levothyroxine) or without drugs during pregnancy. In the ^{131}I group, 112 patients and 18 (13.8%) patients,

Table 1. Comparison of pregnancy outcomes between Graves' disease patients who have undergone ^{131}I therapy or ATD treatment and healthy women

Parameters	Group of Graves hyperthyroidism ($n = 257$)	Group of healthy women ($n = 166$)	t/χ^2 value	P value	OR value	95% CI
Age (years)	28.75 ± 3.66	28.03 ± 3.58	2.678	0.008	–	–
Bearing status						
Delivery	222	154	4.169	0.041	2.023	1.018–4.022
Abortion	35 (13%)	12 (7%)				
Intrauterine growth restriction	8 (3.0%)	2 (1.2%)	0.751	0.386	–	–
Production mode						
Cesarean	100 (42%)	50 (32%)	4.129	0.042	1.552	1.015–2.375
Natural birth	134	104				
Pregnancy week						
Full-term birth	211	142	0.47	0.493	–	–
Preterm birth	23	12				
Neonatal gender						
Male	128	69	3.639	0.056	–	–
Female	106	85				
Birth weight (kg)	3.14 ± 0.50	3.15 ± 0.45	0.261	0.794	–	–
Low birth weight	14 (6.0%)	7 (4.5%)	0.375	0.540	–	–
Birth weight ratio						
Normal weight	213	145	1.276	0.259	–	–
Non-normal weight	21	9				

OR = odds ratio; CI = confidence interval.

respectively, achieved stable disease with and without the use of drugs during pregnancy. In the ATD group, 106 and 21 (16.5%) patients, respectively, achieved stable thyroid function with and without the use of drugs during pregnancy. No significant difference was identified in patients treated with drugs and those treated without drugs during pregnancy in both group ($\chi^2 = 0.368$, $P = 0.548$). On the other hand, the probability of taking levothyroxine in the ^{131}I treatment group was significantly higher (OR = 2.175, 95% CI 1.266–3.739) than in the ATD group.

There was no statistically significant difference in abortion ($\chi^2 = 4.627$, $P = 0.099$), IUGR ($\chi^2 = 3.568$, $P = 0.191$), cesarean delivery ($\chi^2 = 5.551$, $P = 0.062$), preterm birth ($\chi^2 = 0.471$, $P = 0.79$), neonatal gender ($\chi^2 = 4.587$, $P = 0.101$) or birth weight ratio ($\chi^2 = 5.046$, $P = 0.08$) between the three groups. Birth weights in the ^{131}I therapy group, ADT group and healthy group were 3.15 ± 0.58 kg (normal birth weight: $n = 108$; low birth weight: $n = 9$; and fetal macrosomia: $n = 6$), 3.14 ± 0.40 kg (normal birth weight: $n = 105$; low birth weight: $n = 5$ and fetal macrosomia $n = 1$) and 3.15 ± 0.45 kg (normal body weight: $n = 145$; low birth weight: $n = 7$ and fetal macrosomia: $n = 2$), respectively. No significant difference was identified in birth weight between the three groups ($F = 0.037$, $P = 0.964$).

Pregnancy outcomes for the different drugs used in the ^{131}I therapy group during pregnancy

The group who had undergone ^{131}I therapy (130 patients) was divided into three subgroups according to the drugs used, based on the levels of free triiodothyronine (FT3), free thyroxine (FT4), and TSH during pregnancy: PTU (43 cases, 33%), levothyroxine (69 cases, 53%) and no drug (18 cases, 14%). No significant differences were identified in bearing status, production mode, pregnancy week, neonatal gender, birth weight or birth weight ratio among the patients in the three subgroups. From the data in Table 3, we know that no matter what drug was used after ^{131}I treatment during pregnancy, it did not influence the pregnancy outcomes of the patients ($P > 0.05$).

Table 2. Comparison of pregnancy outcomes between Graves' disease patients who have undergone ^{131}I therapy, Graves' disease patients who have undergone ATD treatment, and healthy women

Parameters	Group of ^{131}I therapy (n = 130)	Group of anti-thyroid drug therapy (n = 127)	Group of healthy women (n = 166)	F/χ^2 value	P value
Age (years)	28.90 ± 3.69	29.21 ± 3.90	28.03 ± 3.58	3.790	0.023
Bearing status					
Delivery	114	108	154	4.627	0.099
Abortion	16 (12.3%)	19 (15.0%)	12 (7.2%)		
Intrauterine growth restriction	6 (4.6%)	2 (1.6%)	2 (1.2%)	3.568	0.191
Delivery mode					
Cesarean	57 (46.3%)	43 (38.7%)	50 (32.4%)	5.551	0.062
Natural birth	66	68	104		
Pregnancy week					
Full-term birth	111	100	142	0.471	0.79
Preterm birth	12 (9.8%)	11 (9.9%)	12 (7.8%)		
Neonatal gender					
Male	71	57	69	4.587	0.101
Female	52	54	85		
Birth weight (kg)	3.15 ± 0.58	3.14 ± 0.40	3.15 ± 0.45	0.037	0.964
Low birth weight (kg)	9 (7.9%)	5 (4.7%)	7 (4.7%)	1.276	0.528
Birth weight ratio					
Normal weight	108	105	145	5.046	0.08
Non-normal weight	15	6	9		

$P < 0.05$ was taken to indicate that the difference was statistically significant.

DISCUSSION

Several studies [4, 8] have shown that developing hyperthyroidism before or during pregnancy is associated with an increased risk of maternal and fetal complications, such as miscarriage, stillbirth, preterm birth, induction, and the occurrence of severe preeclampsia, placental abruption or ICU admission. In our research, in cases of Graves' hyperthyroidism where thyroid function was controlled at normal levels prior to conception, no difference in preterm birth rate was observed between the Graves' hyperthyroidism group and the healthy group. Perhaps, as Neelam Aggarawal *et al.* [3] found, women with hyperthyroidism before pregnancy whose condition was well controlled had a lower risk of preterm birth, IUGR and abrupted placentae compared with women whose hyperthyroidism was not well controlled. This study suggested that patients who keep stable thyroid function during pregnancy would have a lower risk of delivery complications. A study by Ohrling *et al.* [10] reported that, 5 years after treatment, mothers with Graves' hyperthyroidism gave birth to children of lower birth weight, shorter birth length, and average head circumference. However, in our study, no differences were observed in terms of preterm birth, IUGR, neonatal gender or body weight, with the exception of abortion and cesarean delivery ($P < 0.05$), between patients with Graves' hyperthyroidism and healthy women. Graves' hyperthyroidism was associated with increased risk of abortion (OR = 2.023) and cesarean delivery (OR = 1.552) compared with the healthy group in our study. This result is consistent with a previous larger population–based study [10]. The inconsistencies among the studies may be derived from an inadequate sample size in our study, the limited follow-up time, the inclusion and exclusion criteria of some patients, lack of sufficiently large datasets, and possibly unadjusted bias. From the numerous studies, it is apparent that hyperthyroidism, whether controlled or uncontrolled, may result in many types of maternal and neonatal complications. Therefore, optimal treatment and management, before and during pregnancy, is of utmost importance for women with hyperthyroidism.

^{131}I is a short-range beta decay radionuclide with a half-life of 8.1 days. When a patient with hyperthyroidism is given therapeutic doses of ^{131}I, nearly all of its energy is absorbed by the thyroid

Table 3. Pregnancy outcomes for different drugs used for the ^{131}I therapy group during pregnancy

Parameters	PTU group ($n = 43$)	Levothyroxine group ($n = 69$)	No medicine group ($n = 18$)	t/χ^2 value	P value
Age (years)	29.99 ± 3.61	27.09 ± 3.79	28.56 ± 2.55	8.850	0.000
Bearing status					
Delivery	38	61	15	0.368	0.832
Abortion	5 (13.1%)	8 (11.6%)	3 (16.7%)		
Delivery mode					
Cesarean	20 (46.3%)	32 (50%)	5 (31.3%)	1.81	0.404
Natural birth	23	32	11		
Pregnancy week					
Full-term birth	40	57	14	0.803	0.757
Preterm birth	3 (6.97%)	7 (10.9%)	2 (12.5%)		
Neonatal gender					
Male	20	42	9	3.867	0.145
Female	23	22	7		
Birth weight (kg)	3.13 ± 0.63	3.11 ± 0.41	3.28 ± 0.71	0.532	0.589
Birth weight ratio					
Normal weight	41	53	14	3.845	0.125
Non-normal weight	2	11	2		

OR = odds ratio; CI = confidence interval; $P < 0.05$ was taken to indicate that the difference was statistically significant.

during decay [11]. The ATA guideline put forward that the general recommendation period for women of childbearing age should not become pregnant <4–6 months following ^{131}Iodine therapy, because that is a sufficient period for complete elimination of the radionuclide [1]. Since ^{131}I is rarely distributed outside the thyroid tissue and has a short residual time [11]. The radiation for a dose of ^{131}I for the treatment of hyperthyroidism is low in the bone marrow, gonads, liver, spleen, and gastrointestinal tract. Edmonds [12] reported that ^{131}I doses in body organs and tissues such as the colon, liver, pancreas, lungs, breast, uterus, ovaries, testis, kidneys and bone marrow were estimated at <10 cGy. Thompson *et al.* [13] pointed out that the dose absorbed by an ovary was 0.2 cGy if 185 MBq ^{131}I was given, approximately equivalent to the X-ray dose delivered by one barium enema, intravenous pyelography or hysterosalpingography, and that such a dose had no influence on fertility. Transient ovarian function failure occurred in thyroid cancer patients after thyroidectomy followed by thyroid remnant ablation with ^{131}I (at least 100 mci), and no correlation was observed between the impairment of ovary function and the radioactive iodine dose absorbed [14].

Patients in our ^{131}I treatment group had controlled, normal thyroid function prior to and during pregnancy, and were treated with small doses of PTU and levothyroxine during pregnancy. Until the termination of pregnancy, there were no statistically significant differences in abortion rates, IUGR, cesarean birth, preterm birth, neonate sex or low birth weight between the ^{131}I therapy group, the ATD group and the healthy group. This suggests that patients with hyperthyroidism treated with ^{131}I can have normal pregnancies and that such therapy has no influence on mothers and newborns. Our study only analyzed birth characteristics for the patients and newborns, however, and lacked long-term follow-up data, so incidences of cancer and leukemia were not identified.

In our study, no difference was seen in the outcomes of pregnancy between the ATD, ^{131}I and healthy groups. ^{131}I therapy has become an increasingly popular treatment for patients of hyperthyroidism because of the adverse effects, such as liver injury and embryopathy, associated with the ATD drugs PTU [15, 16], MMI and carbimazole (CM) [17, 18]. ^{131}I therapy has many advantages over other types of treatments, such as simple application, definitive curative effect, low recurrence rate, and low cost. A number of studies including long-term follow-up of children and adolescents with hyperthyroidism treated with ^{131}I showed that ^{131}I therapy was a safe and effective treatment method, and that the patients' reproductive histories and the health of their offspring were similar to those of the general population. There were no people of deaths, cancer and leukemia in the patients or their offspring [19, 20]. One retrospective study [21] reported that use of ^{131}I therapy prior to pregnancy was associated with a lower incidence of postpartum

thyrotoxicosis compared with their thyroidectomy and ATD groups, which was thought to be due to histological changes, including various degrees of fibrosis in the thyroid gland after radioiodine therapy and a possible decrease in the responsiveness of the remaining cells. However, it must be noted that one study [22] pointed that the risk of stomach cancer did increase over time (follow-up at 15 years) in patients with hyperthyroidism after ^{131}I therapy, but the risk of other types of cancer did not increase appreciably. This suggests that hyperthyroidism patients who have histories of stomach disease would be more prudent when carry out ^{131}I treatment.

We further studied the influence of treatments using PTU, levothyroxine or no additional drug after ^{131}I treatment on the outcomes of pregnancy. Until recently, PTU was traditionally considered as the treatment of choice for Graves' hyperthyroidism during pregnancy [23]. The ATA guideline [24] recommends patients on MMI should be switched to PTU if pregnancy is ascertained in the first trimester. In one survey [25], 96% of responders began treatment of hyperthyroidism of pregnant women with PTU and almost 38% of them will switch to MMI after the first trimester. In our study, patients with relapsing overt or subclinical hyperthyroidism during pregnancy were instructed to use PTU throughout the term of pregnancy, and their liver function was monitored. No hepatotoxicity was observed in these patients. Recently, a large, population-based study [26] showed that in women with gestational thyrotoxicosis using PTU therapy, the frequency of PTU-associated hepatotoxicity was considered low at 1.8 cases per 1000 delivered pregnancies. Levothyroxine is a thyroid hormone replacement drug therapy, and it had no influence on the mother or fetal development. The outcomes of patients who were treated with PTU, levothyroxine in the ^{131}I therapy group showed no statistically significant differences with whom received no additional drug.

The strength of our study is that all of the subjects in our study had Graves' hyperthyroidism and were of reproductive age, which can directly reflect the influence of ^{131}I therapy on pregnancy health. It provides certain reference values for the clinical treatment of women of reproductive age with hyperthyroidism. However, one of the limitations in our study was that details on delivery outcomes were narrow and we had no specific information about the newborns. Another limitation was that the data selected for the healthy women group was based on hospitalized patients, i.e. people who underwent outpatient abortions were not included. Finally, there was a lack of follow-up data, so the subsequent health of patients and whether mental disease occurred in the newborns remains to be investigated in further in-depth studies.

In conclusion, women of childbearing age with Graves' hyperthyroidism were discovered to have normal pregnancies after ^{131}I therapy, as were patients treated with ATD and those in the general population. No differences were seen in the outcomes of pregnancy after ^{131}I therapy, regardless of which, if any, additional drugs were used during pregnancy. In addition, Graves' disease patients who had undergone ^{131}I therapy or ATD treatment had significantly higher rates of abortion and cesarean delivery than the healthy women. From the perspective of prepotency, women with Graves' hyperthyroidism of childbearing age should have normal delivery and newborns as healthy as the general population if they conceive at least six months after ^{131}I therapy, regularly examine their thyroid function, and have antenatal care to maintain a healthy body during pregnancy.

CONFLICT OF INTEREST

The authors report that there are no conflicts of interest.

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