A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors


CRD summary
The review found no evidence to suggest that radioactive iodine had important adverse effects on gonadal function, fertility and pregnancy outcomes beyond 12 months in female survivors of differentiated thyroid cancer, except possibly slightly earlier menopause. The authors’ conclusions were based on the evidence presented, but should be interpreted cautiously due to the poor quality of the included studies.

Authors' objectives
To assess the effects of radioactive iodine on ovarian function and future pregnancy in female differentiated thyroid cancer (DTC) survivors.

Searching
MEDLINE, The Cochrane Library, ACP Journal Club, EBM Reviews, DARE, EMBASE, Cumulative Index to Nursing, Allied Health Literature and HealthSTAR were searched from inception to November 2007. Studies were restricted to those in English. Reference lists of retrieved studies were searched and content experts were contacted for additional papers.

Study selection
Studies were eligible if they were cohort studies, cross-sectional studies, cancer registries, administrative datasets, meta-analyses or case series of more than five patients and a control comparison (either external comparison or comparison to measures prior to radioactive iodine). Participants were required to be females with DTC; women who inadvertently received radioactive iodine during pregnancy were excluded. Eligible outcomes were sex steroid (oestrogen, oestrone, progesterone) or gonadotropin (follicular stimulating hormone, luteinising hormone) levels, ovarian function, menstruation, ovulation, fertility, age of menopause, future fertility, pregnancy and offspring (including live births, spontaneous abortions, induced abortions, stillbirths, preterm birth, infant mortality and congenital defects).

In the included studies, age at first radioactive iodine treatment varied from eight to 50 years. Cumulative dose activities of radioactive iodine administered for treatment varied from 30 to 1,099mCi, where reported. In some studies, patients were also treated with levothyroxine. Comparisons were made with either contemporaneous controls, pre-radioactive iodine data or historical rates. Studies were performed in North America, South America, Europe, Asia and the Middle East.

Two reviewers independently selected studies by examination of abstracts and further review of relevant full text citations. Disagreements were resolved by consensus.

Assessment of study quality
Quality assessment was undertaken according to specific criteria: whether the study had longitudinal follow-up or cross-sectional sampling; type of control group (internal, contemporaneous external controls or historical external controls); whether description of losses to follow up for longitudinal studies was made; presence of a statistical comparison for the outcome of interest.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted on relevant outcomes, with means or medians and standard deviations or ranges calculated for continuous data and percentages for categorical data.
Two reviewers independently extracted data; the authors did not state how disagreements were resolved.

Methods of synthesis
Results for individual studies were displayed in tables and synthesised in narrative format.

Results of the review
Sixteen studies (n=3,023) were included. All studies were observational. Most studies had longitudinal follow-up of clinical cohorts. Eight of the studies included comparisons with contemporaneous controls. Eight longitudinal studies included descriptions of losses to follow-up that ranged from 6% to 15%. Many studies did not have age matching or adjustment in the comparisons or detailed information on confounders.

Transient absence of menstrual periods occurred in 8% to 27% of women within the first year after radioactive iodine (particularly in older women), but resolved within one year in all affected women (three studies). In two studies, radioactive iodine-treated women experienced menopause at a significantly younger age (mean/median late 40s) compared to control (levothyroxine or no radioactive iodine treatment) (mean/median early 50s).

Six studies did not show a significant increase in miscarriage rates in women who had a history of radioactive iodine treatment compared with those who did not receive radioactive iodine treatment. One study reported a significant increase in risk of miscarriage in women exposed to radioactive iodine treatment within one year preceding conception compared with unexposed women (40% versus 18%). Two studies reported an increase in induced abortions within one year of radioactive iodine treatment compared to control (50% versus 16% to 18%).

There was generally no evidence of a significant difference in long term infertility, miscarriages, induced abortions, stillbirths, offspring neonatal mortality and congenital defects in radioactive iodine-treated women compared to control.

Authors’ conclusions
There was little observational evidence to suggest important adverse events of radioactive iodine treatment on gonadal function, fertility or pregnancy outcomes beyond 12 months in female survivors of DTC, with the exception of a possibly slightly earlier age of menopause.

CRD commentary
The review addressed a clear research question. Inclusion criteria were appropriate, although a broad range of study designs were eligible. A wide range of electronic databases were searched. Attempts were made to find additional studies by searching reference lists and consulting with experts. Search terms were not reported, so it was not possible to determine the quality of the search strategy. Eligible studies were restricted to those published in English and no explicit attempts were made to find unpublished studies, so language and publication bias could not be ruled out. Appropriate methods were used for selection of studies and data extraction.

Quality assessment was limited and no methods to minimise bias and reviewer error in this process were reported. No assessments were made for dealing with confounders. Studies were generally of poor quality and most had small sample sizes; a proportion had historical controls, incomplete reporting of relevant data and incomplete or unclear follow-up. The decision to synthesize studies in narrative format was appropriate given the variation in study designs and variety of control groups.

The authors’ conclusions were based on the evidence presented, but should be interpreted cautiously given the poor quality of the included studies.

Implications of the review for practice and research
Practice: The authors stated that recommendations that women treated with radioactive iodine wait at least six to 12 months before conceiving were appropriate. Women considering radioactive iodine treatment for DTC should be counselled that there was little evidence to suggest important adverse effects of radioactive iodine on gonadal function.
and fertility of pregnancy outcomes beyond 12 months after radioactive iodine, except for a possible slightly earlier menopause.

**Research:** The authors stated that future larger controlled prospective studies were needed to assess gonadal and reproductive effects and clinical outcomes in the offspring of women with DTC who received radioactive iodine. Studies should compare short- and long-term outcomes in women who received radioactive iodine who were pre-treated with recombinant thyroid-stimulating hormone compared to those who were hyperthyroid. Any potential protective effect of administration of ovarian suppression should also be explored.

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