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Long-Term Effects of Radioiodine Treatment on Female Fertility in Survivors of Childhood Differentiated Thyroid Carcinoma

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Background: Differentiated thyroid carcinoma (DTC) during childhood is a rare disease. Its excellent survival rate requires a focus on possible long-term adverse effects. This study aimed to evaluate fertility in female survivors of childhood DTC by assessing various reproductive characteristics combined with anti-Müllerian hormone (AMH) levels (a marker of ovarian reserve).

Methods: Female survivors of childhood DTC, diagnosed at ≤18 years of age between 1970 and 2013, were included. Survivors were excluded when follow-up time was less than five years or if they developed other malignancies before or after diagnosis of DTC. Survivors filled out a questionnaire regarding reproductive characteristics (e.g., age at menarche and menopause, pregnancies, pregnancy outcomes, need for assisted reproductive therapy). Survivors aged <18 years during evaluation received an altered questionnaire without questions regarding pregnancy and pregnancy outcomes. These data were combined with information from medical records. AMH levels were measured in serum samples and were compared with AMH levels from 420 women not treated for cancer.

Results: Fifty-six survivors with a median age of 31.0 (interquartile range, IQR, 25.1–39.6) years were evaluated after a median follow-up of 15.4 (IQR 8.3–24.7) years. The median cumulative dose of ^{131}I administered was 7.4 (IQR 3.7–13.0) GBq/200.0 (IQR 100.0–350.0) mCi. Twenty-five of the 55 survivors aged 18 years or older during evaluation reported 64 pregnancies, 45 of which resulted in live birth. Of these 55, 10.9% visited a fertility clinic. None of the survivors reported premature menopause. Age at AMH evaluation did not differ between DTC survivors and the comparison group ($p = 0.268$). Median AMH levels

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did not differ between DTC survivors and the comparison group [2.0 (IQR 1.0–3.7) μg/L vs. 1.6 (IQR 0.6–3.1) μg/L, respectively, $p = 0.244$]. The cumulative dose of ^{131}I was not associated with AMH levels in DTC survivors ($r_s = 0.210$, $p = 0.130$).

Conclusions: Female survivors of DTC who received ^{131}I treatment during childhood do not appear to have major abnormalities in reproductive characteristics nor in predictors of ovarian failure.

Keywords: differentiated thyroid carcinoma, childhood cancer, adverse effects, fertility, radioiodine

Introduction

CHILDHOOD DIFFERENTIATED THYROID CARCINOMA (DTC) is rare, with age-adjusted incidences reported between 0.6 and 1.2 per 100,000 per year (1,2). Up to puberty, the female:male ratio is similar, but after puberty, mainly females are diagnosed with the disease (3). In all age groups, a rise in incidence rates of thyroid cancer has been reported (4). Treatment of pediatric DTC most commonly consists of total thyroidectomy with or without central or lateral neck dissection (5). After surgery, ^{131}I is often administered. Depending on the risk classification of the patient, a certain intensity of thyrotropin (TSH) suppression is pursued. Although this treatment results in excellent survival rates, up to 99% after 30 years of follow-up (6), DTC treatment, especially therapy with ^{131}I, calls for examination of possible long-term adverse effects: reproductive characteristics, secondary cancers, salivary dysfunction, bone marrow suppression, and alterations in quality of life (7–12).

Female fertility after treatment with ^{131}I has been evaluated in survivors of *childhood* and *adult* DTC. Only two studies examined survivors of *childhood* DTC and were limited by small numbers of patients and unclear or ill-defined endpoints (9,13). Studies in survivors of *adult* DTC found conflicting results regarding the effect of ^{131}I on female fertility, although permanent impairment of fertility is not common (14–21).

Anti-Müllerian hormone (AMH) is released by the granulosa cells and is a reflection of the number of antral follicles in the ovaries. Although there is no consensus on the clinical value of AMH, it is a commonly used marker for ovarian reserve in cancer survivors (22), partly because AMH is not influenced by menstrual cycle fluctuations (23,24). AMH levels in adult DTC patients decrease after treatment with ^{131}I (25–27), although it is unclear whether this decrease is transient or permanent or even clinically relevant (21,27). AMH levels show a greater decrease after ^{131}I in women aged 35 years or older during treatment (26).

There is a need for well-defined and systematically performed studies regarding effects on long-term fertility in female survivors of *childhood* DTC. Therefore, the primary aim of the current study was to assess the reproductive characteristics (pregnancies, number of live births, pregnancy outcomes, and health of offspring) in female survivors of *childhood* DTC treated with ^{131}I. The secondary aim was to compare AMH levels (as a measure of ovarian reserve) in female survivors of childhood DTC with a group consisting of women who had not been treated for cancer.

Materials and Methods

This research is part of a nationwide, long-term follow-up study on childhood DTC in the Netherlands, previously described in detail (28). The institutional review board of the University Medical Center Groningen approved the study on behalf of all participating institutions (ABR NL40572.042.12, file number 2012/183). This study has been registered in the Netherlands Trial Registry (trial NL3280). Written informed consent was obtained from all subjects before participation in the study.

Participants

DTC survivors. Included were female patients diagnosed with DTC between 1970 and 2013 at age ≤18 years and treated in the Netherlands. Treatment most commonly consisted of total thyroidectomy, ^{131}I, and TSH suppression therapy (28). Specific exclusion criteria in this study were as follows: less than five years since diagnosis, diagnosis of other malignancy before or after the DTC diagnosis, thyroid hormone withdrawal or recombinant human TSH administration within three months before evaluation, not being able to complete a Dutch questionnaire, and not being treated with ^{131}I for DTC. Patients were evaluated from February 2013 until November 2014.

Fertility assessment. Fertility was assessed by means of a self-administered questionnaire, information from medical records, and a hormonal evaluation.

Questionnaire. Survivors were asked to complete a questionnaire regarding their use of current medication (thyroid hormone, contraceptives, or other medications), smoking, and reproductive characteristics: obstetric and gynecological medical history (menarche, menstrual cycles, age at first pregnancy, children conceived, birth defects and major health problems, and visiting a fertility clinic due to problems with conceiving). Survivors aged <18 years during evaluation received an altered questionnaire without questions regarding pregnancy and pregnancy outcomes.

Medical data. Medical records were accessed to obtain information regarding survivors' characteristics: thyroid carcinoma histology, tumor–node–metastasis (TNM) classification (redefined to the seventh edition of the TNM since the seventh edition was current during initial evaluation), treatment modalities (type of surgery and details of ^{131}I administrations), and survivors' outcomes (remission, recurrence, or persistent disease, defined as previously described) (28). Comorbidities interacting with fertility (e.g., endometriosis or gynecological surgery) were also documented.

Clinical evaluation. Survivors were evaluated during a visit to an outpatient clinic, in the context of the study of long-term treatment effects. Height and weight were

measured by one of the researchers (M.S.K.H.). Fasting blood samples were drawn by venipuncture. Blood samples were subsequently stored in a −80°C environment until processed. Blood sampling was performed at a random time during the menstrual cycle for logistical reasons. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E2) measurements were performed in survivors who did not use contraceptives containing hormones.

AMH, LH, FSH, and E2 analyses of DTC survivors were centrally performed in one run in the laboratory of the University Medical Center Groningen, the Netherlands, by electrochemiluminescence immunoassay on a Roche Cobas analysis platform. Limit of detection (LoD) and intra-assay variation of these assays were 0.010 μg/L and <1.3% for AMH, 0.3 IU/L and <1% for higher ranges and 2.2% for values below 1.0 IU/L for LH, 0.100 IU/L and <2.5% for FSH, and for E2 an LoD of 0.018 nmol/L and an intra-assay coefficient of variability (CV) of 1.1–1.6% over the measuring range, whereas values below 0.07 nmol/L had a CV of 2.4–6.7%. Reference norms per age group (in years) for AMH (in μg/L, 2.5th to 97.5th percentile) were: 15–18.9: 0.34–10.39; 20–24: 1.22–11.7; 25–29: 0.89–9.85; 30–34: 0.58–8.13; 35–39: 0.15–7.49; 40–44: 0.03–5.47; 45–50: 0.01–2.71 (29,30). Smoking and body mass index may influence AMH levels and were therefore also evaluated (31–34).

Comparison group for AMH levels

The comparison group consisted of sisters of childhood cancer survivors ($n = 196$) and women from the general population ($n = 224$) who participated in a previous nationwide cohort study among Dutch female five-year survivors of childhood cancer aiming to evaluate the effects of childhood cancer treatment on fertility (the DCOG-LATER VEVO-study) (35,36). Participants of the comparison group were aged ≥18 years and had not been treated for cancer.

AMH analyses of the comparison group were performed in one run using an ultra-sensitive Elecsys AMH assay (Roche Diagnostics GmbH, Mannheim, Germany) in the laboratory of the VU Medical Center Amsterdam, the Netherlands. The LoD of this assay was 0.01 μg/L, the intra-assay CV of this assay was 0.5–1.8%, and the limit of quantitation of 0.03 μg/L. Reference norms per age group (in years) for AMH (in μg/L, 2.5th–97.5th percentile) were: 15–25: 0.26–11; 25–30: 0.49–14; 30–35: 0.14–13; 35–40: <11; 40–45: <6; 45 and older: <0.48. There was a good agreement between the two AMH assays. The Passing–Bablok regression intercept did not differ significantly from 0 (−0.003, [95% confidence interval −0.075 to 0.021]) and slope 1.092 [95% confidence interval 1.049 to 1.143].

Study definitions

Evaluation date was the date of blood sampling or, in case of lacking blood sample, the date of filling in the questionnaire. Follow-up time was defined as the period between the date of diagnosis and the date of evaluation. Dosages of ^{131}I of 0.9 GBq (25 mCi) or higher were considered as therapeutic doses. Women were considered postmenopausal if they reported 12 months of amenorrhea without any other obvious pathological or physiological cause (22). Premature ovarian insufficiency was defined as start of menopause before the age of 40 years (22).

Statistical analyses

Descriptive statistics regarding disease, treatment, reproductive characteristics, and AMH levels are presented as median (interquartile range [IQR]), unless otherwise specified. Cutoff scores for ''low AMH levels'' were calculated, based on the 10th (0.22 μg/L) and 25th percentile (0.64 μg/L) of AMH levels of the complete comparison group. Categorical variables were compared using chi-square test or Fisher's exact test (if >20% of the cells had an expected count of <5). Mann–Whitney U test was performed for nonnormally distributed continuous or ordinal variables. When variables were normally distributed, an independent sample *t*-test was performed. To correlate two nonnormally distributed continuous and/or ordinal variables, Spearman's rank correlation coefficient (r_s) was used. Simple linear regression analysis was performed to evaluate associations between attained age (in years) and cumulative ^{131}I dose (in GBq) as predictors and AMH as outcome measure. In the first multiple linear regression analysis, log-transformed AMH was predicted by attained age in years and group (coded as 0 = comparison group, 1 = DTC survivors). A second multiple linear regression analysis predicted log-transformed AMH by independent variables: attained age (years) and cumulative dose of ^{131}I (in GBq). A *p*-value of <0.05 was considered statistically significant. All tests were performed two-sided. IBM SPSS Statistics version 23.0.0.3 for Windows (IBM, Armonk, NY) was used for statistical analyses.

Results

Participants

Sixty-two of the 105 survivors of the nationwide follow-up study were eligible for this substudy. Four survivors declined participation, and two were late for inclusion. Thus, 56 of the 62 (90.3%) female survivors were included (Supplementary Fig. S1). Two of the 56 subjects only completed the questionnaire, declining participation in the clinical evaluation. Table 1 shows clinical and treatment characteristics of the included survivors. The median age of survivors at evaluation was 31.0 (IQR 25.1–39.6) years after a median follow-up period of 15.4 (IQR 8.3–24.7) years. The median cumulative activity of ^{131}I administered was 7.4 GBq/200.0 mCi (IQR 3.7–13.0 GBq/IQR 100.0–350.0 mCi, respectively). Half of the survivors received multiple administrations of ^{131}I.

Reproductive characteristics

Fifty-six DTC survivors reported their reproductive characteristics in the administered questionnaire (Table 2). Four (7.1%) women reported being postmenopausal. Ages at menopause were 45, 51, and 52 years, with one age at menopause missing. Of the 55 survivors aged ≥18 years during evaluation, 25 (45.5%) reported one or more pregnancies. The median age at first pregnancy was 25.5 (IQR 22.5–30.0) years. Sixty-four pregnancies were reported (2.6 pregnancies per survivor who reported to ever having been pregnant), of which 1 was a twin pregnancy. Subsequently, 45 live births were reported. Other pregnancy outcomes were miscarriage ($n = 13$), induced abortion ($n = 3$), unknown outcome ($n = 3$), and pregnant at evaluation ($n = 1$). Six (10.9%) survivors had visited a fertility doctor or clinic because of problems with conceiving. Birth defects and major health

Table 1. Characteristics of Survivors of Childhood Differentiated Thyroid Carcinoma

Characteristic	n = *56*
Age at evaluation (years)	31.0 (25.1–39.6)
Age at diagnosis (years)	16.0 (13.7–17.5)
Follow-up duration (years)	15.4 (8.3–24.7)
Histology, *n* (%)	
Papillary	47 (83.9)
Follicular	9 (16.1)
Tumor–node–metastasis stage, *n* (%)	
T	
T1–T2	37 (66.1)
T3–T4	11 (19.6)
Tx	8 (14.3)
N	
N0	27 (48.2)
N1	25 (44.6)
Nx	4 (7.1)
M	
M0	45 (80.4)
M1	6 (10.7)
Mx	5 (8.9)
Cumulative ^{131}I activity (GBq)[a]	7.4 (3.7–13.0)
Cumulative ^{131}I activity (mCi)[a]	200.0 (100.0–350.0)
Multiple ^{131}I administrations, *n* (%)	28 (50.0)

Numbers are presented as median (interquartile range).
[a]Dose of administered ^{131}I unknown in one survivor, therefore $n = 55$.

Table 2. Reproductive Characteristics of Survivors of Childhood Differentiated Thyroid Carcinoma

Characteristic	n = *56*
Age at menarche (years)[a]	13.0 (12.0–13.0)
Postmenopausal, *n* (%)	4 (7.1)
Use of contraceptives, *n* (%)	
Hormonal contraceptives	24 (42.9)
Nonhormonal contraceptives[b]	1 (1.8)
No contraceptives	31 (55.4)
Visited doctor for subfertility (yes), *n* (%)[c]	6 (10.9)
Ever been pregnant (yes), *n* (%)[c]	25 (45.5)
Age at first pregnancy (years)[c,d]	25.5 (22.5–30.0)
No. of pregnancies, *n*[c]	64[e]
Live births, *n*	45
Women reporting miscarriage, *n*	8[f]
Induced abortion, *n*	3
Pregnant during evaluation, *n*	1
Unknown pregnancy outcome, *n*	3

Numbers are presented as median (interquartile range).
[a]$n = 55$ because one missing value.
[b]Copper intrauterine device.
[c]Not applicable in one participant because age <18 years during evaluation, $n = 55$.
[d]$n = 22$ because age at first pregnancy missing for 3 participants.
[e]One twin pregnancy.
[f]Seven women reported one miscarriage, and one woman reported six miscarriages.

problems of children reported by the survivors are shown in Supplementary Table S1.

Hormonal evaluation

Characteristics and AMH levels of the female survivors of childhood DTC and the comparison group are shown in Table 3. DTC survivors who provided blood samples had a median age of 29.4 years ($n = 54$, IQR 24.8–38.3 years) upon evaluation. The median age of the comparison group was 33.1 (IQR 26.8–39.3) years. There were no statistically significant differences between the two groups for nationality (predominantly Dutch, $p = 1.000$, data not shown), age upon evaluation, smoking, and body mass index. The median AMH levels did not differ between DTC survivors and the comparison group (2.0 μg/L vs. 1.6 μg/L, respectively, $p = 0.244$).

The cumulative dosage of ^{131}I did not correlate with AMH levels ($r_s = 0.210$, $p = 0.130$). In the DTC group, age was negatively correlated with AMH levels ($r_s = -0.480$, $p < 0.001$).

Eight (14.8%) and 10 (18.5%) of the DTC survivors had an AMH level below the cutoff value based on the 10th and 25th percentiles of the comparison group, respectively. The number of DTC survivors with ''low AMH levels'' did not significantly differ from those in the comparison group ($p = 0.278$ and $p = 0.296$, respectively) (Supplementary Table S2).

Because the data of AMH were positively skewed, the values were log transformed. Subsequently, all assumptions for linear regression analysis were met. Log-transformed AMH levels did not differ between DTC survivors and the comparison group (median ln(AMH) 0.7 vs. 0.5, respectively, $p = 0.696$; Table 3). Results of the simple and multiple linear regression analyses for log-transformed AMH are shown in Table 4. Simple linear regression showed that age was a significant predictor of log-transformed AMH, but cumulative dose of ^{131}I was not. The first multiple linear regression analysis showed that age was a significant predictor of log-transformed AMH, but group (i.e., survivor vs. comparison group) was not. In model 2, when log-transformed AMH levels in only DTC survivors were predicted by age and cumulative dose of ^{131}I, age remained a significant predictor of log-transformed AMH, but cumulative dose of ^{131}I was not.

There was no difference in AMH levels between DTC survivors who did or did not use contraceptives containing hormones, or between survivors who had received single or multiple doses of ^{131}I (data shown in Supplementary Table S3). LH, FSH, and E2 levels of DTC survivors who did not use contraceptives or used nonhormonal contraceptives, obtained at a random time during the menstrual cycle, were within the reference range (Supplementary Table S4).

Discussion

The current study, focusing on various aspects of female fertility after treatment with ^{131}I for childhood DTC, shows no major abnormalities in reproductive characteristics and no difference in AMH levels between long-term DTC survivors and a comparison group after a median follow-up period of 15 years.

Table 3. Anti-Müllerian Hormone Levels in Survivors of Childhood Differentiated Thyroid Carcinoma Compared with the Comparison Group

	DTC survivors	*Comparison group*	
	n = *54*[a]	n = *420*	p
Age at evaluation (years)	29.4 (24.8 to 38.3)	33.1 (26.8 to 39.3)	0.268[b]
Smoking, *n* (%)			0.392[c]
Current	7 (13.0)	78 (18.6)	
Ever	13 (24.1)	123 (28.8)	
Never	33 (61.1)	221 (52.6)	
Missing	1 (1.9)	0 (0)	
Body mass index (kg/m^2)	23.8 (21.2 to 26.8)[d]	23.0 (21.2 to 25.9)	0.428[b]
Type of control, *n* (%)			
General population	—	224 (53.3)	
Sister	—	196 (46.7)	
AMH level (μg/L)	2.0 (1.0 to 3.7)	1.6 (0.6 to 3.1)	0.244[b]
ln(AMH)	0.7 (0.0 to 1.3)	0.5 (–0.4 to 1.1)	0.696[e]

Numbers are presented as median (interquartile range).
[a]Two participants participated only in questionnaire part of study.
[b]Mann–Whitney U test.
[c]Pearson chi-square test (asymptotic significance).
[d]Length and weight self-reported by two participants.
[e]Independent samples *t*-test.
AMH, anti-Müllerian hormone; DTC, differentiated thyroid carcinoma.

In this unique series of patients, the number of live births per pregnancy in the current study is comparable to those in the normal population: 70% of pregnancies in the DTC survivors resulted in a live birth, which corresponds with the 71% in an earlier prospective register-based study (37). The 10% of female DTC survivors who visited a fertility clinic or doctor because of problems with conception corresponds with that of other couples in the Netherlands who are trying to become pregnant, in whom this percentage is around 15% (38,39).

Comparing current results with findings of previous studies among survivors of *childhood* DTC is complicated by the fact that the earlier studies lack concrete definitions, report on only a small number of patients, or evaluated only a selection of reproductive characteristics (9,13). The cumulative dose of ^{131}I administered to the current survivors is similar to the dose administered in the study of Sarkar *et al.* (13). Overall, no clear impairments of fertility have been observed in the current or previous studies in female survivors of childhood DTC (9,13).

It is unclear whether adverse effects of ^{131}I have similar consequences in *children* and *adults*. Quantitatively, damage to the ovaries caused by ^{131}I could be relatively less severe in younger women, since girls and adolescent women still have a greater number of primary oocytes/primordial follicles than adult women (40). As oocytes decrease in quality with increasing age (41), a higher quality of primary oocytes/primordial follicles in pre-adult women may also be beneficial. Studies in women aged >35 years who were treated with ^{131}I for DTC observed a more pronounced negative effect on AMH levels (26) and birth rates (14). Negative effects on fertility in women treated with chemotherapy for other types of cancer also increase with age at treatment (42).

In this group of *childhood* DTC survivors, evaluation of AMH levels is a measure for ovarian reserve, and this hormone is not significantly affected by menstrual cycle variations (23,24). However, as AMH levels are strongly affected by age, we adjusted our analyses accordingly.

The mere determination of AMH levels as outcome measure in the assessment of female fertility provides an

Table 4. Simple and Multiple Linear Regression Analyses for Log-Transformed Anti-Müllerian Hormone in 54 Survivors of Childhood Differentiated Thyroid Carcinoma

Variable	*Intercept*	β[a]	*CI*	R^2	p
Simple linear regression					
Age at evaluation (years)	4.12	–0.12	[–0.13 to –0.11]	0.418	<0.001
Cumulative ^{131}I activity (GBq)	–0.28	0.06	[–0.01 to 0.12]	0.056	0.089
Multiple linear regression					
1. Age at evaluation (years)	4.13	–0.12	[–0.13 to –0.11]	0.418	<0.001
Group[b]		–0.06	[–0.40 to 0.29]		
2. Age at evaluation (years)[c]	3.73	–0.12	[–0.16 to –0.07]	0.414	<0.001
Cumulative ^{131}I activity (GBq)		0.02	[–0.04 to 0.07]		

[a]Unstandardized coefficients β.
[b]Comparison group = 0, DTC survivors = 1.
[c]"Group" removed from this analysis because comparison group did not receive ^{131}I administrations.
CI, 95% confidence interval.

incomplete representation. AMH levels have been shown to be decreased up to one year after treatment with ^{131}I for DTC in adults (25,26). This reflects damage to the secondary and early antral follicles of the ovary since AMH expression is highest during these follicular stages (Supplementary Table S5) (43,44). Primordial follicles are probably less prone to the effects of ^{131}I treatment, and these unharmed primordial follicles can subsequently develop into secondary and early antral follicles after therapy, resulting in normal AMH expression over the long term. A slight rise in AMH levels in survivors of *adult* DTC one year after ^{131}I treatment was seen in only one study (25); this was not confirmed in another study (26). Seven years after treatment at *adult* ages, AMH levels did not differ between ^{131}I-treated females and their controls (21). In the current study, 15 years after treatment during *childhood*, AMH levels were similar to those of the comparison group. Moreover, studies have also reported recovery of AMH levels after other anticancer treatments (45–47). Evaluation of AMH levels soon after treatment may indicate some form of ovarian damage, but long-term evaluation of AMH levels, combined with reproductive characteristics, is more appropriate in providing information on possible irrecoverable damage to the ovary and subsequent reproductive health.

Unfortunately, we did not evaluate the effects of TSH suppression therapy on fertility in the current survivors (28), although effects of subclinical hyperthyroidism on fertility have not been proven (48,49), other than the well-known effects of overt hyperthyroidism causing, for instance, menstrual disturbances or amenorrhea (50).

Strengths of the present study include the cohort size, given the rarity of DTC in childhood, and the availability of an appropriate comparison group for AMH levels. Minor limitations deserve consideration as well. The reported reproductive characteristics may be subject to change since many of the evaluated survivors in this study were of reproductive age, but may not have conceived yet owing to other factors. The chosen reproductive characteristics were well defined, based on current knowledge. Thereby, we evaluated a broad range of reproductive characteristics that determine fertility, including objective outcome measures, such as live births and hormonal evaluation.

Although no major impact on fertility after ^{131}I treatment for childhood DTC was observed, this does not necessarily imply that ^{131}I can be administered without restriction in young female patients. Sparse data show that ^{131}I therapy seems to have no adverse effects on the risk of congenital abnormalities in offspring of DTC survivors (51). Other adverse effects of ^{131}I (i.e., salivary gland dysfunction, bone marrow suppression) do increase with multiple or higher doses (11,12). This study, in accordance with previous studies, did not find a dose–response relationship between cumulative administrated ^{131}I and AMH levels (21,25,26). Follow-up beyond menopause of the survivors in this cross-sectional study will shed light on the full reproductive period. The current study can serve as a basis for this evaluation.

To conclude, the current study found no abnormalities in fertility in long-term female survivors of childhood DTC. Our conclusions are based on evaluation of a broad range of reproductive characteristics: fertility outcomes, parameters of reproductive health, indications of impaired fertility, and AMH as a marker of ovarian reserve. Altogether, these results regarding long-term reproductive outcomes seem to be reassuring for females receiving ^{131}I for childhood DTC.

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Figure S1
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Supplementary Table S5

References

1. Dermody S, Walls A, Harley EH, Jr. 2016 Pediatric thyroid cancer: an update from the SEER database 2007–2012. Int J Pediatr Otorhinolaryngol **89:**121–126.
2. Steliarova-Foucher E, Stiller CA, Pukkala E, Lacour B, Plesko I, Parkin DM 2006 Thyroid cancer incidence and survival among European children and adolescents (1978–1997): report from the Automated Childhood Cancer Information System project. Eur J Cancer **42:**2150–2169.
3. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE 2009 Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res **156:**167–172.
4. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM 2017 Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA **317:**1338–1348.
5. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S, American Thyroid Association Guidelines Task F 2015 Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid **25:**716–759.
6. Hay ID, Johnson TR, Kaggal S, Reinalda MS, Iniguez-Ariza NM, Grant CS, Pittock ST, Thompson GB 2018 Papillary Thyroid Carcinoma (PTC) in Children and Adults: comparison of Initial Presentation and Long-Term Postoperative Outcome in 4432 Patients Consecutively Treated at the Mayo Clinic During Eight Decades (1936–2015). World J Surg **42:**329–342.
7. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M 2014 Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun **35:**808–817.

8. Klein Hesselink EN, Links TP 2015 Radioiodine treatment and thyroid hormone suppression therapy for differentiated thyroid carcinoma: adverse effects support the trend toward less aggressive treatment for low-risk patients. Eur Thyroid J **4:**82–92.
9. Albano D, Bertagna F, Panarotto MB, Giubbini R 2017 Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer **64:** e26595.
10. Nies M, Klein Hesselink MS, Huizinga GA, Sulkers E, Brouwers AH, Burgerhof JG, van Dam EW, Havekes B, van den Heuvel-Eibrink MM, Corssmit EP, Kremer LC, Netea-Maier RT, van der Pal HJ, Peeters RP, Plukker JT, Ronckers CM, van Santen HM, Tissing WJ, Links TP, Bocca G 2016 Long-term Quality of Life in Adult Survivors of Pediatric Differentiated Thyroid Carcinoma. J Clin Endocrinol Metab **102:**1218–1226.
11. Prinsen HT, Klein Hesselink EN, Brouwers AH, Plukker JT, Sluiter WJ, van der Horst-Schrivers AN, van Imhoff GW, Links TP 2015 Bone marrow function after (131)I therapy in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab **100:**3911–3917.
12. Selvakumar T, Nies M, Klein Hesselink MS, Brouwers AH, van der Horst-Schrivers ANA, Klein Hesselink EN, Tissing WJE, Vissink A, Links TP, Dutch Pediatric Thyroid Cancer Study Consortium 2018 Long-term effects of radioiodine treatment on salivary gland function in adult survivors of pediatric differentiated thyroid carcinoma. J Nucl Med **60:** 172–177.
13. Sarkar SD, Beierwaltes WH, Gill SP, Cowley BJ 1976 Subsequent fertility and birth histories of children and adolescents treated with 131I for thyroid cancer. J Nucl Med **17:**460–464.
14. Wu JX, Young S, Ro K, Li N, Leung AM, Chiu HK, Harari A, Yeh MW 2015 Reproductive outcomes and non-oncologic complications after radioactive iodine ablation for well-differentiated thyroid cancer. Thyroid **25:**133–138.
15. Anderson C, Engel SM, Weaver MA, Zevallos JP, Nichols HB 2017 Birth rates after radioactive iodine treatment for differentiated thyroid cancer. Int J Cancer **141:**2291–2295.
16. Ko KY, Yen RF, Lin CL, Cheng MF, Huang WS, Kao CH 2016 Pregnancy outcome after I-131 therapy for patients with thyroid cancer: a nationwide population-based cohort study. Medicine **95:**e2685.
17. Garsi JP, Schlumberger M, Rubino C, Ricard M, Labbe M, Ceccarelli C, Schvartz C, Henri-Amar M, Bardet S, de Vathaire F 2008 Therapeutic administration of 131I for differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies. J Nucl Med **49:**845–852.
18. Schlumberger M, De Vathaire F, Ceccarelli C, Delisle MJ, Francese C, Couette JE, Pinchera A, Parmentier C 1996 Exposure to radioactive iodine-131 for scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. J Nucl Med **37:**606–612.
19. Sioka C, Fotopoulos A 2011 Effects of I-131 therapy on gonads and pregnancy outcome in patients with thyroid cancer. Fertil Steril **95:**1552–1559.
20. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, Straus S, Thabane L, Gafni A, Ezzat S, George SR, Goldstein DP 2008 A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clin Endocrinol **69:**479–490.
21. Giusti M, Mittica M, Comite P, Campana C, Gay S, Mussap M 2018 Anti-Müllerian hormone in pre-menopausal females after ablative radioiodine treatment for differentiated thyroid cancer. Endocrine **60:**516–523.
22. 1996 Research on the menopause in the 1990s. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser **866:**1–107.
23. La Marca A, Stabile G, Artenisio AC, Volpe A 2006 Serum anti-Mullerian hormone throughout the human menstrual cycle. Hum Reprod **21:**3103–3107.
24. Lambert-Messerlian G, Plante B, Eklund EE, Raker C, Moore RG 2016 Levels of antimullerian hormone in serum during the normal menstrual cycle. Fertil Steril **105:**208–213.e201.
25. Evranos B, Faki S, Polat SB, Bestepe N, Ersoy R, Cakir B 2018 Effects of Radioactive Iodine Therapy on Ovarian Reserve: a Prospective Pilot Study. Thyroid **28:**1702–1707.
26. Yaish I, Azem F, Gutfeld O, Silman Z, Serebro M, Sharon O, Shefer G, Limor R, Stern N, Tordjman KM 2018 A single radioactive iodine treatment has a deleterious effect on ovarian reserve in women with thyroid cancer: results of a prospective pilot study. Thyroid **28:**522–527.
27. Acibucu F, Acibucu DO, Akkar OB, Dokmetas HS 2016 Evaluation of ovarian reserve with AMH level in patients with well-differentiated thyroid cancer receiving radioactive iodine ablation treatment. Exp Clin Endocrinol Diabetes **124:**593–596.
28. Klein Hesselink MS, Nies M, Bocca G, Brouwers AH, Burgerhof JG, van Dam EW, Havekes B, van den Heuvel-Eibrink MM, Corssmit EP, Kremer LC, Netea-Maier RT, van der Pal HJ, Peeters RP, Schmid KW, Smit JW, Williams GR, Plukker JT, Ronckers CM, van Santen HM, Tissing WJ, Links TP 2016 Pediatric differentiated thyroid carcinoma in The Netherlands: a nationwide follow-up study. J Clin Endocrinol Metab **101:**2031–2039.
29. Anckaert E, Oktem M, Thies A, Cohen-Bacrie M, Daan NM, Schiettecatte J, Muller C, Topcu D, Groning A, Ternaux F, Engel C, Engelmann S, Milczynski C 2016 Multicenter analytical performance evaluation of a fully automated anti-Mullerian hormone assay and reference interval determination. Clin Biochem **49:**260–267.
30. Jopling H, Yates A, Burgoyne N, Hayden K, Chaloner C, Tetlow L 2018 Paediatric anti-Müllerian hormone measurement: male and female reference intervals established using the automated Beckman coulter access AMH assay. Endocrinol Diabetes Metab **1:**e00021.
31. Pasternak MC, Christos P, Spandorfer SD 2018 The relationship between body mass index and anti-mullerian hormone levels in reproductive-age women; is there a negative correlation? Fertil Steril **109:**e42–e43.
32. Barriere P, Freour T, Masson D, Mirallie S, Jean M 2007 Normal anti-mullerian hormone (AMH) levels in young smoking women undergoing IVF have no predictive value for ovarian response, inversely to non smokers. Fertil Steril **88:**S172.
33. White AJ, Sandler DP, D'Aloisio AA, Stanczyk F, Whitworth KW, Baird DD, Nichols HB 2016 Antimüllerian hormone in relation to tobacco and marijuana use and sources of indoor heating/cooking. Fertil Steril **106:**723–730.
34. Simoes-Pereira J, Nunes J, Aguiar A, Sousa S, Rodrigues C, Sampaio Matias J, Calhaz-Jorge C 2018 Influence of body mass index in anti-Mullerian hormone levels in 951 non-polycystic ovarian syndrome women followed at a reproductive medicine unit. Endocrine **61:**144–148.

35. van den Berg MH, Overbeek A, Lambalk CB, Kaspers GJL, Bresters D, van den Heuvel-Eibrink MM, Kremer LC, Loonen JJ, van der Pal HJ, Ronckers CM, Tissing WJE, Versluys AB, van der Heiden-van der Loo M, Heijboer AC, Hauptmann M, Twisk JWR, Laven JSE, Beerendonk CCM, van Leeuwen FE, van Dulmen-den Broeder E, DCOG LATER-VEVO study group 2018 Long-term effects of childhood cancer treatment on hormonal and ultrasound markers of ovarian reserve. Hum Reprod **33:**1474–1488.
36. Overbeek A, van den Berg MH, Kremer LC, van den Heuvel-Eibrink MM, Tissing WJ, Loonen JJ, Versluys B, Bresters D, Kaspers GJ, Lambalk CB, van Leeuwen FE, van Dulmen-den Broeder E 2012 A nationwide study on reproductive function, ovarian reserve, and risk of premature menopause in female survivors of childhood cancer: design and methodological challenges. BMC Cancer **12:** 363.
37. Magnus MC, Wilcox AJ, Morken N-H, Weinberg CR, Håberg SE 2019 Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ **364:**l869.
38. Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G 2005 Definition and prevalence of subfertility and infertility. Hum Reprod **20:**1144–1147.
39. Beurskens MP, Maas JW, Evers JL 1995 [Subfertility in South Limburg: calculation of incidence and appeal for specialist care]. Ned Tijdschr Geneeskd **139:**235–238.
40. Scheffer GJ, Broekmans FJ, Looman CW, Blankenstein M, Fauser BC, teJong FH, teVelde ER 2003 The number of antral follicles in normal women with proven fertility is the best reflection of reproductive age. Hum Reprod **18:**700–706.
41. Broekmans FJ, Soules MR, Fauser BC 2009 Ovarian aging: mechanisms and clinical consequences. Endocr Rev **30:** 465–493.
42. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K 2006 American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol **24:** 2917–2931.
43. Weenen C, Laven JS, Von Bergh AR, Cranfield M, Groome NP, Visser JA, Kramer P, Fauser BC, Themmen AP 2004 Anti-Mullerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod **10:**77–83.
44. Andersen CY, Schmidt KT, Kristensen SG, Rosendahl M, Byskov AG, Ernst E 2010 Concentrations of AMH and inhibin-B in relation to follicular diameter in normal human small antral follicles. Hum Reprod **25:**1282–1287.
45. Dillon KE, Sammel MD, Prewitt M, Ginsberg JP, Walker D, Mersereau JE, Gosiengfiao Y, Gracia CR 2013 Pretreatment antimullerian hormone levels determine rate of posttherapy ovarian reserve recovery: acute changes in ovarian reserve during and after chemotherapy. Fertil Steril **99:**477–483.
46. Bedoschi G, Navarro PA, Oktay K 2016 Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol **12:**2333–2344.
47. Decanter C, Cloquet M, Dassonneville A, D'Orazio E, Mailliez A, Pigny P 2018 Different patterns of ovarian recovery after cancer treatment suggest various individual ovarian susceptibilities to chemotherapy. Reprod Biomed Online **36:**711–718.
48. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG 2006 Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol **107:**337–341.
49. Cho MK 2015 Thyroid dysfunction and subfertility. Clin Exp Reprod Med **42:**131–135.
50. Krassas GE 2000 Thyroid disease and female reproduction. Fertil Steril **74:**1063–1070.
51. Clement SC, Peeters RP, Ronckers CM, Links TP, van den Heuvel-Eibrink MM, Nieveen van Dijkum EJ, van Rijn RR, van der Pal HJ, Neggers SJ, Kremer LC, van Eck-Smit BL, van Santen HM 2015 Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma—a systematic review. Cancer Treat Rev **41:**925–934.

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