

Pregnancy Outcome After I-131 Therapy for Patients With Thyroid Cancer

A Nationwide Population-Based Cohort Study

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Abstract: The aim of this study was to evaluate the influence of I-131 therapy on pregnancy outcome in patients that received therapeutic I-131 doses for thyroid cancer in Taiwan.

This nationwide population-based cohort study was based on data from 1998 to 2010 obtained from the Taiwanese National Health Insurance Research Database. We identified 11,708 women with thyroid cancer (≥ 15 and ≤ 50 years of age) by International Classification of Diseases, Ninth Revision, Clinical Modification codes. Patients were divided into 2 cohorts: I-131 therapy cohort and non-I-131 therapy cohort. The mean follow-up period was 6.08 years for the I-131 cohort and 6.87 years for the non-I-131 cohort. The case cohort and the control cohort comprised 775 and 716 pregnant patients, respectively.

The overall incidence of pregnancy was significantly lower in the I-131 cohort (adjusted HR = 0.77, 95% CI = 0.70–0.86) and it was also observed when the patients were stratified according to age (HR = 0.73, 95% CI = 0.64–0.83 in 25–34 years; HR = 0.63, 95% CI = 0.49–0.82 in 35–44 years). Patients in the I-131 cohort had a lower successful delivery rate, particularly among patients in 25 to 34 years (OR = 0.60, 95% CI = 0.45–0.80). No significant difference was observed for adverse pregnancy conditions between 2 cohorts.

I-131 therapy is associated with decreased pregnancy and successful delivery rates. The underlying mechanism likely involves physician recommendation, patient's psychological issue, and potential impact of I-131 treatment on reproductive health. Further investigation is needed.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

INTRODUCTION

The definitive therapy for differentiated thyroid carcinoma is surgical thyroidectomy, coupled with I-131 therapy for treating residual, unresectable, and metastatic tumors.^{1–3} I-131 has been used for the postsurgical treatment of differentiated thyroid carcinoma for over 50 years. Young females comprise the majority of patients with well-differentiated thyroid carcinoma,^{4,5} and most differentiated thyroid carcinoma survivors have a long life expectancy.⁶ The idea that radiation may affect the gonads resulting in genetic damage to the offspring has raised concerns. Because many women are diagnosed with differentiated thyroid cancer during the reproductive years, determining the effect of I-131 on ovarian function and future pregnancy is crucial.

This was a nationwide cohort study of women with thyroid cancer, using data derived from the database of the Taiwanese National Health Insurance (NHI) program to investigate the association between I-131 therapy and pregnancy outcome.

MATERIALS AND METHODS

Data Sources

The NHI program was established in 1995 and covers approximately 99% of the residents of Taiwan. The National Health Insurance Research Database (NHIRD) includes complete ambulatory and inpatient care details and provides researchers with scrambled identification numbers associated with the relevant claim information containing the sex, date of birth, registry of medical services, and medication prescriptions

of the patient. The details of the NHIRD have been described in previous studies.⁷

The insured population with a major disease such as cancer can apply for a catastrophic illness certificate. The Registry for Catastrophic Illness Patient Database (RCIPD) integrates multiple NHI databases to provide comprehensive utilization and enrollment information for all patients with severe diseases who were exempted from copayments.

Codes from the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) were used. Patient consent is not required for accessing the NHIRD; hence, this study was exempted by the Institutional Review Board of China Medical University in Central Taiwan (CMUH-104-REC2-115).

Study Patients

Female patients certified with thyroid cancer catastrophic illness certification (ICD-9-CM code 193) as identified in the RCIPD covering a period of 13 years (1 January 1998 to 31 December 2010) were selected for this study. Patients were divided into 2 cohorts: an I-131 cohort (patients who received I-131 therapy) and a non-I-131 cohort (patients who did not receive any I-131 therapy). The date of I-131 treatment was assigned as the index date for patients in the I-131 cohort. The index date for patients in the non-I-131 cohort was randomly assigned according to the dates in the I-131 cohort. Patients were excluded if they were under 15 years of age or older than 50 years of age. The mean cumulative I-131 dose was 120.1 mCi indirectly calculated from NHI payment code. Figure 1 shows the selection procedure of patients in the study cohorts.

Definitions of End Point, Comorbidities, and Covariables

The primary outcome was the first pregnancy after I-131 treatment. The 2 cohorts were observed until pregnancy, death, withdrawal from the NHI system, or December 31, 2011.

Furthermore, we evaluated several comorbidities which were defined as the history before the index date. They could be related to outcomes, namely, abortion (ICD-9-CM 632, 634, and 637), ectopic pregnancy (ICD-9-CM 633), and infertility (ICD-9-CM 628). The term abortion meant both spontaneous and therapeutic or elective reasons.

Moreover, for pregnancy-related analyses, we considered several covariables, successful delivery (ICD-9-CM 650), low birth weight (ICD-9-CM 765, 765.01–765.08, 765.11–765.18), preterm delivery (ICD-9-CM 644 and 765), gestational hypertension (ICD-9-CM 642.0–642.3 and 642.7–642.9), preeclampsia (ICD-9-CM 642.4–642.7), gestational diabetes (ICD-9-CM 648.0 and 648.8), placenta abruption (ICD-9-CM 641.2),

placenta previa (ICD-9-CM 641.0 and 641.1), and antepartum hemorrhage (ICD-9-CM 641.1, 641.3, 641.8, and 641.9). Here, successful delivery was defined as at least 1 live birth.

Statistical Analysis

The distributions of categorical sociodemographic characteristics and comorbidities were compared between the I-131 and non-I-131 cohorts, and the differences were examined using the Chi-square test. The follow-up person-years were calculated for estimating the incidence rate by using each variable. The I-131 to non-I-131 rate ratio for pregnancy with incidence rate ratio (IRR) and 95% confidence interval (CI) for each variable were calculated. Multivariable Cox proportional hazards regression analyses were used to assess the risk of pregnancy associated with I-131 use after mutually adjusting for age, occupation, comorbidities of abortion, ectopic pregnancy, and infertility. Furthermore, the univariable and multivariable logistic regression model was used to analyze the successful delivery rate between the 2 cohorts. Information about gestation or delivery conditions, such as low birth weight, preterm delivery, gestational hypertension, preeclampsia, gestational diabetes, placenta abruption, and placenta previa, were included in the model. Baseline characteristics variables such as age, occupation, comorbidities of abortion, ectopic pregnancy, and infertility were also included in the multivariable model for adjustment. The Kaplan–Meier analysis was used for calculating cumulative incidence of pregnancy in the 2 cohorts and compared using the log-rank test. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using the SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC).

RESULTS

During the study period, 11,708 patients with thyroid cancer were enrolled. The mean follow-up period was 6.08 years (SD=3.82) for the I-131 cohort and 6.87 years (SD=3.95) for the non-I-131 cohort. The demographic data and comorbidities of the I-131 and non-I-131 cohorts are presented in Table 1. The majority of the study participants were in the age range of 15 to 39 years. Patients in the I-131 cohort were more likely to have had a prior abortion (8.87% vs 6.86%, *P* < 0.001) than those in the non-I-131 cohort.

Of the 11,708 study participants, 1491 patients became pregnant after being diagnosed with thyroid cancer. Among these 1491 patients, 775 patients belonged to the I-131 cohort (incidence rate [IR]=18.7 per 1000 person-year), and 716 belonged to the non-I-131 cohort (IR=21.4 per 1000 person-year) (Table 2). Median time to 1st pregnancy for patients in the I-131 cohort was 3.24 years (SD=2.63) and 2.94 years (SD=2.86) for the non-I-131 cohort. The Kaplan–Meier analysis showed that patients in the I-131 cohort had significantly lower pregnant cumulative incidence than the non-I-131 cohort (Log-rank test, *P* < 0.001) (Figure 2). The incidence of pregnancy was significantly lower in the I-131 cohort than in the non-I-131 cohort (incidence rate ratio [IRR]=0.86, 95% CI=0.79–0.97). The adjusted hazard ratio (HR) for pregnancy was 0.77 (95% CI=0.70–0.86) in the I-131 cohort compared with the non-I-131 cohort. As shown in Table 2, differences in the HR of pregnancy were observed when the patients were stratified according to age. Among in the age range of 25 to 39 years, patients who received I-131 therapy had a significantly lower incidence of pregnancy than those who did not receive I-131 therapy (HR=0.76, 95% CI=0.64–0.90 for patients in

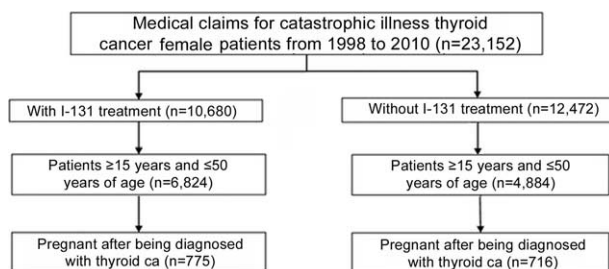


FIGURE 1. Flow chart showing the selection procedure of the study patients.

TABLE 1. Demographic Characteristics and Baseline Comorbidity Between I-131 and non-I-131 Cohorts

	Without I-131 Treatment N = 4884		With I-131 Treatment N = 6824		P-Value
	n	%	n	%	
Age, years					0.001
15–19	121	2.48	183	2.68	
20–24	321	6.57	485	7.11	
25–29	542	11.1	822	12.1	
30–34	712	14.6	11,226	16.5	
35–39	933	19.1	1317	19.3	
≥40	2255	46.2	2891	42.4	
Mean (SD)	37.7	8.32	37.1	8.32	0.01
Occupation					0.07
White collar	2847	(58.3)	4094	(60.0)	
Blue collar	1721	(35.2)	2265	(33.2)	
Others	316	(6.47)	465	(6.81)	
Comorbidity					
Abortion	335	(6.86)	605	(8.87)	<0.001
Ectopic pregnancy	83	(1.70)	145	(2.12)	0.10
Infertility	167	(3.42)	273	(4.00)	0.10

Chi-square test and *t*-test. SD = standard deviation.

the age range of 25–29 years; HR = 0.69, 95% CI = 0.56–0.84 for patients in the age range of 35–34 years; HR = 0.63, 95% CI = 0.46–0.85 for patients in the age range of 35–39 years). As shown in Table 2, patients in the I-131 cohort were less likely to

have pregnancies without comorbidities such as abortion (HR = 0.79, 95% CI = 0.71–0.88), ectopic pregnancy (HR = 0.78, 95% CI = 0.70–0.86), and infertility (HR = 0.78, 95% CI = 0.70–0.86) than those in the non-I-131 cohort.

TABLE 2. IR and HR for Pregnancy Between I-131 and Non-I-131 Cohorts Stratified by Age, Occupation, and Prior Comorbidity

	Without I-131 Treatment				With I-131 Treatment			
	Event	IR	IRR (95% CI)	Adjusted HR (95% CI)	Event	IR	IRR (95% CI)	Adjusted HR (95% CI)
Overall	716	21.4	1 (Reference)	1 (Reference)	775	18.7	0.87 (0.79, 0.97)*	0.77 (0.70, 0.86)**
Age, years								
15–19	33	34.2	1 (Reference)	1 (Reference)	31	25.4	0.74 (0.45, 1.21)	0.91 (0.55, 1.52)
20–24	128	60.6	1 (Reference)	1 (Reference)	150	54.5	0.90 (0.71, 1.14)	0.92 (0.73, 1.17)
25–29	245	86.3	1 (Reference)	1 (Reference)	279	67.8	0.79 (0.66, 0.93)*	0.76 (0.64, 0.90)*
30–34	173	36.5	1 (Reference)	1 (Reference)	190	28.1	0.77 (0.63, 0.95)***	0.69 (0.56, 0.84)*
35–39	91	13.6	1 (Reference)	1 (Reference)	79	9.18	0.69 (0.51, 0.93)***	0.63 (0.46, 0.85)*
≥40	46	2.87	1 (Reference)	1 (Reference)	46	2.55	0.89 (0.59, 1.34)	0.79 (0.52, 1.19)
Occupation								
White collar	427	22.2	1 (Reference)	1 (Reference)	461	18.5	0.83 (0.73, 0.95)*	0.73 (0.64, 0.84)**
Blue collar	225	17.9	1 (Reference)	1 (Reference)	245	17.3	0.97 (0.81, 1.16)	0.86 (0.72, 1.03)
Others	64	36.5	1 (Reference)	1 (Reference)	69	28.3	0.78 (0.55, 1.09)	0.77 (0.54, 1.08)
Comorbidity								
Abortion								
No	645	20.2	1 (Reference)	1 (Reference)	690	17.7	0.88 (0.79, 0.98)***	0.79 (0.71, 0.88)**
Yes	71	46.3	1 (Reference)	1 (Reference)	85	33.0	0.71 (0.52, 0.98)***	0.67 (0.49, 0.93)***
Ectopic pregnancy								
No	695	21.0	1 (Reference)	1 (Reference)	753	18.4	0.88 (0.79, 0.97)***	0.78 (0.70, 0.86)**
Yes	21	58.5	1 (Reference)	1 (Reference)	22	41.5	0.71 (0.39, 1.29)	0.82 (0.44, 1.52)
Infertility								
No	676	20.6	1 (Reference)	1 (Reference)	729	18.0	0.87 (0.79, 0.97)***	0.78 (0.70, 0.86)**
Yes	40	50.5	1 (Reference)	1 (Reference)	46	42.5	0.84 (0.55, 1.29)	0.85 (0.55, 1.32)

P* < 0.05, *P* < 0.01, ****P* < 0.001. CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 person-years, IRR = incidence rate ratio.

Mutually adjusted for age, occupation, prior comorbidities of abortion, ectopic pregnancy, and infertility.

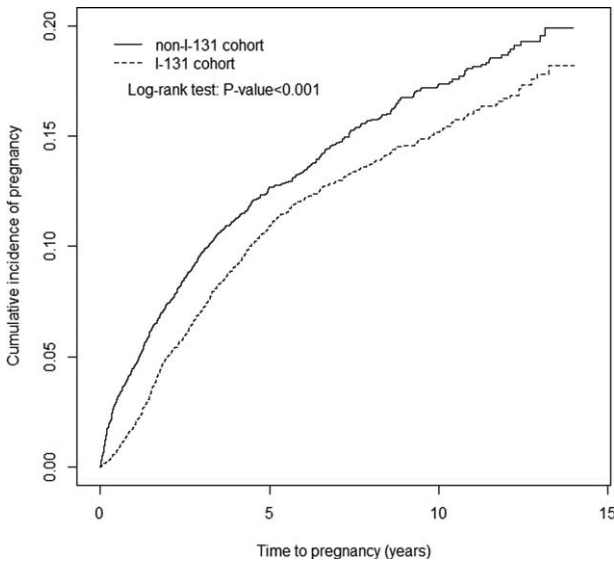


FIGURE 2. Cumulative incidence of pregnancy for patients in the I-131 cohort and in the non-I-131 cohort.

As shown in Tables 3 and 4, we applied logistic regression model analyses to estimate the risk factors of successful delivery and adverse pregnancy outcomes. The results indicated that patients who received I-131 therapy had lower successful delivery rates than those who did not receive I-131 therapy, particularly in the age range of 25 to 34 years (OR = 0.60, 95% CI = 0.45–0.80 for patients in the age range of 25–34 years) (Table 3). When the population was analyzed for gestational disorders, no remarkable differences were observed between patients in both cohorts (Table 4).

DISCUSSION

I-131 and Gonadal Function

For women with differentiated thyroid cancer, the effects of I-131 therapy on gonadal function are an important consideration since most patients are of reproductive age. Female gonads may be affected during I-131 therapy from circulating radioiodine in the blood. A systemic review of 16 papers, containing data from 3023 women or adolescents with differentiated thyroid carcinoma, examining the gonadal and

reproductive effects of I-131 therapy was analyzed.⁸ Transient absence of menstrual periods occurred in 8% to 27% of women within the 1st year after radioactive therapy, particularly in older women. In addition, women who received I-131 therapy experienced menopause at a slightly younger age than those who did not receive I-131 therapy.^{9,10}

Ceccarelli et al⁹ reported that I-131 therapy may contribute to follicular atresia and may induce early menopause. However, a controlled study of 202 patients did not reveal the aforementioned relationship between I-131 therapy and early menopause.¹¹

Sioka et al¹² studied 45 women of child-bearing age with thyroid cancer compared to 83 age-matched control females and reported a significant increase in the number of patients with menstrual cycle and/or menses irregularities after I-131 therapy. Vini et al¹³ reported that transient amenorrhea or menstrual irregularities lasting for up to 10 months were experienced by 83 patients (17%), and no cases of permanent ovarian failure were recorded.¹³ Another study indicated similar results in which 20% of the patients with thyroid cancer who received I-131 therapy experienced amenorrhea during the 1st year, and the elevated FSH levels of 28% of the patients returned to the normal levels by the end of the 1st year.¹⁴ Conversely, Esfahani et al¹⁵ observed that no significant correlation existed between gonadal–hypophyseal hormones and I-131 therapy. Sexual dysfunction, infertility, and abortion were not reported during a 12-month follow-up period. Several studies have indicated that I-131 therapy resulted in transient menstrual cycle abnormalities lasting up to a year and a slightly early menopause, but no permanent ovarian failure.¹⁶ In our study, the overall incidence of pregnancy was significantly lower in the I-131 cohort than in the non-I-131 cohort. When patients were stratified according to age, patients in the age range of 25 to 39 years who received I-131 therapy had lower success rates for getting pregnancy. A bias possibly existed because after receiving I-131 therapy, patients were more likely to use contraception. International clinical practice guidelines for the management of differentiated thyroid cancer recommend that women who receive I-131 therapy wait at least 6 to 12 months before trying to conceive.^{17,18} Thus, this recommendation may lower the pregnancy rates in the I-131 cohort.

I-131 and Pregnancy Outcomes

Most of previous studies in female patients showed no significant effects of I-131 therapy on fertility rate and offspring outcome. Garsi et al¹⁹ obtained data on 2673 pregnancies in

TABLE 3. Successful Delivery for I-131 and Non-I-131 Cohorts Stratified by Age

Outcome	Without I-131 Treatment N = 716		With I-131 Treatment N = 775		OR (95% CI)	
	N	%	n	%	Crude	Adjusted [†]
Successful delivery						
15–24 years	123	76.4	117	64.6	0.56 (0.35, 0.91)*	0.59 (0.36, 0.95)*
25–34 years	304	72.7	289	61.6	0.60 (0.45, 0.80)**	0.60 (0.45, 0.80)**
35+ years	46	33.6	29	23.2	0.60 (0.35, 1.03)	0.55 (0.30, 1.00)*
Overall	473	66.1	435	56.1	0.66 (0.53, 0.81)**	0.61 (0.48, 0.76)**

*P < 0.05, **P < 0.01. CI = confidence interval, OR = odds ratio.

[†] Adjusted for age, occupation, prior comorbidities of abortion, ectopic pregnancy, and infertility.

TABLE 4. Delivery and Gestational Outcomes for I-131 and Non-I-131 Cohorts

Outcome	Without I-131 Treatment N = 716		With I-131 Treatment N = 755		OR (95% CI)	
	n	%	n	%	Crude	Adjusted [†]
Preterm delivery	29	4.05	41	5.29	1.32 (0.81, 2.15)	1.32 (0.81, 2.15)
Low-birth weight	5	0.70	8	1.03	1.48 (0.48, 4.55)	1.48 (0.89, 4.58)
Gestational hypertension	7	0.98	9	1.16	1.19 (0.44, 3.21)	1.17 (0.43, 3.17)
Preeclampsia	12	1.68	11	1.42	0.85 (0.37, 1.93)	0.83 (0.36, 1.90)
Gestational diabetes	52	7.26	50	6.45	0.88 (0.59, 1.32)	0.88 (0.59, 1.32)
Placenta abruption	3	0.42	3	0.39	0.92 (0.19, 4.59)	0.88 (0.18, 4.40)
Placenta praevia	15	2.09	16	2.06	0.99 (0.48, 2.01)	0.97 (0.48, 1.99)
Antepartum hemorrhage	44	6.15	35	4.52	0.72 (0.46, 1.14)	0.71 (0.45, 1.12)

CI = confidence interval, OR = odds ratio.

[†] Adjusted for age, occupation, prior comorbidities of abortion, ectopic pregnancy, and infertility.

women who were treated for thyroid carcinoma, and the data revealed that the incidence of spontaneous abortion was 10% before any treatment, 20% after surgery only, and 19% after I-131 therapy. Spontaneous abortions were not significantly more frequent in women who received I-131 therapy during the year before conception, even in women who had received more than 370 MBq of I-131 during that year. The incidences of stillbirths, preterm births, low birth weight, congenital malformations, and death during the 1st year of life were not significantly different before or after I-131 therapy.¹⁹ Similarly, several studies concluded that there was no evidence of adverse effects of I-131 therapy on the rate of successful delivery, live birth demographics, and the risk of congenital anomalies.^{20–25} In a recent study, Wu et al²⁶ analyzed 18,850 women treated for well-differentiated thyroid cancer and demonstrated that a significant 29% reduction in birthrate among women age 20 to 39 who received I-131 therapy. The results of this study revealed that patients who received I-131 therapy, particularly patients in the age range of 25 to 34 year, had lower successful delivery rates than those who did not receive I-131 therapy. However, similar to previous studies, no remarkable differences regarding preterm birth, low birth weight, and some gestational disorders, such as gestational hypertension, preeclampsia, gestational diabetes, placenta abruption, and placenta previa, were observed between the 2 cohorts.

We observed that the incidence rate of pregnancy and successful delivery rate decreased in thyroid cancer patients with I-131 treatment. These findings might be attributable to not only potential effect of I-131 exposure on subsequent fertility but also an inability to tolerate a delay in childbearing either due to physician recommendation or impact of I-131 therapy on patient’s reproductive choice. Considering the psychological issue, patients might be afraid of being pregnant because worry about adverse impact brought by I-131 therapy. The major strength of our study is that the large sample size in this nationwide study minimized the problem of losing cohort members at follow-up, even if patients were treated at different hospitals because of the coverage of the NHIRD including more than 98% of the population in Taiwan and its reimbursement system.

Study Limitations

Our study had some potential limitations. The NHIRD did not contain detailed information such as pathological

type, disease severity, laboratory data (such as thyroid hormone levels), and maternal comorbidity, as well as it is very difficult to accurately calculate the complete ablation rate after thyroidectomy and I-131 treatment based on the NHIRD.

Tumor Type and Disease Extent

Lack of disease stage is a major limitation in this study. Although we reasonably assumed that most of our study patients had AJCC stage I and stage II differentiated thyroid cancer because the majority of our patients were <45 years old, there was still small percentage of patients over 45 years old. Patients who received I-131 therapy might have advanced tumor stage or higher recurrence risk which might affect the incidence of pregnancy. However, whether the patient received I-131 therapy or not might not precisely reflect the disease severity. Because controversy still exists regarding the role of I-131 therapy of American Thyroid Association (ATA) low to intermediate risk differentiated thyroid cancer patients according to the current ATA guidelines.²⁷ In our country, the use of post-operative I-131 therapy for patients with ATA low to intermediate risk is usually based on physician’s preference and patient’s compliance.

Maternal Comorbidity

It should be noted that the term abortion in our study included both spontaneous and therapeutic abortion, and subsequent therapy as well as comorbidity after I-131 treatment was not documented because such information was not easily available in our database. In our study, we found that previous abortion rate was more frequent in the I-131 treatment group. The possible reason was that some pregnant women terminated the pregnancy when confronted with the need to undergo I-131 therapy. But, “previous abortion” did not influence our result according to stratified analysis.

Diseases diagnosed using the ICD-9-CM codes in the NHIRD. Although the ICD-9-CM codes are among the most popular coding systems used for disease diagnosis in claims, the databases do not always precisely fit the clinical condition of interest. The evidence derived from a retrospective cohort study has a typically lower statistical quality than that of other studies because of the presence of inherent bias.

CONCLUSION

In conclusion, our findings indicate that I-131 treatment is associated with decreased pregnancy and successful delivery rates. The underlying mechanism likely involves physician recommendation, patient's psychological issue, and potential impact of I-131 treatment on reproductive health. Further investigation is needed.

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