Clinical Research

Reproductive function after radioactive iodine treatment for differentiated thyroid carcinoma patients: a systematic review

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ABSTRACT

BACKGROUND Thyroid cancer is one of the most prevalent cancers in the endocrine system, with a rapidly rising incidence over the past 3 decades. Treatment for patients with differentiated thyroid cancer (DTC) typically includes surgery, radioactive iodine (I-131) therapy, and levothyroxine (L-T4) suppressive therapy. This study aimed to explore the potential side effects of I-131 therapy on reproductive function in men and women with DTC.

METHODS A literature search was performed using 4 databases (PubMed, ScienceDirect, BioMed Central, and Google Scholar), limited to English publications since 2013. Clinical trials and observational studies that evaluated I-131 in DTC, focused on reproductive-age patients, and included pre-therapy or during-therapy examinations, administered doses, and treatment frequencies of I-131 were selected. The Joanna Briggs Institute Critical Appraisal Checklist is used as a comprehensive evaluation tool, and the literature quality was categorized as high, moderate, and low.

RESULTS The final 17 articles examined the effect of I-131, with 13 focusing on women's reproductive function and 4 on men's. Women who received I-131 therapy can lower anti-Mullerian hormone levels and disrupt menstrual cycles within the first year, and it does not affect subsequent pregnancies. For men, the therapy led to elevated levels of follicle-stimulating hormone and luteinizing hormone, along with changes in sperm quantity, morphology, and motility, which tend to normalize within a year post-therapy.

CONCLUSIONS The reproductive side effects associated with I-131 therapy are generally transient, with most individuals experiencing a return to normal within 1 year following treatment.

KEYWORDS anti-Mullerian hormone, follicle-stimulating hormone, follicular thyroid carcinoma, luteinizing hormone, papillary thyroid cancer, sperm analysis

Thyroid cancer incidence has shown a significant increase globally over the past three decades despite its infrequency.[1] Based on the 2020 Global Cancer Observatory, thyroid cancer incidence ranked the 10th most common cancer worldwide with 586,202 cases and increased to 7th in 2022 with 821,214 cases.[2–4] In Indonesia, 13,114 cases of thyroid cancer were reported in 2020, which increased to 13,761 new cases in 2022.[5,6] Thyroid carcinoma is estimated to account for 3.78% of all body malignancies,[7] making it the 10th most common malignancy in Indonesia.

The American Thyroid Association (ATA) has recommended radioactive iodine (I-131) ablation therapy for thyroid cancer post-thyroidectomy, particularly for patients with differentiated thyroid carcinoma (DTC, divided into papillary and follicular thyroid carcinoma) at intermediate to high risk.[8] This therapy has demonstrated its efficacy in improving

survival rates, mitigating metastasis, and preventing recurrence in patients with thyroid cancer post-thyroidectomy.[9–11] As a benign carcinoma, DTC has a very high survival rate compared with other carcinomas. Some patients require I-131 therapy only once. However, concerns have arisen regarding its impact on the reproductive functions of patients undergoing this treatment. Some studies have reported temporary adverse effects, such as hypospermia in males and amenorrhea or oligomenorrhea in females, following I-131 administration.[12,13]

This study aimed to comprehensively explore the literature on the reproductive side effects of I-131 in both female and male patients with DTC. By synthesizing existing evidence, this review sought to elucidate I-131 side effects, duration, and reversibility, providing clinicians and patients with a clearer understanding of the reproductive implications of I-131 therapy. Such insights are crucial for informed decision-making and holistic patient care in the management of thyroid cancer.

METHODS

The literature search was conducted using four online databases (PubMed, ScienceDirect, BioMed Central, and Google Scholar) and was limited to publications in English since 2013. The selection of keywords was based on the medical subject headings and involved techniques such as truncation, quotation marks, parentheses, and boolean operators ("AND," "OR," and "NOT"). The selected keywords for this literature study were as follows: PubMed: ("radioactive iodine" OR "radioiodine I-131" OR "radioiodine") AND ("therapy" OR "treatment") AND ("thyroid cancer" OR "carcinoma thyroid") AND ("reproductive function" OR "fertility"); Google Scholar: ("thyroid cancer and radioiodine therapy" OR "radioactive iodine treatment") AND ("reproductive function" OR "fertility") AND ("thyroid cancer").

The inclusion criteria were as follows: (1) clinical trials or observational studies evaluating I-131 administration in patients with DTC; (2) articles published in journals indexed in PubMed and Scopus; (3) availability of full-text articles; (4) articles published in 2013 or later; (5) clinical trials involving reproductive-age patients; and (6) articles including pre- or intra-therapy examinations, administered doses, and treatment frequencies. The exclusion criteria were as follows: (1) secondary or tertiary literature articles, such as guidelines, literature reviews, symposiums, case reports, or case series; and (2) articles available only as abstracts. Data were extracted from the selected studies, including references (author and publisher), study design (research method and sample size), patient characteristics (age, sex, cancer type, and pre- and intra-therapy examinations), I-131 interventions and treatments (dose, frequency, and duration), and primary outcomes. The extracted data were processed using a synthesis matrix to classify and combine elements from the reviewed literature to synthesize a literature study. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist was used as a comprehensive evaluation tool to systematically assess the quality, validity, and reliability of each study or scientific literature. The entire scale in this checklist consists of eight domains for the risk of bias: clarity of inclusion criteria, detailed description of study participants and settings, validity and reliability of exposure measurement, objective and standard criteria for condition measurement, identification of confounding factors, strategies for managing confounding factors, validity and reliability of outcome measurement, and appropriateness of statistical analysis. Each domain was judged on four points: yes, no, unclear, or not applicable. Based on the question in JBI Critical Appraisal Checklist for cross-sectional studies, literature quality was categorized as high, moderate, or low.[14]

The primary outcomes analyzed for female reproductive function included decreased levels of anti-Mullerian hormone (AMH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH); menstrual cycle irregularities; incidence of abortion; pregnancy occurrences; and live birth rates. For male reproductive function, the outcomes analyzed were decreased hormonal levels (FSH and LH) and reduced sperm quality.

RESULTS

Of 632 articles identified, only 17 were included in this review (Figure 1). The sample sizes ranged from 24 to 111,459 in these studies. The Critical Appraisal Checklist indicated that all the studies included in the review met the required quality standards concerning both the risk of bias and applicability domains. A detailed evaluation of each study included

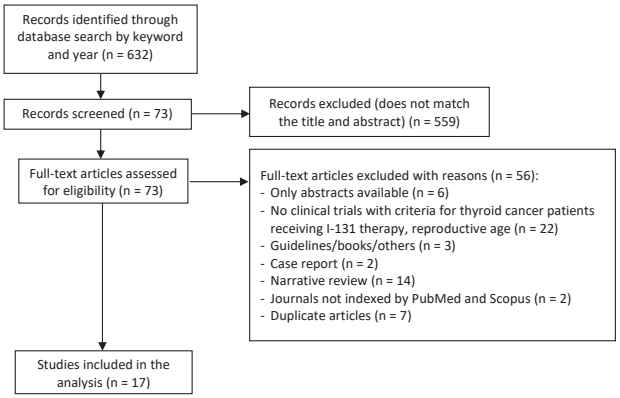

Figure 1. Flow of literature identification and selection

in this systematic review is presented in Table 1. Of 17 articles, 13 addressed the side effects of I-131 on female reproductive function, including menstrual (i.e., amenorrhea and menstrual cycle irregularities) and hormonal (i.e., AMH, FSH, and LH) cycle changes in females (9 articles) and post-therapy pregnancy outcomes (4 articles). The remaining four articles discussed the side effects on male reproductive function, such as hormonal (FSH and LH) changes and their impact on spermatogenesis, including sperm number, motility, and morphology. The data extracted from the included articles were tabulated to summarize the outcomes in Tables 2 and 3.

DISCUSSION

We examined the effects of I-131 therapy on fertility in male and female patients with DTC who had undergone treatment during their reproductive years in the final 17 studies. Assessment of the effects of I-131 therapy on reproductive function involves specific parameters for both males and females. The evaluation focused on AMH, FSH, and LH levels, menstrual cycle patterns, and pregnancy outcomes in females and FSH and LH levels and sperm quality parameters such as sperm motility and morphology in males. These measurements provide a comprehensive understanding of the effect of therapy on reproductive health in both sexes.

This review found that AMH, FSH, and LH levels influenced female reproductive function changes involved in egg cell development, including the menstrual cycle, along with the incidence of abortion, pregnancy, and birth. Nine studies addressed the adverse effects of I-131 on AMH levels: four

Table 1. Literature quality assessment based on the JBI Critical Appraisal Checklist for cross-sectional studies[14]

First author, year	Assessment tool criteria								Total score	Total possible	Summary score	Quality
	1	2	3	4	5	6	7	8				
Adamska,[15] 2021	Y	Y	Y	Y	NA	NA	Y	Y	6	8	0.75	Moderate
Yaish,[16] 2018	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Hosseini,[17] 2023	Y	Y	Y	Y	NA	N	Y	Y	6	8	0.75	Moderate
Evranos,[18] 2018	Y	Y	N	Y	Y	Y	N	Y	6	8	0.75	Moderate
van Velsen,[19] 2020	Y	Y	Y	Y	Y	Y	Y	Y	8	8	0.75	Moderate
Acıbucu,[20] 2016	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Nies,[21] 2020	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Mittica,[22] 2020	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Giusti,[23] 2018	Y	Y	N	N	Y	N	N	Y	5	8	0.63	Moderate
Ko,[24] 2016	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Kim,[25] 2020	Y	Y	N	Y	Y	Y	Y	Y	7	8	0.86	High
Wu,[26] 2015	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Canale,[12] 2015	Y	Y	Y	Y	NA	N	Y	Y	6	8	0.75	Moderate
Soltani,[27] 2023	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Bourcigaux,[28] 2018	Y	Y	Y	Y	Y	Y	Y	Y	8	8	1	High
Nies,[29] 2021	Y	Y	Y	Y	Y	N	Y	Y	7	8	0.86	High
Anderson,[44] 2017	Y	Y	N	Y	Y	Y	Y	Y	7	8	0.86	High

JBI=Joanna Briggs Institute; N=no; NA=not available; Y=yes
Divided literature quality: high: >0.75; moderate: 0.55–0.75; low: <0.55

Table 2. Females reproductive data extraction

First author, year	Research design (method and subjects/patients)	Samples criteria (age and type of cancer)	Intervention (dose, frequencies, and period of research)	Examination before or during therapy	Results
Adamska,[15] 2021	Method: prospective study; sample: 25 patients	Age: 34 (31–38) years; type of cancer: PTC	Dose: single dose (100 mCi); length of research: 2 years	1. Evaluation of the number of antral follicles. 2. Serum FSH and AMH levels 3. Menstrual cycle Evaluated at baseline and 1 year post-therapy	1. There was a decrease in serum AMH concentration (p<0.01) and the number of antral follicles (p = 0.03) after 1 year of therapy. 2. Serum FSH levels after 1 year of therapy did not show any changes (p = 0.23). 3. Menstrual cycle irregularities 1 year after therapy occurred in 16% of patients
Yaish,[16] 2018	Method: prospective study; sample: 25 patients	Age: 20–45 years; type of cancer: PTC	Dose: 6 patients (30 mCi), 2 patients (50 mCi), 4 patients (100 mCi), and 12 patients (150 mC)	1. AMH levels concentrations were assessed at baseline, 3, 6, 9, and 12 months after I-131 treatment. 2. Menstrual cycle	1. A decrease in AMH levels occurred in the first 3 months, 49% of the initial value (p<0.0001) 2. The dose of I-131 is unrelated to the reduction in AMH levels. 3. AMH levels that are stable after 9 months were reported in 82% of patients. 4. Potential factors that might influence the rate of decline: a positive correlation was found between the subject's age (r = 0.51; p = 0.02) and age at menarche (r = 0.48; p = 0.03) 5. Amenorrhea occurred 4 months after therapy in 8.3% (1 patient received 30 mCi and 1 patient received 150 mCi) and improved thereafter; menstrual irregularities after I-131 treatment occurred in 19.2% for approximately 1 year and got better after that.
Hosseini,[17] 2023	Method: prospective study; sample: 60 subjects	Age: 18–35 years; type of cancer: DTC (there is no specific type mentioned)	Dose: 100 mCi (all patient)	Serum AMH concentrations were assessed at baseline, 3, 6, 12 months after I-131 therapy.	AMH levels decreased significantly respectively 49.05% at 3 months, 29.55% at 6 months, and 13.58% at 12 months compared to levels before therapy (p<0.001).
Acıbucu,[20] 2016	Method: study cohort; sample: 85 samples (45 DTC patient receive I-131 therapy and 40 health patient as a control group)	Age: patient = 35.27 (6.66) years; control = 33.37 (6.29) years; type of cancer: DTC (there is no specific type mentioned)	Dose: 100–150 mCi (mean: 104.88 [12.24] mCi); the median (min–max) period from exposure to I-131 to the study was 36 (3–180) months.	1. Examination of serum levels of AMH, FSH, and LH after therapy compared with the control group. 2. Menstrual cycle	1. AMH levels in the treatment group were lower than control (p = 0.038). 2. FSH levels in the treatment group were higher than control (p = 0.028) 3. LH levels in the two groups were similar (p = 0.228). 4. Transient oligomenorrhea lasting 3–5 months was found in 7 patients (15.6% of the patient group) after I-131 treatment. The minimum, maximum, and mean duration of oligomenorrhea were 3, 5, and 3.71 (0.75) months, respectively.

Table 2 continued on next page

Table 2. (Continued)

First author, year	Research design (method and subjects/patients)	Samples criteria (age and type of cancer)	Intervention (dose, frequencies, and period of research)	Examination before or during therapy	Results
Evranos,[18] 2018	Method: prospective study; sample: 33 subjects	Age: 21–38 years; type of cancer: DTC (there is no specific type mentioned)	Dose: 5 patients (75 mCi), 18 patients (100 mCi), and 10 patients (150 mCi)	Serum concentrations of AMH, FSH, and LH were assessed at baseline, 3, 6, and 12 months after I-131 therapy.	1. At the 3 time points, the measurement of AMH levels were similar (p>0.05). 2. At the 3 time points, the measurements of FSH levels showed a p-value of 0.32, and LH levels had a p-value of 0.26.
Mittica,[22] 2020	Method: cross-sectional; sample: 230 subjects divided into three groups (group 1 = 59 [surgery and I-131 therapy]; group 2 = 30 [just surgery]; group 3 = 141 healthy subjects)	Age: group 1 = 41.2 (7.5) (43; 37–47) years, group 2 = 42.4 (9.2) (45; 40–49) years, and group 3 = 33.1 (10.1) (33; 24–42) years; type of cancer: PTC (86%), follicular variant papillary (7%), and FTC (7%)	Dose: 100.1 (117.4) (80; 60–100) mCi	1. AMH levels were checked at baseline, 1, and 2 years after therapy 2. Pregnancy outcome	1. After primary treatment, there was no significant difference in AMH levels between the two groups. 2. Due to differences in age between groups, the number of women who experienced term pregnancies was also different: group 1 (62%), group 2 (47%) and group 3 (23%) (p<0.0001). Six full-term pregnancies occurred after I-131 therapy. 3. There was no difference in abortion rates (p = 0.99). 4. Overall, early menopause was observed in a similar percentage between women with a history of I-131 DTC treatment (21%) and patients who did not receive I-131 17% (p = 0.76).
Giusti,[23] 2018	Method: cohort study; sample: 57 subjects (34 patients received a surgery and I-131 therapy and 23 patients received surgery only as control)	Age: 40.7 (6.7) years; type of cancer: PTC (49 patients), papillary variant follicular (4 patients), and FTC (4 patients)	The specific dose of I-131 given to patients was not stated in this study; patients who received I-131 therapy were categorized as low-risk	1. Analysis of AMH and FSH compared between patients who received I-131 therapy and control patients 2. Menstrual cycle 3. Pregnancy outcome	1. AMH levels in the 2 groups did not show any difference. 2. Menstrual characteristics between the 2 groups did not show any differences (p = 0.43). 3. FSH levels between 2 groups were similar. 4. The number of term pregnancies was similar in both groups (group I-131: in 62% of women; control group: in 61% of women). Six full-term pregnancies (in 5 women) occurred after I-131 therapy.
van Velsen,[19] 2020	Method: longitudinal study; sample: 65 subjects	Age: 32.0 (8.4) years; type of cancer: PTC (59 subjects) and FTC (6 subjects)	Dose: 144 (48–226) mCi; single dose (n = 47) = 50 (30–146) mCi; multiple dose (n = 18) = 291 (284–293) mCi	Serum AMH concentrations were assessed at baseline, 12, 24, 36, and 48 months after I-131 therapy	1. There was a decrease in AMH concentration in both groups, with the lowest value after 12 months (−55%; p<0.0001 vs. −74%; p<0.001). After that, the AMH concentration remained stable. 2. AMH concentrations after 48 months were significantly lower in the multiple-dose group than in the single-dose group (p = 0.005). 3. Cumulative dose of I-131 did not significantly affect AMH concentrations in both groups.
Nies,[21] 2020	Method: cohort study; sample: 56 subjects, 420 control subjects	Age: 31.0 (25.1–39.6) years; type of cancer: PTC (47 subjects) and FTC (9 subjects)	Dose: 200.0 (100.0–350.0) mCi	Evaluation of AMH levels after I-131 therapy compared with the control group	1. Median AMH levels between DTC survivors and the control group showed no difference (2.0 lg/l vs. 1.6 lg/l respectively, p = 0.244) 2. Cumulative dose of I-131 did not correlate with AMH levels (p = 0.130)

Table 2 continued on next page

Table 2. (Continued)

First author, year	Research design (method and subjects/patients)	Samples criteria (age and type of cancer)	Intervention (dose, frequencies, and period of research)	Examination before or during therapy	Results
Ko,[24] 2016	Method: cohort study; sample: 11,708 subjects (6,824 subjects received I-131 and 4,884 subjects received surgery only).	Age: 15 and 39 years; type of cancer: DTC (there is no specific type mentioned)	Cumulative dose: 120.1 mCi	This study focuses on pregnancy outcomes after I-131 therapy in DTC	1. Patients who received I-131 therapy had a much lower incidence of pregnancy after a follow-up period of 6.08 years post-therapy in the I-131 therapy group (775 pregnancies, incidence rate 18.7 per 1,000 person-years) and 6.87 years post-therapy in the non-I-131 therapy group (716 pregnancies, incidence rate 21.4 per 1,000 person-years). 2. Adverse pregnancy conditions between the 2 groups showed no difference.
Wu,[26] 2015	Method: cohort study; sample: 18,850 subjects (9,883 subjects received I-131 <12 months post-surgery)	Age: 45.5 (15.0) years; type of cancer: PTC and FTC	The specific dose of I-131 given to patients was not stated in this study	This study focuses on reproductive outcomes after I-131 therapy in DTC	1. Birth rates between women who received and did not received I-131 therapy showed no difference at 4 years of follow-up (p = 0.81) 2. In subgroup analysis, women aged 35–39 years who received I-131 experienced reduced birth rate compared with women who did not (11.5 vs. 16.3 births per 1,000 woman/years, p<0.001).
Kim,[25] 2020	Method: cohort study; sample: 111,459 subjects (59,483 [53.4%] subjects received surgery only and 51.976 [46.6%] subjects received surgery and I-131).	Age: 20–49 years; type of cancer: DTC (there is no specific type mentioned)	Dose: mean (SD) of cumulative dose 4.44 (3.17) GBq; frequency: 10,367 (19.9%) patient receive more 2 times of the therapy.	This study focuses on the relationship between pregnancy outcomes and I-131 therapy in DTC at 0–5 months, 6–11 months, 12-23 months, and >24 months after therapy.	1. The conception rate in the I-131 group was lower than the surgery-only group at the 0–5 months interval (0.7% vs. 2.0%) and 6–11 months (1.4% vs. 1.9%), and increased at the 12–23 months (3.5% vs 2.6%) 2. Women who became pregnant within 6 months post-I-131 therapy had a higher abortion rate compared with those who became pregnant 12 to 23 months post-I-131 therapy (AOR, 4.08; 95% CI, 3.19–5.22; p<0.001) 3. Cases of congenital malformations observed in women who became pregnant less than 6 months after I-131 therapy occurred in 13.3% of patients, 7.9% in the 6- to 11- month interval, 8.3% in the 12- to 23- month interval, and 9.6% at >24 months interval. 4. I-131 therapy before pregnancy was not associated with an increase in adverse pregnancy outcomes when conception occurred 6 months or more post-therapy.
Anderson,[44] 2017	Method: cohort study; sample: 2,360 subjects	Age: 15–39 years; type of cancer: DTC (there is no specific type mentioned)	The specific dose of I-131 given to patients was not stated in this study	This study focuses on the relationship between birth rate and I-131 therapy in DTC	1. Of 2,360 women identified with DTC, 53% received I-131 2. Overall, birth rates were similar between women who did and did not receive I-131 therapy. 3. The cumulative incidence of birth during a maximum of 14.5 years of follow-up was 30.0% and 29.3% between women who received I-131 therapy and those who did not.

AMH=anti-Mullerian Hormone; AOR=adjusted odds ratio; CI=confidence interval; DTC=differentiated thyroid cancer; FSH=follicle-stimulating hormone; FTC=follicular thyroid carcinoma; GBq=gigabecquerel; I-131=iodine-131; LH=luteinizing hormone; mCi=millicurie; PTC=papillary thyroid cancer; SD=standard deviation

Table 3. Males reproductive data extraction

First author, year	Research design (method and subjects/patients)	Sample criteria (age and type of cancer)	Intervention (dose, frequencies, and period of research)	Examination before or during therapy	Results
Soltani,[27] 2023	Method: cohort study; sample: 18 subjects	Age: 20–45 years; type of cancer: DTC (there is no specific type mentioned)	Dose: 8 subjects received a low dose 30 mCi and 10 subjects received a high dose >150 mCi; length of research: 12 months post-therapy of I-131.	Evaluation of FSH, LH, and testosterone hormones, as well as sperm analysis at baseline 3 weeks before therapy, and follow-up 3, and 12 months post-therapy.	1. There was an increase in LH and FSH levels in the first 3 months, and they tended to return to baseline at the last examination at 12 months after treatment. 2. There is no change in testosterone levels. 3. There is a decrease in sperm count in the first 3 months and returns to normal after 12 months of high-dose therapy. 4. Analysis of sperm motility and morphology after 12 months showed a decrease compared to the initial value.
Canale,[12] 2015	Method: prospective study; sample: 20 subjects	Age: 19–39 years; type of cancer: PTC (18 subjects) and FTC (2 subjects)	Dose: single dose = 1,100 MBq in 10 patients and multiple dose = 4,810–32,190 MBq (mean 12,790 MBq) in 10 patients; length of research: 12 months post-therapy of I-131.	Sperm analysis, and evaluation of FSH, LH, and testosterone hormones at the beginning before therapy, follow-up 6 and 12 months after therapy.	1. There was a significant increase in LH and FSH levels in the first 6 months from the initial condition, at 12 months post-therapy the values returned to basal values. 2. The multiple-dose group experienced a persistent increase in FSH after 12 months post-therapy in 40% of patients. 3. Testosterone hormone levels do not show changes 4. I-131 therapy caused a severe decrease in sperm concentration at 6-month follow-up from basal condition (54,571 vs. 28,877; $p<0.0005$). 5. After 12 months post-therapy, 50% of the multiple-dose group experienced oligozoospermia and 20% of the single-dose group experienced mild oligozoospermia (borderline 13.5 and 14.5 millions/ml). Others returned to normal values. 6. Sperm progressive motility was not reduced compared with basal values, at 6 months (12.7 [3.9] vs. 11.8 [2.4]; $p = 0.77$) or at 12 months (8.8 [1.8]; $p = 0.32$) 7. 25% experienced a persistent decrease in testicular volume (40% of patients on multiple doses and 10% of patients on single doses)

Table 3 continued on next page

Table 3. (Continued)

First author, year	Research design (method and subjects/patients)	Sample criteria (age and type of cancer)	Intervention (dose, frequencies, and period of research)	Examination before or during therapy	Results
Nies,[29] 2021	Method: cross-sectional; sample: 51 subjects.	Age: mean 40.9 (IQR: 34.0–49.6) years; type of cancer: PTC (n = 49), FTC (n = 1), Hürthle cell cancer (n = 1), metastases to lymph nodes (58.8%), and metastases to lungs (5.9%)	Dose: median cumulative dose I-131 = 7.4 (IQR: 5.6–11.1; range: 3.7–23.3) GBq. 20 of 51 patients received cumulative dose I-131 11.1 GBq or more; frequency: 26 subjects received I-131 once, 17 subjects received I-131 twice, 4 subjects received I-131 3 times, and 4 subjects received I-131 4 times; length of research: 2 years (patients were enrolled after a minimum of 2 years post-I-131 therapy)	Semen analysis and hormonal evaluation post I-131 therapy were compared with the 10th percentile of general population-based reference values defined by WHO.	1. Evaluation of LH, FSH, and testosterone showed no difference. 2. No difference in semen quality was observed between patients and the general population based on the 10th percentile. The participants' median semen quality was similar to the median semen quality of the general population, as defined by WHO.
Bourcigaux,[28] 2018	Method: prospective study; sample: 24 subjects	Age: 28–40 years (median = 34); type of cancer: DTC (there is no specific type mentioned)	Dose: single dose 3.7 GBq	Sperm analysis and evaluation of FSH and LH hormones at baseline before therapy (V0), follow-up 3 (V3), and 13 (V13) months post-therapy.	1. There was a significant increase in testosterone, LH, and FSH hormone levels in the first 3 months from the initial condition and the values returned to basal values at 13 months post-therapy. 2. The progressive motility of sperm is the same at each examination. 3. A decrease in sperm concentration and morphology is observed at V3 and returns to normal at V13.

DTC=differentiated thyroid cancer; FSH=follicle-stimulating hormone; FTC=follicular thyroid carcinoma; GBq=gigabecquerel; I-131=iodine-131; IQR=interquartile range; LH=luteinizing hormone; MBq=megabecquerel; mCi=millicurie; PTC=papillary thyroid cancer; WHO=World Health Organization

prospective, three cohort, one cross-sectional, and one longitudinal study. The age of the patients undergoing I-131 treatment varied from 18 to 49 years, and the cumulative dosages of I-131 varied from 30 to 200 mCi. Adamska et al[15] found a decrease in AMH levels in 25 patients 1 year after I-131 treatment compared with the pre-treatment values (base 2.3 [1.5–3.9] *versus* 1 year 2.0 [0.4–3.3] ng/ml; $p<0.01$), but still within the normal range (1.5–4.0 ng/ml). Moreover, Yaish et al[16] identified a significant increase in AMH levels of 29 patients in the first 3 months from 3.25 (2.75) to 1.9 (1.74) ng/ml ($p<0.0001$), which then increased and stabilized after 9 months, but did not return to basal values (2.36 [1.88] ng/ml; $p<0.005$). Hosseini and Lavasani[17] also reported a significant decrease in AMH levels in the first 3 months, which then increased and stabilized after 12 months post-therapy but did not return to basal values ($p<0.001$). Evranos et al[18] examined AMH levels at 3.6 and 12 months after therapy in 33 patients and noticed no significant differences at the three measurement times ($p>0.05$). The median AMH levels were 3.25 (0.32–17.42), 1 (0.01–3.93), 1.13 (0.08–6.12), and 1.37 (0.09–6.1) ng/ml at the first, second, third, and fourth measurements, respectively.[18] van Velsen et al[19] assessed AMH levels by comparing patients who received a single dose and multiple doses. They found a decrease in AMH levels in both groups and discovered that the dose could influence the patient's potential for improvement. The AMH concentrations after 48 months were significantly lower in the multiple-dose group than in the single-dose group ($p = 0.005$). The AMH levels at 48 months after I-131 treatment were 0.95 (1.23), 1.25 (1.23), and 0.52 (1.52) ng/ml, in the total population, single-dose group, and multiple-dose group, respectively.[19]

Acıbucu et al[20] reported that AMH levels in a group receiving therapy were lower than those in a healthy control group. In contrast, Nies et al[21] found no significant difference in AMH levels between DTC survivors and the general population control group (2.0 *versus* 1.6 lg/l, $p = 0.244$). Mittica et al[22] and Giusti et al[23] have found no significant difference in AMH levels between patients with DTC who received only I-131 therapy and those who underwent only surgery. Both studies showed similar results because they examined similar patient age characteristics in research groups that underwent only I-131 therapy or surgery.

Four studies examined the effects of I-131 treatment on FSH and LH levels. Adamska et al[15] reported no significant change in FSH levels 1 year after I-131 therapy compared with the pre-treatment levels. Their findings aligned with Evranos et al[18] who measured FSH and LH levels at baseline, at 3, 6, and 12 months post-therapy and found no significant differences at the three measurement times compared with the initial values. Giusti et al[23] also reported no significant difference in FSH levels between the therapy and control groups. In contrast, Acıbucu et al[20] discovered different results, with higher FSH levels in the group receiving therapy than in the healthy control group. However, none of these studies revealed a significant difference in the LH levels between the two groups.[15,18,20,23]

Recently, Adamska et al[15] reported that menstrual irregularities occurred in 16% of patients 1 year after therapy. However, their study carried out examinations only at two-time points, before and 1 year after therapy; therefore, improvement in the following year is unknown. Acıbucu et al[20] reported that oligomenorrhea occurred approximately 3–5 months after I-131 therapy and improved thereafter. Yaish et al[16] supported this finding by revealing that amenorrhea occurred 4 months after therapy in 8.3% of patients, where one patient received a dose of 30 mCi and another received 150 mCi; menstrual irregularities after I-131 treatment occurred in 19.2% of patients for approximately 1 year. Both parameters improved thereafter. Other patients reported no changes in their menstrual cycle patterns.

Mittica et al[22] researched 230 samples and reported no significant difference in the incidence of abortion between patients who received I-131 therapy and those who did not. Ko et al[24] found no significant differences between the two groups (I-131 therapy and surgery only) after observing pregnancy outcomes, such as the incidence of abortion, ectopic pregnancy, and congenital abnormalities, in 11,708 patients with DTC. Kim et al[25] researched 111,459 patients and reported that women who became pregnant within 6 months of I-131 therapy had a statistically higher abortion rate than those who became pregnant 12–23 months post-therapy. Kim et al[25] also reported a higher rate of congenital abnormalities in the children of women who became pregnant <6 months after I-131 therapy than in those born to women who became pregnant >6 months after therapy.

Four studies evaluated the effect of I-131 therapy on pregnancy rates. Mittica et al[22] observed term pregnancies in different age groups, where patients aged 34–48 years had a higher term pregnancy rate

than those aged above that. Giusti et al[23] showed the same number of term pregnancies in the I-131 and control groups. In contrast, Ko et al[24] found a much lower incidence of pregnancy in patients who received I-131 therapy compared with those who did not. Kim et al[25] showed that the conception rate in the I-131 group was lower than that in the surgery-only group at intervals of 0–5 months and increased at 12–23 months after therapy. Wu et al[26] showed that the birth rates among women who received I-131 therapy and those who did not showed no significant differences at 4 years of follow-up (p = 0.81). In the subgroup analysis, women aged 35–39 years who received I-131 therapy experienced a significantly reduced birth rate compared with those who did not receive therapy (11.5 *versus* 16.3 births per 1,000 women/year, p<0.001), and I-131 therapy can have an impact on birth rates in certain age groups.

This study revealed that male reproductive function is influenced by changes in the levels of hormones involved in the development of egg cells, namely, the hormones FSH and LH, and sperm quality, as assessed by sperm concentration, motility, and morphology. FSH and LH levels were found to be significantly increased in several studies. Soltani et al[27] discovered elevated FSH and LH levels 3 months before therapy, which returned to normal at 12 months post-therapy. Similarly, Bourcigaux et al[28] reported elevated hormonal levels in the first 3 months post-therapy, which returned to normal in 13 months post-therapy. Canale et al[12] found elevated hormonal levels at 6 months post-therapy, which returned to normal at 12 months post-therapy. However, 40% of patients receiving multiple doses experienced persistent improvement 12 months post-therapy.[12] All three studies above had similar observation periods post-therapy, making it possible to detect the same pattern of initial transient improvement and recovery to basal values within 12 months. Nies et al[29] evaluated the FSH, LH, and testosterone levels in patients receiving I-131 therapy. They did not show significant differences compared with the 10th percentile of reference values in the general population defined by the World Health Organization (WHO).[29]

In studies discussing male reproductive effects, changes were also observed. Soltani et al[27] reported significant changes in sperm count in patients receiving high-dose therapy. There was a decrease in the sperm count in the first 3 months, which returned to normal after 12 months post-therapy (basal volume: 38.22 [19.40], volume at 3 months: 32.05 [17.96], and volume at 12 months: 36.66 [18.81] millions/ml; p<0.001). Analysis of sperm motility and morphology after 12 months showed a decrease compared with the initial values. However, due to the limited examination time of only 12 months, improvements were unknown in the following year.[27] Canale et al[12] mentioned that in a group of patients who received multiple doses, I-131 therapy caused a severe decrease in sperm concentration at 6 months follow-up compared with that at basal conditions. After 12 months post-therapy, 50% of the multiple-dose group experienced oligozoospermia, 20% of the single-dose group experienced mild oligozoospermia (borderline 13.5 and 14.5 millions/ml), and others returned to normal values. Progressive sperm motility was not reduced compared with basal values. Among the entire population, 25% experienced a persistent decrease in testicular volume, with 40% receiving multiple doses and 10% receiving single doses.[12] The median semen quality was similar to that of the general population, as defined by the WHO. The progressive motility of the sperm was the same at each examination.[12] In contrast, Nies et al[29] did not find any statistically or clinically relevant differences in semen quality between patients and the general population, based on the 10th percentile.

We examined the impact of I-131 therapy on fertility in male and female patients with DTC who underwent treatment during their reproductive years. AMH level is an indicator to be considered in assessing female reproductive function after I-131 therapy. AMH is produced by granulosa cells that develop ovarian follicles, making it a marker of ovarian reserve. Thus, serum AMH levels correlate with the number of growing follicles.[30,31] I-131 emits charged particles that can damage the ovaries[32] by inhibiting ovarian follicle development, resting, or causing follicle death. When follicles are resting or dead, AMH levels become low or undetectable unless the resting follicles develop again and reach the pre-antral or antral stage to be detected again.[30,33] In addition, AMH levels can recover several months after I-131 treatment. The potential influences for the decrease are the patient's age and age at menarche.[16] In certain situations where the ovaries are exposed to gonadotoxic agents, as the strong and accepted marker of ovarian reserve, AMH level might not accurately reflect the viable primary oocyte pool to indicate recovery potential.[34]

A variation in AMH levels was observed possibly due to the timing difference in the hormonal level assessment of the four studies. If hormonal levels are monitored periodically for several months after therapy, potential improvement will be observed despite not returning to basal values. However, if the observation is only done before and a year after therapy, only AMH levels can be detected with a value lower than its initial level, and no potential improvement can be observed.[16–18] Different periods from I-131 exposure to the study period might contribute to the different results between these studies. The research by Acıbucu et al[20] was carried out for a minimum period of 3 months post-therapy, allowing the influence of radionuclides to persist on cells. However, Nies et al[21] carried out a study for a minimum period of 5 years post-therapy; thus, the effects of the radionuclide disappeared. In contrast, Mittica et al[22] and Giusti et al[23] found no significant difference in AMH levels between patients with DTC who received I-131 therapy and those who underwent only surgery. Both studies showed similar results because they examined similar patient age characteristics in therapy-only and surgery-only groups.

FSH and LH are two hormones closely related to the menstrual cycle because they support the growth of ovarian follicles and ovulation. Elevated FSH and LH levels indicate possible ovarian disorders.[35,36] These are indirect markers of the ovarian reserve, and their blood concentrations increase only when the it is severely compromised.[37] However, other studies have stated that they fluctuate along the menstrual cycle, unlike stable AMH. Therefore, AMH is more accurate than FSH and LH in assessing ovarian reserve and reproductive function. Although AMH can better describe the condition of the ovaries, both AMH and FSH levels should be evaluated using clinical information and other test results to provide a more comprehensive picture of female reproductive health.[33,38]

Damaged or dead ovarian cells can result in a decrease in the production of estrogen and progesterone as sex hormones.[39] Thus, the pituitary gland increases FSH production to stimulate the ovaries to become more active. FSH levels usually elevate in response to reduced ovarian follicular reservation or the inability of the ovaries to respond appropriately to FSH stimulation.[35] In this study, a variation in FSH levels was identified. These differences may have been caused by the large dose administered to the patients. In three studies, a dose of 75–100 mCi was administered to patients, whereas Acıbucu et al[20] administered a dose of 100–150 mCi. In addition, the menstrual cycle of each patient can affect the FSH levels.

Additionally, patients who undergo total thyroidectomy that follows with I-131 therapy receive levothyroxine at a suppressed thyroid-stimulating hormone dose, which may alter the menstrual cycle, and reproductive hormones. Altered hormonal balance post-therapy can influence changes in the menstrual cycle frequency, duration, or volume.[33,35] Some women may experience shorter or longer cycles, or even amenorrhea while the body adapts to hormonal changes.[40] In addition, various doses were administered to patients in three studies in this review, causing various impacts of I-131 therapy on the menstrual cycle between individuals and different improvements approximately a year post-therapy.[15,16,20]

The incidence of abortion and congenital abnormalities could not be confirmed to be caused by I-131 therapy. However, it is recommended to avoid pregnancy in the first year post-therapy to ensure complete elimination of the radionuclide and remission of the disease.[41] Recurrent miscarriages, including those occurring within 6 months of therapy, may be caused by chromosomal abnormalities or immunological incompatibility.[42] The reviewed literature showed no association between an increased risk of miscarriage, premature birth, and congenital abnormalities with I-131 therapy 1 year after treatment. This finding is supported by a systematic review by Moon et al[43] with similar findings. The differences in sample size and examination time between these three studies may have influenced the results. The larger the research sample, the more representative the results are for the general population. The smaller the sample, the greater the likelihood of variability and the less representative the results. These results may reflect special conditions if the examination was conducted at a certain time.[23–25]

The birth rate was not significantly different between women who received and those who did not receive I-131 therapy within a 4-year follow-up period, as Wu et al[26] reported. However, their subgroup analysis found a significantly reduced birth rate in women aged 35–39 years who received I-131 therapy compared with those who did not receive therapy. This finding suggests that I-131 therapy may affect birth rates in certain age groups. In contrast, Anderson et

al[44] reported the same birth rate between women who did and did not receive I-131 therapy, with cumulative incidences of birth of 30.0% and 29.3%, respectively, over a maximum of 14.5 years of follow-up. This birth rate difference may stem from different sample sizes and follow-up times, where longer periods allow researchers to detect post-term births that may not be visible at shorter follow-up times.

The decline in pregnancy and birth rates may be influenced not only by the potential impact of I-131 therapy on reproductive health but also by doctors' recommendations that affect patients' decisions to become pregnant. Clinical practice recommends that patients should not become pregnant or be impregnated for 6–12 months after I-131 therapy. This may alter the incidence of pregnancy in patients who receive I-131 therapy.[8] Additionally, patients' psychological problems can also contribute to reduced pregnancy rates. Further investigations are needed to understand the impact on pregnancy and delivery success in patients receiving I-131 therapy.[26,45]

FSH plays an important role in spermatogenesis, including stimulating the Sertoli cells to help the testicles grow and produce mature sperm. LH stimulates the Leydig cells in the testicles to produce testosterone. Testosterone is a male sex hormone essential for the development and maintenance of male sex organs, such as the testicles and penis, and for maintaining sperm health.[35]

The energy from I-131 may damage the Leydig and Sertoli cells in the testicles.[46] As the Leydig cells produce testosterone and Sertoli cells regulate sperm production, damage to these cells can decrease testosterone production by the testicles. The pituitary gland will then respond by producing more FSH and LH to stimulate the testicles to become more active in testosterone production.[47] This finding is supported by the ATA in 2015, which states that higher cumulative activity (500–800 mCi) in men is associated with the risk of increasing FSH levels. Findings of the ATA suggested that higher cumulative doses may contribute to an increased risk of elevated FSH levels. Therefore, patients receiving multiple or high cumulative doses may have different responses compared with those receiving a single dose. The return of hormonal levels approximately 1 year after therapy allows for improvement, and the damage that occurs to male reproductive function is only reversible depending on the dose received.[8]

The energy of I-131 can damage the sperm in the testicles by inhibiting or even stopping sperm production. Sperms are very sensitive to radiation, and damage can lead to decreased sperm count and quality.[48] The indirect effects of radiation can also increase oxidative stress in the testicles. Oxidative stress can damage sperm cells and disrupt mitochondrial function, which is important for energy and cell function.[49] In this study, a decrease in sperm concentration and morphology was observed in the first 3 months post-therapy, which returned to normal after 12 months, signifying potential improvement in male reproductive function 1 year after therapy.[27] Three studies had similar observation periods post-therapy and sample sizes, making it possible to detect the same pattern of decreasing sperm count in the first 3 months and returning to normal after 12 months post-therapy. These three studies had the same dosing range, confirming that the doses administered can influence the effects.[12,27,28] One article did not report any statistically or clinically relevant differences in semen quality between patients and the general population based on the 10th percentile. This difference may have occurred because of different follow-up times and the characteristics of the doses administered in this study; therefore, researchers could not observe changes in sperm quality.[29]

In conclusion, women who received I-131 therapy experienced reproductive side effects, such as a decrease in AMH levels in approximately the first 12 months without further decrease and temporary changes in the menstrual cycle that improved after the next year, which were influenced by the dose administered. In addition, no effect on pregnancy was observed the following year. Meanwhile, men who received I-131 therapy experienced an increase in FSH and LH levels and a decrease in sperm count and motility with a change in morphology for approximately 6 months after therapy, which improved 1 year after therapy and was influenced by the dose administered. Furthermore, I-131 therapy typically causes temporary reproductive side effects lasting for approximately 1 year in both women and men and possibly influences other reproductive hormones. Further studies should be conducted with a proper research design and should include other types of hormones that could be influenced, demographic conditions, and other more specific factors to reduce high heterogeneity.

This review offers a comprehensive summary of the existing literature, providing clinicians with valuable insights to guide patient counseling regarding the risks involved and the potential need for fertility preservation. Additionally, it highlights the transient nature of the reproductive side effects associated with I-131 therapy, such as changes in hormonal levels and sperm parameters. These findings underscore the importance of monitoring the reproductive health of patients after treatment. Overall, this review serves as a crucial resource for healthcare providers who aim to support their patients in making informed decisions regarding fertility after cancer treatment.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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